uOttawa

L'Université canadienne
Canada's university

FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTOCTORALES

uOttawa

L'Université canadienne
Canada's university

FACULTY OF GRADUATE AND POSDOCTORAL STUDIES

Andrea Catherine Tricco
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

Ph.D. (Population Health)
GRADE / DEGREE

Institute of Population Health
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Publication Bias of Systematic Reviews

TITRE DE LA THÈSE / TITLE OF THESIS

David Moher
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

Jamie Brehaut

Mario Cappelli

Joseph Beyene
(University of Toronto)

Peter Tugwell

Gary W. Slater
Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

Publication Bias of Systematic Reviews

Andrea C. Tricco

Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements
For the PhD degree in Population Health

Institute of Population Health
Faculty of Graduate and Postdoctoral Studies
University of Ottawa

Your file Votre référence
ISBN: 978-0-494-64729-5
Our file Notre référence
ISBN: 978-0-494-64729-5

"*Search for the truth is the noblest occupation of man; its publication is a duty*"

Madame de Stael (1766-1817)

Table of Contents

Title **Page #**

List of tables....vi

List of figures....vii

List of acronyms....viii

Abstract....ix

Acknowledgments....xi

Introduction....xiv

References....xvi

Chapter 1: Background....1

Publication bias at the individual study level....1

Ways of categorizing publication bias....2

Indirect publication bias: Proportion of positive results in the published literature....3

Direct publication bias: Surveys of investigators....3

Direct publication bias: Retrospective cohort studies....4

Direct publication bias: Experimental studies....5

Publication bias at the systematic review level....5

Indirect publication bias: Proportion of positive results in published systematic reviews....5

Direct publication bias: Survey of individual-patient data meta-analysts....6

Relation to population health....7

Figure: The impact of publication and related biases....9

Table 1: Glossary of publication bias definitions....10

Table 2: Examination of publication biases in systematic reviews....11

References.....14

Chapter 2: Conceptual model.....19

Introduction.....19

Methods.....20

Results.....22

Interviewee characteristics.....22

Overview of the conceptual model.....22

Influence of systematic review characteristics on the publication process.....23

Influence of systematic reviewers on the publication process.....24

Influence of journals, journal editors and peer reviewers on the publication process.25

Influence of the funding organization on the publication process.....26

Influence of the public on the publication process.....26

Uptake of systematic review results.....27

Policy/clinical impact of systematic reviews.....27

Effect on health outcomes.....28

Discussion.....28

Figure: Conceptual model for the publication process, dissemination, and utilization of systematic reviews.....30

Table 1: Interviewee characteristics.....31

Table 2: Interviewee responses by categories of the conceptual model.....32

Table 3: Interviewee responses by categories of the conceptual model.....33

Appendix A: Ethics approval for interviews 34

Appendix B: Interview consent form and interview guide.....35

References.....38

Chapter 3: Paper 1.....39

Chapter 4: Paper 2.....40

Chapter 5: Paper 3.....41

Chapter 6: General discussion and conclusion.....42

Table: Variables potentially associated with the publication of systematic reviews..52

References.....53

Chapter 7: Statement of Contributions of Collaborators and/or Co-Authors 54

Cross-sectional study (paper 1).....54

International survey (paper 2).....54

Retrospective cohort study (paper 3).....54

Appendix C: Copyright Permissions.....56

References.....60

List of Tables

Table **Page #**

Chapter 1 Table 1: Glossary of publication bias definitions.....10

Chapter 1 Table 2: Examination of publication biases in systematic reviews.....11

Chapter 2 Table 1: Interviewee characteristics.....31

Chapter 2 Table 2: Interviewee responses by categories of the conceptual model.....32

Chapter 2 Table 3: Interviewee responses by categories of the conceptual model.....33

Chapter 6 Table: Variables potentially associated with the publication of systematic reviews.....52

List of Figures

Figure **Page #**

Chapter 1 Figure: The impact of publication and related biases.....9

Chapter 2 Figure: Conceptual model for the publication process, dissemination, and utilization of systematic reviews.....30

List of acronyms:

CADTH = Canadian Agency for Drugs and Technologies in Health

CIHR = Canadian Institutes for Health Research

CI = confidence interval

CRG = clinical review group

DARE = Database of Abstracts of Reviews of Effectiveness

HR = hazard ratio

ICMJE = International Committee of Medical Journal Editors

IPD = individual patient data

IQR = inter-quartile range

RCT = randomized controlled trial

SR = systematic review

Abstract

Background: Systematic reviews (SRs) are increasingly viewed as useful decision-making tools yet the extent of SR publication bias is under-explored. Through my thesis, I aimed to investigate the extent of SR publication bias.

Methods: A conceptual model was derived from literature searches and one-on-one interviews and three studies were conducted: a cross-sectional study of 296 SRs indexed in MEDLINE and published in November 2004, an international survey of 625 corresponding or first authors of a published SR in 2005, and a retrospective cohort study of 411 Cochrane protocols from Issues 2-4, 2000 and Issue 1, 2001 that were followed until Issue 1, 2008 in The Cochrane Library.

Main findings: The interviewees reported 40 unpublished SRs and the conceptual model showed that publication bias can permeate all steps of the publication process, from conceptualization to ultimate effect on health outcomes. The cross-sectional study identified favourable results in 57.7% of Cochrane reviews and 64.3% of non-Cochrane reviews with a meta-analysis of the primary outcome and non-Cochrane reviews were twice as likely to have positive conclusions as Cochrane reviews (p-value≤0.05). In the international survey, participants reported 1405 published (median: 2.0, range: 1-150) and 199 unpublished (median: 2.0, range: 1-53) SRs. In the retrospective cohort study, 19.1% (71/372) of eligible Cochrane protocols remained unpublished and the median time to publication was 2.4 years (range: 0.15-8.96). A shorter time to publication was associated with the Cochrane review being subsequently updated versus not updated (n=100/372 Cochrane reviews that were updated, hazard ratio: 1.80 [95% confidence interval: 1.39-2.33 years]) and a longer time to publication was associated with the Cochrane review having two published versus one protocol (n=10/372 Cochrane reviews with two published protocols, 0.33 [0.12-0.90 years]).

General conclusions: Over 300 unpublished SRs were identified through the interviews conducted for the conceptual model and the three studies that comprised my thesis. Possible solutions for minimizing or avoiding SR publication bias include registration of SRs at inception, educating the research community about the importance of publishing SRs, and having a general online open-access journal with rapid peer review that is dedicated to only publishing the results of SRs (including their updates).

Acknowledgements

First and foremost I thank my husband Jason Tadros for his love and never-ending support. Jason has always encouraged me to strive for my best at all times. Whenever I doubted myself during my PhD, Jay always believed in me. He was always positive and reminded me about all of the wonderful opportunities that were provided to me. I thank Jay for his patience; he spent endless time proof-reading essays for courses and read every single page of my thesis. If it was not for him, I would not be where I am today. I also thank my son Logan Tadros who allowed me the time to complete this PhD thesis while being just a little baby. The sleepless nights have been worth having such a beautiful and healthy baby who I love so much!

I thank my supervisor Dr David Moher. David, meeting you was truly a blessing. You have provided me with abundant opportunities. You have spent endless hours mentoring me and going over my thesis. I am very grateful to you for everything; you have been the best PhD supervisor that I could ever wish for. You have also been my confidant and friend throughout the years. It's been a lot of fun getting to know you. I truly appreciate your ceaseless support and sense of humour. Thank-you for being so down to earth even though you're a world-renowned researcher; it really is one of your best qualities.

I thank my committee members Drs Jamie Brehaut and Mario Cappelli for their support over the years. I truly appreciate everything you've done for me. You have made my thesis more scientifically rigorous. I know that you have spent a lot of time going over my thesis and publications and for that I'm incredibly grateful. Thank-you for pushing me to be the best I can be. I also thank my examiners Dr Peter Tugwell and Dr Joseph Beyene for their time, useful feedback, encouragement, and support.

...And where would I be without my colleagues? I thank Kristi Adamo, Tanya Horsley, Jennifer Tetzlaff, Simon Dagenais, and Margaret Sampson for their wisdom, encouragement, mentorship, and laughter. I thank my MSc mentor Ba' Pham for introducing me to David Moher and for all of the research and life lessons. I also thank Andrea Anonychuk and Maraki Fikre Merid for all of their encouragement, support, and love. Ladies, it has been great going through our PhD programs together. Being moms at the same time during the process was definitely a bonus!

I thank my sister Shirra Cremer for the daily phone calls, encouragement, love, and advice throughout the years. Shirra, it's so great having you in my life. Not only are you an amazing person but you also understand epidemiology. Your enthusiasm about research is contagious. Always remember the pyramid of evidence! I would never have been able to work from home without being lonely if it wasn't for you. I can't wait for the day for us to work side-by-side.

I thank my PhD classmates for their support and guidance. It's been great getting to know all of you. You have definitely made my PhD experience richer. I especially thank Vivien Runnels for all of her assistance with my one-on-one interviews and teaching me how to be a mom and run a household.

I acknowledge the support from Chalmers Research Group, the Canadian Agency for Technologies in Health, the University of Ottawa, and the Canadian Institutes of Health Research. Your generous financial support has made my thesis more scientifically rigorous and has provided me with many opportunities, such as presenting my research at national and international conferences.

For the first article of my thesis, I thank Dr. Kay Dickersin and Dr. David Gough for pilot-testing the questionnaire and providing invaluable feedback on the original survey. I

also thank Margaret Sampson for validating the literature search and for her assistance with obtaining the random sample, Jennifer Tetzlaff for advice on the survey conduct, Raymond Daniel for assistance with document acquisition, and David Hallett for statistical consultation. Furthermore, I thank Tammy Jakobsen, Beverly MacLaren, and Joan Fawcett for their assistance with survey administration.

For the second article of my thesis, I thank Jacqueline Tetroe and Dr. Mario Cappelli for their input on the original protocol of the study; Margaret Sampson for assistance with the literature searches; Raymond Daniel for assistance with document acquisition; and David Hallett and Maggie Hong Chen for their statistical consultation.

For the third article of my thesis, I thank Dr. Mario Cappelli and Jacqueline Tetroe for their input on the original protocol of the study, Raymond Daniel for assistance with obtaining the sample of Cochrane reviews, and Carmen Ng for her assistance with pilot-testing the data abstraction forms. I also thank Dr. Sally Hopewell of the UK Cochrane Center for her expert advice on the study methods and for lending us the Cochrane CDs, as well as Lisa McGovern of the Canadian Cochrane Network and Centre for lending us the Cochrane CDs.

Introduction

Publication bias occurs when "investigators, reviewers, and editors submit or accept manuscripts for publication based on the direction or strength of the study findings"(1). Studies with particular characteristics (e.g., statistically positive results) have a better chance of being published than those without these characteristics (2). The consequences of publication bias can be severe. A recent meta-analysis showed that publication bias exaggerated the estimate of an anti-depressant's effectiveness by 32% (range: 11-69%), on average (3).

The extent of publication bias among systematic reviews (SRs) is under-explored. Researchers across various disciplines have consistently shown that publication bias may lead to inaccurate answers in randomized controlled trials and observational studies (4). Publication bias of SRs is important because patients, healthcare practitioners, and public policy-makers increasingly use SR results to inform their decisions. SRs are a building block for clinical practice guidelines and decision analyses (5), patient decision-aids (6), and policy briefs (7;8). There are an increasing number of SRs on the determinants of health and health inequities (9-11). Thus, SR publication bias may lead to decisions based on inaccurate information, ranging from individual treatments to population health interventions.

My main objective was to investigate the extent of SR publication bias. Specifically; I aimed to describe the publication process of SRs and its susceptibilities to publication bias through a conceptual model; examine which SR characteristics are associated with favourable results and positive conclusions and determine the level of concordance between the results and conclusions of SRs through a cross-sectional study of 296 SRs; establish the frequency of completed but unpublished SRs and explore factors contributing to their occurrence through an international survey of 625 corresponding authors of published SRs;

and determine the factors that predict the time to publication of SRs through a retrospective cohort study of 411 Cochrane protocols.

References

(1) Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA 1990 Mar 9;263(10):1385-9.

(2) Dickersin K. Publication bias: recognizing the problem, understanding its origins and scope, and preventing harm. In: Rothstein, Sutton, Borenstein, editors. Publication bias in meta-analyses – prevention, assessment and adjustments.New York, New York: John Wiley & Sons Ltd.; 2005.

(3) Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008 Jan 17;358(3):252-60.

(4) Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess 2000;4(10):1-115.

(5) Cook DJ, Greengold NL, Ellrodt AG, Weingarten SR. The relation between systematic reviews and practice guidelines. Ann Intern Med 1997 Aug 1;127(3):210-6.

(6) Elwyn G, O'Connor AM, Bennett C, Newcombe RG, Politi M, Durand MA, et al. Assessing the quality of decision support technologies using the International Patient Decision Aid Standards instrument (IPDASi). PLoS ONE 2009;4(3):e4705.

(7) Lavis J, Davies H, Oxman A, Denis JL, Golden-Biddle K, Ferlie E. Towards systematic reviews that inform health care management and policy-making. J Health Serv Res Policy 2005 Jul;10 Suppl 1:35-48.

(8) Lavis JN, Posada FB, Haines A, Osei E. Use of research to inform public policymaking. Lancet 2004 Oct 30;364(9445):1615-21.

(9) Tugwell P, O'connor A, Andersson N, Mhatre S, Kristjansson E, Jacobsen MJ, et al. Reduction of inequalities in health: assessing evidence-based tools. Int J Equity Health 2006;5:11.

(10) Beach MC, Gary TL, Price EG, Robinson K, Gozu A, Palacio A, et al. Improving health care quality for racial/ethnic minorities: a systematic review of the best evidence regarding provider and organization interventions. BMC Public Health 2006;6:104.

(11) Newmann SJ, Garner EO. Social inequities along the cervical cancer continuum: a structured review. Cancer Causes Control 2005 Feb;16(1):63-70.

Chapter 1: Background

Publication bias occurs when "investigators, reviewers, and editors submit or accept manuscripts for publication based on the direction or strength of the study findings" (1). Studies with particular characteristics (e.g., statistically positive results, large effect sizes) have a better chance of being published than those without these characteristics (2). Consequently, journals might be unwittingly reducing the selection of published articles, potentially leading to decisions that are not based on the full spectrum of evidence. Worse still, some reports might never be published because their results have not met a particular threshold (e.g., $p<0.05$).

Researchers have recognized for centuries that they have a scientific obligation to disseminate the results from their studies (2-4), especially in research environments with scarce resources. However, evidence of the extent of publication bias, as well as its sources, and factors, has only become available within the past few decades (2). The majority of research on publication bias has occurred at the individual study level (e.g., randomized controlled trials - RCTs) while publication bias of systematic reviews (SRs) is under-explored. It is for this reason publication bias of SRs is the focus of my thesis. Evidence for publication bias at the individual study level and SR level will be described below.

Publication bias at the individual study level

The impact of publication bias has been outlined in a conceptual model (Figure) (5). Statistically significant positive results have a higher profile of dissemination versus statistically non-significant results. For example, publication bias exaggerated the estimate of an intervention's effectiveness by 32% (range: 11-69%), on average in a recent meta-analysis (6). An evidence-informed policy-maker or healthcare practitioner may therefore make inappropriate health policy or clinical decisions based on incomplete information from the

published literature. This may lead to wasting limited health resources and inappropriate care of patients.

Many examples of the consequences of publication bias have been documented (5). In one case, a trial showed that acute myocardial infarction patients treated with class 1-antiarrythmic drugs were significantly more likely to die than those in the placebo group. Due to commercial reasons, the trial was stopped early and its results were never published or disseminated. The use of these drugs continued on for another 10 years until two larger trials were subsequently published, confirming that these drugs were associated with increased mortality (7;8). It has been estimated that between 20,000 and 70,000 additional deaths were observed because this evidence was never fully disseminated to healthcare practitioners prescribing these drugs (7). The lack of dissemination of the early trial potentially contributed to some of these deaths.

Ways of categorizing publication bias

A recent SR examined bias and confounding that can occur during a SR (9). Eight different types of publication bias were identified, including full study publication bias (5;10), grey literature bias (5;11), funding bias (12;13), time-lag bias (5;14), abstract to full publication bias (5;15;16), place of publication bias (5), country of conduct bias (5), and language bias (5). In this review, my colleagues and I provided a glossary of definitions (Table 1) and summarized the evidence for the different types of publication bias (Table 2).

According to some researchers, another form of publication bias is outcome reporting bias (17). Outcome reporting bias happens when changes occur between primary outcome(s) reported in the protocol versus those reported in the final publication (18) or when studies measuring multiple outcomes only report those outcomes that were statistically significant (5). Full study publication bias occurs when an entire study is not published while outcome

reporting bias occurs when outcomes that are non-statistically significant are not published. The focus of my thesis is on full study publication bias of SRs.

Evidence for publication bias has been previously classified as being either direct or indirect (5;19). Direct evidence of publication bias comes from researchers admitting the occurrence of publication bias. This information can be obtained through surveys, retrospective cohort studies of registered or funded studies, and experimental studies examining the proportion of studies being accepted or submitted based on the direction or strength of the study results (5). Indirect evidence consists of a higher proportion of positive results or larger effect sizes in small studies in the published literature (5). This evidence is indirect because the true proportion of positive results or large effect sizes for the body of literature that the sample came from is unknown.

Indirect publication bias: Proportion of positive results in the published literature

Sterling (a Canadian researcher) and Smart were among the first to provide indirect evidence of publication bias in 1959 and 1964, respectively. They demonstrated that there were a larger proportion of positive studies published in psychology and education journals than studies with negative or non-statistically significant results (20;21). Sterling updated this research in 1995 and found similar results to those reported previously (22). These results have been confirmed by other studies across medical, social science, and behavioural science research areas (23-30).

Direct publication bias: Surveys of investigators

Surveys of peer reviewers and investigators have consistently found that statistically significant positive studies are more likely to be submitted for publication and accepted for publication (31-35). In one of these surveys, corresponding authors of over 2,400 reports of RCTs were sent a postcard survey asking whether they had any unpublished trials and if so

how many (1). A second more in-depth mail-based survey was sent to clinical trialists, to gather specific information on each identified unpublished trial. Questions included whether statistical significance in favour of the treatment of interest was achieved and reasons for not publishing the trials. Results showed that 14% of unpublished trials favored a new therapy compared to 55% of published reports (p-value <0.001). These results were consistent across studies conducted within the social science, psychology, and medical disciplines (31;33-35).

Direct publication bias: Retrospective cohort studies

The retrospective cohort is a useful study design to examine bias. In a traditional retrospective cohort design, data is reconstructed about persons at historical time intervals. The current status of members within this sample is determined for a condition (e.g., death). Levels of past exposure to risk factors are identified for subsets of the sample. Through analysis, the relationship between past exposure and outcome(s) are determined (36).

At least six retrospective cohort studies of publication bias at the individual study level have been conducted (14;37-43). In these retrospective cohort designs, the publication status of research proposals submitted to either research ethics boards or national funding agencies was determined. Instead of following people, these studies followed studies (e.g., RCTs) over time to determine the relationship between exposures (e.g., statistically significant results, funding status, type of study design) and outcomes (e.g., published versus unpublished). Major findings from these studies included that 1) investigators, peer reviewers, and editors contributed to the existence of publication bias, 2) investigator preferences (e.g., negative results, lack of interest) was the dominant reason for not publishing clinical trials and observational studies, 3) positive results were more likely to get published [49], 4) funded studies as opposed to unfunded studies were more likely to be published, and 5) those with multiple data collection sites were more likely to be published.

Direct publication bias: Experimental studies

Publication bias has been examined in at least two experimental studies (44;45). In both studies, similar manuscripts with positive and negative findings were randomly submitted to journals or peer reviewers to determine whether recommendations to publish the papers differed. Both studies found the manuscripts with positive findings were more likely to be accepted for publication.

The following is apparent from the literature of publication bias at the individual study level: 1) publication bias comes in many forms, some less obvious than others, 2) publication bias is a problem in many types of literature, and 3) there are different points in the process from study proposal to final publication where bias can occur. The totality of research at the individual study level can be used to examine publication bias at the SR level, which will be discussed below.

Publication bias at the systematic review level

Very few studies have studied publication bias at the SR level. Only two studies have examined indirect SR publication bias and one study has examined direct SR publication bias. The results of these three studies will be described below.

Indirect publication bias: Proportion of positive results in published systematic reviews

In one study, the results of Cochrane reviews were compared with SRs published in four general medicine journals and four specialist journals (46). Sixty-nine pairs of Cochrane and journal meta-analyses including at least five controlled clinical trials with binary endpoints were analyzed. The results indicated that journal reviews reported more beneficial results than Cochrane reviews, on average ($p=0.007$, McNemar's paired analysis).

In another study, a sample of 193 SRs published in the Database of Abstracts of Reviews of Effectiveness (DARE) was examined to assess issues and methods relevant to

publication bias (5). SRs were only included if they met DARE's strict criteria. For example, the SR had to have a clear question, appropriate literature search, explicit inclusion/exclusion criteria, and appropriate synthesis of results.

This study examined many factors, such as the number of reviews that searched for and included unpublished studies, and had significant/positive, non-significant/negative, or unclear conclusion statements (5). These factors were compared by whether the SR performed a meta-analysis or did not perform a meta-analysis. The results indicated that searching for unpublished material, discussing publication bias, and assessing publication bias was more commonly reported in meta-analytic reviews than narrative reviews. Furthermore, there were a higher proportion of meta-analytic reviews with positive conclusions compared to narrative reviews (68% vs. 42%).

Direct publication bias: Survey of individual-patient data meta-analysts

One study examined publication bias of SRs by interviewing authors of 38 individual patient data (IPD) meta-analyses of cancer-related topics (47). The researchers found that statistically non-significant results took longer to publish and were published in lower impact journals than statistically significant results. Although informative, the generalizability of this study is limited because IPD meta-analyses account for a small minority of SRs and the included meta-analyses were only within a specific clinical content area.

It is apparent that SR publication bias is under-explored from the literature reviewed above. The studies that examined indirect SR publication bias included a small sample of SRs with strict inclusion criteria, limiting their generalizability (5;46). Furthermore, research examining publication issues surrounding the more common aggregate data SR might find differing results than the study examining IPD meta-analyses (47). Through my thesis, I

aimed to examine publication bias of SRs using a broad spectrum of reviews across many different research areas, such as population health.

Relation to population health

According to Dunn and Hayes, population health is "the health of a population as measured by health status indicators and as influenced by social, economic, physical environments, personal health practices, individual capacity and coping skills, human biology, early childhood development, and health services" (48). The Public Health Agency of Canada identifies population health as "a key concept and approach for policy and program development aimed at improving the health of Canadians" (49). A population health approach involves 1) the determinants of health (50), 2) multi-disciplinary teams, theories, and methods (51), 3) intersectoral collaborations beyond the health sector (52), and 4) evidence-informed decision-making (49). The overall goal of a population health approach is to improve the health and well-being of the entire population (48) and reduce inequities, which can be defined as unfair systematic differences in one or more aspects of health across socially, demographically, or geographically defined groups of the population (53;54).

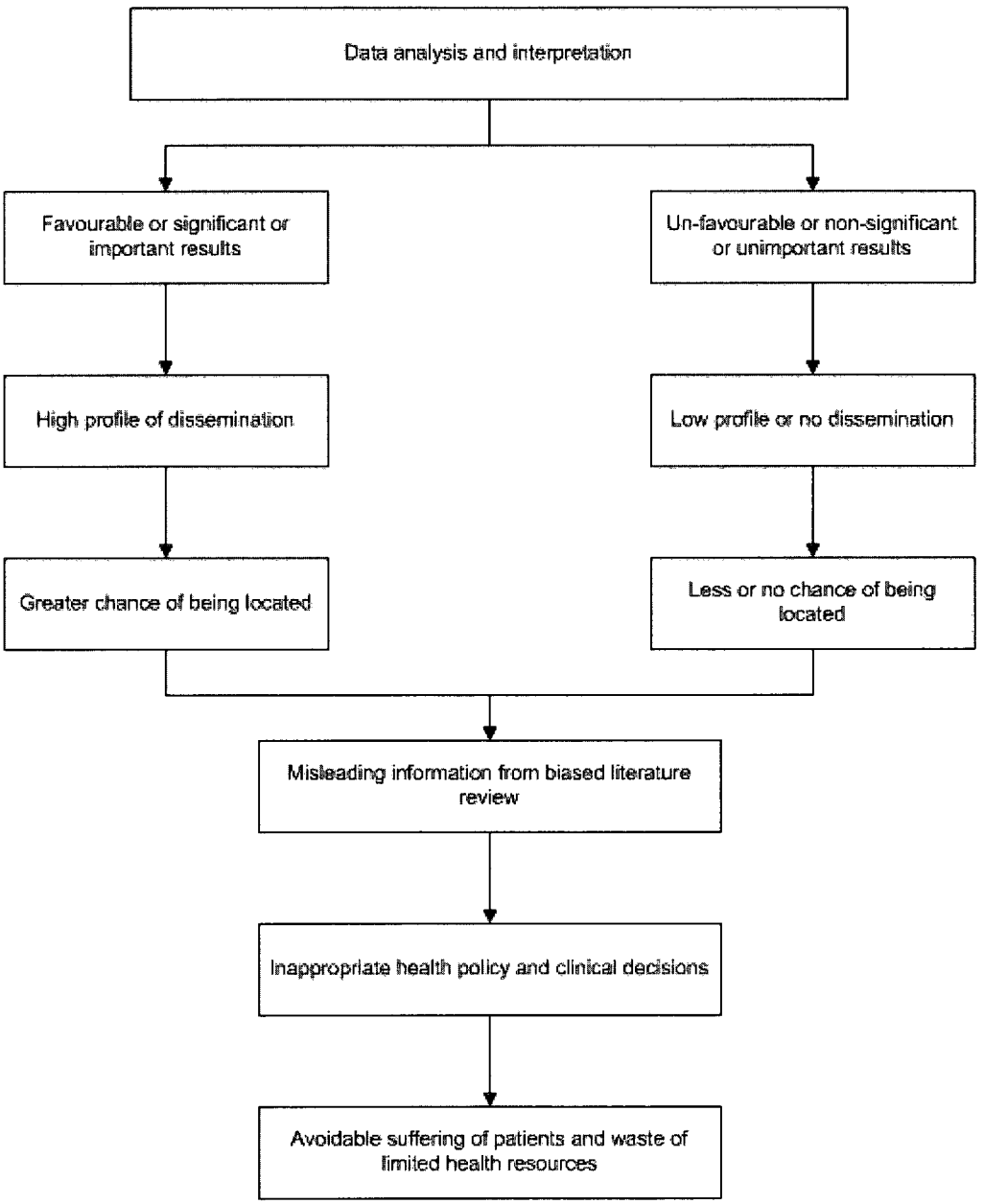
Health policy-makers have little time to effectively keep up with the literature. SRs offer a convenient way for them to keep up-to-date with the current evidence. As such, population health policy-makers increasingly view SRs as a useful decision-informing tool (55-57). The increased utility of SRs has probably contributed to an increase in their publication rates. A recent estimate suggests that 2500 new SRs are published annually in English in MEDLINE (58). This is about 166 times the rate reported in 1991 (59) and is likely an underestimate of the number of SRs being conducted and published annually.

