

Old evidence: survey of meta-analyses of medical interventions

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Abstract

Background

Some evidence on medical interventions may come from old data. We describe how old data are in meta-analyses of medical interventions and whether reviewers probe the relevance of old data for current practice.

Methods

We assessed a 10% random sample of the Cochrane Database of Systematic Reviews (CDRS) (issue 4, 2005) with ≥ 1 meta-analysis. We focused from each review on the primary outcome meta-analysis. We assessed the time since publication of the included trials, whether inferences changed if data were limited to trials published in the last decade, and whether implications of old data were discussed.

Results

For 157 meta-analyses ($n=1,149$ trials), the median year of last search was 2003 (interquartile range [IQR], 2002-2004). Most meta-analyses (64%) had no studies published in 2001-5. Forty-seven meta-analyses had no data published in the last decade, and in another 16 the statistical significance of the summary effects would change, when data were limited to trials published in the last decade.

Only 12 (8%) systematic reviews discussed potential implications of including old studies. We also assessed 22 meta-analyses published in high-impact medical journals in 2005. Only two meta-analyses had no studies published in 2001-2005, while 18 meta-analyses included at least one study published before 1996. Only four meta-analyses discussed implications of including old studies.

Conclusions

For many healthcare interventions evidence from very recent studies is scant. Systematic reviewers and clinicians should be sensitized to the need to discuss the potential implications of some evidence being old.

Background

In the search for best evidence, both systematic reviewers and clinicians often come across studies conducted a long time ago. Old trials may be fully valid despite their age and may still provide conclusive answers. However, effect sizes may sometimes differ between older and more recent studies for various reasons, including both bias and genuine heterogeneity.¹⁻³ Some old studies may be irrelevant,⁴⁻⁶ even if properly conducted at their time, since much may have changed in the meanwhile, including concomitant treatments and disease management.⁷⁻⁹ Therefore, one would like to see some discussion of what the reliability and relevance of old data are, whenever old data are considered in systematic reviews of the evidence.

Here we aimed to describe how recent the synthesized evidence is in a representative random sample of the Cochrane Database of Systematic Reviews (CDSR), the largest and most comprehensive compilation of systematic reviews on medical interventions.¹⁰⁻¹² We also aimed to evaluate whether systematic reviewers discussed how old the trials were and what the implications might be from the inclusion of old trials. A sample of meta-analyses published recently in high-profile medical journals was also analyzed.

Methods

Database of Cochrane meta-analyses

From the CDSR (issue 4, 2005) we selected a random 10% sample of the systematic reviews that had included at least 2 studies in at least one comparison. Of those, we kept those that had not been withdrawn and that had

performed at least one meta-analysis (quantitative synthesis). We kept only one meta-analysis per eligible selected systematic review. When there was more than one eligible meta-analysis in the same systematic review, we retained the one on the primary outcome as defined by the review. If the review included meta-analyses for more than one primary outcome and/or more than one intervention contrasts, we retained the meta-analysis of a primary outcome that had the greatest number of studies. In case of ties, we preferred the meta-analysis with the greatest cumulative sample size. With further ties for a binary outcome we then preferred the meta-analysis with more events. Whenever the same study had been entered as two or more comparisons in the same meta-analysis, we counted them as a single study and calculated its total sample size.

Occasionally, for an intervention contrast more studies may exist than the ones included in the primary outcome meta-analysis.¹³ Typically, these studies have not collected or do not provide primary outcome data, but may have data for other relevant outcomes. This may be common in fields that foster manifold outcomes, e.g. pain or mental health scales. Therefore, we also considered all the studies that had data for any synthesized outcome in the same intervention contrast. When the same study had been considered for more than one outcome, it was counted only once; if the sample size differed for different outcomes, we used the largest listed sample size.

Data extraction from Cochrane meta-analyses

From each selected meta-analysis, we extracted electronically information on the year of publication of each study and number of participants as well as information to calculate the effect size (odds ratio for binary outcomes,

standardized or weighted mean difference for continuous outcomes, as specified in each review) and its variance. We also noted when the last literature search was performed for the systematic review; in 13 reviews where this information was unavailable, we recorded the year of last amendment.

