

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
Corresponding Author	Toshi A. Furukawa
Order of Authors	Yasushi Tsujimoto, Tomoko Fujii, Akira Onishi, Kenji Omae, Yan Luo, Hissei Imai, Sei Takahashi, Takahiro Itaya, Claire Pinson, Sarah Nevitt, Toshi A. Furukawa
Suggested reviewers	Anna Chaimani, Ian Saldanha, Dimitris Mavridis
Opposed reviewers	Spyridon Papageorgiou

Submission Files Included in this PDF

File Name [File Type]

- Cover_letter_final copy.docx [Cover Letter]
- Response letter_revise_3rd.docx [Response to Reviewers]
- Manuscript_JCE_revised_v6_highlighted.docx [Revised Manuscript with Changes Marked]
- What is new_revised.docx [Highlights]
- Manuscript_JCE_revised_v6.docx [Manuscript File]
- Fig 1.jpg [Figure]
- Fig2_revised.jpg [Figure]
- Conflict of interest form.docx [Conflict of Interest]
- Authors statement.docx [Author Statement]
- Supplementary file 1.docx [e-Component]

Submission Files Not Included in this PDF

File Name [File Type]

Supplementary file 3.xlsx [e-Component]

Supplementary file 2_revised.xlsx [e-Component]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
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,

Submitting author: Yasushi Tsujimoto, Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Tel: +81-75-753-9467

Fax: +81-75-753-4644

Email: yssh0108@yahoo.co.jp

Correspondence: Toshi A Furukawa, Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Phone: +81-75-753-9491

Fax: +81-75-753-4641

Email: furukawa@kuhp.kyoto-u.ac.jp

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).

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.

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

Authors:

Yasushi Tsujimoto^{1,2}, yssh0108@yahoo.co.jp

Tomoko Fujii³, tofujii-ky@umin.net

Akira Onishi⁴, telonishi@gmail.com

Kenji Omae^{1,5}, oranz416@gmail.com

Yan Luo⁶, lilaclu@gmail.com

Hissei Imai⁶, hissei.imai@gmail.com

Sei Takahashi¹, heavens.prison.septem@gmail.com

Takahiro Itaya¹, itaya.takahiro.53a@st.kyoto-u.ac.jp

Claire Pinson⁷, clairepinson@college.harvard.edu

Sarah J Nevitt⁸, Sarah.Nevitt@liverpool.ac.uk

Toshi A Furukawa⁶, furukawa@kuhp.kyoto-u.ac.jp

1. Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine, Japan
2. Department of Nephrology and Dialysis, Kyoritsu Hospital, Japan
3. The Australian and New Zealand Intensive Care Research Centre, the School of Public Health and Preventive Medicine, Monash University, Australia
4. Department of Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Japan

5. Department of Innovative Research and Education for Clinicians and Trainees (DiRECT), Fukushima Medical University, Japan
6. Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine, Japan
7. Department of Psychology, Harvard College, USA
8. Department of Biostatistics, University of Liverpool, UK

Corresponding author:

Toshi A Furukawa

Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Phone: +81-75-753-9491

Fax: +81-75-753-4641

Email: furukawa@kuhp.kyoto-u.ac.jp

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 recent 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 , $5 \leq$ to < 10 , or $10 \leq$], 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, Texas, 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, $I^2 = 27\%$, $\tau^2 = 0.044$, 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, $I^2 = 34\%$, $\tau^2 = 0.064$, 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, $I^2 = 47\%$, $\tau^2 = 0.132$, 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, $IF \geq 10$, 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

Reference:

1. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet*. 1993;341:418-22.
2. Tudur Smith C, Marcucci M, Nolan SJ, Iorio A, Sudell M, Riley R, et al. Individual participant data meta-analyses compared with meta-analyses based on aggregate data. *Cochrane Database Syst Rev*. 2016;9:MR000007.
3. Rogozinska E, Marlin N, Thangaratinam S, Khan KS, Zamora J. Meta-analysis using individual participant data from randomised trials: opportunities and limitations created by access to raw data. *Evidence-based medicine*. 2017;22(5):157-62.
4. Rathi V, Dzara K, Gross CP, Hrynaskiewicz I, Joffe S, Krumholz HM, et al. Sharing of clinical trial data among trialists: a cross sectional survey. *BMJ*. 2012;345:e7570.
5. Tudur Smith C, Nevitt S, Appelbe D, Appleton R, Dixon P, Harrison J, et al. Resource implications of preparing individual participant data from a clinical trial to share with external researchers. *Trials*. 2017;18(1):319.

6. Huang Y, Mao C, Yuan J, Yang Z, Di M, Tam WW, et al. Distribution and epidemiological characteristics of published individual patient data meta-analyses. *PLoS One*. 2014;9(6):e100151.
7. Ross JS, Krumholz HM. Ushering in a new era of open science through data sharing: the wall must come down. *JAMA*. 2013;309(13):1355-6.
8. Data CoSfRSOCT. *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk.*: Washington (DC): National Academies Press (US); 2015 Apr 20.
9. Taichman DB, Backus J, Baethge C, Bauchner H, de Leeuw PW, Drazen JM, et al. Sharing Clinical Trial Data--A Proposal from the International Committee of Medical Journal Editors. *N Engl J Med*. 2016;374(4):384-6.
10. Nevitt SJ, Marson AG, Davie B, Reynolds S, Williams L, Smith CT. Exploring changes over time and characteristics associated with data retrieval across individual participant data meta-analyses: systematic review. *BMJ*. 2017;357:j1390.
11. Higgins JP, Green S, (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration. 2011.
12. Huang Y, Tang J, Tam WW, Mao C, Yuan J, Di M, et al. Comparing the Overall Result and Interaction in Aggregate Data Meta-Analysis and Individual Patient Data Meta-Analysis. *Medicine (Baltimore)*. 2016;95(14):e3312.
13. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. *BMJ*. 2012;344:d7762.
14. Riley RD, Simmonds MC, Look MP. Evidence synthesis combining individual patient data and aggregate data: a systematic review identified current

practice and possible methods. *J Clin Epidemiol.* 2007;60(5):431-9.

15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151(4):W65-94.

16. Cooper H, Larry V. Hedges, and Jeffrey C. Valentine. *The handbook of research synthesis and meta-analysis*: Russell Sage Foundation; 2019.

17. Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. *Stat Med.* 2002;21(11):1513-24.

18. De Luca G, Bellandi F, Huber K, Noc M, Petronio AS, Arntz HR, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty-abciximab long-term results (EGYPT-ALT) cooperation: individual patient's data meta-analysis. *J Thromb Haemost.* 2011;9(12):2361-70.

19. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet.* 2014;384(9958):1929-35.

20. Wicherts JM, Bakker M, Molenaar D. Willingness to share research data is related to the strength of the evidence and the quality of reporting of statistical results. *PLoS One.* 2011;6(11):e26828.

21. Vines TH, Albert AYK, Andrew RL, Debarre F, Bock DG, Franklin MT, et al. The availability of research data declines rapidly with article age. *Curr Biol.* 2014;24(1):94-7.

22. Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. *Stat Med*. 1995;14(19):2057-79.
23. Pildal J, Hrobjartsson A, Jorgensen KJ, Hilden J, Altman DG, Gotzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol*. 2007;36(4):847-57.
24. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ*. 2008;336(7644):601-5.
25. Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8:79.
26. Sinclair JC, Bracken MB. Clinically useful measures of effect in binary analyses of randomized trials. *J Clin Epidemiol*. 1994;47(8):881-9.

1
2
3
4
5 **What is new?**
6

7 **Key findings**
8

- 9
- 10 • Trial-level characteristics such as a recent year of publication, large number of
11 participants, high impact factor, and adequate allocation concealment were
12 independently associated with individual participant data (IPD) contribution to
13 systematic reviews (SRs) with IPD meta-analyses.
14
 - 15 • We could not find consistent evidence of a data availability bias; the effect
16 estimates of trials contributing IPD were not statistically different from those not
17 contributing IPD in the same systematic reviews (SRs).
18
19
20
21
22
23
24

25
26
27 **What this study adds to what was known?**
28

- 29 • Methodological qualities of trials were associated with the contribution of IPD to
30 IPD meta-analysis, but effect estimates might not affect this result.
31
- 32 • While previous studies suggested the presence of a data availability bias only
33 narratively or theoretically, we systematically compared the effect estimates
34 between studies with and without IPD contribution and showed that there was no
35 consistent evidence of a data availability bias.
36
37
38
39
40
41
42
43

44 **What is the implication and what should change now?**
45

- 46 • Investigators should be aware of the differences in methodological qualities
47 between RCTs with and without IPD contribution when conducting IPD meta-
48 analyses.
49
- 50 • While we did not detect any systematic data availability bias in the recednt IPD
51 meta-analyses, effect estimates in some IPD meta-analyses might still be biased in
52
53
54
55
56
57
58
59
60

61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120

either direction due to the data availability.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Authors:

Yasushi Tsujimoto^{1,2}, yssh0108@yahoo.co.jp

Tomoko Fujii³, tofujii-ky@umin.net

Akira Onishi⁴, telonishi@gmail.com

Kenji Omae^{1,5}, oranz416@gmail.com

Yan Luo⁶, lilacluogmail.com

Hissei Imai⁶, hissei.imai@gmail.com

Sei Takahashi¹, heavens.prison.septem@gmail.com

Takahiro Itaya¹, itaya.takahiro.53a@st.kyoto-u.ac.jp

Claire Pinson⁷, clairepinson@college.harvard.edu

Sarah J Nevitt⁸, Sarah.Nevitt@liverpool.ac.uk

Toshi A Furukawa⁶, furukawa@kuhp.kyoto-u.ac.jp

1. Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine, Japan
2. Department of Nephrology and Dialysis, Kyoritsu Hospital, Japan
3. The Australian and New Zealand Intensive Care Research Centre, the School of Public Health and Preventive Medicine, Monash University, Australia
4. Department of Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Japan

- 61
62
63
64
65 5. Department of Innovative Research and Education for Clinicians and Trainees
66 (DiRECT), Fukushima Medical University, Japan
67
68
69
70 6. Department of Health Promotion and Human Behavior, Kyoto University Graduate
71 School of Medicine, Japan
72
73
74 7. Department of Psychology, Harvard College, USA
75
76 8. Department of Biostatistics, University of Liverpool, UK
77
78
79

80 **Corresponding author:**

81 Toshi A Furukawa

82
83 Department of Health Promotion and Human Behavior, School of Public Health in the
84 Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto
85
86
87
88 606-8501, Japan

89
90 Phone: +81-75-753-9491

91
92 Fax: +81-75-753-4641

93
94 Email: furukawa@kuhp.kyoto-u.ac.jp
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120

121
122
123
124
125 Abstract (218 words)
126
127

128 *Objectives*
129

130 To assess trial-level factors associated with the contribution of individual
131 participant data (IPD) to IPD meta-analyses, and to quantify the data
132 availability bias, namely the difference between the effect estimates of
133 trials contributing IPD and those not contributing IPD in the same
134 systematic reviews (SRs).
135
136
137
138
139
140
141
142
143
144

145 *Design and Setting*
146

147 We included SRs of randomized controlled trials (RCTs) with IPD meta-
148 analyses since 2011. We extracted trial-level characteristics and examined
149 their association with IPD contribution. To assess the data availability bias,
150 we retrieved odds ratios from the original RCT papers, calculated the ratio
151 of odds ratios (RORs) between aggregate data (AD) meta-analyses of
152 RCTs contributing IPD and those of RCTs not contributing IPD for each
153 SR, and meta-analytically synthesized RORs.
154
155
156
157
158
159
160
161
162
163
164
165
166
167

168 *Results*
169

170 Of 728 eligible RCTs included in 31 SRs, 321 (44%) contributed IPD,
171 while 407 (56%) did not. A recent publication year, larger number of
172
173
174
175
176
177
178
179
180

181
182
183
184
185 participants, adequate allocation concealment, and impact factor ≥ 10 were
186 associated with IPD contribution. We found the SRs yielded widely
187 different estimates of RORs. Overall, there was no significant difference in
188 the pooled effect estimates of AD meta-analyses between RCTs
189 contributing and not contributing IPD (ROR 1.01, 95% confidence interval
190 0.86–1.19).
191
192
193
194
195
196
197
198
199
200
201
202

203 *Conclusions*

204
205 There was no consistent evidence of a data availability bias in recent IPD
206 meta-analyses of RCTs with dichotomous outcomes. Higher
207 methodological qualities of trials were associated with IPD contribution.
208
209
210
211
212
213
214

215 **Keywords**

216
217 Individual participant data, systematic review, meta-analysis, data availability bias
218
219
220

221 **What is new?**

222 **Key findings**

- 223
224
225
226 • Trial-level characteristics such as a recent year of publication, large number of
227 participants, high impact factor, and adequate allocation concealment were
228 independently associated with individual participant data (IPD) contribution to
229 systematic reviews (SRs) with IPD meta-analyses.
230
231
232
233
234 • We could not find consistent evidence of a data availability bias; the effect
235
236
237
238
239
240