It can be argued that publication bias of SRs on population health topics may lead to increased detrimental effects, as their results apply to the broad determinants of health and

have the potential to affect large numbers of individuals in the population. Reasons for publication bias in population health research include vested interests (e.g., passive smoking and the tobacco industry) (60;61), and withholding information due to government suppression (62). A recent systematic review of population health injury prevention programs for children indicated that this body of evidence might be affected by publication bias because interventions with favourable results were more likely to be pubilshed (63). This indicates that publication bias of SRs is an important issue for researchers working within population health as well.

If SR publication bias exists, this may invalidate 1) the SRs themselves, 2) clinical practice guidelines, decision analyses, patient decision aids, and policy briefs, as SRs are often an important building block to their development, and 3) healthcare and policy decisions affecting individuals and entire populations. SR publication bias may also influence primary research, as SRs are often used to justify research at the individual study level (e.g., RCTs) (64). Through my thesis I provided insight into the extent of SR publication bias through the following: 1) a conceptual model that explored the publication process of SRs and its susceptibilities to publication bias, 2) a cross-sectional study of 296 SRs (paper 1), 3) an international survey of 625 corresponding authors of published SRs (paper 2); and 4) a retrospective cohort study of 411 Cochrane protocols (paper 3).

Figure: The impact of publication and related biases



Source: Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ: Publication and related biases. Health Technol Assess 2000, 4: p.23.

Table 1: Glossary of publication bias definitions

Type of publication bias	Definition
Full study publication bias	Occurs when investigators, reviewers, and editors submit or accept manuscripts for publication based on the direction or strength of the study findings [7].
Grey literature bias	Occurs when the results reported in journal articles are systematically different from those presented in other reports, such as working papers, dissertations, or conference abstracts [5].
Funding bias	Biases in the design, outcome, and reporting of industry-sponsored research to show that a drug shows a favorable outcome [22].
Time-lag bias	Occurs when the speed of publication depends on the direction and strength of the trial results [80].
Abstract to full publication bias	Occurs when the full publication of studies that have been initially presented at conferences or in other informal formats is dependent on the direction and/or strength of their findings [5].
Place of publication bias	Occurs when a journal is more enthusiastic toward publishing articles about a given hypothesis than other journals because of editorial policy or readers' preference [41].
Country of conduct bias	Occurs when the country of publication is associated with the strength or direction of research findings [5].
Language bias	Occurs when languages of publication depend on the direction and strength of the study results [81].

Source: Tricco AC, Tetzlaff J, Sampson M, Fergusson D, Cogo E, Horsley T, Moher D. Few systematic reviews exist documenting the extent of bias: a systematic review. J Clin Epidemiol. 2008 May;61(5):422-34.

Table 2: Examination of publication bias in systematic reviews

Author/Year, Reference	Details of biases examined	Pooled results of SR: #comparisons, ES: (95% CI)
1. Sampling bias: biases in identifying studies for the systematic review		
A) Publication bias		
i) Full study publication bias		
Song/2000 (5)	Determining the proportion of statistically significant results in the published literature over time	Not conducted
Song/2000 (5)	Examining the association between type of result (e.g., statistically significant favourable) and publication status (e.g., published)	4 comparisons, adjusted OR for publication bias 2.54 (1.44, 4.47)
Dubben/2005 (10)	Examining the association between type of result and publication status	Not conducted, reported a median reported OR of 2.3
ii) Grey literature bias		
Song/2000 (5)	Examining the association between grey literature and type of result	Not conducted
Hopewell/2002 (11)	Examining the association between grey literature and type of result	Not conducted
iii) Funding bias		
Lexchin/2003 (12)	Examining the association between funding source and publication status	Not conducted
	Examining the association between funding source and type of result	18 comparisons, pharmaceutical sponsorship associated with positive outcomes OR: 4.05 (2.98, 5.51), homogeneity (p=0.17)
	Examining the association between funding source and study quality	Not conducted
Bekelman/2003 (13)	Examining the association between industry sponsorship and type of result	8 comparisons, industry sponsored studies associated with positive results OR:3.60 (2.63, 4.91), homogeneity (p=0.75)
	Examining the association between industry sponsorship and study quality	Not conducted
iv) Time-lag bias		
Song/2000 (5)	Examining the association between time to publication and type of result	Not conducted
Hopewell/2001	Examining the association between time to	Not conducted

(14)	publication and type of result	
v) Abstract to full publication bias		
Song/2000 (5)	Examining the association between abstract characteristics (e.g., basic science, favourable result) and being published in full	Not conducted
von Elm/2003 (15)	Examining the association between abstract characteristics and being accepted for a conference presentation	46% abstracts submitted to meetings were accepted, acceptance when topic was basic vs clinical OR:3.49 (2.50, 4.86) and the outcome was statistically significant favourable vs statistically significant unfavourable OR:1.67 (1.16, 2.39), heterogeneity NR
	Examining the association between abstract characteristics and being published in full	Abstracts were more likely to be published when topic was basic vs clinical OR:2.29 (1.75, 2.98), the outcome was positive vs negative OR:2.07 (1.58, 2.71), and it was an oral presentation vs poster OR:1.53 (1.15, 2.03), heterogeneity NR
	Examining the association between being rejected for a conference presentation and being published in full	27% abstracts published despite meeting rejection
*Scherer/2005 (16)	Examining the association between abstract characteristics and being published in full	44.5% abstracts subsequently published, more likely to be published when there are statistically significant results RR:1.30 (1.14, 1.47, χ^2: p=0.0006), results favour treatment RR:1.17 (1.02, 1.35, χ^2: p=0.01), positive results from RCTs RR:1.18 (1.07, 1.30, χ^2: p=0.14), oral presentation RR:1.28 (1.09, 1.49, χ^2:p<0.0001), accepted for meeting presentation RR:1.78 (1.50, 2.12, χ^2: p<0.0001), RCT design OR:1.24 (1.14, 1.36, χ^2: p=0.56), basic research RR:0.79 (0.70, 0.89, χ^2: p=0.0009), and higher quality RR:1.30 (1.00, 1.71, χ^2: p=0.68)
Scherer/1994 (65)	Examining the association between abstract characteristics and being published in full	11 comparisons, 51% abstracts subsequently published, more likely to be published when there are significant results RR:1.17 (0.99, 1.39) and a sample size above the median RR:1.48 (1.14, 1.94), homogeneity (p=0.01)
vi) Place of publication bias		
Song/2000 (5)	Examining the association between study characteristics (e.g., topic examined, statistically significant favourable result) and being published in different journals	Not conducted
vii) Country of conduct bias		
Song/2000	Examining the association between study	Not conducted

(5)	characteristics and being conducted by researchers from different countries	
viii) Language bias		
Song/2000 (5)	Examining the association between language of publication and study characteristics (e.g., publication status, type of result)	Not conducted

Note: *Represents the major publication of the systematic reviews.
Abbreviations: SR (systematic review), MA (meta-analysis), ES (effect size), CI (confidence intervals), RCTs (randomized controlled trials), OR (odds ratio), RR (relative risk).

Source: Tricco AC, Tetzlaff J, Sampson M, Fergusson D, Cogo E, Horsley T, Moher D. Few systematic reviews exist documenting the extent of bias: a systematic review. J Clin Epidemiol. 2008 May;61(5):422-34.

References

(1) Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA 1990 Mar 9;263(10):1385-9.

(2) Dickersin K. Publication bias: recognizing the problem, understanding its origins and scope, and preventing harm. In: Rothstein, Sutton, Borenstein, editors. Publication bias in meta-analyses – prevention, assessment and adjustments.New York, New York: John Wiley & Sons Ltd.; 2005.

(3) Ferriar J. Medical Histories and Relfexions. London: Cadell and Davies; 1792.

(4) Hall MB. In defense of experimental essays. Robert Boyle on Natural Philosophy. Bloomington: Indiana University Press; 1965.

(5) Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess 2000;4(10):1-115.

(6) Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008 Jan 17;358(3):252-60.

(7) Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. N Engl J Med 1989 Aug 10;321(6):406-12.

(8) Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. The Cardiac Arrhythmia Suppression Trial II Investigators. N Engl J Med 1992 Jul 23;327(4):227-33.

(9) Tricco AC, Tetzlaff J, Sampson M, Fergusson D, Cogo E, Horsley T, et al. Few systematic reviews exist documenting the extent of bias: a systematic review. J Clin Epidemiol 2008 May;61(5):422-34.

(10) Dubben HH, Beck-Bornholdt HP. Systematic review of publication bias in studies on publication bias. BMJ 2005 Aug 20;331(7514):433-4.

(11) Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. Cochrane Database of Methodology Reviews: Reviews 2002;(2).

(12) Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003 May 31;326(7400):1167-70.

(13) Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA 2003 Jan 22;289(4):454-65.

(14) Hopewell S, Clarke M, Stewart L, Tierney J. Time to publication for results of clinical trials. Cochrane Database of Methodology Reviews 2001;(3).

(15) von Elm E, Costanza MC, Walder B, Tramer MR. More insight into the fate of biomedical meeting abstracts: a systematic review. BMC Med Res Methodol 2003 Jul 10;3:12.

(16) Scherer RW, Langenberg P, vonElm E. Full publication of results initially presented in abstracts. Cochrane Database of Methodology Reviews 2005;(2).

(17) Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE 2008;3(8):e3081.

(18) Silagy CA, Middleton P, Hopewell S. Publishing protocols of systematic reviews. Comparing what was done to what was planned. JAMA 2002;287:2831-4.

(19) Sohn D. Publication bias and the evaluation of psychotherapy efficacy in reviews of the research literature. Clin Psychol Rev 1996 Jan 1;16(2):147-56.

(20) Sterling TD. Publication decisions and their possible effects on inferences drawn from tests of significance - or vice versa. J Am Stat Assoc 1959;54:30-4.

(21) Smart RG. The importance of negative results in psychological research. Can Psychol 1964;5:225-32.

(22) Sterling TD, Rosenbaum WL, Weinkam JJ. Publication decisions revisited: The effect of the outcome of statistical tests on the decision to publish and vice versa. American Statistician 1995;49(1):108-12.

(23) Glass GV, McGaw G, Smith ML. Meta-analysis in Social Research. Beverley Hills, California: Sage Publications; 1981.

(24) Smith ML. Publication bias and meta-analysis. Eval Edu 1980;4:22-4.

(25) Smith ML. Sex bias in counseling and psychotherapy. Psychol Bull 1980;87:392-407.

(26) White KR. The relationship between socioeconomic status and academic achievement. Psychol Bull 1982;91:461-81.

(27) Ernst E, Pittler MH. Alternative therapy bias. Nature 1997 Feb 6;385(6616):480.

(28) Moscati R, Jehle D, Ellis D, Fiorello A, Landi M. Positive-outcome bias: comparison of emergency medicine and general medicine literatures. Acad Emerg Med 1994 May;1(3):267-71.

(29) Vickers A, Goyal N, Harland R, Rees R. Do certain countries produce only positive results? A systematic review of controlled trials. Control Clin Trials 1998 Apr;19(2):159-66.

(30) Yaphe J, Edman R, Knishkowy B, Herman J. The association between funding by commercial interests and study outcome in randomized controlled drug trials. Fam Pract 2001 Dec;18(6):565-8.

(31) Coursol A, Wagner EE. Effect of positive findings on submission and acceptance rates: a note on meta-analysis bias. Profess Psych Res Pract 1986;17:136-7.

(32) Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H, Jr. Publication bias and clinical trials. Control Clin Trials 1987 Dec;8(4):343-53.

(33) Greenwald AG. Consequences of prejudice against the null hypothesis. Psychol Bull 1975;82:1-20.

(34) Shadish WR, Doherty M, Montgomery LM. How many studies are in the file drawer? An estimate from the family/marital psychology literature. Clin Psychol Rev 1989;9:589-603.

(35) Sommer B. The file drawer effect and publication rates in menstrual cycle research. Psychol Wom Quart 1987;11:233-42.

(36) Last LM. A Dictionary of Epidemiology: Fourth Edition. Toronto, Canada: Oxford University Press; 2001.

(37) Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991 Apr 13;337(8746):867-72.

(38) Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. JAMA 1992 Jan 15;267(3):374-8.

(39) Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 1997 Sep 13;315(7109):640-5.

(40) Wormald R, Bloom J, Evans J, Oldfield K. Publication bias in eye trials. 1997.

(41) Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998 Jan 28;279(4):281-6.

(42) Dickersin K, Min YI. Publication bias: the problem that won't go away. Ann N Y Acad Sci 1993 Dec 31;703:135-46.

(43) Dickersin K. How important is publication bias? A synthesis of available data. AIDS Educ Prev 1997 Feb;9(1 Suppl):15-21.

(44) Mahoney MJ. Publication prejudices: an experimental study of confirmatory bias in the peer review system. Cog Ther Res 1977;1:161-75.

(45) Epstein WM. Confirmational response bias among social work journals. Sci Tech Hum Val 1990 1990;15:9-37.

(46) Schwarzer G, Antes G, Tallon D, Egger M. Review publication bias? Matched comparative study of Cochrane and journal meta-analyses. 9th International Cochrane Colloquium, Lyon, France, 9-13 October 2001 . 2001.
Ref Type: Abstract

(47) Tierney JF, Clarke M, Stewart LA. Is there bias in the publication of individual patient data meta-analyses? Int J Technol Assess Health Care 2000;16(2):657-67.

(48) Dunn JR, Hayes MV. Toward a lexicon of population health. Can J Public Health 1999 Nov;90 Suppl 1:S7-10.

(49) Public Health Agency of Canada. What is the population health approach? http://www phac-aspc gc ca/ph-sp/phdd/approach/index html 2002 November 29

(50) Etches V, Frank J, Di RE, Manuel D. Measuring population health: a review of indicators. Annu Rev Public Health 2006;27:29-55.

(51) Dunn JR, Hayes MH. Population Health in Canada: A Systematic Review. Ottawa: Canadian Policy Research Networks Inc.; 1998 Mar 6. Report No.: ISBN 1-896703-25-9.

(52) Federal/Provincial/Territorial Advisory Committee on Population Health. Intersectoral action: towards population health. Ottawa: Minister of Supplies and Services Canada; 1999. Report No.: ISBN 0662-64771-9.

(53) Starfield B. Basic concepts in population health and health care. J Epidemiol Community Health 2001 Jul;55(7):452-4.

(54) Robertson A. Shifting discourses on health in Canada: from health promotion to population health. Health Promotion International 1998 Jan 6;13(2):155-66.

(55) Hanney SR, Gonzalez-Block MA, Buxton MJ, Kogan M. The utilisation of health research in policy-making: concepts, examples and methods of assessment. Health Res Policy Syst 2003 Jan 13;1(1):2.

(56) Lavis JN, Posada FB, Haines A, Osei E. Use of research to inform public policymaking. Lancet 2004 Oct 30;364(9445):1615-21.

(57) Lavis JN, Davies HTO, Gruen RL, Walshe K, Farquhar CM. Working within and beyond the Cochrane Collaboration to make systematic reviews more useful to healthcare managers and policymakers. Healthcare Policy 2006;1(2):21-33.

(58) Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and Reporting Characteristics of Systematic Reviews. PLoS Med 2007 Mar 27;4(3):e78.

(59) Chalmers TC. Problems induced by meta-analyses. Stat Med 1991 Jun;10(6):971-9.

(60) Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. JAMA 1998 May 20;279(19):1566-70.

(61) Kawachi I, Colditz GA. Invited commentary: confounding, measurement error, and publication bias in studies of passive smoking. Am J Epidemiol 1996 Nov 15;144(10):909-15.

(62) Samuels A. The toxicity/safety of processed free glutamic acid (MSG): a study in suppression of information. Account Res 1999;6(4):259-310.

(63) Spinks A, Turner C, McClure R, Nixon J. Community based prevention programs targeting all injuries for children. Inj Prev 2004 Jun;10(3):180-5.

(64) Canadian Institutes of Health Research. Randomized Controlled Trials Registration/Application Checklist. http://www cihr-irsc gc ca/e/documents/rct_reg_e pdf 2006 January 12 [cited 2008 Feb 29];

(65) Scherer RW, Dickersin K, Langenberg P. Full publication of results initially presented in abstracts. A meta-analysis. JAMA 1994 Jul 13;272(2):158-62.

Chapter 2: Conceptual model

Introduction

The process of conducting a SR is based on the "evidence-based practice" theory (1). Evidence-based practice can be defined as an approach that decision-makers use to base their decisions on the best available, most scientifically sound evidence (2). This theory might have gained popularity in recent years because evidence suggests that decisions focused on the results of individual studies may be misleading due to bias in their conduct (3). SRs can be used as a tool to interpret the results of individual studies within the context of global evidence (4). As such, SRs have become increasingly important within healthcare. For example, SRs can provide the evidence-base for policy briefs, patient decision aids, and clinical practice guidelines (4). SRs are central to knowledge translation, bridging the gap between research and decision-making (5).

Due to the increased utility of SRs, there has been an exponential increase in the number of SR publications within healthcare (6). However, bias that can occur during the publication of SRs is under-explored. A conceptual model could be used to further understand the publication process of SRs and its susceptibilities to bias.

Conceptual models represent the relationship between logical, analytical or empirical components of a process or system (7). They have been used extensively in healthcare to further the understanding of causal pathways. In order to explain the publication process of SRs and examine how it can be permeated by publication bias, a conceptual model was developed using information from the literature reviewed for the background section of my thesis and from data derived from one-on-one interviews.

Methods

Literature searches were first conducted to gain a better understanding of the publication process for individual studies (e.g., randomized trials, cohort studies), as well as for SRs. A draft conceptual model was derived as a starting point for the interviews. One-on-one interviews were then conducted with systematic reviewers (i.e., those who conduct SRs) between November 2006 and August 2007 and the conceptual model was modified as necessary. Differences between data from the literature search and the interviews were noted. Ethical approval was obtained from the Children's Hospital of Eastern Ontario's Research Ethics Board (Appendix A).

To select the interviewees, a purposeful convenience sample (8) of systematic reviewers who had experience with published and/or unpublished SRs was obtained. The participants were researchers and/or healthcare practitioners from Ottawa, Toronto, and Hamilton, all in Ontario, Canada. These geographical regions were selected to obtain a heterogeneous sample with respect to disciplinary backgrounds and employers. Recruitment was continued until content saturation occurred (i.e., when no new material was obtained) (8).

A semi-structured questionnaire was developed based on literature searches and from consultation with experts in SR methodology and qualitative research. All aspects of SR execution were examined; from the need to conduct SRs to their respective impact. The consent form and interview guide can be found in Appendix B.

Prior to conducting the study interviews, mock interviews were conducted by the interviewer (ACT) and two individuals with experience with SRs and qualitative research. This ensured that the interviewer asked clear, concise, and relevant questions. Information from this exercise was used to modify the interview guide accordingly.

Participants were sent four definitions related to SRs via email prior to their interview. A SR was defined as "a study that aims to summarize research and includes explicit methods (e.g., search terms, inclusion/exclusion criteria) (6;9). Data may be meta-analyzed or qualitatively synthesized". For the purpose of the interview, clinical practice guidelines and health technology assessments (e.g., cost-effectiveness analyses) that begin with a systematic review were included A published SR was defined as "a systematic review reported in one or more journal articles, monographs, books, or chapters in books, available in medical libraries, in documents available from a public archive or in press at the time of questionnaire completion (10).". Unpublished SRs were "completed reviews (i.e., results summarization, and manuscript write-up has been completed) that have not been reported in any of the media described above". An update was "a discrete event aiming to search for and identify 'new evidence' to incorporate into a previously completed systematic review" (11). These definitions ensured that the interviewee understood the terms used during the interview. They were reviewed at the beginning of the interview to ensure concept comprehension.

Confidential, semi-structured, one-on-one interviews were conducted with all participants. Depending on the length of the interviewee's responses, the interviews lasted between 25 and 45 minutes. Written informed consent was obtained at the beginning of the interview (Appendix B). For interviews conducted over the telephone, the consent form was signed and mailed to the interviewer at a later point in time. The interviewer took notes during all interviews, which were audio taped and transcribed. The interviewer contacted the interviewees whenever clarification on responses was required.

Transcripts were content analyzed by one investigator (ACT) to develop coding categories and themes. Through an iterative process, a single coding scheme was developed

and used to code all interviews. The coding scheme was evaluated by another investigator (DM), to ensure its validity.

During the analysis, common themes emerged after reviewing all content. A tree structure was used to develop over-arching themes. The number of interviews by theme and the number of themes covered by each interview were counted.

Results

Interviewee characteristics:

Ten participants were interviewed. They had been conducting SRs for 6 to 20 years and participated in a median of 11 published and 2 unpublished SRs (Table 1). All had at least one university degree and the majority of the participants were female.

Overview of the conceptual model:

It was assumed that the publication process, dissemination, and utilization for SRs within healthcare involves the following seven steps: 1) conceptualization of the issue or problem to be examined by the SR, 2) review protocol, 3) review implementation, 4) dissemination of the review's results (e.g., via conferences or publications), 5) uptake of the research by individuals or groups (e.g., healthcare practitioners, medical societies), 6) policy or clinical impact (e.g., use of evidence within clinical practice guidelines, press releases, consumer websites), and 7) the effect of the SR results on health outcomes over time (e.g., improved health of the population, decreased rich-poor gap; Figure). Individuals or groups of individuals with influence on the publication process include 1) systematic reviewers, 2) journal editors and/or peer reviewers, 3) funding organization(s), 4) and the public (e.g., consumers, patients).

The different types of publication bias that could influence the publication process have been summarized in a recent systematic review (12). They include full study

publication bias (13;14), grey literature bias (13;15), funding bias (16;17), time-lag bias (13;18), abstract to full publication bias (13;19;20), place of publication bias (13), country of conduct bias (13), and language bias (13). The next few sections will describe how the the 7 steps of the conceptual model are populated.

Influence of systematic review characteristics on the publication process (Steps 1-3):

SR characteristics can affect the publication process from conceptualization to review implementation. Characteristics leading to a higher likelihood of being published include if the study (or SR) has funding (10;21), private funding (16;17) (e.g., commercial industry) statistically significant positive results (10;21-24) (e.g., full study publication bias, abstract to full publication bias, time lag bias), and type of study design (or types of study designs included in the SR, for example observational studies versus experimental studies) (21).

A SR may also be susceptible to publication bias if only published studies are included or if evidence of publication bias is observed (e.g., through a funnel plot) (25). Other factors potentially affecting the publication process of SRs include: number of participants (or number of included studies for SRs) (10;21), risk of bias (i.e., study quality) (26), the SR topic (13), assessment of heterogeneity (13), inclusion of unpublished material (13), inclusion of material in languages other than English (e.g., language bias) (13), ability to conduct meta-analysis (13), assessing publication bias in the SR itself (13), and the nature of the reviewers' conclusions (e.g., positive) (13;26).

Of these factors, the interviewees mentioned nature of results as a reason for not submitting their SRs for publication. In addition, proprietary information, lack of rigor in the individual studies or the review, and difficulty obtaining funding for SRs were barriers to publishing SRs. Conversely, facilitators to publishing a SR included high quality of the SR,

ability to conduct meta-analysis, including a large number of studies, and having a clinically relevant/important or controversial SR topic (Table 2).

SR characteristics hindering publication that were brought up by the interviewees and not identified through the literature search included that another SR on the same topic was identified after the review begun, the review being too broad, that some SRs are not done for publishing purposes (e.g., reviews conducted for decision-making, such as the Common Drug Review of the Canadian Agency for Drugs and Technologies in Health), and having to update the review prior to publishing (Table 3). For example, when asked why their SR was unpublished, the interviewee replied "When we actually got into the literature we realized how much had already been done by way of systematic reviews. We ended up having to change paths and we ended up doing a review of reviews ...and that too remains unpublished". Another interviewee stated "That's one of the challenges we always have with the peer-reviewers. You do an AHRQ [Agency for Healthcare Research and Quality] review, finish the report, and by the time you're ready to publish the papers, you're already almost a year behind."

Influence of systematic reviewers on the publication process (Steps 1-5):

Systematic reviewers can influence all stages of the publication process except for the impact and health outcomes stages. Factors that may be associated with an increase in unpublished SRs include lack of time (26), language barriers (13), characteristics of the investigative (or SR) team (e.g., international co-authors with little SR expertise may lead to a longer time to publication) (26), gender of the first or corresponding author (10), country where the SR team is based (13) (e.g., country of conduct bias), and lack of motivation or incentives (e.g., SRs are not recognized as being a unique research endeavour by all organizations). According to interviewees, the most common reason for not publishing SRs was lack of time.

