Reporting of “Theoretical Design” in Explanatory Research: A Critical Appraisal of Research on Early Life Exposure to Antibiotics and the Occurrence of Asthma

Hayat Bentouhami
Lidia Casas
Joost Weyler
University of Antwerp, Social Epidemiology and Health Policy, Wilrijk, 2610, Belgium

Abstract: “Theoretical design” comprises the development of an occurrence relation and the specification of the study domain. In explanatory research, the occurrence relation causally relates one determinant to the occurrence (of an event or a state) taking into account other relevant characteristics (confounders and modifiers). Conflicting results in explanatory research might be (partially) explained by differences in the “theoretical design” or by a mismatch between the “theoretical design” and the “design of data collection”. In this critical review, the reporting of “theoretical design” is assessed in articles on the association between early life antibiotic use and the occurrence of asthma. Articles investigating a relationship between early life antibiotic use and the occurrence of asthma were searched in PubMed and systematically selected for critical review. The full text was read and important elements of study design were extracted (the research question/hypothesis, seven key elements of “theoretical design” (measure of occurrence, case (event or state) definition, conceptualization (and operationalization) of the exposure, temporal relation between outcome and exposure, confounders and effect modifiers taken into account and the domain of the study), the method of data collection and the method of data processing). A comparison was made between articles published before and after the publication of the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) statement (2007). Sixty-three articles were included for review. Thirteen articles reported the seven key elements of “theoretical design” that were questioned. No marked differences in reporting were observed pre- and post-STROBE. All articles reported some key elements of “theoretical design”; however, the reporting is not structured and not linked to the concept of “theoretical design”. Conceptualizing, delineating and explicit reporting of “theoretical design” is quintessential for the quality and transparency of explanatory research.

Keywords: theoretical study design, occurrence function, etiological research, antibiotic use, asthma

Introduction
Conceptualizing, delineating and reporting all elements of study design (the design of the theoretical object, the design of the collection of the data and the design of the processing of the data collected) is quintessential both for the quality and for the interpretability of a study, especially when complex relationships between outcome(s) and exposure(s) are investigated.
In epidemiological research, when specifying study design, researchers often merely refer to the “design of data collection” (eg, cohort study, case-control study, cross-sectional study, …). However, the design of how the data are collected should be considered as only a (be it an important) part of study design. Study design comprises three parts: the design of the “theoretical object” of the study (what will be studied and in what context), the design of how the data are collected (what kind of data will be collected and how will they be collected, ie, defining the study population, the sampling procedures, and the measuring of the characteristics studied) and the design of how the data are processed (the main statistical methods used to process the data from the measurement of the characteristics to the operationalized variables used in the assessment of the association between outcome and exposure).

The development of the “theoretical design” is determined by an appropriate research question that should include the outcome under study, the exposure(s) of interest, and the domain of the study. Central to the “theoretical design” is the translation of this research question/hypothesis into an occurrence relation. Focusing here only on explanatory research, the occurrence relation relates one determinant (the presumed cause) to the (frequency of) occurrence (of an event or a state) taking into account other relevant characteristics (extraneous to the causal pathway: confounders and non-extraneous to the causal pathway: effect modifiers). The application of a theoretical framework for causal inference, eg, the theory of directed acyclic graphs (DAGs) or the sufficient-component cause model can be helpful as a tool for the selection of the relevant characteristics prior to the collection and/or exploration of the data.

Already in the eighties of last century, Miettinen referred to the occurrence relation as being part of “object design”.

Designing the type of end result of an epidemiologic study means making the transition from an informal concept of the research problem to an express definition of the occurrence relation to be studied. This involves designing the nature of the occurrence relation and the domain of the empirical occurrence relation. The nature of the occurrence relation includes: (1) the outcome state(s) or event(s); (2) the parameter of interest; (3) the determinant(s); (4) the time relation between outcome and determinant status; (5) modifiers and (6) potential confounders.

The explicit formulation of this “object design” or “theoretical design”, including the formulation of an occurrence relation and a domain, is crucial for the choice of an appropriate method of data collection and method of data processing. In what follows both “object design” and “theoretical design” will be referred to as “theoretical design”, since these are conceptually similar.

When it comes to the reporting of epidemiological studies, different guidelines have been published. One of these guidelines, the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) statement refers to the importance of reporting the objectives of a study (note that these objectives are not objects as described by Miettinen) and advises to present key elements of study design early in the methods section or at the end of the introduction. In a publication by the Responsible Epidemiological Research Practice (RERP) working group of the Netherlands Epidemiological Society, a guideline also referring to the need for an appropriate design was formulated. This guideline, however, does not discuss details on technical aspects of epidemiological research (eg, study design).

Considering the importance of the formulation of a relevant research question/hypothesis (advised by both STROBE and RERP) and the translation hereof into an explicit “theoretical design” (based on both an occurrence relation and a domain) for the designing of data collection and the designing of data processing, these fundamental elements of study design should be explicitly reported in epidemiological literature.

