Manuscript Details

Manuscript number	JCE_2019_404_R3
Title	No consistent evidence of data availability bias existed in recent individual participant data meta-analyses: A meta-epidemiological study
Article type	Original article

Abstract

Objectives To assess trial-level factors associated with the contribution of individual participant data (IPD) to IPD meta-analyses, and to quantify the data availability bias, namely the difference between the effect estimates of trials contributing IPD and those not contributing IPD in the same systematic reviews (SRs). Design and Setting We included SRs of randomized controlled trials (RCTs) with IPD meta-analyses since 2011. We extracted trial-level characteristics and examined their association with IPD contribution. To assess the data availability bias, we retrieved odds ratios from the original RCT papers, calculated the ratio of odds ratios (RORs) between aggregate data (AD) meta-analyses of RCTs contributing IPD and those of RCTs not contributing IPD for each SR, and meta-analytically synthesized RORs. Results Of 728 eligible RCTs included in 31 SRs, 321 (44%) contributed IPD, while 407 (56%) did not. A recent publication year, larger number of participants, adequate allocation concealment, and impact factor ≥10 were associated with IPD contribution. We found the SRs yielded widely different estimates of RORs. Overall, there was no significant difference in the pooled effect estimates of AD meta-analyses between RCTs contributing and not contributing IPD (ROR 1.01, 95% confidence interval 0.86–1.19). Conclusions There was no consistent evidence of a data availability bias in recent IPD meta-analyses of RCTs with dichotomous outcomes. Higher methodological qualities of trials were associated with IPD contribution.

Keywords	Individual participant data, systematic review, meta-analysis, data availability bias
Manuscript region of origin	Asia Pacific

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Data will be made available on request

Ms. Anneke Germeraad-Uriot

Associate Editor

Journal of Clinical Epidemiology

October 1, 2019

Dear Ms. Germeraad-Uriot,

Thank you for the opportunity to revise our manuscript, "No consistent evidence of data availability bias existed in recent individual participant data meta-analyses: A meta-epidemiological study". As indicated in the editorial comment, we adopt the abstract with 218 words.

We trust that it is now suitable for publication in the *Journal of Clinical Epidemiology*.

Thank you in advance for your kind consideration of this paper.

Sincerely,

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Ms. Anneke Germeraad-Uriot

We are glad to know that our manuscript is almost ready for the publication. As indicated in the editorial comment, we revised abstract as follows:

Abstract (218 words)

Objectives

To assess trial-level factors associated with the contribution of individual participant data (IPD) to IPD meta-analyses, and to quantify the data availability bias, namely the difference between the effect estimates of trials contributing IPD and those not contributing IPD in the same systematic reviews (SRs).

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Results

Of 728 eligible RCTs included in 31 SRs, 321 (44%) contributed IPD, while 407 (56%) did not. A recent publication year, larger number of participants, adequate allocation concealment, and

impact factor ≥10 were associated with IPD contribution. We found the SRs yielded widely different estimates of RORs. Overall, there was no significant difference in the pooled effect estimates of AD meta-analyses between RCTs contributing and not contributing IPD (ROR 1.01, 95% confidence interval 0.86–1.19).

Conclusions

There was no consistent evidence of a data availability bias in recent IPD meta-analyses of RCTs with dichotomous outcomes. Higher methodological qualities of trials were associated with IPD contribution.

No consistent evidence of data availability bias existed in recent individual participant data meta-analyses: A meta-epidemiological study

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To assess trial-level factors associated with the contribution of individual participant data (IPD) to IPD meta-analyses, and to quantify the data availability bias, namely the difference between the effect estimates of trials contributing IPD and those not contributing IPD in the same systematic reviews (SRs).

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Of 728 eligible RCTs included in 31 SRs, 321 (44%) contributed IPD, while 407 (56%) did not. A recent publication year, larger number of

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Conclusions

There was no consistent evidence of a data availability bias in recent IPD meta-analyses of RCTs with dichotomous outcomes. Higher methodological qualities of trials were associated with IPD contribution.

Keywords

Individual participant data, systematic review, meta-analysis, data availability bias

What is new?

Key findings

- Trial-level characteristics such as a recent year of publication, large number of participants, high impact factor, and adequate allocation concealment were independently associated with individual participant data (IPD) contribution to systematic reviews (SRs) with IPD meta-analyses.
- We could not find consistent evidence of a data availability bias; the effect

estimates of trials contributing IPD were not statistically different from those not contributing IPD in the same systematic reviews (SRs).

What this study adds to what was known?

- Methodological qualities of trials were associated with the contribution of IPD to IPD meta-analysis, but effect estimates might not affect this result.
- While previous studies suggested the presence of a data availability bias only narratively or theoretically, we systematically compared the effect estimates between studies with and without IPD contribution and showed that there was no consistent evidence of a data availability bias.

What is the implication and what should change now?

- Investigators should be aware of the differences in methodological qualities between RCTs with and without IPD contribution when conducting IPD meta-analyses.
- While we did not detect any systematic data availability bias in the recednt IPD meta-analyses, effect estimates in some IPD meta-analyses might still be biased in either direction due to the data availability.

Background

Individual participant data (IPD) meta-analyses are considered to increase the statistical power of systematic reviews (SRs) as well as enable more valid subgroup

analyses, in comparison with meta-analyses that are based on aggregate data (AD) extracted from published trial reports [1-3]. Encouragement to share IPD from clinical studies has risen in the scientific literature, and the number of SRs with IPD meta-analyses has increased dramatically over the past few years [4-9].

However, SRs with IPD meta-analyses require the review authors to spend substantial time and effort to contact and request IPD from the authors of the original studies [1, 10, 11] with no certainty that all original authors will contribute their data. Indeed, only 25% of the 760 IPD meta-analyses conducted between 1987 and 2015 retrieved 100% of the data from the relevant trials, and 43% retrieved 80% of the data of relevant trials [10].

The risk of data availability bias increases when all IPD data cannot be procured [2, 10, 12, 13]. The data sharing policy of RCTs might be influenced by the views of the investigators, as well as by the resources or results of the RCTs [5]. If unavailability of IPD is associated with the direction or the size of the intervention effect, studies that are available for IPD analyses may not be representative of the whole evidence, and the results of such IPD meta-analyses may be misleading. However, the difference in characteristics between RCTs contributing and not contributing IPD has not been investigated.

To date, data availability bias has been discussed only anecdotally, narratively or theoretically and there has been no systematic examination aiming to quantify the impact of this bias on the effect estimates of meta-analyses [2, 6, 10, 13, 14]. The purposes of this study were, therefore, two-fold: (i) To assess RCT-level factors associated with the contribution of IPD, and (ii) to examine data availability bias in IPD meta-analysis with less than 100% retrieval rate.

Methods

Design

A meta-epidemiological study

Eligibility criteria

All therapeutic RCTs included in SRs that fulfilled all following criteria were eligible: (i) SRs with IPD meta-analyses, (ii) SRs that included only RCTs comparing an active intervention against a control condition in terms of a dichotomous outcome, (iii) SRs that reported a full reference list of the included RCTs, and (iv) SRs published in English. We excluded the following SRs: (v) SRs published before 2011, (vi) SRs where all included RCTs provided IPD data, (vii) SRs of diagnostic or prognostic studies, and (viii) SRs with network meta-analyses. A cutoff year of 2011 was selected because a reporting guideline for SRs, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, was first published in 2009 [15]. We allowed two years for the dissemination of this guideline.

Search methods

We used the reference list from a recent comprehensive review of IPD meta-analyses conducted by Nevitt et al[10]. We also performed an updated search of MEDLINE via Ovid using the same search strategy as the above review to identify relevant SRs as of 10th March 2018. Supplementary file 1 shows the search terms we used.

Study selection

Two pairs of researchers (YT-TF and KO-AO) independently screened the titles and abstracts of articles identified by the updated search. We pooled the potentially eligible SRs and the reference list from the review conducted by Nevitt et al [10]. We then independently assessed eligibility based on a full-text review.

Data extraction

Eight researchers (YT, TF, KO, AO, ST, TI, YL and CP) independently extracted the following RCT-level factors from the included RCTs; year of publication, sample size, whether the primary outcomes of the RCT was positive or not, allocation concealment, industrial sponsorship, publication status (full-publication or not), data sharing statement (available, unavailable, or unclear), journal impact factor (IF), and language. We selected the primary outcomes of the RCTs using the following hierarchy: an outcome that was mentioned (1) as primary, (2) in the title, (3) in the objective, (4) first in the abstract, (5) first in the text. We defined the primary outcome as positive when the selected primary outcome was statistically significant in superiority trials or within the noninferiority margin in noninferiority trials. We chose not blinding but adequate allocation concealment as a marker of study quality because the feasibility of blinding and its impact on outcomes varies across research questions. We used the IF of the

journal from 2017 Journal Citation Reports® Science Edition (Thomson Reuters, 2018) and assigned an IF of zero to conference abstracts and unpublished studies.