When asked why their SR was not published one respondent replied "Because it's not finished and I don't have a lot of time to finish it; I'm very busy" and another stated "Time. Not having the capacity to just go with it. Priorities – other things – get in the way." The most common facilitator to publishing SRs was working with a team with expertise in SRs. One respondent replied "I think it's been accessibility, so when you're working with groups like the Cochrane group and you have deadlines and people are there to support that process it's a lot easier".

Systematic reviewer characteristics hindering publication, which were brought up by the interviewees and not identified through the literature search, include lack of guidance on the methods, having a workplace that does not conduct SRs, having a first author or corresponding author who is a healthcare practitioner, and not having synthesis skills. Contrastingly, having support with the methods, knowing the format of journals, and having relationships with journals (e.g., knowing journal editors, publishing frequently with a particular journal) were facilitators to publishing SRs that were identified by the interviewees, but not identified in the literature. When asked about what facilitates the publication of SRs one interviewee responded "I don't know, you need support with your methods…". When asked about the barriers to publishing another responded "I think in general although systematic reviews are systematic per say, there's still not a lot of evidence on how to do systematic reviews. Although there's guidance it's still pretty open to interpretation. The guidance is fairly open to interpretation. I think in some cases it's sort of convoluted the field."

Influence of journals, journal editors and peer reviewers on the publication process (Steps 4 and 5):

The journal, journal editors and peer reviewers can influence the dissemination and uptake stages of the publication process. Factors associated with the publication of SRs brought up by the interviewees and identified through the literature searches included the receptiveness of the study (or SR) topic (13) (e.g., place of publication bias). Other factors not identified through the literature included receptiveness of the journal, journal editors, and peer reviewers towards SRs in general, space limitations in journals, the fact that some journals have a time-consuming publishing process, and format of the journal (e.g., online formats might facilitate publication).

The two most commonly reported barriers to publishing SRs were that the journal or peer reviewer(s) may not understand SRs or see the importance of SRs and space limitations in journals. One interviewee replied "There are certain journals where they just don't see the value [of SRs], despite many of the papers that make up the systematic review being published in those journals". Another stated "I think some of the challenges about publishing SRs in paper-based journals are about the length issues...So one issue is space."

Influence of the funding organization on the publication process (Steps 1-2 and 3-4):

The funding organization can influence the conceptualization, study protocol, study implementation, and dissemination of results stages. From research at the individual study level, evidence suggests that published studies with commercial funding are more likely to have statistically significant positive results (e.g., funding bias) (16;17). It is plausible that such is the case for SRs. Interviewees mentioned lack of funding as being a barrier and having funding as being a facilitator to publishing SRs (Table 2).

Influence of the public on the publication process (Steps 1, 5, 6):

The public (e.g., consumers) can affect the study proposal by influencing research topics examined by systematic reviewers and the uptake of research by decision-makers (e.g.,

through lobby groups). Interventions affected by publication bias may have a greater chance of being used at the population level if commercial companies support the public (e.g., pharmaceutical companies who sponsor lobby groups without disclosing their financial support). Interviewees regarded the public as being highly influential to the SR process; 50% reported the public as being their main audience (Table 3). One interviewee replied "I'm most interested in collecting data for consumers and the general public..." while another responded "...actually the consumer are a key target...".

Uptake of systematic review results (Step 5):

If SRs affected by publication bias have a greater chance of being disseminated, then these results will more likely be disseminated and perhaps used by decision-makers (13). It is in this way that all the different types of publication bias can influence the uptake of SR results.

When asked about who uses the results of their SRs (i.e., their main audience), interviewees reported health practitioners, policy-makers, funding organizations, researchers, and the general public (Table 3). One replied "So if it's the American College of Rheumatology it would be rheumatologists, if it's the Canadian Gastroenterology Association it would be gastroenterologists, if it's the American Pain Society that's sponsoring it, it would be pain specialists". Another replied about their SRs "Individual clinicians are interested in them as well, so we have quite a broad readership".

Policy/clinical impact of systematic reviews (Step 6):

SR publication bias can affect the policy/clinical impact if they are more widely disseminated than SRs not affected by publication bias (13). It is in this manner that the types of publication bias that influenced the uptake of results will also influence the policy or clinical impact of SRs. When asked about the impact of SRs, interviewees felt that SRs used in clinical practice guidelines had higher impact, as were SRs directly used for policy-

making (Table 5). One replied "We didn't make the policy decisions but the decisions were based on the information we provided. So there would be a lot of impact if a drug was not funded on the basis of our information or our assessment of the evidence" and another stated "Sometimes they [policy-makers] might not use the information to make the decision but they considered the information in the decision-making process".

Effect on health outcomes (Step 7):

SR publication bias can affect health outcomes if SRs of interventions with favourable results are more widely disseminated than SRs without favourable results (13). It is in this manner that the types of publication bias that influenced the uptake of results and policy or clinical impact of SRs will also affect health outcomes.

Discussion

This is the first conceptual model to examine the publication process of SRs and determine how publication bias can influence it. It was assumed that there are seven steps in the publication process of SRs within healthcare: 1) conceptualization of the issue or problem to be examined by the SR, 2) review protocol, 3) review implementation, 4) dissemination of the review's results, 5) uptake of the research by individuals or groups, 6) policy or clinical impact, and 7) the effect of the SR results on health outcomes over time. From the literature searches and one-on-one interviews, it is clear that the different types of publication bias can permeate any point in the publication process (Figure).

If SRs affected by publication bias have a greater chance of being published, then these results will more likely be disseminated and perhaps used by decision-makers. It is in this manner that the first steps of the publication process of SRs (from conceptualization to dissemination) can affect the last steps of the process (from policy/clinical impact to health outcomes). SR characteristics, systematic reviewer characteristics, the journal, journal

editors, and peer reviewers influence the first steps of the process from conceptualization to dissemination, and can therefore impede or facilitate the entire publication process.

The interviewees reported more factors influencing the publication process than were identified through the literature searches. For example, facilitators to publishing SRs reported by the interviewees that were not identified included reporting guidelines for SRs and knowing the format for journals. A barrier to publishing SRs that was not identified through the literature searches included the lack of recognition of SRs by academia, which was reported by one of the interviewees.

This study has some limitations. Only a small sample of individuals was interviewed, however, their SR experiences were broad and extensive and they identified more factors than were identified through the literature searches. In addition, the interviewee's responses were anecdotal. Due to financial constraints, only one researcher coded all interviews, which may have resulted in bias.

Increased knowledge of the importance of publishing SRs regardless of their characteristics may surmount publication bias of SRs. This could be achieved by educating systematic reviewers, peer reviewers, and journal editors about the importance of SRs in general. Other possible solutions include having an online open-access journal dedicated to only publishing the results of SRs including SR updates across all areas of healthcare (i.e., a general purpose journal), and ensuring that academic institutions realize the importance of SRs for academic endeavours.

Figure: Conceptual model for the publication process, dissemination, and utilization of systematic reviews

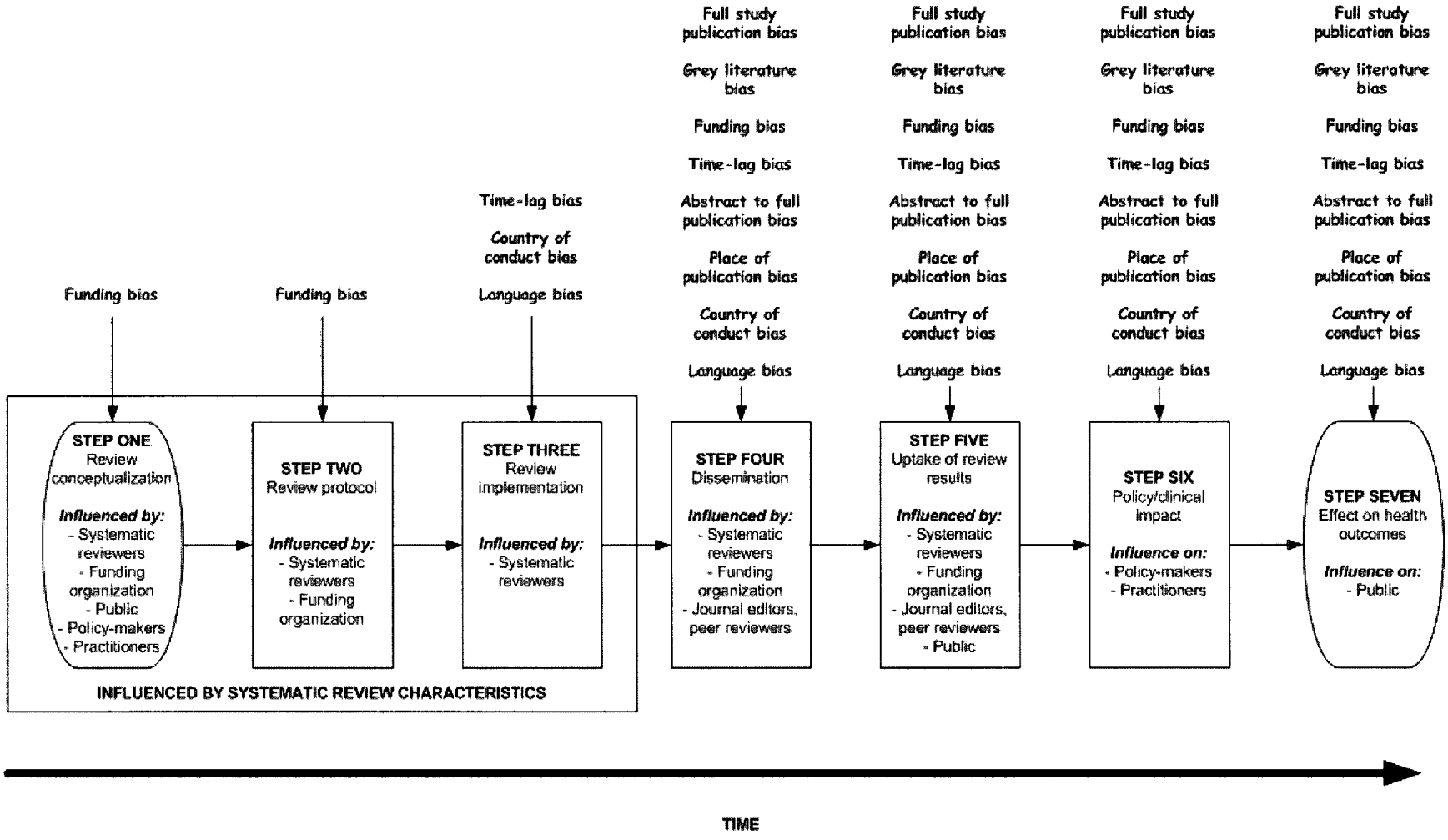


Table 1: Interviewee characteristics

Participant #	Gender	Degree(s)	# years conducting SRs	# published SRs	# unpublished SRs
1	F	PhD candidate	9	20	2
2	F	MD, PhD	6.5	0	25
3	F	MSc candidate	10	7	2
4	F	MD, MSc	20	30	0
5	M	PhD	12	35	4
6	F	PhD candidate	10	25	5
7	F	PhD candidate	13	10	0
8	M	PhD	6	8	1
9	F	MD	15	6	2
10	M	MD, PhD	15	12	1

Abbreviation: SRs (systematic reviews).

Table 2: Characteristics and factors identified by interviewees and the literature search by categories of the conceptual model (Steps One to Four)

Question # [details]	Systematic review characteristics [†]	Systematic reviewer(s) characteristics [†]	Journal, editors, and/or peer review factors [†]
1 [Experience]	Different types of reviews [7]	Workplace/working group [2]	
2, 3 [Reasons for not publishing]	Proprietary information [1] Another review identified [1]* Review was too broad [1]* Non-informative results [1] Not done for publishing purposes [2]*	Language barriers [1] Workplace change [1] Lack of time [3] Having international co-authors [1]	Journal did not like the topic [2]
4 [Facilitators]	A lot of included studies [1] Ability to conduct quantitative analysis [1] Clinically relevant/important /sexy/controversial topic [4] High quality of the review [2] Funding for the review [1]	Having support with methods [2]* Incentives (e.g., career) [2] High expertise of review team [3] Relationships with journals [1]* Knowing the format of journals [1]*	Journal receptiveness to reviews [1]* Online journals [2]*
5 [Barriers]	Proprietary information [1] Lack of rigor in the review [1] Lack of rigor in individual studies [1] Having to update the review prior to publishing [2]* Lack of funding [1]	Lack of time [3] Lack of guidance on methods [1]* Not having synthesis skills [1]* Workplace does not conduct reviews [2]* Corresponding author is a healthcare practitioner [1]	Space limitations in journals [4]* Journal/peer reviewers don't think it's an important topic [7] Journal has a time-consuming publication process [2]*

Notes: * These topics were identified through the interviews and not through the literature search. † # of interviewees offering this response.

Table 3: Factors identified by interviewees and the literature search by categories of the conceptual model (Steps five to seven)

Question # [details]	Response	# interviewees responding
7 [Audience]	Consumers/general public/patients	5
	Health practitioners	10
	Policy-makers	7
	Funding organizations	1
	Researchers	2
	Educators	1
	Journal clubs*	1
	Librarian professionals*	1
	Medical societies	2
8 [Impact]	Not well-evaluated	2
	Has been evaluated	2
	Clinical practice guidelines	3
	Press releases	1
	Consumer websites*	1
	Used for policy making	2
	Impact factor	3
	Been asked to write editorials	1
	Government changed their policy	1

Note: * These topics were identified through the interviews and not through the literature search.

Appendix A: Ethics approval for interviews

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

CHEO RESEARCH ETHICS BOARD APPROVAL – EXPEDITED REVIEW

Principal Investigator:	Dr. David Moher
Proposal Number:	#06/60X
Protocol Title:	Systematic Review Publication Bias: One-on-one Interviews
Department or PSU:	Chalmers Research Group
Approval date:	September 9, 2006
Valid Until:	September 8, 2007
Documents reviewed and approved:	Research protocol submitted August 30, 2006

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval to the above named research study on the date noted above. Your project was reviewed under the expedited stream, which is reserved for projects that involve no more than minimal risk to human subjects.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the REB. Further, investigators are asked to report the following to the REB:

- Proposed changes to the study procedures (including the recruitment strategy, inclusion criteria, etc.);
- Concerns or issues that arise in conducting the research;
- Changes to the consent documents and advertisement notices;
- Changes to the investigators who assume responsibility for the study; &
- An annual report.

Wishing you success in your project.

Regards,

Dr. Carole Gentile, C.Psych.
Chair, Research Ethics Board

CG/smeh 09/09/2006
c.c. Pat Brazeau, Manager, CHEO RI
Andrea Tricco, Chalmers Research Group

This is an official document. Please retain the original for your file *version 11/2003*

401 Smyth Road, Ottawa, ON K1H 8L1, Canada
Tel: (613) 737-7600 www.cheo.on.ca
Making a difference in the lives of children and youth

401, chemin Smyth, Ottawa (ON) K1H 8L1, Canada
Tél.: (613) 737-7600 www.cheo.on.ca
Faire une différence dans la vie des enfants et des adolescents

Appendix B: Interview consent form and interview guide

Interview Consent Form

Title of Study: Systematic review publication bias

Principal Investigators: David Moher, Andrea C. Tricco

Purpose: The purpose of this research is to describe and quantify systematic review publication bias. This survey is a part of a PhD dissertation at the University of Ottawa and will be published in peer review journals.

Procedures: We wish to interview you about your published and unpublished systematic reviews, reasons why some reviews are not published, and the barriers and facilitators of publishing systematic reviews. The interview will be conducted either in person or over the telephone at a time that is convenient for you. The interview may last 45 minutes to an hour and will be tape recorded in order to help the researchers interpret the information accurately.

Risks and Benefits: There are no known risks to you as a participant.

Rights of participant: You are under no obligation to participate in the study and you may withdraw at any time without any repercussions. Research staff will respect your wish to stop the interview at any time. You have a right not to answer any question(s) you so choose. The information collected during the study will be kept confidential. The audiotape will be erased once the transcript has been verified. You will have the opportunity to both review and comment on a draft of the results.

Consent: Please check the appropriate boxes:
Do you agree to be interviewed? __Yes __No
Do you agree to the interview being audio taped? __Yes __No
Do you agree that any material from the interview may be used in presentations/ publications as long as you are not identified by name? __Yes __No
Do you agree to the transcript being kept for a maximum of 5 years? __Yes __No
Do you wish to receive a copy of any reports resulting from the research? __Yes __No
If clarification is required following your interview, may we contact you? __Yes __No

Printed name: _____ **Date:** _____
Signature: _____

May we contact you if we require clarification on your answers? __Yes __No
If 'yes', please provide your name and contact details so that you can be contacted:
Telephone:_____
Email:_____

If you have any additional questions about this study, please call Andrea Tricco (416-483-5034).

Interview Guide:

Prior to the interview, the following definitions will be sent to the participants via email:

A *systematic review* refers to a study that aims to summarize research and includes explicit methods (e.g., search terms, inclusion/exclusion criteria, etc). Data may be meta-analyzed or qualitatively synthesized.

A *published* systematic review refers to systematic reviews reported in one or more journal articles, monographs, books, or chapters in books, available in medical libraries, in documents available from a public archive or in press at the time of questionnaire completion. For example, a Cochrane review would be considered a published systematic review, as it is available on a public archive through the Internet.

Unpublished systematic reviews are completed reviews (i.e., results summarization, and manuscript write-up has been completed) that have not been reported in any of the media described above.

An *update* refers to a discrete event aiming to search for and identify 'new evidence' to incorporate into a previously completed systematic review.

Systematic reviewer details:
Time of interview, date, and place: _____
Systematic reviewer: _____
Systematic reviewer's degree: _____
Systematic reviewer has been conducting reviews for _____ years
Systematic reviewer has _____ published and _____ unpublished reviews

Interview questions:
1. Tell me a bit about your experience with publishing systematic reviews.
Probes: what do you remember the most about your first one? Was it challenging? What drew you into the systematic review field?

2. Why are some of your systematic reviews not published?
Probes: Were any of your unpublished systematic reviews Cochrane reviews?

3. Of these reasons, which was the most significant, in your opinion?
Probe: reiterate the reasons that they provided.

4. Which factors make publishing systematic reviews easier?
Probe: what are the facilitators? Are these different between Cochrane and non-Cochrane?

5. What makes publishing systematic reviews difficult?
Probe: what are the barriers? Are these different between Cochrane and non-Cochrane?

6. What drives you to perform a systematic review?
Probe: does this differ between Cochrane and non-Cochrane?

7. Who is the target audience for your systematic reviews?
Probe: does this differ between published and unpublished reviews? Cochrane and non-Cochrane? How do you know that they've actually used them?

8. In your opinion, what is the impact of your systematic reviews?
Probe: does this differ between published and unpublished reviews? Cochrane and non-Cochrane? Have your reviews been included in guidelines or HTAs?

9. Do you believe that systematic reviews should be updated?
Probe: if yes, how and when? Should the process differ for Cochrane and non-Cochrane? Should updated systematic reviews be published? Would you use a tool (e.g., a decision tree) to help you decide whether systematic reviews should be published or not?

10. From your perspective, who is responsible for updating systematic reviews?
Probe: examples include the original systematic reviewers, journal editors, etc.

11. In your opinion, do you think that the publication process would be different for systematic reviews that mainly focus on population health research versus conventional medicine research and/or other types of research (e.g., complementary and alternative medicine).
Probe: describe what is meant by a population health review versus other types of reviews.

References

(1) Sehon SR, Stanley DE. A philosophical analysis of the evidence-based medicine debate. BMC Health Serv Res 2003 Jul 21;3(1):14.

(2) Naylor CD. Clinical decisions: from art to science and back again. Lancet 2001 Aug 18;358(9281):523-4.

(3) Grimshaw JM, Santesso N, Cumpston M, Mayhew A, McGowan J. Knowledge for knowledge translation: the role of the Cochrane Collaboration. J Contin Educ Health Prof 2006;26(1):55-62.

(4) Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? J Contin Educ Health Prof 2006;26(1):13-24.

(5) Graham ID, Tetroe J. Some theoretical underpinnings of knowledge translation. Acad Emerg Med 2007 Nov;14(11):936-41.

(6) Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and Reporting Characteristics of Systematic Reviews. PLoS Med 2007 Mar 27;4(3):e78.

(7) Last LM. A Dictionary of Epidemiology: Fourth Edition. Toronto, Canada: Oxford University Press; 2001.

(8) Patton MQ. Qualitative research and evaluation methods. Third ed. California: Sage Publications; 2002.

(9) Peters JL, Sutton AJ, Jones DR, Rushton L, Abrams KR. A systematic review of systematic reviews and meta-analyses of animal experiments with guidelines for reporting. J Environ Sci Health B 2006;41(7):1245-58.

(10) Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. JAMA 1992 Jan 15;267(3):374-8.

(11) Moher D, Tsertsvadze A. Systematic reviews: when is an update an update? Lancet 2006 Mar 18;367(9514):881-3.

(12) Tricco AC, Tetzlaff J, Sampson M, Fergusson D, Cogo E, Horsley T, et al. Few systematic reviews exist documenting the extent of bias: a systematic review. J Clin Epidemiol 2008 May;61(5):422-34.

(13) Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess 2000;4(10):1-115.

(14) Dubben HH, Beck-Bornholdt HP. Systematic review of publication bias in studies on publication bias. BMJ 2005 Aug 20;331(7514):433-4.

(15) Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. Cochrane Database of Methodology Reviews: Reviews 2002;(2).

(16) Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003 May 31;326(7400):1167-70.

(17) Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA 2003 Jan 22;289(4):454-65.

(18) Hopewell S, Clarke M, Stewart L, Tierney J. Time to publication for results of clinical trials. Cochrane Database of Methodology Reviews 2001;(3).

(19) von Elm E, Costanza MC, Walder B, Tramer MR. More insight into the fate of biomedical meeting abstracts: a systematic review. BMC Med Res Methodol 2003 Jul 10;3:12.

(20) Scherer RW, Langenberg P, vonElm E. Full publication of results initially presented in abstracts. Cochrane Database of Methodology Reviews 2005;(2).

(21) Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 1997 Sep 13;315(7109):640-5.

(22) Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991 Apr 13;337(8746):867-72.

(23) Dickersin K. How important is publication bias? A synthesis of available data. AIDS Educ Prev 1997 Feb;9(1 Suppl):15-21.

(24) Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998 Jan 28;279(4):281-6.

(25) Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997 Sep 13;315(7109):629-34.

(26) Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA 1990 Mar 9;263(10):1385-9.

Chapter 3: Paper 1

Non-Cochrane versus Cochrane reviews were twice as likely to have positive conclusion statements: Cross-sectional study (1)

ELSEVIER

Journal of Clinical Epidemiology 62 (2009) 380–386

Journal of Clinical Epidemiology

Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study

Andrea C. Tricco[a,b], Jennifer Tetzlaff[a,c], Ba' Pham[a,d], Jamie Brehaut[c,e], David Moher[a,c,*]

[a]*Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute, 401 Smyth Road, Ottawa, Ontario, Canada*
[b]*Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada*
[c]*Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada*
[d]*Toronto Health Economics & Technology Assessment Centre, Toronto, Ontario, Canada*
[e]*Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ontario, Canada*

Accepted 29 August 2008

Abstract

Objectives: To determine which factors predict favorable results and positive conclusions in systematic reviews (SRs) and to assess the level of agreement between SR results and conclusions.

Study Design and Setting: A sample of 296 English SRs indexed in MEDLINE (November, 2004) was obtained. Two investigators independently categorized SR characteristics, results, and conclusions. Descriptive analyses and logistic regression predicting favorable results (nonstatistically significant and statistically significant positive) and positive conclusions were conducted. The level of concordance between results and conclusions was assessed using a weighted-kappa statistic.

Results: Overall, 36.5% of the SRs had favorable results, increasing to 57.7% for Cochrane and 64.3% for non-Cochrane reviews with a meta-analysis of the primary outcome. Non-Cochrane reviews with a meta-analysis of the primary outcome were twice as likely to have positive conclusions as Cochrane reviews with such an analysis (P-value <0.05). The weighted kappa for agreement between SR results and conclusions was 0.55. It was lower for Cochrane (0.41) vs. non-Cochrane (0.67) reviews.

Conclusion: SRs including a meta-analysis of the primary outcome may be affected by indirect publication bias in our sample. Differences between the results and conclusions of Cochrane and non-Cochrane reviews were apparent. Further research on publication-related issues of SRs is warranted.

Keywords: Systematic review; Meta-analysis; Research methodology; Bias; Publication bias; Cross-sectional study

1. Introduction

Publication bias occurs when "investigators, reviewers, and editors submit or accept manuscripts for publication based on the direction or strength of the study findings" [1]. Studies with particular characteristics (e.g., statistically positive results, large effect sizes) are more likely to be published than those without these characteristics [2]. The consequences of publication bias are severe; a recent meta-analysis has shown that publication bias exaggerated the estimate of antidepressant's effectiveness by 32%, on average [3].

Cross-sectional samples of the published literature have found that the proportion of statistically positive results in individual studies (e.g., randomized controlled trials [RCTs]; observational studies) ranges from 35% to 97%, depending on the sample used [4–12]. Only a few studies have examined the proportion of statistically positive results and conclusions in systematic reviews (SRs). In one study, 60% of the 193 included reviews had positive conclusion statements, whereas 13% had negative conclusions [13]. Only 17% assessed for publication bias and 27% included unpublished material [13]. Another study found that SRs published in traditional journals reported more beneficial results compared to those published in the Cochrane Database of Systematic Reviews ($P = 0.007$) [14].

These studies provide *indirect* evidence of publication bias because factors other than publication bias may have

This research was funded by the Canadian Agency for Drugs and Technologies in Health. Ms. Tricco is funded by a Canadian Institutes of Health Research Canada Graduate Scholarship and a University of Ottawa National Excellence Scholarship. Dr. Brehaut is funded by an Ontario Ministry of Health Career Scientist Award. Dr Moher is funded by a University of Ottawa Research Chair.

