Synthesising quantitative evidence in systematic reviews of complex health interventions

Julian P T Higgins,1 José A López-López,1 Betsy J Becker,2 Sarah R Davies,1 Sarah Dawson,1 Jeremy M Grimshaw,3,4 Luke A McGuinness,1 Theresa H M Moore,1,5 Eva A Rehfuess,6 James Thomas,7 Deborah M Caldwell1

ABSTRACT
Public health and health service interventions are typically complex: they are multifaceted, with impacts at multiple levels and on multiple stakeholders. Systematic reviews evaluating the effects of complex health interventions can be challenging to conduct. This paper is part of a special series of papers considering these challenges particularly in the context of WHO guideline development. We outline established and innovative methods for synthesising quantitative evidence within a systematic review of a complex intervention, including considerations of the complexity of the system into which the intervention is introduced. We describe methods in three broad areas: non-quantitative approaches, including tabulation, narrative and graphical approaches; standard meta-analysis methods, including meta-regression to investigate study-level moderators of effect; and advanced synthesis methods, in which models allow exploration of intervention components, investigation of both moderators and mediators, examination of mechanisms, and exploration of complexities of the system. We offer guidance on the choice of approach that might be taken by people collating evidence in support of guideline development, and emphasise that the appropriate methods will depend on the purpose of the synthesis, the similarity of the studies included in the review, the level of detail available from the studies, the nature of the results reported in the studies, the expertise of the synthesis team and the resources available.

BACKGROUND
Public health and health service interventions are typically complex. They are usually multifaceted, with impacts at multiple levels and on multiple stakeholders. Also, the systems within which they are implemented may change and adapt to enhance or dampen their impact.3 Quantitative syntheses (‘meta-analyses’) of studies of complex interventions seek to integrate quantitative findings across multiple studies to achieve a coherent message greater than the sum of their parts. Interest is growing on how the standard systematic review and meta-analysis toolkit can be enhanced to address complexity of interventions and their impact.4 A recent report from the Agency for Healthcare Research and Quality and a series of papers in the Journal of Clinical Epidemiology provide useful background on some of the challenges.5–6

This paper is part of a series to explore the implications of complexity for systematic reviews and guideline development, commissioned by WHO.7 Clearly, and as covered by other papers in this series, guideline development encompasses the consideration of many different aspects,8 such as intervention effectiveness, economic considerations, acceptability9 or certainty of evidence,10 and requires the integration of different types of quantitative as well as qualitative evidence.11 12 This paper is specifically concerned with methods available for the synthesis of quantitative results in the context of a systematic review on the effects of a complex intervention. We aim to point those collating evidence in support...
of guideline development to methodological approaches that will help them integrate the quantitative evidence they identify. A summary of how these methods link to many of the types of complexity encountered is provided in table 1, based on the examples provided in a table from an earlier paper in the series. An annotated list of the methods we cover is provided in table 2.

We begin by reiterating the importance of starting with meaningful research questions and an awareness of the purpose of the synthesis and any relevant background knowledge. An important issue in systematic reviews of complex interventions is that data available for synthesis are often extremely limited, due to small numbers of relevant studies and limitations in how these studies are conducted and their results are reported. Furthermore, it is uncommon for two studies to evaluate exactly the same intervention, in part because of the interventions’ inherent complexity. Thus, each study may be designed to provide information on a unique context or a novel intervention approach. Outcomes may be measured in different ways and at different time points. We therefore discuss possible approaches when data are highly limited or highly heterogeneous, including the use of graphical approaches to present very basic summary results. We then discuss statistical approaches for combining results and for understanding the implications of various kinds of complexity.

In several places we draw on an example of a review undertaken to inform a recent WHO guideline on protecting, promoting and supporting breastfeeding. The review seeks to determine the effects of interventions to promote breast feeding delivered in five types of settings (health services, home, community, workplace, policy context or a combination of settings). The included interventions were predominantly multicomponent, and were implemented in complex systems across multiple contexts. The review included 195 studies, including many from low-income and middle-income countries, and concluded that interventions should be delivered in a combination of settings to achieve high breastfeeding rates.

**THE IMPORTANCE OF THE RESEARCH QUESTION**

The starting point in any synthesis of quantitative evidence is a clear purpose. The input of stakeholders is critical to ensure that questions are framed appropriately, addressing issues important to those commissioning, delivering and affected by the intervention. Detailed discussion of the development of research questions is provided in an earlier paper in the series, and a subsequent paper explains the importance of taking context into account. The first of these papers describes two possible perspectives. A complex interventions perspective emphasises the complexities involved in conceptualising, specifying and implementing the intervention per se, including the array of possibly interacting components and the behaviours required to implement it. A complex systems perspective emphasises the complexity of the systems into which the intervention is introduced, including possible interactions between the intervention and the system, interactions between individuals within the system and how the whole system responds to the intervention.

