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Systematic literature review on which maternal alcohol behaviors are related to Fetal Alcohol Spectrum Disorders (FASD).

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Abstract

Objectives: Fetal Alcohol Spectrum Disorders (FASD) is a worldwide problem. Maternal alcohol consumption is an important risk factor for FASD. It remains unknown which alcohol consumption patterns most strongly predict FASD. The objective of this study was to identify these.

Design: Systematic literature review.

Methods: We searched multiple databases up to April 2017, including English-language studies with human participants reporting maternal drinking behavior(s) related to FASD diagnosis. Substantial variation precluded aggregation of the data and meta-analysis. Instead, data were qualitatively inspected.

Results: All studies that measured both maternal alcohol drinking behaviors and FASD reported retrospective data on maternal drinking patterns, employing both continuous and categorical measures and exhibiting substantial heterogeneity in measures of alcohol consumption (e.g., timing of exposure, quantification of alcohol measure, definition of a standard drink). Study quality improved over time and appeared higher for studies based on active case ascertainment, especially when conducted in schools, and when behavior was assessed through interviews.

Conclusions: We aimed to identify specific maternal drinking behavior(s) related to FASD. The state of the literature precludes such conclusions. Evidence-based preventive measures necessitate identifying which prenatal alcohol drinking behavior(s) are most in need of intervention. Therefore, we formulate three recommendations for future research. First, future studies can optimize the value of the collected

dataset through specifying measurements and reporting of maternal drinking behaviors, and avoiding categorized measures (nominal or ordinal) whenever possible. Second, samples should not be selected based on FASD status, but instead, FASD status as well as maternal alcohol consumption should both be measured in a general population sample. Finally, we provide ten reporting guidelines for FASD research.

Strengths and limitations of this study

- This is the first rigorous systematic synthesis, using extensive queries and a thorough screening procedure, to summarize the data on human maternal alcohol consumption and filial FASD.
- The extant literature precludes insight into the association between those two variables.
- A rich set of recommendations was formulated as to reporting guidelines and measurement principles.

Introduction

Prenatal alcohol exposure is one of the leading causes of mental retardation resulting in irreversible lifelong consequences for the unborn child (e.g., neurocognitive deficits, growth deficiencies, facial dysmorphology). These adverse outcomes are also known as fetal alcohol spectrum disorders (FASD). The spectrum encompasses various diagnostic subtypes: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol related neurodevelopmental disorder (ARND), alcohol related birth defects (ARBD), and neurobehavioral disorder with prenatal alcohol exposure (ND-PAE) [1,2]. Epidemiological research implies that FASD is a worldwide problem. Initial FAS prevalence estimates ranged from 0.5 to 7 per 1,000 livebirths [3,4]. Recent systematic literature reviews [5,6] including multiple meta-analyses reported estimates ranging from 0.11 to 55.42 per 1,000 (FAS), 0.8 to 43.01 per 1,000 (pFAS), 0.12 to 20.25 per 1,000 (ARND), and 1.03 to 10.82 per 1,000 (ARBD), and 1.06 to 113.22 per 1,000 (FASD).

Several review articles identified maternal alcohol consumption to be an important risk factor for FASD [7,8]. Specifically, mothers of children diagnosed in the FASD spectrum reported drinking levels ranging from mild to excessive ('binge drinking') alcohol use [7,9–11] [8,12,13]. The severity of FASD may be dependent on the level, pattern, and timing of prenatal alcohol exposure before and during pregnancy [13,14], along with other confounding factors such as nutritional status of the mother, environmental factors, maternal age, and genetic makeup [14,15]. As yet, there is no known safe amount of alcohol to drink while pregnant [1,13,16,17].

Two systematic literature reviews reported associations between level of alcohol exposure and negative effects on child development [7,11]. Both reviews show the negative effects of higher amounts of alcohol intake related to various neuropsychological outcomes or a FAS diagnosis (daily alcohol consumption up

to 4 or more drinks per occasion before and during pregnancy). Less is known about fetal alterations after smaller amounts of alcohol intake (less than daily drinking). Moreover, other reviews are inconclusive about which behaviors are related to the outcome of FASD [5,7,11].

Planning evidence based health promoting programs requires an adequate understanding of which maternal behavior(s) are associated with FASD. Note that maternal alcohol consumption is not the only factor for filial FASD. Paternal and even grandparental consumption patterns have also been implicated [18,19]. However, for the sake of this review, we limited ourselves to maternal alcohol consumption. Specifically, a first step for designing prevention programs requires defining specific target behavior(s) of the target population related to FASD [6,20]. However, the literature remains inconclusive about which maternal drinking behaviors are related to alterations of the fetal development. Despite this conflicting and inconclusive evidence of the negative effects on the developing fetus, public health recommendations are made nonetheless. These recommendations share one common principle, namely that complete abstinence of alcohol use during pregnancy is the safest approach to prevent any possible risks to the unborn child [1,13,16,17]. However, despite this common thread, there are also many differences between the recommendations. For example, the British Medical Association (BMA) lists four different recommendations that are currently made in the United Kingdom alone [13]. This heterogeneity is problematic because communicating multiple contrasting recommendations is confusing for the target audiences. At the same time, there are good arguments to tailor the recommendations. For example, it is likely that binge drinking is one of the serious risk factors and associated with severe forms of FASD [21]. Therefore, it appears that special attention for specific risk groups such as heavily drinking pregnant women is warranted.

Yet, implementing such a tailored approach is currently hindered by the lack of knowledge regarding the dose-response relationship and potential moderators. On the one hand, insufficient evidence is available about the association of different alcohol-related behaviors to FASD-related risk, especially low doses of alcohol, to adequately delineate target groups to enable tailored communication. This would seem to justify foregoing the heterogeneous recommendations and instead converging on an abstinence recommendation. However, in some target populations, such a total abstinence recommendation does not seem feasible. Especially high-risk populations, for example heavily drinking women, may not be able to completely eliminate their alcohol intake, for example because of personal factors such as self-regulation skills, or environmental factors such as social pressures. Given that a total abstinence recommendation may be unrealistic for some of the highest-risk populations, such a recommendation can be ethically problematic.

Figure 1 about here

To illustrate this, consider Figure 1. This Figure shows two potential dose-response relationships between weekly maternal alcohol consumption and risk of filial FASD. The left panel shows a sigmoid relationship, where risk remains low if less than five units are consumed weekly, whereas in the linear dose-response relationship depicted in the right panel, risk is already considerable at five consumptions weekly. For those subpopulations where abstinence recommendations may be unrealistic, if the dose-response relationship is similar to that shown in the left panel, a harm reduction message such as 'consume at most five units' (the yellow areas in Figure 1) may be easier to defend than if the dose-response relationship is linear. Not only may such a message be easier to defend: it may be more effective at decreasing FASD prevalence. Setting unachievable goals has little behavior change potential [22], and if a more achievable goal can stimulate the target population to moderate their alcohol intake enough to

decrease the risk of FASD, while an abstinence message, being unrealistic, has no effect, the ethics of an abstinence message become questionable. If, however, the risk increases very rapidly even with light alcohol consumption, deviating from an abstinence message may be damaging.

Further research is warranted to identify behaviors for health promotion programs to target on. Developing health promoting programs aiming at reducing alcohol consumption during pregnancy first requires identifying which prenatal alcohol drinking behavior(s) are most in need of intervention. The purpose of the present study is to conduct a systematic literature review and meta-analysis to identify those maternal alcohol drinking behaviors most strongly related to FASD.

Materials and Methods

The PRISMA guideline was followed [23], also available at the Open Science Framework repository for this study https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950.

Ethics statement and patient and public involvement

The current study extracted data from online databases and did not involve participation of participants; therefore, it was not necessary to obtain ethical permission.

Search strategy and criteria

A search was conducted in PubMed, PsychINFO, PsychARTICLES, ERIC, CINAHL, EMBASE and MEDLINE databases up to August 2015 using an extensive query consisting of keywords related to FASD, pregnancy and behavior (e.g., fetal alcohol syndrome, pregnancy, alcohol use, risk factor). We reran the query just before submitting the manuscript including databases up to April 2017. Moreover, gray literature was

inspected through the reference list of included articles (for further inspection see the Open Science Framework repository for this study https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950).

Study selection

Resulting hits from the query were exported and screened by two independent screeners in three rounds. The first screening round was based on titles only; the second, on titles and abstracts; and the third, on the full text articles. Records were included if they were written in English and reported maternal alcohol related behaviors associated with a FASD diagnosis. Records that were duplicates, concerned reviews or meta-analysis, or concerned studies that involved non-human subjects were excluded.

Data extraction

Data were transferred onto extraction forms, which were templated source code files for R [24], using Notepad++. Researcher SR completed all extraction forms including the following variables: sampling method (retrospective versus prospective), sampling selection (select versus aselect), variables on which controls were matched (e.g., age mother, study year of the child), recruitment setting (e.g., school, clinic), descent (native versus nonnative population), geography, year of data collection, sample size, subsamples, method of diagnosis (e.g., IOM, 4-digit), syndrome category (e.g., FAS, ARND), datatype (e.g., aggregate, question), datatype levels (e.g., nominal, logical), confirmed maternal alcohol exposure, method of case ascertainment (active versus passive), data collection method (self-report versus interview). Moreover, variables related to drinking behaviors were extracted. Specifically, period of alcohol consumption (e.g., first trimester, before pregnancy), timeframe (concurrent versus retrospective), intensity specification (e.g., any day, weekend day), specification of units (e.g., oz, mg),

specification of timeframe (e.g., per year, per month), binging, and alcoholism. Also, when no indication of one standard drink was provided, the units in grams were granted depending on country and their national alcohol guidelines (e.g., one standard drink in the United States = 14 gr, Australia = 10 gr; for more detailed information see the Open Science Framework repository for this study https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950). These extraction forms were then read into R and processed by an R script.

Quality assessment

A slightly adapted version of the Newcastle–Ottawa Scale (NOS) was used for assessing the quality of nonrandomized studies for further meta-analysis with a maximum of 10 stars [25] (for more detailed information see the Open Science Framework repository for this study https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950). The quality of each publication was assessed by two independent reviewers (inter rater reliability = 80%). Differences were settled by discussion.

Data synthesis and statistical analysis

In case of sufficient homogeneity, meta-analyses and meta-regressions were to be conducted using metafor, a free package in R [26].

Figure 2 About Here

Results

The systematic literature review resulted in 3047 identified hits (see Figure 2). Twenty hits qualified for further screening and analysis. Hits were excluded because they were duplicates, not written in English, or did not report associations between prenatal alcohol and FASD. The assessment of the included studies using the NOS scale revealed a wide range of quality scores with an average score of 6.55 out of 10 (for more details, see the Open Science Framework repository for this study https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950).

Sample characteristics

Sample characteristics can be inspected in Table 1. First, inspection of the data shows that the included studies were reported from five different countries, including Australia (*n* = 2), Croatia (*n* = 1), Italy (*n* = 2), South Africa (*n* = 12), and United States (*n* = 3). All studies were conducted after the year 1992. Almost all studies relied on interviews (*n* = 16), followed by self-reports (*n* = 3), and medical records (*n* = 1). Moreover, all studies were based on a retrospective sampling method. Behavior was described in terms of maternal alcohol drinking related to a FASD diagnosis. Behaviors were reported before and during pregnancy where the period during pregnancy was specified per trimester (e.g., first, second, third).

Further inspection shows that alcohol consumption was operationalized differently in each study (e.g., drinks per drinking day, BAC levels; a complete table can be found in the supplemental materials, Table 1): in fact, no two studies used the same measure. Some studies reported units, whereas other studies reported subjective estimates (e.g., many, less than). Others used dichotomous measures (e.g., yes or no), a mixture of ordinal measures (e.g., none, mild, moderate, heavy), or interval variables (e.g., percentage). The original author's conclusions on maternal drinking behaviors & FASD can be inspected in the supplemental materials, Table 2.

Dichotomous measures

Dichotomous measures (e.g., yes versus no) were available for 11 studies representing 36 measures (see Table 1). These included questions concerning alcohol consumption before pregnancy [7, 10, 11, 20]. Questions concerning alcohol consumption during pregnancy [2, 8] included the following variables: binge drinking without specifying how this was defined [2, 8], alcoholism [1], binge drinking (3 or more drinks per occasion; 5 or more drinks per occasion) [9, 10, 12, 13], alcohol consumption in general [7, 9, 11, 16, 18], smoking as well as binge drinking (3 or more drinks per occasion; 5 or more drinks per occasion [13]. Moreover, questions were measured if pregnant women drank alcohol during the first trimester of pregnancy [7, 9, 11, 13, 16, 20]; second trimester [7, 9, 11, 13, 16, 20]; and/ or third trimester [7, 9, 11, 13, 16, 20]. For more detailed information see the Open Science Framework repository for this study https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950.

Nominal measures

Although alcohol consumption is in fact a continuous variable, it was still operationalized at the nominal level in six nominal measures used in two studies [4, 16]. For more detailed information see the Open Science Framework repository for this study https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950.

Ordinal measures

In total, 24 ordinal measures were used in eight studies (see Table 1). These incorporated questions concerning alcohol consumption before pregnancy [3], sometimes specified in categories of units e.g., grams a week, stopped during drinking or drank less than current use [3, 5, 6, 8, 19]; and alcohol consumption during pregnancy [1], including variables measuring the categories of alcohol intake in units of e.g., grams a week [3, 14]. Moreover, questions were measured for each trimester of pregnancy;

alcohol consumption during first trimester of pregnancy [5, 8, 19] whereby variables were specified with categories e.g., drank less or drank more than current use [5, 8, 19]; alcohol consumption during second trimester [5, 6, 8, 19] using the categories e.g., drank less or drank more than current use [5, 6, 8, 19]; and alcohol consumption during the third trimester [5, 6, 8, 19] whereby variables were specified with categories e.g., drank less or drank more than current use [5, 6, 8, 19]. For more detailed information see the Open Science Framework repository for this study (https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950.

Continuous measures

Surprisingly, continuous measures were only available for five studies. In total, these studies employed 21 measures (see Table 1). These included questions concerning alcohol consumption before pregnancy [2, 8, 10, 12, 17] where variables were sometimes specified in number of drinks e.g., a day or week [8, 10]; and during pregnancy [10], where variables were sometimes specified in number of drinks e.g., during a drinking day, week, weekend [2, 11, 12, 17]. Moreover, number of alcoholic drinks or drinking days were measured during the first trimester of pregnancy [2, 10, 12], sometimes specified in numbers a day or estimated BAC [8]; number of drinks or drinking days during second trimester [2, 10, 12], sometimes specified in numbers a day or estimated BAC [8]; and/ or number of drinks or drinking days during third trimester [2, 10, 12], sometimes specified in numbers a day or estimated BAC [8].

Table 1 About Here

Table 2 About Here

Integration

Categorical variables were based on different answer options and cut-off values, which precluded further aggregation or integration. Operationalizations on a continuous level of measurement also displayed substantial variation. Where possible, we attempted to transform these continuous measures of alcohol consumption into the same metric (e.g., one standard drink defined in grams). However, even this was hindered by heterogeneity in reported standard sizes (sometimes not reported at all), types of alcohol described, and other variation across countries. Moreover, few studies reported continuous data. Because of these reasons, conducting meta-analyses of the continuous variables alone was not feasible.

Consultation with three independent alcohol experts (e.g., expertise in pharmacology of alcohol and measurements of alcohol drinking behaviors) revealed that aggregation of variables in the current dataset was not feasible. This substantial heterogeneity in operationalizations hindered further meta-analyses, and therefore the data will be described qualitatively below with emphasis on the used operationalizations and timing of exposure.

Because aggregation of the evidence was not possible, we instead sought to explore the heterogeneity exhibited by the included studies. Given the small number of included studies, we decided to inspect visualizations of the associations between study characteristics. We plotted the quality of the studies (NOS scores), study year, measurement level of the alcohol consumption operationalization, recruitment setting, and data collection methods.

These visualizations revealed interesting patterns. The quality of studies (NOS score) seem to improve over the years. Data derived from clinical records were mainly based on ordinal measures. NOS score

appeared higher for studies where maternal alcohol history was based on interviews. Finally, NOS scores appeared higher for samples recruited through active case ascertainment, especially in schools. We have included these visualizations in the Open Science Framework repository for this study (https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950).

