**The reporting quality of individual participant data meta-analyses and the statistical approaches used for subgroup analysis: a scoping review**

**Abstract**

***Introduction***Individual patient data (IPD) meta-analyses are the gold standard of meta-analyses and offer advantages when performing subgroup analysis. However, the quality of the reporting items has not been investigated, since the publication of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) IPD. Additionally, it is not evident which statistical practices are being used when performing subgroup analysis. The aim of this study is to summarize the quality of the statistical practices used and their reporting items when performing subgroup analysis.

***Methods***We perform a systematic review to identify the eligible IPD meta-analyses. We summarize the statistical approaches being used for subgroup analysis along with the quality of their reported items based on PRISMA IPD guideline.

***Results***The adherence to the PRISMA IPD was overall good. The IPD meta-analyses that performed subgroup analysis reported slightly better than IPD meta-analyses that not performed subgroup analysis. However, both groups reported poorly on the risk of bias across studies and IPD integrity.   
When performing subgroup analysis, most studies used a one stage approach with a random effect model. Half of all IPD meta-analyses which investigated subgroup analysis, investigated effect modifiers which were continuous variables, but analyzed as categorical, and already categorical variables.

***Conclusion***The overall reporting quality of IPD meta-analyses is good. However, the quality of reporting for both the process of the IPD systematic reviews and the statistical methods used, still needs improvement. More awareness on the PRISMA IPD together with clear guidelines on what to report when performing subgroup analysis could improve reporting in both these areas.

**Introduction**

Meta-analyses are commonly used in the medical field. They aid towards evidence-based clinical decision making and may be used to create guidelines for modern medicine. The individual participant data (IPD) meta-analysis uses individual data from multiple studies for the synthesis (1). The aim of an IPD meta-analysis is to summarize the evidence on a specific clinical question, and is often used to determine if new treatment options are effective(2).

The main reasons to use the IPD meta-analysis relate to data manipulation and analysis. It allows the researcher to perform time-to-event and subgroup analysis, compare different scales of measurement, and this kind of meta-analysis is less affected by poor reporting quality(3). It allows the researchers to not only use published data, but also to directly contact the trialists and ask for unpublished data. Using the IPD researchers are not dependent on the statistical analysis of published articles, and therefore may reperform poorly performed analyses. Additionally, IPD of trails with poor reporting quality can be used without influencing the outcome of the IPD meta-analysis(3).

Another advantage of the IPD meta-analysis is the ability to perform subgroup analysis with more power and precision. The IPD meta-analysis approach is most practical when investigating whether an intervention is equally effective across well-defined groups of patients. The large number of participants IPD affords greater statistical power, which provides more accurate analyses for detecting treatment differences between patient groups, also known as effect modification (3). Due to the advantages of the IPD meta-analysis, in comparison with the conventional meta-analysis, it can be seen as the gold standard of systematic reviews (4, 5). A study of Simmonds et al., (2015) investigated the statistical approaches in IPD meta-analyses, over a period of ten year. They found a substantial shift in statistical practices used to perform the IPD meta-analysis. However, they did not investigate the practices used for subgroup analysis, and until now no other study has investigated these practices either.

Although the IPD meta-analysis is seen as the gold standard, researchers are only able to judge the credibility and validity of a meta-analysis publication when this publication is reported clearly with all the relevant information. Therefore, in 2009 the preferred reporting items for systematic reviews and meta-analyses (PRISMA) was published (6). This guideline was created to help authors to improve the reporting quality of systematic reviews and meta-analyses. However, Simmonds et al., (2015) investigated the reporting quality of IPD meta-analyses, and concluded that there still was substantial room for improvement (7). They assumed that the publication of the PRISMA-IPD guideline, which is specific to IPD meta-analyses, would improve the overall reporting quality. The PRISMA-IPD was published in 2015 and is similar to the PRISMA. However, it has some additional items focused on the individual data collection and synthesis(8). The PRISMA-IPD is a self-explanatory checklist, which guides the researchers on the minimum amount information that needs to be reported to provide a full and transparent account of how the review was conducted.(9)

Since the publication of the PRISMA-IPD in 2015, no review was published regarding the reporting quality of IPD meta-analyses. Additionally, the methods used to investigate effect modification in current research practice, when performing an IPD meta-analysis, are currently unknown. Therefore, we wanted to evaluate if IPD meta-analyses investigated effect modification and which statistical practices were used when investigating effect modification. The goal of this study is to conduct a scoping review of IPD meta-analyses that have been published in the last 5 years and summarize their reporting quality and the statistical practices used for subgroup analyses.