241
242
243
244
245 estimates of trials contributing IPD were not statistically different from those not
246
247 contributing IPD in the same systematic reviews (SRs).
248
249
250

251 252 **What this study adds to what was known?**

- 253
254 · Methodological qualities of trials were associated with the contribution of IPD to
255
256 IPD meta-analysis, but effect estimates might not affect this result.
257
- 258 · While previous studies suggested the presence of a data availability bias only
259
260 narratively or theoretically, we systematically compared the effect estimates
261
262 between studies with and without IPD contribution and showed that there was no
263
264 consistent evidence of a data availability bias.
265
266
267

268 269 **What is the implication and what should change now?**

- 270
271 · Investigators should be aware of the differences in methodological qualities
272
273 between RCTs with and without IPD contribution when conducting IPD meta-
274
275 analyses.
276
- 277 · While we did not detect any systematic data availability bias in the recednt IPD
278
279 meta-analyses, effect estimates in some IPD meta-analyses might still be biased in
280
281 either direction due to the data availability.
282
283
284
285
286
287
288
289

290 **Background**

291
292 Individual participant data (IPD) meta-analyses are considered to increase the
293
294 statistical power of systematic reviews (SRs) as well as enable more valid subgroup
295
296
297
298
299
300

301
302
303
304
305 analyses, in comparison with meta-analyses that are based on aggregate data (AD)
306 extracted from published trial reports [1-3]. Encouragement to share IPD from clinical
307 studies has risen in the scientific literature, and the number of SRs with IPD meta-
308 analyses has increased dramatically over the past few years [4-9].
309
310
311

312
313
314 However, SRs with IPD meta-analyses require the review authors to spend substantial
315 time and effort to contact and request IPD from the authors of the original studies [1,
316 10, 11] with no certainty that all original authors will contribute their data. Indeed, only
317
318 25% of the 760 IPD meta-analyses conducted between 1987 and 2015 retrieved 100%
319 of the data from the relevant trials, and 43% retrieved 80% of the data of relevant trials
320
321 [10].
322
323
324

325
326
327 The risk of data availability bias increases when all IPD data cannot be procured [2,
328 10, 12, 13]. The data sharing policy of RCTs might be influenced by the views of the
329 investigators, as well as by the resources or results of the RCTs [5]. If unavailability of
330 IPD is associated with the direction or the size of the intervention effect, studies that are
331 available for IPD analyses may not be representative of the whole evidence, and the
332 results of such IPD meta-analyses may be misleading. However, the difference in
333 characteristics between RCTs contributing and not contributing IPD has not been
334 investigated.
335
336
337
338
339
340
341
342

343
344 To date, data availability bias has been discussed only anecdotally, narratively or
345 theoretically and there has been no systematic examination aiming to quantify the
346 impact of this bias on the effect estimates of meta-analyses [2, 6, 10, 13, 14]. The
347 purposes of this study were, therefore, two-fold: (i) To assess RCT-level factors
348 associated with the contribution of IPD, and (ii) to examine data availability bias in IPD
349 meta-analysis with less than 100% retrieval rate.
350
351
352
353
354
355
356
357
358
359
360

361
362
363
364
365
366
367
368
369
370 Methods

371
372 *Design*

373
374 A meta-epidemiological study

375
376
377
378 *Eligibility criteria*

379 All therapeutic RCTs included in SRs that fulfilled all following criteria were eligible:

380
381 (i) SRs with IPD meta-analyses, (ii) SRs that included only RCTs comparing an active
382 intervention against a control condition in terms of a dichotomous outcome, (iii) SRs
383 that reported a full reference list of the included RCTs, and (iv) SRs published in
384 English. We excluded the following SRs: (v) SRs published before 2011, (vi) SRs
385 where all included RCTs provided IPD data, (vii) SRs of diagnostic or prognostic
386 studies, and (viii) SRs with network meta-analyses. A cutoff year of 2011 was selected
387 because a reporting guideline for SRs, Preferred Reporting Items for Systematic
388 Reviews and Meta-Analyses: The PRISMA Statement, was first published in 2009 [15].
389 We allowed two years for the dissemination of this guideline.
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404

405 *Search methods*

406
407 We used the reference list from a recent comprehensive review of IPD meta-analyses
408 conducted by Nevitt et al[10]. We also performed an updated search of MEDLINE via
409 Ovid using the same search strategy as the above review to identify relevant SRs as of
410 10th March 2018. Supplementary file 1 shows the search terms we used.
411
412
413
414
415
416
417
418
419
420

421
422
423
424
425
426
427
428
429 *Study selection*
430

431
432 Two pairs of researchers (YT-TF and KO-AO) independently screened the titles and
433
434 abstracts of articles identified by the updated search. We pooled the potentially eligible
435
436 SRs and the reference list from the review conducted by Nevitt et al [10]. We then
437
438 independently assessed eligibility based on a full-text review.
439
440

441
442
443
444 *Data extraction*
445

446
447
448 Eight researchers (YT, TF, KO, AO, ST, TI, YL and CP) independently extracted the
449
450 following RCT-level factors from the included RCTs; year of publication, sample size,
451
452 whether the primary outcomes of the RCT was positive or not, allocation concealment,
453
454 industrial sponsorship, publication status (full-publication or not), data sharing
455
456 statement (available, unavailable, or unclear), journal impact factor (IF), and language.
457
458 We selected the primary outcomes of the RCTs using the following hierarchy: an
459
460 outcome that was mentioned (1) as primary, (2) in the title, (3) in the objective, (4) first
461
462 in the abstract, (5) first in the text. We defined the primary outcome as positive when
463
464 the selected primary outcome was statistically significant in superiority trials or within
465
466 the noninferiority margin in noninferiority trials. We chose not blinding but adequate
467
468 allocation concealment as a marker of study quality because the feasibility of blinding
469
470 and its impact on outcomes varies across research questions. We used the IF of the
471
472
473
474
475
476
477
478
479
480

481
482
483
484
485 journal from 2017 Journal Citation Reports® Science Edition (Thomson Reuters, 2018)
486
487 and assigned an IF of zero to conference abstracts and unpublished studies.
488
489

490 We also extracted the following SR-level factors from the included SRs: year of
491 publication, the number of included RCTs, types of review (pharmacological or non-
492 pharmacological interventions, adult or pediatric, and Cochrane or non-Cochrane), and
493 funding (yes/no).
494
495
496
497
498