The simplest purpose of a systematic review is to determine whether a particular type of complex intervention (or class of interventions) is effective compared with a ‘usual practice’ alternative. The familiar PICO framework is helpful for framing the review: in the PICO framework, a broad research question about effectiveness is uniquely specified by describing the participants (‘P’), including the setting and prevailing conditions) to which the intervention is to be applied; the intervention (‘I’) and comparator (‘C’) of interest, and the outcomes (‘O’), including their time course) that might be impacted by the intervention. In the breastfeeding review, the primary synthesis approach was to combine all available studies, irrespective of setting, and perform separate meta-analyses for different outcomes.

More useful than a review that asks ‘does a complex intervention work?’ is one that determines the situations in which a complex intervention has a larger or smaller effect. Indeed, research questions targeted by syntheses in the presence of complexity often dissect one or more of the PICO elements to explore how intervention effects vary both within and across studies (ie, treating the PICO elements as ‘moderators’). For instance, analyses may explore variation across participants, settings and prevailing conditions (including context); or across interventions (including different intervention components that may be present or absent in different studies); or across outcomes (including different outcome measures, at different levels of the system and at different time points) on which effects of the intervention occur. In addition, there may be interest in how aspects of the underlying system or the intervention itself mediate the effects, or in the role of intermediate outcomes on the pathway from intervention to impact. In the breastfeeding review, interest moved from the overall effects across interventions to investigations of how effects varied by such factors as intervention delivery setting, high-income versus low-income country, and urban versus rural setting.

**The role of logic models to inform a synthesis**

An earlier paper describes the benefits of using system-based logic models to characterise a priori theories about how the system operates. These provide a useful starting point for most syntheses since they encourage consideration of all aspects of complexity in relation to the intervention or the system (or both). They can help identify important mediators and moderators, and inform decisions about what aspects of the intervention and system need to be addressed in the synthesis. As an example, a protocol for a review of the health effects of environmental interventions to reduce the consumption...
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<tr>
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<th>Synthesis possibilities</th>
<th>Further discussion</th>
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<tbody>
<tr>
<td>What ‘is’ the system? How can it</td>
<td>What are the main influences on the</td>
<td>Map the system, defining pathways and influences. Draw</td>
<td>See companion paper and section 2.1.</td>
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<td>be described?</td>
<td>health problem? How are they created</td>
<td>a logic model based on the key aspects for the research</td>
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<td></td>
<td>and maintained? How do these influences</td>
<td>question at hand as a basis for thinking about the</td>
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<td></td>
<td>interconnect?</td>
<td>quantitative synthesis.</td>
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<tr>
<td>Interactions between components</td>
<td>What is the independent and combined</td>
<td>Consider methods such as meta-regression, network</td>
<td>See sections 5.2 and 6.</td>
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<td>of complex interventions</td>
<td>effect of the individual components?</td>
<td>meta-analysis and component-based approach that</td>
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<td>How do the components work along and in</td>
<td>address intervention components, using models that</td>
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<td>combination to produce effects? (How do</td>
<td>allow investigation of interactions among components.</td>
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<td>they interact to produce outcomes?)</td>
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<td>Interactions of interventions</td>
<td>Do the effects of the intervention appear</td>
<td>Consider subgroup analysis and meta-regression to</td>
<td>See section 5.2.</td>
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<td>with context and adaptation</td>
<td>to be context-dependent?</td>
<td>examine how features of context impact on effect sizes.</td>
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<td>System adaptivity (how does the</td>
<td>(How) does the system change when the</td>
<td>Identify behaviours or actions that might be</td>
<td>See section 8.</td>
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<td>system change?)</td>
<td>intervention is introduced?</td>
<td>affected, and consider these as outcomes in meta-</td>
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<td>Which aspects of the system are affected?</td>
<td>meta-analysis or meta-regression analyses. To account</td>
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<td>Does this potentiate or dampen its</td>
<td>for correlations among them, multivariate methods</td>
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<td>effects?</td>
<td>might be considered.</td>
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<tr>
<td>Emergent properties</td>
<td>What are the effects (anticipated and</td>
<td>Identify other possible effects of the intervention,</td>
<td>See sections 8, box 2</td>
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<td>unanticipated) which follow from this</td>
<td>and consider these as outcomes in meta-analysis or</td>
<td>and 3.</td>
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<td>system change?</td>
<td>meta-regression analyses. Consider model-driven</td>
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<td>meta-analysis or mathematical models (including</td>
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<td>simulation approaches) to investigate these further.</td>
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<td>Non-linearity and phase changes</td>
<td>How do effects change over time?</td>
<td>Identify important time points and address these in</td>
<td>See sections 5 and 8,</td>
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<td>separate meta-analyses, or using meta-regression</td>
<td>and box 3.</td>
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<td>analyses. Consider mathematical models to predict</td>
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<td>how effects might change over time.</td>
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<tr>
<td>Positive (reinforcing) and</td>
<td>What explains change in the effectiveness</td>
<td>Consider model-driven meta-analysis or mathematical</td>
<td>See sections 7 and 8,</td>
</tr>
<tr>
<td>negative (balancing) feedback</td>
<td>of the intervention over time?</td>
<td>models to investigate these.</td>
<td>boxes 2 and 3.</td>
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<td>loops</td>
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<td></td>
<td>Are the effects of an intervention</td>
<td>Consider subgroup analysis and meta-regression to</td>
<td>See section 5.2.</td>
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<td></td>
<td>dampened/suppressed by other aspects of</td>
<td>examine how features of the system impact on effect</td>
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<td>the system (eg, contextual influences)?</td>
<td>sizes.</td>
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### Table 1  Continued

