Systematic Reviews

What, why and how

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Background

- Affiliations
  - Assistant Professor (University Medical Center Utrecht)
  - Honorary Associate Staff (University College London)
  - Honorary Departmental Senior Research Fellow (University of Oxford)
  - Affiliated Researcher (Cochrane Netherlands)
- Edcuation
  - BSc in Computer Science
  - MSc in Artificial Intelligence
  - MSc in Epidemiology
  - PhD in Epidemioloy

Background

- Research focus
  - Developing, evaluating and implementing statistical methodology for meta-analysis & prediction model research
- Project Lead
  - Better predictions using big data sets (**Netherlands**)
  - Zika Virus Consortium individual participant data meta-analysis (**World Health Organization**)
  - Integrated human data repositories for infectious disease-related international cohorts to foster personalized medicine approaches to infectious disease research (**European Comission**)

Acknowledgements

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Keele UNIVERSITY

UNIVERSITY OF OXFORD

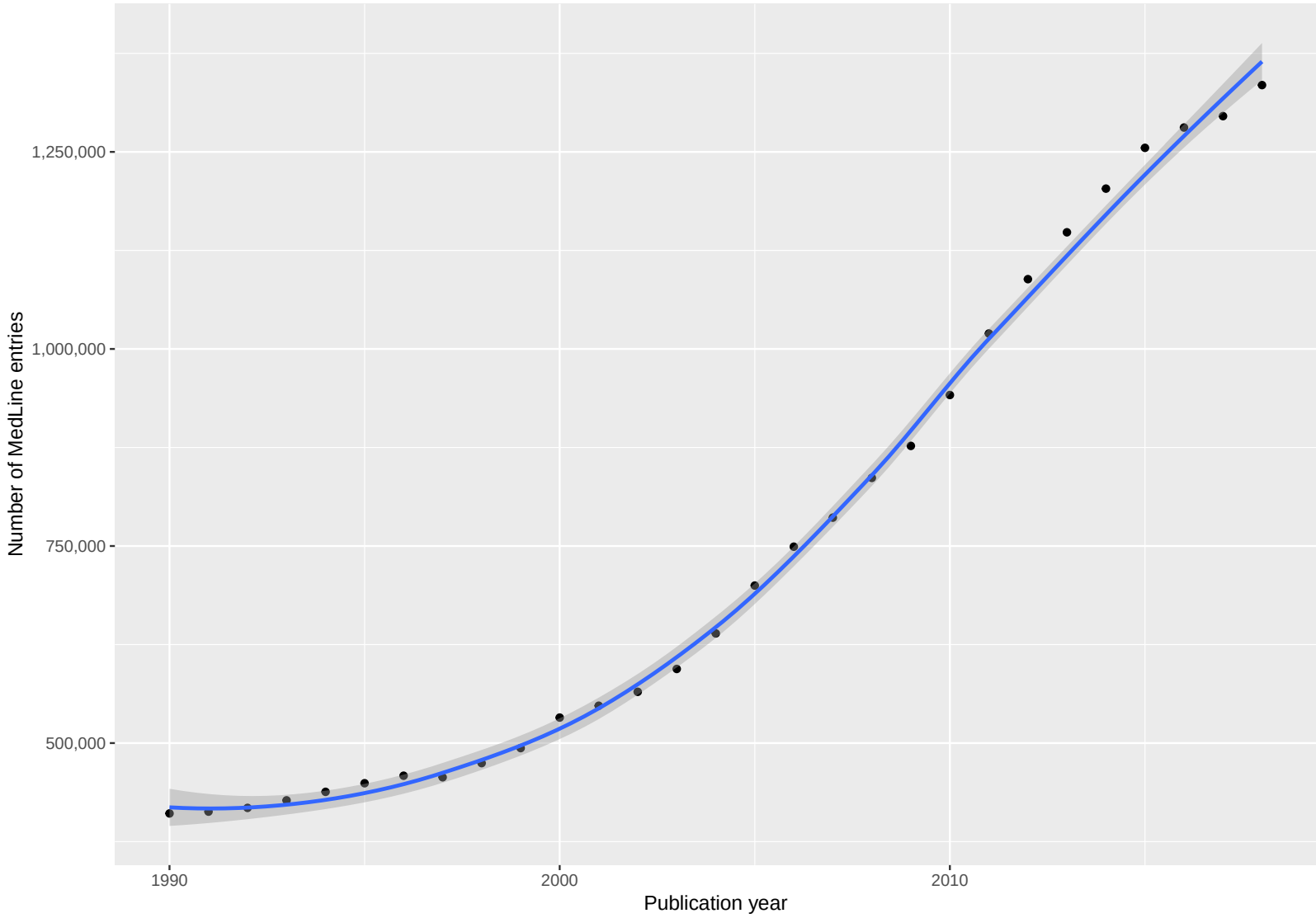
Cochrane

Introduction

Introduction

- Growing number of publications in the medical literature, with
  - differences in quality
  - differences in relevance
- It is unlikely that healthcare providers, consumers, researchers, and policy makers have the time, skills and resources to find, appraise and interpret all this evidence and to incorporate it into healthcare decisions.

Total number of publications in Medline



Why do we need systematic reviews?

- To identify existing studies of relevance and assess their quality
- To assess the generalizability of research findings
- To increase the power and precision of effect estimates