Some studies may disseminate their results in several articles and meeting abstracts, therefore we consistently used the publication year for the main article, as selected by the Cochrane reviewers. In a random sample of 50 studies, there was only a single publication year for 44 studies (single publication $n=43$, all publications in the same year $n=1$), while publications spanned 2 consecutive years for 1 study, 3 consecutive years in another, or a longer period in 4 studies.

For 53 eligible studies where the Cochrane reviewers had not selected a specific article and year of publication or year for data retrieval, we selected the most recent one among the listed articles or abstracts of the study; for seven studies with entirely unpublished data we used the year of the last literature search.

Proportion of recent data in Cochrane meta-analyses

We present descriptive statistics and cumulative curves on the number and proportion of studies across the eligible meta-analyses that have been published in the last 5 years (2001-5), 10 years (1996-2005) and 20 years (1986-2005). Similar analyses examined the number and proportion of included participants. Sensitivity analyses addressed 5-, 10- and 20-year estimates using the year of the literature search rather than 2005 as reference. Using 2005 as the reference year reflects better how recent the evidence is for current clinical

practice, while using the year of the literature search reflects how contemporary the evidence was at the last literature search.

We performed secondary analyses considering all studies on the same intervention contrast, regardless of whether they had been included in the meta-analysis of the selected primary outcome or not. We also estimated for each topic the proportion of the available studies and participants included in the primary outcome meta-analysis.

Conclusions from data published in the last decade in Cochrane meta-analyses

We assessed how many meta-analyses would be affected, if only data published in 1996-2005 were considered. Specifically, we recorded how many meta-analyses had such recent data; and how many would reach different inferences for the statistical significance of the summary effect ($p < 0.05$ or $p \geq 0.05$), as compared with analyses including all data (regardless of year of publication). Summary results were calculated with random effects that allow for variability across studies. We should caution that change in statistical significance does not mean that the estimated effect size is altered beyond chance. Given that most meta-analyses had very limited data overall, there was large uncertainty in the estimated effect size in recent compared to older published data. Direct comparisons of recent against older data would be underpowered to show even major differences in effect sizes in these meta-analyses.

Discussion of implications of including old trials in Cochrane meta-analyses

We examined whether each selected systematic review discussed any implications relating to the fact that some or all of the eligible studies might have

been old. We then examined whether reviews that discussed the implications of including old trials had included overall older trials than those that did not discuss any such issues.

Evaluation of recent meta-analyses published in major medical journals

Meta-analyses published in major medical journals are likely to have a most important impact on current clinical practice. We aimed to examine whether these high-visibility meta-analyses may be comprised of mostly recent trials and whether they discuss appropriately the implications of including old data.

We assessed meta-analyses published in 6 major medical journals (New England Journal of Medicine, Journal of American Medical Association, Lancet, British Medical Journal, Annals of Internal Medicine ,and Public Library of Science Medicine) during the last semester of 2005 (July to December). We excluded systematic reviews where quantitative synthesis was not undertaken, and meta-analyses that included only non-randomized studies. When more than one comparison of intervention contrasts and/or outcomes existed we followed the same procedure as for the CDSR systematic reviews to select one meta-analysis per article.

From each eligible meta-analysis we extracted information on the year of the search strategy, number of synthesized studies, and proportion of studies published in the last five (2001-2005), ten (1996-2005) and twenty years (1986-2006). In seven cases the search strategy year was not reported, and year 2005 was used in all of them. Information on sample size per study and effect size were not available across these published meta-analyses in a standardized enough fashion to allow consistent analyses. Otherwise, we would evaluate the

proportion of recent data and the implications of including old data, as described for the CDSR meta-analyses above.

Analyses were conducted with Intercooled Stata 8.2 (College Station, TX). P-values are two-tailed.

Results

Database of Cochrane systematic reviews and meta-analyses

We randomly sampled 165 of the 1,651 systematic reviews of the CDSR. Of those, 8 were excluded (n=6 withdrawn, n=2 no quantitative synthesis). Of the remaining 157 reviews, the selected outcomes were binary in 133 and continuous in 24 (Appendix table 1).

Overall, 1,149 trials (1,650,701 participants) were included in the analysis considering only one outcome per systematic review and 1,479 trials (2,150,547 participants) were available, when we considered all trials available for the selected intervention contrast, regardless of outcome. Median number (interquartile range, IQR) of trials and participants were 5 (3-7) and 617 (227-1711) for the former analysis and 6 (3-11) and 788 (267-2101) for the latter, respectively.

