

**STRATEGIES TO ADDRESS OVERLAP OF PRIMARY STUDIE
IN OVERVIEWS OF SYSTEMATIC REVIEWS**

Javier Andrés Bracchiglione Pérez

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PhD programme in Biomedical Research Methodology and Public Health

Doctoral Thesis

STRATEGIES TO ADDRESS OVERLAP OF PRIMARY STUDIES IN OVERVIEWS OF SYSTEMATIC REVIEWS

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“El conocimiento del conocimiento obliga. Nos obliga a tomar una actitud de permanente vigilia contra la tentación de la certeza, a reconocer que nuestras certidumbres no son pruebas de verdad, como si el mundo que cada uno ve fuese el mundo y no un mundo que traemos a la mano con nosotros. Nos obliga porque, al saber que sabemos, no podemos negar lo que sabemos.”

El árbol del conocimiento

Humberto Maturana y Francisco Varela

“RESPUESTA DEL ORÁCULO

Hagas lo que hagas te arrepentirás”

Artefactos

Nicanor Parra

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I will take the liberty of writing this section in Spanish, my native tongue.

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Brief personal presentation

I am Javier Andrés Bracchiglione Pérez, a physician from Universidad de Valparaíso, Chile, with a professional path that has gradually evolved from clinical practice to research methodology. My early years were devoted to primary care and family medicine, which was my main job between 2012 and 2018. During that period, I developed a deep appreciation for the complexities of healthcare decision-making and the importance of sound evidence to guide practice. This motivation led me to pursue postgraduate diplomas in *Family Medicine and Primary Care* and *Evidence-Based Medicine* at the Pontifical Catholic University of Chile.

Seeking to strengthen my methodological and analytical skills, I completed a Master of Science in *Clinical Research applied to Health Sciences* at the Autonomous University of Barcelona (UAB), and later a Master's degree in *Biostatistics applied to Health Sciences* at the University of Seville. These experiences consolidated my interest in research methodology and provided the foundations for my current doctoral training in *Biomedical Research Methodology and Public Health*.

My PhD focuses on methodological research applied to evidence synthesis, specifically on developing and assessing methods to evaluate overlap of primary studies among systematic reviews included in overviews. This work has strengthened my commitment to improving transparency, efficiency, and reproducibility in health research.

Throughout these years, I have participated in several projects related to evidence synthesis and guideline development, including collaborations with the World Health Organization (WHO), the European Academy of Allergy and Clinical Immunology (EAACI), the Joint Research Centre of the European Commission (JRC), and international groups such as the Cochrane collaboration, the GRADE working group and the redundancy in systematic reviews initiative. I also take part in academic projects on diverse topics such as environmental health, infertility,

methodological research, and appropriateness of cancer treatments, among others.

Beyond research, I remain closely connected to teaching. Since 2016, I have been a faculty member at Universidad de Valparaíso, where I have chaired the Evidence-Based Medicine and Research Methodology courses. From 2024, I have also joined the teaching staff at UAB.

Originally from Valparaíso, Chile, I continue to value creativity, humour, and social connection in both my personal and professional life. Writing, exchanging ideas, engaging in critical thinking, and spending time with friends and family keep me grounded and inspired. Looking ahead, I hope to pursue a creative academic or research career—leading teams and fostering innovative ideas that contribute to the advancement of evidence-based health care.

Abbreviations

CA	Covered area
CCA	Corrected covered area
GROOVE	Graphical Representation of Overlap for OVERviews
PRIOR	Preferred Reporting Items for Overviews of Reviews
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses

Table of contents

Abstract (English).....	10
Resumen (Español).....	14
Resum (Català).....	18
Introduction.....	22
Research in health sciences.....	22
Systematic reviews and evidence synthesis.....	23
The evidence ecosystem.....	25
Current problems with evidence syntheses.....	28
The need for a broader type of evidence synthesis.....	29
Differences between systematic reviews and overviews.....	30
Particular methodological challenges for overview development.....	31
Definition and importance of overlap of primary studies.....	32
Strategies used to address overlap in overviews.....	34
Methods to describe overlap of primary studies.....	35
Problems with methods to describe overlap.....	41
Objectives.....	45
General objective.....	45
Specific objectives.....	45
Methods.....	46
Study 1: Development of a new tool and approach to describe overlap.....	46
Study 2: Assessment of methods to deal with overlap and to describe overlap using the overall and pairwise CCA approach.....	47
Study 3: Impact of different assumptions for creating matrices of evidence in overlap assessments.....	48
Results.....	50
Article 1: “Graphical Representation of Overlap for OVERviews: GROOVE tool”.....	51
Article 2: “A methodological review finds mismatch between overall and pairwise overlap analysis in a sample of overviews”.....	62
Article 3: “Impact of matrix-construction assumptions on quantitative overlap assessment in overviews: A meta-research study”.....	74
Discussion.....	94
Advancing overlap assessment in overviews.....	94
Integration with previous research.....	95
Overall contributions and implications.....	100
Limitations and strengths.....	101
Future developments.....	103
Rethinking the role of overviews.....	104
Conclusion.....	108
Glossary.....	109
Appendices.....	113
Appendix 1. Accompanying manuscripts for this doctoral thesis.....	113

Appendix 2. Proposal to the Cochrane Collaboration: Pairwise CCA approach for assessing overlap of primary studies in overviews.....	122
Appendix 3. Dissemination of findings related to this thesis.....	127
Appendix 4. List of published articles by the author during the PhD period.....	129
References.....	134

Abstract (English)

Introduction

Systematic reviews play a central role in evidence-informed decision-making. However, their growing number has resulted in redundancy and even discordance. Overviews, defined as systematic reviews of systematic reviews, have emerged as a methodological design to address broader questions than individual systematic reviews, encompassing comparisons across different interventions, populations, outcomes, as well as exploring potential inconsistencies. Yet, overviews face specific methodological challenges, among which the overlap of primary studies is critical. Overlap, defined as the inclusion of the same primary studies across different reviews, can distort findings and misrepresent precision of results if not adequately addressed. Therefore, a crucial first step is to describe overlap. Existing methods include visualisations, which become impractical with large volumes of evidence, and quantitative approaches such as the corrected covered area (CCA), a quantitative metric derived from a matrix of evidence, describing overlap as a percentage. However, overall CCA—a single value for an entire matrix—may mask important patterns of overlap. Besides, there is little guidance on constructing matrices of evidence to underpin its interpretation.

Objectives

This thesis aims to assess existing methodologies to address overlap in overviews and to develop methods for improving the quality and efficiency of their conduct. Specific objectives are:

- To develop a tool and approach for assessing overlap through pairwise CCA analysis.
- To assess methods used in overviews to deal with overlap and to quantify primary study overlap using the CCA formula.

- To describe the impact of different assumptions in matrix construction on overlap estimates.

Methods

This doctoral thesis is presented as a compendium of publications and comprises three studies. First, we developed GROOVE ('Graphical Representation of Overlap for Overviews'), an Excel-based tool to automate overlap assessment. GROOVE provides both overall and pairwise CCA, the latter introduced in this thesis as a complementary metric to capture overlap between specific pairs of reviews. It also outputs adjusted values accounting for structural missingness—impossible intersections within evidence matrices, such as a primary study published after a review—and provides graphical visualisations of the pairwise assessments.

Building on the development of GROOVE, the second study empirically explores the theoretical issue highlighted in the first study: that pairwise overlap assessment may reveal patterns not captured by overall overlap. We conducted a methodological review of 30 intervention-focused overviews published in 2018. We described how overlap was addressed in practice and reanalysed each overview using both overall and pairwise CCA.

Drawing from the first two studies, the third study examines how methodological decisions in constructing evidence matrices affect the calculation of overall and pairwise CCA. This methodological review explicitly defines concepts and assumptions related to matrix construction, including unit of analysis, scope adjustments, publication-thread adjustments, and structural missingness. Using a sample of seven overviews, we tested 16 different scenarios combining these assumptions and compared their impact on overlap estimates.

Results

The studies were published as three independent articles in high-impact indexed journals, each addressing a specific objective of this thesis.

The first article introduced GROOVE, which automated calculations previously done manually, provided visual outputs, and introduced pairwise CCA as a new approach for capturing overlap patterns hidden by overall estimates. Structural missingness was formalised and incorporated into CCA calculation.

The second article empirically showed that overlap was most often ignored or only visually described. Pairwise analysis revealed important discrepancies hidden by overall CCA: some overviews with low overall overlap included a significant proportion of highly overlapping review pairs, while others with high overall overlap contained pairs with little or no overlap.

In the third article, the scenario analysis showed that methodological assumptions may substantially influence overlap estimates. Differences reached up to 13.5% for overall CCA and 15.7% for pairwise CCA, with level of analysis, scope, and structural missingness being the largest contributors. Publication-thread adjustments had little effect.

Discussion

This thesis advances the methodological basis for overviews by deepening the description of overlap. It introduces pairwise CCA, develops GROOVE to automate and visualise assessment, and provides explicit definitions and empirical evidence on how methodological assumptions shape estimates. These contributions highlight the need to move beyond a single overall metric, promote transparency in matrix construction, and standardise reporting.

The thesis does not prescribe thresholds for interpreting overlap as high or low, nor does it dictate methodological decisions once overlap is described. Instead, it provides the definitions, tools, and empirical foundation for future methodological and meta-epidemiological work. Ultimately, overlap should be seen not only as a technical issue but as a defining characteristic of overviews, shaping their role in the evidence synthesis landscape.

Conclusion

This thesis critically evaluated and advanced methodologies to address overlap of primary studies in overviews of systematic reviews. By examining current practices, developing new tools, and clarifying methodological assumptions, it provides a stronger foundation for assessing and interpreting overlap. The contributions of this thesis underscore the importance of routine and detailed overlap assessment, strengthening the role of overviews in selecting the most appropriate reviews for each context and in distinguishing valid replication from research waste.

Resumen (Español)

Introducción

Las revisiones sistemáticas desempeñan un papel central en la toma de decisiones basadas en evidencia. Sin embargo, su número creciente ha generado redundancia e incluso discordancia. Los *overviews* (muchas veces llamados revisiones panorámicas en español), definidos como revisiones sistemáticas de revisiones sistemáticas, han surgido como un diseño metodológico para abordar preguntas más amplias que las de revisiones sistemáticas individuales, incluyendo comparaciones entre diferentes intervenciones, poblaciones y desenlaces, así como la exploración de posibles inconsistencias. No obstante, los *overviews* enfrentan desafíos metodológicos únicos, entre los cuales uno de los más importantes es el solapamiento de estudios primarios. El solapamiento, definido como la inclusión de los mismos estudios primarios en diferentes revisiones, puede sesgar los hallazgos y tergiversar la precisión de los resultados si no se maneja adecuadamente. Por tanto, es crucial que el primer paso sea describir el solapamiento. Entre los métodos existentes están las visualizaciones del solapamiento (que resultan poco prácticas ante grandes volúmenes de evidencia), y los enfoques cuantitativos como el área cubierta corregida (ACC), una métrica derivada de una matriz de evidencia que describe el solapamiento como un porcentaje. Sin embargo, el ACC general —un único valor para toda la matriz— podría ocultar patrones relevantes de solapamiento. Además, existe escasa orientación sobre cómo construir matrices de evidencia que sustenten su interpretación.