- To establish whether (and which type of) new studies are needed
- To identify how future research can be improved
- To optimize health care decisions

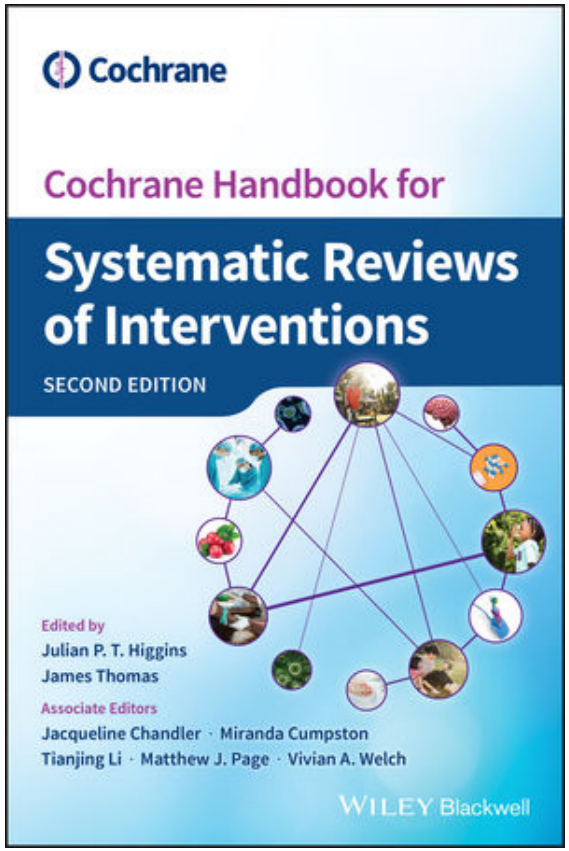
Systematic reviews help to reduce research waste, and to make better use of available research funds

What is a systematic review?

The key characteristics of a systematic review are:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that meet the eligibility criteria;
- a critical appraisal assessment
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.

The Cochrane Handbook



https://www.cochrane.org/news/new-cochrane-handbook-systematic-reviews-interventions

The Cochrane Handbook

Describes the systematic review methods and best practices in

- planning
- conducting
- interpretation

to inform decision-making around the use of health and healthcare interventions.

Types of reviews

- Reviews of the effects of interventions
- Reviews of diagnostic test accuracy
- Reviews of prognosis
- Overview of reviews
- Reviews of methodology

Reviews of the effects of interventions

Key steps

8 steps to summarize intervention effects from published studies

1. Formulating the review question (PICO)

- Choice of population
- Mode of intervention
- Choice of interventions and comparators
- Outcomes

2. Defining the criteria for including studies

- Eligibility criteria for study design
- Eligibility based on publication status and language

Key steps

3. Searching for and selecting studies

- Bibliographic databases
- Ongoing studies and unpublished data sources
- Trials registers and trials results registers
- Regulatory agency sources and clinical study reports
- Grey literature

4. Data extraction

- Study methods and potential sources of bias
- Participants and setting
- Interventions
- Outcomes
- Results

