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Steps in undertaking meta-analysis and addressing heterogeneity in meta-analysis

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Abstract

Evidence-based research is used to generate, summarise, and understand the best available practices to inform decision-making. Systematic reviews (SR) and meta-analysis (MA) have become a valuable tool for these goals in public health, medicine and pharmaceutical research. MA is a statistical procedure for combining the results of multiple studies investigating a common intervention or issue to produce a pooled effect size and evaluate interventions' efficacy across studies. This article outlines the usefulness of systematic reviews and meta-analysis in medicine and public health. Steps in undertaking the systematic reviews and meta-analysis include forming a team, identifying and refining the research question, determining the inclusion and exclusion criteria, registering the SR and MA protocol, searching for the studies, selection of the studies, data extraction, data analysis and presenting the results. The review also outlines the issues that can impact meaningful meta-analysis. The heterogeneity in the included studies, conditions studied, interventions, and end-point measures is one of the major issues encountered in meta-analysis. Quantification of the heterogeneity can be done by I2 statistics and prediction intervals. Sub-group analysis, outlier detection followed by sensitivity analysis, and meta-regression can be applied to explore and reduce heterogeneity. Random effects model, Knapp-Hartung, likelihood estimates, and Bayesian models can be applied in a highly heterogenous meta-analysis.

Keywords: *Meta-analysis, Systematic review, Heterogeneity, Evidence based medicine, Evidence based public health, Evidence synthesis, Sub-group analysis, Meta-regression, Prediction interval, Funnel plot, Egger's test, Random effect model, Fixed effect model*

Introduction

Medical sciences and public health have come a long way in terms of technological advancements and applications. In the earlier centuries, therapy and interventions were administered based on expert opinion, personal observations, and anecdotal evidence. During the latter part of the 20th century, the concept of evidence-based medicine (EBM), initiated by David Sackett in 1981, emerged [1]. EBM has three essential components- best research evidence, the clinical acumen of the practitioner and the patient values [2,3]. Obtaining the best research evidence, in terms of quantity and quality, has been at the forefront of evidence-based and evidence-informed medicine. Expanding the domain of evidence beyond the clinics, Evidence-Based Public Health (EBPH) applied the principles of EBM in public health decisions [4].

EBM and EBPH apply scientific and objective methods to identify, collate, analyse and interpret the currently available evidence to improve the decisions taken in health

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Evidence in Context

Prior Evidence: Meta-analysis helps to estimate the pooled effect size from multiple studies answering the same research question, by applying appropriate statistical methods. Heterogeneity is one of the important issues to be explored and addressed in meta-analysis

Evidence added by this study: Sub-group analysis, outlier detection, sensitivity analysis, and meta-regression can be applied to explore heterogeneity. Prediction intervals must be reported in meta-analysis with high heterogeneity to enable the readers for understanding the heterogeneity extent in terms of outcome measure. Random effects model, Knapp-Hartung, likelihood estimates, and Bayesian models can be applied to improve the robustness of reporting in highly heterogenous meta-analysis.

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[5]. Research studies, especially the Randomized Controlled Trials (RCTs) for positive interventions and Cohort studies, where interventional studies are not possible, are the major study designs employed to collect information on the effect of interventions and exposures on health-related outcomes [6]. Yet, the effect estimates from multiple studies may vary in intensity, direction of the effect, sample sizes and methodological intricacies. Systematic reviews (SR) and meta-analysis (MA) were introduced to address these concerns, to review, collate, analyse, estimate the pooled effects, and interpret and critically analyse all the existing studies under specific topic of interest [7,8]. In the level of evidence, meta-analysis of well-conducted RCTs has been placed at Level IA, the highest level of evidence [5], for answering any clinical or public health questions. Meta-analysis can be done on observational analytical studies (case-control, cohort studies) as well as on cross-sectional prevalence studies. This review enumerates the applications of SR and MA, steps to be followed while undertaking SR and MA, and common methodological issues encountered during the meta-analysis, which will be helpful for beginners in the evidence synthesis. Also, the review elaborately discusses the concept of heterogeneity, its impact on the meta-analysis estimates, techniques to measure heterogeneity and the strategies to address heterogeneity.

Meta-analysis and its applications

Meta-analysis has been defined as "The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings" [9]. Meta-analysis is the statistical extension of the systematic review [10]. By applying appropriate statistical methods, MA helps to estimate the pooled effect size from multiple studies answering the same research question. It improves the statistical power with increased precision of the effect estimates [11,12]. A single estimate will always be better in terms of decision-making in the clinical and public health domains. By pooling the data from multiple studies on the same research question, meta-analysis informs the researchers, clinicians and policymakers whether there was any significant effect of the exposure/interventions on the outcomes, and if so, what is the direction and strength of the effect [13]. Such pooling of the data can also be done while estimating the burden of the diseases in terms of prevalence, indicating the application of meta-analysis in descriptive studies. Thus, meta-analysis can assess the distribution and determinants of health states and diseases, which are the essential components of epidemiology. The outcomes of a meta-analysis may enhance the accuracy of impact estimates, address issues that were not addressed by the individual studies, resolve disputes resulting from seemingly incongruent studies, and provide new hypotheses [14]. Overall, meta-analysis, preceded by systematic review, is the most valuable tool under EBM and EBPH

Steps in meta-analysis

All SR and MAs should follow the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) or "Meta-analyses Of Observational Studies in Epidemiology" (MOOSE) guidelines for maintaining the objectivity and quality in the process [15,16]. The steps involved in conducting an SR and MA, including the tools to assist the process, are discussed in the subsequent section. **[Figure 1]**