Objetivos

Esta tesis tiene como objetivo evaluar las metodologías existentes para abordar el solapamiento en *overviews* y desarrollar métodos para mejorar la calidad y eficiencia en su realización. Los objetivos específicos son:

- Desarrollar una herramienta y un enfoque para evaluar el solapamiento mediante el análisis de ACC por pares de revisiones.
- Evaluar los métodos utilizados en *overviews* para manejar el solapamiento, y cuantificar el solapamiento de estudios primarios utilizando la fórmula del ACC.
- Describir el impacto de distintos supuestos en la construcción de matrices sobre los estimadores de solapamiento.

Métodos

Esta tesis doctoral se presenta como compendio de publicaciones e incluye tres estudios.

En primer lugar, desarrollamos GROOVE (*“Graphical Representation of Overlap for Overviews”*), una herramienta basada en Excel para automatizar la evaluación del solapamiento. GROOVE calcula tanto el ACC general como por pares de revisiones, como una métrica complementaria introducida en esta tesis. Además, permite obtener valores ajustados que consideran las pérdidas estructurales —intersecciones imposibles dentro de las matrices de evidencia, como el caso de un estudio primario publicado después de una revisión—, y proporciona visualizaciones gráficas del solapamiento por pares de revisiones.

A partir del desarrollo de GROOVE, el segundo estudio explora empíricamente el problema teórico descrito en el primer estudio: que el solapamiento por pares de revisiones podría revelar patrones no captados por el solapamiento general. Realizamos una revisión metodológica de 30 *overviews* enfocados en preguntas de intervención, publicados en 2018. Describimos cómo se abordó el solapamiento en la práctica y re-analizamos cada revisión utilizando tanto el ACC general como el ACC por pares de revisiones.

Basado en los primeros dos estudios, el tercer estudio examina cómo las decisiones metodológicas realizadas para construir matrices de evidencia pueden

afectar el cálculo del ACC general y por pares de revisiones. Esta revisión metodológica define de manera explícita conceptos y supuestos relacionados a la construcción de matrices (incluyendo unidad de análisis, ajustes de alcance, ajustes por hilos de publicación y pérdidas estructurales). En una muestra de siete *overviews*, testearon 16 escenarios diferentes que combinaban estos supuestos, y compararon su impacto en las estimaciones de solapamiento.

Resultados

Los estudios se publicaron como artículos independientes en revistas indizadas de alto impacto, cada uno abordando un objetivo específico de la tesis.

El primer artículo introdujo GROOVE, una herramienta que logró automatizar cálculos que antes se realizaban manualmente, proporcionando salidas visuales e introduciendo el ACC por pares como un nuevo abordaje para identificar patrones de solapamiento ocultos por los estimadores generales. Además, introdujo formalmente el concepto de pérdida estructural, incorporándolo en el cálculo del ACC.

El segundo artículo mostró empíricamente que el solapamiento era usualmente ignorado o solo descrito de manera visual. El análisis por pares reveló discrepancias importantes respecto al ACC general: Algunos *overviews* con bajo solapamiento general incluían una proporción importante de pares de revisiones con alto solapamiento, mientras que otros con alto solapamiento general contenían pares con poco o ningún solapamiento.

En el tercer estudio, el análisis de escenarios evidenció que los supuestos metodológicos pueden influir de manera sustancial en las estimaciones de solapamiento. Las diferencias alcanzaron hasta 13,5% para el ACC general y 15,7% para el ACC por pares, siendo altamente influenciadas por el nivel de análisis, el alcance y las pérdidas estructurales. Los ajustes por hilos de publicación tuvieron un impacto mínimo.

Discusión

Esta tesis contribuye al desarrollo metodológico de los *overviews* al profundizar en la descripción del solapamiento. Esta tesis introduce el ACC por pares, desarrolla GROOVE como herramienta para automatizar y visualizar la evaluación de solapamiento, y proporciona definiciones explícitas y evidencia empírica sobre cómo los supuestos metodológicos influyen en las estimaciones de solapamiento. Estas contribuciones resaltan la necesidad de superar el uso de un único indicador global, promover la transparencia en la construcción de matrices y estandarizar los reportes.

La tesis no define umbrales para interpretar el solapamiento como alto o bajo, ni dicta decisiones metodológicas una vez descrito el solapamiento. En cambio, ofrece las definiciones, herramientas y fundamentos empíricos para futuros estudios metodológicos y meta-epidemiológicos. En última instancia, el solapamiento debe entenderse no solo como un aspecto técnico, sino como una característica definitoria de los *overviews*, que determina de forma importante su papel dentro del ámbito de las síntesis de la evidencia.

Conclusión

Esta tesis evaluó críticamente y avanzó las metodologías para abordar el solapamiento de estudios primarios en *overviews* de revisiones sistemáticas. Al examinar las prácticas actuales, desarrollar nuevas herramientas y aclarar los supuestos metodológicos, proporciona una base más sólida para evaluar e interpretar el solapamiento. Las contribuciones de esta tesis subrayan la importancia de una evaluación rutinaria y detallada del solapamiento, reforzando el rol de los *overviews* para seleccionar las revisiones más adecuadas para cada contexto y para distinguir entre replicación válida e investigación redundante.

Resum (Català)

Introducció

Les revisions sistemàtiques juguen un paper central en la presa de decisions basades en l'evidència. No obstant això, el seu nombre creixent ha generat redundància i fins i tot discordança. Els *overviews* (sovint anomenats revisions panoràmiques en català), definits com a revisions sistemàtiques de revisions sistemàtiques, han sorgit com un disseny metodològic per abordar preguntes més àmplies que les de les revisions sistemàtiques individuals, incloent-hi comparacions entre diferents intervencions, poblacions i resultats, així com l'exploració de possibles inconsistències. Tanmateix, els *overviews* afronten reptes metodològics únics, entre els quals un dels més importants és la superposició d'estudis primaris. La superposició, definit com la inclusió dels mateixos estudis primaris en diferents revisions, pot esbiaixar els resultats i tergiversar la precisió de les estimacions si no es gestiona adequadament. Per tant, és crucial que el primer pas sigui descriure la superposició. Entre els mètodes existents hi ha les visualitzacions de la superposició (que resulten poc pràctiques davant grans volums d'evidència), i els enfocaments quantitius com l'àrea coberta corregida (ACC), una mètrica derivada d'una matriu d'evidència que descriu la superposició en forma de percentatge. No obstant això, l'ACC general —un únic valor per a tota la matriu— podria amagar patrons rellevants de superposició. A més, hi ha poca orientació sobre com construir matrius d'evidència que en sustentin la interpretació.

Objectius

Aquesta tesi té com a objectiu avaluar les metodologies existents per abordar la superposició en *overviews* i desenvolupar mètodes per millorar la qualitat i l'eficiència en la seva realització. Els objectius específics són:

- Desenvolupar una eina i un enfocament per avaluar la superposició mitjançant l'anàlisi d'ACC per parelles de revisions.

- Avaluar els mètodes utilitzats en els overviews per gestionar la superposició i quantificar la superposició d'estudis primaris utilitzant la fórmula de l'ACC.
- Descriure l'impacte de diferents supòsits en la construcció de matrius sobre les estimacions de superposició.

Mètodes

Aquesta tesi doctoral es presenta com un compendi de publicacions i inclou tres estudis. En primer lloc, vam desenvolupar GROOVE (*“Graphical Representation of Overlap for Overviews”*), una eina basada en Excel per automatitzar l'avaluació de la superposició. GROOVE calcula tant l'ACC general com l'ACC per parelles de revisions, com a mètrica complementària introduïda en aquesta tesi. A més, permet obtenir valors ajustats que consideren les pèrdues estructurals —interseccions impossibles dins de les matrius d'evidència, com el cas d'un estudi primari publicat després d'una revisió—, i proporciona visualitzacions gràfiques de la superposició per parelles de revisions.

Basant-se en el desenvolupament de GROOVE, el segon estudi explora empíricament la qüestió teòrica destacada en el primer estudi: que la superposició parell a parell pot revelar patrons que no es capturen amb la superposició general. Vam dur a terme una revisió metodològica de 30 overviews enfocats en preguntes d'intervenció, publicats el 2018. Vam descriure com es va abordar la superposició en la pràctica i vam reanalitzar cada revisió utilitzant tant l'ACC general com l'ACC per parelles de revisions.

A partir dels dos primers estudis, el tercer estudi analitza com les decisions metodològiques en la construcció de matrius d'evidència afecten el càlcul del CCA general i parell a parell. Aquesta revisió metodològica defineix explícitament els conceptes i les suposicions relacionats amb la construcció de les matrius (incloent-hi unitat d'anàlisi, ajustos d'abast, ajustos per fils de publicació i pèrdues estructurals). En una mostra de set overviews, vam provar 16 escenaris diferents

que combinaven aquests supòsits, i en vam comparar l'impacte sobre les estimacions de superposició.

Resultats

Els estudis es van publicar com a tres articles independents en revistes indexades d'alt impacte, cadascun abordant un objectiu específic d'aquesta tesi.

El primer article va introduir GROOVE, una eina que va aconseguir automatitzar càlculs que abans es feien manualment, proporcionant sortides visuals i introduint l'ACC per parelles com un nou enfocament per identificar patrons de solapament ocults pels estimadors generals. A més, va introduir formalment el concepte de pèrdua estructural, incorporant-lo en el càlcul de l'ACC.

El segon article va mostrar empíricament que la superposició era habitualment ignorat o només descrit de manera visual. L'anàlisi per parelles va revelar discrepàncies importants respecte a l'ACC general: alguns overviews amb baixa superposició general inclouen una proporció important de parelles de revisions amb alta superposició, mentre que d'altres amb alta superposició general contenen parelles amb poc o gens de superposició.

En el tercer article, l'anàlisi d'escenaris va evidenciar que els supòsits metodològics poden influir de manera substancial en les estimacions de superposició. Les diferències van arribar fins al 13,5% per a l'ACC general i al 15,7% per a l'ACC per parelles, sent altament influenciades pel nivell d'anàlisi, l'abast i les pèrdues estructurals. Els ajustos per fils de publicació van tenir un impacte mínim.

Discussió

Aquesta tesi contribueix al desenvolupament metodològic dels overviews aprofundint en la descripció de la superposició. Aquesta tesi introdueix l'ACC per parelles, desenvolupa GROOVE com a eina per automatitzar i visualitzar l'avaluació de la superposició, i proporciona definicions explícites i evidència

empírica sobre com els supòsits metodològics influeixen en les estimacions de superposició. Aquestes contribucions ressalten la necessitat de superar l'ús d'un únic indicador global, promoure la transparència en la construcció de matrius i estandarditzar els informes.