**Methods**

**Search strategy**

The aim was to investigate the reporting quality of IPD meta-analyses after the publication of the updated PRISMA-IPD. We conducted a search on PubMed using the search strategy presented in Table 1. We restricted our search using the following filters: publication data from 01-01-2015 till 25-11-2019 and only studies written in the English language were selected.

After screening of the title and abstracts, all eligible publications were exported to Endnote, where duplicates were removed.

**Eligibility criteria**

We considered only studies that performed at least one IPD-MA, compared interventions (placebo included), interventions were applied on humans,….etc. In case of a series of studies we included only the last one.

The remaining studies were sorted according to date of publication in an ascending order (older publications first). For full text evaluation, we selected every sixth study. If any study was not eligible we selected the next in order study and so on.

**Extracted information**

After full text evaluation we extracted the following information: Medical field, number of studies included, number of participants included, if quality assessment was performed and the primary outcome association measure.

**((((((("Meta-Analysis" [Publication Type] OR Meta-analys\*[tiab] OR metaanalys\*[tiab]))) AND (((individual participant[tiab] OR individual participants[tiab] OR individual participant’s[tiab] OR individual patient[tiab] OR individual patients[tiab] OR individual patient’s[tiab] OR individualized participant[tiab] OR individualized participants[tiab] OR individualized participant’s[tiab] OR individualized patient[tiab] OR individualized patients[tiab] OR individualized patient’s[tiab] OR individualised participant[tiab] OR individualised participants[tiab] OR individualised participant’s[tiab] OR individualised patient[tiab] OR individualised patients[tiab] OR individualised patient’s[tiab]) AND data[tiab])))) OR (((IPD-MA[tiab] OR IPDMA[tiab]))))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])))**

**Reporting quality**

Meta-analysis query part

("Meta-Analysis" [Publication Type] OR Meta-analys\*[tiab] OR metaanalys\*[tiab])

AND (“individual participant data”[tiab] OR “individual participants data”[tiab] OR “individual participant's data”[tiab] OR “individual patient data”[tiab] OR “individual patients data”[tiab] OR “individual patient's data”[tiab] OR “individualized participant data”[tiab] OR “individualized participants data”[tiab] OR “individualized participant's data”[tiab] OR “individualized patient data”[tiab] OR “individualized patients data”[tiab] OR “individualized patient's data”[tiab] OR “individualized participant data”[tiab] OR “individualized participants data”[tiab] OR “individualized participants data”[tiab] OR “individualised patient data”[tiab] OR “individualized patient data”[tiab] OR “individualized patient's data”[tiab]) OR (IPD-MA[tiab] OR IPDMA[tiab])

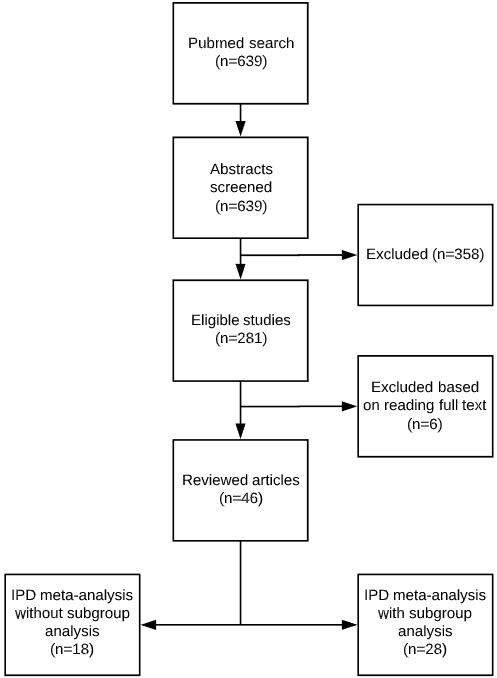
AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]))

To overview the reporting quality of the IPD-MAs we used PRISMA-IPD guideline. The PRISMA-IPD consists of 27 items which are applicable to meta-analysis, and 4 items which are specific for conducting an IPD meta-analysis(9). To assess compliance to the PRISMA-IPD items MB, JH, MR …. . The PRISMA-IPD allows two possible scoring options: reported or not reported. Most of the items adhere to this format, however some items consist of multiple parts that need to be included. The items which contain multiple parts are item 2 on the structured summary, item 10 on the data collection processes, item 14 on the synthesis methods, and item 21 on the results of syntheses. In this study the decision was made that when items had multiple parts, that at least half or more than half of the parts needed to be included to be scored as reported.