We also extracted the following SR-level factors from the included SRs: year of publication, the number of included RCTs, types of review (pharmacological or non-pharmacological interventions, adult or pediatric, and Cochrane or non-Cochrane), and funding (yes/no).

To examine any discrepancy between the effect estimates of RCTs contributing IPD (C-RCTs) and those not contributing IPD (NC-RCTs), we selected a single outcome per SR. As the SR might have reported several outcomes, we selected the single primary outcome that fulfilled all the following criteria: (1) An efficacy outcome measured as a pooled risk ratio (RR) or odds ratio (OR), (2) Not a composite outcome, and (3) Not an outcome of adverse events or subgroup analysis. We did not adopt a composite outcome because the definition or components of the outcome was expected to vary across trials. In cases where the primary outcome did not meet these criteria, we adopted the outcome with the largest number of trials or the first outcome described which met these criteria.

For the single selected outcome in each SR, we extracted the number of events and participants in the intervention and control groups from the original published journal articles or conference abstracts of both C-RCTs and NC-RCTs. If the number of events or participants was missing, or if the selected outcome was not reported in the original RCT but provided in the IPD meta-analysis, we imputed them from the information or outcome data presented in the IPD-SR. We also extracted the pooled RR or OR from the reported IPD meta-analysis. We converted the pooled RR to OR using the observed control event rate [16].

Statistical analysis

We first described RCT characteristics, each classified by whether the RCT contributed IPD to the SR or not. We then explored the RCT-level factors (see Data Extraction) associated with the contribution of IPD using univariable mixed-effect logistic regression with a random intercept for SRs to account for the clustering effects of RCTs within each SR, and a multivariable mixed-effects logistic regression model with fixed factors (year of publication, sample size, positive primary outcome [yes or no], adequate allocation concealment [yes or no], industrial sponsorship [yes or no], publication status [full-publication or not], data sharing statement [available or not), IF [no IF, < 5, 5 ≤ to < 10, or 10 ≤], language [published in English or not]), and a random intercept for SRs.

We calculated odds ratios using the number of events and the number of patients aggregated from the original RCT papers and pooled them in aggregate data (AD) meta-analyses using random-effects models. Each OR was recalculated so that an OR <1 indicated that the intervention arm was favored. To assess data availability bias quantitatively, we calculated and pooled the ratio of odds ratios (ROR) in AD meta-analyses of C-RCTs to those in AD meta-analyses of NC-RCTs using the following two-step approach proposed by Sterne et al [17]. First, we estimated an ROR in each AD meta-analysis by using a random-effect meta-regression. An ROR <1 indicated a larger treatment effect estimate in AD meta-analyses of C-RCTs than in NC-RCTs. We estimated the combined ROR across SRs and the 95 % confidence interval (CI) with a

random-effects meta-analysis model. We used the I^2 statistic, τ^2 –statistic and 95% prediction interval to quantify the heterogeneity between SRs.

We expressed continuous variables as mean (standard deviation) for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data and categorical variables as numbers with the percentage. We considered a two-sided p value < 0.05 as a statistically significant difference. We used Stata/SE, V.14.0 (StataCorp, College Station, TexasX, USA) for all analyses.

Sensitivity analysis

To examine the robustness of the estimated ROR, we performed the following sensitivity analyses. First, we adjusted SR-level factors (year of publication, the number of included studies, types of review [Cochrane or non-Cochrane, pharmacological or not, and pediatric or not], or funding) that assumed to be confounders of the association between IPD contribution and the ROR using the meta-regression model. Second, we excluded RCTs for which we imputed the results of AD meta-analysis with those reported in IPD meta-analysis. Third, we examined a discrepancy between IPD meta-analytic results of C-RCTs and AD meta-analytic results of NC-RCTs using the same methods for the primary outcome.

Additional analyses

As a post-hoc analysis, we used log-transformed data of the number of randomized participants and impact factors instead of categorized data, and added them into the mixed effects multivariable model to examine their associations with the contribution of IPD.

The study was registered in UMIN-CTR as UMIN000028325 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000036147).

Results

Results of searches

Figure 1 shows the flow diagram of the present study. We identified 2349 possible SRs with IPD meta-analyses including 102 references from the previous study [10]. We assessed the eligibility of 268 SRs with IPD meta-analyses that remained after screening of titles and abstracts, and included 37 IPD-SRs for a total of 728 RCTs. For the assessment of data availability bias, six SRs had only one or two RCTs that reported the selected outcome, which made it impossible to calculate the ROR using a random effects meta-regression model. Among 631 RCTs included in the remaining 31 SRs, 264 did not report the selected outcome. Consequently, we included 367 RCTs that reported the selected outcome in the analysis for data availability bias.

Characteristics of included IPD systematic reviews

Supplementary file 2 shows the characteristics of the included IPD-SRs. The number of included RCTs in the IPD-SRs varied from 5 to 103 (median 13, IQR 11 to 21), and the IPD retrieval rate ranged from 10 % to 92 % (median 71 %, IQR 50 % to 81 %). Twenty-five (68 %) IPD-SRs had funding, 21 (57 %) focused on pharmacological interventions, 7 (19%) were Cochrane reviews, and 2 (5 %) were in pediatric areas.

Characteristics of included studies and IPD contribution

Of 728 RCTs included, 321 contributed IPD and 407 did not. Table 1 summarizes the characteristics of the included RCTs and the association with the IPD contribution. C-RCTs were likely to have a recent year of publication, a larger sample size, adequate allocation concealment, full publication status, higher impact factor, and sponsorships as compared to NC-RCTs. We next examined the association between RCT characteristics and IPD contribution with logistic regressions. As shown in Table 1, a recent publication year, larger number of participants randomized, adequate allocation concealment, and high impact factor (≥10) compared to IF <5 were independently associated with IPD contribution. On the other hand, whether the primary outcomes were positive was not associated with IPD contribution (adjusted OR 1.06, 95% CI 0.72 to 1.55). The association of the number of randomized participants or that of impact factors with IPD contribution remained unchanged when we used log-transformed data instead of categorized data (OR 1.34, 95% CI 1.07 to 1.69, and OR 1.28, 95% CI 1.03 to 1.58, respectively)

Table 1 Characteristics of included RCTs and the associations with IPD contribution

Characteristics	C-RCTs (n = 321)	NC-RCTs (n = 407)	Univariable*	Multivariable†
Years since publication, mean (SD)	10.0 (6.9)	11.4 (8.9)	0.94 (0.92 to 0.97)	0.96 (0.93 to 0.99)
Number of randomized participants				
1st quartile	12 to 101	5 to 60	Ref	Ref
2nd quartile	102 to 228	60 to 115	1.85 (1.12 to 3.06)	1.54 (0.90 to 2.63)
3rd quartile	228 to 619	116 to 250	2.89 (1.71 to 4.90)	1.90 (1.07 to 3.37)
4th quartile	620 to 20536	250 to 17354	5.09 (2.83 to 9.15)	2.28 (1.16 to 4.47)
Adequate allocation concealment	230 (57)	107 (33)	3.34 (2.27 to 4.91)	2.33 (1.53 to 3.55)
Publication status				
Full publication	375 (92)	281 (88)	Ref	Ref
Conference abstract	23 (6)	35 (10)	0.37 (0.9 to 0.71)	0.82 (0.27 to 2.51)
Unpublished	9 (2)	5 (2)	0.66 (0.18 to 2.38)	n/a‡
Impact factor§				
<5	142 (35)	161 (50)	Ref	Ref
≥5 to <10	66 (16)	42 (13)	1.57 (0.93 to 2.65)	1.52 (0.87 to 2.65)
≥10	152 (37)	48 (15)	3.13 (1.86 to 5.24)	2.18 (1.22 to 3.88)
No impact factor	47 (12)	70 (22)	0.59 (0.35 to 1.00)	0.84 (0.33 to 2.14)
Industrial sponsorship	119 (29)	68 (21)	2.13 (1.32 to 3.45)	1.40 (0.84 to 2.34)
Published in English	399 (98)	307 (96)	2.29 (0.77 to 6.81)	0.99 (0.26 to 3.81)
Statement to share the data	4 (1)	3 (1)	1.03 (0.19 to 5.56)	0.61 (0.10 to 3.80)
Positive results in the primary outcome‖‖	216 (55)	148 (47)	1.16 (0.82 to 1.66)	1.06 (0.72 to 1.55)