La tesi no defineix llindars per interpretar la superposició com a alt o baix, ni dicta decisions metodològiques un cop descrita la superposició. En canvi, ofereix les definicions, les eines i els fonaments empírics per a futurs estudis metodològics i meta-epidemiològics. En darrera instància, la superposició s'ha d'entendre no només com un aspecte tècnic, sinó com una característica definidora dels overviews, que determina de manera important el seu paper dins de l'àmbit de les síntesis de l'evidència

Conclusió

Aquesta tesi va avaluar críticament i va avançar les metodologies per abordar la superposició d'estudis primaris en els overviews de revisions sistemàtiques. En examinar les pràctiques actuals, desenvolupar noves eines i aclarir els supòsits metodològics, proporciona una base més sòlida per avaluar i interpretar la superposició. Les contribucions d'aquesta tesi subratllen la importància d'una avaluació rutinària i detallada de la superposició, enfortint el paper dels overviews en la selecció de les revisions més adequades per a cada context i en la distinció entre una replicació vàlida i el malbaratament de recerca.

Introduction

Research in health sciences

Health research, understood as any systematic inquiry that aims to improve human health, constitutes the basis of scientific knowledge to inform policy, practice and individual decision-making related to human wellbeing [1]. Depending on its level and object of analysis it can be classified as biomedical research—which studies the conditions, processes, and mechanisms of health and illness mainly at the sub-individual level—, clinical research—focused mainly in the study of preventive, diagnostic and therapeutic effects of interventions or exposures related to individuals' health needs—, and public health research—which studies these phenomena at a population rather than an individual or sub-individual level—, encompassing both epidemiological research (frequency, distribution, and determinants of health needs) and health systems research (the scientific study of the organised social response to health and disease conditions in populations) [2].

The process of generating scientific health knowledge begins with the conduction of primary research, which is understood as the research that assesses the phenomenon of interest directly in the object of analysis (at a sub-individual, individual or population level) [3,4]. Despite being the basis of scientific knowledge, translating primary research directly into health decision-making processes poses several barriers. First, primary research is usually conducted in a limited sample of a specific population, which limits its applicability to different contexts. Second, a specific primary study is prone to both systematic and random error, which can distort the estimates from the theoretical true parameter [5]. Third, it is frequent for different primary studies assessing the same phenomenon to report discordant results or conclusions. It is also possible for a reader not to find all relevant primary studies related to a particular question and, therefore, to be omitting important information for decision-making. Lastly, the continuous growth of primary research has made it nearly impossible—in almost any research field—to keep up with the volume of studies being conducted [6–16]. In the

second half of the 20th century, these problems were detected and, as Sir Archie Cochrane said in the late 1970's, "*It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials*" [17]. These problems constituted the main reasons why systematic reviews were born [18].

Systematic reviews and evidence synthesis

Systematic reviews constitute a methodology for evidence synthesis that aims to answer a research question by identifying, selecting, assessing and summarising all the relevant available primary studies, using explicit, transparent, reproducible and pre-specified methods [19–22]. By definition, a review that uses systematic methods should report its research question, the search sources, the eligibility criteria, methods for selection of the studies, critical appraisal of the included studies, and information about data analysis and synthesis [23]. As a whole, some authors consider evidence synthesis as secondary research, which aims to also generate scientific knowledge but, in contrast to primary research, by collating, assessing and analysing other research as the unit of analysis, and not directly the subjects experiencing the phenomenon of interest [24].

Although initially the scope of systematic reviews was centred in assessing the effects of interventions, the methods quickly evolved to encompass questions regarding diagnosis, prognosis, aetiology, prevalence, incidence, harms, costs, cost-effectiveness, patients' perspectives, among other topics, relying in quantitative or qualitative methods, or both [19,25].

Besides the expansion of their scope, systematic review methods have been constantly developing over time. 'Classical' systematic reviews (that is, systematic reviews that conducted head-to-head comparisons to answer a specific question) are still considered the main methodology for evidence synthesis, and their core methodological principles have been the basis for the development of other specific review designs that have provided useful insights to address other types of questions.

Although currently there is no clear consensus about the specific types of existing reviews [26], some of the most popular review methodologies that use systematic methods include:

- Scoping reviews: An exploratory type of systematic evidence synthesis, aiming to investigate the breadth of the available evidence regarding a specific phenomenon, clarifying its main concepts or characteristics [24,27].
- Mapping reviews: A deductive, aggregative type of evidence synthesis, aiming to describe and categorise the available research in order to clarify what is known or what research exists in a particular topic [24].
- Evidence gap maps: Similar to a mapping review, evidence gap maps use a pre-specified framework as a visual representation of the evidence, in order to identify existing gaps in knowledge [24].
- Qualitative evidence synthesis: A systematic evidence synthesis that uses qualitative methods to collect and analyse data. It can be considered as an umbrella term for several specific type of reviews, depending on their underlying methodology (including phenomenology, ethnography, grounded theory, action research, feminist research, discourse analysis, among others) [25,28]
- Network meta-analysis: A subtype of systematic reviews that, besides direct (head-to-head or pairwise) comparisons, assesses indirect comparisons for three or more interventions being studied through specific statistical methods. Indirect comparisons are conducted using common comparators between two interventions not directly compared within a trial [29–32]

Beyond the standard methods, all these types of reviews may be conducted in either a ‘rapid’ mode—which accelerates the review process by simplifying or omitting selected methodological steps [33–36]— or a ‘living’ mode, in which

evidence is regularly identified and incorporated into the evidence synthesis [36–38].

The evidence ecosystem

Despite several methods available, the generation of primary research, evidence synthesis (including systematic reviews and all the above-mentioned specific types of reviews), and decision-making processes (such as clinical guidelines) is often misaligned and operate in isolation from one another [39,40]. The conceptual frameworks proposed to solve this problem are known as evidence ecosystems [41,42].

Evidence ecosystems aim to improve health care and evidence-informed decision-making by integrating and coordinating the processes of evidence generation, synthesis, and translation [41,43]. The concept of ‘ecosystem’ implies the existence of living organisms (such as professionals, managers, researchers, patients, citizens, payers, politicians, etc), an environment (organisational, sociocultural, economic, political), and nonliving components, such as the evidence itself, standards, methods and frameworks [43–45].

Figure 1 shows the model of evidence ecosystem proposed by the MAGIC (‘Making Grade the Irresistible Choice’) project. This framework puts at the centre the concepts of orchestration, governance and support, which are crucial components that enhance the flow of data from the evidence production to their synthesis, creation of guidance, dissemination to different actors, implementation, evaluation and, finally, again to the evidence production, interpreting the ecosystem as a self-perpetuating cycle [41]. Figure 2 shows the model proposed by Schünemann et al [46], which focuses more on the role of different actors within the ecosystem, and the diversity of criteria needed to be considered to make the best possible evidence-informed decisions, but still following the logic of evidence production, evidence synthesis and decision-making process.

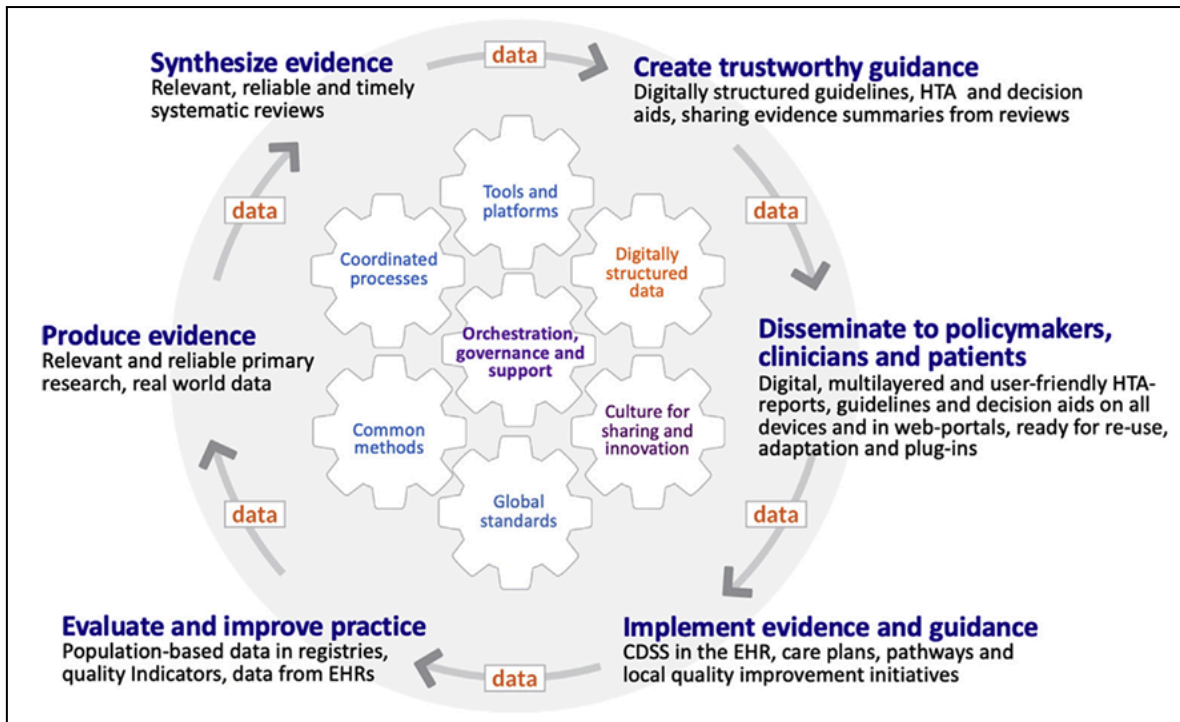


Figure 1. Evidence ecosystem conceptual framework, as proposed by the MAGIC project [41]. CDSS: clinical decision support systems. EHR: electronic health record. HTA: health technology assessment.