<table>
<thead>
<tr>
<th>Aspect of complexity of interest</th>
<th>Examples of potential research question(s)</th>
<th>Synthesis possibilities</th>
<th>Further discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple (health and non-health) outcomes</td>
<td>What changes in processes and outcomes follow the introduction of this system change?</td>
<td>Identify behaviours or actions that might be affected, and consider these as outcomes in meta-analysis or meta-regression analyses. To account for correlations among them, multivariate methods might be considered. Consider meta-regression to examine the mediating effects of intermediate outcomes.</td>
<td>See section 8.</td>
</tr>
<tr>
<td>At what levels in the system are they experienced?</td>
<td>Identify units (eg, individuals or organisations) whose behaviour or actions might be affected, and consider these as outcomes in meta-analysis or meta-regression analyses. Multilevel models might be appropriate to capture the different levels of impact, although may require access to individual participant data.</td>
<td></td>
<td>See section 8.</td>
</tr>
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</table>

#### Considering the types of studies available

Studies of the effects of complex interventions may be difficult to undertake because of the logistical and organisational challenges involved. Randomised controlled trials are the gold standard, but they may be difficult or impossible to perform in the real world. Non-randomised designs, such as interrupted time series or quasi-experimental designs, may provide alternative approaches to evaluating complex interventions. However, these designs may have limitations, such as selection bias and confounding, which need to be addressed carefully.

### Logic models

Logic models are a useful tool for understanding how complex interventions work. They can help to identify potential mechanisms of action and to anticipate potential outcomes. However, they are not a substitute for empirical evidence, and their validity depends on the quality of the data and the methods used to generate them.

A systematic review of community-based interventions for improving access to healthy foods in low-income and middle-income countries was based on a logic model that depicted the potential pathways leading to improved health status. The model included direct effects, such as increased availability and consumption of healthy foods, and indirect effects, such as changes in dietary behaviour and health outcomes. The model also included a framework for assessing the impact of the intervention, which was used to guide the analysis of the findings.

### Causal inference

Causal inference is a fundamental aspect of evaluating complex interventions. In general, observational studies are unable to establish causality, and therefore, the results must be interpreted with caution. Randomised controlled trials, on the other hand, are the gold standard for establishing causality, but they are not always feasible or ethical. In such cases, quasi-experimental designs, such as interrupted time series, may provide a useful alternative.

A quantitative synthesis may draw on a specific proposed framework for how an intervention might work; these are sometimes referred to as a priori frameworks. A qualitative synthesis may adopt and modify the proposed framework as necessary. The choice of approach depends on the nature of the evidence and the research question.

### Subsequent outcomes

The findings of included studies are not always generalisable to other populations or settings. This is particularly true for complex interventions, which are often tailored to specific contexts and may not be replicable in other settings. Therefore, it is important to consider the limitations of the evidence and to draw conclusions with caution.