**Statistical practices for subgroup analysis**

We also wanted to create an overview of the statistical practices that were used when studies investigated effect modification. The first step was to determine if a study performed subgroup analysis. If a study performed subgroup analysis, then the following information would be extracted from the study: If they used a one or two stage approach, the use of a random or fixed effect model, the specific regression method for the primary outcome, the type of effect modifier (e.g. continuous or categorical), and the reporting measure used to determine heterogeneity.

**Results**

**Study selection process**

The literature search resulted in a total of 639 articles. After screening for eligibility, 281 papers could be included. Eventually, after the selection of every sixth or next eligible article, 46 articles were included in this report (10-55).

Figure 1.Flowchart presenting the process of study inclusion. After inclusion a distinction was made between studies that performed subgroup analyses and studies who did not perform subgroup analyses.

**Study characteristics**

Of the 46 included IPDMAs, 28 performed subgroup analyses. Figure 2 provides an overview of the number of IPDMAs per publication year and the percentages that performed subgroup analyses. The medical fields under investigation are shown in figure 3. Cardiovascular disease is the medical field which is investigated the most (n= 16) followed by, oncology (n=6), Psychiatry (n=5) and Obstetrics (n=4). The number of studies that were included in the reviewed IPD meta-analyses varied widely from 2 till 29 studies and the number of participants data included varied from 341 participants to 163,457 participants.

18 IPDMAs used the Cochrane risk-of-bias tool to assess the quality of the included studies, 2 studies used an adjusted version of the Cochrane risk-of-bias tool, 1 study used the Newcastle-Ottawa scale. The other 25 studies did not perform any quality assessment. The studies that investigated effect modification used a quality assessment tool in half of all cases, 14 studies used an assessment tool and 14 studies did not use any quality assessment tool. The studies that did not take effect modification into account used a quality assessment tool in 7 studies and did not use a quality assessment tool in 11 studies.

The association measures that were used for the primary outcome are depicted in figure 4. The most used association measure was hazard ratio, this measure was used in 16 studies. Additionally, relative risk (n=9), odds ratio (n=7) and mean difference (n=8) were used as outcome measure.

Figure 2. The number of publications per year. Distinguished based on if a study performed a subgroup analysis or not.

Figure 3. The medical field that is under investigation. Distinguished based on if a study performed a subgroup analysis or not.

Figure 4. The association measure used to compare the primary outcome. Distinguished based on if a study performed a subgroup analysis or not.

**The PRISMA-IPD guideline adherence**

The adherence regarding to the PRISM-IPD reporting guideline is shown in table 1. The adherence on the items varied widely, with the lowest adherence scores found for the items 15 and 22 both on the risk of bias across studies, and item A3 on the IPD integrity. All 46 papers did follow the guideline regarding the following items: item 2 structured summary, item 3 rationale, item 21 results of synthesis, and item 24 summary of evidence.

The three items with the lowest adherence scores for studies that performed subgroup analyses were item 15 the risk of bias across studies within the method section, item 22 the risk of bias across studies within the results section, and item 5 protocol and registration of the study. The studies that did not perform subgroup analysis scored reported poorly on item 15 risk of bias across studies within their method section, item 22 risk of bias across studies in their results section and item A3 IPD integrity. The average adherence score for the studies that performed subgroup analyses and the studies that did not perform subgroup analyses were 77% and 72% respectively. Table 2 provides a graphical representation of the varying adherence scores for both the studies that performed subgroup analyses and the studies that did not perform subgroup analyses. For the full PRISMA-IPD checklist, filled in for all studies, see Appendix 1.