Note: Values for categorical variables and continuous variables are given as number (percentage) and mean (SD) or median (IQR). *Using univariable mixed effects logistic regression with a random intercept for the systematic review. †Using multivariable mixed effects logistic regression model with fixed factors (year of publication, sample size, adequate allocation concealment, publication status (full-publication or not), impact factor (no impact factor, < 5, 5 ≤ to < 10, or 10 ≤), industrial sponsorship, language (written in English or not), data sharing statement (available or not) and whether the primary outcomes in the RCTs were positive) and a random intercept for the systematic review. ‡No sufficient data was available to conduct the multivariable analysis §Impact factor in 2017. We assigned an impact factor of zero to conference abstracts and unpublished studies. ‖‖Any of the primary outcomes were positive when the selected primary outcome was statistically significant in efficacy trials or within the noninferiority margin in noninferiority trials. Abbreviations: RCT, randomized controlled trial; IPD, individual participant data; C-RCT, RCTs contributing IPD; NC-RCT, RCTs not contributing IPD; SD, standard deviation; IQR, interquartile range.

Data availability bias

Figure 2 shows the RORs that compared AD meta-analyses of C-RCTs and those of NC-RCTs among 31 SRs including 377 RCTs. We found the SRs yielded widely different estimates of RORs. For example, one SR showed a significantly large

treatment effect in C-RCTs compared with NC-RCTs [18], whereas one SR showed a significantly small effect of C-RCTs compared with NC-RCTs [19]. The remaining 29 SRs showed a non-significant difference in treatment effects between C-RCTs and NC-RCTs. Overall, we found no statistically significant association between IPD contribution and the size or direction of treatment effects which could be estimated from AD meta-analyses of the trials within each SR (pooled ROR 1.01, 95 % CI 0.86 to 1.19, I^2 = 27 %, τ^2 = 0.044, and 95% prediction interval 0.60 to 1.42) (Fig 2).

Sensitivity analyses

A sensitivity analysis excluding the data imputed from the IPD meta-analysis showed a consistent result (pooled ROR 1.02, 95% CI 0.85 to 1.22, I^2 = 34 %, τ^2 = 0.064, and 95% prediction interval 0.52 to 1.51). The univariable meta-regression analyses showed that there were no statistically significant associations between any of the SR-level factors and the ROR (Supplementary file 3). There was no statistically significant difference between IPD meta-analytic results of C-RCTs and AD meta-analytic results of NC-RCTs (ROR 1.11, 95% CI 0.83 to 1.48, I^2 = 47 %, τ^2 = 0.132, and 95% prediction interval 0.40 to 1.82).

Discussion

Summary of findings

RCT features reflecting the high methodological quality of RCTs, such as a large number of participants, IF ≥ 10, and adequate allocation concealment, were independently associated with IPD contribution. However, we could not find consistent evidence of data availability bias due to IPD contribution in recent SRs with IPD meta-analyses.

Context with prior studies

Our findings of the RCT characteristics associated with IPD sharing are mostly in line with those from previous studies in the literature. We found that low quality RCTs, that had unclear or high risk of bias in participant selection and had lower impact, might be less likely to provide IPD. A previous research reported a higher prevalence of apparent errors, i.e. low quality, in the reporting of statistical results was associated with authors' reluctance to share research data in high-ranked psychology journals [20]. In addition, old studies might not provide IPD due to limited access to the trial data [21]. These previous findings, however, were based on a univariable analysis. We comprehensively investigated the RCT factors associated with data sharing and examined if the study quality made an independent contribution using a multivariable model. Our data also showed that such trends persisted in more recent cohorts.

Previous studies have raised concerns about data availability bias in effect estimates of meta-analyses using IPD. [2, 10, 13]. For example, a prior study showed a discrepancy of 20% in reporting of statistically significant outcomes between IPD and AD meta-analyses [2]. However, the observed difference might be only due to the different

statistical approaches usually taken in IPD meta-analyses [22]. Unlike previous studies, we directly compared the effect estimates between studies with and without IPD contribution, and showed there was no consistent evidence of data availability bias. Evidence users may be interested in the discrepancy between the IPD meta-analysis of C-RCTs and AD meta-analysis of all available studies as those are the measures presented in papers. However, logically speaking, the ROR of IPD meta-analysis of C-RCTs to AD meta-analysis of all RCTs should be even closer to the unity than the ROR of IPD meta-analysis of C-RCTs to AD meta-analysis of NC-RCTs that was examined in this study. Given the nonsignificant results of our findings, we expect the difference between the IPD meta-analysis of C-RCTs and AD meta-analysis of the whole evidence would be small.

Although we found that significantly more RCTs contributing IPD performed adequate allocation concealment to prevent selection bias that could lead to an overestimation of the intervention effect compared with RCTs not contributing IPD, we could not detect data availability bias in efficacy estimates [23]. A possible explanation for this finding is that most outcomes assessed in this study were objective. A previous study that examined the effects of inadequate allocation concealment on the effect estimates of interventions reported there had been little evidence of bias due to inadequate allocation concealment if a trial adopted objective outcomes [24]. Our findings resemble the previous report; however, the mechanism of this observation was not explained sufficiently. Another explanation might be that other risk of bias domains than allocation concealment may yield unbiased results for C-RCTs, and may cancel out the

data availability bias. Publication bias or outcome reporting bias might also hide the impact of availability bias.

Overall, no general tendency for data availability bias was observed, however, this does not mean "no data availability bias" for each SR. Although the I^2 observed was not substantial (<50%), that might be partly due to a small number of NC-RCTs included in a single SR [25]. The 95% prediction interval was somewhat wide for the combined ROR, which suggested the possible heterogeneity among SRs. Indeed, C-RCTs reported significantly larger effect estimates than NC-RCTs in Emberson 2014 [19]; in turn, C-RCTs reported almost half of the OR which NC-RCTs reported in De Luca 2011 [18]. In future IPD-meta-analyses, reviewers need to examine if such extreme unbalance in effect estimates may be present between C-RCTs and NC-RCTs in their own reviews.

Strengths and limitations of the study

This study has several strengths. This is the first study that assessed the data availability bias quantitatively. As there has been a push to share clinical trial data in many journals and registrations recently, the current study will be useful in understanding current data availability and its impact on effect estimates in IPD meta-analysis. Also, we conducted comprehensive search and rigorous selection of the eligible SRs with IPD meta-analysis and confirmed the robustness of the results using several statistical analyses. Both unadjusted and adjusted analysis showed that a positive result of the primary outcome of RCTs did not appear to affect IPD contribution. The direction or strength of the study findings may not be associated with

the authors' willingness to share the data in any category. Moreover, our detailed data extraction identified RCT features associated with IPD contribution. Readers of IPD meta-analyses would consider that RCTs contributing IPD and those not contributing IPD could be different in terms of a year of publication, number of participants, IF and adequate allocation concealment.

However, we should acknowledge several weaknesses. First, ROR in AD meta-analyses of C-RCTs to those in AD meta-analyses of NC-RCTs is a surrogate measure of availability bias. Data availability bias in the true effect estimates should ideally have been assessed using IPD from both RCTs that contributed IPD and those did not. However, it was infeasible to obtain IPD from RCTs that did not contribute the IPD to the SR. We used AD meta-analytic results to detect data availability bias because, it was previously reported that most results of IPD meta-analysis agreed with those of AD meta-analysis [2]. Thus, IPD of NC-RCTs may not affect the results derived from AD of NC-RCTs even if it was available. We also added a sensitivity analysis that compared IPD meta-analytic results of RCTs contributing IPD and AD meta-analytic results of RCTs not contributing to IPD, and showed a consistent result.

Second, we chose a dichotomous outcome from each SR measured as a pooled RR or OR to calculate ROR. As we needed to mathematically align the direction of intervention effect estimates and as the OR calculated for favorable events is reciprocally related to that which is calculated for unfavorable events, we adopted ROR to assess data availability bias [26]. Although this selection was not likely to confound the association between the efficacy and IPD contribution, further studies using other

outcome measures such as a difference in standardized mean differences for continuous variables would be required.