The wide range of variation in operationalisations provided a unique opportunity to compare them. Continuous measures provide detailed information about specific units (e.g., oz, standard drink, BAC). If reported similarly across studies, these could be further meta-analyzed. However, this requires reporting all information needed to convert the reported statistics into grams or milliliters of alcohol, to enable integration with results from other countries. Other challenges appear to be present for logical, nominal and ordinal measures (e.g., cut-off scores). Some studies reported categories e.g., binge drinking including 3 or more drinks per occasion versus 5 or more drinks per occasion [27]; less than 4 drinks a day versus more than 4 drinks a day [9]. None of the studies reported a description and considerations of why certain cut-off scores were chosen. Cut-off scores likely often followed recommendations by health promotion agencies or suggestions from earlier studies, but without explicit specification this remains unclear. Perhaps the difficulty of establishing sensible cut-off values partly explains this, as doing so requires evidence syntheses to determine where exactly the effects of the relevant behavior becomes qualitatively different. Such evidence (e.g., meta-analyses of maternal alcohol consumption patterns) is not yet available. However, this should lead researchers to employ continuous operationalisations for now, rather than selecting (more or less arbitrary) cut-off scores.

Discussion

In this systematic literature review, we aimed to summarize available data of studies that reported maternal alcohol drinking behaviors in relation to FASD. Data were available for 20 studies. The majority of these 20 studies were based on retrospective self-reports or interviews. A substantial heterogeneity in the applied measures for alcohol consumption was observed. Studies were based on continuous and categorical measures (dichotomous, nominal, and ordinal). Continuous measures included blood alcohol content, percentages of drinking days, and alcohol consumption in grams or ounces. Categorical measures employed a variety of cut-offs to distinguish the different categories. This heterogeneity was so substantial that it precluded meta-analyses. Therefore, it was not possible to answer the original research question: the extant literature does not enable any conclusions as to the relationship between maternal alcohol consumption and the likelihood of infants developing FASD. Instead, however, a wealth of suggestions for future research was distilled from the literature.

The most striking finding was the variation in measurement instruments that were employed to assess maternal drinking behavior. Each of the 20 included studies operationalized measures of alcohol consumption differently. The majority of studies used categorical measures. This is not desirable as these impose a discontinuous scale using cut-off scores. Because, as this review evidences, there exists insufficient evidence to derive whether alcohol consumption (as relating to FASD risk) should be considered as a continuous or discontinuous scale, and where the cut-offs should lie in the case of a discontinuous scale, such cut-off scores are necessarily arbitrary to a degree. In addition, categorizing continuous data discards variance, thereby potentially obfuscating associations between variables [28–30]. The variation in cut-off scores exhibited in the studies included in this review supports this assumption of arbitrariness, and prohibits aggregation of the data collected in those studies. When studies did use continuous measures, studies often did not report how much grams of alcohol were in one standard drink. By making assumptions (e.g., based on the standard drink size in the country of data

collection) we were able to convert most standard drink-based measures into grams of alcohol, but this was not always feasible.

One of the reasons for this heterogeneity may be that none of the included studies was conducted primarily to investigate the association between maternal drinking behavior and FASD: although both variables were frequently measured and reported, most studies were designed to determine prevalence or FASD symptoms. It appears that few or no attempts have been made to empirically establish how maternal alcohol consumption is related to the likelihood of FASD. Given the comprehensive set up of this literature review, it is unlikely that such attempts have been overlooked. The search query was very extensive, rendering omission of relevant keywords unlikely. Screening was conducted in three screening rounds, by two independent screeners, and all records flagged for inclusion by one screener were retained for closer inspection. In addition, the ascendency and descendency approach was applied. Given that reports of studies where these variables were secondary measures preclude conclusions about this relationship, it is as yet not possible to establish which recommendations can be empirically justified. In other words, even though in some target populations a total abstinence recommendation does not seem feasible. Available literature as yet offers no clear guidance that enables exploring a recommendation that could balance feasibility for the target population with dangers to health. Also Mamluk et al. [31] underlined the lack of data to make robust conclusions on the harmful effects of prenatal alcohol exposure and the unborn child. However, our inspection of the literature did yield a number of valuable recommendations for future research.

Recommendations

The first recommendation is addressed specifically to epidemiological researchers, and is based on the observation that the majority of studies assessed maternal drinking as part of a prevalence study. Because these studies form the largest part of the available data regarding associations between

maternal alcohol consumption and FASD outcomes it is important to pay close attention to the measurement of alcohol consumption, even in epidemiological studies with different primary aims.

Second, in general, researchers should anticipate the need to aggregate their measures of alcohol consumption with measures from other studies: in other words, conversion to consumption in metric units, such as grams of alcohol, in a specified time period such as week or month, should be possible. If such conversion cannot be performed, the study cannot contribute to an accumulation of evidence. For example, many studies did not specify what exactly constituted a unit of alcohol (i.e. one standard drink). This means that it was necessary to try and identify the definition of a unit of alcohol in the country where the data were collected, in the period where the data were collected, but even then the obtained definition was unreliable as sometimes researchers conduct studies away from their home country yet use their home countries' unit definitions when reporting the results. Another example is that if timing of exposure was not specified, it is not clear whether the behavior occurred during the first, second, or third trimester (or was an aggregate of those periods).

This recommendation translates into a number of specific suggestions. Most of these are covered by following guidelines for the measurement of alcohol consumption, such as those specified by Dawson [32] and Sobell and Sobell [33], but specifically, it is recommended that future studies assessing specific maternal drinking behaviors should report at least the following (see below for the recommended approach in each case):

(i) how the sample was selected (e.g., retrospective) and which method was used (e.g., convenience sampling method),

(ii) the maternal characteristics variables (e.g., age, descent, educational level),

(iii) which method (or specific questions) was used to assess maternal alcohol consumption (e.g., alcohol timeline follow back approach),

(iv) the timing of exposure when assessing maternal alcohol consumption (e.g., first trimester pregnancy) ,

(v) the frequency of exposure when assessing maternal alcohol consumption (e.g., number of exposure sessions per week or month),

(vi) the amount of alcohol consumed per exposure session [either following the quantify/frequency or the graded frequency systems; ,32],

(vii) the sample size,

(viii) what was considered as one standard drink using International System of Units (i.e. grams or milliliters of alcohol),

(ix) if discontinuous (categorical) measures cannot be avoided, , clear justification of the employed cut-offs.

The third recommendation refers to the complexity of exploring the association between maternal alcohol consumption and filial FASD. One cannot recruit children with FASD and then proceed to select children without FASD. This is not helpful because the *number* of children without FASD but with parents with matched alcohol consumption patterns is the variable of interest. The proportion of children with FASD within each group of parents with a given alcohol consumption pattern is the dependent variable to measure. For example, let us assume that in the left panel of Figure 1 (showing the sigmoid relationship), the probability of FASD is 1% if alcohol consumption is lower than 5 units; 25% if alcohol consumption is between 5 and 10 units; 75% if alcohol consumption is between 10 and 15 units; and 99% if alcohol consumption exceeds 15 units. Similarly, let us assume that in the right panel (showing the linear relationship), the probability of FASD is 12.5% is alcohol consumption is lower than 5 units; 37.5% is alcohol consumption is between 5 and 10 units; 62.5% is alcohol consumption is between 10 and 15 units; and 87.5% is alcohol consumption exceeds 15 units. This means that for 1000 parents consuming between 0 and 5 units (the yellow area), in the sigmoid scenario, 10 children will develop FASD and 990

(99 times more) will not, while in the linear scenario, 125 children develop FASD and 875 will not (7 times more). Now, imagine that a researcher visits a school and screens all children for FASD, and 10 children screen positive for FASD. For simplicity's sake, let us assume that the parents of all these children happened to consume less than 5 units per week during pregnancy. Now, this researcher will not know whether to create a matched control group that is 99 times larger (as would be the case in the sigmoid scenario) or 7 times larger (as would be the case in the linear scenario). It is exactly the relative sizes of these groups that is the variable to measure, and the only way to do so is to measure both maternal alcohol consumption patterns and filial FASD in a large sample.

Based on these recommendations, the ideal design would be a large-scale[1] prospective study where maternal and paternal alcohol consumption patterns would be assessed both using self-reports (conform the recommendations made earlier) as well as objective measures such as biomarkers for alcohol consumption [e.g., ethyl glucuronide which can be detected in blood; ,34]. Infants would then be assessed for FASD according to the revised IOM guidelines [1] and other recommendations provided by Roozen et al. [6], and the FASD prevalence would be related to alcohol consumption patterns of both parents separate and in conjunction. This design also enables examination of potential confounders such as social economic status or age. Such an ideal design may not always be feasible. After all, learning about the association of parental drinking patterns to filial FASD requires assessing drinking patterns in all pregnancies: it is not possible to start from identified FASD cases, as we explained earlier. However, even when other designs are utilized, it is important that researchers anticipate data aggregation over studies, and therefore attempt to provide alcohol measures in metric units.

[1] Note that what constitutes "large-scale" depends on the expected FASD prevalence in a population as well as the target behavior under investigation, e.g. abstinence versus moderated drinking, or abstinence versus regular drinking patterns. These two parameters determine the effect size of the association that is to be estimated, which in turn enables computation of the required sample size for accurate estimation of that effect size using Accuracy in Parameter Estimation (AIPE) methods.

The present review focused on reported data on maternal drinking behaviors. Some of the included studies also reported paternal drinking patterns or grandparental drinking patterns. The role of paternal drinking and transgenerational toxicity on fetal development and FASD is not well understood. A recent review study by Gupta and colleagues [18] reported that paternal alcoholism alters the gene expression for fetal susceptibility to FAS. In another review, Resendiz and colleagues [19] argue that transgenerational toxicity may play a role in FASD etiology. Moreover, social facilitation by paternal drinking is significantly associated with maternal drinking [35]. The origin of FASD is therefore not only based on maternal drinking behaviors but by many other factors (e.g., genetic and epigenetic predisposition, maternal body makeup, and lifestyle). Gupta and colleagues [18] emphasized that FAS etiology, and also other diagnosis within the FASD spectrum, is based on a complex interaction of different factors whereby cautious interpretation is warranted.

Conclusion

The current knowledge on maternal alcohol drinking behaviors in relation to FASD is limited. Behaviors were measured using various techniques and operationalized differently. For evidence-based preventive measures it is necessary to identify which prenatal alcohol drinking behavior(s) are most in need of intervention. Several recommendations have been made that can facilitate accumulation of evidence over studies. Following these recommendations can contribute to establishing the evidence base required for the development of effective preventive health promoting programs.

Contributors

Authors SR, GJYP, GK, LC designed the study and directed its implementation, including quality assurance and control. Authors DT, JN, and GK helped supervising the field activities. Authors SR and GJYP conducted the literature review and analyses and prepared the Materials and Methods and the Discussion sections of the text. All other co-authors contributed to successive drafts. All authors gave significant input in preparation of the article and approved the manuscript and submission.

Availability of data and materials

All data, analysis scripts, and other materials are publicly available at the Open Science Framework repository for this study (https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950).

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Figure captions:

Figure 1. Two examples of possible dose-response relationships between maternal alcohol consumption and probability of filial FASD.

Figure 2. Flow chart of publications measuring maternal behavior(s) related to FASD included in the review. Considerations during the inclusion and exclusion process can also be inspected at https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950

Table 1. Overview of characteristics of included studies in this review

	Authors (year)	Geography	Sample year	Cases	Controls	Assessment methods	Number of measurement levels[1]				NOS score[2]
							Dich.	Nom.	Ord.	Cont.	
1	*Cannon and colleagues*[9]	United States	1995-1997	353	3894874	record documentation	1		2		4
2	*Ceccanti and colleagues* [36]	Italy	2014	39	108	interview	1			6	9
3	*Coyne and colleagues*[37]	Australia	1994-2006	54	56	self-report			2		5
4	*Davies and colleagues* [38]	South Africa	2002-2003	39	36	interview		1			6
5	*May and colleagues*[39]	South Africa		46	42	interview			4		6
6	*May and colleagues* [40]	South Africa	1999-2001	53	116	interview			4		7
7	*May and colleagues* [41]	South Africa		61	133	interview	5				7
8	*May and colleagues*[42]	South Africa	2002	49 FAS, 15 pFAS	133	interview	1		4	7	6
9	*May and colleagues* [43]	Italy	2011	8 FAS, 34 pFAS, 30 FASD	122	interview	4				9
10	*May and colleagues* [44]	South Africa	2013	63 FAS, 48 pFAS, 32 ARND	81	interview	4				7

11	*May and colleagues*[45]	South Africa	2013	68 FAS, 52 pFAS, 35 ARND	90	interview	7		1		7
12	*May and colleagues*[46]	United States	2010-2011	30	80	interview	2		4		7
13	*May and colleagues*[27]	South Africa		43	85	interview	5				7
14	*Miller and colleagues*[47]	United States	1992-1994	22	214499	*unknown*		1			7
15	*O'Leary and colleagues*[48]	Australia	1995-1997			self-report		3			6
16	*Petković and Barišić*[49]	Croatia		55	769	self-report				5	7
17	*Suttie and colleagues* [50]	South Africa	2013	22 FAS, 26 pFAS	69	interview			3		5
18	*Urban and colleagues*[51]	South Africa	2001-2004	82	74	interview	1				6
19	*Viljoen and colleagues*[52]	South Africa	2001	31	31	interview		4			6
20	*Viljoen and colleagues*[53]	South Africa	2005	53	116	interview	5				7

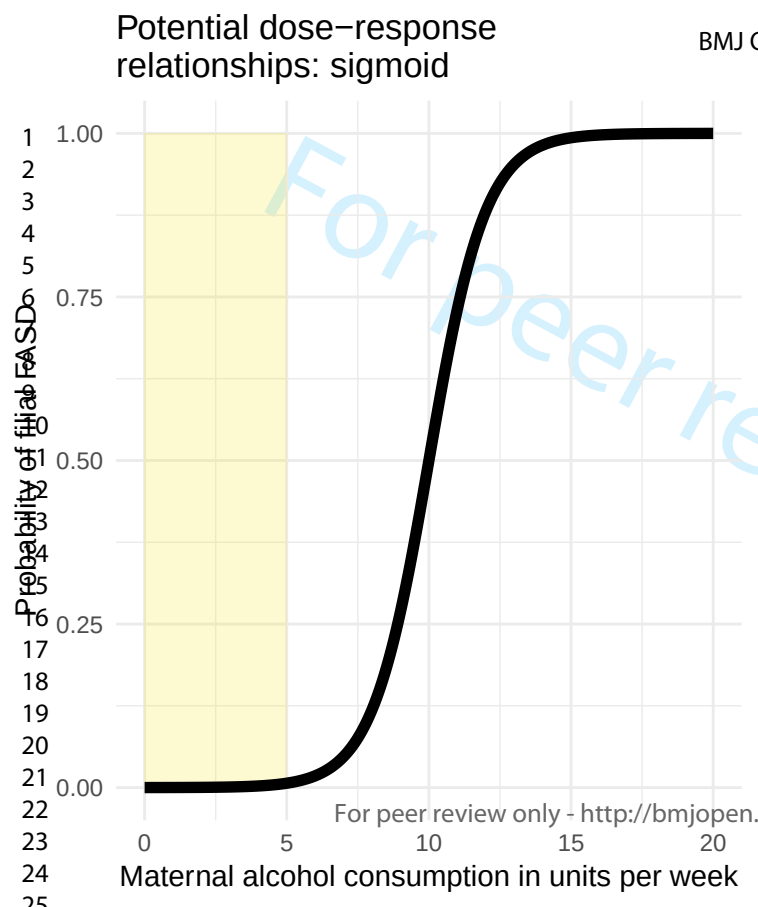
note [1]measurements of maternal alcohol drinking behavior are categorized in three different levels: dichotomous ('Dich.', e.g., yes/no), nominal ('Nom.', e.g., admitted, negative, unanswered), ordinal ('Ord.', e.g., < 4 drinks, > 4 drinks), continuous ('Cont.', e.g., %). The measures represent the different questions asked for each category (e.g., "drank during the first trimester of pregnancy"). [2]Each study was assessed using the adapted version of the Newcastle – Ottawa Scale (NOS). Scores were allocated from a scale from 0 (poor quality) to a maximum of 10 stars (excellent quality). For more detailed information see https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950