Table 1. PRISMA-IPD guideline adherence. The three columns from left to right represent the overall adherence of all studies, the adherence of studies that performed subgroup analysis and the adherence of studies that did not perform subgroup analysis. The numbers are given as n (%) with n as number of studies within that specific group, and % as percentage of that group.

|  |  |  |  |
| --- | --- | --- | --- |
| PRISMA item | Adherence  (n=46) | Adherence  IPDMA with subgroup analyses (n=28) | Adherence  IPDMA without subgroup analyses (n=18) |
| **Title** |  |  |  |
| 1. Title | 32 (69.6%) | 20(71.4%) | 12(66.7%) |
| **Abstract** |  |  |  |
| 1. Structured summary | 46(100%) | 28(100%) | 18(100%) |
| **Introduction** |  |  |  |
| 1. Rationale | 46(100%) | 28(100%) | 18(100%) |
| 1. Objective | 45(97.8%) | 27(96.4%) | 18(100%) |
| **Methods** |  |  |  |
| 1. Protocol and registration | 18(39.1%) | 11(39.3%) | 7(38.9%) |
| 1. Eligibility criteria | 43(93.5%) | 28(100%) | 15(83.3%) |
| 1. Identifying studies – information sources | 37(80.4%) | 24(85.7%) | 13(72.2%) |
| 1. Identifying studies - search | 22(47.8%) | 12(42.9%) | 10(55.6%) |
| 1. Study selection processes | 32(69.6%) | 21(75%) | 11(61.1%) |
| 1. Data collection processes | 30(65.2%) | 17(60.7%) | 13(72.2%) |
| 1. Data items | 38(82.6%) | 22(78.6%) | 16(88.9%) |
| A1 IPD integrity | 27(58.7%) | 17(60.7%) | 10(55.6%) |
| 1. Risk of bias assessment in individual studies | 22(47.8%) | 15(53.6%) | 7(38.9%) |
| 1. Specification of outcomes and effect measures | 44(95.7%) | 27(96.4%) | 17(94.4%) |
| 1. synthesis methods | 36(78.3%) | 24(85.7%) | 12(66.7%) |
| A2 Exploration of variation in effects | 33(71.7%) | 24(85.7%) | 9(50%) |
| 1. Risk of bias across studies | 12(26.1%) | 8(28.6%) | 4(22.2%) |
| 1. Additional analyses | 40(87.0%) | 27(96.4%) | 13(72.2%) |
| **Results** |  |  |  |
| 1. Study selection and IPD obtained | 45(97.8%) | 27(96.4%) | 18(100%) |
| 1. Study characteristics | 42(91.3%) | 24(85.7%) | 18(100%) |
| A3 IPD integrity | 17(37%) | 13(46.4%) | 4(22.2%) |
| 1. Risk of bias within studies | 18(39.1%) | 13(46.4%) | 5(27.8%) |
| 1. Results of individual studies | 30(65.2%) | 18(64.3%) | 12(66.7%) |
| 1. Results of Synthesis | 46(100%) | 28(100%) | 18(100%) |
| 1. Risk of bias across studies | 9(19.6%) | 6(21.4%) | 3(16.7%) |
| 1. Additional analyses | 41(89.1%) | 27(96.4%) | 14(77.8%) |
| **Discussion** |  |  |  |
| 1. Summary of evidence | 46(100%) | 28(100%) | 18(100%) |
| 1. Strengths and limitations | 42(91.3%) | 25(89.3%) | 17(94.4%) |
| 1. Conclusions | 45(97.8%) | 28(100%) | 17(94.4%) |
| A4 Implications | 45(97,8%) | 27(96.4%) | 18(100%) |
| **Funding** |  |  |  |
| 1. Funding | 38(82.6%) | 24(85.7%) | 14(77.8%) |

Table 2. Graphical representation of the PRISMA-IPD adherence. Left column shows adherence for studies that performed subgroup analysis. Right column shows adherence for studies that did not perform subgroup analysis. The percentage that is given represents the adherence within that group.