* Corresponding author. Clinical Epidemiology Program, Ottawa Health Research Institute, Box 208, 501 Smyth Road, Ottawa, Ontario, Canada.

E-mail address: dmoher@ohri.ca (D. Moher).

0895-4356/09/$ – see front matter
doi: 10.1016/j.jclinepi.2008.08.008

What's new?

1. Indirect evidence of publication bias occurs when a large proportion of the published literature has positive results and conclusion statements. Few studies have examined indirect publication bias of systematic reviews using a broad sample of systematic reviews and a variety of characteristics predicting the occurrence of positive results and conclusions.
2. In a sample of 296 systematic reviews published in English in MEDLINE, the proportion of published results and conclusions was about 1/3. This increased to approximately 2/3 for systematic reviews with a meta-analysis of the primary outcome, indicating that these reviews may be affected by indirect publication bias.
3. Non-Cochrane reviews versus Cochrane reviews were twice as likely to have positive conclusions. However, Cochrane reviews had a lower level of agreement between their results and conclusion statements. This suggests that differences exist between the results and conclusions of Cochrane and non-Cochrane reviews.
4. Future research examining publication issues surrounding systematic reviews is warranted, such as a survey examining the frequency of unpublished systematic reviews and a retrospective cohort study of factors associated with the time to publication of systematic reviews.

led to a higher proportion of studies with statistically positive results and positive conclusions [13]. For example, in individual studies it may indicate that the sample included studies with high power (e.g., included a large number of participants), which were able to show a true difference of the null hypothesis [15]. For SRs, it may indicate that the individual studies included had high power. Previous research examining indirect publication bias for SRs used a specific sample of SRs (e.g., SRs reported in four general medicine journals and four specific medicine journals [14]) and only examined a few "predictors" (i.e., SR characteristics that predict positive results and conclusions). Furthermore, only one independent investigator categorized the results and conclusions in these studies.

Indirect evidence of SR publication bias is particularly important, as decision makers increasingly rely on SRs [16,17]. If evidence of SR publication bias exists, this may influence the utility of SRs. We aimed to examine a broad spectrum of "predictors" to determine which SR characteristics were associated with favorable results and positive conclusions and to determine the level of concordance between the results and conclusions in this sample of SRs using a large sample of all SRs published in MEDLINE in November 2004.

2. Methods

2.1. Sample of SRs

We identified a sample of SRs indexed in MEDLINE (November 2004) and published in English. The methods of ascertaining this sample have been described elsewhere [18]. Briefly, the SRs were identified through a modified version of Montori's strategy (see Appendix A on the journal's web site at www.elsevier.com) [19]. Two independent reviewers (A.C.T., J.T.) first screened the citations (i.e., titles and abstracts) from the literature search. Subsequently, one reviewer screened full-text articles with a second reviewer screening a 10% random sample. Eligibility was determined using the following definition of a SR: "the authors' objective was to summarize evidence and the article described explicit methods" [18]. The report was excluded whenever it was clear that the authors' intent was to conduct a literature review instead of a SR. For the current study, reviews of non–health-related topics were excluded.

2.2. Categorizing the SRs

Characteristics of the SRs that may predict favorable results or positive conclusions were abstracted. The first "predictor" was whether a meta-analysis was performed. According to the Cochrane Handbook for Systematic Reviews of Interventions, a meta-analysis is inappropriate if the included studies in the SR are clinically diverse, methodologically different, or statistically inconsistent [20]. As such, SRs in this study were also categorized as whether they assessed between-study inconsistency. Further predictors included SR component study designs (e.g., experimental, observational), Cochrane status (i.e., Cochrane or non-Cochrane review), and funding source(s). Methodological aspects of the SRs (e.g., assessment of publication bias, eligibility criteria based on publication status, or language of publication) were also assessed. All of these factors have been associated with the publication status of SRs in previous research [13].

The primary SR outcome was sometimes reported by the SR authors; however, in those cases where the primary outcome was not stated, a decision-tree approach was used [10]; if available, the outcome highlighted in the title or objectives was considered the primary outcome. If this was not available, the most serious outcome (e.g., mortality) was chosen. If multiple interventions were present, we chose the comparison with the "experimental" treatment vs. placebo or standard of care for the primary outcome.

The results of the SRs were categorized based on the primary outcome (Fig. 1), which was determined as follows

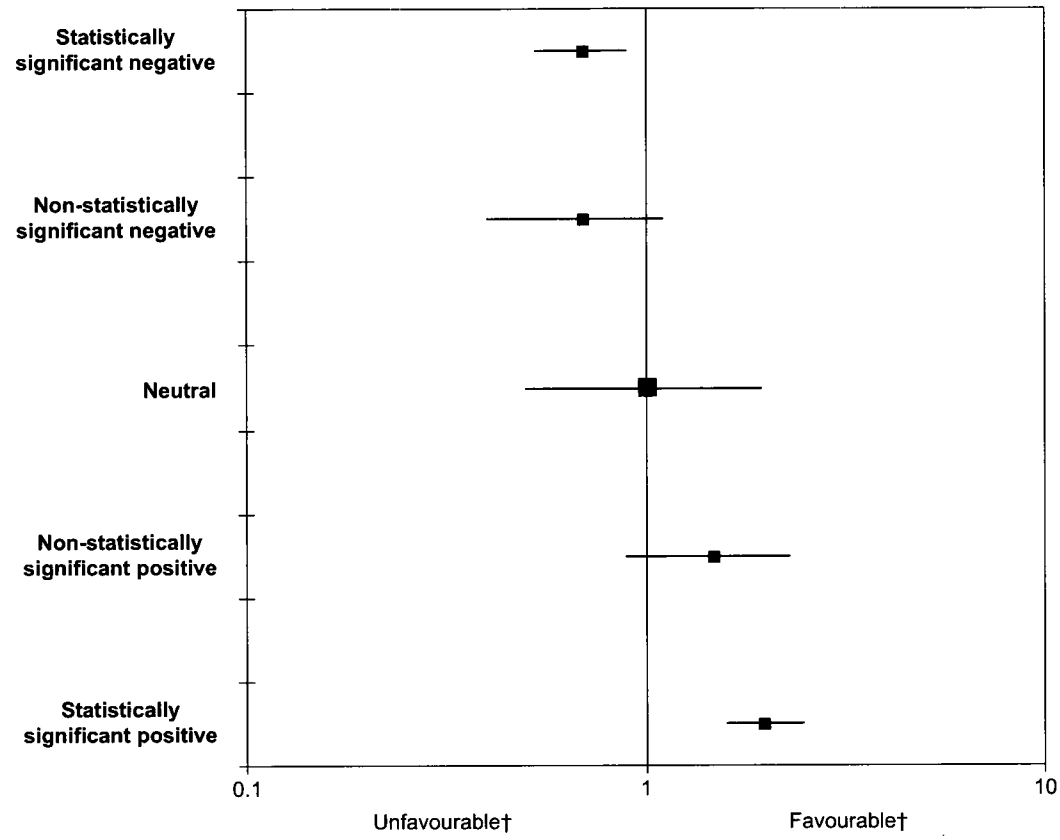


Fig. 1. Systematic review (SR) results*. Notes: *Point estimates and 95% confidence intervals. †"Unfavorable" represents SR results favoring the control or comparison intervention, while "favorable" represents SR results favoring the intervention of interest.

(using the example of a SR hypothesizing a benefit of an intervention vs. a comparator): unfavorable, namely, there is an effect in favor of the nonintervention comparator (i.e., statistically significant negative with an associated P-value ≤ 0.05 and nonstatistically significant negative); neutral (effect size between 0.95 and 1.05 and the confidence interval (CI) crosses 1); favorable (i.e., nonstatistically significant positive and statistically significant positive with an associated P-value ≤ 0.05); indeterminate (i.e., not able to judge; e.g., the SR lists 10 primary outcomes, all of which have different results) or noncomparative (e.g., SRs of prevalence).

The conclusions of the SRs as stated in the abstract or discussion section were categorized (using the example of a SR hypothesizing a benefit of an intervention vs. a comparator) as: positive (i.e., authors stated that there is evidence of effectiveness), negative (i.e., authors advised against the use of the intervention or it was not recommended), neutral (no evidence of effectiveness or they reported no opinion), indeterminate (i.e., stated that there is insufficient evidence or that more research is required), and noncomparative [13].

A categorization guide was developed by the investigative team. To ensure that the guide was adequate it was pilot tested using a separate set of articles. The guide was then revised, as necessary (See Appendix B on the journal's web site at www.elsevier.com). Two members of the team independently categorized the entire sample of SRs (A.C.T., J.T.). Discrepancies were resolved through discussion or the involvement of a third member of the team (D.M.).

2.3. Statistical analysis

Data were analyzed descriptively in SAS using frequencies and proportions. To determine whether any of the "predictors" described above led to SRs with favorable results and/or positive conclusions, a series of logistic regressions were conducted for those SRs for which a meta-analysis of the primary outcome was conducted. The degree of concordance between the results and conclusions of the SRs was examined using a weighted kappa and its 95% CI [21]. To calculate a weighted-kappa statistic in SAS, default weights are applied. Generally, close misses (e.g., 1–2) are more heavily weighted than misses that are further apart (e.g., 1–3) in SAS [22].

3. Results

3.1. Sample acquisition

A total of 1,046 records were identified and screened. Of these, 758 full-text articles were obtained and 300 SRs met the eligibility criteria for the previous study [18]. Four SRs

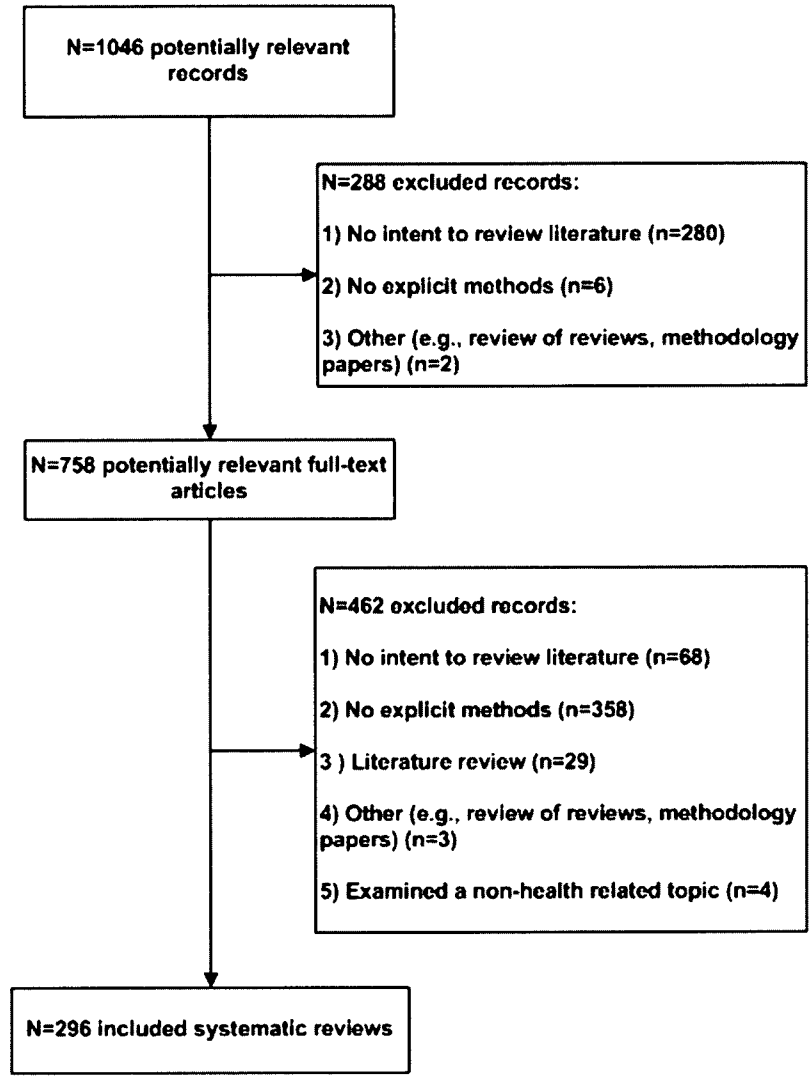


Fig. 2. Study flow.

were excluded from the present study, as they were not health related, leaving 296 SRs in our sample (Fig. 2).

3.2. SR characteristics

A little less than half of the SRs (141/296, 47.6%) included a meta-analysis of the primary outcome, the majority of which assessed between-study inconsistency (134/141, 95.0%; Table 1). Cochrane reviews were more likely to conduct a meta-analysis of the primary outcome (78/129, 60.5%) than non-Cochrane reviews (63/167, 37.7%). A funding source was not reported in 39.9% (118/296) of the SRs and the funder was reported as being a not-for-profit organization in 48.6% (144/296) of the SRs. Of those authors reporting publication status eligibility criteria (188/296, 63.5%), about one third of the SRs (66/188, 35.1%) were limited to published material only. Of those authors reporting on language of publication eligibility criteria (164/296, 55.4%), about one third (48/164, 29.3%) were limited to English language reports only.

Most SRs included studies with experimental designs (178/296, 60.2%), whereas 20.6% (61/296) included only observational designs (Table 1). For SRs including a meta-analysis of the primary outcome (141/296, 47.6%), only 39.7% (56/141) of the authors reported assessing publication bias and 36.9% (52/141) discussed their results in relation to publication bias.

3.3. SR results and reviewers' conclusions

Overall, 57.8% (171/296) of SR results were classified as noncomparative; indeterminate or neutral (Table 2). Few SRs had unfavorable results (17/296, 5.8%) and over a third had favorable results (36.5%, 108/296). A slightly higher proportion of non-Cochrane reviews with a meta-analysis of the primary outcome had unfavorable (9.6%, 6/63) and favorable (64.3%, 41/63) results compared to Cochrane reviews with such an analysis (favorable: 57.7%, 45/78 and unfavorable: 9.0%, 7/78). Similarly, non-Cochrane reviewers made negative conclusion

Table 1
Systematic review "predictors" of favorable results and positive conclusions

Item	Total (%)	SRs without a meta-analysis of the primary outcome (%)	SRs with a meta-analysis of the primary outcome (%)
#SRs	296 (100.0)	155/296 (52.4)	141/296 (47.6)
Between-study inconsistency assessment			
Inconsistency assessed	204/296 (68.9)	70/155 (45.2)	134/141 (95.0)
Inconsistency not assessed	92/296 (31.1)	85/155 (54.8)	7/141 (5.0)
Cochrane vs. non-Cochrane			
Cochrane review	129/296 (43.6)	51/155 (32.9)	78/141 (55.3)
Non-Cochrane	167/296 (56.4)	104/155 (67.1)	63/141 (44.7)
Source of funding			
None	3/296 (1.0)	2/155 (1.3)	1/141 (0.7)
No for profit	144/296(48.6)	62/155 (40.0)	82/141 (58.2)
For profit	7/296 (2.4)	2/155 (1.3)	5/141 (3.5)
Mixed	19/296 (6.4)	11/155 (7.1)	8/141 (5.7)
Can't tell	5/296 (1.7)	1/155 (0.6)	4/141 (2.8)
NR	118/296 (39.9)	77/155 (49.7)	41/141 (29.1)
Authors made an explicit statement regarding inclusion/exclusion of published or unpublished material			
No such statement	108/296 (36.5)	66/155 (42.6)	42/141 (29.8)
Yes: published only	66/296 (22.3)	35/155 (22.6)	31/141 (22.0)
Yes: published and unpublished	122/296 (41.2)	54/155 (34.8)	68/141 (48.2)
Authors made an explicit statement regarding inclusion/exclusion of studies based on language			
No	132/296 (44.6)	73/155 (47.1)	59/141 (41.8)
Yes: English only	48/296 (16.2)	31/155 (20.0)	17/141 (12.1)
Yes: Mixed	6/296 (2.0)	4/155 (2.6)	2/141 (1.4)
Yes: All languages	109/296 (36.9)	46/155 (29.7)	63/141 (44.7)
NR/can't tell	1/296 (0.3)	1/155 (0.6)	0 (0)
Design of studies included in the SR			
Experimental	178/296 (60.2)	73/155 (47.1)	105/141 (74.5)
Observational	61/296 (20.6)	38/155 (24.5)	23/141 (16.3)
Both	43/296 (14.5)	31/155 (20.0)	12/141 (8.5)
Unclear/NR	14/296 (4.7)	13/155 (8.4)	1/141 (0.7)
Authors reported assessing publication bias			
No	225/296 (76.0)	140/155 (90.3)	85/141 (60.3)
Yes	67/296 (22.6)	11/155 (7.1)	56/141 (39.7)
Not relevant	4/296 (1.4)	4/155 (2.6)	0 (0)
Authors discussed results in relation to publication bias			
No	215/296 (72.6)	126/155 (81.3)	89/141 (63.1)
Yes	70/296 (23.7)	18/155 (11.6)	52/141 (36.9)
Not relevant	11/296 (3.7)	11/155 (7.1)	0 (0)

Abbreviations: SRs systematic reviews, NR not reported.

statements (8.4%, 14/167) slightly more than Cochrane reviewers (7.0%, 9/129). However, non-Cochrane reviewers were significantly more likely to make positive conclusions (32.3%, 54/167) than Cochrane reviewers (24.0%, 31/129), on average. Descriptive analysis revealed no difference between the proportion of favorable results and positive conclusions for SR component study designs (e.g., experimental, observational) or different funding sources.

None of the predictors for which we collected data were associated with favorable results (Table 3). However, non-Cochrane reviews with a meta-analysis of the primary outcome were more than twice as likely to have positive conclusions compared to Cochrane reviews with such an analysis (odds ratio = 2.35, 95% CI: 1.01, 5.48).

3.4. Level of agreement between SR results and reviewers' conclusions

Overall, the weighted kappa for agreement between SR results and conclusions was 0.55 (95% CI: 0.47, 0.64). Cochrane reviews had less agreement (weighted kappa = 0.41; 95% CI: 0.28, 0.55) between the results and conclusions than non-Cochrane reviews (weighted kappa = 0.67; 95% CI: 0.55, 0.78), although the CIs overlapped slightly.

4. Discussion

Indirect publication bias occurs when one observes a high proportion of statistically positive results and/or conclusions in the published literature [13]. In our sample of SRs, approximately 1/3 had favorable results and positive conclusions, which increased to approximately 2/3 for SRs including a meta-analysis of the primary outcome. To evaluate whether indirect publication bias is present in our sample of SRs, comparison with other cross-sectional studies is likely beneficial.

In our study, the proportion of favorable results for Cochrane and non-Cochrane reviews with a meta-analysis of the primary outcome (64.3% and 57.7%, respectively) was inconsistent with another study of 138 meta-analyses that found more beneficial results in non-Cochrane reviews ($P = 0.007$) [14]. The overall proportion of positive conclusions from our study (28.7%) is much lower than a previous cross-sectional study of 193 SRs published in the Database of Abstracts of Reviews of Effects (60.0%); however, the proportion of positive conclusions for non-Cochrane reviews including a meta-analysis of the primary outcome is similar (57.2% and 68%, respectively) [13]. Furthermore, the proportion of favorable results for SRs with a meta-analysis of the primary outcome was much higher than a study examining favorable results of individual studies (35%) [12], yet similar to other studies examining samples of individual studies (71–75%) [4,8,10]. Based on these comparisons, the SRs including a meta-analysis of the primary outcome in our sample potentially are affected by indirect publication bias.

Our results indicate that non-Cochrane reviews are more than twice as likely to have positive conclusion statements as Cochrane reviews. Although the CIs overlapped slightly, Cochrane reviews had a lower level of agreement between SR results and reviewer conclusions than non-Cochrane reviews. This suggests that differences exist between the results and conclusions of Cochrane and non-Cochrane reviews.

The lower level of agreement for Cochrane review results and conclusions might be because a higher proportion

Table 2
Results and conclusions of non-Cochrane and Cochrane reviews

Item	Total Cochrane and non-Cochrane reviews (%)	Non-Cochrane reviews without a meta-analysis of the primary outcome (%)	Non-Cochrane reviews with a meta-analysis of the primary outcome (%)	Cochrane reviews without a meta-analysis of the primary outcome (%)	Cochrane reviews with a meta-analysis of the primary outcome (%)
#Systematic reviews	296 (100.0)	104/167 (62.3)	63/167 (37.7)	51/129 (39.5)	78/129 (60.5)
Review results					
Indeterminate	92/296 (31.0)	27/104 (26.0)	13/63 (20.6)	31/51 (60.7)	21/78 (26.9)
Noncomparative	64/296 (21.6)	64/104 (61.5)	0 (0)	0 (0)	0 (0)
Unfavorable[a]	*17/296 (5.8)*	*1/104 (1.0)*	*6/63 (9.6)*	*3/51 (5.9)*	*7/78 (9)*
Nonstatistically significant negative	12/296 (4.1)	1/104 (1.0)	3/63 (4.8)	2/51 (3.9)	6/78 (7.7)
Statistically negative	5/296 (1.7)	0 (0)	3/63 (4.8)	1/51 (2.0)	1/78 (1.3)
Neutral	15/296 (5.1)	1/104 (1.0)	3/63 (4.8)	6/51 (11.8)	5/78 (6.4)
Favorable[†]	*108/296 (36.5)*	*11/104 (10.5)*	*41/63 (64.3)*	*11/51 (21.6)*	*45/78 (57.7)*
Nonstatistically significant positive	43/296 (14.5)	7/104 (6.7)	9/63 (14.3)	6/51 (11.8)	21/78 (26.9)
Statistically positive	65/296 (22.0)	4/104 (3.8)	32/63 (50.7)	5/51 (9.8)	24/78 (30.8)
Reviewers' conclusions					
Indeterminate	103/296 (34.8)	15/104 (14.4)	16/63 (25.4)	40/51 (78.4)	32/78 (41.0)
Noncomparative	64/296 (21.6)	64/104 (61.5)	0 (0)	0 (0)	0 (0)
Neutral	21/296 (7.1)	2/104 (2.0)	2/63 (3.2)	5/51 (9.8)	12/78 (15.4)
Negative	23/296 (7.8)	5/104 (4.8)	9/63 (14.3)	1/51 (2.0)	8/78 (10.3)
Positive	85/296 (28.7)	18/104 (17.3)	36/63 (57.2)	5/51 (9.8)	26/78 (33.3)

[a] Includes nonstatistically significant negative and statistically negative.
[†] Includes nonstatistically significant positive and statistically positive.

of Cochrane reviews had indeterminate conclusions, stating that more research is required than non-Cochrane reviews. This may indicate that Cochrane reviewers are more cautious; they may not make definitive conclusions unless the data are 100% clear-cut. It may also indicate that our rating criteria for a "favorable" or "unfavorable" result may not match the criteria used by The Cochrane Collaboration.

In our study, approximately 50% of the SRs reported a not-for-profit funding source and our logistic regression analyses did not identify funding as being a predictor of favorable results or positive conclusions. This may suggest that differences exist between the SR and individual-study level. The factors and pressures to publish primary research (e.g., randomized trials) have been shown to be influenced by funding source. Specifically, for-profit funding sources have been associated with positive results and conclusions in clinical research [23–25]. However, almost 40% of the SRs did not report a funding source, which may have affected our findings.

Table 3
Characteristics predicting favorable results and positive conclusions among systematic reviews performing a meta-analysis of the primary outcome

Characteristic	Review results[a]	Reviewers' conclusions[a]
Did not assess between-study inconsistency vs. did	0.65 (0.11, 3.89)	1.05 (0.19, 5.66)
Non-Cochrane vs. Cochrane	0.53 (0.23, 1.27)	2.35 (1.01, 5.48*)
Not funded/not reported vs. funded	0.59 (0.27, 1.29)	0.88 (0.40, 1.91)
Included English reports only vs. included all languages	3.89 (0.39, 39.0)	0.20 (0.03, 1.33)
Included mixed language reports only vs. included all languages	2.99 (0.31, 28.79)	0.61 (0.10, 3.8)
No explicit statement on publication status inclusion vs. included published material only	1.15 (0.47, 2.70)	1.41 (0.58, 3.46)
Included published material only vs. included published and unpublished material	0.92 (0.33, 2.63)	2.25 (0.79, 6.36)
Assessed publication bias vs. did not	1.38 (0.66, 2.89)	0.78 (0.36, 1.65)

*$P < 0.05$.
[a] Presented as odds ratios (95% confidence intervals).

Our results suggest that some methodological aspects of SRs have not improved over time. In our sample of SRs, 41.2% included unpublished material and 38.9% included non-English articles, which is similar to a study conducted by Song et al. and published in 2000 (34.0% and 30.0%, respectively) [13]. Approximately 23% of the SRs assessed for publication bias and discussed publication bias in our study, whereas 17% assessed for publication bias and 36% discussed publication bias in this other study [13]. However, our sample has shown improvements in the use of protocols and quality assessment in SRs over time [18].

Our study has some limitations. The cross-sectional sample comprised only English reviews from 1 month of a single database and we relied on what the authors reported in the SR publication [18]. Furthermore, we used a broad definition of what constitutes a SR and we did not assess the individual studies included in the SRs. Assessing the primary outcome, results, and conclusions of the SRs was often difficult; over half of the included SRs did not report a primary outcome or reported multiple primary outcomes. However, two independent investigators classified the entire sample and resolved discrepancies through discussion, which increases the validity of our results.

Confusion with reporting primary outcomes may indicate that outcome-reporting bias may affect our sample of SRs [26]. Our results suggest that systematic reviewers would benefit from training on how to select and report primary outcomes before conducting their SR. Registration of SRs at inception is a possible mechanism for decreasing reporting bias among SRs and may also minimize or avoid unpublished SRs [18,27]. International, collaborative efforts toward such an initiative are required.