The explicit formulation of an appropriate “study object” or “theoretical design” (both in the setting up of a study as well as in the reporting) is essential for the justification of the choice for the method of data collection and method of data processing. Diverging results in research on complex exposure–outcome relationships might be (at least partially) explained by differences in the object of the study (different underlying ‘theoretical designs’) or by a mismatch between the object of the study (”theoretical design”) and the way data are collected (“design of data collection”). The relationship between early life antibiotic use and the occurrence of asthma is such a complex exposure–outcome relationship and studies on this relationship have been showing diverging results. Several studies refer to reversed causation and confounding-by-indication as a possible
explanation of the associations found between early life antibiotic use and the occurrence of asthma. Asthma is a complex disease whose etiological mechanisms are not fully understood. Potential risk factors for asthma can act in the prenatal period, at birth and later in life. As a consequence, the unraveling of the etiology of asthma is challenging, since historical reconstruction (ie, prior to asthma onset) of relevant exposures, risk factors and other relevant characteristics is not straightforward. Early life exposures might also not be as relevant for adult onset asthma as for childhood onset asthma as the time interval between the exposure and the outcome differs.

So far, existing methodological reviews on the association between early life antibiotic use and the occurrence of asthma, mainly focus on the design of data collection (cohort, case control, retrospective, prospective, …) and on how outcome definition for asthma, reversed causation and confounding-by-indication could affect this association. Marra et al advise in their review that future research on the association between early life antibiotic use and the occurrence of asthma should address other methodological flaws. To our knowledge, no methodological reviews have been conducted focusing on the explicit reporting of “theoretical design” in explanatory research. Therefore, the aim of this critical review was to gain insight (factual knowledge) in the “current” explicit reporting of “theoretical design” as an “intercept only” function in (English language) articles published in scientific peer reviewed journals indexed in the PubMed database on the association between early life antibiotic use and the occurrence of asthma.

2. To what extent does the use and reporting of “theoretical design” differ between articles published before vs after STROBE (2007)?

“Theoretical design”: Current explicit reporting of “theoretical design” as a function of the era of publication (pre- vs post-STROBE) in (English language) articles published in scientific peer reviewed journals indexed in the PubMed database on the association between early life antibiotic use and the occurrence of asthma.

Search Strategy and Selection of Articles
A search in PubMed was conducted using the following medical subject headings (MeSH): “asthma” AND ‘antibiotics’. To assess current explicit reporting of “theoretical design”, “current” was defined as the era including all (English language) articles published in a scientific peer reviewed journal indexed in the PubMed database on the association between antibiotic use and the occurrence of asthma. The search was performed on the 7th of January 2019 and a selection was made from all articles resulting from the search in PubMed reaching over the predefined period. This selection was based on a three-step procedure.

First, in the screening phase, the title and the aim or research question/hypothesis reported in the abstract was read. Articles were excluded if it was clear from the information provided that the interest was not in investigating a causal relationship between early life antibiotic use and the occurrence of asthma. If this information was ambiguous or missing in the abstract, the article was not excluded in this first step. Secondly, the full abstract of the remaining articles was read. In this step, articles were excluded if (1) the articles did not report on a study investigating a causal relationship between early life antibiotic use and the occurrence of asthma, (2) the causal relationship between early life antibiotic use and the occurrence of asthma was investigated in vitro or in animals and (3) no full (English language) text of the article was accessible or available. Articles remaining after this screening phase were assessed for

Methods
Theoretical Design
The (factual) research questions and corresponding theoretical designs are:

1. To what extent do researchers explicitly report a “theoretical design” in (English language) articles published in scientific peer-reviewed journals indexed in the PubMed database on the association between early life antibiotic use and the occurrence of asthma?
eligibility by reading the full text of the articles. After reading the full text of the remaining articles, articles were excluded if they were not primary publications (e.g., review articles) or they did not report on a study investigating a causal relationship between early life antibiotic use and the occurrence of asthma after all. This implies that the abstract was missing or the information provided in the abstract was incomplete or ambiguous. The remaining (English language) articles reporting on a study that investigated a causal relationship between early life antibiotic use and the occurrence of asthma were included for review.

No abstract domain was specified for this critical review. The aim was to gain factual knowledge about current explicit reporting of a “theoretical design” in (English language) articles published in scientific peer reviewed journals indexed in the PubMed database on the causal relationship between early life antibiotic use and the occurrence of asthma (observation period from June 1998 until the 7th of January 2019, i.e., the era between the publication of the oldest article indexed in PubMed on the association between early life antibiotic use and the occurrence of asthma and the day the search was performed). Occurrence of asthma was not restricted to occurrence in childhood, but articles investigating occurrence of asthma in adolescence or adulthood were included as well.