|  |  |  |
| --- | --- | --- |
| PRISMA item | Adherence  IPDMA with subgroup analyses  (n=28) | Adherence  IPDMA without subgroup analyses  (n=18) |
| **Title** |  |  |
| 1. Title |  |  |
| **Abstract** |  |  |
| 1. Structured summary |  |  |
| **Introduction** |  |  |
| 1. Rationale |  |  |
| 1. Objective |  |  |
| **Methods** |  |  |
| 1. Protocol and registration |  |  |
| 1. Eligibility criteria |  |  |
| 1. Identifying studies – information sources |  |  |
| 1. Identifying studies - search |  |  |
| 1. Study selection processes |  |  |
| 1. Data collection processes |  |  |
| 1. Data items |  |  |
| A1 IPD integrity |  |  |
| 1. Risk of bias assessment in individual studies |  |  |
| 1. Specification of outcomes and effect measures |  |  |
| 1. synthesis methods |  |  |
| A2 Exploration of variation in effects |  |  |
| 1. Risk of bias across studies |  |  |
| 1. Additional analyses |  |  |
| **Results** |  |  |
| 1. Study selection and IPD obtained |  |  |
| 1. Study characteristics |  |  |
| A3 IPD integrity |  |  |
| 1. Risk of bias within studies |  |  |
| 1. Results of individual studies |  |  |
| 1. Results of Synthesis |  |  |
| 1. Risk of bias across studies |  |  |
| 1. Additional analyses |  |  |
| **Discussion** |  |  |
| 1. Summary of evidence |  |  |
| 1. Strengths and limitations |  |  |
| 1. Conclusions |  |  |
| A4 Implications |  |  |
| **Funding** |  |  |
| 1. Funding |  |  |

**Statistical practices used when performing subgroup analyses**

Studies that performed subgroup analyses used a one stage approach in 19 (70%) studies and a two stage approach in 8 (30%) studies. When studies performed a one stage approach, they used a random effect (n=9), fixed effect (n=6), both (n=1) or it was not described clearly what they used (n= 3). When using the two stage approach these numbers were: random effect (n=4), fixed effect (n=2) or did not describe clearly (n=2). One study applied both a one stage and two stage approach, but it was unclear if they used a random or fixed effect.

Figure 5. The left circle presents the number of studies that performed subgroup analysis versus studies which did not investigate subgroup analysis. The right circle represents the usage of a one stage or two stage model, when investigating subgroup analysis. One study did not report if they used a one or two stage approach. Therefore, this study is not included in the figure, and not included in the percentages.

When performing subgroup analyses several methods have been used. The most used method was the one stage IPD meta-analysis method (n=18). In addition, the meta-analysis of interaction terms (n=4), per subgroup meta-analysis (n=2) and the one stage ignoring clustering (n=2) were used. Two studies did not explicitly mention which methods were used.

Figure 6. Methods used to investigate effect modification. 1= one stage IPD meta-analysis, 2= meta-analysis of interaction terms, 3= per subgroup meta-analysis, 4= one stage ignoring clustering and 5= not reported.

The type of effect modifiers that were found in the different studies are shown in figure 7. The three types of effect modifiers were continuous variables analyzed either as continuous or categorical, and already categorical variables. As can be seen in figure 7, most studies used a combination of the effect modifying types. The combination that was most often found, in 48% of all studies, was the use of continuous variables that were analyzed as categorical together with already categorical variables.

Figure7. Type of effect modifier used in analysis. 1= continuous variable, which is analyzed as continuous, 2= continuous variable, which is analyzed as categorical, 3= categorical variable, 4= both 1&3, 5= both 2&3 and 6= 1,2 &3.

Within the studies that performed subgroup analyses heterogeneity was only assessed in 16 studies for certain, using I2 (n=15), tau2 (n=2) and Q (n=2). In two studies it was clearly mentioned that heterogeneity was not assessed and for the remaining 10 studies it was unclear what they performed.

**Discussion**

The goal of this scoping review was to summarize the overall reporting quality of the IPD meta-analyses that have been published since PRISMA-IPD was officially launched, and to study which statistical practices have been used when one of the aims was to identify potential relevant subgroups. Over the past five years a small increase in IPD meta-analysis publications can be seen. This could be the result of the fact that IPD meta-analyses receive more attention due to the methodological advantages and tools like the PRISMA-IPD. The medical areas that mostly use IPD meta-analysis are the cardiovascular and oncology areas, which is in line with previous research(7, 56). However, the use of IPD meta-analysis in the cardiovascular area is more dominant in this review. When investigating the association measures, it was clear that the hazard ratio was used more frequently than all the other association measures.

Although not all studies mentioned the use of the PRISMA-IPD guideline to write their IPD meta-analysis, the overall adherence was good. In this review we distinguished two groups: the IPD meta-analyses that performed subgroup analyses and the IPD meta-analyses that did not perform subgroup analyses. Both groups had a comparable adherence rate.