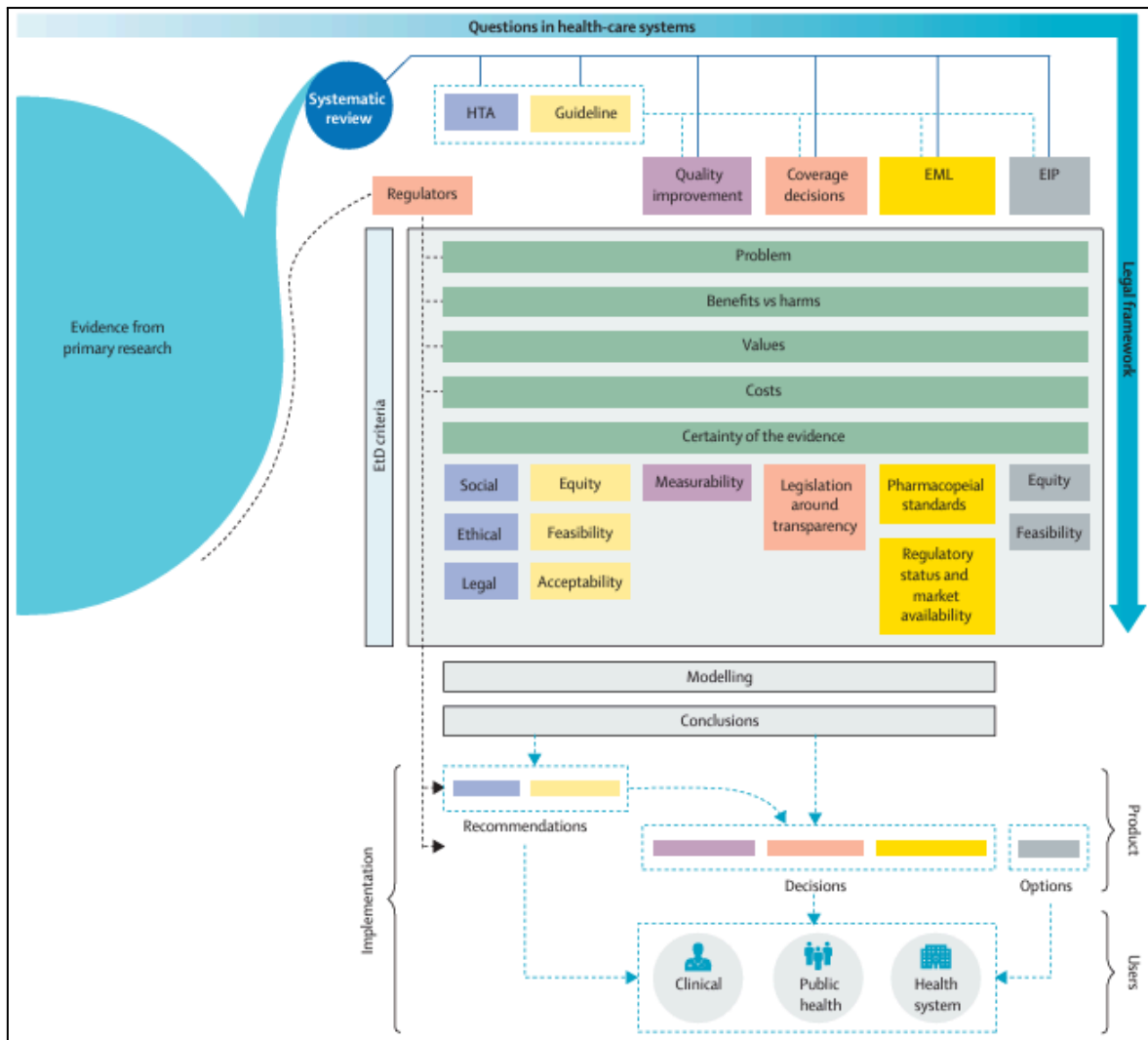


Figure 2. Evidence ecosystem conceptual framework, as proposed by Schünemann et al [46]. EML: essential medicines list. EIP: evidence-informed policy making. EtD: evidence-to-decision. HTA: health technology assessment.

Evidence ecosystem conceptual frameworks —such as the ones shown and others [47–50]— assign a key role to evidence synthesis, especially systematic reviews. In these models, systematic reviews represent a crucial step to move from primary evidence to decision-making, with new methodologies and softwares to enhance their conduction constantly developing [42,51].

Current problems with evidence syntheses

However, the idea of evidence ecosystems is not globally implemented, and evidence syntheses have increasingly been subject to similar problems of those previously described for primary research.

The first problem is the vast quantity of systematic reviews currently available [6,52]. Some authors have estimated that 80 systematic reviews are being published every day, which represents a 20-fold increase in the last 20 years [53]. As shown in figure 3, the Epistemonikos foundation estimates an important yearly increase in the amount of systematic reviews, with more than 115,000 systematic reviews published in 2025, and no signs of decline in this trend [52].

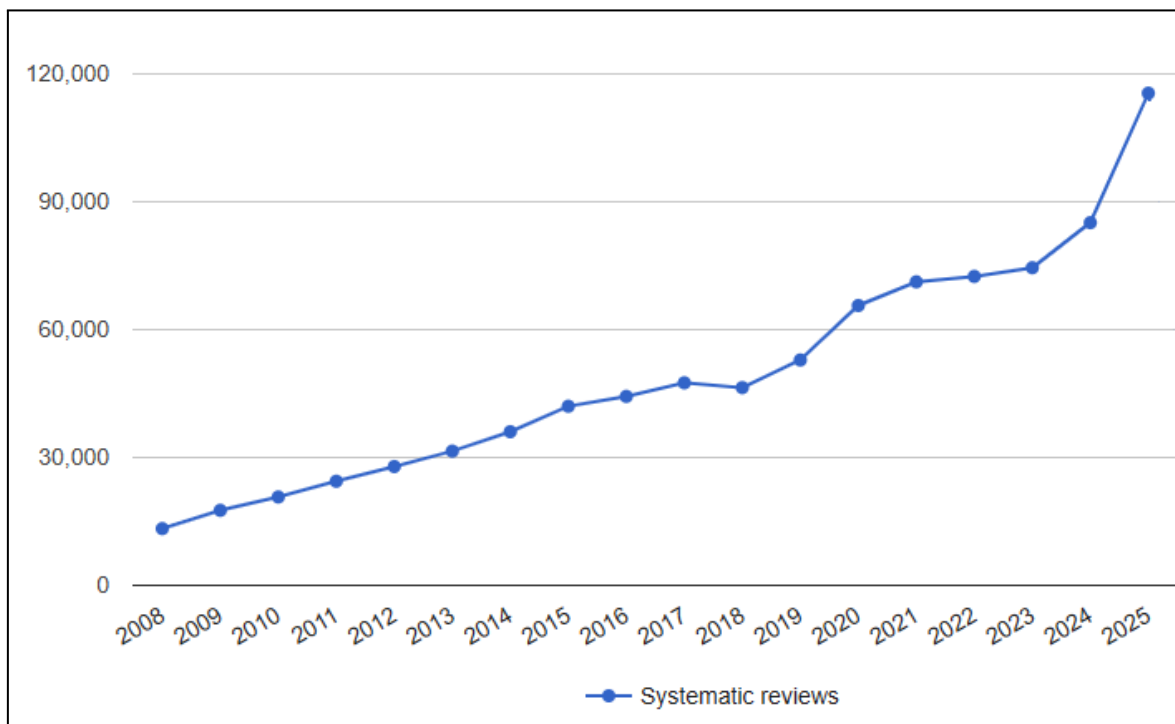


Figure 3. Trends in systematic review production by year, according to the Epistemonikos database [consulted on November 14, 2025] [52].

Second, several systematic reviews being published are redundant [54,55]. Although replication is an important process in science, the concept of redundancy relates to the unnecessary or low-quality replication, especially when addressing a non-priority question, with no resolution of possible controversies or uncertainties,

no clear impact on the population or future research, and with no consideration of opportunity costs. Redundancy is currently an important problem in evidence synthesis, since it represents an important source of waste in research [56–63].

In third place, systematic reviews are prone to problems affecting their reliability or validity. These problems can be related to the comprehensiveness, rigourness, transparency or objectivity in the conduction of the review. Some of these problems may be comparable to those potentially affecting primary research (such as high risk of bias, low reporting quality, or errors in data analysis), but others are specific to evidence syntheses (such as language restriction among the eligibility criteria, risk of publication bias, or inadequate search strategies) [64].

Lastly—and influenced by all the above-mentioned reasons—, it is frequent for systematic review assessing the same question to report inconsistent or even discrepant results [65–72]. In an attempt to solve this, Jadad et al proposed a decision tool to select one systematic review among multiple discordant ones [73], but this approach has shown not to be successfully reproducible [74]. To this date, no consensus guidance has been developed about how to approach scenarios where multiple, discordant systematic reviews are available, although most clinicians and methodologists prefer relying on the highest quality systematic review (excluding redundant reviews) [75].

The need for a broader type of evidence synthesis

Since the previously mentioned problems with evidence syntheses have become progressively more frequent, researchers, clinicians and decision-makers started to discuss the necessity for a broader type of synthesis that could identify, summarise and analyse all relevant systematic reviews within a topic. This newer type of research has been called ‘overviews’ [32,76].

Overviews (also known as umbrella reviews, overview of reviews, overview of systematic reviews, review of reviews, review of systematic reviews, meta-reviews, among others) can be defined, in its simplest form, as a systematic review of systematic reviews [25,32,76–80]. As such, overviews are a type of

evidence synthesis based on the same systematic principles as systematic reviews (i.e. explicit methods for formulating and reporting the research question, search sources, eligibility criteria, selection of the studies, critical appraisal, and data analysis and synthesis), but considering systematic reviews (and not primary studies) as their main unit of inclusion and analysis [25,32].

Overviews attempt to answer broad questions by compiling and collating the evidence from multiple systematic reviews, providing an efficient and many times user-friendly product of evidence synthesis [81]. Overviews can help decision-makers, clinicians, researchers, politicians, patients and other relevant interest-holders to approach the quantity of research and overall findings of the body of evidence synthesis available for a specific or multiple phenomena, by adopting a broad scope [32,70,80,82].

Differences between systematic reviews and overviews

Although both systematic reviews and overviews are a systematic research design of evidence synthesis, their differences derive mainly from two key characteristics: their scope and their unit of analysis [80].

Overviews' research questions usually have a broader scope than those of particular systematic reviews, although sometimes it may be difficult for authors to decide whether a question would be better answered by an overview or by a systematic review [32,83]. For questions of interventions, the Cochrane Collaboration has proposed that an overview may be appropriate if there are at least two potentially eligible systematic reviews available, and the research question addresses: i) different interventions (or modes of delivery of the interventions) for the same population; ii) the same intervention for different populations; iii) adverse events of interventions across different conditions or populations; or iv) different outcomes (or time points) across systematic reviews, for the same interventions and populations [32]. Other authors have also highlighted the role of overviews in mapping the existing systematic reviews and examining possible discordancies [82,84,85]. Altogether, the underlying concept

still holds: Overviews are meant to address broader questions than systematic reviews.

The second key difference between systematic reviews and overviews is their unit of analysis. While systematic reviews identify, include and analyse primary studies, an overview identifies, includes and analyses systematic reviews [32,86,87]. This difference adds an additional layer of complexity in the conduct of overviews, that demands the development of new methodologies.

Particular methodological challenges for overview development

The development of overviews has required the refinement of generic systematic methods for evidence synthesis, tailored for this specific study design. Among these, some authors have methodologically addressed strategies to improve efficiency in the identification of relevant systematic reviews [88–90], and others have developed critical appraisal tools to assess systematic reviews [91,92]. In terms of reporting, a specific guideline for overviews called PRIOR ('Preferred Reporting Items for Overviews of Reviews') has been developed, largely based on the principles previously stated by PRISMA ('Preferred Reporting Items for Systematic reviews and Meta-Analyses') for systematic reviews [22,77]. Although all these advancements are critical for an optimal development of overview methods, it is also true that the nature of overviews —the analysis of already synthesised evidence— also brings a plethora of particular methodological challenges, among which three should be highlighted: risk of bias assessment, certainty of evidence assessment, and overlap of primary studies [93,94].

Risk of bias assessment is a critical step in most evidence syntheses, since it allows to estimate the likelihood of systematic error within the findings. In systematic reviews, risk of bias is usually assessed using critical appraisal tools according to the design of the included primary studies [95–99]. Therefore, an overall assessment of low risk of bias with these tools provides more confidence in the estimates. In overviews, authors can also use critical appraisal tools to assess their included systematic reviews [91,92,100]. However, an overall low risk of bias of the included systematic reviews (i.e. an overall high quality of the methods used

in the conduction of the systematic review) does not assure that the primary studies in the assessed systematic reviews are also of high quality. In other words, the risk of bias assessment in overviews may have two independent layers of assessment: The included systematic reviews, and the body of primary evidence included within those systematic reviews [101].