Timing of last search in Cochrane meta-analyses

The median (IQR) year of the last search across the 157 systematic reviews was 2003 (2002-2004). There were 11 reviews where the year of last search was before 2000. In six of those 11 reviews the most recent included trial had been published at least 3 years or more before the last search.

Evidence from studies included in the selected Cochrane meta-analyses

Table 1 shows what data were published within 5, 10, or 20 years from the reference year (2005 or year of last search). Overall, very few meta-analyses had a substantial representation of recently published data (Figure 1). Most (64%) meta-analyses had absolutely no data published in the period 2001-5, and on median only a quarter of the data had been published within 5 years of the literature search. For the median meta-analysis, one third of the data had been published in the last 10 years and two thirds had been published within 10 years of the literature search. A 20-year window usually captured most or all the included data.

The picture was very similar, when we considered all available studies in each intervention contrast (Appendix table 3 and Appendix figure 1). The proportion of the recent evidence did not change. Most (61%) reviews had no data published in the period 2001-5 and on median only 23% of the data had been published within 5 years of the literature search. However, for 93 reviews (59%) the amount of the available evidence was larger than the amount of evidence included in the meta-analysis of the selected primary outcome. In 75 reviews, there were additional trials that had not been included in the selected meta-analysis (they had no data for the specific outcome); and in 18 reviews, there were no additional trials, but there were additional patients in some trials. The median (IQR) proportion of the available studies and participants included in the meta-analysis of the selected primary outcome was 100% (71-100%) and 94% (68-100%), respectively. For 18 reviews (11%), there were more than double available participants on the intervention contrast compared with the

information that could be synthesized in the selected meta-analysis.

Conclusions from data published in the last decade in Cochrane meta-analyses

Of the 157 meta-analyses, 47 did not have any data published in the last decade. Of the other 110 meta-analyses, 21 had all their data published in the last decade. In the remaining 89, exclusion of the data published before 1996 changed the level of statistical significance of the summary effects in 16 meta-analyses: in 9 cases the summary effects became non-statistically significant while they were statistically significant when all data were included; the opposite change was seen in 7 cases.

Discussion of implications of including old studies in Cochrane meta-analyses

Only 12 (8%) systematic reviews discussed possible implications stemming from the fact that some or all of the included trials had been published several years ago and the evidence may have been quite dated. Two of them concluded that year of publication was unlikely to matter. The other 10 expressed some concerns and 2 also clearly stated the importance of revisiting the clinical question currently with new trials (Table 2).

The median year of publication for the trials included in these 12 meta-analyses was older than in the other 145 that did not discuss the age of the studies ($p=0.003$, Mann-Whitney U test). However, 61 of the 70 reviews that included trials published before 1986 and 124 of the 136 reviews that included trials published before 1996 did not discuss at all the age of the included studies.

Evaluation of meta-analyses published in peer-reviewed journals

Twenty-five meta-analyses were identified, of which 22 had data available on the publication year of the synthesized studies (Appendix table 2). The

median (IQR) of the search strategy and number of synthesized studies were 2005 (2004-2005) and 11 (8-15), respectively. Median proportions of studies (IQR) published in the last 5, 10, or 20 years since 2005 were 39 (17-50), 68 (45-90), and 100 (92-100), respectively. Two meta-analyses had no studies published in the previous five years (2001-2005), while all had at least one study published in the last decade (1996-2005). Eighteen meta-analyses included at least one study published before 1996.

Four meta-analyses discussed implications of including old data (Table 2). One of these 4 meta-analyses also performed a sensitivity analysis with recent studies only (those published in the last decade).

The median year of publication for the trials included in the 4 meta-analyses was not statistically significantly different than in the other 19 that did not discuss the age of the studies ($p=0.46$, Mann-Whitney U test). Overall 7 of the 9 meta-analyses that included trials published before 1986, and 14 of the 18 meta-analyses that included trials published before 1996 did not discuss at all the age of the included studies.

Discussion

Our analysis suggests that even with the best intentions, evidence-based medicine has to rely on some old evidence. The majority of the analyzed Cochrane systematic reviews had been updated in the last two years. Even when results were corrected for the year of the last literature search, typically very limited data had been published within 5 years of the last search. Almost a third of the Cochrane meta-analyses had no data published in the last decade.