However, the adherence of the IPD meta-analyses that performed subgroup analysis tended to be higher. Especially, the items additional analysis, risk of bias within studies, IPD integrity and exploration of variation in effects were better adhered to. An explanation for this could be that the IPD meta-analyses that performed subgroup analyses are more interested in the variation of effects, and therefore better investigated these items. Both groups tend to score high on the basic processes of a systematic review such as offering a structured summary, rationale, results of synthesis and summary of evidence. However, there are also some areas with potential room for improvement, such as the items risk of bias across studies and IPD integrity. Only a little over half of all studies explained if they checked the data they received, on completeness and possible problems. The review of Simmonds et al also established this problem and hoped that the PRISMA-IPD would solve this problem, unfortunately this was not the case (7).

Our results are in agreement with Simmonds et al., (2015) regarding the use of the one stage approach (7). In addition to their research we also investigated the type of effect modifier used for subgroup analysis. The most frequently used effect modifying variables were continuous but analyzed as categorical together with already categorical variables.

After investigating the specific regression methods used for the primary outcomes, we can conclude that there is a lot of variation. The variation was thus large that we decided to not present them in the results since it would not inform on the current practice. Every article used different names for their analysis and there was a lot of uncertainty. There are no clear guidelines on how to perform these analyses, and what needs to be reported. The PRISMA-IPD is a useful tool which could offer a framework for the reporting part of the analysis. Unfortunately, the number of studies that mention the PRISMA-IPD is little.

The major strength of our scoping review is that this is the first study that investigated the reporting quality after the publication of the PRISMA-IPD. Additionally, no article had created an overview of the statistical practices that are used when performing subgroup analysis in an IPD meta-analysis. However, some limitations should also be discussed. First, due to the limited amount of time, we could only include 50 articles instead of 100, which is the amount we wanted to include initially. Second, the assessment of the articles and which statistical practices were applied has proven to be difficult. There were lots of uncertainties due to incomplete reporting in the methods and results sections.

**Conclusion**

Our results suggest that PRISMA-IPD is adhered to by most authors reporting on individual participant data, but there is still considerable room for improvement. Additionally, when performing subgroup analysis there was great variety in the methods presented, and there seems no current standard on what to report. The PRISMA-IPD should be implemented more, and future studies should try to find a uniform solution for the reporting of statistical analysis.

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**APPENDIX 1**

PRISMA-IPD checklist adherence for all articles.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | 1.Title | 2.Structured summary | 3.Rationale | 4.Objectives | 5.Protocol and registration | 6.Eligibility criteria | 7.Identifying studies/ sources | 8.Identifying studies -search |
| 6. Breugom et al., 2015 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| 12. Egerup et al., 2015 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 19. Katz et al., 2015 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
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| 126. Jolly et al., 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| 132. Lambertini et al., 2017 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| 138. Maund et al., 2017 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 144. Palmerini et al., 2017 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| 150. Powell et al., 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
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| 163. van Vliet et al., 2017 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
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| 228. Neonatal Vitamin A Supplementation Evidence group., 2019 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| 234. Bernard et al., 2019 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
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| 264. Rosenfield et al., 2019 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
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| Study | 9.Study selection processes | 10.Data collection processes | 11.Data items | A1.IPD intergrity | 12.Risk of bias assessment  in individual studies | 13.Specification of  outcomes and effect measures | 14.Synthesis methods |
| 6. Breugom et al., 2015 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 12. Egerup et al., 2015 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
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| 126. Jolly et al., 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| 132. Lambertini et al., 2017 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
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| Study | A2. Exploration of  variation in effects | 15.Risk of bias across studies | 16.additional analyses | 17.Study selection and  IPD obtained | 18.Study characteristics | A3.IPD intergrity | 19.Risk of bias  within studies | 20.Results of individual studies |
| 6. Breugom et al., 2015 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 1 |
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| Study | 21.Results of syntheses | 22.Risk of bias across studies | 23.Additional analyses | 24.Summary of evidence | 25.Strengths and limitations | 26.Conclusions | A4.Implications | 27.Funding |
| 6. Breugom et al., 2015 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 |
| 12. Egerup et al., 2015 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 19. Katz et al., 2015 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
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