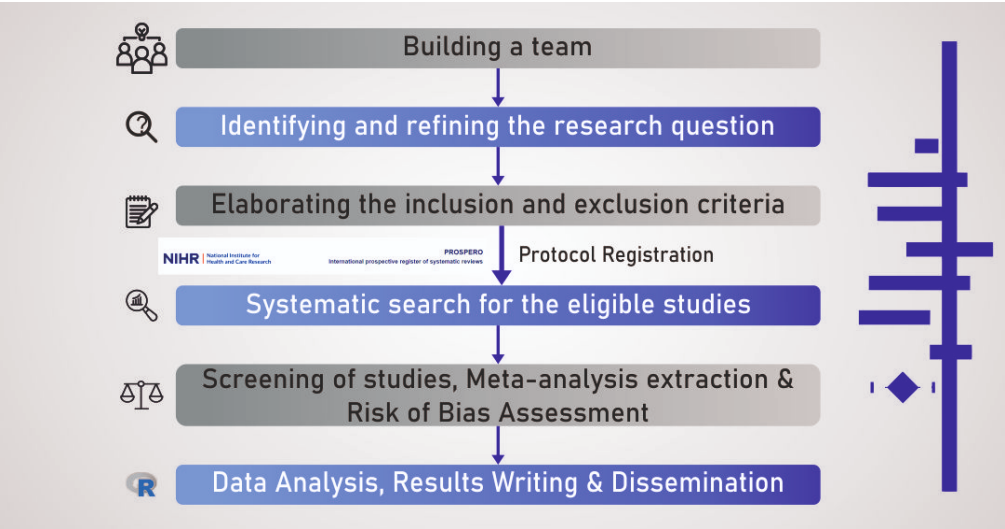

Figure 1: Major steps in conducting the meta-analysis

Building a team:

Systematic review and meta-analysis require forming a group with a minimum of three researchers (reviewers), to enable independent data extraction and adjudication of the contradictions. The group should consist of expert(s) of the domain in which the research is being undertaken. For instance, SR and MA on the effect of a clinical intervention on neonatal mortality should include a neonatologist or a paediatrician. At-least one of the members should be well-versed with the stepwise process of the SR and MA and the statistical methods employed under various aspects of meta-analysis. These domain experts and methodological experts should have a consultative working through all SR and MA stages to achieve methodologically robust and policy-influencing outcomes.

Identifying and refining the research question

Research question is one of the most critical steps in the SR and MA since it drives the whole exercise. Answering the research question is the overall objective of the SR and MA. The research question may be initiated in a broader sense. A preliminary literature search and review should be undertaken to refine and ensure the research question is ethical, specific, feasible and novel [17]. The answer to this research question should be interesting for clinicians and policymakers, as it will have practical implications. While the domain expert can bring in the broader idea for the research question, the methodological expert can enable refining the research question by providing relevant literature and review techniques.

Determining the inclusion and exclusion criteria

Once the research question is finalised, specific inclusion and exclusion criteria for the studies to be included in the review shall be listed out [18]. These inclusion and exclusion criteria shall be made according to the components in the research questions. For interventional studies, the acronym PICO is used to denote the components [19,20]. It included **P**opulation in which the primary studies are conducted and on whom the investigators want to apply their findings, **I**ntervention which needs to be evaluated, **C**omparator group which needs to be compared with the intervention (placebo-control or active control) and the **O**utcome, which is the effect of the intervention that needs to be assessed. For instance, El Dib et al. in their SR and MA on the effect of probiotics on depression and anxiety, defined their research questions in terms of PICO [21]. The criteria can be modified as PECO (Population, Exposure, Control, Outcomes) for the observational, analytical studies and only PO (Population and outcomes) for the descriptive, prevalence studies [22]. Other important aspects to be prespecified under the inclusion/exclusion criteria are the study designs, language of the articles, geography and the time period of the eligible studies [23,24].

Registration of the SR and MA protocol

The SR and MA protocol should contain the plan the reviewers intend to follow for the exercise. Protocol should consist of rationality for the SR and MA, research question, inclusion and exclusion criteria, databases included, search strategy, screening and data extraction plan, risk of bias assessments, data analysis and dissemination plans. The protocol needs to be registered prospectively with one of the registering organisations. Multiple registries such as International Prospective Register of Systematic Reviews (PROSPERO), Cochrane Collaboration, INPLASY, Registry of Systematic Reviews/Meta-Analyses in Research Registry, Open Science Framework Registries and protocols.io are available [25,26]. PROSPERO is the most widely used open-access database for registering the SR and MA protocols [27,28]. While the SR and MA on the interventional studies must be prospectively registered, it is also strongly recommended to register the SR and MA protocols on the observational studies. Guidelines on the reporting of SR and MA protocols are also available [26].

Systematic Search for the studies

The relevant and potentially eligible studies to answer the research question can be identified from the multiple databases. With 35 million citations, PubMed is the largest open-access search engine for studies undertaken in medical sciences [29]. It enables a search of studies indexed in MEDLINE and those deposited with PubMed Central. Other important databases include Scopus, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PsycInfo, CINAHL, OVID, Web of Science, ProQuest and EBSCOHost [30–37]. At least three primary databases appropriate for the research question need to be searched to identify the relevant studies [38]. Based on the pre-determined PICO criteria, a suitable search strategy needs to be formulated for each database, and the search must be undertaken. Google Scholar can be used as a secondary search source. Pre-print servers such as medRxiv, arXiv, bioRxiv, BioRN, ChemRxiv, and SSRN can also be searched for unpublished literature.[39–43] Hand search of the references in eligible primary research papers, reviews and relevant speciality journals can also be done [44,45]. MEDLINE, Embase and Web of Science as the primary databases with Google Scholar as the secondary search source has been reported to be the best combination of databases for retrieving the relevant studies [46]. Duplicates from multiple databases shall be deleted to have a unique list of studies [47,48]. Various tools are available to enable the systematic search process and removal of duplication. Ovid platform facilitates systematic search and downloading results from multiple databases such as Medline, Embase, Cochrane etc., and also assists in deduplication of the results obtained [49,50]. Other tools useful in the deduplication of the studies from multiple databases are Mendeley, EndNote, Rayyan and COVIDENCE. Among these, Mendeley and Rayyan are free-of-cost applications.