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### Conclusion

Complex interventions are challenging to evaluate, but they are also essential for addressing many public health challenges. Logic models can help to understand how these interventions work, but they are just one part of a broader evidence-based approach to evaluating complex interventions.
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<th>Methodological approach</th>
<th>Data requirements from each study</th>
<th>Main strengths</th>
<th>Main limitations</th>
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</thead>
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<tr>
<td>Forest plot (without overall effect)</td>
<td>Effect size and CI on the same metric</td>
<td>Widely familiar; each study clearly identified</td>
<td>Replication (of similar research questions) across studies is uncommon; effect size data may not be available</td>
</tr>
<tr>
<td>Albatross plot</td>
<td>P value, sample size and direction of effect</td>
<td>Data requirements are basic, so usually met; possibility of making indirect inferences on underlying effect sizes</td>
<td>Does not provide estimate of effect size; studies not clearly identified</td>
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<tr>
<td>Harvest plot</td>
<td>Conclusion of statistical test for effect; study feature(s) of interest</td>
<td>Data requirements are basic, so usually met; multiple outcomes can easily be displayed</td>
<td>Arbitrary distinction of studies according to statistical test; does not provide estimate of effect size</td>
</tr>
<tr>
<td>Effect direction plot</td>
<td>Conclusion of statistical test for effect; study feature(s) of interest</td>
<td>Data requirements are basic, so usually met; multiple outcomes can easily be displayed</td>
<td>Arbitrary distinction of studies according to statistical test; does not provide estimate of effect size; studies not clearly identified</td>
</tr>
<tr>
<td>Bubble plot</td>
<td>Conclusion of statistical analysis for effect; study feature(s) of interest</td>
<td>Data requirements are basic, so usually met; multiple outcomes can easily be displayed</td>
<td>Arbitrary distinction of studies according to result of statistical analysis; does not provide estimate of effect size; studies not clearly identified</td>
</tr>
<tr>
<td>Binomial test</td>
<td>Direction of effect</td>
<td>Data requirements are basic, so usually met</td>
<td>Does not provide estimate of effect size</td>
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<tr>
<td>Combining p values</td>
<td>P value and direction of effect</td>
<td>Data requirements are basic, so usually met</td>
<td>Does not provide estimate of effect size</td>
</tr>
<tr>
<td>Standard meta-analysis (eg, weighted average)</td>
<td>Effect size and CI (or equivalent) on the same metric</td>
<td>Widely familiar; produces effect sizes (important for decision making)</td>
<td>Replication (of similar research questions) across studies is uncommon; effect size data may not be available</td>
</tr>
<tr>
<td>Multiple outcomes meta-analysis (multivariate methods)</td>
<td>Effect size and CI (or equivalent) on the same metric for each outcome; data on correlations between outcomes</td>
<td>Can strengthen analysis of one outcome by ‘borrowing strength’ from other outcomes</td>
<td>Requires reasonably large number of studies for reliable results</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td>Effect size and CI (or equivalent) on the same metric; study feature(s) of interest</td>
<td>Straightforward and widely familiar; flexible approach appropriate for examining impact of context, settings, participants, intervention characteristics</td>
<td>Addresses one study feature at a time; requires reasonably large number of studies for reliable results; high risk of false-positive conclusions; often has low power to detect true impacts of the features examined</td>
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<tr>
<td>Meta-regression</td>
<td>Effect size and CI (or equivalent) on the same metric; study feature(s) of interest</td>
<td>Allows multiple study features to be examined together; flexible approach appropriate for examining impact of context, settings, participants, intervention characteristics and for mediating effects of intermediate outcomes</td>
<td>Requires reasonably large number of studies for reliable results; high risk of false-positive conclusions; often has low power to detect true impacts of the features examined</td>
</tr>
<tr>
<td>Multiple interventions meta-analysis (network meta-analysis)</td>
<td>Effect size and CI (or equivalent) on the same metric; category to place each intervention</td>
<td>Facilitates rank ordering of interventions for the outcome</td>
<td>Requires interventions to be grouped into (reasonably homogenous) categories; requires similar target population for all studies; requires all categories of interventions to be ‘connected’ in the network</td>
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### Table 2 Continued

<table>
<thead>
<tr>
<th>Methodological approach</th>
<th>Data requirements from each study</th>
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<th>Main limitations</th>
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<tbody>
<tr>
<td>Components-based approach to intervention complexity</td>
<td>Effect size and CI (or equivalent) on the same metric; components present in each intervention</td>
<td>Facilitates identification of most important component(s) of complex intervention</td>
<td>Requires reasonably large number of studies for reliable results; Assumptions required about whether components act additively or otherwise</td>
</tr>
<tr>
<td>Qualitative comparative analysis</td>
<td>Effect size estimates and study features of interest</td>
<td>Supports non-linear effects; multiple pathways to effectiveness; operates in ‘small n’ scenarios</td>
<td>Produces explanatory, rather than predictive, findings</td>
</tr>
<tr>
<td>Model-driven meta-analysis</td>
<td>Assumed causal model (logic model); effect size information for each relevant path in the model</td>
<td>Flexible approach to combining evidence; forces thinking about how effects arise</td>
<td>Dependent on appropriate assumptions being made in the causal model and availability of data</td>
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<tr>
<td>Mathematical models and system science methods</td>
<td>Assumed model; variable data requirements</td>
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Figure 1  Example graphical displays of data from a review of interventions to promote breast feeding, for the outcome of continued breast feeding up to 23 months.\textsuperscript{15} Panel A: Forest plot for relative risk (RR) estimates from each study. Panel B: Albatross plot of p value against sample size (effect contours drawn for risk ratios assuming a baseline risk of 0.15; sample sizes and baseline risks extracted from the original papers by the current authors); Panel C: Harvest plot (heights reflect design: randomised trials (tall), quasi-experimental studies (medium), observational studies (short); bar shading reflects follow-up: longest follow-up (black) to shortest follow-up (light grey) or no information (white)). Panel D: Bubble plot (bubble sizes and colours reflect design: randomised trials (large, green), quasi-experimental studies (medium, red), observational studies (small, blue); precision defined as inverse of the SE of each effect estimate (derived from the CIs); categories are: “Potential Harm”: RR <0.8; “No Effect”: RRs between 0.8 and 1.25; “Potential Benefit”: RR >1.25 and CI includes RR=1; “Benefit”: RR >1.25 and CI excludes RR=1).

OPTIONS WHEN EFFECT SIZE ESTIMATES CANNOT BE OBTAINED OR STUDIES ARE TOO DIVERSE TO COMBINE

Graphical approaches

Graphical displays can be very valuable to illustrate patterns in results of studies.\textsuperscript{27} We illustrate some options in figure 1. Forest plots are the standard illustration of the results of multiple studies (see figure 1, panel A), but require a similar effect size estimate from each study. For studies of complex interventions, the diversity of approaches to the intervention, the context,\textsuperscript{1} evaluation approaches and reporting differences can lead to considerable variation across studies in what results are available. Some novel graphical approaches have been proposed for such situations. A recent development is the albatross plot, which plots p values against sample sizes, with approximate effect-size contours superimposed (see figure 1, panel B).\textsuperscript{28} The contours are computed from the p values and sample sizes, based on an assumption about the type of analysis that would have given rise to the p values. Although these plots are designed for situations when effect size estimates are not available, the contours can be used to infer approximate effect sizes from studies that are analysed and reported in highly diverse ways. Such an advantage may prove to be a disadvantage, however, if the contours are overinterpreted.