Extraction of Relevant Information
For every article selected, the following information (Table 1) was extracted after reading the full text twice (HB).

Critical Review of the Articles
As study design starts with the formulation of an appropriate research question/hypothesis which is then translated into a “theoretical design”, the presence of such an appropriate research question/hypothesis referring to the outcome, the exposure(s) and the domain of the study was first assessed.

Secondly, the presence of an explicitly formulated “theoretical design” (including the occurrence relation, an explicit temporal structure and the formulation of the domain of the study) was assessed. When no explicit “theoretical design” was reported, the presence/absence of seven key elements of “theoretical design” was discussed (HB and JW):

(a) Measure of occurrence.
(b) Case (event or state) definition (for asthma).
(c) Conceptualization and operationalization of the exposure.
(d) Temporal relation between outcome and exposure derivable from the research question/hypothesis or from the combination of the case (event or state) definition and conceptualization of the exposure. This means that by reading the research question/hypothesis or the reported case (event or state) definition and the conceptualization of the exposure, it should be clear how the exposure was situated in time in relation to the outcome (as an “antecedent” or as a “starting point”).
(e) Confounders that were considered.
(f) Effect modifiers that were taken into account.
(g) Domain of the study.

Derivation of the Theoretical Design
For all articles where the temporal relation between the outcome and the exposure could be derived from the aim or from the case (event or state) definition and the conceptualization of the exposure, a “theoretical design” was formulated. In order to formulate this “theoretical design” all information extracted from the article (specified in Table 1) was considered. The “theoretical design” was formulated first by HB and JW separately. In case of divergent interpretations, the “theoretical design” was discussed and assigned “in consensus”.

Comparison Based on the Year of Publication
The explicit reporting of a “theoretical design” (or the seven key elements (cfr supra) of “theoretical design” in case no explicit “theoretical design” was reported) was compared between articles published before and after the publication of the STROBE statement in 2007 by categorizing the articles in two groups: articles published between 1998 and 2007 and articles published between 2008 and 2019.

Processing of the Extracted Information
For the presence of all reviewed elements (presence of the outcome, exposure and domain in the research question/hypothesis, explicit reporting of “theoretical design”, presence/absence of seven key elements of “theoretical design”) absolute numbers are presented for all articles together. For the comparison based on the year of

https://doi.org/10.2147/CLEP.S318287

DovePress

Clinical Epidemiology 2021:13

Bentouhami et al

DovePress

Clinical Epidemiology 2021:13

758
| Information Extracted                                                                 | Explanation                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Journal                                                                          | Needs no further explanation                                                                                                                                                                               |
| 2. Year of publication                                                               | Needs no further explanation.                                                                                                                                                                             |
| 3. Title of the article                                                              | Needs no further explanation.                                                                                                                                                                             |
| 4. Aim of the study                                                                  | The aim of the study reported at the end of the introduction section was copied.                                                                                                                                 |
| 5. Research question or hypothesis of the study                                      | The research question/hypothesis reported was copied.                                                                                                                                                     |
| 6. Whether the authors mentioned the word(s) “(study) design” in the text (including the location in the text) | Needs no further explanation.                                                                                                                                                                             |
| 7. The case (event or state) definition for asthma                                   | Needs no further explanation.                                                                                                                                                                             |
| 8. Scientific \(T_0\) (and whether this was explicitly mentioned) and (theoretical) temporal aspects | \(T_0\) refers to scientific (reference) time. If the interest is in studying “future occurrence of asthma as a function of current exposure to antibiotics”, then the moment of realization of exposure is the reference \(T_0\). If the interest is in studying the “current occurrence of asthma as a function of a history of antibiotic use”, then the moment of occurrence (asthma onset/diagnosis) is the reference \(T_0\). If the \(T_0\) was not explicitly mentioned, a decision was made after discussion (HB and JW) on what \(T_0\) could have been after taking into account the aim or research question/hypothesis of the study, the measure of occurrence, the method of data collection, the method of data processing and the abstract (theoretical) temporal aspects of confounders. The following example refers to the process of defining \(T_0\):  
**Aim:** “… to assess what the association is between the exposure to antibiotics in the first year of life and later risk on asthma occurrence by age 7.”  
**Measure of occurrence:** Future incidence  
**Method of data collection:** Longitudinal study  
**Method of data processing:** Cox proportional hazards regression  
**Abstract temporal aspect of confounders:** Confounders were assessed in the first year of life of the child  
\(T_0\) in this case would be at the age of 1 year. Incident cases of asthma would be detected from this point in time and onwards (= future occurrence). |
| 9. The measure of disease occurrence (eg: prevalence, incidence) and the abstract (theoretical) temporal aspect hereof (current-, future-)\(^a\) | Needs no further explanation.                                                                                                                                                                             |
| 10. The conceptualization of the exposure and the abstract (theoretical) temporal aspect hereof (past-, current-)\(^a\) | The conceptualization of the exposure to antibiotics as reported by the authors was extracted. In case the exposure was conceptualized in multiple ways (eg antibiotic use during pregnancy, antibiotic use during the first year of life, …), all conceptualizations were extracted. Additionally the temporal aspect (past exposure to antibiotics if the interest was in the current occurrence of asthma or current exposure to antibiotics if the interest was in the future occurrence of asthma) was extracted from the article. |