Similarly, certainty of evidence assessment in overviews has two layers of complexity. Although a systematic review may provide an estimate derived from a meta-analysis for a particular relevant outcome, in the context of overviews it is possible to have a multiplicity of estimates for the same outcome, derived from multiple meta-analyses within the included systematic reviews. Pooling the effects of different meta-analysis (also known as second-order meta-analysis) is difficult and highly discouraged [84,102–104]. Although some authors have made proposals about how to assess certainty of evidence in overviews [25,105,106], the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group has still no official guidance in this topic, and a multiplicity of options are still under discussion, from translating systematic review methods for assessing certainty to overviews, to only describe (or even not present) the results of certainty of evidence of each individual systematic review [101].

However, among all the specific challenges in overview methods, several authors agree that the overlap of primary studies among systematic reviews—a problem constantly highlighted but not sufficiently addressed—is amongst the main ones [32,76,77,80,82–86,93,94,101,103,107–111].

Definition and importance of overlap of primary studies

As shown in figure 4, since an overview includes and analyses multiple systematic reviews assessing similar phenomena, it is possible for those systematic reviews to include a proportion of overlapping primary studies. Although overlap can also happen in an individual systematic review when double-counting data from the same population across individual studies—especially when synthesising real-world evidence [112–115]—, this issue is far more frequent and magnified in

overviews. For purposes of this thesis, we will define overlap of primary studies among systematic reviews (which may be referred simply as ‘overlap’, from now on) as the consideration of data from the same set of primary studies across two or more systematic reviews within a specific overview [77,80,83,85,86,93,108].

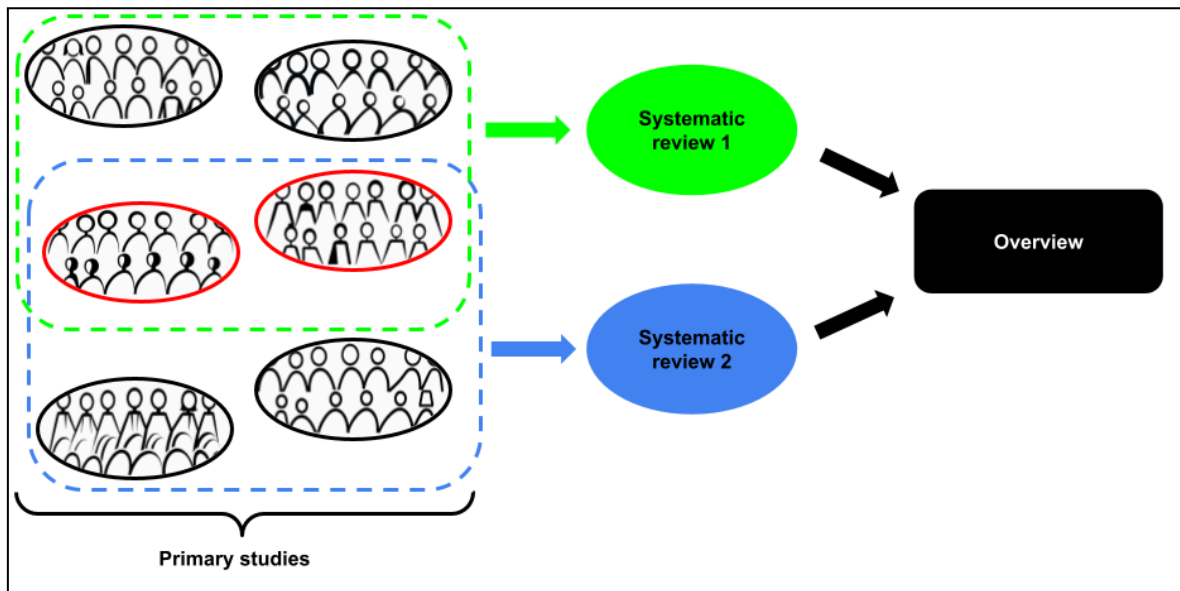


Figure 4. Representation of the two layers of unit of analysis for an overview. Primary studies are summarised across systematic reviews, which in turn are included in overviews. Overlap occurs when a subset of the total primary studies (marked in red) is included in multiple systematic reviews within the same overview. Source: Prepared by the author.

Overlap assessments may enhance meta-epidemiological research, serving as a measure of waste research or detection of appropriate replication for systematic reviews and facilitating the explanation of possible discrepancies in the findings across different systematic reviews [103,107]. On the downside, overlap is a complex phenomenon for overview conduction that can mislead overview authors if not correctly addressed. Overlap may induce authors to analyse data from overlapped primary studies multiple times within the same overview, which can result in an artificial increase in the precision of the estimates of effect due to the double-counting of outcome data from the same original population, which impacts both the narrative interpretation and the statistical estimates of the overview [32,109,116–118]. Additionally, overlap may be considered a form of bias since it

systematically deviates the results towards the direction of the most overlapped primary studies across the included systematic reviews [82], although some authors consider it just a precision problem related to sampling, and not a bias itself [109]. Therefore, it is imperative for overview authors to adequately detect, describe and address the overlap of primary studies across the identified systematic reviews.

Strategies used to address overlap in overviews

Although some meta-epidemiological studies indicate that an important proportion of overview authors ignore overlap [94,108,111,119], several authors have empirically used strategies regarding overlap at different stages within their overview process [86,101,109,120]:

- As part of their eligibility criteria, for example, by selecting one among multiple overlapped systematic reviews according to their methodological quality (or other prespecified decision rules), or by excluding systematic reviews not providing unique primary studies [84,121–124].
- At the data extraction step, by choosing to extract data from all systematic reviews (irrespective of overlap), or by extracting only from a subset of reviews, based on a priori criteria (e.g. most recent, most included studies) [81,82,84,125].
- At the time of synthesis and analysis, by deciding whether to consider all the reviews or only a subset using decision rules (e.g. most included studies, most complete information) [82,84].
- At the step of description of the results, by using visual representations [123,126] or methods to quantify the degree of overlap [108,123].
- At data analysis [82,84,122], whether using decision rules (e.g. using the most recent meta-analysis, or the highest quality review) [127], excluding

reviews with no unique primary studies, using specific algorithms [73], or trying to statistically deal with overlap [84,102,104,117,128].

- At the discussion, by incorporating overlap as a limitation [82]

Remarkably and although empirically used, several of the above-mentioned strategies are probably not methodologically appropriate. For example, deciding the inclusion of systematic reviews using predefined criteria may be prone to subjectivity and bias, and some may argue that this strategy violates the principles of systematic evidence synthesis since it may result in a loss of relevant information [85]. On the other hand, trying to statistically deal with overlap without clear methods to describe it may be misleading. Overall, current methodological recommendations highlight the need to describe overlap across systematic reviews, either visually or quantitatively, as a key step for the conduct of overviews [108,120,126].

Methods to describe overlap of primary studies

Visual representations of overlap

The most basic methods to graphically display overlap are Venn and Euler diagrams. Applied to overviews, both diagrams represent the systematic reviews as circles (or ellipses), with overlap represented as the intersection among these shapes. Venn diagrams show all possible intersection areas, whereas Euler diagrams depict only intersections where overlap is present (figure 5) [126,129].

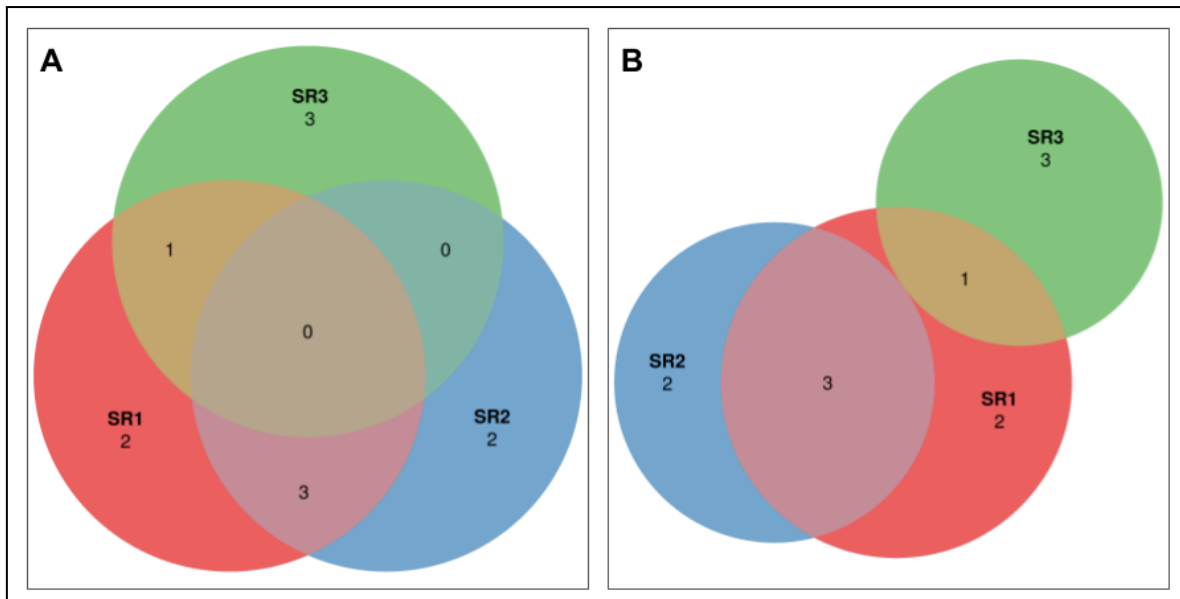


Figure 5. Visual representation of overlap using Venn and Euler diagrams for three systematic reviews (SR). Venn diagram (panel A) includes all possible intersections, even if they are empty, whereas Euler diagram (panel B) includes only those intersections with at least one element included. Source: Prepared by the author, using the set explorer by iMetaLab [130].

Node-link graphs can represent a citation network including all relevant systematic reviews [126,131]. These graphs can include both the systematic reviews and their included primary studies (directly linking the reviews with the primary research), or only the systematic reviews, representing the degree of overlap among SRs with the thickness of each link (figure 6) [126].