The results of the current study along with the results of a recent survey [27] suggest that further research examining publication issues surrounding SRs is warranted. This survey found that unpublished SRs do exist; participants reported 1,405 published (median per respondent: 2.0, range 1–150) and 199 unpublished (median per respondent: 2.0, range 1–33) SRs [27]. The most commonly reported reasons for not publishing were lack of time, the article being rejected, and operational issues. Members of the investigative team are currently involved with research endeavors within this area.

In conclusion, SRs including a meta-analysis of the primary outcome may be affected by indirect publication bias. Differences between the results and conclusions of Cochrane and non-Cochrane reviews were also apparent. Further research on publication-related issues at the SR level is warranted.

Acknowledgments

This research was funded by the Canadian Agency for Drugs and Technologies in Health. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The research was conducted as part of a PhD dissertation in Population Health at the University of Ottawa.

We thank Jacqueline Tetroe and Dr. Mario Cappelli for their input on the original protocol of this study; Margaret Sampson for assistance with the literature searches; Raymond Daniel for assistance with document acquisition; and David Hallett and Maggie Hong Chen for their statistical consultation.

Potential conflict of interest: All of the authors are members of the Cochrane Collaboration.

References

[1] Dickersin K. How important is publication bias? A synthesis of available data. AIDS Educ Prev 1997;9:15–21.

[2] Dickersin K. Publication bias: recognizing the problem, understanding its origins and scope, and preventing harm. In: Rothstein, Sutton, Borenstein, editors. Publication bias in meta-analyses—prevention, assessment and adjustments. New York, New York: John Wiley & Sons Ltd.; 2005.

[3] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358:252–60.

[4] Smart RG. The importance of negative results in psychological research. Can Psychol 1964;5:225–32.

[5] Bozarth JD, Roberts RR. Signifying significant significance. Am Psychol 1972;27:774–5.

[6] Hubbard R, Armstrong JS. Publication bias against null results. Psychol Rep 1997;80:337–8.

[7] Greenwald AG. Consequences of prejudice against the null hypothesis. Psychol Bull 1975;82:1–20.

[8] Davidson RA. Source of funding and outcome of clinical trials. J Gen Intern Med 1986;1:155–8.

[9] Moscati R, Jehle D, Ellis D, Fiorello A, Landi M. Positive-outcome bias: comparison of emergency medicine and general medicine literatures. Acad Emerg Med 1994;1:267–71.

[10] Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. JAMA 1994;272:122–4.

[11] Mulward S, Gøtzshe P. Sample-size of randomized double-blind trials 1976-1991. Dan Med Bull 1996;43:96–8.

[12] Csada RD, James PC, Espie RHM. The file drawer problem of non-significant results—does it apply to biological research? Oikos 1996; 76:591–3.

[13] Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess 2000;4:1–115.

[14] Schwarzer G, Antes G, Tallon D, Egger M. Review publication bias? Matched comparative study of Cochrane and journal meta-analyses. 9th International Cochrane Colloquium, Lyon, France, 9–13 October 2001. 2001. Ref Type: Abstract.

[15] Sohn D. Publication bias and the evaluation of psychotherapy efficacy in reviews of the research literature. Clin Psychol Rev 2007; 16:147–56.

[16] Lavis JN, Davies HTO, Gruen RL, Walshe K, Farquhar CM. Working within and beyond the Cochrane Collaboration to make systematic reviews more useful to healthcare managers and policymakers. Healthc Policy 2006;1:21–33.

[17] Lavis J, Davies H, Oxman A, Denis JL, Golden-Biddle K, Ferlie E. Towards systematic reviews that inform health care management and policy-making. J Health Serv Res Policy 2005;10(Suppl 1): 35–48.

[18] Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med 2007;4:e78.

[19] Montori VM, Wilczynski NL, Morgan D, Haynes RB. Optimal search strategies for retrieving systematic reviews from Medline: analytical survey. BMJ 2005;330:68.

[20] Cochrane Handbook for Systematic Reviews of Interventions 4.2.6. [updated September 2006]. The Cochrane library edn. Chichester, UK: John Wiley & Sons, Ltd.; 2006.

[21] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.

[22] SAS Online Doc, Version 8. Cary, NC: SAS Institute Inc.; 2008. Available at: http://www.uc.edu/sashtml. Accessed July 11, 2008.

[23] Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003;326:1167–70.

[24] Lexchin J. Statistics can affect treatment decisions. Can Fam Physician 2003;49:1587–8.

[25] Lexchin JR. Implications of pharmaceutical industry funding on clinical research. Ann Pharmacother 2005;39:194–7.

[26] Silagy CA, Middleton P, Hopewell S. Publishing protocols of systematic reviews. Comparing what was done to what was planned. JAMA 2002;287:2831–4.

[27] Tricco AC, Pham B, Brehaut J, Tetroe J, Cappelli M, Hopewell S, et al. An international survey suggested that unpublished systematic reviews do exist. 2008. Ref Type: Unpublished Work

[28] Last LM. A dictionary of epidemiology: fourth edition. Toronto, Canada: Oxford University Press; 2001.

[29] Shadish W, Cook T, Campbell D. Quasi-experimental and experimental designs for generalized causal inference. Boston, MA: Houghton Mifflin Company; 2002.

Appendix A

Montori's search strategy

1. 200411.ed.
2. cochrane database of systematic reviews.jn. or search.tw. or meta-analysis.pt. or medline.tw. or systematic review.tw. or ((meta-analysis.mp,pt. or review.pt. or search$.tw.) and methods$.ab.)
3. 1 and 2
4. limit 3 to English

Appendix B

Categorization guide

1. Discern whether the systematic review (SR) is relevant or not. We will only include SRs on health-related topics. For example, SRs on animal studies and plant studies will be excluded.
2. Establish whether the SR includes a meta-analysis. The definition of a meta-analysis is "a statistical synthesis of the data from separate but similar studies, leading to a quantitative summary of the pooled results" [28].
3. Establish whether the SR includes experimental studies or observational studies. Experimental studies are those under the direct control of the investigator [28]. They include randomized controlled trials (RCTs), quasi-RCTs, controlled trials, and quasi-experimental studies (matching instead of randomization is used; examples include interrupted or noninterrupted time series, one-group posttest only, one-group pretest posttest, removed treatment design, repeated treatment design). Observational studies are those that do not involve any intervention, experimental, or otherwise [29]. Examples of observational studies include cohort, case–control, and cross-sectional studies (e.g., ecological studies). Some studies include MAs and/or other SRs (e.g., clinical practice guidelines). In these situations, SRs and MAs should be classified as observational studies.
4. Distinguish whether the RESULTS of the SR were statistically negative (unfavorable: $P > 0.05$), nonstatistically negative (unfavorable: $P \leq 0.05$), neutral, nonstatistically positive (favorable: $P > 0.05$), statistically positive (favorable: $P \leq 0.05$), indeterminate/unclear, or noncomparative. For nonsignificant and negative results:
   a. SRs that are examining incidence, prevalence, or other noncomparative topics should be classified as noncomparative.
   b. The decision tree should be used to classify negative results [10]. This should also be used to determine the primary outcome of the SR, whenever unclear. The stated primary outcome should be used, however, if that's not available, use the one in the title/objective or the most serious outcome (e.g., mortality) [10].
   c. Qualitative SRs that do not use outcomes, yet the topic is comparative in nature should be classified as indeterminate.
   d. If a diagnostic SR uses diagnostic odds ratios, these should be used to determine the category of the results. If not, judge how their test compared with another test/gold standard to determine the status of their results (e.g., A vs. B in the presence of gold standard, A vs. gold).
   e. If they compare across multiple treatments, discern the results of the primary outcome based on the treatment vs. placebo or standard of care. Try to determine the intervention and the comparator. Judge positive/negative, etc. based on this. If the intervention and comparator are unclear, then the newest intervention will be considered the intervention and the standard of care/gold standard/placebo will be considered the comparator.
   f. If the effect size is between 0.95 and 1.05 and the confidence interval crosses 1, then we will classify this as a neutral result.
5. Discern whether the CONCLUSIONS of the authors of the SR were negative, neutral, positive, indeterminate, or noncomparative, regardless of what their results were [13]. For example, if the authors state that there is evidence of effectiveness then we would consider this to be a positive conclusion. If the authors advised against the intervention/comparison or it is not recommended then we would classify this as negative. If they state that there is no evidence of effectiveness or had no opinion, then this would be considered a neutral conclusion. Classify the SR as indeterminate if they state that there is evidence, yet it's inconclusive or that more research is required. If there are mixed conclusions, try to use the conclusion from the primary outcome/primary comparison of interest to determine the status of the conclusions. We should use the decision tree [10] to help determine the primary outcome/primary comparison of interest in these situations. If there are mixed conclusions and the primary outcome/comparison can't be deciphered, classify the SR's conclusions as indeterminate.

Chapter 4: Paper 2

An international survey indicated that unpublished systematic reviews exist (2)

ELSEVIER

Journal of Clinical Epidemiology 62 (2009) 617–623

Journal of Clinical Epidemiology

ORIGINAL ARTICLES

An international survey indicated that unpublished systematic reviews exist

Andrea C. Tricco[a,b], Ba' Pham[a,c], Jamie Brehaut[d,e], Jacqueline Tetroe[f], Mario Cappelli[g,h], Sally Hopewell[i], John N. Lavis[j], Jesse A. Berlin[k], David Moher[a,d,*]

[a]*Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada*
[b]*Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada*
[c]*Toronto Health Economics & Technology Assessment Centre, University of Toronto, Toronto, Ontario, Canada*
[d]*Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada*
[e]*Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ontario, Canada*
[f]*Canadian Institutes of Health Research, Ottawa, Ontario, Canada*
[g]*Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada*
[h]*School of Psychology, University of Ottawa, Ottawa, Ontario, Canada*
[i]*UK Cochrane Centre, Oxford, UK*
[j]*Department of Clinical Epidemiology & Biostatistics and Department of Political Science, McMaster University, Hamilton, Ontario, Canada*
[k]*Pharmacoepidemiology Department, Johnson & Johnson Pharmaceutical Research and Development, Titusville, New Jersey, United States*

Accepted 15 September 2008

Abstract

Objective: To determine the frequency of unpublished systematic reviews (SRs) and explore factors contributing to their occurrence.

Study Design and Setting: First or corresponding authors from a sample of SRs published in 2005 were asked to participate in a 26-item survey administered through the Internet, facsimile, and postal mail. Outcomes included median and range of published and unpublished SRs, and barriers, facilitators, and reasons for not publishing SRs. Descriptive analyses were performed.

Results: 55.7% (348 of 625) of those invited participated, half of which were from Europe and 22.7% were from the United States. Participants reported 1,405 published (median: 2.0, range: 1–150) and 199 unpublished (median: 2.0, range: 1–33) SRs. Lack of time and lack of funding and organizational support were barriers, whereas time availability and self-motivation were facilitators to publishing reviews. For most recent unpublished SRs ($n = 52$), the reasons for not publishing included lack of time (12 of 52, 23.0%), the manuscript being rejected (10 of 52, 19.0%), and operational issues (six of 52, 11.5%).

Conclusion: Unpublished SRs do exist. Lack of time, funding, and organizational support were consistent reasons for not publishing SRs. Statistical significance of SR results was not reported as being a major barrier or reason for not publishing. Further research on unpublished SRs is warranted.

Keywords: Systematic review; Meta-analysis; Publication bias; Bias; Survey; Barriers and facilitators

1. Introduction

Publication bias occurs when "investigators, reviewers, and editors submit or accept manuscripts for publication based on the direction or strength of the study findings" [1]. Primary research studies with particular characteristics (e.g., statistically positive results, large effect sizes) have a better chance of being published than those without these characteristics [2]. Consequently, journals might be the unwitting conduit of a biased selection of articles, potentially leading to decisions that are not based on the full spectrum of evidence. Worse still, some reports might never be

This research was funded by the Canadian Agency for Drugs and Technologies in Health (CADTH). It was presented as a poster presentation at the 2007 CADTH Invitational Symposium on April 23, 2007, in Ottawa, Ontario, Canada, and as an oral presentation at the Society for Research Synthesis Methodology, Evanston, IL, United States, on July 10, 2007. Ms Tricco is funded by a Canadian Institutes of Health Research Canada Graduate Scholarship and a University of Ottawa Excellence Scholarship. Dr Brehaut is funded by an Ontario Ministry of Health Career Scientist Award. Dr Lavis is funded by a Canada Research Chair in Knowledge Transfer and Exchange. Dr Moher is funded by a University of Ottawa Research Chair. Dr Berlin's time was donated by his employer, Johnson & Johnson Pharmaceutical Research and Development.

A.C.T., B.P., J.B., S.H., J.N.L., and D.M. are all members of the Cochrane Collaboration.

* Corresponding author. Clinical Epidemiology Program, Ottawa Health Research Institute, Box 208, 501 Smyth Road, Ottawa, Ontario, K1H 8L6 Canada. Tel.: +613-738-3591; fax: +613-738-4800.

E-mail address: dmoher@ohri.ca (D. Moher).

0895-4356/09/$ – see front matter
doi: 10.1016/j.jclinepi.2008.09.014

What is new?

1. Few studies have examined the occurrence of publication bias at the systematic review level and the frequency of unpublished systematic reviews is unclear.
2. Our results indicate that unpublished systematic reviews exist and the median number of reported unpublished reviews per respondent is similar to that of published SRs.
3. The reasons for not publishing systematic reviews are different than reasons for not publishing individual studies (e.g., clinical trials). The most common reasons for not publishing systematic reviews included lack of time and the manuscript being rejected.
4. Mechanisms for minimizing or avoiding unpublished reviews include registration of SRs at inception, training on how to conduct a thorough scoping exercise before conducting a review, creating methods to fast-track the peer-review process, and encouraging journals to publish SRs without word limitations.
5. Future research examining publication issues surrounding systematic reviews is warranted, such as a retrospective cohort study of factors associated with the time to publication of systematic reviews.

published because their results have not met a particular threshold of statistical significance. The consequences of publication bias can be severe; it can exaggerate the estimate of an intervention's effectiveness by 20% or more in clinical research [3]. Surveys of peer reviewers and investigators have consistently found that statistically positive trials and observational studies are more likely to be submitted for publication and accepted for publication [4–8]. One study examining 38 individual patient data (IPD) meta-analyses in cancer [9] found that nonsignificant results took longer to publish and were published in lower-impact journals than significant results.

The extent of publication bias for the more common non-IPD systematic review (SR) across all areas of research is underexplored. This issue is particularly important, as decision makers increasingly rely on SR results [10–12]. We aimed to determine the frequency of completed but unpublished SRs and explore factors contributing to their occurrence.

2. Methods

2.1. Survey design

SRs were identified through an electronic search of MEDLINE, EMBASE, and CINAHL (OVID Interface) using a modified Montori search strategy (Appendix A; available on the journal's website at www.jclinepi.com) [13]. The search was limited to reviews indexed in 2005 and published in English. The search strategy was developed by an experienced information specialist and implemented by a member of the research team (A.C.T.) on June 8, 2006.

One investigator (A.C.T.) screened a computer-generated random sample of records (i.e., title and abstract) from the literature search to determine its eligibility based on the following definition of an SR: "the authors' objective was to summarize evidence and the article described explicit methods" [14,15]. SR abstracts not published in full and those on nonhuman, non–health-related topics (e.g., plant and animal studies) were excluded. Our definition of a published SR included those reported in one or more journal articles, monographs, or books, available in libraries, in documents available from a public archive, or in press at the time of questionnaire completion [16]. Records deemed relevant were obtained in full text and subsequently screened by the same member of the team (A.C.T.). A second member of the team was consulted whenever relevance was unclear (D.M.). Based on a previous survey on the publication practices of trialists [5], it was determined that a sample of at least 15% of first or corresponding authors should be drawn.

2.2. Development and pretesting

The survey was developed and pilot-tested by the investigative team along with a five-member international panel. To increase the overall response rate, standard survey methods for performing mail- and Internet-based surveys were used. The effectiveness of these methods has been verified [17–19].

The survey consisted of 26 questions, which were based on past surveys identified in the literature [4–8], and discussion with experts in survey design, SR methodology, and/or publication bias (Appendix B; available on the journal's website at www.jclinepi.com). To minimize position bias, the order of responses was randomized in the rows of questions for which no order was required, which occurred for eight of the 26 survey questions. All survey questions provided nonresponse options (e.g., undecided), and participants were allowed to skip questions they did not wish to answer.

There were two parts to the survey: (1) issues related to published SRs; and (2) issues related to unpublished SRs. Major themes of the survey included eliciting authors' reasons for conducting SRs, examining facilitators and barriers to publishing SRs, obtaining details about unpublished SRs in general, and more detailed information on the most recent unpublished SR. We defined an unpublished SR as a completed review (i.e., results synthesized and manuscript completed) that was not reported through any of these means described above.

2.3. Survey administration

Ethics approval was obtained from the Research Ethics Board of the Children's Hospital of Eastern Ontario. To ensure that authors of multiple SRs published in 2005 were not oversampled, corresponding or first authors on the

relevant SRs were contacted. A short prenotification e-mail was sent 2 days before survey implementation, informing participants about the survey objective and that it would take approximately 20 minutes to complete. A link to the survey was e-mailed to all participants through "Survey Monkey," an Internet survey tool [20]; available at www.surverymonkey.com.

The Survey Monkey tool was chosen because of its versatility in survey design and execution. The survey can be easily customized, or preexisting survey templates can be used. The survey question options can be randomized or sorted. A unique identification number is automatically assigned to every individual contacted, which allows participants and nonrespondents to be easily tracked. Custom e-mail invitations including a simple web link to the survey can be created and follow-up reminders to only those who have not responded can be easily sent. Furthermore, it allows participants to review their answers to check for accuracy even after survey completion.

A reminder along with the Survey Monkey link was sent 1 week after survey implementation through e-mail to nonrespondents. Another reminder along with the questionnaire was sent 3 weeks later through facsimile to nonrespondents. The last contact involved sending the cover letter and survey package approximately 7 weeks later to nonrespondents by postal mail with a prepaid mail return envelope for those working in Canada. The questionnaire was consistent across survey modalities. Invitees were offered a small token of appreciation (i.e., a US$10 gift certificate from www.amazon.com) in the introduction letter. Participants were offered the final survey results on the last Internet screen (or page) of the survey. Data were collected between November 2006 and April 2007.

2.4. Data analysis

Data from "Survey Monkey" were collected automatically, whereas the data from facsimile and postal mail were manually entered into a database. Quality checks on the manually entered data were conducted to ensure its accuracy. All data were analyzed descriptively using statistical software produced by the SAS Institute Inc. (Cary, NC, USA). The response rate was calculated as the number of unique responses received divided by the number of individuals who were sent the survey (i.e., a total of 625 systematic reviewers) [18]. All unique responses from the survey participants were analyzed and incomplete surveys were included.

3. Results

3.1. Sampling process

Our electronic search yielded a total of 35,795 records. The OVID Interface only allows duplicates to be removed from 6,000 records at a time across databases. As such, a computer-generated random sample of 6,000 records was drawn (Appendix A). These records were downloaded and duplicates were removed by the information specialist to ensure that articles indexed in more than one of the databases did not have multiple chances of being sampled. The resulting set included 3,340 unique records. The 3,340 records were screened for eligibility, and 819 SRs met the eligibility criteria. Some of the first or corresponding authors had published more than one SR in the database of 819 reviews. Duplicate authors were removed, and this resulted in a total of 625 unique first or corresponding authors that were used as our sample of systematic reviewers (Fig. 1).

3.2. Response rate

Overall, 64.5% (403 of 625) of those invited responded; 348 (55.7%) participated in the survey, and 55 (8.8%) explicitly declined (Fig. 1). Throughout their careers, the 348 participants reported being the lead on a total of 1,405 published SRs, with a median of 2.0 published SRs per reviewer (range: 1–150). In contrast, 54 participants (54 of 348, 15.5%) reported participating in 199 unpublished SRs with a median of 2.0 unpublished SRs per reviewer (range: 1–33).

3.3. Systematic reviewer characteristics

From the published SR report, 50% (174 of 348) of the participants were based in Europe, 22.7% (79 of 348) were from the United States, 9.5% (33 of 348) were from Canada, 8.6% (30 of 348) were from Australia, 4.9% (17 of 348) were from Asia, 2.9% (10 of 348) were from South America, and 1.4% (five of 348) were from Africa (Table 1). Although we identified all respondents as being the first or corresponding author on a published SR, 6.3% (22 of 348) reported that they have never been the lead on

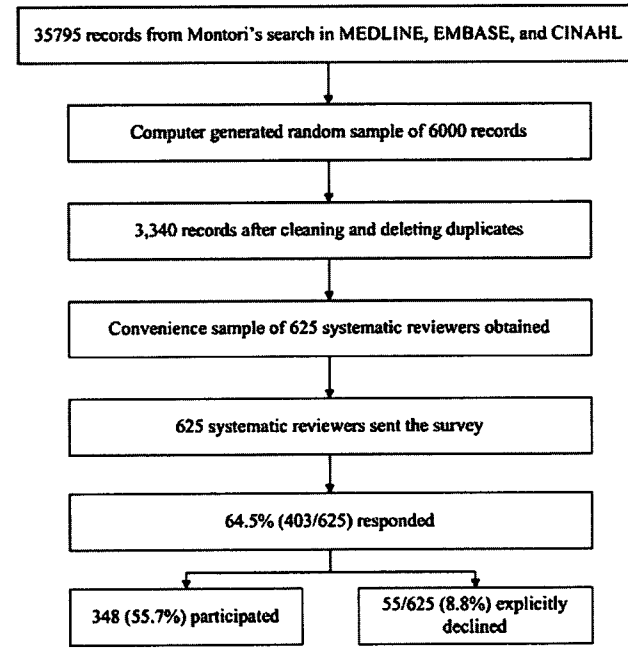


Fig. 1. Survey flow.

Table 1
Characteristics of systematic reviews (SRs) published by group[a]

Characteristics	Participants ($n = 348$)	Participants reporting never being the lead on a published SR ($n = 26$)[b]	Nonparticipants ($n = 277$)[c]
Number of authors—median: range	3: 1–22	4: 1–16	3: 1–31
Study funding (%)			
NFP	33.9	33.3	23.6
PI	3.7	7.4	5.2
None	10.1	7.4	17.0
NR	52.3	51.9	53.5
Mixed	0	0	0.7
Publication type (%)			
SR	95.7	88.9	96.0
CPG	1.4	11.1	2.9
HTA	2.9	0	1.1
SR type (%)			
Non-Cochrane	79.9	96.3	90.6
Cochrane	18.7	3.7	9.1
NIHR HTA	1.4	0	0.3
Location (%)			
Europe	50.0	29.6	23.6
United States	22.7	29.6	37.6
Canada	9.5	7.4	11.3
Other	17.8	33.4	27.5

Abbreviations: SR, systematic review; NFP, not-for-profit organization; PI, private industry; NR, not reported; CPG, clinical practice guideline; NIHR HTA, National Institute for Health Research Health Technology Assessment programme.

[a] This information was gleaned from the full-text systematic review article.

[b] These are included in the participants' analysis.

[c] This category includes declines ($n = 55$). Includes reviews with mixed private industry and not-for-profit funders.

a published SR or unpublished SR, and 1.1% (four of 348) reported only being the lead on an unpublished SR. Most of the respondents were the leads on published SRs only (72.4% [252 of 348]), whereas 14.4% (50 of 348) reported being the lead on published and unpublished SRs.

There were some small differences between the responders and nonresponders, although we believe they are not of methodological importance (Table 1). For example, 79.9% (278 of 348) of participants were non-Cochrane reviewers vs. 90.6% (251 of 277) of nonparticipants.

3.4. Reasons for conducting systematic reviews

Common reasons for conducting their published SRs included an area of interest (always or frequently: 91.0% [282 of 310]), a gap in the literature or controversial area (84.8% [263 of 310]), and justification of new research initiatives (38.8% [118 of 304]; Table 2). Unpublished SRs were more likely to be conducted to justify new research (always or frequently: 51% [26 of 51]) and because of requests from a consumer group (12.0% [six of 50]; Table 2).

3.5. Barriers and facilitators

Barriers to publishing SRs included lack of time (most significant and significant: 54.7% [164 of 300]), lack of funding (36.1% [109 of 302]), and lack of organizational support (29.6% [89 of 301]; Table 3). Significant facilitators to publishing SRs included self-motivation (most significant and significant: 85.0% [256 of 301]), time availability (81.5% [246 of 302]), and influencing practice or informing policy (80.5% [243 of 302]; Table 3).

3.6. Main audience

The main intended audience of published and unpublished SRs was health care practitioners (76.2% [230 of 302] and 65.4% [34 of 52], respectively), researchers (7.3% [22 of 302] and 3.8% [two of 52]), and policy makers (7.0% [21 of 302] and 7.7% [four of 52]). Unpublished SRs were more likely to have no specific audience (9.6% [five of 52) compared with published SRs (5.0% [15 of 302]).

3.7. Degree of impact

Approximately one-fifth of the participants (20.9% [63 of 302]) were not sure of their published SR's impact on the health of the population. Among the rest, 28.8% (87 of 302) reported much, 28.5% (86 of 302) reported some, and 10.9% (33 of 302) reported little impact.