Selection of the studies and meta-analysis extraction

The screening process in SR and MA is done in two stages: Title-abstract screening and full-text review. Each unique study obtained after deduplication must be screened independently by at least two reviewers based on the title and abstract by applying the pre-determined eligibility criteria and identifying potential studies for full-text review. The full text of these eligible studies obtained from the title-abstract should be reviewed by two reviewers independently, applying the precise PICO eligibility criteria. Finally, the studies eligible for the data extraction need to be short-listed [51,52]. Studies for which full text could not retrieved should be recorded and excluded from the review. Online tools such as Covidence, Rayyan and {NESTED} Knowledge are available to enable the screening of eligible studies [53,54]. A data extraction sheet should be made according to the variables required for the research question. It should also include the basic demographic details reported by the studies. The data from the final eligible studies shall be extracted according to the data extraction sheet. There should be a plan to remove the contradictions and differences of opinion between the reviewers during the screening and data extraction process. Such strategies include adjudication by the third reviewer and consensus meetings between the independent extractors. With the advent of Artificial Intelligence (AI), platforms such as {NESTED} Knowledge facilitate the screening and data extraction process [55].

Other Machine Learning (ML) tools have also been explored in search, screening and extraction steps of the SR and MAs [56–62].

Risk of bias assessment

The quality of the eligible and included studies in the SR and MA shall be assessed using design-specific quality assessment tools. Cochrane risk-of-bias tool for randomised trials (RoB 2) for RCTs, New Castle Ottawa quality assessment scales for cohort and case-control studies, JBI quality assessment tool and NHLBI tools for prevalence and case series studies are a few of the most applied and recommended quality assessment tools. Based on the evaluation, the studies are declared as good or poor quality to be included/excluded in the sensitivity analysis.

Data analysis and software for analysis

Outcomes assessed and the type of outcome (rate, ratio, proportion, time to event, mean difference etc.,) should be mentioned [63,64]. Primary analysis plan, statistical methods used to determine the heterogeneity and the pooled estimate, any sensitivity analysis [65,66], and sub-group analysis planned, methods and tools to assess the risk of bias [67,68], and publication bias in the included studies shall be explicitly mentioned before initiating the SR and MA [69–72], and the same shall be executed at the data analysis stage. Software available for meta-analysis include R studio, STATA, RevMan 5 and Comprehensive Meta-Analysis (CMA). While RevMan 5 and CMA are menu-based applications, R Studio is a command-based application, and STATA is a combination of menu-based and command-based application. Depending on the heterogeneity levels in the study, fixed-effect model (FEM) or random-effects model (REM) can be applied [73]. As a rule of thumb, if the heterogeneity is substantially high (I^2 >50%), then REM can be applied. Publication bias in the MA can be explored by means of the funnel plot and Egger's test [69]. Recently, novel and better measures of publication bias, such as the Doi plot and LFK index, have been introduced [74,75]. The certainty assessment of the effect estimate from the meta-analysis needs to be assessed using standard tools such as "Grading of Recommendations, Assessment, Development, and Evaluations" (GRADE[76]) [77–79].

Presenting the results

The eligible studies and their characteristics (author, place of study, year of study, age, sex, outcomes of interest, total sample and key findings) shall be tabulated. A PRISMA flow chart denoting the reasons for the exclusion of studies at each stage of the screening needs to be presented. The pooled estimate of the primary outcome with its 95% confidence interval and heterogeneity statistics shall be reported along with a forest plot [80,81]. Risk of bias assessment of each domain must be presented in a table or figuratively, along with the overall quality of the study. All sensitivity and sub-group analyses must be reported. Publication bias depiction as funnel plots or Doi plots shall be included in the results [82,83]. The overall certainty of the pooled estimates from the SR and MA must be presented as very low, low, moderate or high [76].

Implications and recommendations

The pooled estimate, quality of the studies included, and the generalisability of the findings must be critically discussed with the existing evidence and practices. The strengths and limitations of the SR and MA must be articulated. Recommendations based on the pooled estimates and the certainty of the estimate obtained shall be made to the clinicians, public health professionals, policymakers and researchers.

Common issues in meta-analysis

Although a single estimate will always be better from a decision-making point of view, there are certain issues, mostly methodological, which need to be acknowledged and addressed while analysing and interpreting the meta-analysis. Foremost is deciding when to go beyond the systematic review (qualitative synthesis of the results from many studies) and undertake the meta-analysis (quantitative synthesis) of the results to have a pooled estimate. Meta-analysis is recommended when the outcomes are presented quantitatively rather than only qualitative findings, outcomes which can be construed as standardised effect sizes from similar study designs reporting a simple and similar construct of relationship between two variables [84]. Other major issues include errors of exclusion of studies which may not have been included in the databases and sources which the investigators searched for their SR and MA, quality of the included studies in terms of risk of bias, publication bias, language bias, small study effects, heterogeneity between the included studies and overall generalizability of the results [85,86]. While each of these issues is important and can be addressed using different statistical and methodological strategies, in this review, we will focus on the concept of heterogeneity and the methods to address it.

Heterogeneity: integral part or an inherent problem?