(Continued)
### Table 1 (Continued).

| Information Extracted | Explanation |
|------------------------|-------------|
| 11. The operationalization of the exposure | Operationalization of the exposure to antibiotics refers to how the authors operationalized exposure to antibiotics when the data were processed. This could be for example dichotomous (exposed vs non-exposed), but also in several categories of exposure (per class of antibiotic, per number of courses, ...). |
| 12. The measurement method for the exposure | The method used to assess the exposure to antibiotics in the study was extracted. This can be for example a questionnaire. |
| 13. The measure of association | The estimate calculated by means of the statistical method applied to assess the strength of the association between antibiotic use and the occurrence of asthma was extracted from the article. This could be a hazard ratio, an odds ratio, an incidence density ratio, a causal fraction, .... |
| 14. Confounders taken into account (including the abstract (theoretical) temporal aspects) | All confounders taken into account and reported by the authors (including the timing of assessment) were extracted. |
| 15. Effect modifiers taken into account (including the abstract (theoretical) temporal aspects) | All effect modifiers taken into account and reported by the authors (including the timing of assessment) were extracted. |
| 16. The justification for the selection of confounders and/or effect modifiers | If any justification for the selection of confounders and/or effect modifiers (e.g., selection based on prior knowledge, selection based on the construction of a DAG, sufficient-component cause model) was reported in the article, this was extracted. |
| 17. The domain of the study | The domain refers to the population to whom the results can be applied on. After reading the full text, the domain of the study reported (either explicitly or implicitly) was extracted. |
| 18. The design of data collection | The method used to collect the data for the study was extracted. This could be for example by means of a (birth) cohort, a case-control study, .... Example from a reviewed article: "The Home Allergens and Asthma Study is a prospective birth cohort study of children with a parental history of asthma or allergies in the Boston metropolitan area." In this study the association between antibiotic use and the occurrence of asthma was assessed by using data from a prospective birth cohort. Therefore the design of data collection is a prospective birth cohort. |
| 19. The design of data processing | The main statistical methods used to process the data and to assess the association between antibiotic use and the occurrence of asthma was extracted from the article. |
| 20. Whether there is any referral to a methodological paper or work supporting the used methods or referral to a reporting guideline | If any referral was made to a methodological article, a theoretical work or a reporting guideline supporting the applied epidemiological methods in the study or the reporting, this was indicated with “yes”. |

**Notes:** *Temporal aspects refer to the time structure between the occurrence of asthma and the exposure to antibiotics. In etiologic research, a causal relationship between an outcome and an exposure can only be assessed when the exposure occurred before onset of the outcome under study; Italic font indicates text quoted from an article.*

---

Publication (pre- vs post-STROBE) absolute numbers and percentages were calculated per group. No statistical tests were performed as the aim was limited to the reporting of the facts in the selected articles (based on topic and era), and not to make any inference with respect to eventual differences found pre- vs post-STROBE.
For each of the assessed elements of “theoretical design” (in case no explicit “theoretical design” was reported), two examples are provided in Appendix 3, one in case the assessed element was considered to be present and one in case the same element was considered absent. All examples are taken from the reviewed articles, but are anonymized. Also, for the derivation of “theoretical design” anonymized examples are presented in Appendix 4 to explain this process. Text quoted literally from the articles is written in italic and between quotation marks. Reporting was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.  

Deviations from the Methodology

Any deviations from the described methodology (cfr supra) are indicated and explained in the results section.

Results

Selection of Articles

The search in PubMed yielded 3973 articles. In Figure 1 the selection procedure for the articles is presented. The observation period was defined as the era between the publication of the oldest article (investigating a causal relationship between early life antibiotic use and the occurrence of asthma) and the day the search was performed (ie, the 7th of January 2019). Within this observation period, the oldest article investigating a causal relationship between early life antibiotic use and the occurrence of asthma and indexed in PubMed was published in June 1998. The most recent article was published in August 2018. After the exclusion of 3910 articles (explained in detail in Figure 1), 63 articles were included (see Appendix 1).

Critical Review of the Extracted Information

Detailed extracted information (cfr Table 1) for all 63 articles can be consulted in Appendix 2. Examples are provided in Appendix 3 to explain how the extracted information was reviewed.