499 To examine any discrepancy between the effect estimates of RCTs contributing IPD
500 (C-RCTs) and those not contributing IPD (NC-RCTs), we selected a single outcome per
501 SR. As the SR might have reported several outcomes, we selected the single primary
502 outcome that fulfilled all the following criteria: (1) An efficacy outcome measured as a
503 pooled risk ratio (RR) or odds ratio (OR), (2) Not a composite outcome, and (3) Not an
504 outcome of adverse events or subgroup analysis. We did not adopt a composite outcome
505 because the definition or components of the outcome was expected to vary across trials.
506
507 In cases where the primary outcome did not meet these criteria, we adopted the outcome
508 with the largest number of trials or the first outcome described which met these criteria.
509
510
511
512
513
514
515
516
517
518

519 For the single selected outcome in each SR, we extracted the number of events and
520 participants in the intervention and control groups from the original published journal
521 articles or conference abstracts of both C-RCTs and NC-RCTs. If the number of events
522 or participants was missing, or if the selected outcome was not reported in the original
523 RCT but provided in the IPD meta-analysis, we imputed them from the information or
524 outcome data presented in the IPD-SR. We also extracted the pooled RR or OR from
525 the reported IPD meta-analysis. We converted the pooled RR to OR using the observed
526 control event rate [16].
527
528
529
530
531
532
533
534
535
536
537
538
539
540

541
542
543
544
545
546
547
548
549 *Statistical analysis*
550
551

552 We first described RCT characteristics, each classified by whether the RCT contributed
553 IPD to the SR or not. We then explored the RCT-level factors (see Data Extraction)
554 associated with the contribution of IPD using univariable mixed-effect logistic
555 regression with a random intercept for SRs to account for the clustering effects of RCTs
556 within each SR, and a multivariable mixed-effects logistic regression model with fixed
557 factors (year of publication, sample size, positive primary outcome [yes or no], adequate
558 allocation concealment [yes or no], industrial sponsorship [yes or no], publication status
559 [full-publication or not], data sharing statement [available or not], IF [no IF, < 5 , $5 \leq$ to
560 < 10 , or $10 \leq$], language [published in English or not]), and a random intercept for SRs.
561
562
563
564
565
566
567
568
569
570
571

572 We calculated odds ratios using the number of events and the number of patients
573 aggregated from the original RCT papers and pooled them in aggregate data (AD) meta-
574 analyses using random-effects models. Each OR was recalculated so that an OR < 1
575 indicated that the intervention arm was favored. To assess data availability bias
576 quantitatively, we calculated and pooled the ratio of odds ratios (ROR) in AD meta-
577 analyses of C-RCTs to those in AD meta-analyses of NC-RCTs using the following
578 two-step approach proposed by Sterne et al [17]. First, we estimated an ROR in each
579 AD meta-analysis by using a random-effect meta-regression. An ROR < 1 indicated a
580 larger treatment effect estimate in AD meta-analyses of C-RCTs than in NC-RCTs. We
581 estimated the combined ROR across SRs and the 95 % confidence interval (CI) with a
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600

601 random-effects meta-analysis model. We used the I^2 statistic, τ^2 -statistic and 95%
602
603
604
605
606 prediction interval to quantify the heterogeneity between SRs.
607
608

609
610 We expressed continuous variables as mean (standard deviation) for normally
611 distributed data or median (interquartile range [IQR]) for non-normally distributed data
612
613 and categorical variables as numbers with the percentage. We considered a two-sided p
614
615 value < 0.05 as a statistically significant difference. We used Stata/SE, V.14.0
616
617
618 (StataCorp, College Station, TexasX, USA) for all analyses.
619
620

621 622 623 624 625 *Sensitivity analysis* 626

627
628 To examine the robustness of the estimated ROR, we performed the following
629 sensitivity analyses. First, we adjusted SR-level factors (year of publication, the number
630
631 of included studies, types of review [Cochrane or non-Cochrane, pharmacological or
632
633 not, and pediatric or not], or funding) that assumed to be confounders of the association
634
635 between IPD contribution and the ROR using the meta-regression model. Second, we
636
637 excluded RCTs for which we imputed the results of AD meta-analysis with those
638
639 reported in IPD meta-analysis. Third, we examined a discrepancy between IPD meta-
640
641 analytic results of C-RCTs and AD meta-analytic results of NC-RCTs using the same
642
643 methods for the primary outcome.
644
645
646
647
648
649
650

651 652 *Additional analyses* 653 654 655 656 657 658 659 660

661
662
663
664
665 As a post-hoc analysis, we used log-transformed data of the number of randomized
666 participants and impact factors instead of categorized data, and added them into the
667 mixed effects multivariable model to examine their associations with the contribution of
668
669
670
671 IPD.
672

673
674
675
676
677 The study was registered in UMIN-CTR as UMIN000028325
678
679 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000036147).
680
681
682
683
684

685 686 Results

687 688 689 *Results of searches*

690
691
692
693 Figure 1 shows the flow diagram of the present study. We identified 2349 possible
694 SRs with IPD meta-analyses including 102 references from the previous study [10]. We
695 assessed the eligibility of 268 SRs with IPD meta-analyses that remained after screening
696 of titles and abstracts, and included 37 IPD-SRs for a total of 728 RCTs. For the
697 assessment of data availability bias, six SRs had only one or two RCTs that reported the
698 selected outcome, which made it impossible to calculate the ROR using a random
699 effects meta-regression model. Among 631 RCTs included in the remaining 31 SRs,
700 264 did not report the selected outcome. Consequently, we included 367 RCTs that
701 reported the selected outcome in the analysis for data availability bias.
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720

721
722
723
724
725 *Characteristics of included IPD systematic reviews*
726
727

728
729 Supplementary file 2 shows the characteristics of the included IPD-SRs. The number of
730 included RCTs in the IPD-SRs varied from 5 to 103 (median 13, IQR 11 to 21), and the
731 IPD retrieval rate ranged from 10 % to 92 % (median 71 %, IQR 50 % to 81 %).
732

733
734 Twenty-five (68 %) IPD-SRs had funding, 21 (57 %) focused on pharmacological
735 interventions, 7 (19%) were Cochrane reviews, and 2 (5 %) were in pediatric areas.
736
737
738
739
740
741
742