In a meta-analysis conducted by Gandhi et al. to estimate the prevalence of oral lesions in mpox (formerly known as monkeypox), a high heterogeneity level (I^2= 98.24%) was observed [87]. What is this heterogeneity, and what is its significance in the meta-analysis? Heterogeneity refers to any type of variation that exists between the studies included in the SR and MA [64]. It is inevitable in these types of analyses since SR and MA bring together multiple studies conducted in different settings. Visually, it can be identified by looking at the point estimates varying widely between the studies and their confidence interval not overlapping, indicating a variance between the studies [88]. Broadly, heterogeneity can be classified into clinical, methodological and statistical heterogeneity. The biological characteristics of the participants included in the studies (eg. age, sex), type of intervention and the outcomes assessed may contribute towards clinical heterogeneity.

Methodological heterogeneity comprises variations in the tools used to assess the outcomes, risk of bias and the research design used in the studies. Statistical heterogeneity refers to the variation in the magnitude of the effects measured between the studies [89]. Statistical heterogeneity is caused due to the clinical and/or methodological heterogeneity present in the study [64].

Effect of heterogeneity on the study estimates and interpretation

The meta-analysis aims to club the samples and effects obtained from multiple studies, critically analyse, and estimate a single effect with improved power. The single pooled estimate obtained from the meta-analysis is only as good as its generalisability to all populations, interventions and tools employed in the included studies. Heterogeneity poses a challenge in interpreting the pooled estimate from the meta-analysis [90]. Meta-analysis undertaken with studies that harbours high heterogeneity may be less interpretable in a broader sense [91].

Addressing heterogeneity

However, the mere presence of heterogeneity will not make the meta-analysis unnecessary or useless. The other school of thought is that heterogeneity is inevitable in meta-analysis, since the objective of meta-analysis itself is to pool the effects of multiple studies from different settings. This is more so when the meta-analysis addresses a broader question eg., the effect of a class of drug on a particular disease, rather than focussing on a single drug within the class [64]. In the past, almost one-third of the SR and MAs did not consider or address the problem of high heterogeneity between the included studies [92]. It is imperative that the investigators recognise the potential factors responsible for the heterogeneity at various levels, followed by adopting strategies to address the heterogeneity [92,93].

Clinical and methodological heterogeneity can be identified and addressed by restriction at the time of planning and identifying the eligible studies. This can be achieved by clearly defined research questions, and inclusion and exclusion criteria. For instance, "What is the effect of physician-administered cognitive behavioural therapy (CBT) on depression in adolescents without any comorbidities?". In this, the tool used for measuring depression should be the same and objective (Eg PHQ9), across the studies. However, restriction may be an overtly exclusionary concept. Another method to address this type of heterogeneity is sub-group analysis, which is planned a priori in the protocol. Sub-group analysis involves dividing and clubbing the studies into groups according to the potential and known factors causing heterogeneity [73,94,95]. For instance, grouping the study according to geography, which may be a proxy for the biological factor (genetics) and environmental factors, grouping the studies according to the age of the population (adults/adolescents/children), grouping the studies according to the type of intervention used (CBT by psychologist/CBT by primary care physician), grouping the studies according to the tool used for measuring the outcomes (PHQ 9/DASS) are few sub-group analyses which can be done to explain the heterogeneity.

Meta-regression is another method to identify and explain the heterogeneity. But, sub-group analysis and meta-regression can only be done for the known/potential factors of heterogeneity. Also, in the meta-analysis of RCTs, these methods suffer from the limitation that the explanatory factors based on which sub-group analysis and meta-regression are conducted were not randomised, unlike the actual intervention under study [88].

Statistical heterogeneity is the most mentioned heterogeneity while discussing the meta-analysis. It denotes the variations in the outcomes between the studies more than which can occur by chance. Various tests are available to determine the levels of heterogeneity between the studies. Cochran's Q test employs the chi-square distribution and applies a null hypothesis that outcomes across the included studies are same with only chance being the reason for any variations [96]. A p value of <0.05 is taken as the level of significance for rejecting the null hypothesis. However, it does not apply to meta-analysis involving few studies [97]. Tests to quantitatively measure the heterogeneity among the studies are also available. These have come from the assumption that heterogeneity always exists between the studies of a meta-analysis qualitatively. Hence, there is a necessity to quantify the heterogeneity [64], and determine the levels as low and high heterogeneity. Based on the following cut-offs of 25%, 50% and 75% of I^2 values, a low, moderate, or high heterogeneity is assigned to the studies included in the study. When the I^2 value is >50%, considerable heterogeneity can be attributed to the analysis [96]. In those meta-analyses with high heterogeneity, techniques such as sub-group analysis and meta-regression can be applied to identify and address the heterogeneity.

In a simulation of a model analysis created by the authors, the pooled risk ratio of an outcome following an intervention from multiple studies was estimated. The heterogeneity level was high (I^2=87%) **[Figure 2]**.

In order to identify the variable causing the heterogeneity, we undertook a sub-group analysis by clubbing the studies according to the age group (≥18 years and <18 years) included in the study. Sub-grouping by age led to the elimination of heterogeneity (I^2=0%). **[Figure 3]**

Dropping the few studies with the effect estimate that appears to be outliers can also reduce the heterogeneity [64]. In order to identify the outliers, various tests such as Baujat plot, leave-one-out analysis, Graphical display of study heterogeneity (GOSH) plots, radial plot and diagnostic tests can be applied [98–102]. The outliers identified can be excluded, and the pooled estimate with the remaining studies can be determined, which might reduce the heterogeneity. In the following model, heterogeneity between the studies was found to be significantly high (I^2=91%) [Figure 4].