None of the 63 articles reported a research question and only 16 reported a hypothesis. All articles reported the aim(s) of the study. As a consequence the presence of the outcome, the exposure and the domain was assessed from the formulation of the aim(s) (instead of from the formulation of the research question/hypothesis). For 46 articles, the aim(s) comprised the outcome, the exposure and the domain of the study. None of the 63 articles explicitly reported a “theoretical design”. Therefore, all articles were assessed on the presence of seven key elements of “theoretical design” (measure of occurrence, case (event or state) definition, conceptualization (and operationalization) of the exposure, temporal relation between outcome and exposure, confounders and effect modifiers taken into account and the domain of the study). Thirteen out of 63 articles reported all seven key elements of “theoretical design” questioned. The other 50 articles reported only three to six out of the seven key elements of “theoretical design” (cfr supra). Table 2 shows the absolute number of articles that (implicitly) reported the listed key elements of the “theoretical design”.

Fifty-seven out of 63 articles reported the measure of occurrence (prevalence or incidence of asthma). Out of 63 articles, 59 reported a case (event or state) definition. Fifty-seven out of 63 articles reported the conceptualization and operationalization of the exposure. For 50 articles, the temporal relation between the outcome and the exposure could be derived from the aim or the case (event or state) definition and conceptualization of the exposure. Regarding confounders and effect modifiers, 56 out of 63 articles reported the confounders that were considered and only 24 out of 63 articles reported to have taken effect modifiers into account. All articles reported the domain of the study. However, none of the authors explicitly referred to this as the “domain”.

Derivation of the “Theoretical Design”

For 50 out of 63 articles, the temporal relation between outcome and exposure could be derived from the aim or the case definition and conceptualization of the exposure. For those 50 articles, HB and JW independently formulated a “theoretical design”.

For 15 articles, there was consensus that the authors were interested in investigating “current occurrence of asthma as a function of past exposure to antibiotics”. For another 24 articles, there was consensus that the authors were interested in investigating the “future occurrence of asthma as a function of current exposure to antibiotics”. For the remaining 11 articles, there was initially no consensus on what the “theoretical design” could be. After discussion, consensus on the “theoretical design” was reached between HB and JW. For 10 articles HB agreed that the “theoretical design” was that formulated by JW and for one article JW agreed with the “theoretical design” to be that formulated by HB. The
information reported in these articles was often ambiguous or even missing. Formulating a “theoretical design” was therefore not straightforward. For all scenarios, an example is provided in Appendix 4 to explain this in detail.

**Comparison Based on Before/After the Publication of STROBE (2007)**

Out of 63 articles, 16 were published between 1998 and 2007 and 47 were published between 2008 and 2019.

Between articles published before and after STROBE, no marked differences were observed neither in the reporting of all seven key elements of “theoretical design” questioned (3/16 vs 10/47, respectively), nor in the reporting of the outcome, exposure and domain in the aim (pre-STROBE: 11/16 vs post-STROBE: 35/47).

For the reporting of the individual key elements of “theoretical design” (a-g), there were no marked differences in the articles published after the publication of the STROBE statement (ie, from 2008 onwards), except for reporting the measure of occurrence and the specification of effect modifiers (Table 3).
Discussion

In this critical review, the reporting of a “theoretical design” in (English language) articles published in scientific peer reviewed journals indexed in the PubMed database investigating the relationship between early life antibiotic use and the occurrence of asthma was assessed (within the observation period from June 1998 until the 7th of January 2019). To our knowledge, no methodological reviews on this topic were published before. Some reviews, investigating only some of the elements of “theoretical design” questioned in this review, were published. For example, a review by Pocock et al pointed out that the selection of confounders and the justification for the selection of confounders was poorly reported in the reviewed articles.21 In concordance, another study showed that 22% of the articles examined did not report confounders, and that 33% of the articles did not specify the domain of the study.22

The results presented in this critical review are based on our own interpretation of the reported information in the articles. The text of the articles was read twice to ensure that no reported information was overlooked. If there was doubt on the reporting of some of the elements questioned, this was discussed (HB and JW).

None of the articles explicitly reported a “theoretical design”, although the concept of “theoretical/object design” has been clearly and repeatedly defined since decades.6,9 Even when the “theoretical design” is not explicitly reported, it can be expected that key elements of the “theoretical design” are reported. We assessed to what extent seven of these key elements were explicitly or implicitly reported in 63 articles. In 13 articles, all seven key elements were present. In all other articles at least three key elements were present. One of these seven key elements reported by all articles was the domain of the study. However, none of the articles explicitly referred to the concept of “domain”.

Even though none of the articles explicitly referred to the concept of “theoretical design”, referral to the concept of “(study) design” would be expected, since it is an essential element (apart from relevance) both for the justification of the conduct of the study for the authors as for the understanding and interpretation of the findings for the reader. However, only half of the articles (n = 31) explicitly referred to this concept. Of these 31 articles, 16 referred to the concept of “(study) design” in the methods section of the article. Because study design starts after the formulation of an appropriate research question or hypothesis, which is then translated into a theoretical design,6 it can also be expected that a research question or hypothesis is reported. However, none of the articles reported a research question and 16 out of 63 reported a research hypothesis.