For unpublished SRs, 15.3% (eight of 52) were unsure about the impact of their SRs whereas 23.1% (12 of 52) reported their reviews as having much, 30.8% (16 of 52) some, and 7.7% (four of 52) little impact. A higher proportion of participants felt that their unpublished SRs had no

Table 2
Reasons for conducting published and unpublished systematic reviews[a,b]

Item	Always or frequently		Sometimes		Never	
	Published SRs	Unpublished SRs	Published SRs	Unpublished SRs	Published SRs	Unpublished SRs
An area of interest to you	282/310 (91.0)	42/53 (79.2)	20/310 (6.5)	6/53 (11.3)	8/310 (2.6)	5/53 (9.4)
A gap in the literature or a controversial area	263/310 (84.8)	39/52 (75.0)	38/310 (12.3)	10/52 (19.2)	9/310 (2.9)	3/52 (5.8)
Justification of new research initiatives (e.g., trials)	118/304 (38.8)	26/51 (51.0)	98/304 (32.2)	14/51 (27.5)	88/304 (28.9)	11/51 (21.6)
An area of interest to your employer	85/304 (28.0)	11/51 (21.6)	64/304 (21.0)	11/51 (21.6)	155/304 (51.0)	29/51 (56.9)
A health care practitioner suggested that you conduct the review	42/303 (13.9)	7/51 (13.7)	89/303 (29.4)	12/51 (23.5)	172/303 (56.8)	32/51 (62.8)
You received peer-reviewed funding	31/304 (10.2)	7/51 (13.7)	55/304 (18.1)	6/51 (11.8)	218/304 (71.7)	38/51 (74.5)
Commissioned by a not-for-profit health organization	30/303 (9.9)	9/51 (17.6)	47/303 (15.5)	9/51 (17.7)	226/303 (74.6)	33/51 (64.7)
Commissioned by a government organization	29/303 (9.6)	9/51 (17.6)	53/303 (17.5)	4/51 (7.8)	221/303 (72.9)	38/51 (74.5)
You received pharmaceutical company or other industry funding	7/303 (2.3)	3/51 (5.9)	19/303 (6.3)	5/51 (9.8)	277/303 (91.4)	43/51 (84.3)
A consumer group (e.g., patients) asked you to conduct the review	7/302 (2.3)	6/50 (12.0)	28/302 (9.3)	4/50 (8.0)	267/302 (88.4)	40/50 (80.0)

[a] Question 1: Based on your experience, please rank the following reasons that you conduct your published systematic reviews for, in general. Tick the appropriate box for each reason. Question 2: Based on your experience, please rank the following reasons that you conduct your unpublished systematic reviews for, in general. Tick the appropriate box for each reason.
[b] Presented as *n*/total respondents who answered the question (%).

impact (25.0% [13 of 52]) compared with published SRs (8.9% [27 of 302]).

3.8. Details about most recent unpublished systematic review and unpublished systematic reviews in general

When asked about the completion date of their most recent unpublished SR, 3.9% (two of 52) reported it being completed in 1995–1999, 21.2% (11 of 52) in 2000–2004, and 75.0% (39 of 52) in 2005. There was a median of 3.0 (range: 1–27) authors and a median of 12.0 (range: 0–140) studies included in the most recent unpublished SR.

A meta-analysis was conducted in 36.5% (19 of 52) of the most recent unpublished SRs, 68.4% (13 of 19) of which had a statistically significant result for their primary outcome. Only 32.7% (17 of 52) of the most recent unpublished SRs were presented at a conference. Of all 199 unpublished SRs, participants reported a total of 36 reviews that were submitted for publication but rejected by a journal.

Table 3
Rank of barriers and facilitators to publishing systematic reviews[a, b]

Item	Most significant or significant	Undecided	Least significant
Barriers to publishing systematic reviews			
Lack of time to invest in the publication process	164/300 (54.7)	47/300 (15.7)	89/300 (29.7)
Lack of funding or study funding ends before publication	109/302 (36.1)	52/302 (17.2)	141/302 (46.7)
Lack of organizational support	89/301 (29.6)	46/301 (15.3)	166/301 (55.2)
Often rejected by peer-reviewed journals	78/299 (26.1)	77/299 (25.8)	144/299 (48.2)
Operational issues	52/301 (17.3)	56/301 (18.6)	193/301 (64.1)
Noninformative or nonsignificant results	47/298 (15.8)	78/298 (26.2)	173/298 (58.1)
Workplace or study funder does not want to publish the results of your SRs	13/300 (4.3)	29/300 (9.7)	258/300 (86.0)
You are often contractually obliged not to publish the results	9/300 (3.0)	15/300 (5.0)	276/300 (92.0)
Facilitators to publishing systematic reviews			
Self-motivation	256/301 (85.0)	25/301 (8.3)	20/301 (6.6)
You have the ability to invest time into preparing SRs for publication	246/302 (81.5)	36/302 (11.9)	20/302 (6.6)
Influencing practice or informing policy	243/302 (80.5)	45/302 (14.9)	14/302 (4.6)
Informative or statistically significant results	195/300 (65.0)	48/300 (16.0)	57/300 (19.0)
Often accepted by peer-reviewed journals	192/301 (63.8)	68/301 (22.6)	41/301 (13.6)
Organizational support	166/300 (55.3)	50/300 (16.7)	84/300 (28.0)
Ease in getting funding for them	68/299 (22.7)	65/299 (21.7)	166/299 (55.5)

[a] Question 1: based on your experience, how do you rank the following barriers to publishing your systematic reviews? Please tick the appropriate box for each reason. Question 2: based on your experience, how do you rank the following facilitators to publishing your systematic reviews? Please tick the appropriate box for each reason.
[b] Presented as *n*/total respondents who answered the question (%).

Respondents cited lack of time (23.0% [12 of 52]) and the manuscript being rejected (19.0% [10 of 52]) as being the main reasons for not publishing their most recent unpublished SR, which was similar for their unpublished SRs in general (Fig. 2).

3.9. Cochrane vs. non-Cochrane systematic reviews

Post hoc descriptive analysis found no differences between the responses of participants who were the lead or corresponding authors of published Cochrane reviews ($n = 65$) vs. non-Cochrane reviews ($n = 283$).

4. Discussion

Our results indicate that unpublished SRs do exist; the median number of reported unpublished reviews per respondent is similar to that of published SRs. Through our survey, 199 unpublished SRs and 1,405 published SRs were identified, leading to a 12.4% [199/(199 + 1405)] nonpublication rate of SRs. This extrapolates to approximately 310 unpublished SRs per year from MEDLINE alone (i.e., 12.4% nonpublication rate from this study × 2,500 published SRs per year in MEDLINE from another study [14]), possibly containing over 344,720 participants (assuming 1,112 participants per SR, on average) [14]. This is a large amount of potentially meaningful data missing from the literature and implies enormous wasted time and resources. We cannot ascertain whether the studies included in the unpublished SRs were included in other published reviews.

Nearly 8% of respondents did not take "ownership" of their SR. We know that these individuals were the lead on an SR, as we identified them as such from our sample. The International Committee of Medical Journal Editors (ICMJE), have outlined criteria for authorship credit [21]. Surveys of university hospital faculty concluded that the knowledge and use of ICMJE criteria was low [22,23]. Our survey may provide evidence that confusion about authorship exists among systematic reviewers as well.

Lack of time was the most commonly reported reason for not publishing SRs. This was followed by the manuscript being rejected, yet participants reported that only

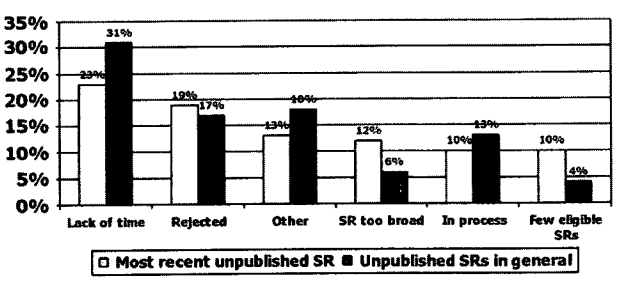


Fig. 2. Main reasons for not publishing most recent systematic reviews and systematic reviews in general. Question 1: What is the main reason that your most recent unpublished systematic review was not published? Please tick one of the following. Question 2: In general, what is the main reason for not publishing your systematic reviews? Please tick one of the following. *Abbreviation*: SR, systematic review.

36 unpublished SRs had been rejected. Similar to a previous survey of IPD meta-analysts [9], statistical significance did not appear to be an important driver of nonpublication of traditional summary data SRs. These results differ from the reasons of publication bias reported for individual studies [5,24]. Here, statistically significant results were the most common reason for publishing trials and psychology-related research [5,24]. However, 65.0% of respondents reported significant results as being the most significant or a significant facilitator for publishing SRs.

According to respondents, unpublished SRs were more likely to be conducted for consumers or have no specific intended audience, and less impact, compared with published SRs. Some participants felt that their unpublished reviews did have impact on the health of the population, which may be because they were conducted for a government organization to change health policy but were never published. A little over one-third of participants reported always or frequently conducting their published SRs to justify new research initiatives, whereas half reported always or frequently doing so for unpublished SRs. These results parallel recent efforts to put clinical research into context, by beginning and ending with up-to-date SRs in publications of trial reports [25–27]. Our results suggest that perhaps SRs are being conducted before performing clinical research, but the SR results are rarely reported in publications.

Registration of SRs at inception is a possible mechanism for minimizing or avoiding unpublished SRs [14]. Approximately 12% of participants reported the SR being too broad, and 10% reported that few studies were eligible as reasons for not publishing their most recent SR. Perhaps, systematic reviewers would benefit from training on how to conduct a thorough scoping exercise before conducting their SR. Other possible solutions to decreasing the frequency of unpublished SRs include creating methods to fast-track the peer-review process and encouraging journals to publish SRs without word limitations.

Our research had some limitations. The results are only generalizable to SRs published in English. Only 64.3% responded to our survey and nonrespondents may have different publication practices vs. respondents. However, our response rate is similar to a survey of trialists [5], and in line with expected response rates from Internet surveys [18]. Furthermore, our definition of an SR was quite broad and some of our participants may have only intended to do a literature review. However, this definition has been used in the past [14,15], and there is no reason to believe that the publication practices of systematic reviewers and literature reviewers is different. Our definition of a published SR was also quite broad [16,28]. As such, the number of unpublished SRs may be underestimated. Our results are based on self-report; sophisticated respondents may have downplayed the possibility that their lack of publication was because of statistically significant results.

Because of the exploratory nature of this study, future research on SR publication practices is warranted. Such

an endeavor could examine factors (e.g., statistically significant results, funding source of the SR, SR quality) that discriminate between published and nonpublished SRs. Such a study could be conducted by obtaining the unpublished SRs identified through our survey and comparing them with a random sample of the published SRs.

Acknowledgments

This research was funded by Canadian Agency for Drugs and Technologies in Health (CADTH). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The research was conducted as part of a PhD dissertation in Population Health at the University of Ottawa. We thank Dr. Kay Dickersin and Dr. David Gough for pilot-testing the questionnaire and providing invaluable feedback on the original survey. We also thank Margaret Sampson for validating the literature search and for her assistance with obtaining the random sample. We thank Jennifer Tetzlaff for advice on the survey conduct, Raymond Daniel for assistance with document acquisition, and David Hallett for statistical consultation. Furthermore, we thank Tammy Jakobsen, Beverly MacLaren, and Joan Fawcett for their assistance with survey administration.

Potential conflict of interest: Authors A.C.T., B.P., J.B., J.T., S.H., J.N.L., and D.M. are members of the Cochrane Collaboration.

References

[1] Dickersin K. How important is publication bias? A synthesis of available data. AIDS Educ Prev 1997;9:15–21.

[2] Dickersin K. Publication bias: recognizing the problem, understanding its origins and scope, and preventing harm. In: Rothstein H, Sutton A, Borenstein M, editors. Publication bias in meta-analyses—prevention, assessment and adjustments. New York: John Wiley & Sons Ltd.; 2005.

[3] Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess 2000;4:1–115.

[4] Coursol A, Wagner EE. Effect of positive findings on submission and acceptance rates: a note on meta-analysis bias. Prof Psychol Res Pr 1986;17:136–7.

[5] Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H Jr. Publication bias and clinical trials. Control Clin Trials 1987;8:343–53.

[6] Greenwald AG. Consequences of prejudice against the null hypothesis. Psychol Bull 1975;82:1–20.

[7] Shadish WR, Doherty M, Montgomery LM. How many studies are in the file drawer? An estimate from the family/marital psychology literature. Clin Psychol Rev 1989;9:589–603.

[8] Sommer B. The file drawer effect and publication rates in menstrual cycle research. Psychol Wom Quart 1987;11:233–42.

[9] Tierney JF, Clarke M, Stewart LA. Is there bias in the publication of individual patient data meta-analyses? Int J Technol Assess Health Care 2000;16:657–67.

[10] Lavis JN, Posada FB, Haines A, Osei E. Use of research to inform public policymaking. Lancet 2004;364:1615–21.

[11] Lavis J, Davies H, Oxman A, Denis JL, Golden-Biddle K, Ferlie E. Towards systematic reviews that inform health care management and policy-making. J Health Serv Res Policy 2005;10(Suppl. 1):35–48.

[12] Lavis JN, Davies HTO, Gruen RL, Walshe K, Farquhar CM. Working within and beyond the Cochrane Collaboration to make systematic reviews more useful to healthcare managers and policymakers. Healthcare Policy 2006;1:21–33.

[13] Montori VM, Wilczynski NL, Morgan D, Haynes RB. Optimal search strategies for retrieving systematic reviews from Medline: analytical survey. BMJ 2005;330:68.

[14] Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med 2007;4:e78.

[15] Peters JL, Sutton AJ, Jones DR, Rushton L, Abrams KR. A systematic review of systematic reviews and meta-analyses of animal experiments with guidelines for reporting. J Environ Sci Health B 2006;41:1245–58.

[16] Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. JAMA 1992;267:374–8.

[17] Kellerman SE, Herold J. Physician response to surveys. A review of the literature. Am J Prev Med 2001;20:61–7.

[18] Dillman DA. Internet and interactive voice response surveys. In: Mail and Internet surveys: the tailored design method. New York: John Wiley & Sons Inc.; 2000.

[19] Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, et al. Methods to increase response rates to postal questionnaires. Cochrane Database Methodol Rev 2007;18.

[20] Survey Monkey. www.surveymonkey.com. 2006.

[21] International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. http://www.icmje.org/#author. Accessed 01.02.2006

[22] Pignatelli B, Maisonneuve H, Chapuis F. Authorship ignorance: views of researchers in French clinical settings. J Med Ethics 2005;31:578–81.

[23] Dhaliwal U, Singh N, Bhatia A. Awareness of authorship criteria and conflict: survey in a medical institution in India. MedGenMed 2006;8:52.

[24] Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991;337:867–72.

[25] Young C, Horton R. Putting clinical trials into context. Lancet 2005;366:107–8.

[26] Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. J R Soc Med 2007;100:187–90.

[27] Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357:1191–4.

[28] Wager E. Publishing clinical trial results: the future beckons. PLoS Clin Trials 2006;1:e31.

Appendix A

Montori's search strategy

Search strategy for phase 2 of the research

1. 2005$.yr.
2. Cochrane database of systematic reviews.jn. or search.tw. or meta-analysis.pt. or medline.tw. or systematic review.tw. or ((meta-analysis.mp.pt. or review.pt. or search$.tw.) and methods$.ab.)
3. 1 and 2
4. Limit 3 to English
5. From 4 keep 2, 45 .... (numbers from the computer-generated random sample were entered here).

Appendix B

Survey instrument

Systematic reviewer publication practices survey

Section 1

This section relates to published systematic reviews.

In this survey, a **systematic review** refers to a study that aims to summarize research and includes explicit methods (e.g., search terms, inclusion/exclusion criteria). Data may be meta-analyzed and/or qualitatively synthesized.

A **published systematic review** refers to a systematic review reported in one or more journal articles, monographs or books, available in libraries, in documents available from a public archive or currently in press. For example, a Cochrane or a Campbell review would be considered a published systematic review, as it is available on a public archive through the Internet.

1. Using the definitions above, have you ever been a **lead author** (i.e., first or corresponding author) on a **published** systematic review? Please tick **one** of the following choices:

—Yes
—No
—Other
(i.e., you've done something related that doesn't exactly fit the definitions).
Please describe:_____

→If you answered NO, please skip to Section 2, question #11.

2. **How many** systematic reviews have you **published** for which you were the **lead author** (i.e., first or corresponding author)? Please tick **one** of the following choices:

—1
—2
—3
—4
—5
—6
—7
—8
—9
—10
—11
—12
—13
—14
—15
—16
—17
—18
—19
—≥20

Please write the exact amount in here: _____

3. Based on your experience, please **rank** the following **reasons** that you conduct your systematic reviews, **in general**. Tick the appropriate box for **each** reason.

In this survey, a **health-care practitioner** refers to individuals that see patients and work in the health-care field (e.g., doctors, nurses, psychologists, chiropractors).

	Always	Frequently	Sometimes	Never
A consumer group (e.g., patients, general population) asked you to conduct the review				
Justification of new research initiatives (e.g., a randomized controlled trial)				
You received pharmaceutical company or other industry funding				
An area of interest to you				
Commissioned by a not-for-profit health organization				
An area of interest to your employer				
A health-care practitioner suggested that you conduct the review				
You received peer-reviewed funding				
A gap in the literature or a controversial area				
Commissioned by a government organization				

4. Based on your experience, how do you **rank** the following **barriers** to **publishing** your systematic reviews? Please tick the appropriate box for **each** reason.

	Most significant	Significant	Undecided	Least significant
Workplace or study funder does not want to publish the results of your systematic reviews				
Operational issues (e.g., first author of the systematic review moves on to another job)				
You are often contractually obliged not to publish the results				
Lack of organizational support (e.g., publishing systematic reviews is not part of your workplace's mandate)				
Lack of funding or study funding ends prior to publication				
Lack of time to invest in the publication process				
Non-informative or nonsignificant results				
Often rejected by peer-reviewed journals				

Based on your experience, how do you **rank** the following **facilitators** to **publishing** your systematic reviews? Please tick the appropriate box for **each** reason.

	Most significant	Significant	Undecided	Least significant
Organizational support (e.g., publishing systematic reviews is part of your workplace's mandate)				
Self-motivation (e.g., building your CV)				
Ease in getting funding for them				
You have the ability to invest time into preparing the systematic review for publication				
Influencing practice or informing policy				
Informative or statistically significant results				
Often accepted by peer-reviewed journals				

6. Who is the main audience of your published systematic reviews, in general? Please tick one of the following:

—Consumers
(e.g., patients, general population)
—No specific target audience
—Managers/executives of not-for-profit organizations (e.g., the government)
—Health-care practitioners
—Managers/executives of for-profit organizations
(e.g., pharmaceutical companies)
—Policy-makers
(e.g., politicians, civil servants)
—Other (please specify: _____)

7. What degree of **impact** do your published systematic reviews have on the **health of the population**, in general? Please tick **one** of the following:

—Much impact
(e.g., affected the international, national or provincial/state level)
—Some impact
(e.g., affected the community level)
—Little impact
(e.g., affected a local organization, such as a community hospital)
—No impact that you're aware of
—Not sure
—Other (please specify: _____)

8. **When** should a systematic review be **updated**? Please tick **one** of the choices below.

In this survey, an **update** refers to a discrete event aiming to search for and identify "new evidence" to incorporate into a previously completed systematic review.

—Never
—When sufficient evidence has emerged, rendering the previous review out-of-date
—When a pre-specified period of time has gone by since the previous review (e.g., every 2 years)
—Other (please specify: _____)

→If you answered NEVER, please skip to Section 2, question #11.

9. In your opinion, who is **responsible for updating** a previously published systematic review? Please tick **one** of the following:

—Authors who conducted the previous systematic review
—Journals that publish them
—People or decision-makers who want to use the systematic review's results
—The systematic review community in general
—The editorial group responsible for the review (e.g., Cochrane musculoskeletal group)
—The funding organization of the previous review
—A combination of authors and journals
—A combination of authors, journals, and editorial groups
—A combination of authors, journals, and funding organizations
—A combination of authors, journals, editorial groups, and funding organizations
—Other (please specify):

10. Do you think that **updated systematic reviews** should be **published** in peer-reviewed journals? Please tick **one** of the following:

—Yes
—Yes, with what the update adds to the literature clearly highlighted
—No
—Other (please specify):

Section 2.

This section relates to **unpublished** systematic reviews.

In this survey, **unpublished systematic reviews** are **completed** systematic reviews (i.e., results summarization and manuscript write-up has been completed) that have not been reported in one or more journal articles, monographs or books, available in libraries, in documents available from a public archive or currently in press.

11. Using the definition above, do you have any **unpublished systematic reviews** for which you were the **lead author** (i.e., first or corresponding author) that you won't be submitting for publication within the next year? Please tick **one** of the following:

—Yes
—No
—Other (i.e., you've done something related that doesn't exactly fit the definition). Please describe:

→ If no, please skip to question #27, page 9.

12. **How many unpublished** systematic reviews do you have for which you were the **lead author** (i.e., first or corresponding author)? Please tick **one** of the following:

—1
—2
—3
—4
—5
—6
—7
—8
—9
—10
—11
—12
—13
—14
—15
—16
—17
—18
—19
—≥20

Please write the exact amount in here:

13. Based on your experience, please **rank** the following **reasons** that you conduct your **unpublished** systematic reviews, **in general**. Tick the appropriate box for **each** reason.

In this survey, a **health-care practitioner** refers to individuals that see patients and work in the health-care field (e.g., doctors, nurses, psychologists, chiropractors).

	Always	Frequently	Sometimes	Never
A consumer group (e.g., patients, general population) asked you to conduct the review				
Justification of new research initiatives (e.g., a randomized controlled trial)				
You received pharmaceutical company or other industry funding				
An area of interest to you				
Commissioned by a not-for-profit health organization				
An area of interest to your employer				
A health-care practitioner suggested that you conduct the review				

(Continued)

(Continued)

	Always	Frequently	Sometimes	Never
You received peer-reviewed funding				
A gap in the literature or a controversial area				
Commissioned by a government organization				

You will now be asked about your **most recent unpublished** systematic review for which you were the **lead author** (i.e., first or corresponding author).

14. What **year** was your **most recent** unpublished systematic review **completed** for which you were the **lead author**? Please tick **one** of the following:

—Before 1980
—1980–1984
—1985–1989
—1990–1994
—1995–1999
—2000–2004
—After 2005

15. In your **most recent unpublished** systematic review, **how many researchers** were involved, including yourself? Please tick **one** of the following:

—1
—2
—3
—4
—5
—6
—7
—8
—9
—≥10—Please write the exact amount in here: _____

16. What **topic** was examined (e.g., disease, condition, effectiveness of a drug, quality improvement strategy) in your **most recent unpublished** systematic review? Please write your answer in here: _____

17. How many **studies** passed all of your inclusion criteria and were **included** in this unpublished systematic review? Please tick **one** of the following:

—0
—1
—2
—3
—4
—5
—6
—7
—8

(Continued)

(Continued)

—9
—10
—11
—12
—13
—14
—15
—16
—17
—18
—19
—≥20

Please write the exact amount in here: _____

18. Was a **primary outcome** specified for this systematic review? Please tick **one** of the following:

—Yes
—No
—Other (please specify): _____

19. Was **statistical combining** (i.e., a meta-analysis) conducted in this unpublished systematic review? Please tick **one** of the following:

—Yes
—No
—Other (please specify: _____

→ If no, please skip to question #21.

20. Was **statistical significance** (defined as P value ≤ 0.05) in favour of your hypothesis achieved for the **primary outcome**? Please tick **one** of the following:

—Yes
—No, but a trend of significance was observed ($0.05 < P$ value ≤ 0.10)
—No and a trend of significance was not observed
—Other (please specify: _____

21. Was this **unpublished** systematic review **presented** at a conference? Please tick **one** of the following:

—Yes
—No
—Other (please specify: _____

22. What is the **main reason** that this systematic review was **not published**? Please tick **one** of the following

—No studies (or very few studies) were eligible for inclusion in the review
—Authors lacked interest
—The review was of a broad scope, rendering it difficult to conduct and publish
—Operational issues (e.g., first author of the systematic review moves on to another job)
—The review was of low quality
—The results were not significant
—You were contractually obliged not to publish the results
—Lack of study funding or study funding ended
—Not sure
—Other (please specify:

The past few questions dealt with your most recent unpublished systematic review.

You will now be asked a few questions about your **unpublished systematic reviews in general**.

23. Who is the **main audience** of your **unpublished** systematic reviews? Please tick **one** of the following:

—Policy-makers (e.g., politicians, civil servants)
—Managers/executives of for-profit organizations (e.g., pharmaceutical companies)
—Managers/executives of not-for-profit organizations (e.g., the government)
—Health-care practitioners
—No specific target audience
—Consumers (e.g., patients, general population)
—Other (please specify):

24. What degree of **impact** do your **unpublished** systematic reviews have, **in general**? Please tick **one** of the following:

—Much impact (e.g., affected the international, national or provincial/state level)
—Some impact (e.g., affected the community level)
—Little impact (e.g., affected a local organization, such as a community hospital)
—No impact that you're aware of
—Not sure
—Other (please specify:

25. Of all your **unpublished** systematic reviews for which you were the **lead author** (i.e., first or corresponding author), how many were submitted for publication but **rejected** by at least one journal? Please tick **one** of the following:

—0
—1
—2
—3
—4
—5
—6
—7
—8
—9
—≥10—Please write the exact amount in here:

26. **In general**, what is the **main** reason for **not publishing** your systematic reviews? Please tick **one** of the following:

—Lack of study funding or study funding ended
—The study funder does not want to publish the results of the review
—The results are not significant
—The manuscript was rejected
—You are often contractually obliged not to publish the results
—Authors lacked interest
—The review was of low quality
—The review was of a broad scope, rendering it difficult to conduct
—Your workplace does not want to publish the results of the review
—Another systematic review on the same topic or question was identified
—No studies (or very few studies) are eligible for inclusion in the review
—Operational issues (e.g., first author of the systematic review moves on to another job)
—Not sure
—Other (please specify:

27. May we contact you within the next 12 months for further information if we require clarification on your responses?

—No
—Yes

28. Your responses are very much appreciated. You will receive your $10Amazon.com gift certificate via email when the survey responses have been compiled.