Key steps

5. Choosing effect measures and computing estimates of effect

- Risk ratio, an odds ratio, a risk difference (binary outcomes)
- (Standardized) mean difference (continuous outcomes)

6. Critical appraisal

- Cochrane risk-of-bias tool for randomized trials (RoB 2)
- ROBINS-I (non-randomized studies)

Key steps

7. Quantitative synthesis

- Meta-analysis: calculating a weighted average
- Investigating sources of heterogeneity
- R packages (metafor, mvmeta)

8. Interpretation of results

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

A recent example

Cochrane Library

Cochrane Database of Systematic Reviews

Screening for breast cancer with mammography (Review)

Gøtzsche PC, Jørgensen KJ

10.1002/14651858.CD001877.pub5

A recent example

Background

- Breast cancer is an important cause of death among women
- Early detection through mass screening with mammography has the potential to find breast cancer before a lump can be felt.
- The goal of breast cancer screening is to treat cancer earlier, when a cure is more likely.
- There is wide variation in screening policies between different countries
- Mass screening may lead to unnecessary treatment of overdiagnosed tumours

A Cochrane review was conducted to assess the effect of screening for breast cancer with mammography on mortality and morbidity

A recent example

Review strategy

- Types of studies:
  - Randomised clinical trials
- Types of participants:
  - Women without previously diagnosed breast cancer
- Types of interventions:
  - Experimental: screening with mammography
  - Control: no screening with mammography
- Primary outcome measure:
  - Mortality from breast cancer

A recent example

Results

- The review includes 7 trials that involved 600,000 women in the age range 39 to 74 years
- The largest reported effect resulted in an absolute reduction in breast cancer mortality of 0.1% after 10 years
- The studies which provided the most reliable information did not find evidence that screening reduced breast cancer mortality.
- Because of substantial advances in treatment and greater breast cancer awareness since the trials were carried out, it is likely that the absolute effect of screening today is smaller than in the trials.

Need to re-assess whether universal mammography screening should be recommended for any age group (Review findings are used in 11 guidelines)

Reviews of prognosis

Background

Key prognosis questions:

- "What is the most likely course (outcome) of people with this health condition?" (**Average/overall prognosis**)
- "What factors are associated with that outcome?" (**Prognostic factors**)
- "Are there risk groups who are likely to have different outcomes?" (**Prognostic prediction models**)

Also for prognosis, the literature is inundated by numerous publications that are based on small and local studies

Key guidance papers

Debray *et al. Diagnostic and Prognostic Research* (2019) 3:13
https://doi.org/10.1186/s41512-019-0059-4

Diagnostic and Prognostic Research

METHODOLOGY Open Access

Evidence synthesis in prognosis research

Thomas P.A. Debray[1,2*†], Valentijn M.T. de Jong[1†], Karel G.M. Moons[1,2] and Richard D. Riley[3]

Abstract

Over the past few years, evidence synthesis has become essential to investigate and improve the generalizability of medical research findings. This strategy often involves a meta-analysis to formally summarize quantities of interest, such as relative treatment effect estimates. The use of meta-analysis methods is, however, less straightforward in prognosis research because substantial variation exists in research objectives, analysis methods and the level of reported evidence.

We present a gentle overview of statistical methods that can be used to summarize data of prognostic factor and prognostic model studies. We discuss how aggregate data, individual participant data, or a combination thereof can be combined through meta-analysis methods. Recent examples are provided throughout to illustrate the various methods.

Keywords: Prediction, Meta-analysis, Prognosis, Validation, IPD

Key guidance papers

thebmj Research Education News & Views Campaigns Archive

Research Methods & Reporting

A guide to systematic review and meta-analysis of prognostic factor studies

BMJ 2019 ; 364 doi: https://doi.org/10.1136/bmj.k4597 (Published 30 January 2019)
Cite this as: *BMJ* 2019;364:k4597

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Accepted 8 October 2018

Key guidance papers

thebmj Research Education News & Views Campaigns Archive

Research Methods & Reporting

A guide to systematic review and meta-analysis of prediction model performance

BMJ 2017 ; 356 doi: https://doi.org/10.1136/bmj.i6460 (Published 05 January 2017)
Cite this as: *BMJ* 2017;356:i6460