Table 2 Critical Review of 63 Articles on the Presence of Seven Key Elements of “Theoretical Design”

| Measure of occurrence | N (total = 63) |
|-----------------------|---------------|
| Case (event or state) definition | 59 |
| Conceptualization and operationalization of the exposure | 57 |
| Temporal relation between outcome and exposure derivable from aim and/or case (event or state) definition and conceptualization of the exposure | 50 |
| Confounders considered | 56 |
| Effect modifiers taken into account | 24 |
| Domain of the study (implicitly) reported | 63 |

Table 3 Comparison Articles Published Pre- and Post-STROBE (2007) for Reporting the Seven Key Elements of “Theoretical Design”

| Measure of occurrence | 1998–2007 (n = 16) | 2008–2019 (n = 47) |
|-----------------------|--------------------|--------------------|
| Case (event or state) definition | 14 (87) | 45 (96) |
| Conceptualization and operationalization of the exposure | 15 (94) | 42 (89) |
| Temporal relation between outcome and exposure derivable from aim and/or case (event or state) definition and conceptualization of the exposure | 12 (75) | 38 (81) |
| Confounders considered | 14 (87) | 42 (89) |
| Effect modifiers taken into account | 4 (25) | 20 (53) |
| Domain of the study (implicitly) reported | 16 (100) | 47 (100) |
The reporting of the key elements of “theoretical design” questioned was never linked to the concept of “theoretical design”. The extraction of the information mentioned in Table 1 was not straightforward as this information (including the seven key elements of “theoretical design” questioned) was in most articles unstructured, unclear or even missing. The aim(s) of the study should be stated at the end of the introduction section, preferably followed by the formulation of an appropriate research question or hypothesis. The first paragraph of the methods section should repeat (or formulate) the research question or hypothesis and include the translation thereof into an explicitly formulated “theoretical design”. This “theoretical design” should explicitly specify the occurrence relation and the domain of the study. The remaining paragraphs in the methods section should then be dedicated to detailed definition and description of the key elements of “theoretical design” questioned in this critical review (measure of occurrence, case (event or state) definition, conceptualization and operationalization of the exposure, temporal relation between outcome and exposure, confounders that were considered, effect modifiers that were taken into account and the domain of the study), the design of data collection and the design of data processing.

Concerning the directionality of explanatory research, two opinions within explanatory research exist. One approaches the “theoretical design” in explanatory research as “the future occurrence of the outcome as a function of current exposure in a specific domain”, which is inspired by intervention research. This design specifically aims at controlling confounding at scientific reference time T₀ (i.e., moment of realization of the exposure) by making prognostic profiles comparable to each other. The other approaches “theoretical design” in explanatory research as “the current occurrence of an outcome as a function of past exposure in a specific domain”, which is inspired by observational research (case-control studies). This approach aims at controlling confounding throughout the whole trajectory prior to the onset of the event or the state (scientific reference time T₀) by reconstructing exposures and other relevant characteristics prior to T₀. This approach has been theoretically elaborated by Miettinen since the eighties of last century: the “object design” (“theoretical design”) of explanatory research should be the current occurrence of an outcome as a function of past exposure to a determinant, taking into account relevant covariates (extraneous to the causal pathway: confounders, non-extraneous to the causal pathway: effect modifiers) in a specific domain. 23–26

Conceptualizing and delineating the “theoretical design” of a study should include the specification of the directionality of the research in the occurrence relation. This is essential for the choice of an appropriate method of data collection, method of data processing and the interpretation of the findings of a study. When the interest is in studying the “current occurrence of an outcome (a state or an event) as a function of past exposure”, the scientific reference time T₀ would be at the moment of occurrence of the outcome. When collecting data, the occurrence of the outcome will be identified in the study base and a probe of population time is drawn from the study base. Data on exposure and other relevant characteristics prior to the occurrence of the outcome or selection as a probe of population time must be collected. On the other hand, when the interest is in studying the “future occurrence of an outcome as a function of current exposure profile”, scientific reference time T₀ would be at realization (or at the moment of the assessment) of the exposure. The (future) occurrence of the outcome under study would then be compared in the group of exposed and non-exposed (taking into account confounders and modifiers at the moment of the exposure assessment). The data collection method and as a consequence the nature of the data (exposed can become unexposed) thus depends on the chosen “theoretical design”. Therefore, conflicting findings may (at least partly) be explained by a different underlying “theoretical design” or a mismatch between the “theoretical design” and the design of data collection. Delineating the directionality of explanatory research is essential and explicit reporting of this directionality as part of the occurrence relation of the “theoretical design” would increase quality and transparency of explanatory research. Although the concept of directionality is important, none of the articles reviewed explicitly reported the directionality of the research.