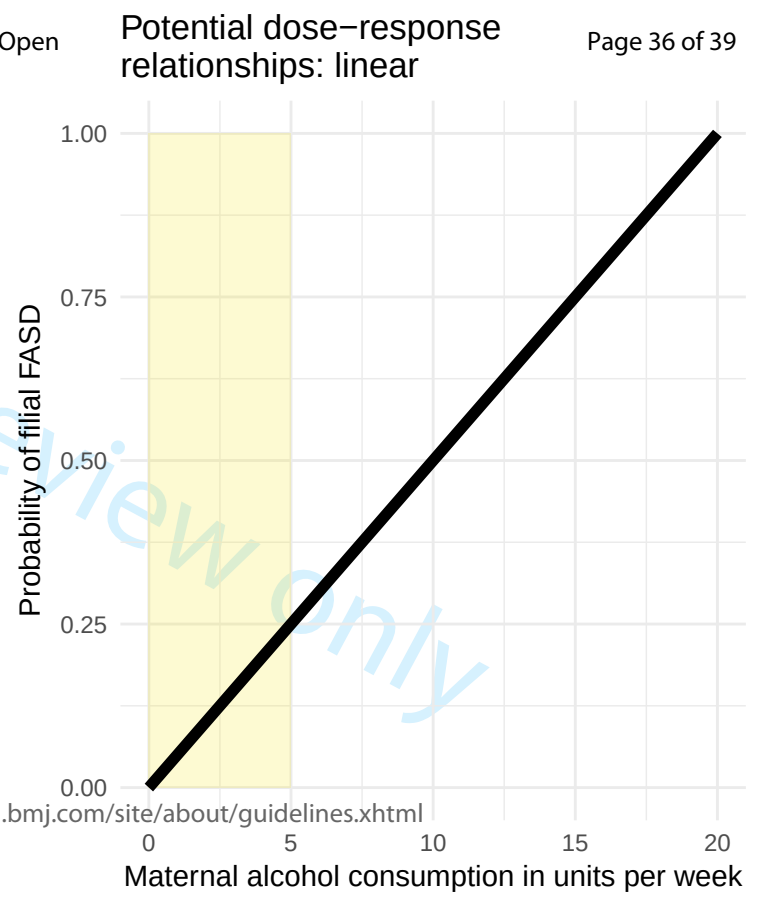
Table 2. Conclusions made by authors of included studies on maternal drinking behaviors and FASD

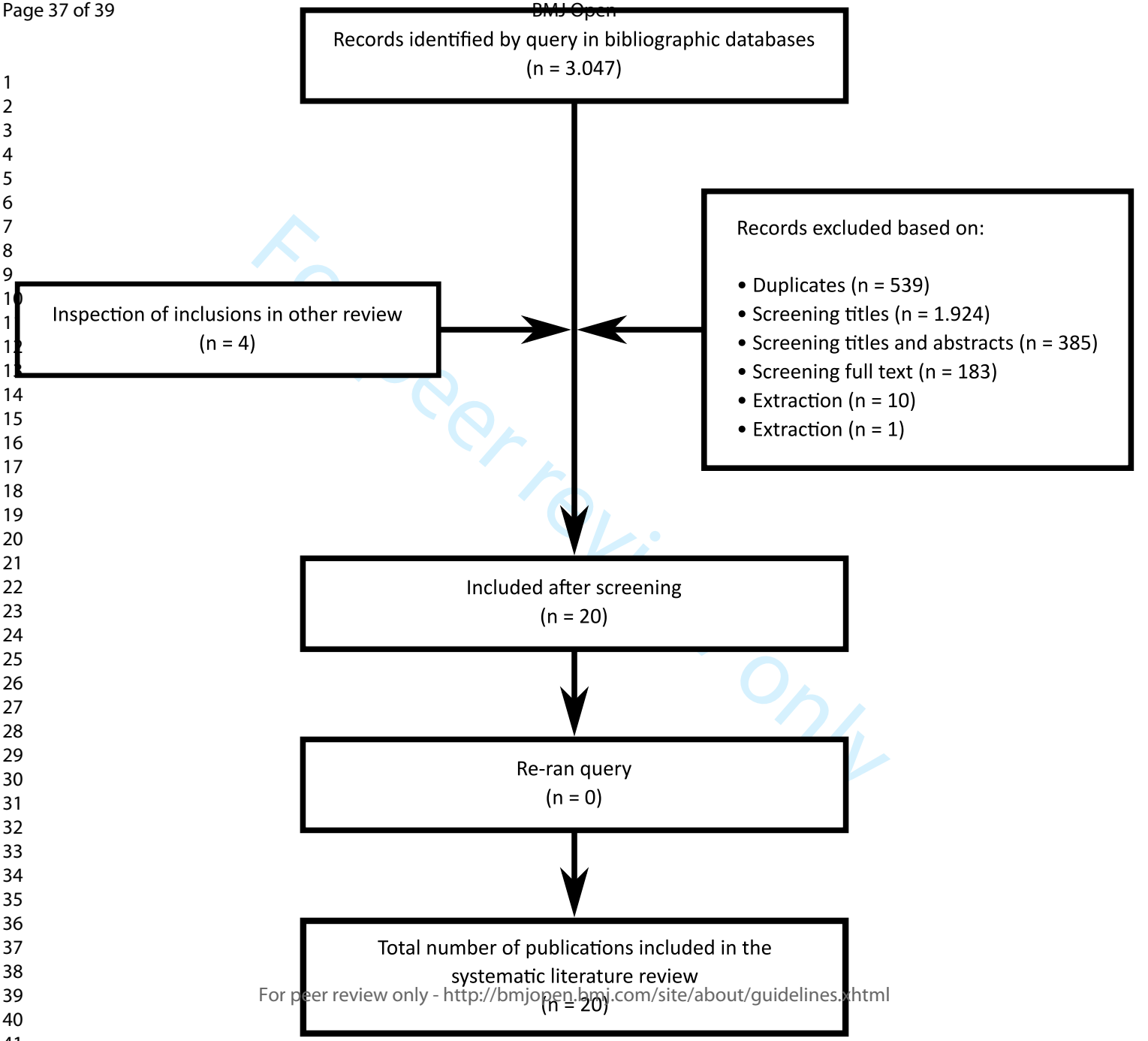
Authors (year)	Original authors' conclusions
Cannon and colleagues[9]	"Mothers of children with FAS have severe substance abuse behaviors including daily drinking, binge drinking"
Ceccanti and colleagues [36]	"Mothers of children with a FASD reported more drinking three months prior to pregnancy, more current drinking, and endorsed questionnaire items indicating that solitary drinking was more common"
Coyne and colleagues[37]	"Mothers of children with FAS reported heavy alcohol intake during pregnancy"
Davies and colleagues [38]	"Twenty five mothers with a FASD diagnosed child (69%) reported drinking alcohol, on average, every week during their pregnancy"
May and colleagues[39]	"Most drinking is binge drinking. Even though the current drinking quantities reported by both subjects and controls were not high in absolute standards, the most important interpretation of the data is the large differential between subjects and controls. There is no doubt, however, that these mothers drank sufficiently to produce verifiable cases of fetal alcohol syndrome as severe as we have seen anywhere in the United States"
May and colleagues [40]	"Alcohol consumption was much greater for case mothers than for control mothers in all comparisons. Control mothers were more likely to have been abstainers or Light drinkers compared with case mothers, who showed significantly heavier drinking patterns and reported drinking at the same level (53%-55%) or higher during pregnancy (32%-34%) compared with current drinking levels"
May and colleagues [41]	"Measures of drinking during the index pregnancies are significantly associated with low intelligence and frequent behavioral problems in the children. Reported drinking during pregnancy (.59), drinks per day (.48), three drinks or more per occasion (.51), and five drinks or more per occasion (.45), correlate highly with total dysmorphology in the children"
May and colleagues[42]	"In most every variable of maternal alcohol use and abuse, a spectrum emerged based on the final diagnosis of the child with FAS, PFAS, and control. Alcohol use was greatest in quantity, frequency, and duration among the mothers of FAS children, and generally next most severe among mothers of PFAS children, while lowest among controls"
May and colleagues [43]	"Mothers of children with FASD report heavy current drinking and drinking during the 2nd and 3rd trimesters of the index pregnancy"
May and colleagues [44]	"Binge drinking of at least two days a week during all trimesters in this population may produce FAS or PFAS, while mothers of children with ARND and exposed children without an FASD are most likely to reduce their average and peak alcohol consumption in the later trimesters"

May and colleagues[45]	"Mean number of drinks per week and drinking 3 and 5 or more drinks per occasion during pregnancy both illustrate the significant difference between mothers of FASD children and those of normal children"
May and colleagues[46]	"Mothers of children who had a FASD reported more drinking 3 months before pregnancy, and heavy drinking by the father of children who had FASD"
May and colleagues[27]	"With patterns of heavy episodic (binge) drinking being the most harmful to the fetus"
Miller and colleagues[47]	"Mothers of FAS cases were more likely to drink alcohol during pregnancy"
O'Leary and colleagues[48]	"Heavy PAE in the first trimester was associated with a more than fourfold increased risk of ARBDs. This association was specific to PAE in the first trimester. The finding of twofold increased odds of ARBDs after moderate levels of PAE during late pregnancy is likely because many women also had heavy first trimester exposure and reduced their alcohol intake as pregnancy progressed"
Petković and Barišić[49]	"Confirmed pregnancy alcohol consumption in the FAS/PFAS group was higher (18.2%) to observed frequency in the whole sample of questioned mothers (11.5%) and significantly higher when compared to non-FAS/PFAS mothers (10.4%)"
Suttie and colleagues [50]	"No differences were found for prenatal alcohol exposure between the HE subgroup with FAS/PFAS affinity (nonsyndromal heavy exposed with FAS/PFAS-like face signature [HE1]) versus theHE subgroup with control affinity (nonsyndromal heavy exposed with more control-like face signature [HE2]) (P < .10)"
Urban and colleagues[51]	"Maternal drinking during pregnancy was much more frequently reported in mothers of children with FAS/PFAS than in controls"
Viljoen and colleagues[52]	"Mothers of children with FAS drank significantly heavier than controls, especially for continues drinking heavily (and/or increasing) throughout pregnancy. Control mothers drank less and drinking levels declined during pregnancy. Episodic drinking on weekends was modal for both groups with bingeing 5+ drinks was normative during 2 constructive days for FAS mothers "
Viljoen and colleagues[53]	"Mothers of children with FAS drink more than controls, drink rapidly and drink heavily in an episodic fashion. Moreover, they do not quit or cut down during pregnancy"

Note For more detailed information see https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950







PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Systematic literature review on which maternal alcohol behaviors are related to Fetal Alcohol Spectrum Disorders (FASD).

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Abstract

Objectives: Fetal Alcohol Spectrum Disorders (FASD) is a worldwide problem. Maternal alcohol consumption is an important risk factor for FASD. It remains unknown which alcohol consumption patterns most strongly predict FASD. The objective of this study was to identify these.

Design: Systematic literature review.

Methods: We searched in PubMed, PsychINFO, PsycARTICLES, ERIC, CINAHL, EMBASE and MEDLINE up to August 2018. The query consisted of keywords and their synonyms related to FASD, pregnancy, and behavior. Studies were excluded when not published in English, were reviews, or involved non-human subjects. Substantial heterogeneity precluded aggregation or meta-analysis of the data. Instead, data were qualitatively inspected.

Results: In total, 21 studies were eligible for further data analysis. All studies that measured both maternal alcohol drinking behaviors and FASD reported retrospective data on maternal drinking patterns, employing both continuous and categorical measures and exhibiting substantial heterogeneity in measures of alcohol consumption (e.g., timing of exposure, quantification of alcohol measure, definition of a standard drink). Study quality improved over time and appeared higher for studies based on active case ascertainment, especially when conducted in schools, and when behavior was assessed through interviews.

Conclusions: We aimed to identify specific maternal drinking behavior(s) related to FASD. The state of the literature precludes such conclusions. Evidence-based preventive measures necessitate identifying

which prenatal alcohol drinking behavior(s) are most in need of intervention. Therefore, we formulate three recommendations for future research. First, future studies can optimize the value of the collected dataset through specifying measurements and reporting of maternal drinking behaviors, and avoiding categorized measures (nominal or ordinal) whenever possible. Second, samples should not be selected based on FASD status, but instead, FASD status as well as maternal alcohol consumption should both be measured in a general population sample. Finally, we provide ten reporting guidelines for FASD research.

Strengths and limitations of this study

- This systematic literature review uses a comprehensive search strategy to cover the published literature
- We did not consult grey literature
- Consultation about data aggregation took place with three independent alcohol experts
- Substantial heterogeneity prevented synthesis but yielded a rich set of recommendations as to reporting guidelines and measurement principles

Introduction

Prenatal alcohol exposure is one of the leading causes of mental retardation resulting in irreversible lifelong consequences for the unborn child (e.g., neurocognitive deficits, growth deficiencies, facial dysmorphology) [1]. These adverse outcomes are also known as fetal alcohol spectrum disorders (FASD). The spectrum encompasses various diagnostic subtypes: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol related neurodevelopmental disorder (ARND), alcohol related birth defects (ARBD), and neurobehavioral disorder with prenatal alcohol exposure (ND-PAE) [1,2]. Epidemiological research implies that FASD is a worldwide problem. Initial FAS prevalence estimates ranged from 0.5 to 7 per 1,000 livebirths [3,4]. Recent systematic literature reviews [5,6] including multiple meta-analyses reported estimates ranging from 0.11 to 55.42 per 1,000 (FAS), 0.8 to 43.01 per 1,000 (pFAS), 0.12 to 20.25 per 1,000 (ARND), 1.03 to 10.82 per 1,000 (ARBD), and 1.06 to 113.22 per 1,000 (FASD).

FASD, as its name implies, is caused by alcohol use. Several reviews have aimed to further elucidate the relationship between alcohol use and filial FASD [7,8]. Specifically, mothers of children diagnosed in the FASD spectrum reported drinking levels ranging from mild to excessive ('binge drinking') alcohol use [7,9–11] [8,12,13]. The severity of FASD may be dependent on the level, pattern, and timing of prenatal alcohol exposure before and during pregnancy [13,14], along with other confounding factors such as nutritional status of the mother (e.g. vitamin or mineral intake), environmental factors (e.g., social relationships, stress),maternal age, and genetic makeup [14–16]. As yet, there is no known safe amount of alcohol to drink while pregnant [1,13,17,18].

Two systematic literature reviews reported associations between level of alcohol exposure and negative effects on child development [7,11]. Both reviews show the negative effects of higher amounts of alcohol intake (daily alcohol consumption up to 4 or more drinks per occasion before and during pregnancy) related to various neuropsychological outcomes (including but not specific for a FASD diagnosis. However, these reviews are inconclusive about behaviors related to the outcome of FASD specifically [5,7,11], or the effects of consumption of lower amounts of alcohol.

Planning evidence based health promoting programs requires an adequate understanding of which maternal behavior(s) are associated with FASD. Note that maternal alcohol consumption is not the only factor for filial FASD. Paternal and even grandparental consumption patterns have also been implicated [19,20], but as yet it remains undecided whether paternal and grandparental consumption should also be included in the FASD definition (effects of paternal and grandparental consumption are considered necessarily either genetic or through influencing maternal alcohol consumption, whereas maternal alcohol consumption has a direct teratogenic effect). However, for the sake of this review, we limited ourselves to maternal alcohol consumption. Specifically, a first step for designing prevention programs requires defining specific target behavior(s) of the target population related to FASD [6,21]. However, the literature remains inconclusive about which maternal drinking behaviors are related to alterations of the fetal development. Despite this conflicting and inconclusive evidence of the negative effects on the developing fetus, public health recommendations are made nonetheless. These recommendations share one common principle, namely that complete abstinence of alcohol use during pregnancy is the safest approach to prevent any possible risks to the unborn child [1,13,17,18]. However, despite this common thread, there are also many differences between the recommendations. For example, the British Medical Association (BMA) lists four different recommendations that are currently made in the United Kingdom alone [13]. This heterogeneity is problematic because communicating multiple contrasting

recommendations is confusing for the target audiences. At the same time, there are good arguments to tailor the recommendations. For example, it is likely that although any alcohol consumption may entail risks, binge drinking (BAC to .08 grams percent or above; 4 or more drinks in about 2 hours)is one of the serious risk factors and associated with severe forms of FASD [22]. Therefore, it appears that special attention for specific risk groups such as heavily drinking pregnant women is warranted.

