Individual participant data meta-analysis. When? Why? How? A scoping review

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Abstract

Background

Individual participant data(IPD) meta-analysis(MA) is considered the gold standard for evidence based inference. It is well established that IPD-MA offers great advantages compared to aggregate MA and single studies, thus systematic reviews have been conducted in order to investigate current practice and propose guidance. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines help authors in reporting systematic reviews and meta-analyses. Nevertheless, the extended PRISMA guidelines were introduced in 2015 and no review has been performed since then.

Objective: Our goal is to conduct a scoping review of IPD-MA and summarise their reporting quality and statistical approaches used. Consequently, we aim to inform how IPD-MA are performed, what is their goal, which statistical approach they use and whether reporting was described according to PRISMA guidelines and/or to the level that the analysis can be reproduced.

Methods

We searched MEDLINE, PubMed and Cochrane IPD-MA Library for IPD-MAs related articles published the last five years. We screened the titles and abstracts and extracted where possible the size of the meta-analysis, their primary goal, type of outcome(s), study designs, statistical analysis and modelling approaches performed. Subsequently we excluded diagnostic, network, predictive and opportunistic IPD-MAs and articles with poor reporting and sampled the remaining for full text consideration. Finally, we assessed the quality of -within full text- reporting according to the PRISMA-IPD guidelines.

Results

Our search resulted in 1538 articles, after exclusion criteria we ended with *702*. We sampled 100 and considered their full texts. IPD-MAs have seen considerable growth over the last five years. Random-effects are most often used and one-stage are almost equally performed as two-stage approaches. Most IPD-MAs have not clearly stated the goal, statistical approach and characteristics of their meta-analysis in their abstract and title.

Temporary

Most of the IPD-MAs had as a goal to investigate for subgroups effects. Reporting type of

Conclusions

Not yet

Introduction

Meta-analysis (MA) is a statistical method that involves combining information from multiple sources. While initially, meta-analyses were limited in aggregated data (AD) in the early 1990s individual participant data meta-analysis (IPD-MA or IPDMA) was introduced (CHALMERS 1993). In IPD-MA the participant level information is available and therefore evidence from multiple studies can be analysed as a whole. Collecting the IPD may be a difficult and time consuming task, but IPD-MA is considered the gold standard in evidence synthesis (Stewart and Parmar 1993 ; and 1995 ; Stewart and Tierney 2002) and offers great opportunities (Walraven 2010) that in AD-MA may be inevitable. Besides when investigating overall treatment effects where AD-MA and IPD-MA are mathematically equivalent, IPD-MA offers (1) the possibility to standardize subgroup definitions and outcomes across studies, (2) higher validity and credibility of subgroup findings, (3) increased flexibility to search for subgroups based on combinations of patient and/or disease characteristics (4) the possibility to avoid ecological BIAS (5) investigate non-linear functional forms (6) training better prediction models and (7) efficiently synthesizing evidence from different designs.

Given these advantages systematic reviews were typically applied to inform of how are IPD from multiple sources analysed and what for. For instance, Simmonds et al (Simmonds et al. 2005) identified 44 IPD-MAs performed during 2000-2005 time period and 1) summarized whether IPD-MAs obtained all the data they sought 2) reported the types of approaches that were used in the analysis 3) and whether the effects of covariates have been investigated and 4) report which medical field was their topic. On a subsequent paper, 10 years later Simmonds et al. (Simmonds, Stewart, and Stewart 2015) identified 1371 potential IPD-MAs performed during 2010-2015 time period, sampled 184 of them and after obtaining full texts included 100 IPD-MAs. Then they investigated along with the topics investigated in the initial paper they investigated also the quality of IPD-MA reporting. Riley et al. (Riley, Lambert, and Abo-Zaid 2010) identified 383 IPD-MAs performed form instance until 2009 and summarised only: 1) their medical field topic and 2) whether they assessed risk or prognostic factors. Finally, Schuit and Ioannidis (Schuit, Li, and Ioannidis 2018) identified 327 IPD-MAs performed from inception until 2014. Nevertheless, they restricted their interest in subgroup effects investigation. Our objective is to conduct a systematic review of IPD-MA from 2015 onwards and and summarise their properties. Furthermore, we aim to inform when and how IPD-MA are performed, whether state-of the art methods are used and whether they are clearly described.

Nevertheless far systematic reviews over the IPD-MA practices are limited until 2014.