In this critical appraisal, we did not assess to what extent a difference in “theoretical designs” or a mismatch between “theoretical design” and design of data collection would contribute to conflicting results. We propose that future reviews should take this into account.

All (English language) articles published in scientific peer-reviewed journals indexed in the PubMed database and investigating the relationship between early life antibiotic use and the occurrence of asthma were included, resulting in a time period from 1998 to 2019. This allowed to assess
reporting based on the year of publication (pre- and post-STROBE). The reporting of key elements of “theoretical design” could also be assessed in articles published before STROBE, because the concept of “theoretical design” is not new and has been introduced early, even before the publication of the oldest article included in this review.

No marked differences were observed, when assessing to what extent the reporting of the seven key elements of “theoretical design” questioned differed after the publication of STROBE. The proportion of articles reporting a measure of occurrence was even smaller post-STROBE compared to pre-STROBE. Although the authors of STROBE advise the reporting of the outcome, the exposure and the domain of the study in the research question (note that in this critical appraisal the presence of outcome, exposure and the domain was assessed in the aim(s) because none of the articles reported a research question), no difference in reporting was observed after STROBE. STROBE was published as a response to the need for reporting guidelines for observational studies. Although STROBE advises the reporting of “key elements of study design”, no specification of what these elements are is provided and no explicit referral to the concept of “theoretical design” is made. Moreover, none of the articles included in this review and published after 2007 reported to have used STROBE as a reporting guideline. In total, according to the Web of Science, STROBE was cited approximately 16,555 times over a period of almost 13 years. As STROBE was published as a response to the need for reporting guidelines for observational studies, it would be expected that authors would use this guideline in order to improve reporting and therefore would refer to STROBE to support their methodological approach.

When using MeSH terms in PubMed, a selection of articles is made, showing articles that were indexed with these specific terms. Depending on what terms were entered in the PubMed search engine, only a selection is made of all articles indexed in the database and the more specific the terms, the more tailored the search result. To get a broad picture of the current practice in the use of “theoretical design” we kept the search strategy very broad. We only used “asthma” AND “antibiotics” as MeSH terms in the PubMed search engine, which resulted in the highest possible number of articles. Neither the domain nor the term “theoretical design” was included as MeSH term, because this would have led to a more detailed selection of articles that were also indexed with these terms and other articles investigating a relationship between early life antibiotic use and the occurrence of asthma would have been overlooked.

We are aware that articles must undergo a reviewing process before publication. As a consequence of the reviewing process, changes could have been made to the first manuscript. This process could have influenced the reporting of the elements questioned in our review. Therefore, we did not intend to draw conclusions about the knowledge of the authors of the articles. We merely wanted to gain insight into the reporting in the final product resulting from this process, which is the published article.

The aim of this critical review was to gain factual knowledge in the reporting of “theoretical design” in (English language) articles published in scientific peer reviewed journals indexed in the PubMed database investigating the relationship between early life antibiotic use and the occurrence of asthma in a well-defined (20.5 years) time period and to assess whether differences in reporting can be observed before and after the publication of STROBE. Therefore, we considered the application of inferential statistics redundant. Nevertheless, it would be instructive to assess reporting in other areas of research assessing a causal relationship between an outcome and an exposure in order to assess whether the same findings can be observed when other outcome–exposure relationships are considered.

Conclusions

This critical appraisal of research on early life exposure to antibiotics and the occurrence of asthma demonstrated that reporting of the seven key elements of “theoretical design” questioned is still incomplete in explanatory research on the association between early life antibiotic use and the occurrence of asthma. None of the articles reported a “theoretical design” and only one-fourth reported the seven key elements of “theoretical design”. No marked differences were observed in the reporting of the seven key elements of “theoretical design” after the publication of STROBE.

Although guidelines do not advise to report an explicit “theoretical design”, they do specify important elements of “theoretical design” and how they should be reported (early in the methods section and as specific as possible). “Theoretical design” is a crucial part of study design, setting the scene for the “design of data collection” and the “design of data processing”, which is on its turn the backbone for the interpretation of the findings. Conceptualizing, delineating and reporting of “theoretical design” would increase the quality and transparency of
explanatory research. This would allow researchers to choose the appropriate method of data collection and method of data processing and would facilitate accurate reporting about their study. Additionally, reporting the “theoretical design” would allow other researchers to reflect on and discuss the quality of the study and what the added value is in the area of research in a more informed way.

**Abbreviations**

GINA, Global Initiative for Asthma; IIS, The Infant Immune Study; MD, medical diagnosis; MeSH, medical subject headings; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RERP, Responsible Epidemiological Research Practice; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

**Data Sharing Statement**

All articles reviewed are listed in Appendix 1. All data generated during this study are included in this published article in Appendix 2.