Harvest plots have been proposed by Ogilvie \textit{et al} as a graphical extension of a vote counting approach to synthesis (see figure 1, panel C).\textsuperscript{29} However, approaches based on vote counting of statistically significant results have been criticised on the basis of their poor statistical properties, and because statistical significance is an outdated and unhelpful notion.\textsuperscript{30} The harvest plot is a matrix of small illustrations, with different outcome domains defining rows and different qualitative conclusions (negative effect, no effect, positive effect) defining columns. Each study is represented by a bar that is positioned according to its measured outcome and qualitative conclusion. Bar heights and shadings can depict features of the study, such as objectivity of the outcome measure, suitability of the study design and study quality.\textsuperscript{29} 31 A similar idea to the harvest plot is the effect direction plot proposed by Thomson and Thomas.\textsuperscript{32}
A device to plot the findings from a large and complex collection of evidence is a bubble plot (see figure 1, panel D). A bubble plot illustrates the direction of each finding (or whether the finding was unclear) on a horizontal scale, using a vertical scale to indicate the volume of evidence, and with bubble sizes to indicate some measure of credibility of each finding. Such an approach can also depict findings of collections of studies rather than individual studies, and was used successfully, for example, to summarise findings from a review of systematic reviews of the effects of acupuncture on various indications for pain.35

**Statistical methods not based on effect size estimates**

We have mentioned that a frequent problem is that standard meta-analysis methods cannot be used because data are not available in a similar format from every study. In general, the core principles of meta-analysis can be applied even in this situation, as is highlighted in the Cochrane Handbook, by addressing the questions: ‘What is the direction of effect?; ‘What is the size of effect?; ‘Is the effect consistent across studies?; and ‘What is the strength of evidence for the effect?’.34

Alternatives to the estimation of effect sizes could be used more often than they are in practice, allowing some basic statistical inferences despite divergently reported results. The most fundamental analysis is to test the overall null hypothesis of no effect in any of the studies. Such a test can be undertaken using only minimally reported information from each study. At its simplest, a binomial test can be performed using only the direction of effect observed in each study, irrespective of its CI or statistical significance.35 Where exact p values are available as well as the direction of effect, a more powerful test can be performed by combining these, for example, Fisher’s combination of p values.36 It is important that these p values are computed appropriately, however, accounting for clustering or matching of participants within the studies. Rejecting the null model based on such tests provides no information about the magnitude of the effect, providing information only on whether at least one study shows an effect is present, and if so, its direction.37

**STANDARD SYNTHESIS METHODS**

**Meta-analysis for overall effect**

Probably the most familiar approach to meta-analysis is that of estimating a single summary effect across similar studies. This simple approach lends itself to the use of forest plots to display the results of individual studies as well as syntheses, as illustrated for the breastfeeding studies in figure 1 (panel A). This analysis addresses the broad question of whether evidence from a collection of studies supports an impact of the complex intervention of interest, and requires that every study makes a comparison of a relevant intervention against a similar alternative. In the context of complex interventions, this is described by Caldwell and Welton as the ‘lumping’ approach,38 and by Guise et al as the ‘holistic’ approach.34 One key limitation of the simple approach is that it requires similar types of data from each study. A second limitation is that the meta-analysis result may have limited relevance when the studies are diverse in their characteristics. Fixed-effect models, for instance, are unlikely to be appropriate for complex interventions because they ignore between-studies variability in underlying effect sizes. Results based on random-effects models will need to be interpreted by acknowledging the spread of effects across studies, for example, using prediction intervals.39

A common problem when undertaking a simple meta-analysis is that individual studies may report many effect sizes that are correlated with each other, for example, if multiple outcomes are measured, or the same outcome variable is measured at several time points. Numerous approaches are available for dealing with such multiplicity, including multivariate meta-analysis, multilevel modelling, and strategies for selecting effect sizes.40

A very simple strategy that has been used in systematic reviews of complex interventions is to take the median effect size within each study, and to summarise these using the median of these effect sizes across studies.41

**Exploring heterogeneity**

Diversity in the types of participants (and contexts), interventions and outcomes are key to understanding sources of complexity.9 Many of these important sources of heterogeneity are most usefully examined—to the extent that they can reliably be understood—using standard approaches for understanding variability across studies, such as subgroup analyses and meta-regression.42

A simple strategy to explore heterogeneity is to estimate the overall effect separately for different levels of a factor using subgroup analyses (referring to subgrouping studies rather than participants).42 As an example, McFadden et al conducted a systematic review and meta-analysis of 73 studies of support for healthy breastfeeding mothers with healthy term babies.43 They calculated separate average effects for interventions delivered by a health professional, a lay supporter or with mixed support, and found that the effect on cessation of exclusive breastfeeding at up to 6 months was greater for lay support compared with professionals or mixed support (p=0.02). Guise et al provide several ways of grouping studies according to their interventions, for example, grouping studies by key components, by function or by theory.44