If you would like to say anything else about publishing systematic reviews, please use the space provided below:

Chapter 5: Paper 3

Following 411 Cochrane protocols to completion: A retrospective cohort study (3)

Following 411 Cochrane Protocols to Completion: A Retrospective Cohort Study

Andrea C. Tricco[1,2], Jamie Brehaut[3,4], Maggie H. Chen[5], David Moher[1,3]*

1 Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada, **2** Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada, **3** Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, **4** Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ontario, Canada, **5** Department of Biostatistics, University of Toronto, Toronto, Ontario, Canada

Abstract

Background: Cochrane reviews are regarded as being scientifically rigorous and are increasingly used by a variety of stakeholders. However, factors predicting the publication of Cochrane reviews have never been reported. This is important because if a higher proportion of Cochrane protocols with certain characteristics (e.g., funding) are being published, this may lead to inaccurate decisions. We examined the frequency of published and unpublished Cochrane reviews and protocol factors that predict the publication of Cochrane reviews.

Methodology/Principal Findings: Retrospective cohort study of Cochrane protocols published in 2000 (Issues 2 to 4) and 2001 (Issue 1). The publication status of these reviews was followed up to Issue 1, 2008 in The Cochrane Library. Survival analysis of the time from protocol publication to the first review publication and protocol factors predicting the time to publication was conducted. There were 411 new Cochrane protocols in the cohort. After excluding 39; 71/372 (19.1%) were unpublished and 301/372 (80.9%) were published as full Cochrane reviews at the time of study analysis (January 2008). The median time to publication was 2.4 years (range: 0.15 to 8.96). Multivariate analyses revealed that shorter time to publication was associated with the review subsequently being updated (hazard ratio, HR: 1.80 [95% confidence interval, CI: 1.39 to 2.33 years]) and longer time to publication was associated with the review having two published protocols, indicating changes to the review plan (HR: 0.33 [95% CI: 0.12 to 0.90 years]).

Conclusions/Significance: Only about 80% Cochrane protocols were published as full reviews after over 8 years of follow-up. The median time to publication was 2.4 years and some reviews took much longer. Strategies to decrease time to publication should be considered, such as streamlining the review process, increased support for authors when protocol amendments occur, and better infrastructure for updating Cochrane reviews.

Citation: Tricco AC, Brehaut J, Chen MH, Moher D (2008) Following 411 Cochrane Protocols to Completion: A Retrospective Cohort Study. PLoS ONE 3(11): e3684. doi:10.1371/journal.pone.0003684

Editor: Hany Abdel-Aleem, Assiut University Hospital, Egypt

Received July 15, 2008; **Accepted** October 16, 2008; **Published** November 10, 2008

Funding: Andrea C. Tricco is funded by a Canadian Institutes of Health Research Canada Graduate Scholarship and University of Ottawa Excellence Scholarship. Dr. Brehaut is funded by an Ontario Ministry of Health Career Scientist Award. Dr. Moher is funded by a University of Ottawa Research Chair.

Competing Interests: ACT and DM are members of the Cochrane Collaboration. JB and MHC have no competing interests.

* E-mail: dmoher@uottawa.ca

Introduction

The mission of the Cochrane Collaboration is to conduct systematic reviews in all areas of healthcare [1]. Currently, the Collaboration includes more than 10,000 members globally organized into clinical review groups (CRGs; e.g., schizophrenia group), methods groups (e.g., bias methods group), and fields (e.g., child health field) [1]. Evidence suggests that Cochrane reviews are the most scientifically reported systematic reviews [2]. They are also increasingly being used by consumers, clinicians, and policy-makers as part of their decision-making process [3]. Although these reviews are highly regarded, their frequency of publication and factors associated with their publication remains unknown. If factors such as funding are associated with subsequent publication this may imply that Cochrane reviews are also subject to publication bias.

Publication bias occurs when "investigators, reviewers, and editors submit or accept manuscripts for publication based on the direction or strength of the study findings"[4]. Publication bias also occurs when studies with certain characteristics (e.g., favourable results, funding from organizations with vested interests, such as pharmaceutical companies or the tobacco industry) are published quicker than those without these characteristics [5]. Publication bias has been extensively examined for individual studies (e.g., randomized trials) [4,6–11], but is under-explored for systematic reviews [12–14].

Cochrane reviews can be followed over time to examine whether certain factors are associated with their publication. The process for publishing a Cochrane review includes the following: 1) title (or topic) registration to ensure that the review is unique to The Cochrane Library, 2) publication of a protocol, which outlines the review plan, 3) conduct of the review, 4) publication of the review report, and 5) update of the review, which usually occurs every two years [1]. Cochrane reviews can be published elsewhere, yet they should be published in The Cochrane Library first. All Cochrane protocols and their respective reviews are provided with a unique Cochrane identification number, which allows both to be followed over time. We conducted a retrospective cohort study to

examine the frequency of published and unpublished Cochrane reviews and determine the protocol factors that predict the publication of Cochrane reviews.

Methods

Cohort sample acquisition

A new issue of The Cochrane Library is published quarterly along with a CD with all of its contents. We obtained all Cochrane Library CDs from inception from the UK Cochrane Centre and Canadian Cochrane Network and Centre. In order to allow time for publication, we selected all new protocols from 2000 (Issues 2 to 4) and 2001 (Issue 1) [4,8–11]. The CD indicates when a Cochrane protocol is new to that particular issue.

The unique Cochrane identification number was entered into Issue 1, 2008 of The Cochrane Library to determine the publication status. Authors of Cochrane protocols that could no longer be found in The Cochrane Library were contacted for further information. When a response from the authors was not received, the CRG coordinator responsible for the Cochrane protocol was contacted.

The new protocols arising from the Cochrane CDs were subsequently screened to ensure that they were eligible for the study. Cochrane protocols that were split into more than one Cochrane review, taken over by another review group, published in the same issue as the corresponding Cochrane review itself, published later than the review publication or published prior to Issue 2, 2000 were excluded.

Data abstraction

A 37-item data abstraction form was developed by two investigators (ACT, DM) and pilot-tested. Descriptive characteristics (country of conduct, population examined, number of authors, number of protocols [multiple protocols indicating that changes to the original review plan occurred], number of unique Cochrane identification numbers [some of the reviews had multiple numbers]), planned methodology (observational versus experimental study inclusion, number of databases searched, number of primary outcomes, inclusion of unpublished material, language inclusion, assessment of publication bias, assessment of heterogeneity), and other characteristics (gender of corresponding author and whether they were a healthcare provider, number of updates, funding) were abstracted from the Cochrane protocols by one investigator (ACT). Data were also abstracted from the original version of the Cochrane review, such as the timing of publication and whether it was subsequently updated. Random data checks were made by two investigators, independently (ACT, MHC).

Two time points were abstracted for the analysis from all included protocols and their subsequent reviews. The first was the *version first published online* date of publication from The Cochrane Library citation and the second was the *most recent substantive amendment date* from the cover page of the Cochrane protocol and associated completed review. As Cochrane reviews are published quarterly, the *version first published online* date is truncated to four time points per year. As such, it was decided that the *most recent substantive amendment date* would be used for the primary analyses while the *version first published online date* would be used for sensitivity analyses. The most recent substantive amendment date always occurs prior to the publication date, resulting in more than eight years of follow-up data.

Data analysis

Time-to-publication analyses were conducted using the Kaplan-Meier method, which is often used to estimate time-related events and takes into account censored data (i.e., losses to the sample that occur prior to the final outcome) [15]. Cochrane reviews that remained unpublished at the time of study were censored on January 23, 2008 (i.e., the publication date of Cochrane Library, Issue 1, 2008). Cox proportional hazards models (regression models often used to examine time-dependent factors) were then used to predict the time to publication of Cochrane reviews. Hazard ratios and 95% confidence intervals were calculated. The hazard ratio is the effect of an explanatory variable on the hazard or risk of an event and can be thought of as an estimate of the relative risk (i.e., the risk of an event, in this case the risk of being unpublished, relative to exposure, such as, lack of funding, negative results). Variables chosen for the univariate and multivariate analyses were based on *a priori* consideration of most plausible predictors for time to publication. Both univariate and multivariate models and interactions between variables were assessed. Statistical analyses were conducted with SAS, version 9.0 (SAS Institute, Cary, North Carolina). This analysis is consistent with research on the publication status of individual studies (e.g., randomized trials) [4,8–11], providing the opportunity to compare our results with these studies.

Results

Frequency of published Cochrane reviews

There were a total of 411 Cochrane protocols published in Issues 2 to 4, 2000 and Issue 1, 2001 of The Cochrane library. After excluding 39 protocols 372 (90.5%) remained in our sample (Figure 1). Of these protocols, 19.1% (71/372) were not published as full Cochrane reviews at the time of this study while 80.9% (301/372) were published in full. Only 33.2% (100/372) of the reviews were subsequently updated.

Reasons for non-publication as final reviews included that the protocol is still active in The Cochrane Library and a corresponding review has never been conducted (52.1%, 37/71), the review authors acknowledged that the review is incomplete but no reason was provided (14.1%, 10/71), the protocol was withdrawn due to out-datedness (12.7%, 9/71), the Cochrane review authors lacked time or interest (9.9%, 7/71), the reviewers experienced operational issues (e.g., the lead author changed jobs; 5.6%, 4/71), and the Cochrane Collaboration rejected the review (2.8%, 2/71). Information about two protocols (2.8%) was not provided after contacting the corresponding author of the review.

We contacted the corresponding author or CRG coordinator for the 71 reviews that were unpublished as of January 2008 to determine the stage that the review was at, as well as to inquire whether the review was ever published elsewhere. Sixty-eight responses (96%) were received. The review was incomplete (stage not reported, 52.9%, 36/68), complete but never published in Cochrane (10.3%, 7/68), a draft manuscript was compiled (8.8%, 6/68), at the literature search stage (7.4%, 5/68), in peer review (7.4%, 5/68), at the analysis stage (5.8%, 4/68), and at the data abstraction stage (7.4%, 5/68). Only 13.2% (9/68) of the reviews were published elsewhere, one of which was published as a book chapter.

Cochrane protocol characteristics

The majority of the corresponding authors were based in the United Kingdom (39.5%, 147/372), while 13.4% (50/372) were based in Australia, 7.3% (27/372) in Canada, and 7.0% in the United States (26/373; Table 1). The median number of authors per protocol was 3 (range: 1–22). Almost 3% (10/372) of the reviews had two published protocols. Approximately 7% (27/372) of the protocols had two unique Cochrane identification numbers, possibly indicating inconsistent editorial practices.

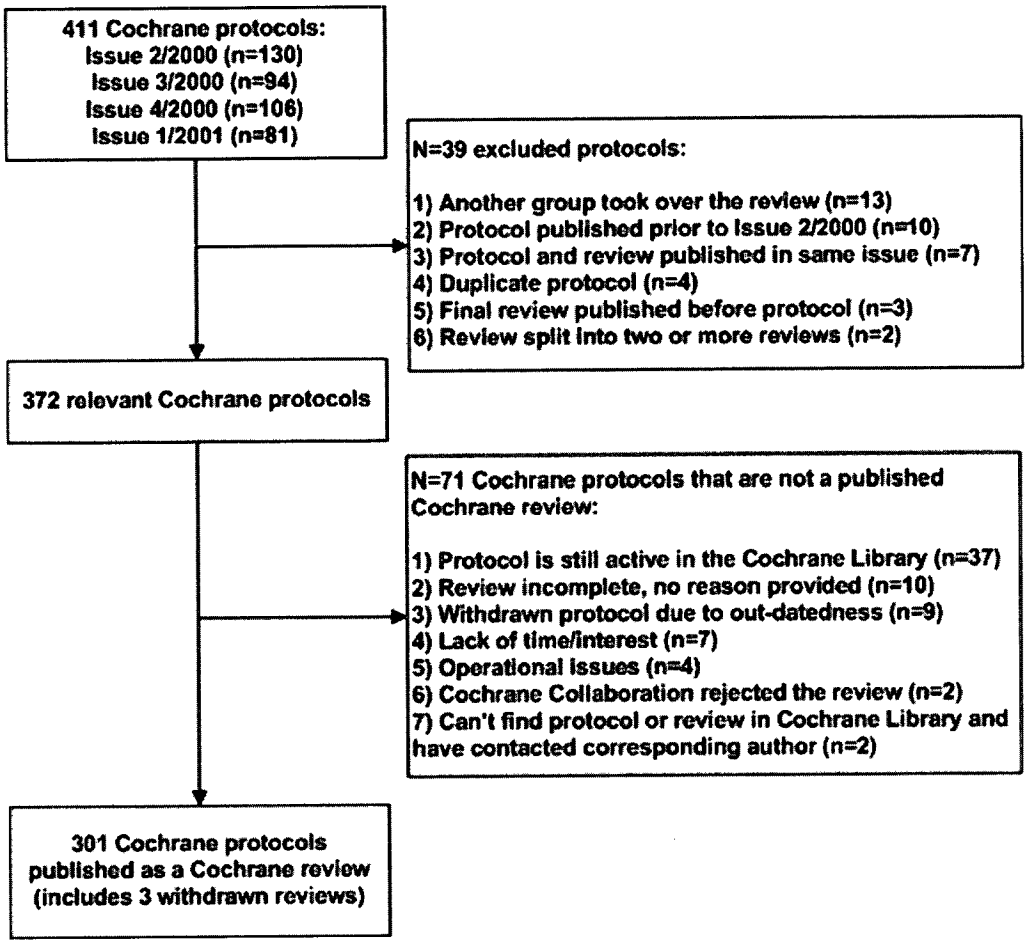


Figure 1. Study flow. The cohort included a total of 411 Cochrane protocols and 379 (90.5%) remained after excluding 39. Of these protocols, 19.1% (71/372) were never published as full Cochrane reviews while 80.9% (301/372) were published in full.
doi:10.1371/journal.pone.0003684.g001

The majority of the protocols indicated a plan to include experimental (e.g., randomized controlled trials) and quasi-experimental (e.g., interrupted time series) primary studies (96.2%, 358/372; Table 1). Almost 75% of the protocols reported a planned primary outcome (73.7%, 274/372) and the median number of planned primary outcomes per protocol was 1 (range: 1–22). When reported, the majority of the protocols planned to include all languages (34.4%, 128/372) and assess for heterogeneity (75.8%, 282/372), yet only 20.2% (75/372) planned to assess for publication bias.

A little over half of the protocols reported a funding source (58.1%, 216/372; Table 1). This was predominantly a not-for-profit funder (46.3%, 100/216); while 27.3% (59/216) reported funding from a government agency and 23.6% (51/216) reported joint government and not-for-profit funding. Few protocols reported for-profit organization funding, which is a Cochrane mandate [1] and few of the corresponding authors reported being a healthcare provider (20.4%, 76/372).

Survival analysis

The median time to publication using the *most recent substantive amendment date* was 2.4 years (range: 0.15 to 8.96 years; interquartile range, IQR: 3.8 years; Figure 2). This was similar to the sensitivity analysis (i.e., the *version first published online date*), which was 2.24 years (range: 0.25 to 7.75 years; IQR: 3.7 years). Of the variables chosen for the univariate analyses, four were significant and entered into the multivariate analyses: having two protocols ($p = 0.001$); an updated review ($p < 0.0001$), number of authors ($p = 0.008$); and number of primary outcomes ($p = 0.002$). There was also a trend towards significance for the language inclusion variable ($p = 0.06$). These five factors were subsequently used in the Cox proportional hazard model (Table 2).

In the multivariate analyses only two of the variables were significant. A shorter time to publication was associated with the review being an update (hazard ratio, HR 1.80 [95% CI: 1.39, 2.33)] and a longer time to publication was associated with the review having two published protocols (HR 0.33 [95% CI: 0.12, 0.90]; Table 2). Sensitivity analysis based on the *version first published online* date produced similar results.

Discussion

We conducted a retrospective cohort study of Cochrane protocols to provide data on the average time to publication of Cochrane reviews and factors associated with their publication. Our results indicate that for every four published Cochrane reviews, one review remained unpublished based on one year of Cochrane protocols. As Cochrane reviews are regarded as being scientifically rigorous, this finding is disquieting. As a major contributor to the systematic review literature, we believe that all Cochrane protocols should be completed and published as

Table 1. Cochrane review characteristics.

Item	Total: 372 Cochrane reviews
Descriptive characteristics	
Country of conduct: n (%)	
United Kingdom	147 (39.5)
Australia and New Zealand	50 (13.4)
Canada	27 (7.3)
United States of America	26 (7.0)
Italy	14 (3.8)
Netherlands	12 (3.2)
Brazil	9 (2.4)
France	8 (2.2)
China	7 (1.9)
Denmark	7 (1.9)
South Africa	7 (1.9)
Spain	7 (1.9)
Other	38 (10.2)
Not reported	13 (3.4)
Population examined: n (%)	
Neonates only	21 (5.6)
Children only	11 (3.0)
Adolescents only	1 (0.3)
Adults only	61 (16.3)
Women only	49 (13.2)
Men only	4 (1.1)
Elderly only	4 (1.1)
Children and adolescents	13 (3.5)
Children, adolescents and adults	2 (0.5)
Adolescents and adults	5 (1.3)
Adolescents, adults and elderly	1 (0.3)
All	200 (53.8)
Number of authors: median (range)	3 (1, 22)
Review had two protocols: n (%)	10 (2.7)
Review had two unique Cochrane identification numbers: n (%)	27 (7.3)
Methodological characteristics	
Type of reports to be included in the reviews: n (%)	
Observational only	0 (0)
Experimental and quasi-experimental only	358 (96.2)
Both	14 (3.8)
Number of databases to be searched: median (range)	4 (1, 22)
A primary outcome was reported: n (%)	274 (73.7)
Number of primary outcomes: median (range)	1 (1, 20)
*Reviews with multiple primary outcomes: n (%)**	135 (49.3)
Language inclusion: n (%)	
English only	6 (1.6)
Mixed languages only	5 (1.4)
All languages	128 (34.4)
Not reported	233 (62.6)
Publication bias was to be assessed: n (%)	75 (20.2)
Heterogeneity was to be assessed: n (%)	282 (75.8)
Other characteristics	
Gender of corresponding author: n (%)	
Female	132 (35.5)
Male	192 (51.6)
Unclear	48 (12.9)
Corresponding author was a healthcare provider: n (%)	76 (20.4)
Number of reviews with funding: n (%)	216 (58.1)
Type of funding source: n (%)‡	
Government only	59 (27.3)
Not-for-profit organization only	100 (46.3)
Insurance company only	1 (0.5)
Government and not-for-profit organization	51 (23.6)
For-profit organization and government	2 (0.9)
For-profit and government and not-for-profit	3 (1.4)

Notes: * Denominator is number of reviews with a primary outcome (n = 274), † denominator is published reviews (n = 301), ‡ denominator is number of reviews with funding (n = 216).

doi:10.1371/journal.pone.0003684.t001

Cochrane reviews. For the unpublished Cochrane reviews, only a minority (13.2%) were published elsewhere, indicating a major loss of information being publicly available, as well as wasted scarce resources.

A little more than half (52.1%) of the unpublished reviews were still active Cochrane protocols in The Cochrane Library. This indicates a lack of consistency in the Cochrane Collaboration's editorial procedures, as some of the protocols were withdrawn due

Figure 2. Kaplan-Meier Curve for the time to publication of Cochrane reviews and 95% confidence intervals. The Kaplan-Meier Curve displays that the proportion of unpublished Cochrane reviews decreases over time.

doi:10.1371/journal.pone.0003684.g002

Table 2. Factors predicting the time to publication of Cochrane reviews

Factor	Univariate Hazard Ratio* (95% CI)	p-value	Multivariate Hazard Ratio* (95% CI)	p-value
Language inclusion (including all vs. including mixed languages and not reported)	1.27 (1.00, 1.61)	0.04	1.31 (0.69, 2.50)	0.42
Language inclusion (not reported vs. reported)	0.78 (0.62, 0.98)	0.03	1.00 (0.52, 1.91)	0.10
Review has two published protocols vs. one published protocol	0.27 (0.10, 0.72)	0.01	0.33 (0.12, 0.90)	0.03
Number of primary outcomes reported in the protocol	1.05 (0.77, 1.44)	0.00	1.02 (0.98, 1.05)	0.23
Number of authors on the protocol	0.90 (0.84, 0.98)	0.01	0.94 (0.86, 1.03)	0.17
Review subsequently being updated	1.87 (1.47, 2.35)	<0.001	1.78 (1.39, 2.33)	<0.0001

Note: * Hazard ratios indicate the relative hazard to the time to publication. Numbers above 1 indicate an decreased time to publication, numbers below 1 indicate an increased time to publication.
Abbreviation: CI confidence interval.
doi:10.1371/journal.pone.0003684.t002

to out-datedness while others were not. Another editorial inconsistency was the finding that 7% of the included protocols had two unique identification numbers. The Cochrane Library is unusual in that there is no single person directly responsible for its quality assurance. We hope that with the appointment of the Library's new editor-in-chief, the number of unpublished Cochrane reviews will decrease substantially.

Our results indicated that the median time to publication of the completed Cochrane review from the published protocol was 2.4 years, and some reviews took as long as 9 years to be published (using the *most recent substantive amendment date*). Our results are consistent with another study that examined the time to publication from submission to final publication of the review [14]. However, our time frame is double that reported elsewhere [15], as this study examined a different time period than this study did [15].

In this study, a longer time to publication was associated with the review having two protocols. Strategies to decrease time to publication should be considered. These may include providing support to reviewers when protocol changes occur and streamlining the publication process to decrease the time to publication of Cochrane reviews [16].

As noted elsewhere, updating systematic reviews is of paramount importance because some health care interventions currently known to be effective may be shown to be ineffective or harmful in the future and new interventions or health outcomes may emerge [17,18]. Our results indicate a shorter time to publication associated with the review subsequently being updated. This could be due to a variety of reasons, such as a quickly evolving clinical content area or a highly motivated Cochrane review team. A recent study examined indicators predicting when systematic reviews go out of date [15]. These analyses found that shorter time to update was associated with the cardiovascular content area (i.e., indicating a quickly evolving clinical area) and heterogeneity being present or suspected in the review (i.e., indicating a motivation to examine unstable results).

The current Cochrane guidance is to update their reviews every 2 years [1]. Although our cohort spans over 8 years, only a third of the reviews were updated and only 2 out of the entire sample had 3 updates. For Cochrane reviews (as any other systematic reviews) to maintain their currency, a more active policy should be considered to ensure that a much higher proportion is kept up-to-date. This could include international harmonization of aspects of the updating process and having other authors finish the update when too much time has elapsed.

The reasons for unpublished Cochrane reviews seem to be different than the reasons for unpublished individual studies (e.g., trials). For clinical trials, there is a trend towards shorter time to publication when they are sponsored by private industry (e.g., pharmaceutical companies) [9,11] and a higher likelihood of publication when they are funded [19]. Our findings are consistent with a recent survey on the publication practices of systematic reviewers. In this survey, the most commonly reported reasons for not publishing Cochrane reviews included lack of time, the manuscript being rejected, and operational issues (Andrea Tricco personal communication). Members of the investigative team are currently involved with research exploring these issues.

This study has some limitations. Only one investigator abstracted all of the data, which could have led to inaccuracies. Furthermore, we did not examine all of the review factors associated with the time to publication and the reasons for publishing Cochrane reviews elsewhere often were not provided by the review authors. However, our cohort includes one year of data with a large number of Cochrane protocols, a high response rate was attained for the 71 unpublished reviews, and two investigators performed random data checks and resolved any issues with the data. Furthermore, the Cochrane review factors associated with the time to publication have been examined elsewhere recently (Andrea Tricco, personal communication).

In conclusion, only about 80% of Cochrane protocols were published as full reviews after more than 8 years of follow-up. The median time to publication was nearly two and a half years and some reviews took considerably longer. We recommend that the Cochrane Collaboration have consistent editorial policies, streamline the review process to decrease the time to publication, provide support for review authors when changes to the protocol occur, and provide a better infrastructure for updating Cochrane reviews.

Acknowledgments

The research was conducted as part of a PhD dissertation in Population Health at the University of Ottawa. We thank Dr. Mario Cappelli and Jacqueline Tetroe for their input on the original protocol of this study, Raymond Daniel for assistance with obtaining the sample of Cochrane reviews, and Carmen Ng for her assistance with pilot-testing the data abstraction forms. We also thank Dr. Sally Hopewell of the UK Cochrane Centre for her expert advice on the study methods and for lending us the Cochrane CDs, as well as Lisa McGovern of the Canadian Cochrane Network and Centre for lending us the Cochrane CDs.

Author Contributions

Conceived and designed the experiments: ACT JB DM. Performed the experiments: ACT. Analyzed the data: ACT MHC. Wrote the paper: ACT. Edited and approved the paper: DM JB MHC.

References

1. (2008) Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration. Available.
2. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG (2007) Epidemiology and Reporting Characteristics of Systematic Reviews. PLoS Med 4: e78.
3. Lavis JN, Davies HTO, Gruen RL, Walshe K, Farquhar CM (2006) Working within and beyond the Cochrane Collaboration to make systematic reviews more useful to healthcare managers and policymakers. Healthcare Policy 1: 21–33.
4. Dickersin K (1990) The existence of publication bias and risk factors for its occurrence. JAMA 263: 1385–1389.
5. Hopewell S, Clarke M, Stewart L, Tierney J (2001) Time to publication for results of clinical trials. Cochrane Database of Methodology Reviews.
6. Begg CB, Berlin JA (1989) Publication bias and dissemination of clinical research. J Natl Cancer Inst 81: 107–115.
7. Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H Jr (1987) Publication bias and clinical trials. Control Clin Trials 8: 343–353.
8. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR (1991) Publication bias in clinical research. Lancet 337: 867–872.
9. Ioannidis JP (1998) Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 279: 281–286.
10. Simes RJ (1987) Confronting publication bias: a cohort design for meta-analysis. Stat Med 6: 11–29.
11. Stern JM, Simes RJ (1997) Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 315: 640–645.
12. Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ (2000) Publication and related biases. Health Technol Assess 4: 1–115.
13. Schwarzer G, Antes G, Tallon D, Egger M (2001) Review publication bias? Matched comparative study of Cochrane and journal meta-analyses. 9th International Cochrane Colloquium, Lyon, France, 9–13 October 2001.
14. Tierney JF, Clarke M, Stewart LA (2000) Is there bias in the publication of individual patient data meta-analyses? Int J Technol Assess Health Care 16: 657–667.
15. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, et al. (2007) How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 147: 224–233.
16. Sampson M, Shojania KG, Garritty C, Horsley T, Ocampo M, et al. (2008) Systematic reviews can be produced and published faster. J Clin Epidemiol 61: 531–536.
17. Moher D, Tsertsvadze A, Tricco AC, Eccles M, Grimshaw J, et al. (2007) A systematic review identified few methods and strategies describing when and how to update systematic reviews. J Clin Epidemiol 60: 1095–1104.
18. Moher D, Tsertsvadze A, Tricco AC, Eccles M, Grimshaw J, et al. (2008) When and how to update systematic reviews. Cochrane Database Syst Rev MR000023.
19. Dickersin K, Min YI, Meinert CL (1992) Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. JAMA 267: 374–378.