Reporting IPD-MA may be conducted in either one stage or two stages. In one-stage IPD-MA, a statistical model of choice is applied and IPD from all studies are analysed simultaneously, whilst accounting for within-studies clustering of the participants. On the other hand, in two-stage IPD-MA a statistical model of choice is fitted per study. Subsequently the estimates extracted are pooled using inverse-variance meta-analytical methods. Both approaches have a variety of parameters and results that should be reported in the abstract, the methods and the results section. An extended version of PRISMA for IPD (Stewart et al. 2015) offers guidance on how to report results in IPD-MA. For instance, in two-stage IPD-MA 1) heterogeneity measures (I^2 , Cochran's Q, τ^2) 2) and their corresponding methods used 3) forest plots (if applicable) and 4) use of fixed or random effects models and any other model assumptions should be described in the Methods section. Furthermore, in't Hout (IntHout et al. 2016) suggested that prediction intervals of estimates are also a valuable information and should be included. On the other hand, in one-stage IPD-MA 1) specification of one-stage models 2) use of fixed-effect, stratified or random-effects in the terms of the model and 3) how clustering of patients within studies was accounted for should be reported in the methods section.

Effect modification Simmonds et al. (Simmonds, Stewart, and Stewart 2015) showed that IPD-MA are frequently performed in order to detect treatment effect modification. The approaches that were mostly used were one aggregated data meta-analysis approach 'meta-regression' and three IPD-MA approaches, per-subgroup meta-analysis, meta-analysis of interaction terms and one-stage IPD-MA. Guidance on which method to choose is available. Specifically, Simmonds and Higgins (Simmonds and Higgins 2007) mathematically proved that, given some unrealistic assumptions, one-stage IPD-MA is always more powerful than meta-analysis of interaction terms and meta-regression. Fisher et al. (Fisher et al. 2011) also critically reviewed all four approaches. They concluded that one-stage IPD-MA allows for more complex analysis, but is more difficult to perform than pooling within-trial interaction terms. Furthermore, Hua et al. (Hua et al. 2016) noted that these one-stage IPD-MA using mixed-effects modelling should also centre the effect

modifiers to their mean, in order to separate across and within trial information and therefore accounting for ecological bias.

Modelling functional forms IPD-MA may be performed in order to investigate the role of risk-factors in the prevalence of a disease. In that case observational studies are typically meta-analysed. Thereto, IPD-MA may involve modelling also non-linear functional forms. Sauerbrei and Royston (Sauerbrei and Royston 2011) suggested the use of a two stage approach. As a first stage a fractional polynomial is selected and pooling their estimates through a point-wise weighted meta-analytical process. Subsequently they extended these non-linear associations to include interactions (Royston and Sauerbrei 2013). Furthermore, splines may also be applied to detect non-linear associations.

Methods

This study is a scoping review of current practices in IPD-MAs. We report our study according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. *(bold are checkpoints in the PRISMA-ScR check-list)*

Protocol and registration No formal protocol exists for this study.

Information sources A MEDLINE, PubMed and Cochrane library search was performed in 1^{st} of May using the following search terms: *(("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 IPDMA[tiab] OR IPD-MA[tiab] AND ("2015/01/01"[PDat] : "2019/05/01"[PDat])*

Eligibility criteria We included studies describing an IPD-MA published between 01/01/2015 and 01/05/2019. We removed duplicate papers and from series of articles we included only the most recent.

PRISMA-IPD offers guidance in the reporting of the title, abstract ,introduction, methods, results, discussion and funding section of an article. Therefore, our scoping review has been performed into two stages, one evaluating the title and abstract of all IPD-MAs and one evaluating the full text of a subset of them. For instance, in the first stage we considered all available IPD-MAs and screened their titles and abstracts. Thereto, we extracted information -if present- over the year, medical field, number of included studies and participants, the goal, types of outcomes and statistical approaches preferred. Subsequently, we excluded diagnostic test and predictive IPD-MAs. Other reasons for further exclusion were: 1) full text was not published in English, 2) IPD-MAs were given as examples (for instance in methodological, health-technology assessments and cost-effectiveness studies) 3) we had no access to full text and 4) the studies were protocols. Finally, we sampled 100 of these eligible studies and extracted information over the statistical analysis and evaluated the reporting quality according to the PRISMA-IPD guidelines.