Meta-regression provides a flexible generalisation to subgroup analyses, whereby study-level covariates are included in a regression model using effect size estimates as the dependent variable.44 Both continuous and categorical covariates can be included in such models; with a single categorical covariate, the approach is essentially equivalent to subgroup analyses. Meta-regression with continuous covariates in theory allows the extrapolation of relationships to contexts that were not examined in any of the studies, but this should generally be avoided.
For example, if the effect of an interventional approach appears to increase as the size of the group to which it is applied decreases, this does not mean that it will work even better when applied to a single individual. Generally, the mathematical form of the relationship modelled in a meta-regression requires careful selection. Most often a linear relationship is assumed, but a linear relationship does not permit step changes such as might occur if an interventional approach requires a particular level of some feature of the underlying system before it has an effect.

Several texts provide guidance for using subgroup analysis and meta-regression in a general context and for complex interventions. In principle, many components have been described by Welton, Ivers, and created covariates to code the presence of particular features in each intervention implementation. As an example, Blakemore et al analysed 39 intervention comparisons from 33 independent studies aiming to reduce urgent healthcare use in adults with asthma. Effect size estimates were coded according to components used in the interventions, and the authors found that multicomponent interventions including skills training, education and relapse prevention appeared particularly effective. In another example, of interventions to support family caregivers of people with Alzheimer’s disease, the authors used methods for decomposing complex interventions proposed by Czaja et al, and created covariates that reduced the complexity of the interventions to a small number of features about the intensity of the interventions. More sophisticated models for examining components have been described by Welton et al, Ivers et al, and Madan et al.

A component-level approach may be useful when there is a need to disentangle the ‘active ingredients’ of an intervention, for example, when adapting an existing intervention for a new setting. However, component-based approaches require assumptions, such as whether individual components are additive or interact with each other. Furthermore, the effects of components can be difficult to estimate if they are used only in particular contexts or populations, or are strongly correlated with use of other components. An alternative approach is to treat each combination of components as a separate intervention. These separate interventions might then be compared in a single analysis using network meta-analysis. A network meta-analysis combines results from studies comparing two or more of a larger set of interventions, using indirect comparisons via common comparators to rank-order all interventions. As an example, Achan et al examined the effectiveness of safety interventions on the uptake of three poisoning prevention practices in households with children. Each singular combination of intervention components was defined as a separate intervention in the network. Network meta-analysis may also be useful when there is a need to compare multiple interventions to answer an ‘in principle’ question of which intervention is most effective. Consideration of the main goals of the synthesis will help those aiming to prepare guidelines to decide which of these approaches is most appropriate to their needs.

A case study exploring components is provided in box 1, and an illustration is provided in figure 2. The component-based analysis approach can be likened to

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## Box 1 Example of understanding components of psychosocial interventions for coronary heart disease

Welton et al reanalysed data from a Cochrane review of randomised controlled trials assessing the effects of psychological interventions on mortality and morbidity reduction for people with coronary heart disease. The Cochrane review focused on the effectiveness of any psychological intervention compared with usual care, and found evidence that psychological interventions reduced non-fatal reinfarctions and depression and anxiety symptoms. The Cochrane review authors highlighted the large heterogeneity among interventions as an important limitation of their review.

Welton et al were interested in the effects of the different intervention components. They classified interventions according to which of five key components were included: educational, behavioural, cognitive, relaxation and psychosocial support. Their reanalysis examined the effect of each component in three different ways: (1) An additive model assuming no interactions between components. (2) A two-factor interaction model, allowing for interactions between pairs of components. (3) A network meta-analysis, defining each combination of components as a separate intervention, therefore allowing for full interaction between components. Results suggested that interventions with behavioural components were effective in reducing the odds of all-cause mortality and non-fatal myocardial infarction, and that interventions with behavioural and/or cognitive components were effective for reducing depressive symptoms.
a factorial trial, in that it attempts to separate out the effects of individual components of the complex interventions, and the network meta-analysis approach can be likened to a multiarm trial approach, where each complex intervention in the set of studies is a different arm in the trial. Deciding between the two approaches can leave the analyst caught between the need to ‘split’ components to reflect complexity (and minimise heterogeneity) and ‘lump’ to make an analysis feasible. Both approaches can be used to examine other features of interventions, including interventions designed for delivery at different levels. For example, a review of the effects of interventions for children exposed to domestic violence and abuse included studies of interventions targeted at children alone, parents alone, children and parents together, and parents and children separately.

A network meta-analysis approach was taken to the synthesis, with the people targeted by the intervention used as a distinguishing feature of the interventions included in the network.