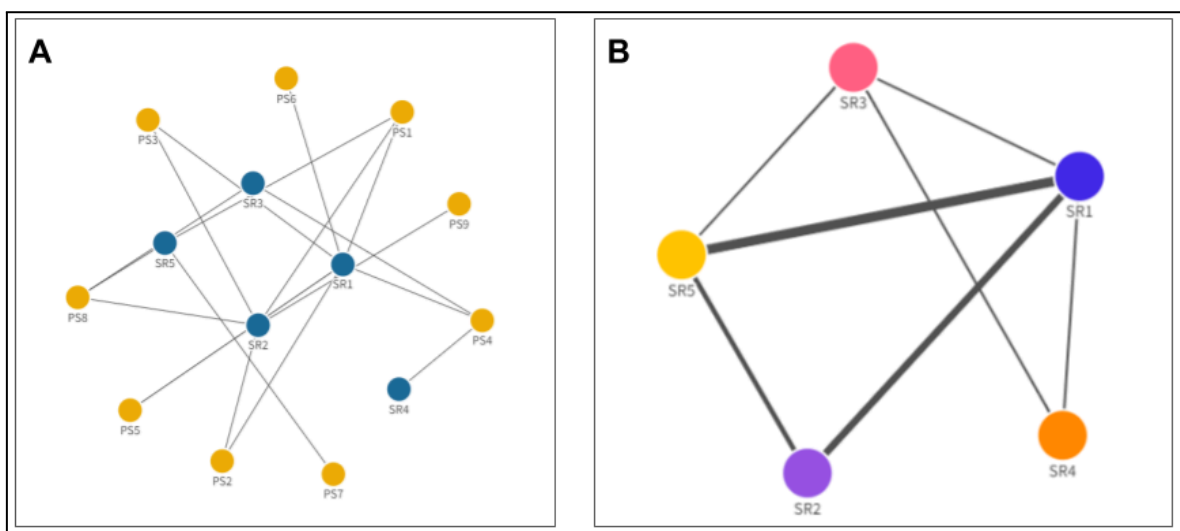


Figure 6. Visual representation of overlap using node-link graphs. In panel A, the citation network includes both primary studies (PS, in yellow) and systematic reviews (SR, in blue). In panel B, the graph includes only systematic reviews, and the overlap degree is represented by the thickness of each line. Source: Prepared by the author, using Flourish [132].

Another option to represent overlap, especially when high volumes of evidence are available, is a bar plot. As shown in figure 7, a bar plot can summarise the total number of unique primary studies, the total number of overlapped primary studies and the number of non-included primary studies for each systematic review [126]. However, the utility of this plot is very limited, since it provides no information about which systematic reviews overlap, and which primary studies are included in each review.

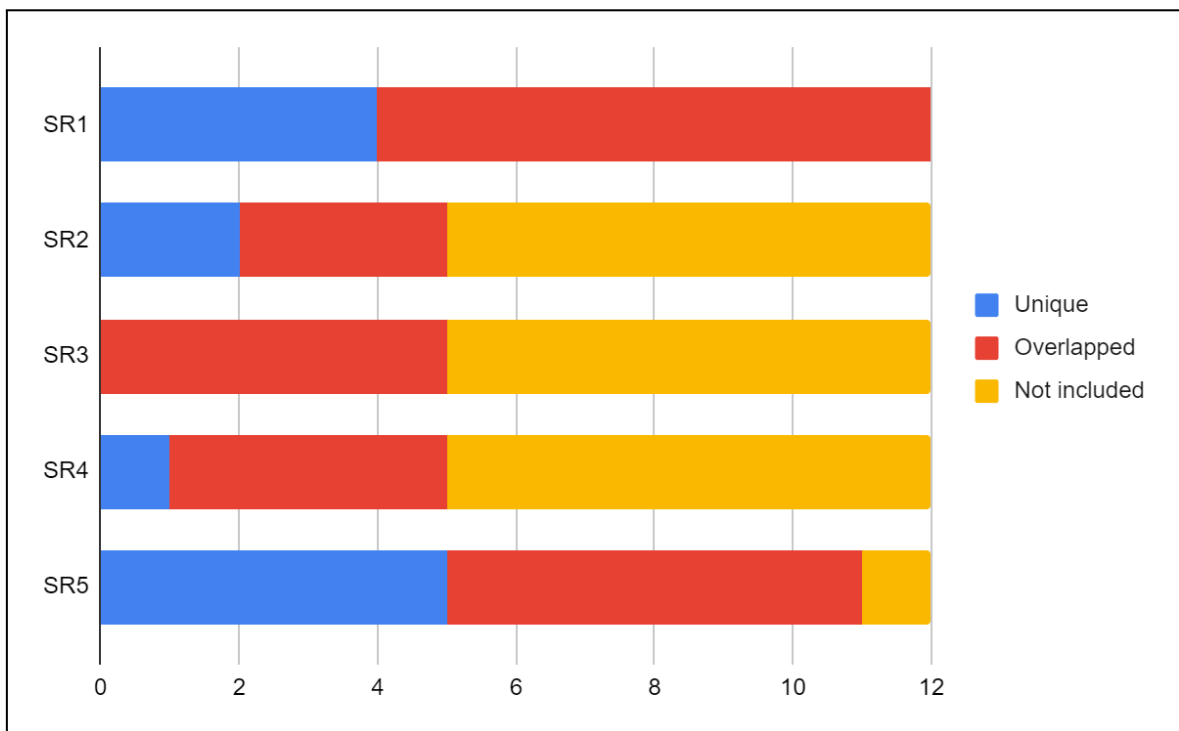


Figure 7. Visual representation of overlap using a bar plot. This plot aggregates the total number of unique, overlapped and non-included primary studies for each included systematic review (SR). Source: Prepared by the author.

But above all, matrix-based techniques have been widely used to graphically display overlap. Upset plots can provide information about the amount of overlap

for each possible set of reviews, although they are usually not used for overlap assessment due to their difficult interpretation and the required expertise (figure 8). On the other hand, matrices of evidence (also known as citation matrices) are currently the most recommended method to visually describe overlap [32,71,126,133–137]. Matrices of evidence are grids that represent the identified systematic review in the columns, and each included primary studies within those reviews in the rows (or vice-versa), allowing to individually link each primary study with their respective systematic reviews (figure 9) [108,126].

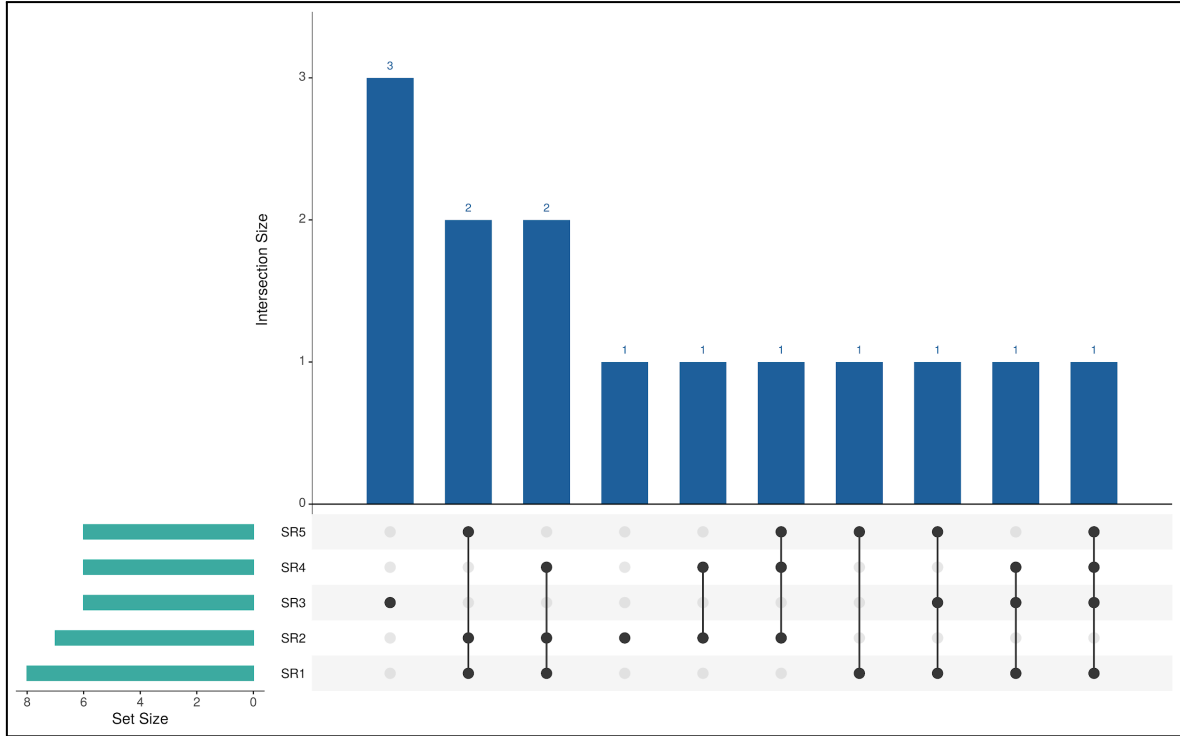


Figure 8. Visual representation of overlap using an upset plot. This plot displays the set of systematic reviews (SR, in teal) and the total number of included primary studies within each one, as well as a bar plot representing intersection sets and their magnitude (in blue). Source: Prepared by the author, using the set explorer by iMetaLab [130].

	SR1	SR2	SR3	SR4	SR5
PS1					
PS2					
PS3					
PS4					
PS5					
PS6					
PS7					
PS8					
PS9					

Figure 9. Visual representation of overlap using a matrix of evidence. The matrix is a grid representing the included systematic reviews (SR) in the columns and the primary studies (PS) in the rows. This matrix allows to clearly cross-link each systematic review with their respective included primary studies (green cells). Source: Prepared by the author.

Quantitative descriptions of overlap

Besides describing the absolute total number of primary studies repeated among the included systematic reviews, the only method developed to quantitatively describe overlap is the corrected covered area (CCA) [108], which currently is amongst the most recommended overall methods to describe overlap [32,103,117,120].

The CCA calculates the degree of overlap as a percentage derived from a matrix of evidence [108]. This matrix includes the following parameters:

- c : the total number of included systematic reviews (columns).
- r : the total number of unique index publications (rows).

- N : the total number of primary studies (including multiple counting [see green cells in Figure 9]).

These parameters allow the calculation of the covered area (CA) of the matrix:

$$CA = \frac{N}{rc}$$

However, the CA reflects only the proportion of the matrix that is filled, without distinguishing whether the same study is counted multiple times. Therefore, the formula needs a correction to accurately measure overlap, which is achieved by subtracting the first appearance of each primary study from both the numerator and the denominator. This corrected formula is the CCA, which is calculated as follows:

$$CCA = \frac{N - r}{rc - r}$$

This formula provides an estimate that quantifies the extent of overlap among the systematic reviews by normalising the double-counted studies against the total potential overlaps within the matrix. Per definition, a CCA of 0% represents no overlap, and a CCA of 100% represents total overlap. In their original publication, the authors proposed four categories for overlap interpretation: Slight overlap (CCA between 0% and 5%), moderate overlap (CCA between 6 and 10%), high overlap (CCA between 11 and 15%), and very high overlap (CCA above 15%) [108], although they provided no rationale for setting these thresholds.

Problems with methods to describe overlap

Data visualisation methods may be intuitive, easy to create, and appealing for the readers; however, they usually share a major flaw: large volumes of evidence hinder their interpretation, mainly due to a distortion or oversaturation of shapes and lines (figure 10) [126]. Even matrices of evidence, the most recommended method to visually depict overlap, become harder to read as the number of

systematic reviews or primary studies increases, with the overlap interpretation being highly dependent on the order in which the studies are included in the matrix. For these reasons, visual representations of overlap are usually restricted to overviews with a limited number of studies since their utility diminishes as the amount of evidence increases.