743 *Characteristics of included studies and IPD contribution*
744
745

746
747 Of 728 RCTs included, 321 contributed IPD and 407 did not. Table 1 summarizes the
748 characteristics of the included RCTs and the association with the IPD contribution. C-
749 RCTs were likely to have a recent year of publication, a larger sample size, adequate
750 allocation concealment, full publication status, higher impact factor, and sponsorships
751 as compared to NC-RCTs. We next examined the association between RCT
752 characteristics and IPD contribution with logistic regressions. As shown in Table 1, a
753 recent publication year, larger number of participants randomized, adequate allocation
754 concealment, and high impact factor (≥ 10) compared to IF < 5 were independently
755 associated with IPD contribution. On the other hand, whether the primary outcomes
756 were positive was not associated with IPD contribution (adjusted OR 1.06, 95% CI 0.72
757 to 1.55). The association of the number of randomized participants or that of impact
758 factors with IPD contribution remained unchanged when we used log-transformed data
759 instead of categorized data (OR 1.34, 95% CI 1.07 to 1.69, and OR 1.28, 95% CI 1.03
760 to 1.58, respectively)
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780

781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840

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

841
842
843
844
845 treatment effect in C-RCTs compared with NC-RCTs [18], whereas one SR showed a
846
847 significantly small effect of C-RCTs compared with NC-RCTs [19]. The remaining 29
848
849 SRs showed a non-significant difference in treatment effects between C-RCTs and NC-
850
851 RCTs. Overall, we found no statistically significant association between IPD
852
853 contribution and the size or direction of treatment effects which could be estimated from
854
855 AD meta-analyses of the trials within each SR (pooled ROR 1.01, 95 % CI 0.86 to 1.19,
856
857 $I^2 = 27\%$, $\tau^2 = 0.044$, and 95% prediction interval 0.60 to 1.42) (Fig 2).
858
859
860
861
862
863

864 *Sensitivity analyses*

865
866
867 A sensitivity analysis excluding the data imputed from the IPD meta-analysis showed a
868
869 consistent result (pooled ROR 1.02, 95% CI 0.85 to 1.22, $I^2 = 34\%$, $\tau^2 = 0.064$, and
870
871 95% prediction interval 0.52 to 1.51). The univariable meta-regression analyses showed
872
873 that there were no statistically significant associations between any of the SR-level
874
875 factors and the ROR (Supplementary file 3). There was no statistically significant
876
877 difference between IPD meta-analytic results of C-RCTs and AD meta-analytic results
878
879 of NC-RCTs (ROR 1.11, 95% CI 0.83 to 1.48, $I^2 = 47\%$, $\tau^2 = 0.132$, and 95%
880
881 prediction interval 0.40 to 1.82).
882
883
884
885
886
887
888

889 Discussion

892 *Summary of findings*

901 RCT features reflecting the high methodological quality of RCTs, such as a large
902 number of participants, $IF \geq 10$, and adequate allocation concealment, were
903 independently associated with IPD contribution. However, we could not find consistent
904 evidence of data availability bias due to IPD contribution in recent SRs with IPD meta-
905 analyses.
906
907
908
909
910
911
912
913
914

915 *Context with prior studies*

916
917
918
919

920 Our findings of the RCT characteristics associated with IPD sharing are mostly in line
921 with those from previous studies in the literature. We found that low quality RCTs, that
922 had unclear or high risk of bias in participant selection and had lower impact, might be
923 less likely to provide IPD. A previous research reported a higher prevalence of apparent
924 errors, i.e. low quality, in the reporting of statistical results was associated with authors'
925 reluctance to share research data in high-ranked psychology journals [20]. In addition,
926 old studies might not provide IPD due to limited access to the trial data [21]. These
927 previous findings, however, were based on a univariable analysis. We comprehensively
928 investigated the RCT factors associated with data sharing and examined if the study
929 quality made an independent contribution using a multivariable model. Our data also
930 showed that such trends persisted in more recent cohorts.
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947

948 Previous studies have raised concerns about data availability bias in effect estimates of
949 meta-analyses using IPD. [2, 10, 13]. For example, a prior study showed a discrepancy
950 of 20% in reporting of statistically significant outcomes between IPD and AD meta-
951 analyses [2]. However, the observed difference might be only due to the different
952
953
954
955
956
957
958
959
960

961
962
963
964
965 statistical approaches usually taken in IPD meta-analyses [22]. Unlike previous studies,
966
967 we directly compared the effect estimates between studies with and without IPD
968
969 contribution, and showed there was no consistent evidence of data availability bias.
970
971 Evidence users may be interested in the discrepancy between the IPD meta-analysis of
972
973 C-RCTs and AD meta-analysis of all available studies as those are the measures
974
975 presented in papers. However, logically speaking, the ROR of IPD meta-analysis of C-
976
977 RCTs to AD meta-analysis of all RCTs should be even closer to the unity than the ROR
978
979 of IPD meta-analysis of C-RCTs to AD meta-analysis of NC-RCTs that was examined
980
981 in this study. Given the nonsignificant results of our findings, we expect the difference
982
983 between the IPD meta-analysis of C-RCTs and AD meta-analysis of the whole evidence
984
985 would be small.
986
987
988
989

990 Although we found that significantly more RCTs contributing IPD performed adequate
991
992 allocation concealment to prevent selection bias that could lead to an overestimation of
993
994 the intervention effect compared with RCTs not contributing IPD, we could not detect
995
996 data availability bias in efficacy estimates [23]. A possible explanation for this finding
997
998 is that most outcomes assessed in this study were objective. A previous study that
999
1000 examined the effects of inadequate allocation concealment on the effect estimates of
1001
1002 interventions reported there had been little evidence of bias due to inadequate allocation
1003
1004 concealment if a trial adopted objective outcomes [24]. Our findings resemble the
1005
1006 previous report; however, the mechanism of this observation was not explained
1007
1008 sufficiently. Another explanation might be that other risk of bias domains than
1009
1010 allocation concealment may yield unbiased results for C-RCTs, and may cancel out the
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020

1021
1022
1023
1024
1025 data availability bias. Publication bias or outcome reporting bias might also hide the
1026
1027 impact of availability bias.
1028
1029

1030
1031 Overall, no general tendency for data availability bias was observed, however, this
1032 does not mean “no data availability bias” for each SR. Although the I^2 observed was not
1033 substantial (<50%), that might be partly due to a small number of NC-RCTs included in
1034 a single SR [25]. The 95% prediction interval was somewhat wide for the combined
1035 ROR, which suggested the possible heterogeneity among SRs. Indeed, C-RCTs reported
1036 significantly larger effect estimates than NC-RCTs in Emberson 2014 [19]; in turn, C-
1037 RCTs reported almost half of the OR which NC-RCTs reported in De Luca 2011 [18].
1038
1039 In future IPD-meta-analyses, reviewers need to examine if such extreme unbalance in
1040 effect estimates may be present between C-RCTs and NC-RCTs in their own reviews.
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050