Yet, implementing such a tailored approach is currently hindered by the lack of knowledge regarding the dose-response relationship and potential moderators. On the one hand, insufficient evidence is available about the association of different alcohol-related behaviors to FASD-related risk, especially low doses of alcohol, to adequately delineate target groups to enable tailored communication. This would seem to justify foregoing the heterogeneous recommendations and instead converging on an abstinence recommendation. However, in some target populations, such a total abstinence recommendation does not seem feasible. Especially high-risk populations, for example heavily drinking women, may not be able to completely eliminate their alcohol intake, for example because of personal factors as self-regulation skills, or environmental factors such as social pressures. Given that a total abstinence recommendation may be unrealistic for some of the highest-risk populations, such a recommendation can be ethically problematic.

Figure 1 about here

To illustrate this, consider Figure 1. This Figure shows two potential dose-response relationships between weekly maternal alcohol consumption and risk of filial FASD for a given individual (note that individual vulnerabilities can vary). The left panel shows a sigmoid relationship, where risk remains low if less than five units are consumed weekly, whereas in the linear dose-response relationship depicted in the right

panel, risk is already considerable at five consumptions weekly. For those subpopulations where abstinence recommendations may be unrealistic, if the dose-response relationship is similar to that shown in the left panel, a harm reduction message such as 'consume at most five units' (the yellow areas in Figure 1) may be easier to defend than if the dose-response relationship is linear. Not only may such a message be easier to defend: it may be more effective at decreasing FASD prevalence. Setting unachievable goals has little behavior change potential [23], and if a more achievable goal can stimulate the target population to moderate their alcohol intake enough to decrease the risk of FASD, while an abstinence message, being unrealistic, has no effect, the ethics of an abstinence message become questionable. If, however, the risk increases very rapidly even with light alcohol consumption, deviating from an abstinence message may be damaging.

Animal models have provided some evidence as to potential dose-response relationships. However, such models are not fully translatable to humans [16], and especially given that the present research question concerns not simply whether a dose-response relationship exists, but what the *nature* of this relationship is, relying on animal models does not seem appropriate.

Further research is warranted to identify behaviors for health promotion programs to target on. Developing health promoting programs aiming at reducing alcohol consumption during pregnancy first requires identifying which prenatal alcohol drinking behavior(s) are most in need of intervention. The purpose of the present study is to conduct a systematic literature review and meta-analysis to identify those maternal alcohol drinking behaviors most strongly related to FASD.

Materials and Methods

Protocol and data repository

Data will be reported following the PRISMA guideline [24]. All materials and supporting documents are publicly available at the Open Science Framework repository at https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950 (NOTE TO REVIEWERS, EDITOR AND TYPESETTERS: THIS WILL BE REPLACED WITH THE PUBLIC, NON-ANONYMIZED URL ON ACCEPTANCE). In this repository, we have numbered the directories that organize the materials. Hereafter, we will refer to materials in this repository as ''resource 1" through "resource 8", which correspond to these directories.

Ethics statement and patient and public involvement

The current study extracted data from online databases and did not involve participation of participants; therefore, it was not necessary to obtain ethical permission.

Search strategy

A search was conducted in PubMed, PsychINFO, PsychARTICLES, ERIC, CINAHL, EMBASE and MEDLINE databases up to August 2015 using an extensive query consisting of keywords related to FASD, pregnancy and behavior (e.g., fetal alcohol syndrome, pregnancy, alcohol use, risk factor). We reran the query just before submitting the manuscript in August 2018 and performed a cursory inspection to scan for newly added papers. Moreover, we applied the ascendancy approach by inspecting the reference lists of included articles (the complete queries are included in resource 1).

Study selection

Resulting hits from the query were exported and screened by two independent screeners in three rounds. The first screening round was based on titles only; the second, on titles and abstracts; and the third, on the full text articles. Records were included if they were written in English and reported maternal alcohol related behaviors associated with a FASD diagnosis. Records that were duplicates, concerned reviews or meta-analysis, or concerned studies that involved non-human subjects were excluded. An extensive list of inclusion and exclusion criteria is located in the screening instructions (resource 2).

Data extraction

Data were transferred onto extraction forms, which were templated source code files for R [25], using Notepad++. Researcher SR completed all extraction forms including the following variables: sampling method (retrospective versus prospective), sampling selection (select versus aselect), variables on which controls were matched (e.g., age mother, study year of the child), recruitment setting (e.g., school, clinic), descent (native versus nonnative population), geography, year of data collection, sample size, subsamples, method of diagnosis (e.g., IOM, 4-digit), syndrome category (e.g., FAS, ARND), datatype (e.g., aggregate, question), datatype levels (e.g., nominal, logical), confirmed maternal alcohol exposure, method of case ascertainment (active versus passive), data collection method (self-report versus interview). Moreover, variables related to drinking behaviors were extracted. Specifically, period of alcohol consumption (e.g., first trimester, before pregnancy), timeframe (concurrent versus retrospective), intensity specification (e.g., any day, weekend day), specification of units (e.g., oz, mg), specification of timeframe (e.g., per year, per month), binging, and alcoholism. Also, when no indication of one standard drink was provided, the units in grams were granted depending on country and their

national alcohol guidelines (e.g., one standard drink in the United States = 14 gr, Australia = 10 gr; see resource 5). These extraction forms were then read into R and processed by an R script.

Quality assessment

A slightly adapted) version of the Newcastle–Ottawa Scale (NOS) was used for assessing the quality of nonrandomized studies for further meta-analysis with a maximum of 10 stars [26] (see resource 4 for the complete assessment and comparison to the original version) The quality of each publication was assessed by two independent reviewers (inter rater reliability = 80%) who settled differences by discussion.. No studies were excluded based on this quality assessment.

Data synthesis and statistical analysis

In case of sufficient homogeneity, meta-analyses and meta-regressions were to be conducted using metafor, a free package in R [27].

Figure 2 About Here

Results

The systematic literature review resulted in 3404 identified hits (see Figure 2). Twenty-one hits qualified for further screening and analysis. Hits were excluded because they were duplicates, not written in English, or did not report associations between prenatal alcohol and FASD. The assessment of the included studies using the NOS scale revealed a wide range of quality scores with an average score of 6.57 out of 10 (for more details, see resource 5).

Sample characteristics

Sample characteristics can be inspected in Table 1. First, inspection of the data shows that the included studies were reported from five different countries, including Australia (*n* = 2), Croatia (*n* = 1), Italy (*n* = 2), South Africa (*n* = 12), and United States (*n* = 4). All studies were conducted after the year 1992. Almost all studies relied on interviews (*n* = 17), followed by self-reports (*n* = 3), and medical records (*n* = 1). Moreover, all studies were based on a retrospective sampling method. Behavior was described in terms of maternal alcohol drinking related to a FASD diagnosis. Behaviors were reported before and during pregnancy where the period during pregnancy was specified per trimester (e.g., first, second, third).

Further inspection shows that alcohol consumption was operationalized differently in each study (e.g., dichotomous measures; a complete table can be found in Table 1): in fact, no two studies used the same measure. Some studies reported units, whereas other studies reported subjective estimates (e.g., many, less than). Others used dichotomous measures (e.g., yes or no), a mixture of ordinal measures (e.g., none, mild, moderate, heavy), or interval variables (e.g., percentage). The original author's conclusions on maternal drinking behaviors & FASD can be inspected in Table 2.

Dichotomous measures

Dichotomous measures (e.g., yes versus no) were available for 12 studies representing 44 measures (see Table 1). These included questions concerning alcohol consumption before pregnancy [7, 10, 11, 20]. Questions concerning alcohol consumption during pregnancy [2, 8, 14] included the following variables: binge drinking without specifying how this was defined [2, 8], alcoholism [1], binge drinking (3 or more drinks per occasion; 5 or more drinks per occasion) [9, 10, 12, 13, 14], alcohol consumption in general [7, 9, 11, 17, 19], smoking as well as binge drinking (3 or more drinks per occasion; 5 or more drinks per occasion [13]. Moreover, questions were measured if pregnant women drank alcohol during the first

trimester of pregnancy [7, 9, 11, 13, 14, 17, 21]; second trimester [7, 9, 11, 13, 14, 17, 21]; and/ or third trimester [7, 9, 11, 13, 14, 17, 21]. For more detailed information see resource 5.

Nominal measures

Although alcohol consumption is in fact a continuous variable, it was still operationalized at the nominal level in six nominal measures used in two studies [4, 17]. For more detailed information see resource 5.

Ordinal measures

In total, 24 ordinal measures were used in eight studies (see also the numbered studies in Table 1). These incorporated questions concerning alcohol consumption before pregnancy [3], sometimes specified in categories of units e.g., grams a week, stopped during drinking or drank less than current use [3, 5, 6, 8, 20]; and alcohol consumption during pregnancy [1], including variables measuring the categories of alcohol intake in units of e.g., grams a week [3, 15]. Moreover, questions were measured for each trimester of pregnancy; alcohol consumption during first trimester of pregnancy [5, 8, 20] whereby variables were specified with categories e.g., drank less or drank more than current use [5, 8, 20]; alcohol consumption during second trimester [5, 6, 8, 20] using the categories e.g., drank less or drank more than current use [5, 6, 8, 20]; and alcohol consumption during the third trimester [5, 6, 8, 20] whereby variables were specified with categories e.g., drank less or drank more than current use [5, 6, 8, 20]. For more detailed information see resource 5.

Continuous measures

Surprisingly, continuous measures were only available for six studies. In total, these studies employed 29 measures (see Table 1). These included questions concerning alcohol consumption before pregnancy [2, 8, 10, 12, 18] where variables were sometimes specified in number of drinks e.g., a day or week [8, 10, 14]; and during pregnancy [10, 14], where variables were sometimes specified in number of drinks e.g.,

during a drinking day, week, weekend [2, 11, 12, 14, 18]. Moreover, number of alcoholic drinks or drinking days were measured during the first trimester of pregnancy [2, 10, 12, 14], sometimes specified in numbers a day or estimated BAC [8]; number of drinks or drinking days during second trimester [2, 10, 12, 14], sometimes specified in numbers a day or estimated BAC [8]; and/ or number of drinks or drinking days during third trimester [2, 10, 12, 14], sometimes specified in numbers a day or estimated BAC [8].

Table 1 About Here

Table 2 About Here

Integration

Categorical variables were based on different answer options and cut-off values, which precluded further aggregation or integration. Operationalizations on a continuous level of measurement also displayed substantial variation. Where possible, we attempted to transform these continuous measures of alcohol consumption into the same metric (e.g., one standard drink defined in grams). However, even this was hindered by heterogeneity in reported standard sizes (sometimes not reported at all), types of alcohol described, and other variation across countries. Moreover, few studies reported continuous data. Because of these reasons, conducting meta-analyses of the continuous variables alone was not feasible.

Consultation with three independent alcohol experts (e.g., expertise in pharmacology of alcohol and measurements of alcohol drinking behaviors) revealed that aggregation of variables in the current dataset was not feasible. This substantial heterogeneity in operationalizations hindered further meta-

analyses, and therefore the data will be described qualitatively below with emphasis on the used operationalizations and timing of exposure.

Because aggregation of the evidence was not possible, we instead sought to explore the heterogeneity exhibited by the included studies (note that all 230 extracted effect sizes are available in file 'effectsizes.csv', and an overview of the used operationalisations in 'Alcohol use variables.csv', both in resource 6). Given the small number of included studies, we decided to inspect visualizations of the associations between study characteristics. We plotted the quality of the studies (NOS scores), study year, measurement level of the alcohol consumption operationalization, recruitment setting, and data collection methods.

These visualizations revealed interesting patterns. The quality of studies (NOS score) seem to improve over the years. Data derived from clinical records were mainly based on ordinal measures. NOS score appeared higher for studies where maternal alcohol history was based on interviews. Finally, NOS scores appeared higher for samples recruited through active case ascertainment, especially in schools. We have included these visualizations in resource 6).

The wide range of variation in operationalisations provided a unique opportunity to compare them. Continuous measures provide detailed information about specific units (e.g., oz, standard drink, BAC). If reported similarly across studies, these could be further meta-analyzed. However, this requires reporting all information needed to convert the reported statistics into grams or milliliters of alcohol, to enable integration with results from other countries. Other challenges appear to be present for logical, nominal and ordinal measures (e.g., cut-off scores). Some studies reported categories e.g., binge drinking including 3 or more drinks per occasion versus 5 or more drinks per occasion [28]; less than 4 drinks a day versus more than 4 drinks a day [9]. None of the studies reported a description and considerations of why certain cut-off scores were chosen. Cut-off scores likely often followed recommendations by health

promotion agencies or suggestions from earlier studies, but without explicit specification this remains unclear. Perhaps the difficulty of establishing sensible cut-off values partly explains this, as doing so requires evidence syntheses to determine where exactly the effects of the relevant behavior becomes qualitatively different. Such evidence (e.g., meta-analyses of maternal alcohol consumption patterns) is not yet available. However, this should lead researchers to employ continuous operationalisations for now, rather than selecting (more or less arbitrary) cut-off scores.

Discussion

In this systematic literature review, we aimed to summarize available data of studies that reported maternal alcohol drinking behaviors in relation to FASD. Data were available for 21 studies. The majority of these 20 studies were based on retrospective self-reports or interviews. A substantial heterogeneity in the applied measures for alcohol consumption was observed. Studies were based on continuous and categorical measures (dichotomous, nominal, and ordinal). Continuous measures included blood alcohol content, percentages of drinking days, and alcohol consumption in grams or ounces. Categorical measures employed a variety of cut-offs to distinguish the different categories. This heterogeneity was so substantial that it precluded meta-analyses. Therefore, it was not possible to answer the original research question: the extant literature does not enable any conclusions as to the relationship between maternal alcohol consumption and the likelihood of infants developing FASD. Instead, however, a wealth of suggestions for future research was distilled from the literature.

The most striking finding was the variation in measurement instruments that were employed to assess maternal drinking behavior. Each of the 20 included studies operationalized measures of alcohol consumption differently. The majority of studies used categorical measures. This is not desirable as these

impose a discontinuous scale using cut-off scores. Because, as this review evidences, there exists insufficient evidence to derive whether alcohol consumption (as relating to FASD risk) should be considered as a continuous or discontinuous scale, and where the cut-offs should lie in the case of a discontinuous scale, such cut-off scores are necessarily arbitrary to a degree. In addition, categorizing continuous data discards variance, thereby potentially obfuscating associations between variables [29–31]. The variation in cut-off scores exhibited in the studies included in this review supports this assumption of arbitrariness, and prohibits aggregation of the data collected in those studies. When studies did use continuous measures, studies often did not report how many grams of alcohol were in one standard drink. By making assumptions (e.g., based on the standard drink size in the country of data collection) we were able to convert most standard drink-based measures into grams of alcohol, but this was not always feasible.

Strengths and limitations

One of the reasons for this heterogeneity may be that none of the included studies were conducted primarily to investigate the association between maternal drinking behavior and FASD: although both variables were frequently measured and reported, most studies were designed to determine prevalence or FASD symptoms. It appears that few or no studies have been designed specifically to empirically establish how maternal alcohol consumption in humans is related to the likelihood of FASD. Given the comprehensive set up of this literature review, it is unlikely that such attempts have been overlooked. The search query was very extensive, rendering omission of relevant keywords unlikely. Screening was conducted in three screening rounds, by two independent screeners, and all records flagged for inclusion by one screener were retained for closer inspection. In addition, the ascendency approach was applied. Given that reports of studies where these variables were secondary measures preclude conclusions about this relationship, it is as yet not possible to establish which recommendations can be empirically

justified. In other words, even though in some target populations a total abstinence recommendation does not seem feasible. Available literature as yet offers no clear guidance that enables exploring a recommendation that could balance feasibility for the target population with dangers to health. Also Mamluk et al. [32] underlined the lack of data to make robust conclusions on the harmful effects of prenatal alcohol exposure and the unborn child. However, our inspection of the literature did yield a number of valuable recommendations for future research.