Data items

We summarised our results using frequency tables, barplots and

Results

Our search identified 1538 potential records. We removed 61 duplicates and series of articles. We screened the titles and abstracts of the remaining 1477 studies. Approximately 36% of the papers were not identified as a systematic review, or meta-analysis or meta-analysis of individual participant data.

Table 1: Percentage of articles indicating that they perform and IPD-MA

IPD reference in title	Frequency	Percentage
Yes	943	63.85%
No	534	36.15%

We showed an increasing trend over the years of articles involved with IPD-MA. IPD methods seem to gain popularity in medical fields such as pregnancy and childbirth, mental health and neurology

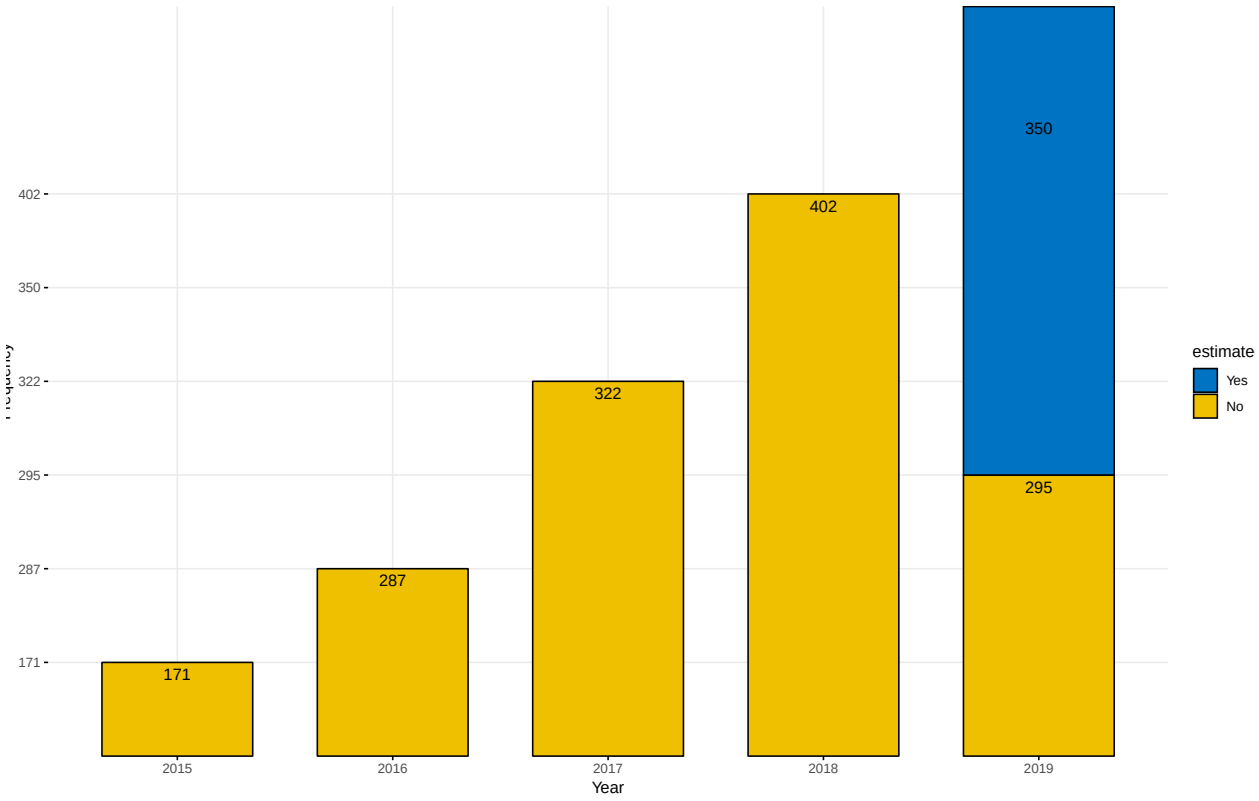

Figure 1.