Article Related content Metrics Responses Peer review

Thomas P A Debray, assistant professor[1 2], Johanna A A G Damen, PhD fellow[1 2], Kym I E Snell, research fellow[3], Joie Ensor, research fellow[3], Lotty Hooft, associate professor[1 2], Johannes B Reitsma, associate professor[1 2], Richard D Riley, professor[3], Karel G M Moons, professor[1 2]

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Accepted 25 November 2016

A recent example

Damen *et al. BMC Medicine* (2019) 17:109
https://doi.org/10.1186/s12916-019-1340-7

BMC Medicine

RESEARCH ARTICLE Open Access

Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis

Johanna A. Damen[1,2*], Romin Pajouheshnia[2], Pauline Heus[1,2], Karel G. M. Moons[1,2], Johannes B. Reitsma[1,2], Rob J. P. M. Scholten[1,2], Lotty Hooft[1,2] and Thomas P. A. Debray[1,2]

A recent example

Background

- The Framingham risk (FRS) models and pooled cohort equations (PCE) are widely used and advocated in guidelines for predicting 10-year risk of developing coronary heart disease and cardiovascular disease in the general population.
- Over the past few decades, these models have been extensively validated within different populations

Objectives

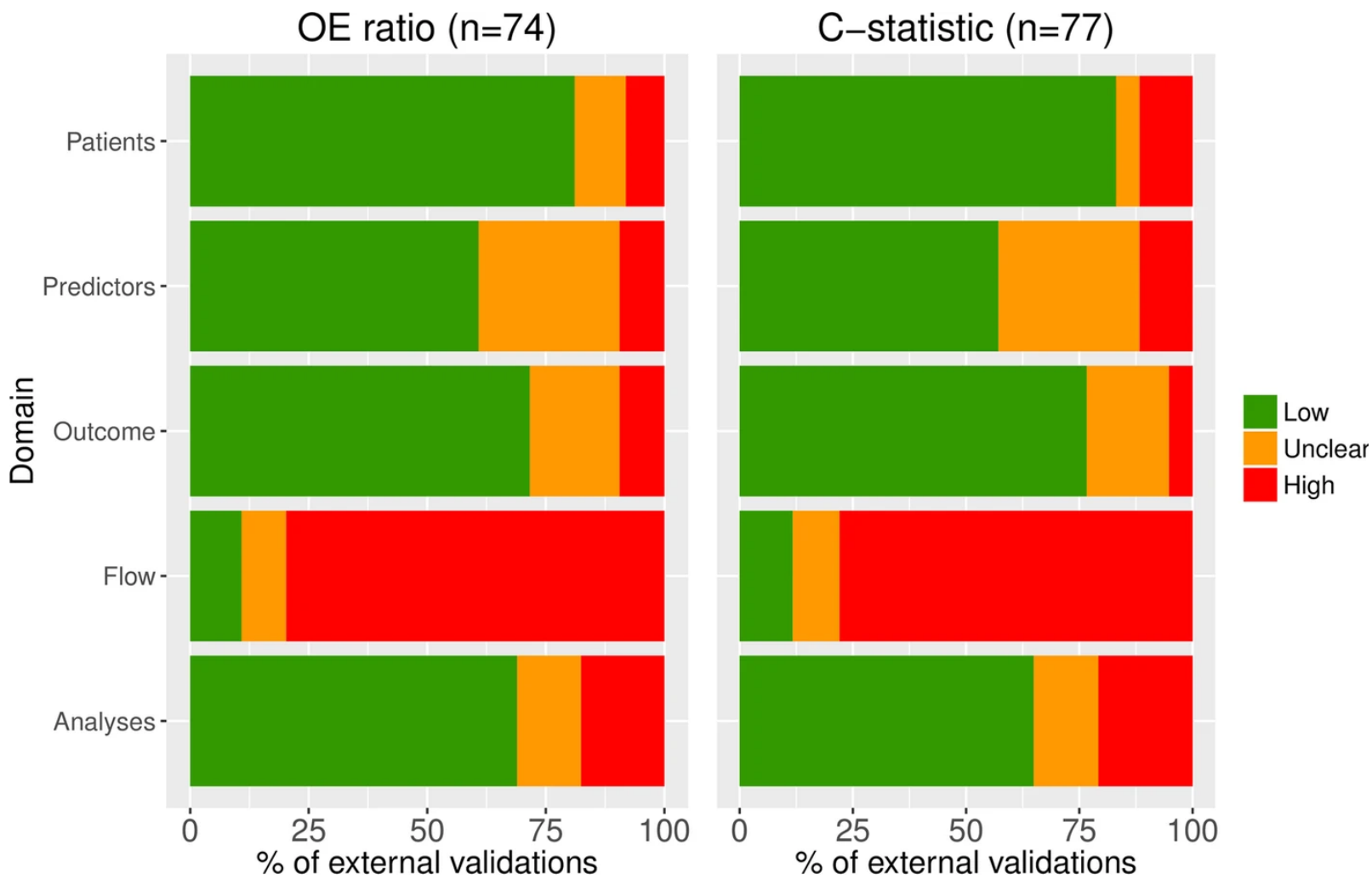
- To systematically review and summarize the predictive performance of FRS and PCE in men and women separately
- To assess the generalizability of performance across different subgroups and geographical regions
- To determine sources of between-study heterogeneity