1051 1052 1053 *Strengths and limitations of the study* 1054 1055

1056
1057 This study has several strengths. This is the first study that assessed the data
1058 availability bias quantitatively. As there has been a push to share clinical trial data in
1059 many journals and registrations recently, the current study will be useful in
1060 understanding current data availability and its impact on effect estimates in IPD meta-
1061 analysis. Also, we conducted comprehensive search and rigorous selection of the
1062 eligible SRs with IPD meta-analysis and confirmed the robustness of the results using
1063 several statistical analyses. Both unadjusted and adjusted analysis showed that a
1064 positive result of the primary outcome of RCTs did not appear to affect IPD
1065 contribution. The direction or strength of the study findings may not be associated with
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080

1081
1082
1083
1084
1085 the authors' willingness to share the data in any category. Moreover, our detailed data
1086 extraction identified RCT features associated with IPD contribution. Readers of IPD
1087 meta-analyses would consider that RCTs contributing IPD and those not contributing
1088 IPD could be different in terms of a year of publication, number of participants, IF and
1089 adequate allocation concealment.
1090
1091

1092
1093
1094
1095
1096
1097 However, we should acknowledge several weaknesses. First, ROR in AD meta-
1098 analyses of C-RCTs to those in AD meta-analyses of NC-RCTs is a surrogate measure
1099 of availability bias. Data availability bias in the true effect estimates should ideally have
1100 been assessed using IPD from both RCTs that contributed IPD and those did not.
1101
1102 However, it was infeasible to obtain IPD from RCTs that did not contribute the IPD to
1103 the SR. We used AD meta-analytic results to detect data availability bias because, it was
1104 previously reported that most results of IPD meta-analysis agreed with those of AD
1105 meta-analysis [2]. Thus, IPD of NC-RCTs may not affect the results derived from AD
1106 of NC-RCTs even if it was available. We also added a sensitivity analysis that
1107 compared IPD meta-analytic results of RCTs contributing IPD and AD meta-analytic
1108 results of RCTs not contributing to IPD, and showed a consistent result.
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119

1120
1121 Second, we chose a dichotomous outcome from each SR measured as a pooled RR or
1122 OR to calculate ROR. As we needed to mathematically align the direction of
1123 intervention effect estimates and as the OR calculated for favorable events is
1124 reciprocally related to that which is calculated for unfavorable events, we adopted ROR
1125 to assess data availability bias [26]. Although this selection was not likely to confound
1126 the association between the efficacy and IPD contribution, further studies using other
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140

1141
1142
1143
1144
1145 outcome measures such as a difference in standardized mean differences for continuous
1146
1147 variables would be required.
1148

1149
1150 Thirdly, our study was possibly underpowered to detect the statistically significant
1151 difference. We intentionally retrieved all published SRs with pairwise IPD meta-
1152 analysis of interventional RCTs after 2011, because we aimed to obtain data from
1153 properly conducted SRs after the PRISMA reporting guideline was disseminated [15].
1154
1155 Thereby, having a threshold of a statistical significance using p-value < 0.05 in the
1156 pooled analysis might have had only low power to assess the data availability bias,
1157 given the limited number of SRs with IPD meta-analysis.
1158
1159
1160
1161
1162
1163
1164

1165
1166 Lastly, our evidence may not be applied to the IPD meta-analyses of non-RCTs that
1167 are known to have a low IPD retrieval rate [10]. This issue should be investigated in
1168 future research.
1169
1170
1171

1172 1173 1174 1175 1176 1177 Conclusion

1178
1179
1180 Higher quality RCTs tended to contribute IPDs than lower quality RCTs. However, we
1181 found no consistent evidence of data availability bias in recent IPD meta-analyses. This
1182 does not mean the absence of availability bias in each and every single IPD meta-
1183 analysis. Further work that uses other effect measures such as subjective outcomes or
1184 continuous outcomes or that incorporates IPD meta-analyses of non-RCTs is warranted.
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194

1195 List of abbreviations

1196
1197
1198
1199
1200

1201
1202
1203
1204
1205 SR, systematic review; IPD, individual participant data; AD, aggregated data; RCT,
1206 randomized controlled trial; IF, impact factor; RR, risk ratio; OR, odds ratio; ROR, ratio
1207 of odds ratio; CI, confidence interval; IQR, interquartile range;
1208
1209
1210
1211

1212 1213 1214 1215 1216 Ethics approval and consent to participate 1217

1218
1219 Ethics approval is not applicable. This study is a research on research study.
1220
1221

1222 1223 1224 1225 Consent for publication 1226

1227
1228 Not applicable
1229
1230

1231 1232 1233 1234 1235 Availability of data and material 1236

1237
1238 The data are available to academic researchers upon request.
1239
1240

1241 1242 1243 1244 Competing interests 1245

1246
1247
1248 None declared
1249

1250 1251 1252 1253 Funding 1254

1261
1262
1263
1264
1265 None declared
1266
1267
1268
1269
1270

1271 Authors' contributions

1272
1273
1274
1275 YT had full access to all the data in the study and take responsibility for the integrity of
1276 the data and the accuracy of the data analysis. Study concept and design: YT, TF, AO,
1277 KO, SJN, and TAF. Acquisition of data: YT, TF, AO, KO, HI, ST, TI, YL, and CP.
1278
1279 Analysis and interpretation of data: YT, TF, AO, KO, SJN and TAF. Drafting of the
1280 manuscript: YT, TF, AO, KO, and TAF. Critical revision of the manuscript for
1281 important intellectual content: SJN and TAF. All authors gave final approval of the
1282 version to be published and agreed to be accountable for all aspects of this work.
1283
1284
1285
1286
1287
1288
1289
1290

1291 Acknowledgements

1292
1293
1294 We thank Ms. Keiko Fujii and Aya Ichizawa for obtaining the full-text articles.
1295
1296
1297
1298
1299
1300

1301 Figure titles and legends

1302
1303
1304
1305
1306
1307 Figure 1. Flow diagram of the present study
1308

1309
1310 Abbreviations: IPD, individual participant data; RCT, randomized controlled trial; SR,
1311 systematic review; MA, meta-analysis; RR, risk ratio; OR, odds ratio; NMA, network
1312 meta-analysis
1313
1314
1315
1316
1317
1318
1319
1320

1321
1322
1323
1324
1325
1326
1327
1328 Figure 2. Comparison of treatment effect estimates between studies providing IPD or
1329
1330 not

1331
1332
1333
1334 Difference in treatment effect estimates is expressed as ROR. An ROR <1 indicates
1335
1336 larger treatment effect estimates in studies contributing IPD. Abbreviations: IPD,
1337
1338 individual participant data; ROR, ratio of odds ratio
1339
1340
1341
1342
1343