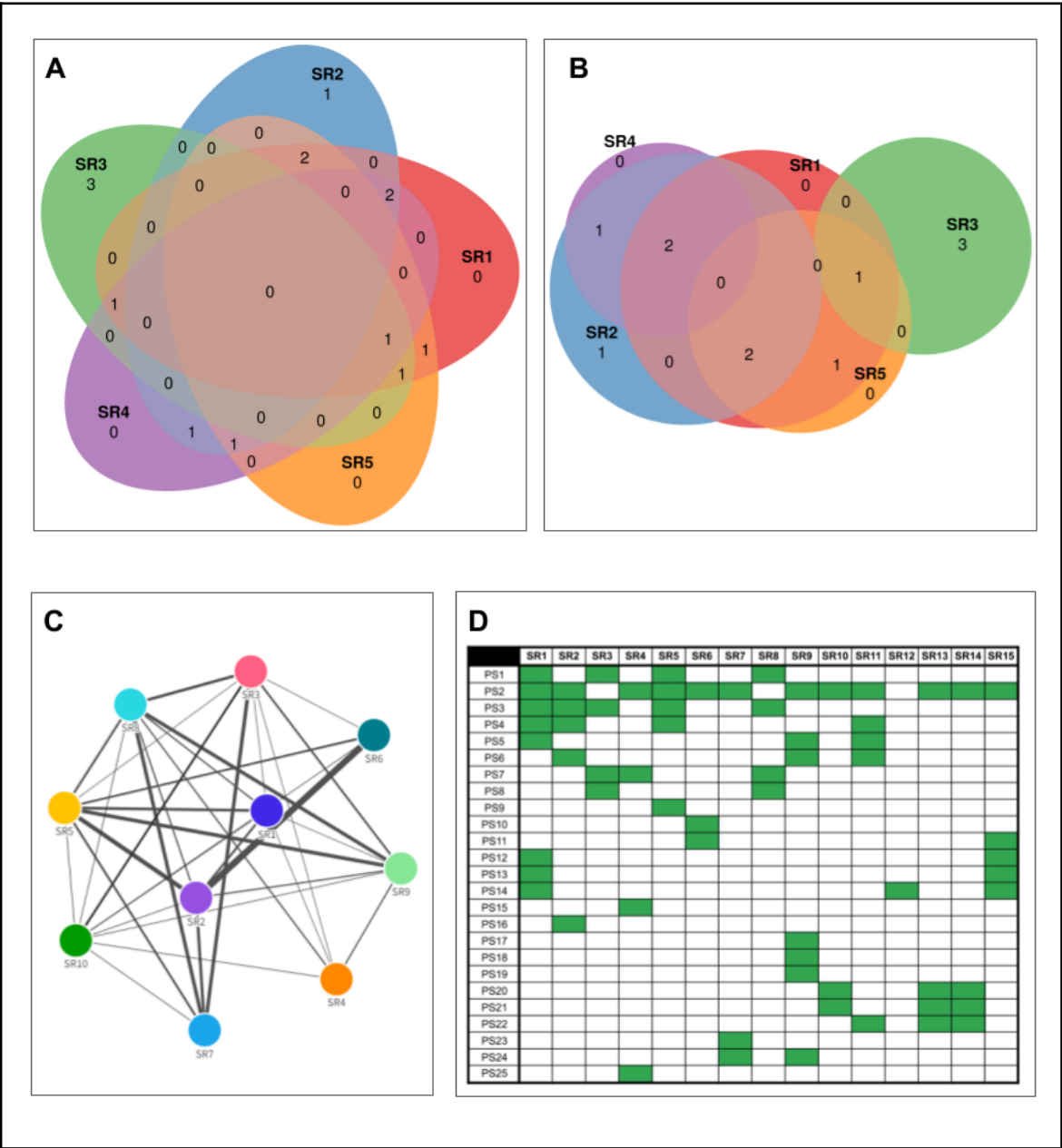


Figure 10. Visual representations of overlap when large volumes of evidence are included, using a Venn diagram (panel A), an Euler diagram (panel B), a citation network (panel C), and a matrix of evidence (panel D). Compared to figures 5, 6 and 9, interpretation becomes more difficult due to distortion of shapes or

oversaturation of data. Source: Prepared by the author using the set explorer by iMetaLab, and Flourish [130,132].

Although CCA provides an appropriate quantitative measure of overlap for a matrix of evidence, it provides one unique estimate irrespective of the size of the matrix. In case of large matrices (e.g., more than five systematic reviews) it is possible that a CCA fails to detect significant overlap between a specific pair of systematic reviews, due to a dilution effect of the other systematic reviews in the matrix (figure 11).

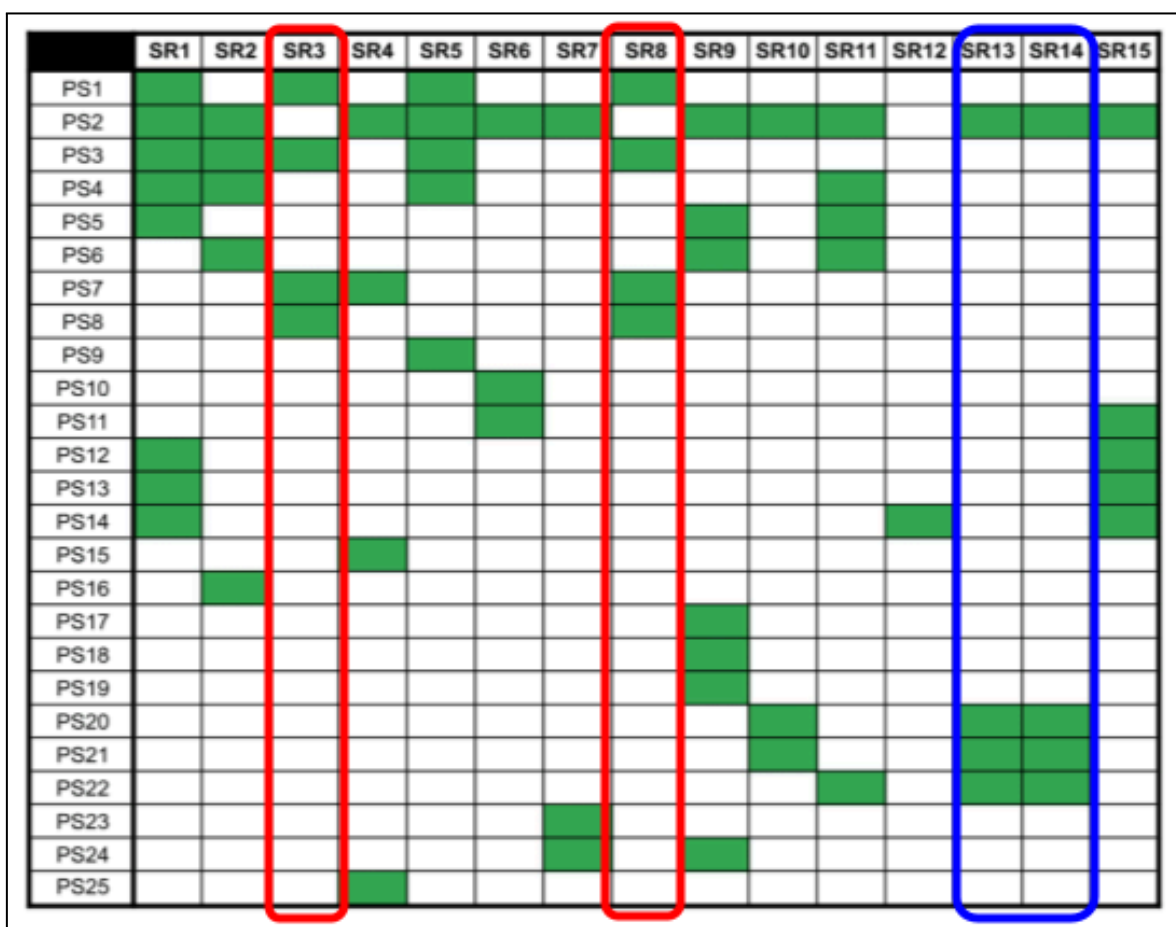


Figure 11. Matrix of evidence with a CCA of 11.4%, but with total overlap between two specific pairs of systematic reviews (SR): 3 and 8 (in red), and 13 and 14 (in blue). In this case, overall CCA fails to detect this overlap since the other systematic reviews dilute the estimate by providing additional empty area to the matrix.

Besides, there is no clear guidance about how to construct a matrix of evidence, and authors may take different (mostly implicit) assumptions to create them. For example, a matrix could include all the primary studies within the identified systematic reviews, or only those that provide relevant data for the overview. The rows could be considered as each reference, or as a publication-thread (i.e., the set of references providing data for the same study). Also, matrices could be constructed at an overview or outcome level. All these assumptions probably impact how matrices are built and interpreted, and, therefore, can potentially affect the CCA estimates. In sum, current methods and guidance for overviews are insufficient to adequately describe overlap of primary studies among systematic reviews.

Objectives

General objective

- To assess methodologies currently used in overviews to deal with overlap of primary studies, and to develop methods for improving the quality and efficiency of overview conduct.

Specific objectives

- To develop a tool and approach for assessment of primary study overlap in overviews through a pairwise CCA analysis (study 1).
- To assess methods used in overviews to deal with primary study overlap and to quantify primary study overlap using the CCA formula (study 2).
- To describe the impact of different assumptions in the development of matrices of evidence and calculation of CCA in overviews (study 3).

Methods

This doctoral thesis is presented as a compendium of publications and comprises three studies. This section outlines the overarching rationale and methodological approaches applied in each study, corresponding to each specific objective of this thesis.

Study 1: Development of a new tool and approach to describe overlap

Since methods and tools to describe overlap of primary studies in overviews seem to be insufficient, this study focused on the development of a tool that could both automate the process of calculation overall CCA, and also provide a new approach for overlap quantification and visualisation.

Building upon previous experience of the research team with overviews including large volumes of evidence [138,139], we detected that assessing overlap was critical for both data analysis and interpretation of the findings, but at the same time it was a very burdensome task. Large matrices of evidence (with over 50 systematic reviews and hundreds of primary studies) were almost impossible to be visually interpreted, and overall CCA did not seem to accurately describe the full complexity of the overlap phenomenon.

To solve this problem, we implemented a new strategy to describe overlap: the pairwise CCA calculation. This approach consisted in complementing the overall CCA calculation (i.e., the CCA for a whole matrix of evidence) with a CCA estimate for each possible pair of systematic reviews within the matrix. Additionally, we aimed to present these CCA estimates in a visually-friendly display that could be both easy to interpret and useful for overview authors. This strategy would allow the detection of specific highly overlapped or non-overlapped pairs of systematic reviews.

The idea was first presented in the 26th Cochrane Colloquium [140]. After receiving expert feedback about this approach and through an iterative process of testing and discussion, we started the development of a tool that could automate both the process of calculation of pairwise CCA, and its graphical display. This first study presents this approach and tool, providing guidance on how to use it and formulating new proposals for CCA calculation methods.

Study 2: Assessment of methods to deal with overlap and to describe overlap using the overall and pairwise CCA approach

Although the first study highlighted a theoretical problem with the overall CCA analysis (the lack of detection of specific highly-overlapped or non-overlapped pairs of systematic reviews), there had been no description of the magnitude of this problem in real overviews. This second study is a methodological review with two objectives: to describe how overview authors addressed overlap, and to assess the overlap degree comparing the overall and the pairwise CCA approach.