A recent example

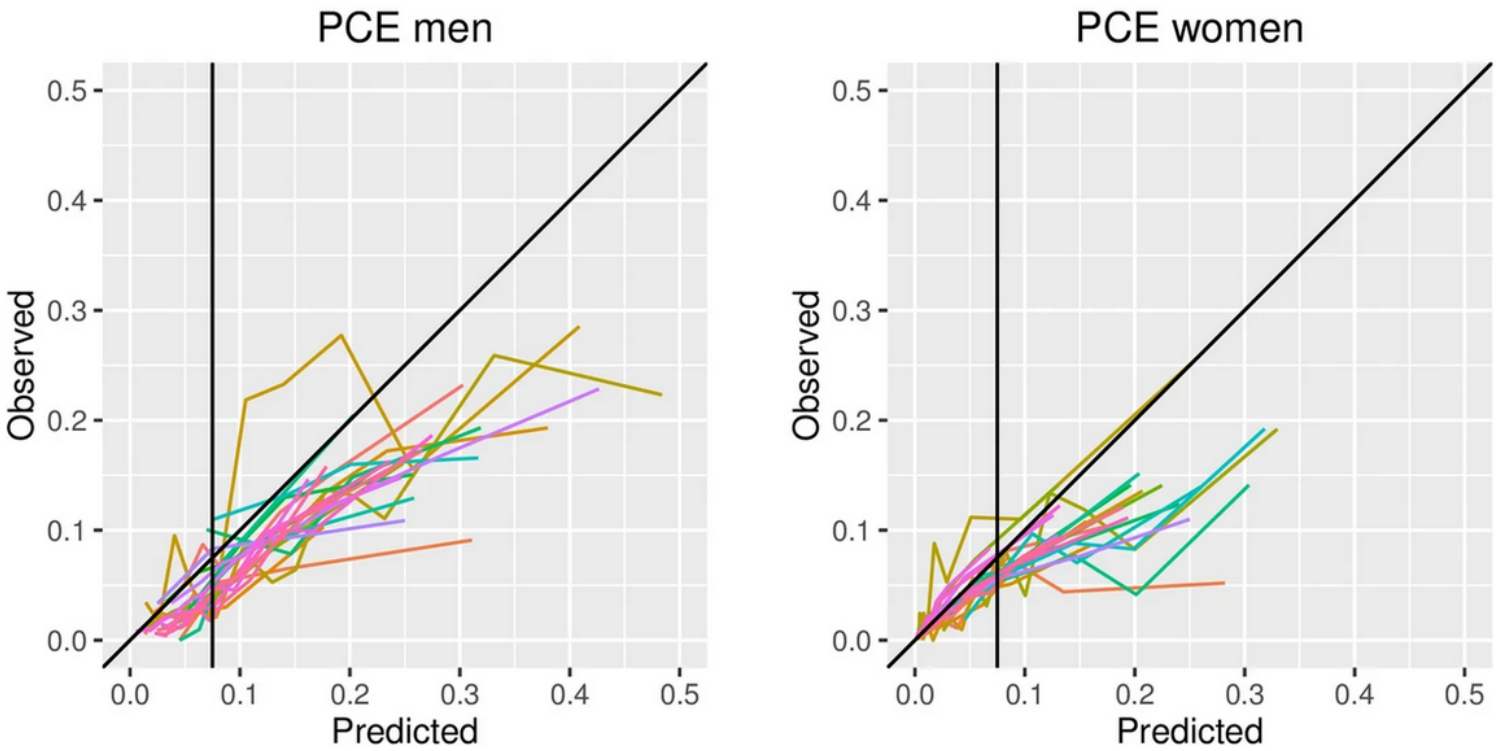
Results

- 304 potentially eligible studies
- Inclusion of 38 studies (112 validations) in the review
- Study participants
  - recruited between 1965 and 2008
  - originated from North America (56), Europe (29), Asia (25) and Australia (2)
- Extracted (or reconstructed) data:
  - Total OE ratio (N = 74)
  - Concordance statistic (N = 77)

A recent example



A recent example



A recent example

Main findings

- Small differences in pooled performance (except between men and women)