1344 Reference:

- 1345
1346
1347 1. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual
1348 patient data: is there a difference? *Lancet*. 1993;341:418-22.
1349
1350
1351 2. Tudur Smith C, Marcucci M, Nolan SJ, Iorio A, Sudell M, Riley R, et al.
1352
1353 Individual participant data meta-analyses compared with meta-analyses based on
1354
1355 aggregate data. *Cochrane Database Syst Rev*. 2016;9:MR000007.
1356
1357
1358 3. Rogozinska E, Marlin N, Thangaratinam S, Khan KS, Zamora J. Meta-
1359 analysis using individual participant data from randomised trials: opportunities and
1360
1361 limitations created by access to raw data. *Evidence-based medicine*. 2017;22(5):157-62.
1362
1363
1364 4. Rathi V, Dzara K, Gross CP, Hrynaskiewicz I, Joffe S, Krumholz HM, et al.
1365
1366 Sharing of clinical trial data among trialists: a cross sectional survey. *BMJ*.
1367
1368 2012;345:e7570.
1369
1370
1371 5. Tudur Smith C, Nevitt S, Appelbe D, Appleton R, Dixon P, Harrison J, et al.
1372
1373 Resource implications of preparing individual participant data from a clinical trial to
1374
1375 share with external researchers. *Trials*. 2017;18(1):319.
1376
1377
1378
1379
1380

- 1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
6. Huang Y, Mao C, Yuan J, Yang Z, Di M, Tam WW, et al. Distribution and epidemiological characteristics of published individual patient data meta-analyses. *PLoS One*. 2014;9(6):e100151.
 7. Ross JS, Krumholz HM. Ushering in a new era of open science through data sharing: the wall must come down. *JAMA*. 2013;309(13):1355-6.
 8. Data CoSfRSOCT. *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk.*: Washington (DC): National Academies Press (US); 2015 Apr 20.
 9. Taichman DB, Backus J, Baethge C, Bauchner H, de Leeuw PW, Drazen JM, et al. Sharing Clinical Trial Data--A Proposal from the International Committee of Medical Journal Editors. *N Engl J Med*. 2016;374(4):384-6.
 10. Nevitt SJ, Marson AG, Davie B, Reynolds S, Williams L, Smith CT. Exploring changes over time and characteristics associated with data retrieval across individual participant data meta-analyses: systematic review. *BMJ*. 2017;357:j1390.
 11. Higgins JP, Green S, (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration. 2011.
 12. Huang Y, Tang J, Tam WW, Mao C, Yuan J, Di M, et al. Comparing the Overall Result and Interaction in Aggregate Data Meta-Analysis and Individual Patient Data Meta-Analysis. *Medicine (Baltimore)*. 2016;95(14):e3312.
 13. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. *BMJ*. 2012;344:d7762.
 14. Riley RD, Simmonds MC, Look MP. Evidence synthesis combining individual patient data and aggregate data: a systematic review identified current

1441
1442
1443
1444
1445
1446 practice and possible methods. *J Clin Epidemiol.* 2007;60(5):431-9.

1447
1448 15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et
1449 al. The PRISMA statement for reporting systematic reviews and meta-analyses of
1450 studies that evaluate health care interventions: explanation and elaboration. *Ann Intern*
1451 *Med.* 2009;151(4):W65-94.

1452
1453
1454
1455 16. Cooper H, Larry V. Hedges, and Jeffrey C. Valentine. *The handbook of*
1456 *research synthesis and meta-analysis*: Russell Sage Foundation; 2019.

1457
1458
1459 17. Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical
1460 methods for assessing the influence of study characteristics on treatment effects in
1461 'meta-epidemiological' research. *Stat Med.* 2002;21(11):1513-24.

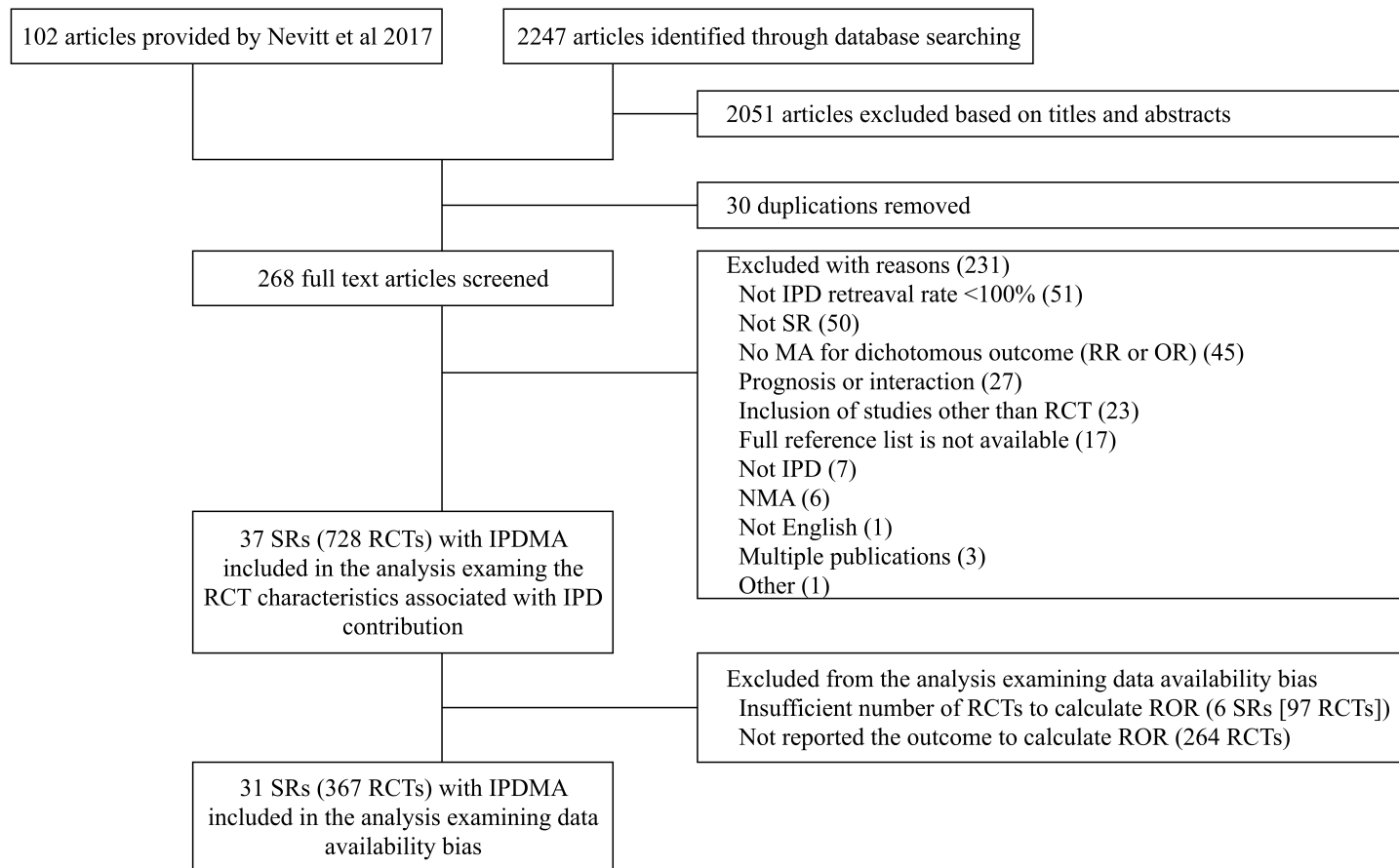
1462
1463
1464
1465 18. De Luca G, Bellandi F, Huber K, Noc M, Petronio AS, Arntz HR, et al. Early
1466 glycoprotein IIb-IIIa inhibitors in primary angioplasty-abciximab long-term results
1467 (EGYPT-ALT) cooperation: individual patient's data meta-analysis. *J Thromb Haemost.*
1468
1469
1470
1471
1472
1473 2011;9(12):2361-70.