Recommendations

The original aim of this review was to provide a first step on the road to theory- and evidence-based intervention development. We had hoped that after identifying the risk related to different behavioral patterns, we could provide guidelines for prevention workers working with different target populations (e.g. alcohol-dependent pregnant women or teenage mothers). The next step could then be to map the determinants of those behaviors in those populations (i.e. why individuals engage in the relevant undesirable and desirable behaviors)[33]; so that these can be targeted by behavior change principles [34] that are then integrated into prevention campaigns [35]. However, it seems that the literature as yet has little guidance to offer. Because designing effective interventions first and foremost requires a thorough understanding of the target behavior(s), it is therefore important that future research considers the limitations identified in this review so that in the future, a clearer picture may emerge.

The first recommendation is addressed specifically to epidemiological researchers, and is based on the observation that the majority of studies assessed maternal drinking as part of a prevalence study. Because these studies form the largest part of the available data regarding associations between maternal alcohol consumption and FASD outcomes it is important to pay close attention to the measurement of alcohol consumption, even in epidemiological studies with different primary aims.

Second, in general, researchers should anticipate the need to aggregate their measures of alcohol consumption with measures from other studies: in other words, conversion to consumption in metric units, such as grams of alcohol, in a specified time period such as week or month, should be possible. If such conversion cannot be performed, the study cannot contribute to an accumulation of evidence. For example, many studies did not specify what exactly constituted a unit of alcohol (i.e. one standard drink). This means that it was necessary to try and identify the definition of a unit of alcohol in the country where the data were collected, in the period where the data were collected, but even then the obtained definition was unreliable as sometimes researchers conduct studies away from their home country yet use their home countries' unit definitions when reporting the results. Another example is that if timing of exposure was not specified, it is not clear whether the behavior occurred during the first, second, or third trimester (or was an aggregate of those periods).

This recommendation translates into a number of specific suggestions. Most of these are covered by following guidelines for the measurement of alcohol consumption, such as those specified by Dawson [36] and Sobell and Sobell [37], but specifically, it is recommended that future studies assessing specific maternal drinking behaviors should report at least the following (see below for the recommended approach in each case):

(i) how the sample was selected (e.g., retrospective) and which method was used (e.g., convenience sampling method),

(ii) the maternal characteristics variables (e.g., age, descent, educational level),

(iii) which method (or specific questions) was used to assess maternal alcohol consumption (e.g., alcohol timeline follow back approach),

(iv) the timing of exposure when assessing maternal alcohol consumption (e.g., first trimester pregnancy),

(v) the frequency of exposure when assessing maternal alcohol consumption (e.g., number of exposure sessions per week or month),

(vi) the amount of alcohol consumed per exposure session [36],

(vii) the sample size,

(viii) what was considered as one standard drink using International System of Units (i.e. grams or milliliters of alcohol),

(ix) if discontinuous (categorical) measures cannot be avoided, clear justification of the employed cut-offs.

The third recommendation refers to the complexity of exploring the association between maternal alcohol consumption and filial FASD. One cannot recruit children with FASD and then proceed to select children without FASD. This is not helpful because the *number* of children without FASD but with parents with matched alcohol consumption patterns is the variable of interest. The proportion of children with FASD within each group of parents with a given alcohol consumption pattern is the dependent variable to measure. For example, let us assume that in the left panel of Figure 1 (showing the sigmoid relationship), the probability of FASD is 1% if alcohol consumption is lower than 5 units; 25% if alcohol consumption is between 5 and 10 units; 75% if alcohol consumption is between 10 and 15 units; and 99% if alcohol consumption exceeds 15 units. Similarly, let us assume that in the right panel (showing the linear relationship), the probability of FASD is 12.5% is alcohol consumption is lower than 5 units; 37.5% is alcohol consumption is between 5 and 10 units; 62.5% is alcohol consumption is between 10 and 15 units; and 87.5% is alcohol consumption exceeds 15 units. This means that for 1000 parents consuming between 0 and 5 units (the yellow area), in the sigmoid scenario, 10 children will develop FASD and 990 (99 times more) will not, while in the linear scenario, 125 children develop FASD and 875 will not (7 times more). Now, imagine that a researcher visits a school and screens all children for FASD, and 10 children

screen positive for FASD. For simplicity's sake, let us assume that the parents of all these children happened to consume less than 5 units per week during pregnancy. Now, this researcher will not know whether to create a matched control group that is 99 times larger (as would be the case in the sigmoid scenario) or 7 times larger (as would be the case in the linear scenario). It is exactly the relative sizes of these groups that is the variable to measure, and the only way to do so is to measure both maternal alcohol consumption patterns and filial FASD in a large sample.

Based on these recommendations, the ideal design would be a large-scale[1] prospective study where maternal and paternal alcohol consumption patterns would be assessed both using self-reports (conform the recommendations made earlier) as well as objective measures such as biomarkers for alcohol consumption [38]. Infants would then be assessed for FASD according to the revised IOM guidelines [1] and other recommendations provided by Roozen et al. [6], and the FASD prevalence would be related to alcohol consumption patterns of both parents separate and in conjunction. This design also enables examination of potential confounders such as social economic status or age. Such an ideal design may not always be feasible. After all, learning about the association of parental drinking patterns to filial FASD requires assessing drinking patterns in all pregnancies: it is not possible to start from identified FASD cases, as we explained earlier. However, even when other designs are utilized, it is important that researchers anticipate data aggregation over studies, and therefore attempt to provide alcohol measures in metric units.

The present review focused on reported data on maternal drinking behaviors. Some of the included studies also reported paternal drinking patterns or grandparental drinking patterns. The role of paternal

[1] Note that what constitutes "large-scale" depends on the expected FASD prevalence in a population as well as the target behavior under investigation, e.g. abstinence versus moderated drinking, or abstinence versus regular drinking patterns. These two parameters determine the effect size of the association that is to be estimated, which in turn enables computation of the required sample size for accurate estimation of that effect size using Accuracy in Parameter Estimation (AIPE) methods.

drinking and transgenerational toxicity on fetal development and FASD is not well understood. A recent review study by Gupta and colleagues [19] reported that paternal alcoholism alters the gene expression for fetal susceptibility to FAS. In another review, Resendiz and colleagues [20] argue that transgenerational toxicity may play a role in FASD etiology. Moreover, social facilitation by paternal drinking is significantly associated with maternal drinking [39]. The origin of FASD is therefore not only based on maternal drinking behaviors but by many other factors (e.g., genetic and epigenetic predisposition, maternal body makeup, and lifestyle). Gupta and colleagues [19] emphasized that FAS etiology, and also other diagnosis within the FASD spectrum, is based on a complex interaction of different factors whereby cautious interpretation is warranted.

Conclusion

The current knowledge on maternal alcohol drinking behaviors in relation to FASD is limited. Behaviors were measured using various techniques and operationalized differently. For evidence-based preventive measures it is necessary to identify which prenatal alcohol drinking behavior(s) are most in need of intervention. Several recommendations have been made that can facilitate accumulation of evidence over studies. Following these recommendations can contribute to establishing the evidence base required for the development of effective preventive health promoting programs.

Contributors

Authors SR, GJYP, GK, LC designed the study and directed its implementation, including quality assurance and control. Authors DT, JN, and GK helped supervising the field activities. Authors SR and GJYP conducted the literature review and analyses and prepared the Materials and Methods and the Discussion sections of the text. All other co-authors contributed to successive drafts. All authors gave significant input in preparation of the article and approved the manuscript and submission.

Availability of data and materials

All data, analysis scripts, and other materials are publicly available at the Open Science Framework repository for this study (https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950).

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Figure captions:

Figure 1. Two examples of possible dose-response relationships between maternal alcohol consumption and probability of filial FASD.

Figure 2. Flow chart of publications measuring maternal behavior(s) related to FASD included in the review. Details regarding the screening procedure and number of exclusions per exclusion criterion can be inspected at resource 2.

Table 1. Overview of characteristics of included studies in this review

	Authors (year)	Geography	Sample year	Cases	Controls	Assessment methods	Number of measurement levels[1]				NOS score[2]
							Dich.	Nom.	Ord.	Cont.	
1	*Cannon and colleagues*[9]	United States	1995-1997	353	3894874	record documentation	1		2		4
2	*Ceccanti and colleagues* [40]	Italy	2014	39	108	interview	1			6	9
3	*Coyne and colleagues*[41]	Australia	1994-2006	54	56	self-report			2		5
4	*Davies and colleagues* [42]	South Africa	2002-2003	39	36	interview		1			6
5	*May and colleagues*[43]	South Africa		46	42	interview			4		6
6	*May and colleagues* [44]	South Africa	1999-2001	53	116	interview			4		7
7	*May and colleagues* [45]	South Africa		61	133	interview	5				7
8	*May and colleagues*[46]	South Africa	2002	49 FAS, 15 pFAS	133	interview	1		4	7	6
9	*May and colleagues* [47]	Italy	2011	8 FAS, 34 pFAS, 30 FASD	122	interview	4				9
10	*May and colleagues* [48]	South Africa	2013	63 FAS, 48 pFAS, 32 ARND	81	interview	4				7

11	*May and colleagues*[49]	South Africa	2013	68 FAS, 52 pFAS, 35 ARND	90	interview	7		1		7
12	*May and colleagues*[50]	United States	2010-2011	30	80	interview	2		4		7
13	*May and colleagues*[28]	South Africa		43	85	interview	5				7
14	*May and colleagues*[51]	South Africa	2011	118 FAS, 91 pFAS, 55 ARND	100	interview	11		8		7
15	*Miller and colleagues*[52]	United States	1992-1994	22	214499	*unknown*		1			7
16	*O'Leary and colleagues*[53]	Australia	1995-1997			self-report		3			6
17	*Petković and Barišić*[54]	Croatia		55	769	self-report			5		7
18	*Suttie and colleagues* [55]	South Africa	2013	22 FAS, 26 pFAS	69	interview			3		5
19	*Urban and colleagues*[56]	South Africa	2001-2004	82	74	interview	1				6
20	*Viljoen and colleagues*[57]	South Africa	2001	31	31	interview		4			6
21	*Viljoen and colleagues*[58]	South Africa	2005	53	116	interview	5				7

note [1]measurements of maternal alcohol drinking behavior are categorized in three different levels: dichotomous ('Dich.', e.g., yes/no), nominal ('Nom.', e.g., admitted, negative, unanswered), ordinal ('Ord.', e.g., < 4 drinks, > 4 drinks), continuous ('Cont.', e.g., %). The measures represent the different questions asked for each category (e.g., "drank during the first trimester of pregnancy"). [2]Each study was assessed using the adapted version of the Newcastle – Ottawa Scale (NOS). Scores were allocated from a scale from 0 (poor quality) to a maximum of 10 stars (excellent quality). For more detailed information see resource 5.

Table 2. Conclusions made by authors of included studies on maternal drinking behaviors and FASD

Authors (year)	Original authors' conclusions
Cannon and colleagues[9]	"Mothers of children with FAS have severe substance abuse behaviors including daily drinking, binge drinking"
Ceccanti and colleagues [40]	"Mothers of children with a FASD reported more drinking three months prior to pregnancy, more current drinking, and endorsed questionnaire items indicating that solitary drinking was more common"
Coyne and colleagues[41]	"Mothers of children with FAS reported heavy alcohol intake during pregnancy"
Davies and colleagues [42]	"Twenty five mothers with a FASD diagnosed child (69%) reported drinking alcohol, on average, every week during their pregnancy"
May and colleagues[43]	"Most drinking is binge drinking. Even though the current drinking quantities reported by both subjects and controls were not high in absolute standards, the most important interpretation of the data is the large differential between subjects and controls. There is no doubt, however, that these mothers drank sufficiently to produce verifiable cases of fetal alcohol syndrome as severe as we have seen anywhere in the United States"
May and colleagues [44]	"Alcohol consumption was much greater for case mothers than for control mothers in all comparisons. Control mothers were more likely to have been abstainers or Light drinkers compared with case mothers, who showed significantly heavier drinking patterns and reported drinking at the same level (53%-55%) or higher during pregnancy (32%-34%) compared with current drinking levels"
May and colleagues [45]	"Measures of drinking during the index pregnancies are significantly associated with low intelligence and frequent behavioral problems in the children. Reported drinking during pregnancy (.59), drinks per day (.48), three drinks or more per occasion (.51), and five drinks or more per occasion (.45), correlate highly with total dysmorphology in the children"
May and colleagues[46]	"In most every variable of maternal alcohol use and abuse, a spectrum emerged based on the final diagnosis of the child with FAS, PFAS, and control. Alcohol use was greatest in quantity, frequency, and duration among the mothers of FAS children, and generally next most severe among mothers of PFAS children, while lowest among controls"
May and colleagues [47]	"Mothers of children with FASD report heavy current drinking and drinking during the 2nd and 3rd trimesters of the index pregnancy"
May and colleagues [48]	"Binge drinking of at least two days a week during all trimesters in this population may produce FAS or PFAS, while mothers of children with ARND and exposed children without an FASD are most likely to reduce their average and peak alcohol consumption in the later trimesters"

May and colleagues[49]	"Mean number of drinks per week and drinking 3 and 5 or more drinks per occasion during pregnancy both illustrate the significant difference between mothers of FASD children and those of normal children"
May and colleagues[50]	"Mothers of children who had a FASD reported more drinking 3 months before pregnancy, and heavy drinking by the father of children who had FASD"
May and colleagues[28]	"With patterns of heavy episodic (binge) drinking being the most harmful to the fetus"
May and colleagues[51]	"Outcomes, both physical and cognitive/behavioral, are especially poor among children who were exposed to the highest quantity and frequency of drinking, especially drinks per drinking day and three or more drinks per occasion in both the case control comparisons and the correlation analysis"
Miller and colleagues[52]	"Mothers of FAS cases were more likely to drink alcohol during pregnancy"
O'Leary and colleagues[53]	"Heavy PAE in the first trimester was associated with a more than fourfold increased risk of ARBDs. This association was specific to PAE in the first trimester. The finding of twofold increased odds of ARBDs after moderate levels of PAE during late pregnancy is likely because many women also had heavy first trimester exposure and reduced their alcohol intake as pregnancy progressed"
Petković and Barišić[54]	"Confirmed pregnancy alcohol consumption in the FAS/PFAS group was higher (18.2%) to observed frequency in the whole sample of questioned mothers (11.5%) and significantly higher when compared to non-FAS/PFAS mothers (10.4%)"
Suttie and colleagues [55]	"No differences were found for prenatal alcohol exposure between the HE subgroup with FAS/PFAS affinity (nonsyndromal heavy exposed with FAS/PFAS-like face signature [HE1]) versus theHE subgroup with control affinity (nonsyndromal heavy exposed with more control-like face signature [HE2]) (P < .10)"
Urban and colleagues[56]	"Maternal drinking during pregnancy was much more frequently reported in mothers of children with FAS/PFAS than in controls"
Viljoen and colleagues[57]	"Mothers of children with FAS drank significantly heavier than controls, especially for continues drinking heavily (and/or increasing) throughout pregnancy. Control mothers drank less and drinking levels declined during pregnancy. Episodic drinking on weekends was modal for both groups with bingeing 5+ drinks was normative during 2 constructive days for FAS mothers "
Viljoen and colleagues[58]	"Mothers of children with FAS drink more than controls, drink rapidly and drink heavily in an episodic fashion. Moreover, they do not quit or cut down during pregnancy"

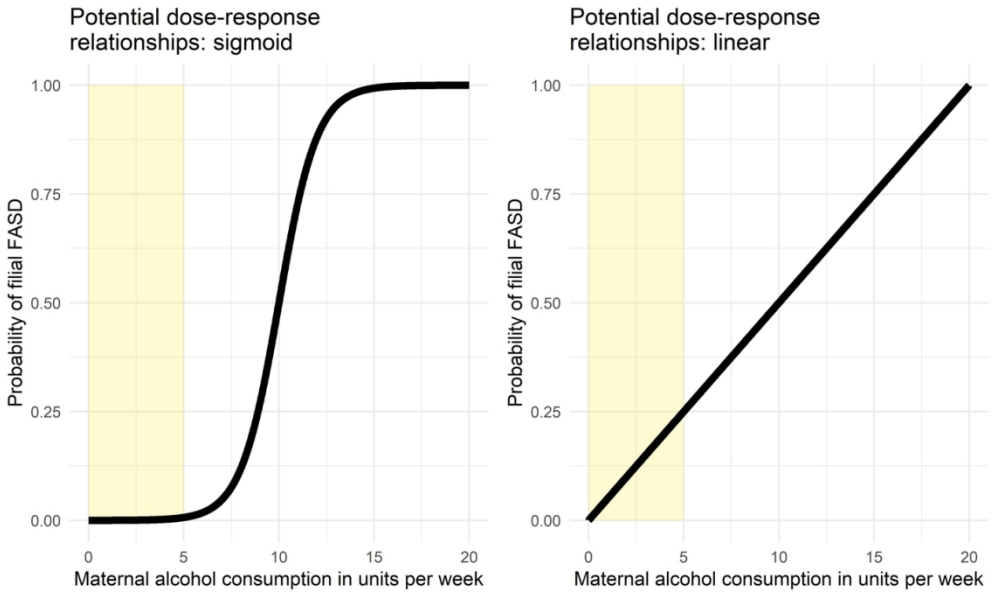

Figure 1. Two examples of possible dose-response relationships between maternal alcohol consumption and probability of filial FASD.