- Mis-calibration appears to occur in baseline risk only
  - Overestimation of risk in EU populations
  - Underestimation of risk in some Asian populations
- Discrimination increases as populations become more diverse

Conclusion: Framingham models appear adequate for risk prediction, but local revisions are necessary.

Next-generation reviews

Overview

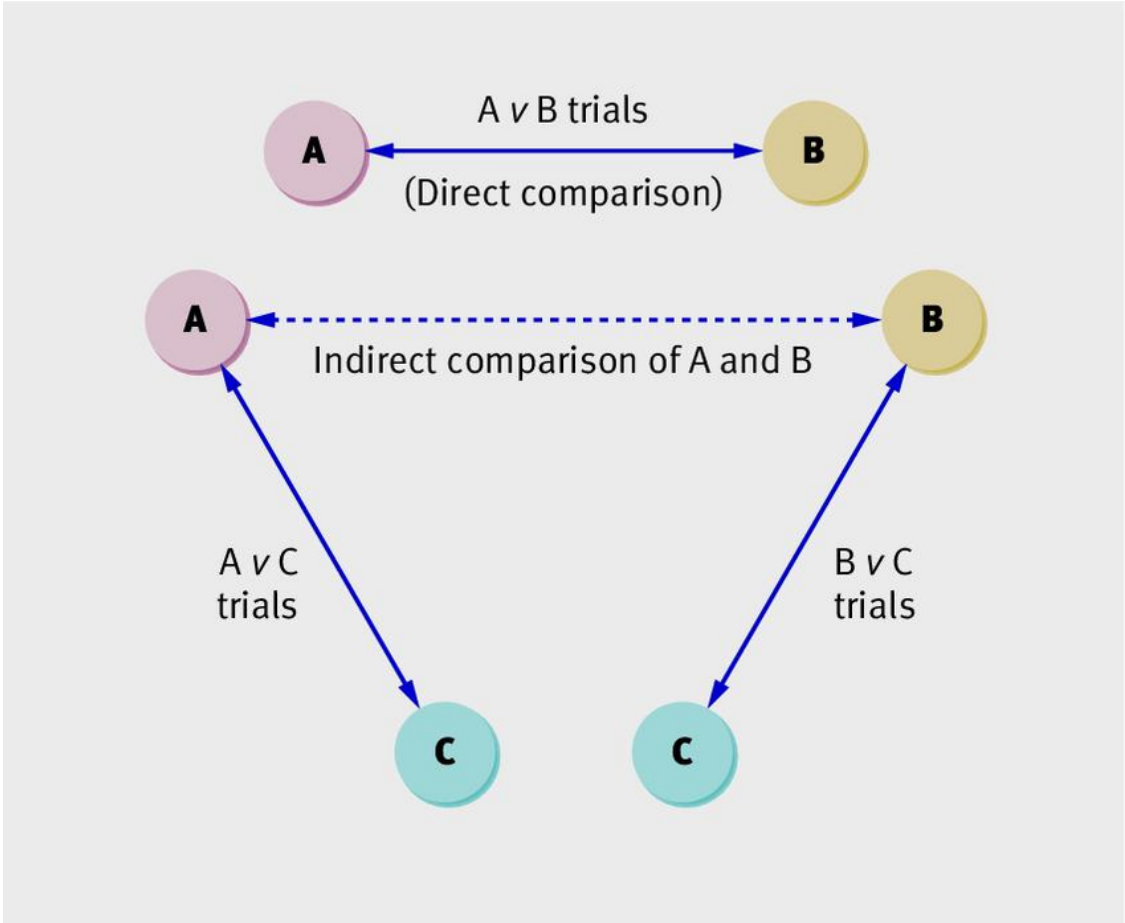
- Network meta-analysis
- Individual patient data meta-analysis (IPD-MA)
- Prospective meta-analysis