Thirdly, our study was possibly underpowered to detect the statistically significant difference. We intentionally retrieved all published SRs with pairwise IPD meta-analysis of interventional RCTs after 2011, because we aimed to obtain data from properly conducted SRs after the PRISMA reporting guideline was disseminated [15]. Thereby, having a threshold of a statistical significance using p-value < 0.05 in the pooled analysis might have had only low power to assess the data availability bias, given the limited number of SRs with IPD meta-analysis.

Lastly, our evidence may not be applied to the IPD meta-analyses of non-RCTs that are known to have a low IPD retrieval rate [10]. This issue should be investigated in future research.

Conclusion

Higher quality RCTs tended to contribute IPDs than lower quality RCTs. However, we found no consistent evidence of data availability bias in recent IPD meta-analyses. This does not mean the absence of availability bias in each and every single IPD meta-analysis. Further work that uses other effect measures such as subjective outcomes or continuous outcomes or that incorporates IPD meta-analyses of non-RCTs is warranted.

List of abbreviations

SR, systematic review; IPD, individual participant data; AD, aggregated data; RCT, randomized controlled trial; IF, impact factor; RR, risk ratio; OR, odds ratio; ROR, ratio of odds ratio; CI, confidence interval; IQR, interquartile range;

Ethics approval and consent to participate

Ethics approval is not applicable. This study is a research on research study.

Consent for publication

Not applicable

Availability of data and material

The data are available to academic researchers upon request.

Competing interests

None declared

Funding

None declared

Authors' contributions

YT had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YT, TF, AO, KO, SJN, and TAF. Acquisition of data: YT, TF, AO, KO, HI, ST, TI, YL, and CP. Analysis and interpretation of data: YT, TF, AO, KO, SJN and TAF. Drafting of the manuscript: YT, TF, AO, KO, and TAF. Critical revision of the manuscript for important intellectual content: SJN and TAF. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of this work.

Acknowledgements

We thank Ms. Keiko Fujii and Aya Ichizawa for obtaining the full-text articles.

Figure titles and legends

Figure 1. Flow diagram of the present study

Abbreviations: IPD, individual participant data; RCT, randomized controlled trial; SR, systematic review; MA, meta-analysis; RR, risk ratio; OR, odds ratio; NMA, network meta-analysis

Figure 2. Comparison of treatment effect estimates between studies providing IPD or not

Difference in treatment effect estimates is expressed as ROR. An ROR <1 indicates larger treatment effect estimates in studies contributing IPD. Abbreviations: IPD, individual participant data; ROR, ratio of odds ratio

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What is new?

Key findings

- Trial-level characteristics such as a recent year of publication, large number of participants, high impact factor, and adequate allocation concealment were independently associated with individual participant data (IPD) contribution to systematic reviews (SRs) with IPD meta-analyses.
- We could not find consistent evidence of a data availability bias; the effect estimates of trials contributing IPD were not statistically different from those not contributing IPD in the same systematic reviews (SRs).

What this study adds to what was known?

- Methodological qualities of trials were associated with the contribution of IPD to IPD meta-analysis, but effect estimates might not affect this result.
- While previous studies suggested the presence of a data availability bias only narratively or theoretically, we systematically compared the effect estimates between studies with and without IPD contribution and showed that there was no consistent evidence of a data availability bias.

What is the implication and what should change now?

- Investigators should be aware of the differences in methodological qualities between RCTs with and without IPD contribution when conducting IPD meta-analyses.
- While we did not detect any systematic data availability bias in the recednt IPD meta-analyses, effect estimates in some IPD meta-analyses might still be biased in

either direction due to the data availability.

No consistent evidence of data availability bias existed in recent individual participant data meta-analyses: A meta-epidemiological study

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Abstract (218 words)

Objectives

To assess trial-level factors associated with the contribution of individual participant data (IPD) to IPD meta-analyses, and to quantify the data availability bias, namely the difference between the effect estimates of trials contributing IPD and those not contributing IPD in the same systematic reviews (SRs).

Design and Setting

We included SRs of randomized controlled trials (RCTs) with IPD meta-analyses since 2011. We extracted trial-level characteristics and examined their association with IPD contribution. To assess the data availability bias, we retrieved odds ratios from the original RCT papers, calculated the ratio of odds ratios (RORs) between aggregate data (AD) meta-analyses of RCTs contributing IPD and those of RCTs not contributing IPD for each SR, and meta-analytically synthesized RORs.

Results

Of 728 eligible RCTs included in 31 SRs, 321 (44%) contributed IPD, while 407 (56%) did not. A recent publication year, larger number of

participants, adequate allocation concealment, and impact factor ≥10 were associated with IPD contribution. We found the SRs yielded widely different estimates of RORs. Overall, there was no significant difference in the pooled effect estimates of AD meta-analyses between RCTs contributing and not contributing IPD (ROR 1.01, 95% confidence interval 0.86–1.19).

Conclusions

There was no consistent evidence of a data availability bias in recent IPD meta-analyses of RCTs with dichotomous outcomes. Higher methodological qualities of trials were associated with IPD contribution.

Keywords

Individual participant data, systematic review, meta-analysis, data availability bias

What is new?

Key findings

- Trial-level characteristics such as a recent year of publication, large number of participants, high impact factor, and adequate allocation concealment were independently associated with individual participant data (IPD) contribution to systematic reviews (SRs) with IPD meta-analyses.
- We could not find consistent evidence of a data availability bias; the effect

estimates of trials contributing IPD were not statistically different from those not contributing IPD in the same systematic reviews (SRs).

What this study adds to what was known?

- Methodological qualities of trials were associated with the contribution of IPD to IPD meta-analysis, but effect estimates might not affect this result.
- While previous studies suggested the presence of a data availability bias only narratively or theoretically, we systematically compared the effect estimates between studies with and without IPD contribution and showed that there was no consistent evidence of a data availability bias.

What is the implication and what should change now?

- Investigators should be aware of the differences in methodological qualities between RCTs with and without IPD contribution when conducting IPD meta-analyses.
- While we did not detect any systematic data availability bias in the recednt IPD meta-analyses, effect estimates in some IPD meta-analyses might still be biased in either direction due to the data availability.

Background

Individual participant data (IPD) meta-analyses are considered to increase the statistical power of systematic reviews (SRs) as well as enable more valid subgroup

analyses, in comparison with meta-analyses that are based on aggregate data (AD) extracted from published trial reports [1-3]. Encouragement to share IPD from clinical studies has risen in the scientific literature, and the number of SRs with IPD meta-analyses has increased dramatically over the past few years [4-9].

However, SRs with IPD meta-analyses require the review authors to spend substantial time and effort to contact and request IPD from the authors of the original studies [1, 10, 11] with no certainty that all original authors will contribute their data. Indeed, only 25% of the 760 IPD meta-analyses conducted between 1987 and 2015 retrieved 100% of the data from the relevant trials, and 43% retrieved 80% of the data of relevant trials [10].

The risk of data availability bias increases when all IPD data cannot be procured [2, 10, 12, 13]. The data sharing policy of RCTs might be influenced by the views of the investigators, as well as by the resources or results of the RCTs [5]. If unavailability of IPD is associated with the direction or the size of the intervention effect, studies that are available for IPD analyses may not be representative of the whole evidence, and the results of such IPD meta-analyses may be misleading. However, the difference in characteristics between RCTs contributing and not contributing IPD has not been investigated.

To date, data availability bias has been discussed only anecdotally, narratively or theoretically and there has been no systematic examination aiming to quantify the impact of this bias on the effect estimates of meta-analyses [2, 6, 10, 13, 14]. The purposes of this study were, therefore, two-fold: (i) To assess RCT-level factors associated with the contribution of IPD, and (ii) to examine data availability bias in IPD meta-analysis with less than 100% retrieval rate.

Methods

Design

A meta-epidemiological study

Eligibility criteria

All therapeutic RCTs included in SRs that fulfilled all following criteria were eligible: (i) SRs with IPD meta-analyses, (ii) SRs that included only RCTs comparing an active intervention against a control condition in terms of a dichotomous outcome, (iii) SRs that reported a full reference list of the included RCTs, and (iv) SRs published in English. We excluded the following SRs: (v) SRs published before 2011, (vi) SRs where all included RCTs provided IPD data, (vii) SRs of diagnostic or prognostic studies, and (viii) SRs with network meta-analyses. A cutoff year of 2011 was selected because a reporting guideline for SRs, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, was first published in 2009 [15]. We allowed two years for the dissemination of this guideline.

Search methods

We used the reference list from a recent comprehensive review of IPD meta-analyses conducted by Nevitt et al[10]. We also performed an updated search of MEDLINE via Ovid using the same search strategy as the above review to identify relevant SRs as of 10th March 2018. Supplementary file 1 shows the search terms we used.