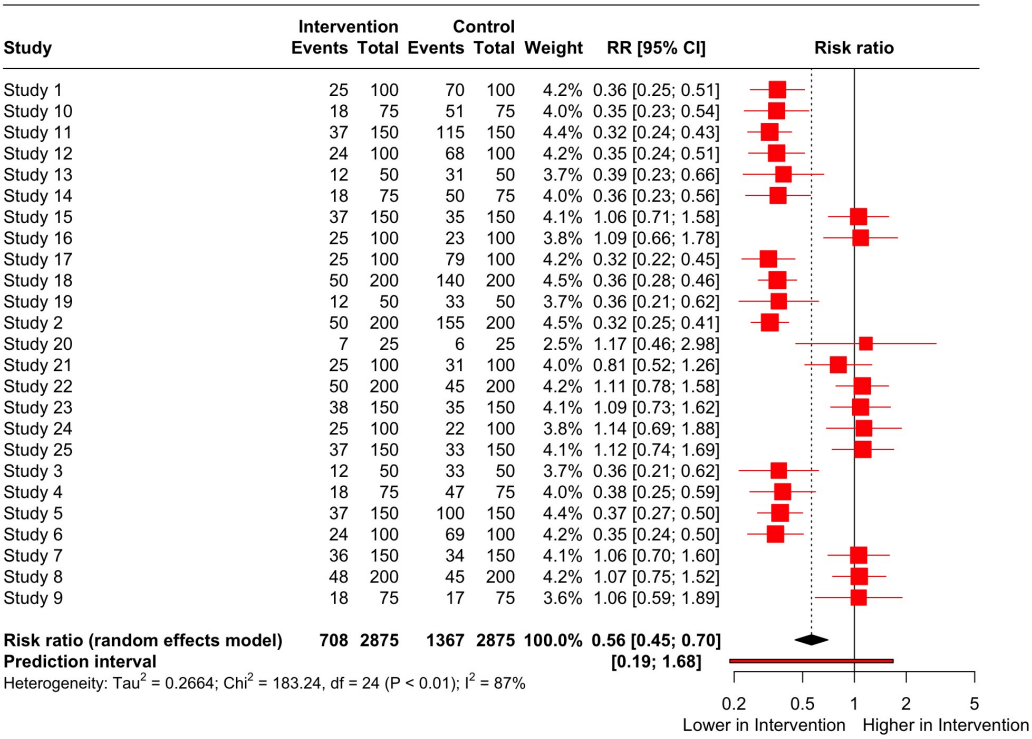

Figure 2: Pooled risk ratio of an outcome among the study population

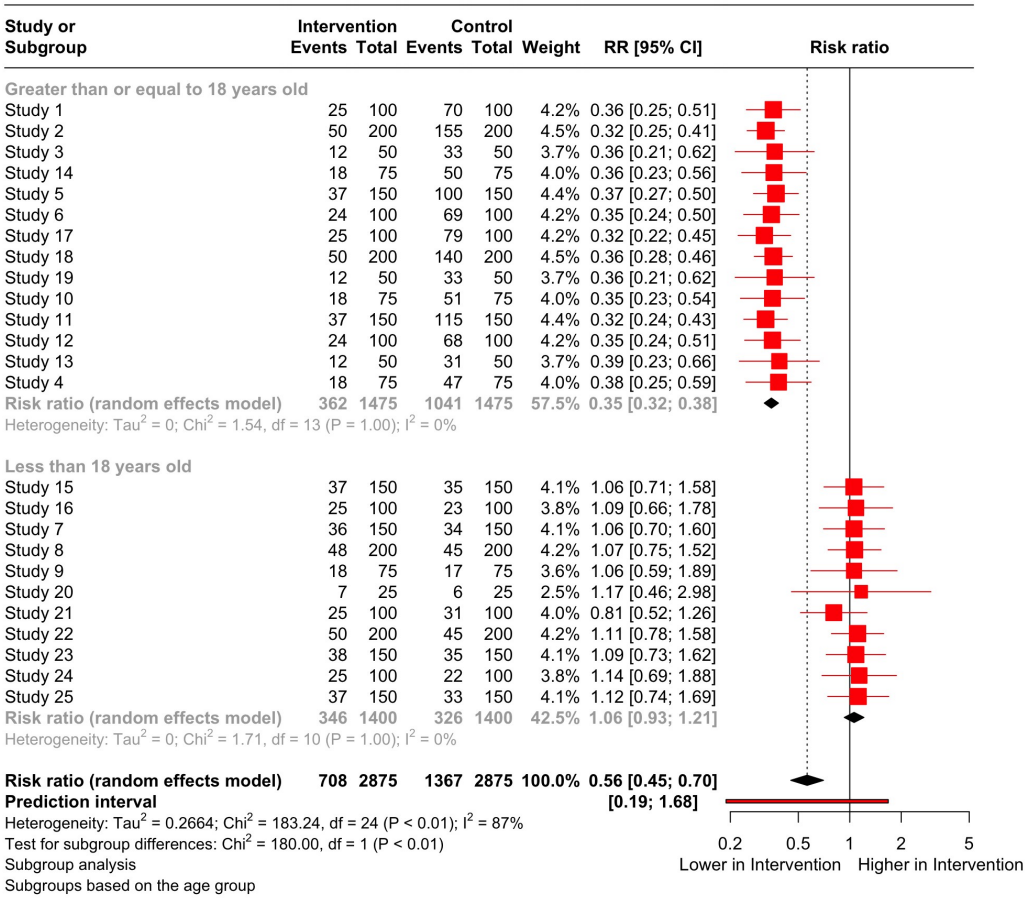

Figure 3: Pooled estimates and heterogeneity of the studies grouped according to the age