Title results
Synthesis of results

Table 2: Individual participant meta-analysis per medical field

General Medical Field	Frequency	Percentage
Cardiovascular diseases	58	18.3%
Cancer	47	14.83%
Neurology	33	10.41%
Mental health	29	9.15%
Pregnancy and childbirth	25	7.89%
Child health	24	7.57%

General Medical Field	Frequency	Percentage
Endocrine and metabolism	16	5.05%
Gastroenterology	14	4.42%
Orthopedics	11	3.47%
Lungs and airways	8	2.52%
Psychology	7	2.21%
Geriatrics	6	1.89%
Infectious diseases	5	1.58%
Pain	5	1.58%
Generic Care	4	1.26%
Ear, nose & throat	3	0.95%
Other	3	0.95%
Critical care	2	0.63%
Gynaecology	2	0.63%
Nutrition	2	0.63%
Renal Disease	2	0.63%
Review	2	0.63%
Vaccines	2	0.63%
Wound	2	0.63%
Anaesthesiology	1	0.32%
Dermatology	1	0.32%
Pharmakokinetics	1	0.32%
Renal disease	1	0.32%
Stastical	1	0.32%

Table 3: Individual participant meta-analysis per medical field

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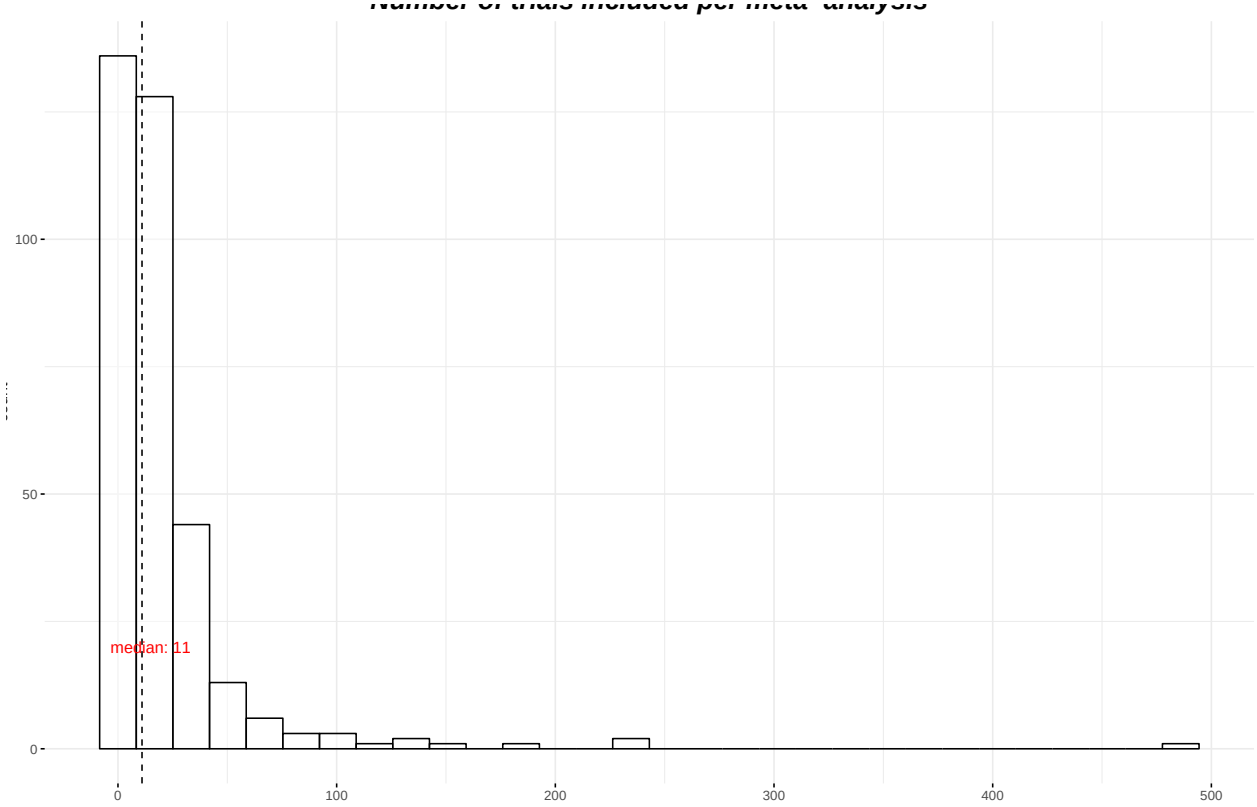
Pharmakokinetics	1	0.32%
Renal disease	1	0.32%
Stastical	1	0.32%

The medical fields with the most articles were Cardiovascular diseases, cancer, neurology and mental health.