119x71mm (300 x 300 DPI)

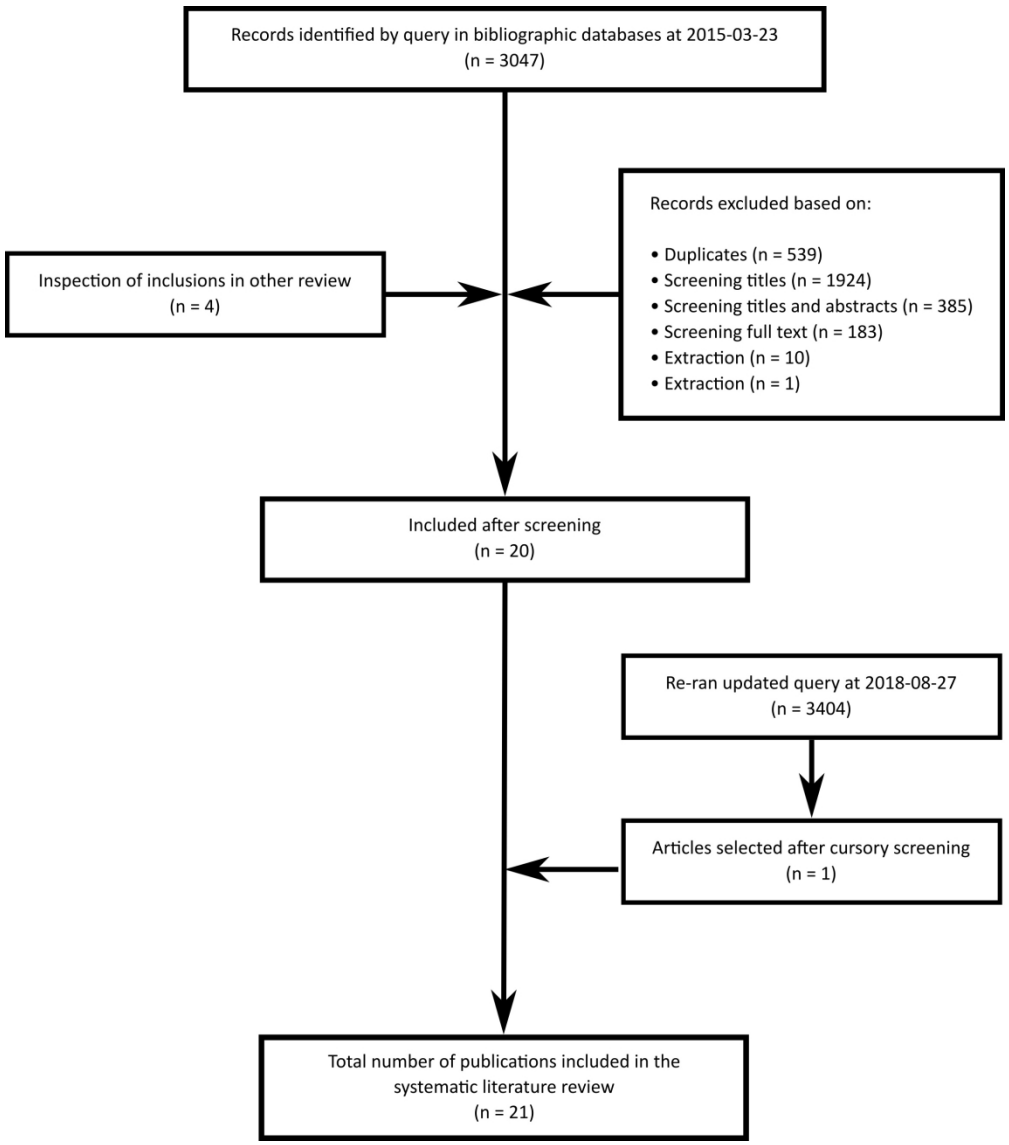

Figure 2. Flow chart of publications measuring maternal behavior(s) related to FASD included in the review. Details regarding the screening procedure and number of exclusions per exclusion criterion can be inspected at resource 2.

615x697mm (96 x 96 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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The PRISMA for Abstracts Checklist

TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	1
BACKGROUND		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	4
METHODS		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	4
4. Information sources:	Key databases searched and search dates.	4
5. Risk of bias:	Methods of assessing risk of bias.	NA
RESULTS		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	4
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	4
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	NA
DISCUSSION		
9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	5
10. Interpretation:	General interpretation of the results and important implications	5
OTHER		
11. Funding:	Primary source of funding for the review.	NA
12. Registration:	Registration number and registry name.	NA

BMJ Open

Systematic literature review on which maternal alcohol behaviors are related to Fetal Alcohol Spectrum Disorders (FASD).

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Systematic literature review on which maternal alcohol behaviors are related to Fetal Alcohol Spectrum Disorders (FASD).

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Abstract

Objectives: Fetal Alcohol Spectrum Disorders (FASD) is a worldwide problem. Maternal alcohol consumption is an important risk factor for FASD. It remains unknown which alcohol consumption patterns most strongly predict FASD. The objective of this study was to identify these.

Design: Systematic literature review.

Methods: We searched in PubMed, PsychINFO, PsycARTICLES, ERIC, CINAHL, EMBASE and MEDLINE up to August 2018. The query consisted of keywords and their synonyms related to FASD, pregnancy, and behavior. Studies were excluded when not published in English, were reviews, or involved non-human subjects. Substantial heterogeneity precluded aggregation or meta-analysis of the data. Instead, data were qualitatively inspected.

Results: In total, 21 studies were eligible for further data analysis. All studies that measured both maternal alcohol drinking behaviors and FASD reported retrospective data on maternal drinking patterns, employing both continuous and categorical measures and exhibiting substantial heterogeneity in measures of alcohol consumption (e.g., timing of exposure, quantification of alcohol measure, definition of a standard drink). Study quality improved over time and appeared higher for studies based on active case ascertainment, especially when conducted in schools, and when behavior was assessed through interviews.

Conclusions: We aimed to identify specific maternal drinking behavior(s) related to FASD. The state of the literature precludes such conclusions. Evidence-based preventive measures necessitate identifying

which prenatal alcohol drinking behavior(s) are most in need of intervention. Therefore, we formulate three recommendations for future research. First, future studies can optimize the value of the collected dataset through specifying measurements and reporting of maternal drinking behaviors, and avoiding categorized measures (nominal or ordinal) whenever possible. Second, samples should not be selected based on FASD status, but instead, FASD status as well as maternal alcohol consumption should both be measured in a general population sample. Finally, we provide ten reporting guidelines for FASD research.

Strengths and limitations of this study

- This systematic literature review uses a comprehensive search strategy to cover the published literature
- We did not consult grey literature
- Consultation about data aggregation took place with three independent alcohol experts
- Substantial heterogeneity prevented synthesis but yielded a rich set of recommendations as to reporting guidelines and measurement principles

Introduction

Prenatal alcohol exposure is one of the leading causes of mental retardation resulting in irreversible lifelong consequences for the unborn child (e.g., neurocognitive deficits, growth deficiencies, facial dysmorphology) [1]. These adverse outcomes are also known as fetal alcohol spectrum disorders (FASD). The spectrum encompasses various diagnostic subtypes: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol related neurodevelopmental disorder (ARND), alcohol related birth defects (ARBD), and neurobehavioral disorder with prenatal alcohol exposure (ND-PAE) [1,2]. Epidemiological research implies that FASD is a worldwide problem. Initial FAS prevalence estimates ranged from 0.5 to 7 per 1,000 livebirths [3,4]. Recent systematic literature reviews [5,6] including multiple meta-analyses reported estimates ranging from 0.11 to 55.42 per 1,000 (FAS), 0.8 to 43.01 per 1,000 (pFAS), 0.12 to 20.25 per 1,000 (ARND), 1.03 to 10.82 per 1,000 (ARBD), and 1.06 to 113.22 per 1,000 (FASD).

FASD, as its name implies, is caused by alcohol use. Several reviews have aimed to further elucidate the relationship between alcohol use and filial FASD [7,8]. Specifically, mothers of children diagnosed in the FASD spectrum reported drinking levels ranging from mild to excessive ('binge drinking') alcohol use [7,9–11] [8,12,13]. The severity of FASD may be dependent on the level, pattern, and timing of prenatal alcohol exposure before and during pregnancy [13,14], along with other confounding factors such as nutritional status of the mother (e.g. vitamin or mineral intake), environmental factors (e.g., social relationships, stress),maternal age, and genetic makeup [14–16]. As yet, there is no known safe amount of alcohol to drink while pregnant [1,13,17,18].

Two systematic literature reviews reported associations between level of alcohol exposure and negative effects on child development [7,11]. Both reviews show the negative effects of higher amounts of alcohol intake (daily alcohol consumption up to 4 or more drinks per occasion before and during pregnancy) related to various neuropsychological outcomes (including but not specific for a FASD diagnosis. However, these reviews are inconclusive about behaviors related to the outcome of FASD specifically [5,7,11], or the effects of consumption of lower amounts of alcohol.

Planning evidence based health promoting programs requires an adequate understanding of which maternal behavior(s) are associated with FASD. Note that maternal alcohol consumption is not the only factor for filial FASD. Paternal and even grandparental consumption patterns have also been implicated [19,20], but as yet it remains undecided whether paternal and grandparental consumption should also be included in the FASD definition (effects of paternal and grandparental consumption are considered necessarily either genetic or through influencing maternal alcohol consumption, whereas maternal alcohol consumption has a direct teratogenic effect). However, for the sake of this review, we limited ourselves to maternal alcohol consumption. Specifically, a first step for designing prevention programs requires defining specific target behavior(s) of the target population related to FASD [6,21]. However, the literature remains inconclusive about which maternal drinking behaviors are related to alterations of the fetal development. Despite this conflicting and inconclusive evidence of the negative effects on the developing fetus, public health recommendations are made nonetheless. These recommendations share one common principle, namely that complete abstinence of alcohol use during pregnancy is the safest approach to prevent any possible risks to the unborn child [1,13,17,18]. However, despite this common thread, there are also many differences between the recommendations. For example, the British Medical Association (BMA) lists four different recommendations that are currently made in the United Kingdom alone [13]. This heterogeneity is problematic because communicating multiple contrasting

recommendations is confusing for the target audiences. At the same time, there are good arguments to tailor the recommendations. For example, it is likely that although any alcohol consumption may entail risks, binge drinking (BAC to .08 grams percent or above; 4 or more drinks in about 2 hours)is one of the serious risk factors and associated with severe forms of FASD [22]. Therefore, it appears that special attention for specific risk groups such as heavily drinking pregnant women is warranted.

Yet, implementing such a tailored approach is currently hindered by the lack of knowledge regarding the dose-response relationship and potential moderators. On the one hand, insufficient evidence is available about the association of different alcohol-related behaviors to FASD-related risk, especially low doses of alcohol, to adequately delineate target groups to enable tailored communication. This would seem to justify foregoing the heterogeneous recommendations and instead converging on an abstinence recommendation. However, in some target populations, such a total abstinence recommendation does not seem feasible. Especially high-risk populations, for example heavily drinking women, may not be able to completely eliminate their alcohol intake, for example because of personal factors as self-regulation skills, or environmental factors such as social pressures. Given that a total abstinence recommendation may be unrealistic for some of the highest-risk populations, such a recommendation can be ethically problematic.

Figure 1 about here

To illustrate this, consider Figure 1. This Figure shows two potential dose-response relationships between weekly maternal alcohol consumption and risk of filial FASD for a given individual (note that individual vulnerabilities can vary). The left panel shows a sigmoid relationship, where risk remains low if less than five units are consumed weekly, whereas in the linear dose-response relationship depicted in the right

panel, risk is already considerable at five consumptions weekly. For those subpopulations where abstinence recommendations may be unrealistic, if the dose-response relationship is similar to that shown in the left panel, a harm reduction message such as 'consume at most five units' (the yellow areas in Figure 1) may be easier to defend than if the dose-response relationship is linear. Not only may such a message be easier to defend: it may be more effective at decreasing FASD prevalence. Setting unachievable goals has little behavior change potential [23], and if a more achievable goal can stimulate the target population to moderate their alcohol intake enough to decrease the risk of FASD, while an abstinence message, being unrealistic, has no effect, the ethics of an abstinence message become questionable. If, however, the risk increases very rapidly even with light alcohol consumption, deviating from an abstinence message may be damaging.

Animal models have provided some evidence as to potential dose-response relationships. However, such models are not fully translatable to humans [16], and especially given that the present research question concerns not simply whether a dose-response relationship exists, but what the *nature* of this relationship is, relying on animal models does not seem appropriate.

Further research is warranted to identify behaviors for health promotion programs to target on. Developing health promoting programs aiming at reducing alcohol consumption during pregnancy first requires identifying which prenatal alcohol drinking behavior(s) are most in need of intervention. The purpose of the present study is to conduct a systematic literature review and meta-analysis to identify those maternal alcohol drinking behaviors most strongly related to FASD.

Materials and Methods

Protocol and data repository

Data will be reported following the PRISMA guideline [24]. All materials and supporting documents are publicly available at the Open Science Framework repository at https://osf.io/whq45/. In this repository, we have numbered the directories that organize the materials. Hereafter, we will refer to materials in this repository as ''resource 1" through "resource 8", which correspond to these directories.

Ethics statement and patient and public involvement

The current study extracted data from online databases and did not involve participation of participants; therefore, it was not necessary to obtain ethical permission.

Search strategy

A search was conducted in PubMed, PsychINFO, PsychARTICLES, ERIC, CINAHL, EMBASE and MEDLINE databases up to August 2015 using an extensive query consisting of keywords related to FASD, pregnancy and behavior (e.g., fetal alcohol syndrome, pregnancy, alcohol use, risk factor). We reran the query just before submitting the manuscript in August 2018 and performed a cursory inspection to scan for newly added papers. Moreover, we applied the ascendancy approach by inspecting the reference lists of included articles (the complete queries are included in resource 1).

Study selection

Resulting hits from the query were exported and screened by two independent screeners in three rounds. The first screening round was based on titles only; the second, on titles and abstracts; and the

third, on the full text articles. Records were included if they were written in English and reported maternal alcohol related behaviors associated with a FASD diagnosis. Records that were duplicates, concerned reviews or meta-analysis, or concerned studies that involved non-human subjects were excluded. An extensive list of inclusion and exclusion criteria is located in the screening instructions (resource 2).

Data extraction

Data were transferred onto extraction forms, which were templated source code files for R [25], using Notepad++. Researcher SR completed all extraction forms including the following variables: sampling method (retrospective versus prospective), sampling selection (select versus aselect), variables on which controls were matched (e.g., age mother, study year of the child), recruitment setting (e.g., school, clinic), descent (native versus nonnative population), geography, year of data collection, sample size, subsamples, method of diagnosis (e.g., IOM, 4-digit), syndrome category (e.g., FAS, ARND), datatype (e.g., aggregate, question), datatype levels (e.g., nominal, logical), confirmed maternal alcohol exposure, method of case ascertainment (active versus passive), data collection method (self-report versus interview). Moreover, variables related to drinking behaviors were extracted. Specifically, period of alcohol consumption (e.g., first trimester, before pregnancy), timeframe (concurrent versus retrospective), intensity specification (e.g., any day, weekend day), specification of units (e.g., oz, mg), specification of timeframe (e.g., per year, per month), binging, and alcoholism. Also, when no indication of one standard drink was provided, the units in grams were granted depending on country and their national alcohol guidelines (e.g., one standard drink in the United States = 14 gr, Australia = 10 gr; see resource 5). These extraction forms were then read into R and processed by an R script.