Study selection

Two pairs of researchers (YT-TF and KO-AO) independently screened the titles and abstracts of articles identified by the updated search. We pooled the potentially eligible SRs and the reference list from the review conducted by Nevitt et al [10]. We then independently assessed eligibility based on a full-text review.

Data extraction

Eight researchers (YT, TF, KO, AO, ST, TI, YL and CP) independently extracted the following RCT-level factors from the included RCTs; year of publication, sample size, whether the primary outcomes of the RCT was positive or not, allocation concealment, industrial sponsorship, publication status (full-publication or not), data sharing statement (available, unavailable, or unclear), journal impact factor (IF), and language. We selected the primary outcomes of the RCTs using the following hierarchy: an outcome that was mentioned (1) as primary, (2) in the title, (3) in the objective, (4) first in the abstract, (5) first in the text. We defined the primary outcome as positive when the selected primary outcome was statistically significant in superiority trials or within the noninferiority margin in noninferiority trials. We chose not blinding but adequate allocation concealment as a marker of study quality because the feasibility of blinding and its impact on outcomes varies across research questions. We used the IF of the

journal from 2017 Journal Citation Reports® Science Edition (Thomson Reuters, 2018) and assigned an IF of zero to conference abstracts and unpublished studies.

We also extracted the following SR-level factors from the included SRs: year of publication, the number of included RCTs, types of review (pharmacological or non-pharmacological interventions, adult or pediatric, and Cochrane or non-Cochrane), and funding (yes/no).

To examine any discrepancy between the effect estimates of RCTs contributing IPD (C-RCTs) and those not contributing IPD (NC-RCTs), we selected a single outcome per SR. As the SR might have reported several outcomes, we selected the single primary outcome that fulfilled all the following criteria: (1) An efficacy outcome measured as a pooled risk ratio (RR) or odds ratio (OR), (2) Not a composite outcome, and (3) Not an outcome of adverse events or subgroup analysis. We did not adopt a composite outcome because the definition or components of the outcome was expected to vary across trials. In cases where the primary outcome did not meet these criteria, we adopted the outcome with the largest number of trials or the first outcome described which met these criteria.

For the single selected outcome in each SR, we extracted the number of events and participants in the intervention and control groups from the original published journal articles or conference abstracts of both C-RCTs and NC-RCTs. If the number of events or participants was missing, or if the selected outcome was not reported in the original RCT but provided in the IPD meta-analysis, we imputed them from the information or outcome data presented in the IPD-SR. We also extracted the pooled RR or OR from the reported IPD meta-analysis. We converted the pooled RR to OR using the observed control event rate [16].

Statistical analysis

We first described RCT characteristics, each classified by whether the RCT contributed IPD to the SR or not. We then explored the RCT-level factors (see Data Extraction) associated with the contribution of IPD using univariable mixed-effect logistic regression with a random intercept for SRs to account for the clustering effects of RCTs within each SR, and a multivariable mixed-effects logistic regression model with fixed factors (year of publication, sample size, positive primary outcome [yes or no], adequate allocation concealment [yes or no], industrial sponsorship [yes or no], publication status [full-publication or not], data sharing statement [available or not), IF [no IF, < 5, 5 ≤ to < 10, or 10 ≤], language [published in English or not]), and a random intercept for SRs.

We calculated odds ratios using the number of events and the number of patients aggregated from the original RCT papers and pooled them in aggregate data (AD) meta-analyses using random-effects models. Each OR was recalculated so that an OR <1 indicated that the intervention arm was favored. To assess data availability bias quantitatively, we calculated and pooled the ratio of odds ratios (ROR) in AD meta-analyses of C-RCTs to those in AD meta-analyses of NC-RCTs using the following two-step approach proposed by Sterne et al [17]. First, we estimated an ROR in each AD meta-analysis by using a random-effect meta-regression. An ROR <1 indicated a larger treatment effect estimate in AD meta-analyses of C-RCTs than in NC-RCTs. We estimated the combined ROR across SRs and the 95 % confidence interval (CI) with a

random-effects meta-analysis model. We used the I^2 statistic, τ^2 –statistic and 95% prediction interval to quantify the heterogeneity between SRs.

We expressed continuous variables as mean (standard deviation) for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data and categorical variables as numbers with the percentage. We considered a two-sided p value < 0.05 as a statistically significant difference. We used Stata/SE, V.14.0 (StataCorp, College Station, TexasX, USA) for all analyses.

Sensitivity analysis

To examine the robustness of the estimated ROR, we performed the following sensitivity analyses. First, we adjusted SR-level factors (year of publication, the number of included studies, types of review [Cochrane or non-Cochrane, pharmacological or not, and pediatric or not], or funding) that assumed to be confounders of the association between IPD contribution and the ROR using the meta-regression model. Second, we excluded RCTs for which we imputed the results of AD meta-analysis with those reported in IPD meta-analysis. Third, we examined a discrepancy between IPD meta-analytic results of C-RCTs and AD meta-analytic results of NC-RCTs using the same methods for the primary outcome.

Additional analyses

As a post-hoc analysis, we used log-transformed data of the number of randomized participants and impact factors instead of categorized data, and added them into the mixed effects multivariable model to examine their associations with the contribution of IPD.

The study was registered in UMIN-CTR as UMIN000028325 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000036147).

Results

Results of searches

Figure 1 shows the flow diagram of the present study. We identified 2349 possible SRs with IPD meta-analyses including 102 references from the previous study [10]. We assessed the eligibility of 268 SRs with IPD meta-analyses that remained after screening of titles and abstracts, and included 37 IPD-SRs for a total of 728 RCTs. For the assessment of data availability bias, six SRs had only one or two RCTs that reported the selected outcome, which made it impossible to calculate the ROR using a random effects meta-regression model. Among 631 RCTs included in the remaining 31 SRs, 264 did not report the selected outcome. Consequently, we included 367 RCTs that reported the selected outcome in the analysis for data availability bias.

Characteristics of included IPD systematic reviews

Supplementary file 2 shows the characteristics of the included IPD-SRs. The number of included RCTs in the IPD-SRs varied from 5 to 103 (median 13, IQR 11 to 21), and the IPD retrieval rate ranged from 10 % to 92 % (median 71 %, IQR 50 % to 81 %). Twenty-five (68 %) IPD-SRs had funding, 21 (57 %) focused on pharmacological interventions, 7 (19%) were Cochrane reviews, and 2 (5 %) were in pediatric areas.

Characteristics of included studies and IPD contribution

Of 728 RCTs included, 321 contributed IPD and 407 did not. Table 1 summarizes the characteristics of the included RCTs and the association with the IPD contribution. C-RCTs were likely to have a recent year of publication, a larger sample size, adequate allocation concealment, full publication status, higher impact factor, and sponsorships as compared to NC-RCTs. We next examined the association between RCT characteristics and IPD contribution with logistic regressions. As shown in Table 1, a recent publication year, larger number of participants randomized, adequate allocation concealment, and high impact factor (≥10) compared to IF <5 were independently associated with IPD contribution. On the other hand, whether the primary outcomes were positive was not associated with IPD contribution (adjusted OR 1.06, 95% CI 0.72 to 1.55). The association of the number of randomized participants or that of impact factors with IPD contribution remained unchanged when we used log-transformed data instead of categorized data (OR 1.34, 95% CI 1.07 to 1.69, and OR 1.28, 95% CI 1.03 to 1.58, respectively)

Table 1 Characteristics of included RCTs and the associations with IPD contribution