In another 10% statistical significance would change if data were limited to the last decade. Most Cochrane reviews did not address the implications of including potentially old data.

Typically, recent evidence was not lacking because Cochrane reviews were not up-to-date. Review updates are demanding and their performance may have to be explicitly justified.¹⁴⁻¹⁶ However, we should caution that although the average CDSR is probably up-to-date, for some rapidly moving fronts, even 1 year may bring major changes. This was recently highlighted in an interesting empirical evaluation by Shojania et al. that described a wide spectrum in the extent of outdateding of systematic reviews.¹⁷ There is increasing awareness that systematic reviews need to do their best to be and remain clinically relevant.¹⁸ The most recent, last-minute evidence often attracts wide attention from clinicians, as suggested by the popularity that late breaker sessions enjoy in major meetings. When coupled with fast-track publication in major journals,¹⁹ such studies may have a major impact in clinical practice. Systematic reviews need to find a way to remain relevant in such rapidly moving fronts, without sacrificing quality and without succumbing to unquestioned acceptance of each piece of new evidence without careful scrutiny.

Meta-analyses published in high-profile peer-reviewed journals tend to address newer interventions than the average CDSR review. Therefore they are expected to include mostly recent studies. Accordingly, almost all of them had included some trials published in the last 5 years and all of them included some trials published in the last decade. Nevertheless, even in these meta-analyses,

their large majority also included one or more older trials. Again, very few discussed the implications of including older evidence.

Evidence should not be undervalued simply because of its age. The amount of data, regardless of year of publication, is limited for most healthcare topics.^{20,21} We don't have the luxury of discarding trials simply because of their calendar year. For topics where well-designed old clinical trials are still relevant and conclusive, it is imprudent, and even unethical, to conduct new trials. For many topics, no new trials are performed because the issues may be considered settled or, conversely, the treatments may have become outdated. The question is whether old trials are as reliable as newer ones and whether treatments, management, and patient populations have changed in the interim. Occasionally early published results may differ compared to later publications.¹⁻³ This may reflect bias,²²⁻²⁴ time-dependent efficacy,²⁵ quality differences,^{26,27} or chance. However, one cannot generalize: old trials are not necessarily of worse quality,^{28,29} smaller,³⁰ or less externally valid^{7,8} than newer ones.⁵ Each topic needs a careful case-by-case scrutiny of whether the available evidence is relevant to current practice. Nevertheless, few systematic reviews discussed the implications of the time of publication on the relevance of the evidence. Systematic reviewers and clinicians should be sensitized to the potential importance of this issue.

For many interventions assessed in CDSR either no data were available that were published in the last decade, or the nominal statistical significance of the effect would change, if data were limited only to the last decade. We should

caution that decision-making based on nominal statistical significance is precarious.^{31,32} Our sample was too limited to evaluate formally whether the treatment effect size also differed significantly in older versus recent trials. However, previous empirical evidence suggests that in some fields decreasing treatment effects may be encountered in more recent trials.^{1-4,33}

The availability of evidence is sometimes further restricted by the lack of standardized outcomes across trials. Most meta-analyses could not use data from all participants even for the primary outcome. Consideration of trials with different outcomes would not increase the proportion of recent evidence, but sometimes it would increase considerably the amount of both recent and older evidence. Selective reporting of “positive” outcome results is a particular threat.^{34,36} Even if selective reporting is not guided by the nature of the results the availability of too many outcomes may still cause confusion.³⁷

Some caveats should be discussed. We used a consistent approach for selecting the year of publication to maximize objectivity. Nevertheless, a trial may have been conducted many years before it is published. Most trials don't specify when they started and when they completed enrollment and follow-up. Efficacy trials may take 3-10 or more years from the start of enrollment to publication.²² For smaller trials, the respective time frame may still amount to 1-4 years or more. Therefore, the proportion of recently conducted trials is even smaller than what we report based on publication year.