A common limitation when implementing these quantitative methods in the context of complex interventions is that replication of the same intervention in two or more studies is rare. Qualitative comparative analysis (QCA) might overcome this problem, being designed to address the ‘small N; many variables’ problem. QCA involves: (1) Identifying theoretically driven thresholds for determining intervention success or failure. (2) Creating a ‘truth table’, which takes the form of a matrix, cross-tabulating all possible combinations of conditions (eg, participant and intervention characteristics) against each study and its associated outcomes. (3) Using Boolean algebra to eliminate redundant conditions and to identify configurations of conditions that are necessary and/or sufficient to trigger intervention success or failure. QCA can usefully complement quantitative integration, sometimes in the context of synthesising diverse types of evidence.

SYNTHESIS METHODS FOR UNDERSTANDING MECHANISMS OF ACTION

An alternative purpose of a synthesis is to gain insight into the mechanisms of action behind an intervention, to inform its generalisability or applicability to a particular context. Such syntheses of quantitative data may complement syntheses of qualitative data, and the two forms might be integrated. Logic models, or theories of action, are important to motivate investigations of mechanism. The synthesis is likely to focus on intermediate outcomes reflecting intervention processes, and on mediators of effect (factors that influence how the intervention affects an outcome measure). Two possibilities for analysis are to use these intermediate measurements as predictors of main outcomes using meta-regression methods, or to use multivariate meta-analysis to model the intermediate and main outcomes simultaneously, exploiting and estimating the correlations between them. If the synthesis suggests that hypothesised chains of outcomes hold, this lends weight to the theoretical model underlying the hypothesis.

An approach to synthesis closely identified with this category of interventions is model-driven meta-analysis, in which different sources of evidence are integrated within a causal path model akin to a directed acyclic graph. A model-driven meta-analysis is an explanatory analysis. It attempts to go further than a standard meta-analysis or meta-regression to explore how and why an intervention works, for whom it works, and which aspects of the intervention (factors) are driving overall effect. Such syntheses have been described in frequentist and Bayesian frameworks and are variously known as model-driven meta-analysis, linked meta-analysis, meta-mediation analysis and meta-analysis of structural equation models. In their simplest form, standard meta-analyses estimate a summary correlation independently for each pair of variables in the model. The approach is inherently multivariate, requiring the estimation of multiple correlations (which, if obtained from a single study, are also not independent). Each study is likely to contribute fragments of the correlation matrix. A summary correlation matrix, combined either by fixed-effects or random-effects methods, then serves as the input for subsequent analysis via a standardised regression or structural equation model.
An example is provided in box 2. The model in figure 3 postulates that the effect of ‘Dietary adherence’ on ‘Diabetes complications’ is not direct but is mediated by ‘Metabolic control’.

SYNTHESIS APPROACHES FOR UNDERSTANDING COMPLEXITIES OF THE SYSTEM

Syntheses may seek to address complexities of the system to understand either the impact of the system on the effects of the intervention or the effects of the intervention on the system. This may start by modelling the salient features of the system’s dynamics, rather than focusing on interventions. Subgroup analysis and meta-regression are useful approaches for investigating the extent to which an intervention’s effects depend on baseline features of the system, including aspects of the context. Sophisticated meta-regression models might investigate multiple baseline features, using similar approaches to the component-based meta-analyses described earlier. Specifically, aspects of context or population characteristics can be regarded as ‘components’ of the system into which the intervention is introduced, and similar statistical modeling strategies used to isolate effects of individual factors, or interactions between them.

When interventions act at multiple levels, it may be important to understand the effects at these different levels. Outcomes may be measured at different levels (eg, at patient, clinician and clinical practice levels) and analysed separately. Qualitative research plays a particularly important role in identifying the outcomes that should be assessed through quantitative synthesis. Care is needed to ensure that the unit of analysis issues are addressed. For example, if clinics are the unit of randomisation, then outcomes measured at the clinic level can be analysed using standard methods, whereas outcomes measured at the level of the patient within the clinic would need to account for clustering. In fact, multiple dependencies may arise in such data, when patients receive care in small groups. Detailed investigations of effect at different levels, including interactions between the levels, would lend themselves to multilevel (hierarchical) models for synthesis. Unfortunately, individual participant data at all levels of the hierarchy are needed for such analyses.

Model-based approaches also offer possibilities for addressing complex systems; these include economic models, mathematical models and systems science methods generally. Broadly speaking, these provide mathematical representations of logic models, and analyses may involve incorporation of empirical data (eg, from systematic reviews), computer simulation, direct computation or a mixture of these. Multiparameter evidence synthesis methods might be used. Approaches include models to represent systems (eg, systems dynamics models) and approaches that simulate individuals within the system (eg, agent-based models). Models can be particularly useful when empirical evidence does not address all important considerations, such as ‘real-world’ contexts, long-term effects, non-linear effects and complexities such as feedback loops and threshold effects. An example of a model-based approach to synthesis is provided in box 3. The challenge when adopting these approaches is often in the identification of system components, and accurately estimating causes and effects (and uncertainties). There are few examples of the use of these analytical tools in systematic approaches.

Figure 3  Theoretical diabetes care model (adapted from Brown et al).