Quality assessment

A slightly adapted) version of the Newcastle–Ottawa Scale (NOS) was used for assessing the quality of nonrandomized studies for further meta-analysis with a maximum of 10 stars [26] (see resource 4 for the complete assessment and comparison to the original version) The quality of each publication was assessed by two independent reviewers (inter rater reliability = 80%) who settled differences by discussion.. No studies were excluded based on this quality assessment.

Data synthesis and statistical analysis

In case of sufficient homogeneity, meta-analyses and meta-regressions were to be conducted using metafor, a free package in R [27].

Figure 2 About Here

Results

The systematic literature review resulted in 3404 identified hits (see Figure 2). Twenty-one hits qualified for further screening and analysis. Hits were excluded because they were duplicates, not written in English, or did not report associations between prenatal alcohol and FASD. The assessment of the included studies using the NOS scale revealed a wide range of quality scores with an average score of 6.57 out of 10 (for more details, see resource 5).

Sample characteristics

Sample characteristics can be inspected in Table 1. First, inspection of the data shows that the included studies were reported from five different countries, including Australia (*n* = 2), Croatia (*n* = 1), Italy (*n* =

2), South Africa (*n* = 12), and United States (*n* = 4). All studies were conducted after the year 1992. Almost all studies relied on interviews (*n* = 17), followed by self-reports (*n* = 3), and medical records (*n* = 1). Moreover, all studies were based on a retrospective sampling method. Behavior was described in terms of maternal alcohol drinking related to a FASD diagnosis. Behaviors were reported before and during pregnancy where the period during pregnancy was specified per trimester (e.g., first, second, third).

Further inspection shows that alcohol consumption was operationalized differently in each study (e.g., dichotomous measures; a complete table can be found in Table 1): in fact, no two studies used the same measure. Some studies reported units, whereas other studies reported subjective estimates (e.g., many, less than). Others used dichotomous measures (e.g., yes or no), a mixture of ordinal measures (e.g., none, mild, moderate, heavy), or interval variables (e.g., percentage). The original author's conclusions on maternal drinking behaviors & FASD can be inspected in Table 2.

Dichotomous measures

Dichotomous measures (e.g., yes versus no) were available for 12 studies representing 44 measures (see Table 1). These included questions concerning alcohol consumption before pregnancy [7, 10, 11, 20]. Questions concerning alcohol consumption during pregnancy [2, 8, 14] included the following variables: binge drinking without specifying how this was defined [2, 8], alcoholism [1], binge drinking (3 or more drinks per occasion; 5 or more drinks per occasion) [9, 10, 12, 13, 14], alcohol consumption in general [7, 9, 11, 17, 19], smoking as well as binge drinking (3 or more drinks per occasion; 5 or more drinks per occasion [13]. Moreover, questions were measured if pregnant women drank alcohol during the first trimester of pregnancy [7, 9, 11, 13, 14, 17, 21]; second trimester [7, 9, 11, 13, 14, 17, 21]; and/ or third trimester [7, 9, 11, 13, 14, 17, 21]. For more detailed information see resource 5.

Nominal measures

Although alcohol consumption is in fact a continuous variable, it was still operationalized at the nominal level in six nominal measures used in two studies [4, 17]. For more detailed information see resource 5.

Ordinal measures

In total, 24 ordinal measures were used in eight studies (see also the numbered studies in Table 1). These incorporated questions concerning alcohol consumption before pregnancy [3], sometimes specified in categories of units e.g., grams a week, stopped during drinking or drank less than current use [3, 5, 6, 8, 20]; and alcohol consumption during pregnancy [1], including variables measuring the categories of alcohol intake in units of e.g., grams a week [3, 15]. Moreover, questions were measured for each trimester of pregnancy; alcohol consumption during first trimester of pregnancy [5, 8, 20] whereby variables were specified with categories e.g., drank less or drank more than current use [5, 8, 20]; alcohol consumption during second trimester [5, 6, 8, 20] using the categories e.g., drank less or drank more than current use [5, 6, 8, 20]; and alcohol consumption during the third trimester [5, 6, 8, 20] whereby variables were specified with categories e.g., drank less or drank more than current use [5, 6, 8, 20]. For more detailed information see resource 5.

Continuous measures

Surprisingly, continuous measures were only available for six studies. In total, these studies employed 29 measures (see Table 1). These included questions concerning alcohol consumption before pregnancy [2, 8, 10, 12, 18] where variables were sometimes specified in number of drinks e.g., a day or week [8, 10, 14]; and during pregnancy [10, 14], where variables were sometimes specified in number of drinks e.g., during a drinking day, week, weekend [2, 11, 12, 14, 18]. Moreover, number of alcoholic drinks or drinking days were measured during the first trimester of pregnancy [2, 10, 12, 14], sometimes specified in numbers a day or estimated BAC [8]; number of drinks or drinking days during second trimester [2, 10, 12, 14], sometimes specified in numbers a day or estimated BAC [8]; and/ or number of drinks or

drinking days during third trimester [2, 10, 12, 14], sometimes specified in numbers a day or estimated BAC [8].

Table 1 About Here

Table 2 About Here

Integration

Categorical variables were based on different answer options and cut-off values, which precluded further aggregation or integration. Operationalizations on a continuous level of measurement also displayed substantial variation. Where possible, we attempted to transform these continuous measures of alcohol consumption into the same metric (e.g., one standard drink defined in grams). However, even this was hindered by heterogeneity in reported standard sizes (sometimes not reported at all), types of alcohol described, and other variation across countries. Moreover, few studies reported continuous data. Because of these reasons, conducting meta-analyses of the continuous variables alone was not feasible.

Consultation with three independent alcohol experts (e.g., expertise in pharmacology of alcohol and measurements of alcohol drinking behaviors) revealed that aggregation of variables in the current dataset was not feasible. This substantial heterogeneity in operationalizations hindered further meta-analyses, and therefore the data will be described qualitatively below with emphasis on the used operationalizations and timing of exposure.

Because aggregation of the evidence was not possible, we instead sought to explore the heterogeneity exhibited by the included studies (note that all 230 extracted effect sizes are available in file

'effectsizes.csv', and an overview of the used operationalisations in 'Alcohol use variables.csv', both in resource 6). Given the small number of included studies, we decided to inspect visualizations of the associations between study characteristics. We plotted the quality of the studies (NOS scores), study year, measurement level of the alcohol consumption operationalization, recruitment setting, and data collection methods.

These visualizations revealed interesting patterns. The quality of studies (NOS score) seem to improve over the years. Data derived from clinical records were mainly based on ordinal measures. NOS score appeared higher for studies where maternal alcohol history was based on interviews. Finally, NOS scores appeared higher for samples recruited through active case ascertainment, especially in schools. We have included these visualizations in resource 6).

The wide range of variation in operationalisations provided a unique opportunity to compare them. Continuous measures provide detailed information about specific units (e.g., oz, standard drink, BAC). If reported similarly across studies, these could be further meta-analyzed. However, this requires reporting all information needed to convert the reported statistics into grams or milliliters of alcohol, to enable integration with results from other countries. Other challenges appear to be present for logical, nominal and ordinal measures (e.g., cut-off scores). Some studies reported categories e.g., binge drinking including 3 or more drinks per occasion versus 5 or more drinks per occasion [28]; less than 4 drinks a day versus more than 4 drinks a day [9]. None of the studies reported a description and considerations of why certain cut-off scores were chosen. Cut-off scores likely often followed recommendations by health promotion agencies or suggestions from earlier studies, but without explicit specification this remains unclear. Perhaps the difficulty of establishing sensible cut-off values partly explains this, as doing so requires evidence syntheses to determine where exactly the effects of the relevant behavior becomes qualitatively different. Such evidence (e.g., meta-analyses of maternal alcohol consumption patterns) is

not yet available. However, this should lead researchers to employ continuous operationalisations for now, rather than selecting (more or less arbitrary) cut-off scores.

Discussion

In this systematic literature review, we aimed to summarize available data of studies that reported maternal alcohol drinking behaviors in relation to FASD. Data were available for 21 studies. The majority of these 20 studies were based on retrospective self-reports or interviews. A substantial heterogeneity in the applied measures for alcohol consumption was observed. Studies were based on continuous and categorical measures (dichotomous, nominal, and ordinal). Continuous measures included blood alcohol content, percentages of drinking days, and alcohol consumption in grams or ounces. Categorical measures employed a variety of cut-offs to distinguish the different categories. This heterogeneity was so substantial that it precluded meta-analyses. Therefore, it was not possible to answer the original research question: the extant literature does not enable any conclusions as to the relationship between maternal alcohol consumption and the likelihood of infants developing FASD. Instead, however, a wealth of suggestions for future research was distilled from the literature.

The most striking finding was the variation in measurement instruments that were employed to assess maternal drinking behavior. Each of the 20 included studies operationalized measures of alcohol consumption differently. The majority of studies used categorical measures. This is not desirable as these impose a discontinuous scale using cut-off scores. Because, as this review evidences, there exists insufficient evidence to derive whether alcohol consumption (as relating to FASD risk) should be considered as a continuous or discontinuous scale, and where the cut-offs should lie in the case of a discontinuous scale, such cut-off scores are necessarily arbitrary to a degree. In addition, categorizing

continuous data discards variance, thereby potentially obfuscating associations between variables [29–31]. The variation in cut-off scores exhibited in the studies included in this review supports this assumption of arbitrariness, and prohibits aggregation of the data collected in those studies. When studies did use continuous measures, studies often did not report how many grams of alcohol were in one standard drink. By making assumptions (e.g., based on the standard drink size in the country of data collection) we were able to convert most standard drink-based measures into grams of alcohol, but this was not always feasible.

Strengths and limitations

One of the reasons for this heterogeneity may be that none of the included studies were conducted primarily to investigate the association between maternal drinking behavior and FASD: although both variables were frequently measured and reported, most studies were designed to determine prevalence or FASD symptoms. It appears that few or no studies have been designed specifically to empirically establish how maternal alcohol consumption in humans is related to the likelihood of FASD. Given the comprehensive set up of this literature review, it is unlikely that such attempts have been overlooked. The search query was very extensive, rendering omission of relevant keywords unlikely. Screening was conducted in three screening rounds, by two independent screeners, and all records flagged for inclusion by one screener were retained for closer inspection. In addition, the ascendency approach was applied. Given that reports of studies where these variables were secondary measures preclude conclusions about this relationship, it is as yet not possible to establish which recommendations can be empirically justified. In other words, even though in some target populations a total abstinence recommendation does not seem feasible. Available literature as yet offers no clear guidance that enables exploring a recommendation that could balance feasibility for the target population with dangers to health. Also Mamluk et al. [32] underlined the lack of data to make robust conclusions on the harmful effects of

prenatal alcohol exposure and the unborn child. However, our inspection of the literature did yield a number of valuable recommendations for future research.

Recommendations

The original aim of this review was to provide a first step on the road to theory- and evidence-based intervention development. We had hoped that after identifying the risk related to different behavioral patterns, we could provide guidelines for prevention workers working with different target populations (e.g. alcohol-dependent pregnant women or teenage mothers). The next step could then be to map the determinants of those behaviors in those populations (i.e. why individuals engage in the relevant undesirable and desirable behaviors)[33]; so that these can be targeted by behavior change principles [34] that are then integrated into prevention campaigns [35]. However, it seems that the literature as yet has little guidance to offer. Because designing effective interventions first and foremost requires a thorough understanding of the target behavior(s), it is therefore important that future research considers the limitations identified in this review so that in the future, a clearer picture may emerge.

The first recommendation is addressed specifically to epidemiological researchers, and is based on the observation that the majority of studies assessed maternal drinking as part of a prevalence study. Because these studies form the largest part of the available data regarding associations between maternal alcohol consumption and FASD outcomes it is important to pay close attention to the measurement of alcohol consumption, even in epidemiological studies with different primary aims.

Second, in general, researchers should anticipate the need to aggregate their measures of alcohol consumption with measures from other studies: in other words, conversion to consumption in metric units, such as grams of alcohol, in a specified time period such as week or month, should be possible. If such conversion cannot be performed, the study cannot contribute to an accumulation of evidence. For example, many studies did not specify what exactly constituted a unit of alcohol (i.e. one standard drink).

This means that it was necessary to try and identify the definition of a unit of alcohol in the country where the data were collected, in the period where the data were collected, but even then the obtained definition was unreliable as sometimes researchers conduct studies away from their home country yet use their home countries' unit definitions when reporting the results. Another example is that if timing of exposure was not specified, it is not clear whether the behavior occurred during the first, second, or third trimester (or was an aggregate of those periods).

This recommendation translates into a number of specific suggestions. Most of these are covered by following guidelines for the measurement of alcohol consumption, such as those specified by Dawson [36] and Sobell and Sobell [37], but specifically, it is recommended that future studies assessing specific maternal drinking behaviors should report at least the following (see below for the recommended approach in each case):

(i) how the sample was selected (e.g., retrospective) and which method was used (e.g., convenience sampling method),

(ii) the maternal characteristics variables (e.g., age, descent, educational level),

(iii) which method (or specific questions) was used to assess maternal alcohol consumption (e.g., alcohol timeline follow back approach),

(iv) the timing of exposure when assessing maternal alcohol consumption (e.g., first trimester pregnancy),

(v) the frequency of exposure when assessing maternal alcohol consumption (e.g., number of exposure sessions per week or month),

(vi) the amount of alcohol consumed per exposure session [36],

(vii) the sample size,

(viii) what was considered as one standard drink using International System of Units (i.e. grams or milliliters of alcohol),

(ix) if discontinuous (categorical) measures cannot be avoided, clear justification of the employed cut-offs.

The third recommendation refers to the complexity of exploring the association between maternal alcohol consumption and filial FASD. One cannot recruit children with FASD and then proceed to select children without FASD. This is not helpful because the *number* of children without FASD but with parents with matched alcohol consumption patterns is the variable of interest. The proportion of children with FASD within each group of parents with a given alcohol consumption pattern is the dependent variable to measure. For example, let us assume that in the left panel of Figure 1 (showing the sigmoid relationship), the probability of FASD is 1% if alcohol consumption is lower than 5 units; 25% if alcohol consumption is between 5 and 10 units; 75% if alcohol consumption is between 10 and 15 units; and 99% if alcohol consumption exceeds 15 units. Similarly, let us assume that in the right panel (showing the linear relationship), the probability of FASD is 12.5% is alcohol consumption is lower than 5 units; 37.5% is alcohol consumption is between 5 and 10 units; 62.5% is alcohol consumption is between 10 and 15 units; and 87.5% is alcohol consumption exceeds 15 units. This means that for 1000 parents consuming between 0 and 5 units (the yellow area), in the sigmoid scenario, 10 children will develop FASD and 990 (99 times more) will not, while in the linear scenario, 125 children develop FASD and 875 will not (7 times more). Now, imagine that a researcher visits a school and screens all children for FASD, and 10 children screen positive for FASD. For simplicity's sake, let us assume that the parents of all these children happened to consume less than 5 units per week during pregnancy. Now, this researcher will not know whether to create a matched control group that is 99 times larger (as would be the case in the sigmoid scenario) or 7 times larger (as would be the case in the linear scenario). It is exactly the relative sizes of

these groups that is the variable to measure, and the only way to do so is to measure both maternal alcohol consumption patterns and filial FASD in a large sample.

Based on these recommendations, the ideal design would be a large-scale[1] prospective study where maternal and paternal alcohol consumption patterns would be assessed both using self-reports (conform the recommendations made earlier) as well as objective measures such as biomarkers for alcohol consumption [38]. Infants would then be assessed for FASD according to the revised IOM guidelines [1] and other recommendations provided by Roozen et al. [6], and the FASD prevalence would be related to alcohol consumption patterns of both parents separate and in conjunction. This design also enables examination of potential confounders such as social economic status or age. Such an ideal design may not always be feasible. After all, learning about the association of parental drinking patterns to filial FASD requires assessing drinking patterns in all pregnancies: it is not possible to start from identified FASD cases, as we explained earlier. However, even when other designs are utilized, it is important that researchers anticipate data aggregation over studies, and therefore attempt to provide alcohol measures in metric units.