Characteristics	C-RCTs (n = 321)	NC-RCTs (n = 407)	Univariable*	Multivariable†
Years since publication, mean (SD)	10.0 (6.9)	11.4 (8.9)	0.94 (0.92 to 0.97)	0.96 (0.93 to 0.99)
Number of randomized participants				
1st quartile	12 to 101	5 to 60	Ref	Ref
2nd quartile	102 to 228	60 to 115	1.85 (1.12 to 3.06)	1.54 (0.90 to 2.63)
3rd quartile	228 to 619	116 to 250	2.89 (1.71 to 4.90)	1.90 (1.07 to 3.37)
4th quartile	620 to 20536	250 to 17354	5.09 (2.83 to 9.15)	2.28 (1.16 to 4.47)
Adequate allocation concealment	230 (57)	107 (33)	3.34 (2.27 to 4.91)	2.33 (1.53 to 3.55)
Publication status				
Full publication	375 (92)	281 (88)	Ref	Ref
Conference abstract	23 (6)	35 (10)	0.37 (0.9 to 0.71)	0.82 (0.27 to 2.51)
Unpublished	9 (2)	5 (2)	0.66 (0.18 to 2.38)	n/a‡
Impact factor§				
<5	142 (35)	161 (50)	Ref	Ref
≥5 to <10	66 (16)	42 (13)	1.57 (0.93 to 2.65)	1.52 (0.87 to 2.65)
≥10	152 (37)	48 (15)	3.13 (1.86 to 5.24)	2.18 (1.22 to 3.88)
No impact factor	47 (12)	70 (22)	0.59 (0.35 to 1.00)	0.84 (0.33 to 2.14)
Industrial sponsorship	119 (29)	68 (21)	2.13 (1.32 to 3.45)	1.40 (0.84 to 2.34)
Published in English	399 (98)	307 (96)	2.29 (0.77 to 6.81)	0.99 (0.26 to 3.81)
Statement to share the data	4 (1)	3 (1)	1.03 (0.19 to 5.56)	0.61 (0.10 to 3.80)
Positive results in the primary outcome‖‖	216 (55)	148 (47)	1.16 (0.82 to 1.66)	1.06 (0.72 to 1.55)

Note: Values for categorical variables and continuous variables are given as number (percentage) and mean (SD) or median (IQR). *Using univariable mixed effects logistic regression with a random intercept for the systematic review. †Using multivariable mixed effects logistic regression model with fixed factors (year of publication, sample size, adequate allocation concealment, publication status (full-publication or not), impact factor (no impact factor, < 5, 5 ≤ to < 10, or 10 ≤), industrial sponsorship, language (written in English or not), data sharing statement (available or not) and whether the primary outcomes in the RCTs were positive) and a random intercept for the systematic review. ‡No sufficient data was available to conduct the multivariable analysis §Impact factor in 2017. We assigned an impact factor of zero to conference abstracts and unpublished studies. ‖‖Any of the primary outcomes were positive when the selected primary outcome was statistically significant in efficacy trials or within the noninferiority margin in noninferiority trials. Abbreviations: RCT, randomized controlled trial; IPD, individual participant data; C-RCT, RCTs contributing IPD; NC-RCT, RCTs not contributing IPD; SD, standard deviation; IQR, interquartile range.

Data availability bias

Figure 2 shows the RORs that compared AD meta-analyses of C-RCTs and those of NC-RCTs among 31 SRs including 377 RCTs. We found the SRs yielded widely different estimates of RORs. For example, one SR showed a significantly large

treatment effect in C-RCTs compared with NC-RCTs [18], whereas one SR showed a significantly small effect of C-RCTs compared with NC-RCTs [19]. The remaining 29 SRs showed a non-significant difference in treatment effects between C-RCTs and NC-RCTs. Overall, we found no statistically significant association between IPD contribution and the size or direction of treatment effects which could be estimated from AD meta-analyses of the trials within each SR (pooled ROR 1.01, 95 % CI 0.86 to 1.19, I^2 = 27 %, τ^2 = 0.044, and 95% prediction interval 0.60 to 1.42) (Fig 2).

Sensitivity analyses

A sensitivity analysis excluding the data imputed from the IPD meta-analysis showed a consistent result (pooled ROR 1.02, 95% CI 0.85 to 1.22, I^2 = 34 %, τ^2 = 0.064, and 95% prediction interval 0.52 to 1.51). The univariable meta-regression analyses showed that there were no statistically significant associations between any of the SR-level factors and the ROR (Supplementary file 3). There was no statistically significant difference between IPD meta-analytic results of C-RCTs and AD meta-analytic results of NC-RCTs (ROR 1.11, 95% CI 0.83 to 1.48, I^2 = 47 %, τ^2 = 0.132, and 95% prediction interval 0.40 to 1.82).

Discussion

Summary of findings

RCT features reflecting the high methodological quality of RCTs, such as a large number of participants, IF ≥ 10, and adequate allocation concealment, were independently associated with IPD contribution. However, we could not find consistent evidence of data availability bias due to IPD contribution in recent SRs with IPD meta-analyses.

Context with prior studies

Our findings of the RCT characteristics associated with IPD sharing are mostly in line with those from previous studies in the literature. We found that low quality RCTs, that had unclear or high risk of bias in participant selection and had lower impact, might be less likely to provide IPD. A previous research reported a higher prevalence of apparent errors, i.e. low quality, in the reporting of statistical results was associated with authors' reluctance to share research data in high-ranked psychology journals [20]. In addition, old studies might not provide IPD due to limited access to the trial data [21]. These previous findings, however, were based on a univariable analysis. We comprehensively investigated the RCT factors associated with data sharing and examined if the study quality made an independent contribution using a multivariable model. Our data also showed that such trends persisted in more recent cohorts.

Previous studies have raised concerns about data availability bias in effect estimates of meta-analyses using IPD. [2, 10, 13]. For example, a prior study showed a discrepancy of 20% in reporting of statistically significant outcomes between IPD and AD meta-analyses [2]. However, the observed difference might be only due to the different

statistical approaches usually taken in IPD meta-analyses [22]. Unlike previous studies, we directly compared the effect estimates between studies with and without IPD contribution, and showed there was no consistent evidence of data availability bias. Evidence users may be interested in the discrepancy between the IPD meta-analysis of C-RCTs and AD meta-analysis of all available studies as those are the measures presented in papers. However, logically speaking, the ROR of IPD meta-analysis of C-RCTs to AD meta-analysis of all RCTs should be even closer to the unity than the ROR of IPD meta-analysis of C-RCTs to AD meta-analysis of NC-RCTs that was examined in this study. Given the nonsignificant results of our findings, we expect the difference between the IPD meta-analysis of C-RCTs and AD meta-analysis of the whole evidence would be small.

Although we found that significantly more RCTs contributing IPD performed adequate allocation concealment to prevent selection bias that could lead to an overestimation of the intervention effect compared with RCTs not contributing IPD, we could not detect data availability bias in efficacy estimates [23]. A possible explanation for this finding is that most outcomes assessed in this study were objective. A previous study that examined the effects of inadequate allocation concealment on the effect estimates of interventions reported there had been little evidence of bias due to inadequate allocation concealment if a trial adopted objective outcomes [24]. Our findings resemble the previous report; however, the mechanism of this observation was not explained sufficiently. Another explanation might be that other risk of bias domains than allocation concealment may yield unbiased results for C-RCTs, and may cancel out the

data availability bias. Publication bias or outcome reporting bias might also hide the impact of availability bias.

Overall, no general tendency for data availability bias was observed, however, this does not mean "no data availability bias" for each SR. Although the I^2 observed was not substantial (<50%), that might be partly due to a small number of NC-RCTs included in a single SR [25]. The 95% prediction interval was somewhat wide for the combined ROR, which suggested the possible heterogeneity among SRs. Indeed, C-RCTs reported significantly larger effect estimates than NC-RCTs in Emberson 2014 [19]; in turn, C-RCTs reported almost half of the OR which NC-RCTs reported in De Luca 2011 [18]. In future IPD-meta-analyses, reviewers need to examine if such extreme unbalance in effect estimates may be present between C-RCTs and NC-RCTs in their own reviews.

Strengths and limitations of the study

This study has several strengths. This is the first study that assessed the data availability bias quantitatively. As there has been a push to share clinical trial data in many journals and registrations recently, the current study will be useful in understanding current data availability and its impact on effect estimates in IPD meta-analysis. Also, we conducted comprehensive search and rigorous selection of the eligible SRs with IPD meta-analysis and confirmed the robustness of the results using several statistical analyses. Both unadjusted and adjusted analysis showed that a positive result of the primary outcome of RCTs did not appear to affect IPD contribution. The direction or strength of the study findings may not be associated with

the authors' willingness to share the data in any category. Moreover, our detailed data extraction identified RCT features associated with IPD contribution. Readers of IPD meta-analyses would consider that RCTs contributing IPD and those not contributing IPD could be different in terms of a year of publication, number of participants, IF and adequate allocation concealment.

However, we should acknowledge several weaknesses. First, ROR in AD meta-analyses of C-RCTs to those in AD meta-analyses of NC-RCTs is a surrogate measure of availability bias. Data availability bias in the true effect estimates should ideally have been assessed using IPD from both RCTs that contributed IPD and those did not. However, it was infeasible to obtain IPD from RCTs that did not contribute the IPD to the SR. We used AD meta-analytic results to detect data availability bias because, it was previously reported that most results of IPD meta-analysis agreed with those of AD meta-analysis [2]. Thus, IPD of NC-RCTs may not affect the results derived from AD of NC-RCTs even if it was available. We also added a sensitivity analysis that compared IPD meta-analytic results of RCTs contributing IPD and AD meta-analytic results of RCTs not contributing to IPD, and showed a consistent result.