Box 2  Example of a model-driven meta-analysis for type 2 diabetes

Brown et al present a model-driven meta-analysis of correlational research on psychological and motivational predictors of diabetes outcomes, with medication and dietary adherence factors as mediators. In a linked methodological paper, they present the a priori theoretical model on which their analysis is based. The model is simplified in figure 3, and summarised for the dietary adherence pathway only. The aim of their full analysis was to determine the predictive relationships among psychological factors and motivational factors on metabolic control and body mass index (BMI), and the role of behavioural factors as possible mediators of the associations among the psychological and motivational factors and metabolic control and BMI outcomes.

The analysis is based on a comprehensive systematic review. Due to the number of variables in their full model, 775 individual correlational or predictive studies reported across 739 research papers met eligibility criteria. Correlations between each pair of variables in the model were summarised using an overall average correlation, and homogeneity assessed. Multivariate analyses were used to estimate a combined correlation matrix. These results were used, in turn, to estimate path coefficients for the predictive model and their standard errors. For the simplified model illustrated here, the results suggested that coping and self-efficacy were strongly related to dietary adherence, which was strongly related to improved glycaemic control and, in turn, a reduction in diabetic complications.
It may be desirable to learn about a specific setting, intervention type or outcome measure more directly than others. For example, to inform a decision for a low-income setting, emphasis should be placed on results of studies performed in low-income countries. One option is to restrict the synthesis to these studies. An alternative is to model the dependence on an intervention’s effect on some feature(s) related to the income setting, and extract predictions from the model that are most relevant to the setting of interest. This latter approach makes fuller use of available data, but relies on stronger assumptions.

Often, however, the accumulated studies are too few or too disparate to draw conclusions about the impact of bias or relevance. On rare occasions, syntheses might implement formal adjustments of individual study results for likely biases. Such adjustments may be made by imposing prior distributions to depict the magnitude and direction of any biases believed to exist. The choice of a prior distribution may be informed by formal assessments of risk of bias, by expert judgement, or possibly by empirical data from meta-epidemiological studies of biases in randomised and/or non-randomised studies. For example, Wolf et al implemented a prior distribution based on findings of a meta-epidemiological study to adjust for lack of blinding in studies of interventions to improve quality of point-of-use water sources in low-income and middle-income settings. Unfortunately, empirical evidence of bias is mostly limited to clinical trials, is weak for trials of public health and social care interventions, and is largely non-existent for non-randomised studies.

CONCLUSION

Our review of quantitative synthesis methods for evaluating the effects of complex interventions has outlined many possible approaches that might be considered by those collating evidence in support of guideline development. We have described three broad categories: (1) Non-quantitative methods, including tabulation, narrative and graphical approaches. (2) Standard meta-analysis methods, including meta-regression to investigate study-level moderators of effect. (3) More advanced synthesis methods, in which models allow exploration of intervention components, investigation of both moderators and mediators, examination of mechanisms, and exploration of complexities of the system.

The choice among these approaches will depend on the purpose of the synthesis, the similarity of the studies included in the review, the level of detail available from the studies, the nature of the results reported in the studies, the expertise of the synthesis team, and the resources available. Clearly the advanced methods require more expertise and resources than the simpler methods. Furthermore, they require a greater level of detail and typically a sizeable evidence base. We therefore expect them to be used seldomly; our aim here is largely to articulate what they can achieve so that they
can be adopted when they are appropriate. Notably, the choice among these approaches will also depend on the extent to which guideline developers and users at global, national or local levels understand and are willing to base their decisions on different methods. Where possible, it will thus be important to involve concerned stakeholders during the early stages of the systematic review process to ensure the relevance of its findings.

Complexity is common in the evaluation of public health interventions at individual, organisational or community levels. To help systematic review and guideline development teams decide how to address this complexity in syntheses of quantitative evidence, we summarise considerations and methods in tables 1 and 2. We close with the important remark that quantitative synthesis is not always a desirable feature of a systematic review. Whereas some sophisticated methods are available to deal with a variety of complex problems, on many occasions—perhaps even the majority in practice—the studies may be too different from each other, too weak in design or have data too sparse, for statistical methods to provide insight beyond a commentary on what evidence has been identified.

Author affiliations

1Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
2Department of Educational Psychology and Learning Systems, College of Education, Florida State University, Tallahassee, Florida, USA
3Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada
4Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada
5NIHR Collaboration for Leadership in Applied Health Care (CLAHRC) West, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
6Institute for Medical Information Processing, Biometry and Epidemiology, Pettenkofer School of Public Health, LMU Munich, Munich, Germany
7EPPi-Centre, Department of Social Science, University College London, London, UK

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Contributors

JPTH co-led the project, conceived the paper, led discussions and wrote the first draft. JAL-L undertook analyses, contributed to discussions and contributed to writing the manuscript. BJF drafted material on mechanisms, contributed to discussions and contributed extensively to writing the manuscript. SRD screened and categorised the results of the literature searches, collated examples and contributed to discussions. SD undertook searches to identify relevant literature and contributed to discussions. JMG contributed to discussions and commented critically on drafts. LAM undertook analyses, contributed to discussions and commented critically on drafts. THMM contributed examples, contributed to discussions and commented critically on drafts. EAR and JT contributed to discussions and commented critically on drafts. DMC co-led the project, contributed to discussions and drafted extensive parts of the paper. All authors approved the final version of the manuscript.

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