Second, we used CDSR for our primary analyses, because it is widely considered the most all-encompassing and up-to-date source for current

evidence on healthcare interventions across all medical fields. However, even CDSR represents work in progress and it does not capture all interventions yet.³⁸ Several old topics have not been addressed and may never be addressed, as they are not considered worth performing systematic reviews on. This is not a disadvantage, as it focuses the analysis on relevant clinical topics. Our evaluation of meta-analyses published in medical journals was unavoidably more restricted, since some information is not standardized and readily available in the same detail as in Cochrane reviews.

Acknowledging these caveats, our survey suggests that even though updating has been quite recent in most (but not all) examined reviews, for most healthcare interventions evidence from very recently published studies is scant. Old trials should not be discarded. However, clinicians should interpret medical evidence paying also attention the applicability and relevance of old data for current clinical practice.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JPAI had the original idea and both authors developed the protocol. NAP organized the databases and performed the analyses with help from JPAI. Both authors interpreted the data and the analyses and both wrote the manuscript.

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Figures

Figure 1 Plots of cumulative proportions of meta-analyses for proportion of trials and participants published in the last 5, 10, or 20 years from the reference year (Cochrane meta-analyses). The reference year is 2005 in the left panels and year of the last literature search in the right panels.

Tables

Table 1 Absolute numbers and proportion of data published within 5, 10, or 20 years from the reference year – Cochrane meta-analyses

Studies	Amount of data included in meta-analysis that were published in the time interval, median (IQR)			
	Reference year	Last 5 years	Last 10 years	Last 20 years
Absolute number	2005	0 (0-1)	2 (0-4)	3 (2-6)
	Last search	1 (0-3)	2 (1-5)	4 (2-6)
Proportion	2005	0 (0-17)	33 (0-71)	100 (60-100)
	Last search	25 (0-50)	69 (33-100)	100 (92-100)
Participants				
Absolute number	2005	0 (0-106)	127 (0-604)	419 (141-1379)
	Last search	84 (0-509)	275 (88-1056)	474 (173-1451)
Proportion	2005	0 (0-16)	50 (0-84)	100 (74-100)
	Last search	24 (0-67)	80 (30-100)	100 (94-100)

Table 2 Extracts from meta-analyses that discussed any implication of how old the included studies were

Topic	Publication years for trials: median (range)	Text
<i>Meta-analyses from Cochrane Database of Systematic Reviews</i>		
Chlorpromazine for schizophrenia*	1965 (1955-2000)	1.1 Adding the old to the new: This work includes studies that span nearly five decades of evaluative studies within psychiatry. It is possible that the rigour of these experiments has changed over time, as have the participants and even the formulation of the drug; it was thought that introduction of impurities in early formulations ...led to jaundice...the quality of schizophrenia trial reporting has not changed much over time [ref] or ...may even have declined [ref]. We have found no time-related differences in reporting of studies within this review and no suggestion of a change of the effect size over time. Synthesis of the results of studies seems justified.
Length of hospitalisation for severe mental illness	1975 (1975-1976)	The fact that all these trials were published in the 1970s... These trials... would be difficult to repeat today in the 'West' where large institutions have closed.
Systems for routine surveillance for people with diabetes mellitus*	1989 (1982-1994)	Heterogeneity could be due to a deterioration in hospital care since the early study by Hayes 1984. Again, this is unlikely given that hospital care compared favourably with the routine general practice care arm of the Hoskins 1992 trial.
Aversive smoking for smoking cessation†	1978 (1973-1987)	This is primarily due to the inadequacy of the methodology of smoking cessation studies from the 1970s and the beginning of 1980s when aversive smoking was a fashionable research topic. However, the crucial methodological developments including techniques for objective validation of self-reported smoking status, a recognition of the importance of sample size, and longer follow ups, became widespread only over the last 10 to 15 years... There is a clear need to revisit promising