Study	Intervention Events	Intervention Total	Control Events	Control Total	Weight	RR [95% CI]
Study A	25	100	70	100	7.3%	0.36 [0.25; 0.51]
Study B	50	200	155	200	7.4%	0.32 [0.25; 0.41]
Study C	20	500	480	500	7.1%	0.04 [0.03; 0.06]
Study D	18	75	50	75	7.1%	0.36 [0.23; 0.56]
Study E	37	150	100	150	7.4%	0.37 [0.27; 0.50]
Study F	24	100	69	100	7.2%	0.35 [0.24; 0.50]
Study G	25	100	79	100	7.3%	0.32 [0.22; 0.45]
Study H	50	200	140	200	7.4%	0.36 [0.28; 0.46]
Study I	12	50	33	50	6.9%	0.36 [0.21; 0.62]
Study J	36	150	6	150	6.1%	6.00 [2.61; 13.82]
Study K	37	150	115	150	7.4%	0.32 [0.24; 0.43]
Study L	24	100	68	100	7.2%	0.35 [0.24; 0.51]
Study M	12	50	31	50	6.9%	0.39 [0.23; 0.66]
Study N	18	75	47	75	7.1%	0.38 [0.25; 0.59]
Risk ratio (random effects model)	**388**	**2000**	**1443**	**2000**	**100.0%**	**0.36 [0.22; 0.58]**
Prediction interval						**[0.05; 2.59]**

Heterogeneity: $Tau^2 = 0.7632$; $Chi^2 = 137.85$, df = 13 (P < 0.01); $I^2 = 91\%$

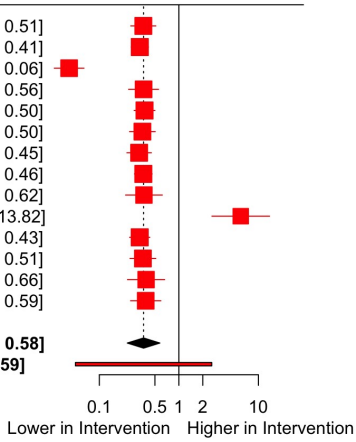

Figure 4: Pooled risk ratio of the outcomes from 14 studies

Based on the above methods, studies C and J were identified as outliers **[Figures 5 and 6]**.

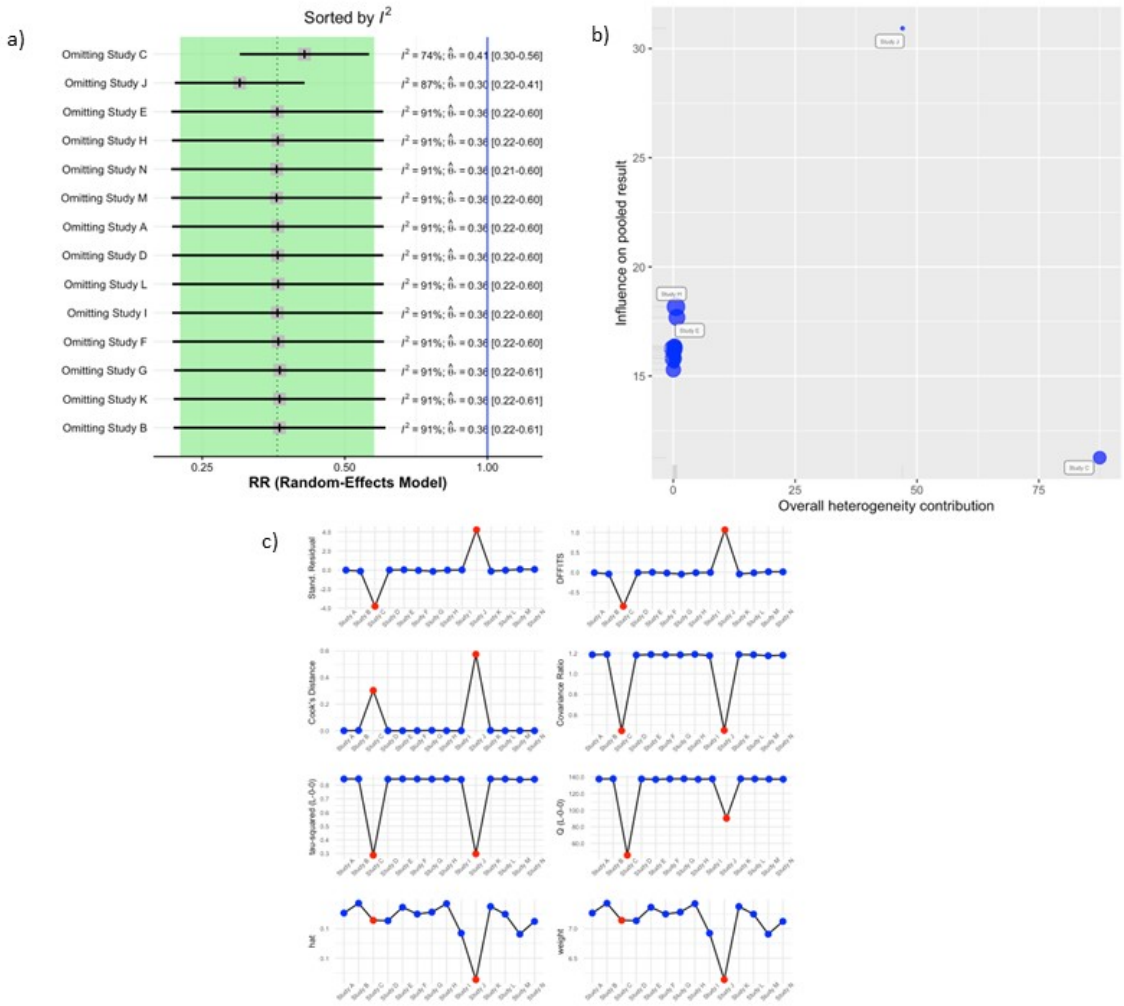

Figure 5: Outlier analysis: a) Leave one out analysis; b) Baujat plot; c) Radial plot