**Acknowledgment**

We would like to thank prof Dr Diederick Grobbee from Julius Clinical for his time and advice.

**Author Contributions**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

**Funding**

There is no funding to report.

**Disclosure**

The authors declare that they have no conflicts of interest for this work.

**References**

1. Beaglehole R, Bonita R, Kjellström T. Basic Epidemiology. 1st ed. Geneva: World Health Organization; 1993.

2. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic Research: Principles and Quantitative Methods. 1st ed. Belmont, California: Lifetime Learning Publications; 1982.

3. Lilienfield A. Foundations of Epidemiology. 3rd ed. New York: Oxford University Press, Inc.; 1994.

4. MacMahon B, Pugh TF. Epidemiology: Principles and Methods. 1st ed. Boston: Little, Brown and Company; 1970.

5. Rothman KJ. Modern Epidemiology. Boston, Massachusetts: Little, Brown and Company; 1986.

6. Grobbee DE, Hoes AW. Clinical Epidemiology: Principles, Methods and Applications for Clinical Research. 1st ed. Sudbury, Massachusetts: Jones and Bartlett Publishers; 2009.

7. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37–48. doi:10.1097/00001648-199901000-00008

8. Rothman KJ. Epidemiology: An Introduction. 2nd ed. New York: Oxford University Press, Inc.; 2012.

9. Miettinen OS. Theoretical Epidemiology: Principles of Occurrence Research in Medicine. 1st ed. Albany, New York: Delmar Publishers Inc.; 1985.

10. Miettinen OS, Karp I. Epidemiological Research: An Introduction. 1st ed. Dordrecht: Springer; 2012.

11. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Epidemiology. 2007;18(6):805–835. doi:10.1097/EDE.0b013e3181775111

12. Swaen GMH, Langendam M, Weyler J, et al. Responsible epidemiologic research practice: a guideline developed by a working group of the netherlands epidemiological society. J Clin Epidemiol. 2018;100:111–119. doi:10.1016/j.jclinepi.2018.02.010

13. von Elm E, Altman DG, Egger M, et al. The strengthening of reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–1457. doi:10.1016/S0140-6736(07)61602-X

14. Celenlo JC, Litonjua AA, Ryan L, et al. Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years. Am J Respir Crit Care Med. 2002;166(1):72–75. doi:10.1164/rcrm.2109074

15. Ahmadizar F, Vijverberg SJH, Arets HGM, et al. Early life antibiotic use and the risk of asthma and asthma exacerbations in children. Pediatr Allergy Immunol. 2017;28(5):430–437. doi:10.1111/pai.12725

16. Marra F, Lynd L, Coombes M, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest. 2006;129(3):610–618. doi:10.1378/ chest.129.3.610

17. Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. Pediatrics. 2011;127(6):1125–1138. doi:10.1542/peds.2010-2092

18. Silverwood RJ, Rutter CE, Mitchell EA, et al. Are environmental risk factors for current wheeze in the international study of asthma and allergies in children (ISAAC) phase three due to reverse causation? Clin Exp Allergy. 2019;49(4):430–441. doi:10.1111/cea.13325

19. Penders J, Kummeling I, Thijs C. Infant antibiotic use and wheeze and asthma risk: a systematic review and meta-analysis. Eur Respir J. 2011;38(2):295–302. doi:10.1183/09031936.0010510

20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100. doi:10.1371/journal.pmed.1000100

21. Pocock SJ, Collier TJ, Dandreo KJ, et al. Issues in the reporting of epidemiological studies: a survey of recent practice. BMJ. 2004;329(7471):883. doi:10.1136/bmj.38250.571088.55
22. Tooth L, Ware R, Bain C, et al. Quality of reporting of observational longitudinal research. *Am J Epidemiol*. 2005;161(3):280–288. doi:10.1093/aje/kwi042

23. Miettinen OS. Etiologic research: needed revisions of concepts and principles. *Scand J Work Environ Health*. 1999;25(6):484–490. doi:10.5271/sjweh.470

24. Miettinen OS. Etiologic study vis-a-vis intervention study. *Eur J Epidemiol*. 2010;25(10):671–675. doi:10.1007/s10654-010-9486-9

25. Miettinen OS. On progress in epidemiologic academia. *Eur J Epidemiol*. 2017;32(3):173–179. doi:10.1007/s10654-017-0227-1

26. Miettinen OS. “Directionality” in epidemiologic research. *J Clin Epidemiol*. 1989;42(9):825–826. doi:10.1016/0895-4356(89)90093-0

27. Clarivate Analytics. Web of Science [homepage on the Internet]. Available from: https://www.webofscience.com/wos/woscc/citation-report/5983465e-3688-43d2-bc03-b0d4201206c9-04422281. Accessed September 7, 2020.