Second, we chose a dichotomous outcome from each SR measured as a pooled RR or OR to calculate ROR. As we needed to mathematically align the direction of intervention effect estimates and as the OR calculated for favorable events is reciprocally related to that which is calculated for unfavorable events, we adopted ROR to assess data availability bias [26]. Although this selection was not likely to confound the association between the efficacy and IPD contribution, further studies using other

outcome measures such as a difference in standardized mean differences for continuous variables would be required.

Thirdly, our study was possibly underpowered to detect the statistically significant difference. We intentionally retrieved all published SRs with pairwise IPD meta-analysis of interventional RCTs after 2011, because we aimed to obtain data from properly conducted SRs after the PRISMA reporting guideline was disseminated [15]. Thereby, having a threshold of a statistical significance using p-value < 0.05 in the pooled analysis might have had only low power to assess the data availability bias, given the limited number of SRs with IPD meta-analysis.

Lastly, our evidence may not be applied to the IPD meta-analyses of non-RCTs that are known to have a low IPD retrieval rate [10]. This issue should be investigated in future research.

Conclusion

Higher quality RCTs tended to contribute IPDs than lower quality RCTs. However, we found no consistent evidence of data availability bias in recent IPD meta-analyses. This does not mean the absence of availability bias in each and every single IPD meta-analysis. Further work that uses other effect measures such as subjective outcomes or continuous outcomes or that incorporates IPD meta-analyses of non-RCTs is warranted.

List of abbreviations

SR, systematic review; IPD, individual participant data; AD, aggregated data; RCT, randomized controlled trial; IF, impact factor; RR, risk ratio; OR, odds ratio; ROR, ratio of odds ratio; CI, confidence interval; IQR, interquartile range;

Ethics approval and consent to participate

Ethics approval is not applicable. This study is a research on research study.

Consent for publication

Not applicable

Availability of data and material

The data are available to academic researchers upon request.

Competing interests

None declared

Funding

None declared

Authors' contributions

YT had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YT, TF, AO, KO, SJN, and TAF. Acquisition of data: YT, TF, AO, KO, HI, ST, TI, YL, and CP. Analysis and interpretation of data: YT, TF, AO, KO, SJN and TAF. Drafting of the manuscript: YT, TF, AO, KO, and TAF. Critical revision of the manuscript for important intellectual content: SJN and TAF. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of this work.

Acknowledgements

We thank Ms. Keiko Fujii and Aya Ichizawa for obtaining the full-text articles.

Figure titles and legends

Figure 1. Flow diagram of the present study

Abbreviations: IPD, individual participant data; RCT, randomized controlled trial; SR, systematic review; MA, meta-analysis; RR, risk ratio; OR, odds ratio; NMA, network meta-analysis

Figure 2. Comparison of treatment effect estimates between studies providing IPD or not

Difference in treatment effect estimates is expressed as ROR. An ROR <1 indicates larger treatment effect estimates in studies contributing IPD. Abbreviations: IPD, individual participant data; ROR, ratio of odds ratio

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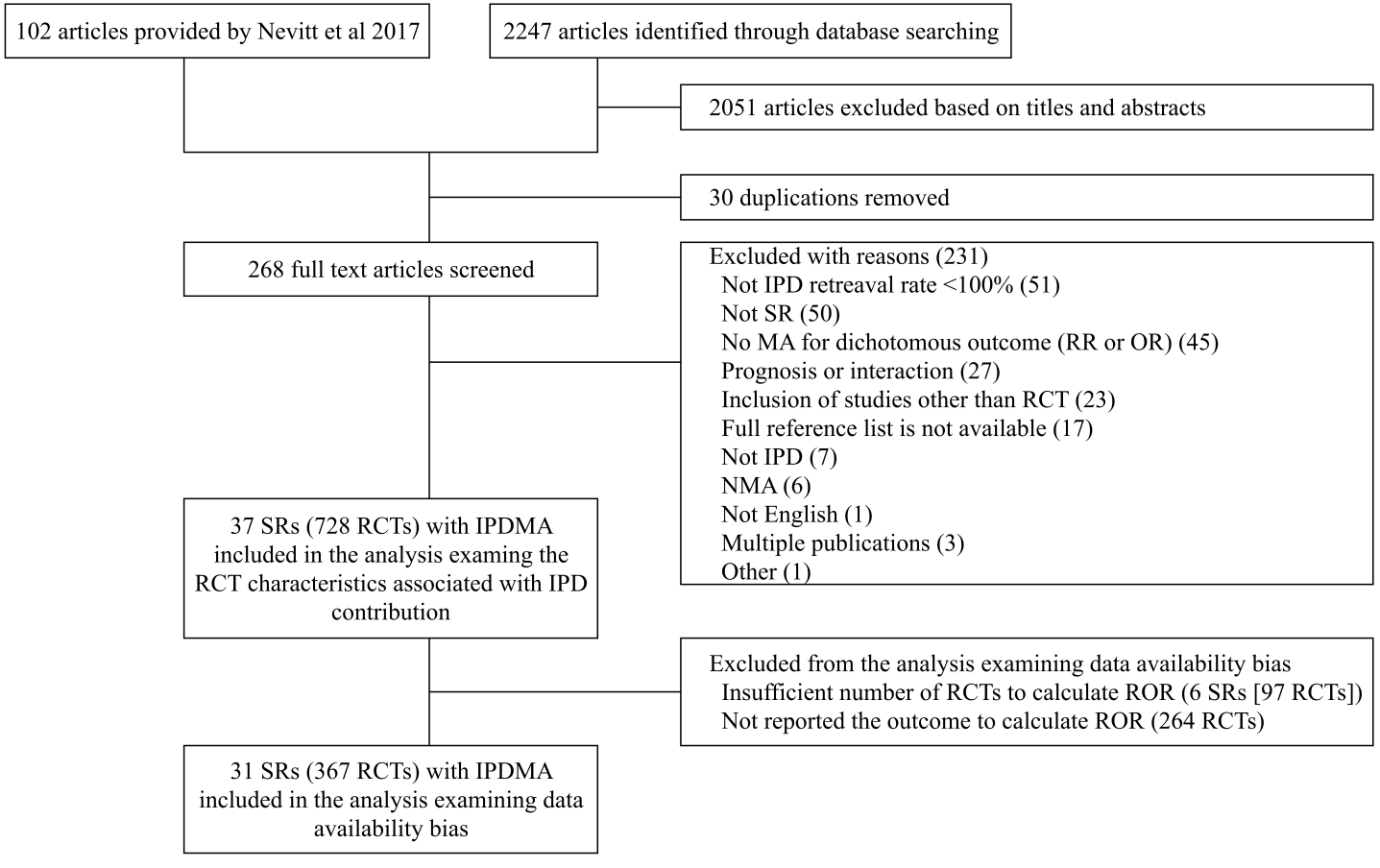
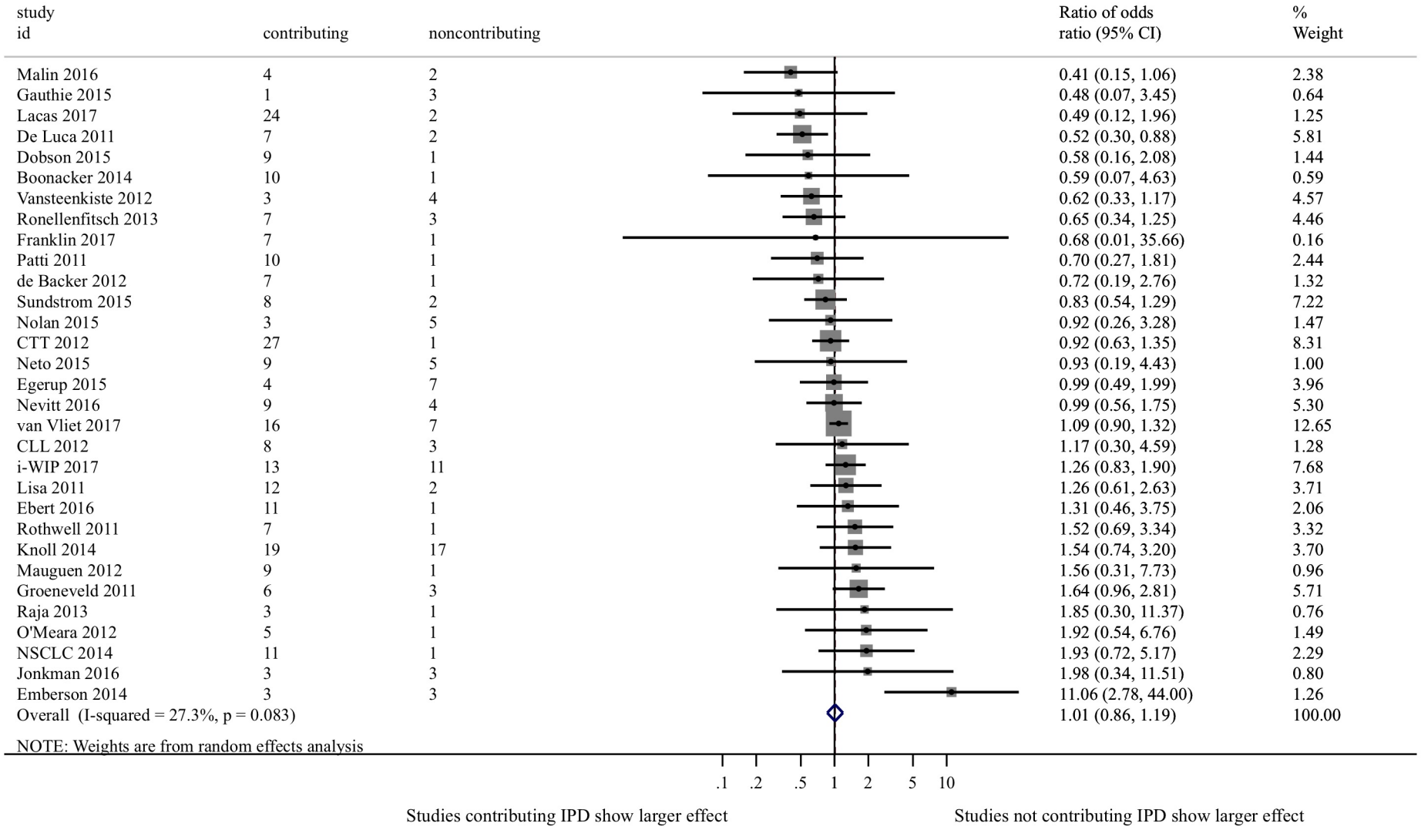