These types of meta-analysis are increasingly common, and best integrated in a systematic review

Network meta-analysis

- Intervention questions relevant for clinical practice often involve multiple treatment comparisons:
  - What is the best drug for depression?
  - What is the best therapy for advanced colon cancer?
  - What is the optimal aspirin dose to prevent stroke?
- Network meta-analysis
  - examines all treatments for a given condition or disease and all the possible comparisons between them
  - combines direct and indirect evidence

Network meta-analysis



Network meta-analysis guidance

Tutorial

Research Synthesis Methods

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(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1195

GetReal in network meta-analysis: a review of the methodology

Orestis Efthimiou,[a*] Thomas P. A. Debray,[b,c] Gert van Valkenhoef,[d] Sven Trelle,[e,f] Klea Panayidou,[e] Karel G. M. Moons,[b,c] Johannes B. Reitsma,[b,c] Aijing Shang[g] and Georgia Salanti[a,†] on behalf of GetReal Methods Review Group[‡]

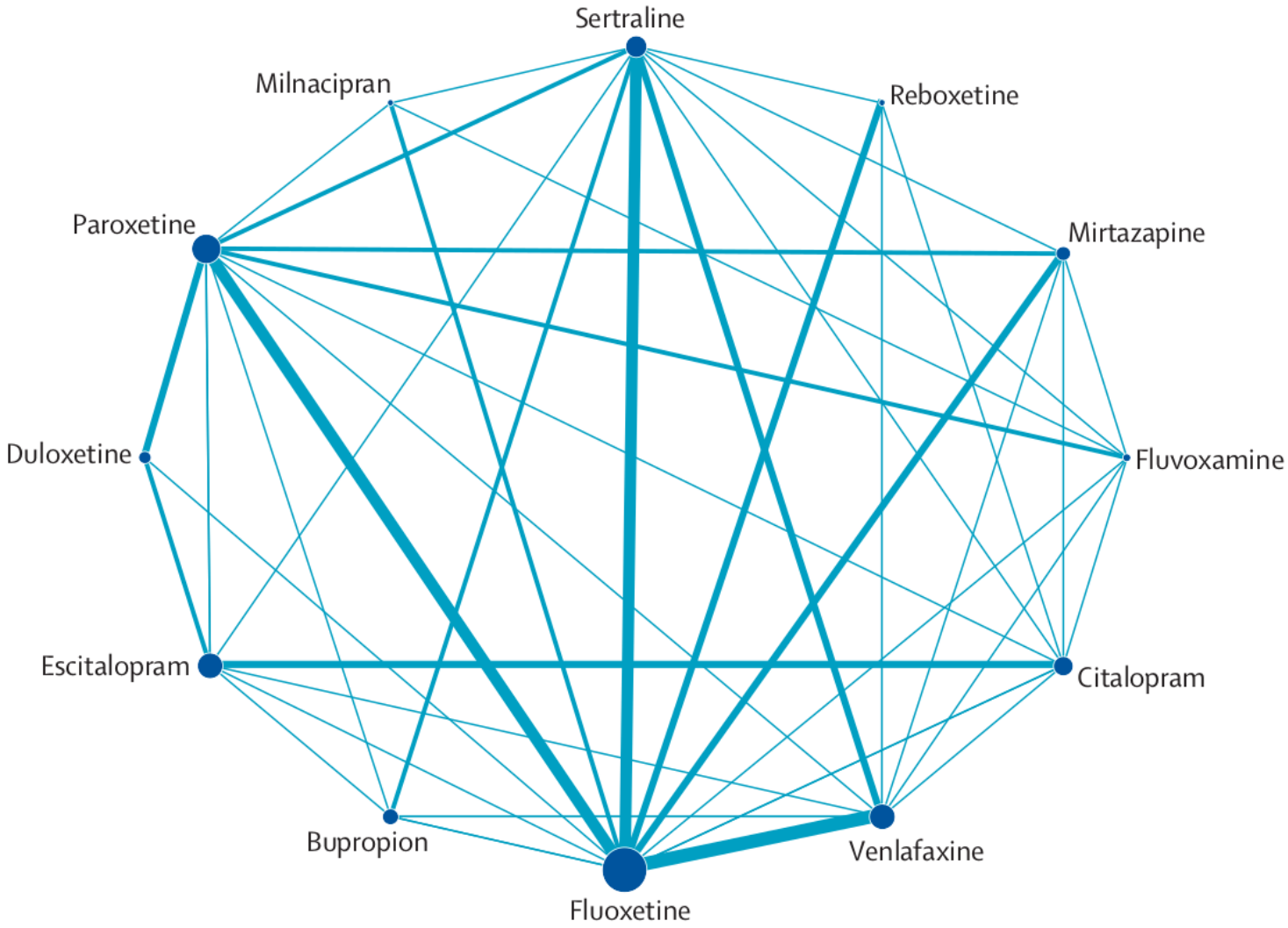
10.1002/jrsm.1195

Network meta-analysis example

- Conventional (pairwise) meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants
- Selective publication of placebo-controlled antidepressant trials
- Clinicians need to know whether (and to what extent) treatments work within a clinically reasonable period
- Cipriani *et al* systematically reviewed 117 randomised controlled trials from 1991 to 2007, which compared antidepressants for the acute treatment of unipolar major depression in adults
- The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment

Source: 10.1016/S0140-6736(09)60046-5 (Lancet 2009)

Network meta-analysis example



Network meta-analysis example

Main findings

- Response: mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine
- Acceptability: escitalopram, sertraline, citalopram, and bupropion were better tolerated than other new-generation antidepressants
- Two of the most efficacious treatments (mirtazapine and venlafaxine) might not be the best for overall acceptability
- Sertraline appears better than other new-generation drugs in terms of efficacy and acceptability, and could be used as a standard comparator in phase III trials