Number of trials included per meta-analysis
100
50
0
median: 11
0
100
200
300
400
500
Trials per Meta−analysis

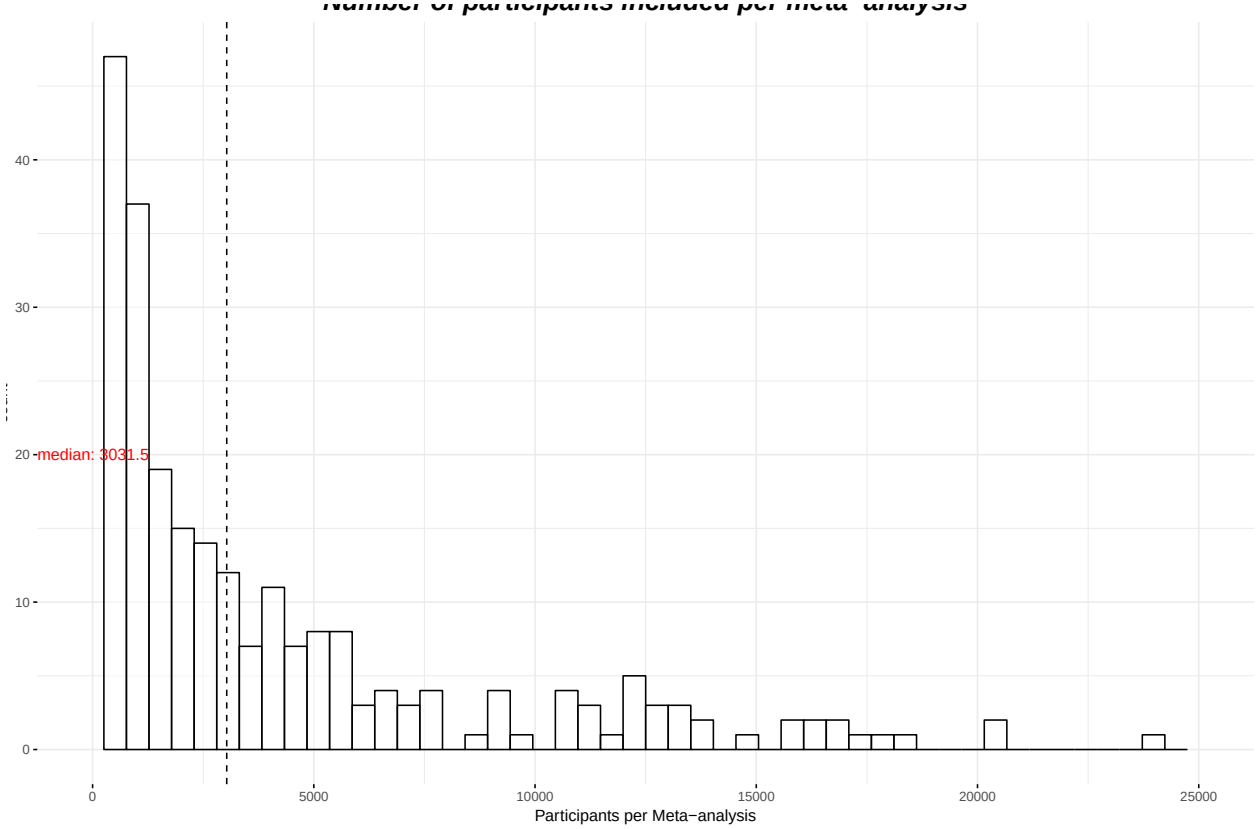

Number of participants included per meta-analysis
40
30
20
10
0
median: 3031.5
0
5000
10000
15000
20000
25000
Participants per Meta−analysis

Table 4: Table 2. Type of outcomes investigated

Binary	Continuous	Time-to-event
362	113	265

Table 5: Table 3

	One-stage IPD-MA	Meta-analysis of interaction terms	Per subgroup meta-analysis	Meta-regression	Centered one-stage IPD-MA
		Fixed vs	random effects		
Fixed effect	x	x	x	x	x
Random effects	x	x	x	x	x
		Reporting of	heterogeneity		
I^2	x	x	x	x	x
Cochran's Q (without I^2)	x	x	x	x	x
τ^2	x	x	x	x	x
Prediction intervals	x	x	x	x	x
From one-stage model	x	x	x	x	x
Other	x	x	x	x	x
Not reported	x	x	x	x	x

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