102 articles provided by Nevitt et al 2017
2247 articles identified through database searching
2051 articles excluded based on titles and abstracts
30 duplications removed
268 full text articles screened
Excluded with reasons (231)
Not IPD retreaval rate <100% (51)
Not SR (50)
No MA for dichotomous outcome (RR or OR) (45)
Prognosis or interaction (27)
Inclusion of studies other than RCT (23)
Full reference list is not available (17)
Not IPD (7)
NMA (6)
Not English (1)
Multiple publications (3)
Other (1)
37 SRs (728 RCTs) with IPDMA included in the analysis examing the RCT characteristics associated with IPD contribution
Excluded from the analysis examining data availability bias
Insufficient number of RCTs to calculate ROR (6 SRs [97 RCTs])
Not reported the outcome to calculate ROR (264 RCTs)
31 SRs (367 RCTs) with IPDMA included in the analysis examining data availability bias


study id
contributing
noncontributing
Ratio of odds ratio (95% CI)
% Weight
Malin 2016 4 2 0.41 (0.15, 1.06) 2.38
Gauthie 2015 1 3 0.48 (0.07, 3.45) 0.64
Lacas 2017 24 2 0.49 (0.12, 1.96) 1.25
De Luca 2011 7 2 0.52 (0.30, 0.88) 5.81
Dobson 2015 9 1 0.58 (0.16, 2.08) 1.44
Boonacker 2014 10 1 0.59 (0.07, 4.63) 0.59
Vansteenkiste 2012 3 4 0.62 (0.33, 1.17) 4.57
Ronellenfitsch 2013 7 3 0.65 (0.34, 1.25) 4.46
Franklin 2017 7 1 0.68 (0.01, 35.66) 0.16
Patti 2011 10 1 0.70 (0.27, 1.81) 2.44
de Backer 2012 7 1 0.72 (0.19, 2.76) 1.32
Sundstrom 2015 8 2 0.83 (0.54, 1.29) 7.22
Nolan 2015 3 5 0.92 (0.26, 3.28) 1.47
CTT 2012 27 1 0.92 (0.63, 1.35) 8.31
Neto 2015 9 5 0.93 (0.19, 4.43) 1.00
Egerup 2015 4 7 0.99 (0.49, 1.99) 3.96
Nevitt 2016 9 4 0.99 (0.56, 1.75) 5.30
van Vliet 2017 16 7 1.09 (0.90, 1.32) 12.65
CLL 2012 8 3 1.17 (0.30, 4.59) 1.28
i-WIP 2017 13 11 1.26 (0.83, 1.90) 7.68
Lisa 2011 12 2 1.26 (0.61, 2.63) 3.71
Ebert 2016 11 1 1.31 (0.46, 3.75) 2.06
Rothwell 2011 7 1 1.52 (0.69, 3.34) 3.32
Knoll 2014 19 17 1.54 (0.74, 3.20) 3.70
Mauguen 2012 9 1 1.56 (0.31, 7.73) 0.96
Groeneveld 2011 6 3 1.64 (0.96, 2.81) 5.71
Raja 2013 3 1 1.85 (0.30, 11.37) 0.76
O'Meara 2012 5 1 1.92 (0.54, 6.76) 1.49
NSCLC 2014 11 1 1.93 (0.72, 5.17) 2.29
Jonkman 2016 3 3 1.98 (0.34, 11.51) 0.80
Emberson 2014 3 3 11.06 (2.78, 44.00) 1.26
Overall (I-squared = 27.3%, p = 0.083) 1.01 (0.86, 1.19) 100.00
NOTE: Weights are from random effects analysis
.1 .2 .5 1 2 5 10
Studies contributing IPD show larger effect
Studies not contributing IPD show larger effect

Conflict of interests declaration

Yasushi Tsujimoto

Competing interests: None

Tomoko Fujii

Competing interests: None

Akira Onishi

Competing interests: None

Kenji Omae

Competing interests: None

Yan Luo

Competing interests: None

Hissei Imai

Competing interests: None

Sei Takahashi

Competing interests: None

Takahiro Itaya

Competing interests: None

Claire Pinson

Competing interests: None

Sarah J Nevitt

Competing interests: None

Toshi A Furukawa

Competing interests: None

Authorship statement

Yasushi Tsujimoto: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing - original draft. Tomoko Fujii: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing - original draft. Akira Onishi: Conceptualization, Data cu- ration, Investigation, Methodology, Project administration, Writing - review & editing. Kenji Omae: Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. Yan Luo: Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. Hissei Imai: Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. Sei Takahashi: Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. Takahiro Itaya: Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. Claire Pinson: Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. Sarah J Nevitt: Conceptualization, Investigation, Supervision, Writing - review & editing. Toshi A. Furukawa: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing - review & editing

Supplementary file 1. Search strategy of the present study

1. (individual patient$ adj6 data).ti,ab.
2. (individual patient$ adj6 report$).ti,ab.
3. (individual patient$ adj6 outcome$).ti,ab.
4. (individual patient$ adj6 level$).ti,ab.
5. individual participant data.ti,ab.
6. ipd.ti,ab.
7. (individual subject$ adj6 data).ti,ab.
8. (individual subject$ adj6 report$).ti,ab.
9. (individual subject$ adj6 outcome$).ti,ab.
10. (individual subject$ adj6 level$).ti,ab.
11. (raw patient$ adj6 data).ti,ab.
12. (raw patient$ adj6 report$).ti,ab.
13. (raw patient$ adj6 outcome$).ti,ab.
14. (raw patient$ adj6 level$).ti,ab.
15. (raw subject$ adj6 data).ti,ab.
16. (raw subject$ adj6 report$).ti,ab.
17. (raw subject$ adj6 outcome$).ti,ab.
18. (raw subject$ adj6 level$).ti,ab.

19. idiopathic.ti,ab.

20. immediate pigment darkening.ti,ab.

21. intermittent peritoneal dialysis.ti,ab.

22. invasive pneumococcal disease.ti,ab.

23. indirect photometric detection.ti,ab.

24. interaural phase disparity.ti,ab.

25. or/1-18

26. or/19-24

27. 25 not 26

28. limit 27 to ed=20140611-20180310