		behavioural treatments...
Antibiotic prophylaxis regimens and drugs for cesarean section	1988 (1981-1989)	It is interesting to note that very few trials have been published since the late 1980s on this subject.
Regular vs as needed inhaled short acting b2-agonist (chronic asthma)	1998 (1992-2001)	...Concerns... can be traced back to the study of Sears in 1990... coming at a time when there was natural concern about peaks in asthma mortality, fears were raised that regular use of short acting beta agonists was a contributory factor.
Chemotherapy for non-small cell lung cancer	1990 (1972-1995)	...Clearly, such regimens are not used today, but the result could have implications for other disease sites, albeit that the administration of chemotherapy and the drugs used have changed considerably over the past twenty years.
Vitamin E supplementation for prevention of morbidity and mortality in preterm infants	1998 (1991-2002)	The majority of the clinical trials available in this systematic review were conducted in the 1980s or earlier... recommendations based on the available subjects must be viewed with caution when applied to the group of preterm infants inhabiting the modern neonatal unit. The current population includes many infants who are more premature and smaller than the infants on whom the recommendations were based. Furthermore, the only major long-term benefit of vitamin E supplementation demonstrated in this review was the prevention of blindness in very low birth weight infants, the incidence of which has been substantially reduced with laser photo coagulation.
Interventions in sexual dysfunction in women post pelvic radiotherapy†	1984 (1981-1987)	The evidence for the use of topical oestrogen or benzydamine in this situation is less clear due to date, quality and size of studies. In order to support their implementation these trials should be repeated with larger numbers to confirm the benefit.
Betamimetics for inhibiting preterm labour	1980 (1976-1992)	All trials were conducted before 1990, when antenatal corticosteroids were not widely used.
Long vs. short inspiratory times in	1989 (1980-1992)	These studies were performed at a time when mortality rates for ventilated infants with hypoxic respiratory failure were considerably higher than current rates [ref]. Major changes since their

neonates receiving mechanical ventilation		publication may reduce the applicability of the results of these meta- analyses. These changes include the routine use of antenatal steroids and postnatal surfactant. The major complications of HMD seen at the time of these studies (namely hypoxia and air leak despite intervening with IPPV) have been significantly reduced by surfactant replacement therapy [ref]. Although both these interventions have significantly altered the treatment of HMD, the risk of mortality has been markedly reduced but has not been removed. Morbidities such as air leak and BPD continue to occur. The classical definition of BPD by Northway 1967 was based on larger and more mature (>30 weeks) newborns and has been replaced by oxygen and/or ventilator dependency at 36 weeks post conceptual age to reflect the present population of newborn infants with HMD. These extremely low birth weight, extremely premature infants continue to have significantly high rates of BPD. None of the studies in this systematic review looked at ventilatory or oxygen requirements at 36 weeks.
Neoadjuvant chemotherapy for invasive bladder cancer	1999 (1991-2004)	These three trials are among the earliest trials of neoadjuvant chemotherapy and may be less relevant in today's context, where combination regimens are preferred.
<i>Meta-analyses from major medical journals</i>		
Risk for stroke for β blockers vs other antihypertensives	2000 (1985-2005)	Why has this suboptimum effect of blockers not influenced the people who draw up hypertension guidelines? One reason could be that blockers have been analysed together with diuretics, assuming that so called old drugs or conventional treatment—ie, drugs synthesised around the same time—would have the same treatment effects. Another reason could be that the largest studies, consisting of more than 69 000 of about 127 000 patients, have been published fairly recently (since 2002).. Second, since the trials were published during two decades, patient characteristics and hypertension care might have changed, aspects that are difficult to account for.

Prophylactic amiodarone after cardiac surgery for atrial fibrillation/flutter	2001 (1993-2003)	Two meta-analyses found no difference in the incidence of stroke in patients who received amiodarone therapy [ref]. Our apparent discrepant results may be due to the fact that we included recent studies that were not included in the earlier reviews [ref].
Warfarin plus aspirin after myocardial Infarction	2001 (1990-2004)	All studies were conducted in the 1990s before coronary artery stenting became widespread. As a result of several comparative trials, warfarin is not considered a standard of care in stented patients [ref].
Long- vs short-term anticoagulant in venous thromboembolism	1995 (1972-2004)	When only recent (within the last 10 years)..... were included, the risk of recurrence was still less with long term anticoagulation.

* Reviewers conclude that year of the studies does not influence results. †Reviewers suggest revisiting the question with new trials

ref: reference mentioned

Additional files

appendix.doc – List of Cochrane reviews, references from peer-reviewed journals meta-analyses, secondary analyses tables, and appendix figure legend.

appendix_fig1.pdf – **Appendix figure.** Plots of cumulative proportions of meta-analyses for proportion of trials and participants published in the last 5, 10, or 20 years from the reference year for all available data in each intervention contrast. The reference year is 2005 in the left panel and year of the last literature search in the right panel.