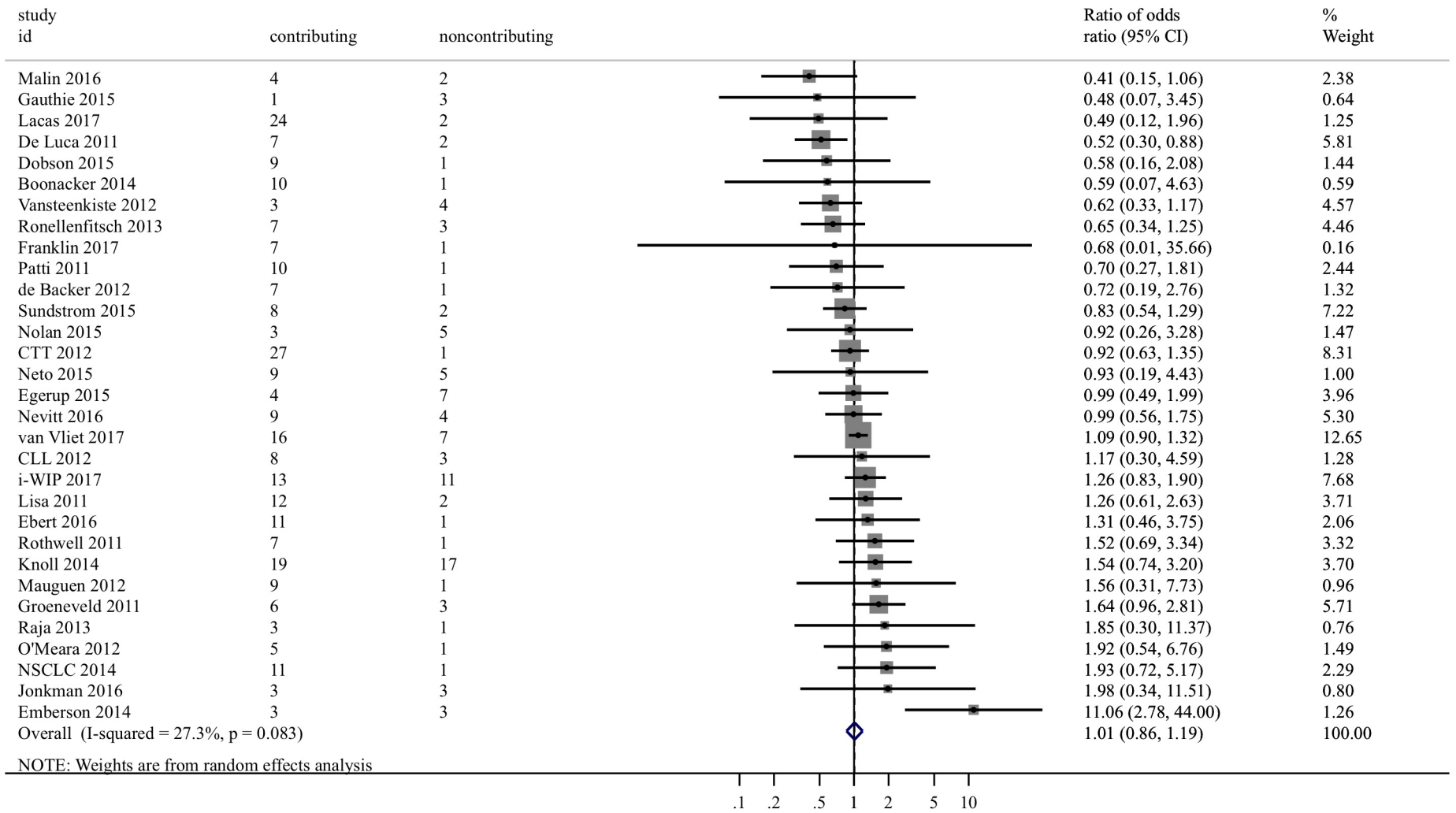
1474
1475 19. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al.
1476
1477 Effect of treatment delay, age, and stroke severity on the effects of intravenous
1478 thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual
1479 patient data from randomised trials. *Lancet.* 2014;384(9958):1929-35.

1480
1481
1482
1483 20. Wicherts JM, Bakker M, Molenaar D. Willingness to share research data is
1484 related to the strength of the evidence and the quality of reporting of statistical results.
1485
1486
1487 *PLoS One.* 2011;6(11):e26828.

1488
1489
1490 21. Vines TH, Albert AYK, Andrew RL, Debarre F, Bock DG, Franklin MT, et
1491 al. The availability of research data declines rapidly with article age. *Curr Biol.*
1492
1493
1494 2014;24(1):94-7.

- 1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
22. Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. *Stat Med*. 1995;14(19):2057-79.
23. Pildal J, Hrobjartsson A, Jorgensen KJ, Hilden J, Altman DG, Gotzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol*. 2007;36(4):847-57.
24. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ*. 2008;336(7644):601-5.
25. Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8:79.
26. Sinclair JC, Bracken MB. Clinically useful measures of effect in binary analyses of randomized trials. *J Clin Epidemiol*. 1994;47(8):881-9.





NOTE: Weights are from random effects analysis

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 curation, 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