Chapter 6: General discussion and conclusion

In order to investigate the extent of SR publication bias I developed a conceptual model and conducted the following studies: a cross-sectional study of SRs (1), an international survey (2), and a retrospective cohort study of Cochrane reviews (3). The results of these studies, as well as a general discussion and conclusions will follow.

The publication process of SRs and its susceptibilities to publication bias was explored through a conceptual model. Seven steps in the publication process of SRs within healthcare were assumed: 1) conceptualization of the issue or problem to be examined by the SR, 2) review protocol, 3) review implementation, 4) dissemination of the review's results, 5) uptake of the research by individuals or groups, 6) policy or clinical impact, and 7) the effect of the SR results on health outcomes over time. The interviewees reported more factors influencing the publication of SRs than were identified through the literature searches. It was apparent through the conceptual model that the different types of publication bias can permeate all steps of the publication process of SRs.

In the cross-sectional study of 296 SRs indexed in MEDLINE circa 2004, 36.5% of the overall sample including meta-analyses and non-meta-analytic reviews had favorable results (1). This increased to 57.7% for Cochrane and 64.3% for non-Cochrane reviews with a meta-analysis of the primary outcome. Non-Cochrane reviews with a meta-analysis of the primary outcome were twice as likely to have positive conclusions as Cochrane reviews with such an analysis (p-value<0.05). The weighted kappa for agreement between SR results and conclusions was 0.55. It was lower for Cochrane (0.41) vs. non-Cochrane (0.67) reviews, which could be because Cochrane reviewers make more conservative conclusion statements (e.g., they report that more research is required if there is a trend towards a favourable result).

In the international survey of systematic reviewers, 55.7% (348 of 625) of those invited participated (2). Half of the participants were from Europe and 22.7% were from the United States. They reported 1405 published (median: 2.0, range: 1-150) and 199 unpublished (median: 2.0, range: 1-33) SRs. Commonly reported barriers to publishing SRs included lack of time, lack of funding, and lack of organizational support. Commonly reported facilitators included time availability and self-motivation. Common reasons for not publishing most recent unpublished SRs (n=52) were lack of time (12 of 52, 23.0%), the manuscript being rejected (10 of 52, 19.0%), and operational issues (six of 52, 11.5%).

In the retrospective cohort study of 411 Cochrane protocols published in 2000 (Issues 2 to 4) and 2001 (Issue 1), 71/372 (19.1%) were unpublished and 301/372 (80.9%) were published as full Cochrane reviews after excluding 39 protocols (3). The median time to publication was 2.4 years (range: 0.15 to 8.96). Multivariate analyses revealed that shorter time to publication was associated with the review subsequently being updated (hazard ratio, HR: 1.80 [95% confidence interval, CI: 1.39 to 2.33 years]) and longer time to publication was associated with the review having two published protocols, indicating changes to the review plan (HR: 0.33 [95% CI: 0.12 to 0.90 years]).

From the research comprising my thesis, it is apparent that some of the studies provide evidence of publication bias of SRs. For example, interviewees mentioned nature of results (e.g., non-statistically significant) as a reason for not submitting their SRs for publication in the conceptual model paper. In the cross-sectional study of 296 SRs, a high proportion of meta-analytic SRs had favourable results, possibly providing indirect evidence of publication bias within this sample of SRs (1). Non-Cochrane reviews were twice as likely to have positive conclusion statements as Cochrane reviews, which may also provide evidence of bias in this sample (1). In the international survey 65% of participants reported

significant results as being a significant facilitator for publishing SRs (2). However, in the retrospective cohort study, funding source was not associated with a longer time to publication of Cochrane reviews (3).

Over 300 unpublished SRs were identified through this research. For the conceptual model paper, interviewees reported over 40 unpublished SRs. In the international survey, 199 unpublished SRs were identified (2). The median number of reported unpublished SRs per survey respondent was similar to that of published SRs and a 12.4% non-publication rate of SRs was identified (2). Furthermore, 71 (19.1%) unpublished Cochrane reviews were identified in the retrospective cohort study (3). These studies confirm that a large amount of potentially meaningful data is missing from the literature and implies enormous wasted time and resources. For example, few of the unpublished Cochrane reviews were ever published elsewhere in the retrospective cohort study (3).

SRs can also be a source of unpublished individual studies, including RCTs. Cochrane reviews often search for and include unpublished and grey literature (i.e., difficult-to-access materials, such as conference abstracts, dissertations, and institutional reports (4)). This furthers the argument that SRs should be published. We could not ascertain whether the studies included in the unpublished SRs were included in other published reviews. This should be examined in the future.

Many factors associated with the publication of SRs were identified through the literature searches and individual interviews for the conceptual model. As the research progressed, other factors potentially associated with the publication of SRs were identified. These included number of authors on the review, number of review protocols, number of unique identification numbers, population examined, number of databases searched, number of primary outcomes, and the level of agreement between the results and conclusions. Other

variables identified from another study that I conducted with some colleagues on the publication of SRs included an author change between the protocol and subsequent review and number of pages of the review (5). An exhaustive list of all the variables potentially associated with the publication of SRs can be found in Table.

Registration of SRs at inception is a possible mechanism for minimizing or avoiding unpublished SRs (6). International, collaborative efforts toward such an initiative are required. This could be accomplished by leveraging the successful registration of clinical trials (7). For example, some evidence suggests that large increases in the number of clinical trial registrations and more complete records were observed in one study that examined the Clinicaltrials.gov database over time (8).

Another possible solution to decreasing the frequency of unpublished SRs might entail educating systematic reviewers, peer reviewers, and journal editors about the importance of publishing SRs regardless of the review characteristics. Other possible solutions include creating methods to fast-track the peer-review process, having an online journal dedicated to only publishing the results of SRs, and ensuring that academic institutions recognize the importance of SRs.

In the retrospective cohort study, a longer time to publication was associated with a Cochrane review having two protocols (3). In a similar study examining the review factors associated with Cochrane review publication, a longer time to publication was associated with an author change between the protocol and subsequent review (5). Strategies to decrease time to publication of Cochrane reviews may include providing support to reviewers when protocol changes or author changes occur and streamlining the publication process of Cochrane reviews (9).

The totality of evidence from this thesis suggests that systematic reviewers would benefit from training on how to conduct a SR. In the cross-sectional study, over half of the included SRs either did not report a primary outcome or reported multiple primary outcomes, perhaps implying that systematic reviewers do not fully understand how to report primary outcomes in SRs (1). Furthermore, reasons for not publishing SRs brought up by participants in the international survey included that the SR was too broad and that few eligible studies were identified (2). Another commonly reported reason for lack of publication in the survey was that a SR on the same topic was identified after the review was started (2), which was also brought up in the one-on-one interviews.

Results of the retrospective cohort study indicate that the median time to publication of the completed Cochrane review from the published protocol was 2.4 years, and some reviews took as long as 9 years to be published (3). Within this time, the knowledge included in a SR may become out-of-date. Outdated SRs are problematic, as some healthcare interventions known to be effective may be shown to be ineffective or harmful in the future and new interventions or health outcomes may emerge (10). Therefore, SRs should be published, and published as quickly as possible. Evidence suggests that SRs can be produced and published quicker than they currently are (9).

In the retrospective cohort study, a shorter time to publication was associated with the review subsequently being updated (hazard ratio: 1.80, confidence interval: 1.39 to 2.33 years) (3). These results were confirmed in another study that used a sub-sample of the protocols used in study three to examine the Cochrane review factors predicting the time to publication of Cochrane reviews (5). Over 30 review factors were examined, including statistically significant results, positive conclusions, and funding source. The results show that an author change between the protocol and final review was associated with a longer

time to publication (p=0.002), while an updated review was associated with a shorter time to publication (p=0.03).

A shorter time to publication when a SR is subsequently updated could be due to a variety of reasons. Examples include a quickly evolving clinical content area or a highly motivated SR team. A recent study examined indicators predicting when SRs go out of date (11). The results indicated that a shorter time to update was associated with the cardiovascular content area and the presence or suspicion of heterogeneity in the SR. These factors may indicate that SRs involving quickly evolving clinical areas and unstable SR results require frequent updating.

Although updating SRs is an important issue, current evidence suggests that only a small proportion of them are updated. A recent study identified few updated SRs in a cross-sectional sample of 300 SRs indexed in MEDLINE (6). A survey of 195 healthcare organizations within the international SR community revealed that although the majority of the organizations recognized the importance of updating SRs, updating practices were reported as being irregular and inconsistent (12). In the retrospective cohort study, only 1/3 of the eligible Cochrane reviews were updated after 8 years of follow-up, even though the Cochrane Collaboration's mandate is to update their reviews every two years (3).

For SRs to maintain their currency, a more active updating policy should be considered. This may ensure that a much higher proportion of SRs are kept up-to-date. Such a policy should be explicitly and formally incorporated into organizational research mandates. International harmonization of aspects of the updating process should be considered, as well as having other authors conduct an update when too much time has elapsed.

From the research comprising my thesis, the reasons for unpublished SRs seem to be different than the reasons for unpublished individual studies, such as RCTs. For clinical trials, there is a trend towards shorter time to publication when they are sponsored by commercial industry (e.g., pharmaceutical companies) (13;14) and a higher likelihood of publication when they are funded (15) or have statistically significant results (15-18). In the cross-sectional study of SRs, the logistic regression analyses did not identify funding as being a predictor of favorable results or positive conclusions, although this was based on a small number of studies (1). In the international survey, participants did not report statistically significant results as being a major driver for unpublished SRs (2). Furthermore, funding source had no impact on the time to publication of Cochrane reviews in the retrospective cohort study, which included a large number of studies (3). Instead, important factors for unpublished SRs include type of review (Cochrane vs. non-Cochrane), meta-analytic vs. non-meta-analytic, number of published protocols, and the review subsequently being updated.

Results from another study are consistent with the three studies that comprise this thesis (5). In this study, statistically significant results, positive conclusions, and funding source were not associated with the time to publication of Cochrane reviews. Instead, an author change between the protocol and the review and the review subsequently being updated were the only factors associated with the time to publication of Cochrane reviews. These results are not surprising, as the sample used in this study overlapped with the sample used in the retrospective cohort study.

My thesis has some limitations above and beyond those brought up in the individual papers. One limitation is that a high proportion of the SRs included in the three studies were the traditional SR of RCTs addressing the "what works" question, thus other types of reviews

relevant to population health might have been excluded. For example, policy-makers might need information about the effectiveness of certain interventions in different settings. This type of information might be more readily available in other types of reviews, such as realist reviews or meta-ethnography reviews. Realist reviews are useful to answer how complex programs work or why do they fail in certain contexts (19) while meta-ethnography reviews use qualitative evidence to explain differences apparent between complex interventions (20). Although these types of reviews may also be relevant to population health, they are fairly new and examples of their application are difficult to locate. Furthermore, there is little methodological research validating these approaches. Future research examining the publication of these types of reviews is warranted when a larger sample is available.

The use of SRs as a tool for decision-makers also is limited. There is some evidence suggesting that SRs still may be used infrequently by healthcare practitioners. For example, a SR of the information seeking behaviour of physicians found that textbooks (many of which do not rely on evidence from SRs) and advice from colleagues are still the most frequent source of information (21). The SR question may not entirely be relevant to a decision-maker and the SR may lack the clinical or policy contextual details required to make a decision (22). Furthermore, the best presentation of a SR to enhance the uptake of its results by a decision-maker has not been widely examined.

Current efforts are trying to improve the utility of systematic review by making them more user-friendly. Resources for clinicians include Clinical Evidence in the UK (http://clinicalevidence.bmj.com/ceweb/index.jsp) and Up-to-Date in the USA (http://www.uptodate.com/home/index.html). Resources for policy-makers include Rx for Change in Canada (http://www.cadth.ca/index.php/en/compus/optimal-ther-resources/interventions) and the Program in Policy Decision-Making/Canadian Cochrane

Network and Centre (PPD/CCNC) database (http://www.researchtopolicy.ca/Search/Reviews.aspx), which is also based in Canada. In addition, enabling The Cochrane Library to be publicly available may increase the uptake of Cochrane reviews by healthcare providers, patients, and policy makers.

Current terminology has moved away from evidence-based practice towards evidence-*informed* practice. Sometimes a decision-maker is faced with a question that has yet to be answered by the evidence and there is no time to conduct a new study (23). The practitioner might have to therefore use their clinical judgment in conjunction with evidence that is not entirely applicable to their current situation.

Future research might entail determining how to make SRs more relevant to decision-makers and how to increase their uptake by decision-makers. Furthermore, the influence of risk of bias on the publication of SRs requires further assessment. This could be done by examining the association between the risk of bias of the included studies in a review, as well as the risk of bias of the SR itself and the time to publication of SRs. Another issue that requires further investigation is determining the number of unpublished studies that are reported in unpublished SRs. Publication issues surrounding other types of reviews (e.g., realist reviews) is warranted when a larger sample of these reviews is available. Finally, more research on updating SRs is required.

In conclusion, some of the studies comprising my thesis provided evidence of SR publication bias and a high proportion of unpublished SRs were identified. Possible solutions for minimizing or avoiding SR publication bias include registration of SRs at inception, educating systematic reviewers, peer reviewers, and journal editors about the importance of publishing SRs, creating methods to fast-track the peer-review process, having an online open-access journal dedicated to only publishing the results of SRs (including their updates),

and ensuring that academic institutions recognize the importance of SRs. Strategies to decrease time to publication of Cochrane reviews may include providing support to reviewers when protocol changes or author changes occur and streamlining the publication process.

Table: Variables potentially associated with the publication of systematic reviews

Systematic review characteristics	Systematic reviewer characteristics	Journal, journal editor, and peer reviewer characteristics
Nature of results	Lack of time	Receptiveness of topic
Nature of conclusions	Language barriers	Receptiveness of SRs in general
Number of included studies	International SR authors	Journal format
Total number of participants	Number of authors	
Study design of included studies	Healthcare practitioner vs. non-healthcare practitioner	
Publication bias of included studies	Author change between protocol and final review	
Quality of included studies	Motivation/incentives	
Assessment of heterogeneity	Guidance on methods	
Language of included studies	Synthesis skills	
Assessment of publication bias	Relationships with journals	
Another SR identified	Workplace interest/priority	
SR too broad in scope	Gender of corresponding author	
SR updates	Country of SR authors	
Publication status of included studies		
SR not done for publishing purposes		
Meta-analysis vs. no meta-analysis		
Funding		
Funding source		
Number of review protocols		
Number of unique identification numbers		
Population examined		
Number of databases searched		
Primary outcome to be assessed		
Number of primary outcomes		
Number of pages of the review		
Level of agreement between review results and reviewer conclusions		
Quality of the SR		
SR topic		

Abbreviation: SR (systematic review).

References

(1) Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol 2009 Apr;62(4):380-6.

(2) Tricco AC, Pham B, Brehaut J, Tetroe J, Cappelli M, Hopewell S, et al. An international survey indicated that unpublished systematic reviews exist. J Clin Epidemiol 2009 Jun;62(6):617-23.

(3) Tricco AC, Brehaut J, Chen MH, Moher D. Following 411 Cochrane protocols to completion: a retrospective cohort study. PLoS ONE 2008;3(11):e3684.

(4) Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. Cochrane Database of Methodology Reviews: Reviews 2002;(2).

(5) Tricco AC, Moher D, Chen MH, Daniel R. Factors predicting publication of Cochrane reviews. 2009.
Ref Type: Unpublished Work

(6) Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and Reporting Characteristics of Systematic Reviews. PLoS Med 2007 Mar 27;4(3):e78.

(7) Zarin DA, Ide NC, Tse T, Harlan WR, West JC, Lindberg DA. Issues in the registration of clinical trials. JAMA 2007 May 16;297(19):2112-20.

(8) Zarin DA, Tse T, Ide NC. Trial Registration at ClinicalTrials.gov between May and October 2005. N Engl J Med 2005 Dec 29;353(26):2779-87.

(9) Sampson M, Shojania KG, Garritty C, Horsley T, Ocampo M, Moher D. Systematic reviews can be produced and published faster. J Clin Epidemiol 2008 Jun;61(6):531-6.

(10) Moher D, Tsertsvadze A. Systematic reviews: when is an update an update? Lancet 2006 Mar 18;367(9514):881-3.

(11) Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007 Aug 21;147(4):224-33.

(12) Garritty C, Tsertsvadze A, Tricco AC, Sampson M, Moher D. Updating systematic reviews: an international survey. 2009.
Ref Type: Unpublished Work

(13) Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003 May 31;326(7400):1167-70.

(14) Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA 2003 Jan 22;289(4):454-65.

(15) Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. JAMA 1992 Jan 15;267(3):374-8.

(16) Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991 Apr 13;337(8746):867-72.

(17) Dickersin K, Min YI. Publication bias: the problem that won't go away. Ann N Y Acad Sci 1993 Dec 31;703:135-46.

(18) Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998 Jan 28;279(4):281-6.

(19) Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist review--a new method of systematic review designed for complex policy interventions. J Health Serv Res Policy 2005 Jul;10 Suppl 1:21-34.

(20) Atkins S, Lewin S, Smith H, Engel M, Fretheim A, Volmink J. Conducting a meta-ethnography of qualitative literature: lessons learnt. BMC Med Res Methodol 2008;8:21.

(21) Dawes M, Sampson U. Knowledge management in clinical practice: a systematic review of information seeking behavior in physicians. Int J Med Inform 2003 Aug;71(1):9-15.

(22) Glasziou P, Shepperd S. Ability to apply evidence from systematic reviews. 2007.

(23) Tannahill A. Beyond evidence--to ethics: a decision-making framework for health promotion, public health and health improvement. Health Promot Int 2008 Dec;23(4):380-90.

Chapter 7: Statement of contributions of collaborators and/or co-authors

Cross-sectional study (paper 1) (1):

ACT conceptualized the research, designed the questionnaire, conducted the survey, gathered the data, analyzed the results, wrote the manuscript, and approved the final version of the manuscript. ACT had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. BP, JB, JT and MC helped conceptualize the research question, designed the questionnaire, edited the manuscript, and approved the final version of the manuscript. SH, JNL and JAB pilot-tested the questionnaire, edited the manuscript, and approved the final version of the manuscript. DM conceptualized the research, designed the questionnaire, edited the manuscript, and approved the final version of the manuscript.

International survey (paper 2) (2):

ACT conceptualized the research, helped obtain the sample of SRs, designed the categorization guide, categorized the SRs, analyzed the results, wrote the manuscript, and approved the final version of the manuscript. ACT had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. JMT obtained the sample of SRs, helped design the categorization guide, categorized the SRs, analyzed the results, and approved the final version of the manuscript. BP and JB helped conceptualize the research, edited the manuscript, and approved the final version of the manuscript. DM conceptualized the research, designed the categorization guide, edited the manuscript, and approved the final version of the manuscript.

Retrospective cohort study (paper 3) (3):

ACT conceptualized the research, obtained the sample of Cochrane reviews, designed the data abstraction form, abstracted all of the data from the reviews, verified the quality of the

data, analyzed the results, wrote the manuscript, and approved the final version of the manuscript. ACT had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. JB helped conceptualize the research, edited the manuscript, and approved the final version of the manuscript. MHC verified the quality of the data, helped analyze the results, edited the manuscript, and approved the final version of the manuscript. DM conceptualized the research, designed the data abstraction form, edited the manuscript, and approved the final version of the manuscript.

Appendix C: Copyright permissions

Permission to use Figure 1:

From: "Simons P.P." <P.P.Simons@soton.ac.uk>
Subject: RE: Copyright permission
Date: Wed, 26 November, 2008 9:53 am
To: "'atric060@uottawa.ca'" <atric060@uottawa.ca>

Dear Andrea Tricco

Permission is granted on a one-time, non-exclusive basis to use the materials specified below for the purpose described below.

Please acknowledge the source.

Phillip

Phillip Simons
Programme Manager (Communications)
NCCHTA
Alpha House, Enterprise Road
Southampton Science Park, Chilworth
Southampton SO16 7NS

tel: 023 8059 5619
fax: 023 8059 5639
e-mail: pps@southampton.ac.uk

-----Original Message-----
From: Andrea C. Tricco [mailto:atric060@uottawa.ca]
Sent: 25 November 2008 23:45
To: hta
Subject: Copyright permission

Dear HTA journal,

I am a PhD candidate at the University of Ottawa in the Population Health program. My PhD dissertation deals with issues surrounding the publication of systematic reviews. I would like written permission to publish Figure 3: The impact of publication and related biases from Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ: Publication and related biases. Health Technol Assess 2000, 4: p.23 in my PhD dissertation.

Many thanks for your considerations and looking forward to hearing back

from you soon.

All the best,
Andrea

Permission to use Table 1, Table 2, Paper 1, Paper 2:

Dear Dr Tricco

As per your letter dated 10 December 2008, we hereby grant you permission to reprint the aforementioned material at no charge **in your thesis** subject to the following conditions:

1. If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies.

2. Suitable acknowledgment to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows: "This article was published in Publication title, Vol number, Author(s), Title of article, Page Nos, Copyright Elsevier (or appropriate Society name) (Year)."

3. Your thesis may be submitted to your institution in either print or electronic form.

4. Reproduction of this material is confined to the purpose for which permission is hereby given.

5. This permission is granted for non-exclusive world **English** rights only. For other languages please reapply separately for each one required. Permission excludes use in an electronic form other than submission. Should you have a specific electronic project in mind please reapply for permission.

6. This includes permission for the Library and Archives of Canada to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission.

Yours sincerely

Laura Gould

Rights Assistant

-----Original Message-----
From: Tricco, Andrea
Sent: Wed 12/10/2008 12:47 PM
To: healthpermissions@elsevier.co.uk
Subject: FW: JCE 7471 and JCE 7499

To whom it may concern,

I would like to ask the JCE for written permission to publish two articles that are *In Press* at the JCE in my PhD dissertation. They were conducted for my dissertation and I need to therefore publish them in my dissertation. The citations are:

Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane versus Cochrane reviews were twice as likely to have positive conclusion statements: Cross-sectional study. Journal of Clinical Epidemiology. *In press*, July 2008.

Tricco AC, Pham B, Brehaut J, Tetroe J, Cappelli M, Hopewell S, Lavis JN, Berlin JA, Moher D. An international survey suggested that unpublished systematic reviews do exist. Journal of Clinical Epidemiology. *In press*, September 2008

Also, I would like to ask for written permission to publish Table 5 and the glossary from the following article in my PhD dissertation: **Tricco, A.C.**; Tetzlaff, J.; Sampson, M.; Fergusson, D.; Cogo, E.; Horsley, T.; Moher, D. Few systematic reviews exist documenting the extent of bias: a systematic review. J Clin Epidemiol. 2008 May;61(5):422-434.

Many thanks for your consideration and looking forward to your reply.

All the best,
Andrea

Permission to use Paper 3:

Subject: FW: Copyright permission
From: "Lindsay King" <lking@plos.org>
Date: Mon, 1 December, 2008 7:49 am
To: atric060@uottawa.ca
Dear Andrea,

Thank you for your email and my apologies for the delayed response. Everything that the Public Library of Science publishes is freely available online throughout the world, to read, download, copy, distribute, and use (with attribution) any way you wish; with no permission required. All PLoS ONE articles are published under the Creative Commons Attribution License <http://www.plos.org/journals/license.html> and so by definition, authors retain ownership of the copyright for their article, but also allow anyone to download, reuse, reprint, modify, distribute, and/or copy articles in PLoS journals, so long as the original authors and source are cited. You therefore do not need written permission from us to

submit the paper cited below as part of your PhD dissertation (provided that you cite it in full). Although; please do also check your institutional guidelines for their policy on students publishing materials in multiple journals.

I hope this clarifies any concerns that you may have had; however, please do contact me again should you like any further information as I will be happy to help.

Thanks and best wishes,
Lindsay

Lindsay King
Publications Manager
PLoS ONE
7 Portugal Place
Cambridge
CB5 8AF
www.plosone@plos.org <http://www.plosone@plos.org/>

-----Original Message-----
From: Andrea C. Tricco [mailto:atric060@uottawa.ca]
Sent: 25 November 2008 23:53
To: Nisha Doshi
Subject: Copyright permission

Dear PLoS ONE Medicine,

I would like to ask the PLoS ONE journal for written permission to publish the following article in my PhD dissertation: Tricco AC, Brehaut J, Chen M, Moher D. Following 411 Cochrane protocols to completion: A retrospective cohort study. PLoS ONE. 2008;3(11):e3684. This study was conducted for my dissertation and I need to therefore publish it in my dissertation.

Many thanks for your consideration and looking forward to your reply.

All the best,
Andrea

References

(1) Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol 2009 Apr;62(4):380-6.

(2) Tricco AC, Pham B, Brehaut J, Tetroe J, Cappelli M, Hopewell S, et al. An international survey indicated that unpublished systematic reviews exist. J Clin Epidemiol 2009 Jun;62(6):617-23.

(3) Tricco AC, Brehaut J, Chen MH, Moher D. Following 411 Cochrane protocols to completion: a retrospective cohort study. PLoS ONE 2008;3(11):e3684.