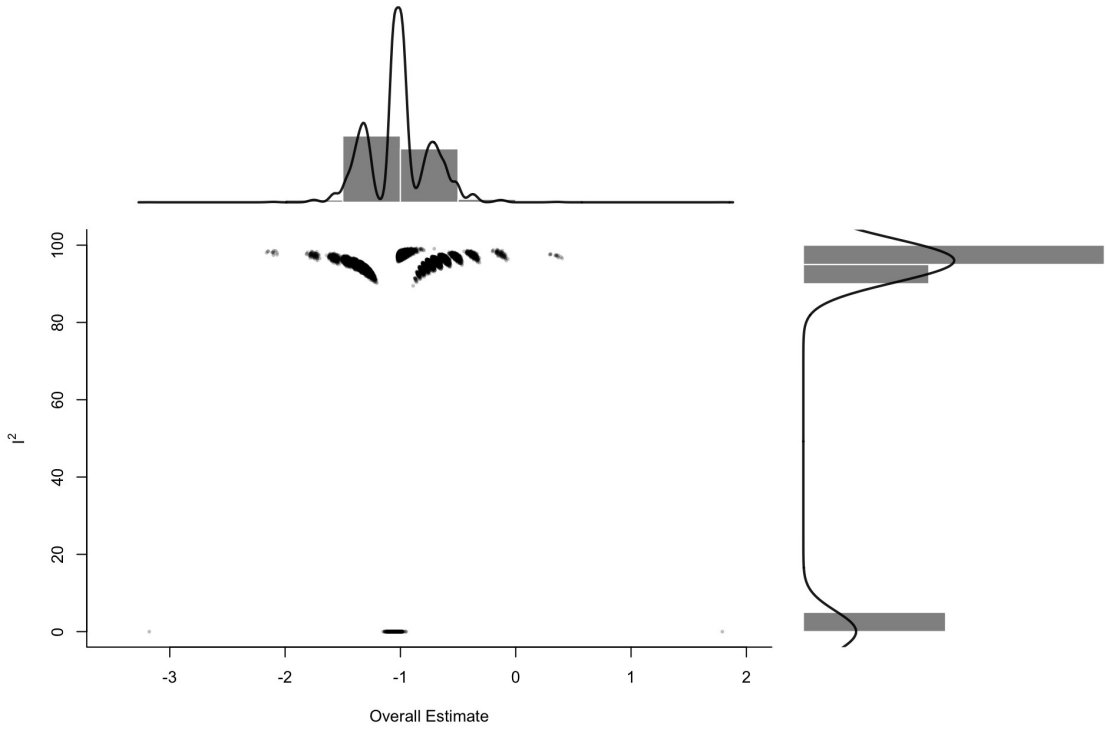

Figure 6: Graphical display of study heterogeneity (GOSH) plots

Sensitivity analysis conducted after removing the outliers eliminated the heterogeneity (I^2=0%) [Figure 7].

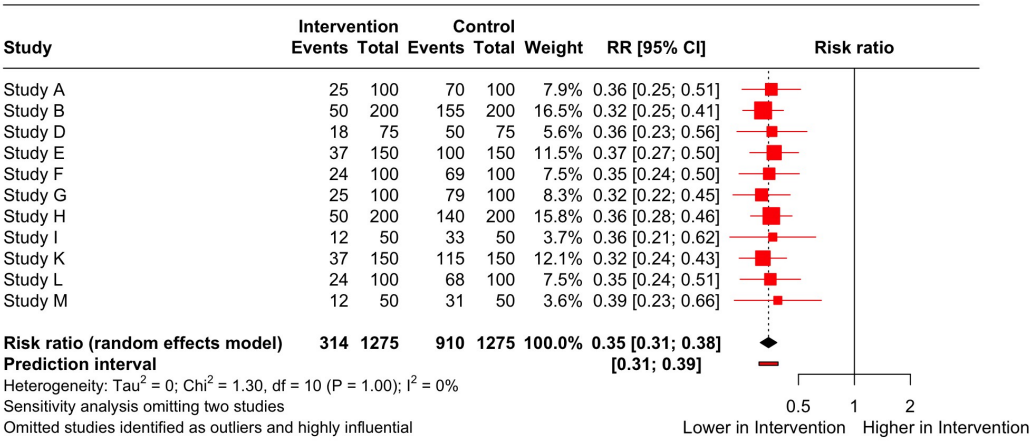

Figure 7: Sensitivity analysis after removing the outliers (studies C & J)

Meta-regression is another way to explain the heterogeneity depicted by the bubble plots [94,103,104]. A model analysis depicts the pooled prevalence of a condition with high heterogeneity(I^2=84%) **[Figure 8].**