The present review focused on reported data on maternal drinking behaviors. Some of the included studies also reported paternal drinking patterns or grandparental drinking patterns. The role of paternal drinking and transgenerational toxicity on fetal development and FASD is not well understood. A recent review study by Gupta and colleagues [19] reported that paternal alcoholism alters the gene expression for fetal susceptibility to FAS. In another review, Resendiz and colleagues [20] argue that transgenerational toxicity may play a role in FASD etiology. Moreover, social facilitation by paternal

[1] Note that what constitutes "large-scale" depends on the expected FASD prevalence in a population as well as the target behavior under investigation, e.g. abstinence versus moderated drinking, or abstinence versus regular drinking patterns. These two parameters determine the effect size of the association that is to be estimated, which in turn enables computation of the required sample size for accurate estimation of that effect size using Accuracy in Parameter Estimation (AIPE) methods.

drinking is significantly associated with maternal drinking [39]. The origin of FASD is therefore not only based on maternal drinking behaviors but by many other factors (e.g., genetic and epigenetic predisposition, maternal body makeup, and lifestyle). Gupta and colleagues [19] emphasized that FAS etiology, and also other diagnosis within the FASD spectrum, is based on a complex interaction of different factors whereby cautious interpretation is warranted.

Conclusion

The current knowledge on maternal alcohol drinking behaviors in relation to FASD is limited. Behaviors were measured using various techniques and operationalized differently. For evidence-based preventive measures it is necessary to identify which prenatal alcohol drinking behavior(s) are most in need of intervention. Several recommendations have been made that can facilitate accumulation of evidence over studies. Following these recommendations can contribute to establishing the evidence base required for the development of effective preventive health promoting programs.

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Competing interests

None declared.

Contributors

Authors SR, GJYP, GK, LC designed the study and directed its implementation, including quality assurance and control. Authors DT, JN, and GK helped supervising the field activities. Authors SR and GJYP conducted the literature review and analyses and prepared the Materials and Methods and the Discussion sections of the text. All other co-authors contributed to successive drafts. All authors gave significant input in preparation of the article and approved the manuscript and submission.

Availability of data and materials

All data, analysis scripts, and other materials are publicly available at the Open Science Framework repository for this study (https://osf.io/whq45/).

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Figure captions:

Figure 1. Two examples of possible dose-response relationships between maternal alcohol consumption and probability of filial FASD.

Figure 2. Flow chart of publications measuring maternal behavior(s) related to FASD included in the review. Details regarding the screening procedure and number of exclusions per exclusion criterion can be inspected at resource 2.

Table 1. Overview of characteristics of included studies in this review

	Authors (year)	Geography	Sample year	Cases	Controls	Assessment methods	Number of measurement levels[1]				NOS score[2]
							Dich.	Nom.	Ord.	Cont.	
1	*Cannon and colleagues*[9]	United States	1995-1997	353	3894874	record documentation	1		2		4
2	*Ceccanti and colleagues* [40]	Italy	2014	39	108	interview	1			6	9
3	*Coyne and colleagues*[41]	Australia	1994-2006	54	56	self-report			2		5
4	*Davies and colleagues* [42]	South Africa	2002-2003	39	36	interview		1			6
5	*May and colleagues*[43]	South Africa		46	42	interview			4		6
6	*May and colleagues* [44]	South Africa	1999-2001	53	116	interview			4		7
7	*May and colleagues* [45]	South Africa		61	133	interview	5				7
8	*May and colleagues*[46]	South Africa	2002	49 FAS, 15 pFAS	133	interview	1		4	7	6
9	*May and colleagues* [47]	Italy	2011	8 FAS, 34 pFAS, 30 FASD	122	interview	4				9
10	*May and colleagues* [48]	South Africa	2013	63 FAS, 48 pFAS, 32 ARND	81	interview	4				7

11	*May and colleagues*[49]	South Africa	2013	68 FAS, 52 pFAS, 35 ARND	90	interview	7			1		7
12	*May and colleagues*[50]	United States	2010-2011	30	80	interview	2			4		7
13	*May and colleagues*[28]	South Africa		43	85	interview	5					7
14	*May and colleagues*[51]	South Africa	2011	118 FAS, 91 pFAS, 55 ARND	100	interview	11			8		7
15	*Miller and colleagues*[52]	United States	1992-1994	22	214499	*unknown*			1			7
16	*O'Leary and colleagues*[53]	Australia	1995-1997			self-report			3			6
17	*Petković and Barišić*[54]	Croatia		55	769	self-report		5				7
18	*Suttie and colleagues* [55]	South Africa	2013	22 FAS, 26 pFAS	69	interview				3		5
19	*Urban and colleagues*[56]	South Africa	2001-2004	82	74	interview	1					6
20	*Viljoen and colleagues*[57]	South Africa	2001	31	31	interview			4			6
21	*Viljoen and colleagues*[58]	South Africa	2005	53	116	interview	5					7

note [1]measurements of maternal alcohol drinking behavior are categorized in three different levels: dichotomous ('Dich.', e.g., yes/no), nominal ('Nom.', e.g., admitted, negative, unanswered), ordinal ('Ord.', e.g., < 4 drinks, > 4 drinks), continuous ('Cont.', e.g., %). The measures represent the different questions asked for each category (e.g., "drank during the first trimester of pregnancy"). [2]Each study was assessed using the adapted version of the Newcastle – Ottawa Scale (NOS). Scores were allocated from a scale from 0 (poor quality) to a maximum of 10 stars (excellent quality). For more detailed information see resource 5.

Table 2. Conclusions made by authors of included studies on maternal drinking behaviors and FASD

Authors (year)	Original authors' conclusions
Cannon and colleagues[9]	"Mothers of children with FAS have severe substance abuse behaviors including daily drinking, binge drinking"
Ceccanti and colleagues [40]	"Mothers of children with a FASD reported more drinking three months prior to pregnancy, more current drinking, and endorsed questionnaire items indicating that solitary drinking was more common"
Coyne and colleagues[41]	"Mothers of children with FAS reported heavy alcohol intake during pregnancy"
Davies and colleagues [42]	"Twenty five mothers with a FASD diagnosed child (69%) reported drinking alcohol, on average, every week during their pregnancy"
May and colleagues[43]	"Most drinking is binge drinking. Even though the current drinking quantities reported by both subjects and controls were not high in absolute standards, the most important interpretation of the data is the large differential between subjects and controls. There is no doubt, however, that these mothers drank sufficiently to produce verifiable cases of fetal alcohol syndrome as severe as we have seen anywhere in the United States"
May and colleagues [44]	"Alcohol consumption was much greater for case mothers than for control mothers in all comparisons. Control mothers were more likely to have been abstainers or Light drinkers compared with case mothers, who showed significantly heavier drinking patterns and reported drinking at the same level (53%-55%) or higher during pregnancy (32%-34%) compared with current drinking levels"
May and colleagues [45]	"Measures of drinking during the index pregnancies are significantly associated with low intelligence and frequent behavioral problems in the children. Reported drinking during pregnancy (.59), drinks per day (.48), three drinks or more per occasion (.51), and five drinks or more per occasion (.45), correlate highly with total dysmorphology in the children"
May and colleagues[46]	"In most every variable of maternal alcohol use and abuse, a spectrum emerged based on the final diagnosis of the child with FAS, PFAS, and control. Alcohol use was greatest in quantity, frequency, and duration among the mothers of FAS children, and generally next most severe among mothers of PFAS children, while lowest among controls"
May and colleagues [47]	"Mothers of children with FASD report heavy current drinking and drinking during the 2nd and 3rd trimesters of the index pregnancy"
May and colleagues [48]	"Binge drinking of at least two days a week during all trimesters in this population may produce FAS or PFAS, while mothers of children with ARND and exposed children without an FASD are most likely to reduce their average and peak alcohol consumption in the later trimesters"

May and colleagues[49]	"Mean number of drinks per week and drinking 3 and 5 or more drinks per occasion during pregnancy both illustrate the significant difference between mothers of FASD children and those of normal children"
May and colleagues[50]	"Mothers of children who had a FASD reported more drinking 3 months before pregnancy, and heavy drinking by the father of children who had FASD"
May and colleagues[28]	"With patterns of heavy episodic (binge) drinking being the most harmful to the fetus"
May and colleagues[51]	"Outcomes, both physical and cognitive/behavioral, are especially poor among children who were exposed to the highest quantity and frequency of drinking, especially drinks per drinking day and three or more drinks per occasion in both the case control comparisons and the correlation analysis"
Miller and colleagues[52]	"Mothers of FAS cases were more likely to drink alcohol during pregnancy"
O'Leary and colleagues[53]	"Heavy PAE in the first trimester was associated with a more than fourfold increased risk of ARBDs. This association was specific to PAE in the first trimester. The finding of twofold increased odds of ARBDs after moderate levels of PAE during late pregnancy is likely because many women also had heavy first trimester exposure and reduced their alcohol intake as pregnancy progressed"
Petković and Barišić[54]	"Confirmed pregnancy alcohol consumption in the FAS/PFAS group was higher (18.2%) to observed frequency in the whole sample of questioned mothers (11.5%) and significantly higher when compared to non-FAS/PFAS mothers (10.4%)"
Suttie and colleagues [55]	"No differences were found for prenatal alcohol exposure between the HE subgroup with FAS/PFAS affinity (nonsyndromal heavy exposed with FAS/PFAS-like face signature [HE1]) versus theHE subgroup with control affinity (nonsyndromal heavy exposed with more control-like face signature [HE2]) (P < .10)"
Urban and colleagues[56]	"Maternal drinking during pregnancy was much more frequently reported in mothers of children with FAS/PFAS than in controls"
Viljoen and colleagues[57]	"Mothers of children with FAS drank significantly heavier than controls, especially for continues drinking heavily (and/or increasing) throughout pregnancy. Control mothers drank less and drinking levels declined during pregnancy. Episodic drinking on weekends was modal for both groups with bingeing 5+ drinks was normative during 2 constructive days for FAS mothers "
Viljoen and colleagues[58]	"Mothers of children with FAS drink more than controls, drink rapidly and drink heavily in an episodic fashion. Moreover, they do not quit or cut down during pregnancy"

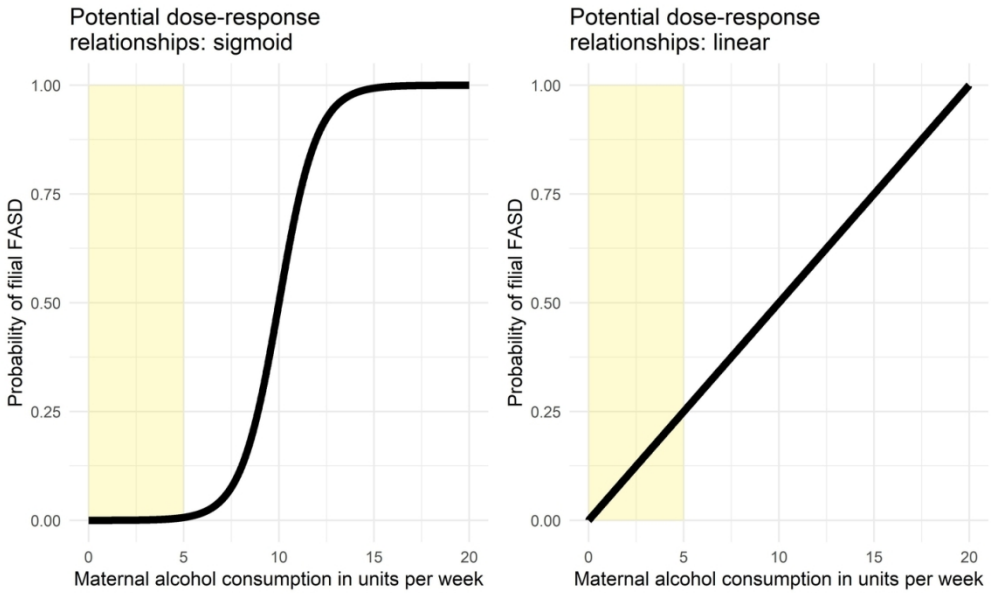

Figure 1. Two examples of possible dose-response relationships between maternal alcohol consumption and probability of filial FASD.

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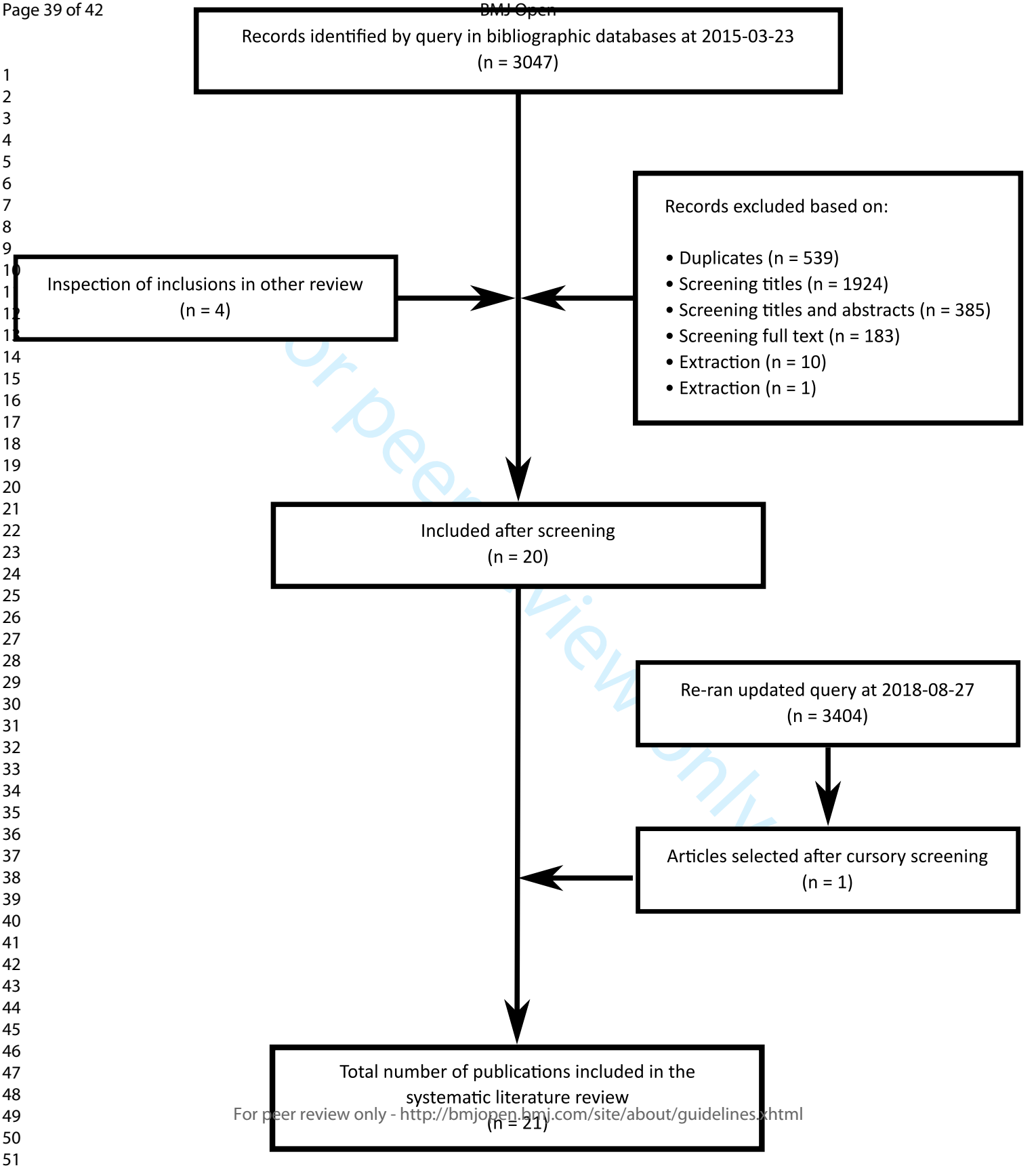

The PRISMA for Abstracts Checklist

TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	1
BACKGROUND		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	4
METHODS		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	4
4. Information sources:	Key databases searched and search dates.	4
5. Risk of bias:	Methods of assessing risk of bias.	NA
RESULTS		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	4
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	4
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	NA
DISCUSSION		
9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	5
10. Interpretation:	General interpretation of the results and important implications	5
OTHER		
11. Funding:	Primary source of funding for the review.	NA
12. Registration:	Registration number and registry name.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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