Meta-analysis of individual participant data

- Traditional meta-analysis is based on published summary results, hence its validity limited by the format and completeness of reported aggregate data
- Meta-analysis of individual participant data (IPD-MA)
  - avoids many reporting problems
  - facilitates quality control
  - improves comparability of study results
  - allows use of additional data
  - allows more flexibility and can increase statistical power
- IPD-MA is particularly relevant for research questions focusing on individual patient characteristics
  - examination of treatment-effect modifiers
  - development and validation of prediction models

Guidance on IPD-MA

Reviews of the effects of interventions

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GUIDELINES AND GUIDANCE

Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use

Jayne F. Tierney, Claire Vale, Richard Riley, Catrin Tudur Smith, Lesley Stewart, Mike Clarke, Maroeska Rovers

Published: July 21, 2015 • https://doi.org/10.1371/journal.pmed.1001855

Guidance on IPD-MA

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Get real in individual participant data (IPD) meta-analysis: a review of the methodology

Thomas P. A. Debray,[a,b]* Karel G. M. Moons,[a,b] Gert van Valkenhoef,[c] Orestis Efthimiou,[d] Noemi Hummel,[e] Rolf H. H. Groenwold,[a] Johannes B. Reitsma[a,b] and on behalf of the GetReal methods review group

Guidance on IPD-MA

Reviews of prognosis

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GUIDELINES AND GUIDANCE

Individual Participant Data (IPD) Meta-analyses of Diagnostic and Prognostic Modeling Studies: Guidance on Their Use

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¶ Membership of the Cochrane IPD Meta-analysis Methods group is listed in the Acknowledgments.
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Final remarks

Take-home message

Systematic reviews and meta-analysis are of great relevance

- Considered the highest level of evidence
- Summarize findings from reported data, individual participant data, or both
- Methods, guidance and software widely available in the public domain
- Prospective registration & collection of IPD may help to overcome many pitfalls associated with meta-analysis
- Adequate reporting of systematic reviews remains important (PRISMA)