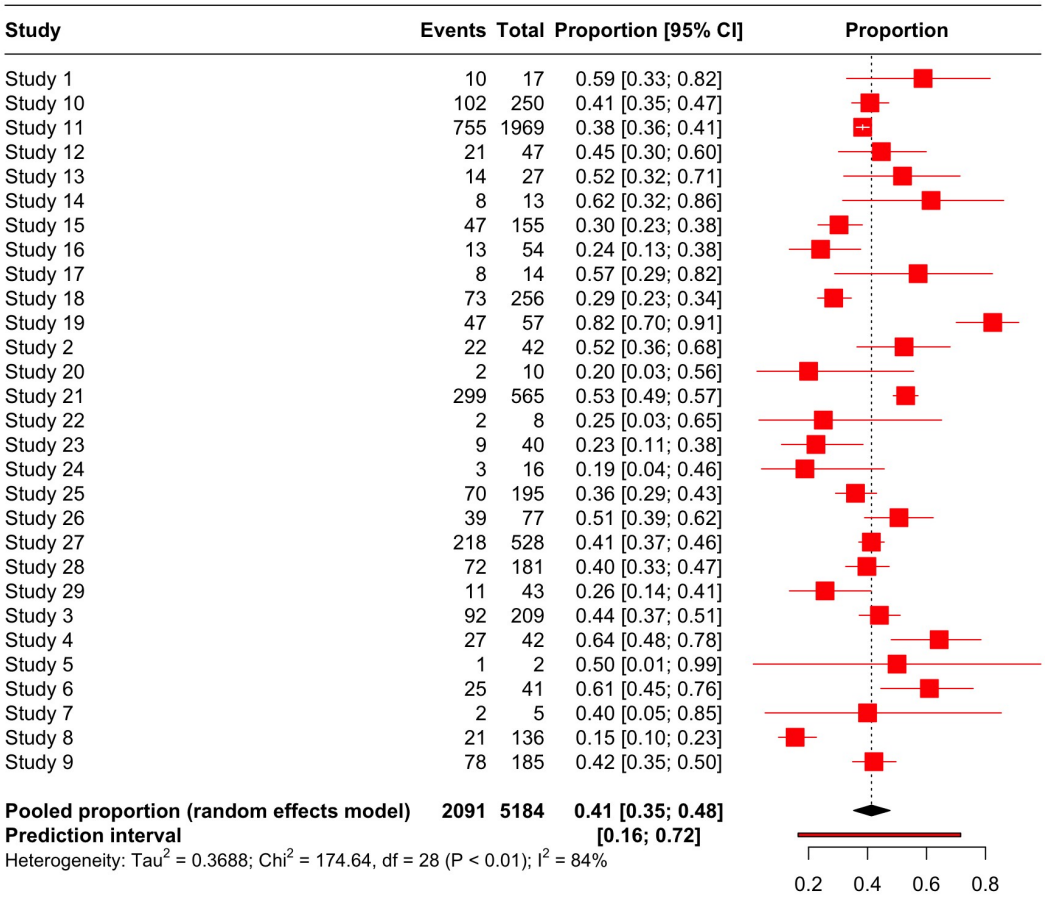

Figure 8: Pooled prevalence of the outcomes from 29 studies

Meta-regression was undertaken where the prevalence was plotted against the mean age of the study participants and the proportion of males in the included studies [Figures S1 and S2]. While the mean age showed no significant relationship (beta=-0.03, p=0.41), the proportion of males have a direct relationship with the prevalence of the condition (beta=0.04, p=0.01) i.e., studies with a higher proportion of males had a higher prevalence of the condition. Thus, the proportion of male patients in the studies is a potential factor causing the heterogeneity in the pooled estimates from the studies.

Alternatively, when these techniques (sub-group analysis, meta-regression and sensitivity) cannot identify or eliminate the heterogeneity considerably, or the number of studies is not large enough to allow for sub-group analysis, then the random effects model can be applied in the meta-analysis to estimate the pooled outcome [96,105]. Yet, the random effects model is not an elixir for the heterogeneity problem. Caution must be taken while generalising the results to the broader population [91], with robust measures and statistics provided by the investigators to further address the high heterogeneity in their study. The most commonly used method to undertake the random-effects model is the DerSimonian-Laird method (DL method) [105]. However, it is not an optimal method, especially when there is a low number of studies and high heterogeneity. Alternative and better approaches such as the Knapp-Hartung, Likelihood estimates, and Bayesian models can be applied to estimate the pooled outcomes by the random effects model [106,107]. Inthout et al., in their simulation, found that Hartung-Knapp-Sidik-Jonkman method of the random effects model had more adequate error rates than the DL method [108]. An increasingly large number of meta-analyses are applying the Bayesian models to improve the robustness of the random effects analysis [109].

Additionally, statistics describing the quantum of variation between the studies, tau^2 (τ^2), may be calculated, and the prediction interval (PI) can be provided along with the pooled outcome estimate and other heterogeneity statistics. PI can assist in better presenting the pooled effect estimates in the meta-analysis of studies that harbour high heterogeneity [110]. It helps the readers understand and interpret the extent of the heterogeneity in the same measure as the study's outcome (prevalence, risk ratio etc.,), unlike I^2 [110]. PI also estimates the range within which the outcomes of 95% of the studies (similar to the ones included in the index meta-analysis) conducted in future will occur [111]. Sahoo et al. in their SR and MA estimated the pooled prevalence of suicidal ideation among adolescents in India to be 11% but with a high heterogeneity (I^2=98%). This level of heterogeneity was expressed as PI in terms of the outcome measure (proportion of suicidal ideation), ranging from 2% to 45% [22]. This will enable the readers to understand the extent of variation existing in the studies and arrive at a meaningful interpretation of whether to take the pooled estimate as a reliable measure or with caveats [64,105].

Conclusion

Systematic review and meta-analysis can be efficient tools for researchers and policymakers in evidence-based practice when the steps enumerated are followed sequentially and systematically. Methodological and interpretative issues of the analysis and results exists in the meta-analysis of studies. Due consideration must be given by the reviewers towards the issue of heterogeneity of the included studies in their meta-analysis. If substantially high heterogeneity is present, all methodological and statistical efforts must be taken by the reviewers to identify, eliminate, acknowledge, and address it. Adequate discussion on the meaningful interpretation of the pooled estimates in the context of heterogeneity must be provided by the reviewers to facilitate the comprehension of the readers.

Supporting information
None

Ethical Considerations
None

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Author contribution statement

Aravind P Gandhi: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). **Muhammad Aaqib Shamim**: Conceptualization, Software (lead); writing – review and editing (equal). **Bijaya Kumar Padhi**: Methodology; writing – review and editing (equal).

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List of supplementary figures
Figure S1: Bubble plot in which the prevalence of a condition is plotted against age of the study participants in the studies

Figure S2: Bubble plot in which the prevalence of a condition is plotted against percentage of males in the included studies

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