We aimed to identify overviews that reported an explicit search strategy, with intervention-focused questions and an effectiveness-oriented objective, that included only systematic reviews (and provided the list of those reviews) as units of analysis, and that were published during 2018. We searched MEDLINE using previously validated filters to retrieve overviews, and two reviewers independently screened the references.

From the total studies fulfilling the eligibility criteria, we analysed a random sample of 30 overviews. We described the approaches that authors used to deal with overlap using the following framework:

- Use of a decision rule based on overlap presence or degree.
- Use of visual representation of overlap.
- Quantification of overlap not using CCA.
- Quantification of overlap using CCA.
- Consideration of overlap as a limitation.

- Not specifying any approach to deal with overlap.

Then, we constructed a *de novo* matrix of evidence for each one of the sampled overviews. Using the tool developed in study 1, we calculated overlap describing both the overall and pairwise CCA for each overview. This analysis aimed to identify any discrepancies between the two approaches, thereby providing evidence to support the hypothesis that the pairwise CCA can complement the overall CCA calculation.

Study 3: Impact of different assumptions for creating matrices of evidence in overlap assessments

With the first two articles, we accumulated vast experience constructing evidence matrices and calculating CCA. However, despite proposing and studying the pairwise CCA method and its relevance as a complement to the overall CCA description, we realised there was no clear guidance (or even terminology) about how to construct a matrix of evidence in the first place. We hypothesised that varying assumptions considered at the moment of creating an evidence matrix may lead to significantly different CCA estimations and, therefore, to heterogeneous conclusions about overview findings. In this study, we aimed to examine how different assumptions for evidence matrices construction influence CCA calculations.

We conducted a focused search strategy in MEDLINE (January 2023 to April 2023). Similarly to study 2, we only included overviews focused on health interventions that reported an explicit list of the included systematic reviews. For all the identified overviews, we described the median included systematic reviews, scope of the overview, reporting guideline used, and methods for assessing overlap.

In this study, we explicitly proposed and defined critical terms related to overlap assessments. These concepts were classified as:

- General concepts:
 - Matrix of evidence.
 - CCA.
- Unit of analysis for the overlap assessment:
 - Overview-level overlap assessment.
 - Outcome-level overlap assessment.
- Assumptions for creating a matrix of evidence and calculating CCA:
 - Scope adjustment.
 - Publication-thread adjustment.
 - Structural missingness adjustment.
- CCA calculation approach:
 - Overall CCA calculation.
 - Pairwise CCA calculation.

These concepts have been summarised in the 'Glossary' section of this thesis.

After defining these terms, we created 16 possible scenarios, representing all possible combinations of units of analysis and different assumptions for calculating CCA. We then took a purposive sample of seven overviews, and conducted an overall and pairwise CCA assessment under these different scenarios. We descriptively compared the CCA results under different scenarios, and discussed the potential impact that different assumptions for creating evidence matrices may have on overlap assessments.

Results

This section includes the main results of this doctoral thesis in the form of three published scientific manuscripts, one for each of the previously described studies. Additionally, appendix 1 provides five publications as accompanying manuscripts, representing opinion papers and relevant applied examples of the methods developed within this thesis, authored or co-authored by the doctoral candidate [80,135,141–143].

Article 1: “Graphical Representation of Overlap for OVERviews: GROOVE tool”

Main results

The first study was published in the manuscript titled “Graphical Representation of Overlap for OVERviews: GROOVE tool” [144]. This article formally introduced the pairwise CCA analysis as a complementary approach for describing the overlap of primary studies among systematic reviews.

As thoroughly described in this thesis, the manuscript briefly introduces the available methods to describe overlap—focusing on matrices of evidence and CCA—, and highlights their main problems: the difficulty of interpreting matrices of evidence in the presence of large volumes of evidence and the possibility of having specific pairs of highly overlapped systematic reviews in the context of low overall CCA (and vice versa).

GROOVE is an Excel-based tool that allows the automation of the overall and pairwise CCA calculations. The tool includes a sheet where the user needs to construct the matrix of evidence. From this input, the tool automatically provides several outputs:

- The overall parameters of the matrix: the total number of reviews (“ c ”), the total number of unique primary studies (“ r ”), the total number of studies within the matrix (including double counting) (“ N ”), the CA, the CCA and the interpretation of the CCA (according to predefined thresholds [108]).
- The absolute number of non-overlapped and overlapped primary studies
- A graphical representation of the pairwise CCA analysis as a heatmap, where the intersections represents each possible pair of systematic reviews, and the value represents the CCA for a hypothetical matrix including only those two systematic reviews. The figure distinguishes the CCA values according to predefined thresholds using different colours (colour-blind friendly) or in a grayscale.

Also, in this article we introduce the concept of structural missingness (or structural zeros) as an alternative consideration for creating matrices of evidence. We define structural missingness as the impossibility of a certain intersection in the matrix to acquire a value of 1, due to an intrinsic reason. For example, it would be impossible for a primary study to be included in a systematic review that was published before that study; therefore, this would be a structural missingness.

Based on this concept, in this article we proposed an adjustment to the original CCA formula based on considering the previously disregarded structural missingness:

$$CCA_{adj-sm} = \frac{N - r}{rc - r - X}$$

Where CCA_{adj-sm} is the CCA adjusted by structural missingness, and X is the total number of structural missingness in the matrix. If users consider structural missingness in their matrices, GROOVE provides the CCA adjusted by structural missingness as a complementary calculation.

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Graphical Representation of Overlap for OVERviews: GROOVE tool

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Abstract

Overlap of primary studies among systematic reviews (SRs) is one of the main methodological challenges when conducting overviews. If not assessed properly, overlapped primary studies may mislead findings, since they may have a major influence either in qualitative analyses or in statistical weight. Moreover, overlapping SRs may represent the existence of duplicated efforts. Matrices of evidence and the calculation of the overall corrected covered area (CCA) are appropriate methods to address this issue, but they seem to be not comprehensive enough. In this article we present Graphical Representation of Overlap for OVERviews (GROOVE), an easy-to-use tool for overview authors. Starting from a matrix of evidence, GROOVE provides the number of included primary studies and SRs included in the matrix; the absolute number of overlapped and non-overlapped primary studies; and an overall CCA assessment. The tool also provides a detailed CCA assessment for each possible pair of SRs (or “nodes”), with a graphical and easy-to-read representation of these results. Additionally, it includes an advanced optional usage, incorporating structural missingness in the matrix. In this article, we show the details about how to use GROOVE, what results it achieves and how the tool obtains these results. GROOVE is intended to improve the overlap assessment by making it easier, faster, and more friendly for both authors and readers. The tool is freely available at <http://doi.org/10.17605/OSF.IO/U2MS4> and <https://es.cochrane.org/es/groovetool>

KEYWORDS

corrected covered area, overlap, overviews of systematic reviews, systematic reviews as topic

Highlights

- The development of overviews of reviews has brought new methodological challenges, such as the assessment of overlap of primary studies among systematic reviews.
- Current methods and guidance for addressing overlap still have important limitations, especially when assessing a large body of evidence.
- This new and freely-available tool named GROOVE provides a simpler and more comprehensive way for assessing the overlap of primary studies among systematic reviews included in an overview.

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1 | INTRODUCTION

The increasing number of systematic reviews (SRs) published during the last years has led to the development of new methods for broader evidence synthesis, such as overviews.^{1–4} An overview can be defined as a SR of SRs instead of primary studies, and constitutes a relatively new approach for broad evidence synthesis.^{4,5} Nevertheless, some methodological challenges have arisen with the development of this research design, with one of the most important being the assessment of overlap of primary studies among SRs.

The overlap of primary studies among SRs (also named as overlapping SRs) refers to the double counting of the same primary study included in at least two (or more) SRs. Overviews including overlapping SRs are complex and, if not assessed properly, overlapped primary studies could have a major influence either in qualitative analyses or in statistical weight,⁵ which could lead to misleading findings due to the undue influence of the results of the studies with greater overlap in the global assessment of the effect of the intervention of interest. For example, if an overview does not correctly assess the overlap of primary studies, it could wrongly obtain overly precise estimates of the effect of certain interventions.⁶ Moreover, neglecting the analysis of overlap among SRs may disregard the opportunity of identifying duplicated efforts that may constitute a research waste phenomenon, with implications ranging from the existence of redundant findings, to the misuse of funds and resources.⁷

2 | METHODS AND ISSUES WHEN ASSESSING OVERLAP

There are several ways to deal with overlap at different stages during the development of the overview.^{8–11} Overview authors may decide about eligibility, data extraction, risk of bias assessment and synthesis/presentation of the results, based on the overlap of primary studies among the included SRs. Indeed, a variety of tools has been proposed for guiding these decisions.^{5,12–14} Nevertheless, currently, most authors of overviews do not report any method for handling overlap.¹⁵ Although some methods for assessing overlap have been proposed, these are not widely used, and there is considerable heterogeneity among guidelines considering this issue.^{11,16,17}

Matrices of evidence and the calculation of the corrected covered area (CCA) are probably among the most exhaustive methods for measuring overlap.^{10,17,18} Matrices of evidence are grids that link SRs with their included primary studies. This method is very useful when the analysed body of evidence is relatively small since it displays a visual image that allows to capture (sensory impression) the overlap of studies between the different SRs that are being analysed within the overview. On the other hand, CCA is a formula that quantitatively assesses the overlap degree, gathering its variables from a matrix of evidence (Figure 1). According to the original publication, a CCA of 0%–5% represents a slight overlap, 6%–10% a moderate overlap, 11%–15% a high overlap, and above 15% a very high overlap.¹⁸

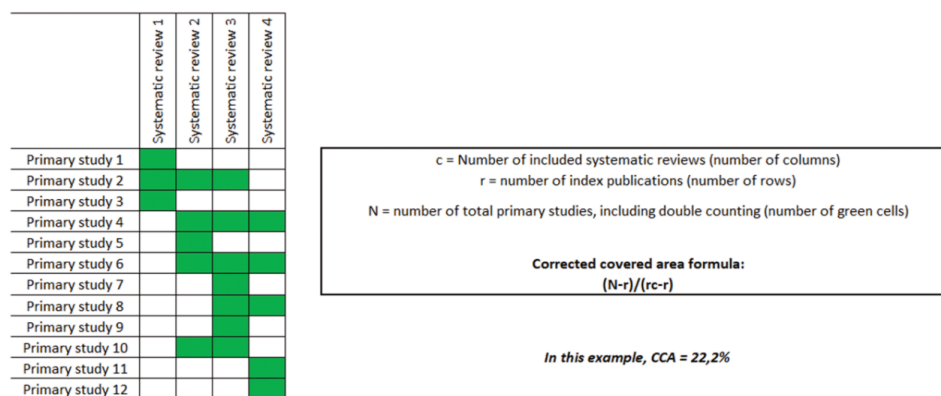


FIGURE 1 Matrix of evidence and calculation of corrected covered area (CCA) formula.¹⁸ Ticked cells represent a primary study included in the respective SR [Colour figure can be viewed at wileyonlinelibrary.com]

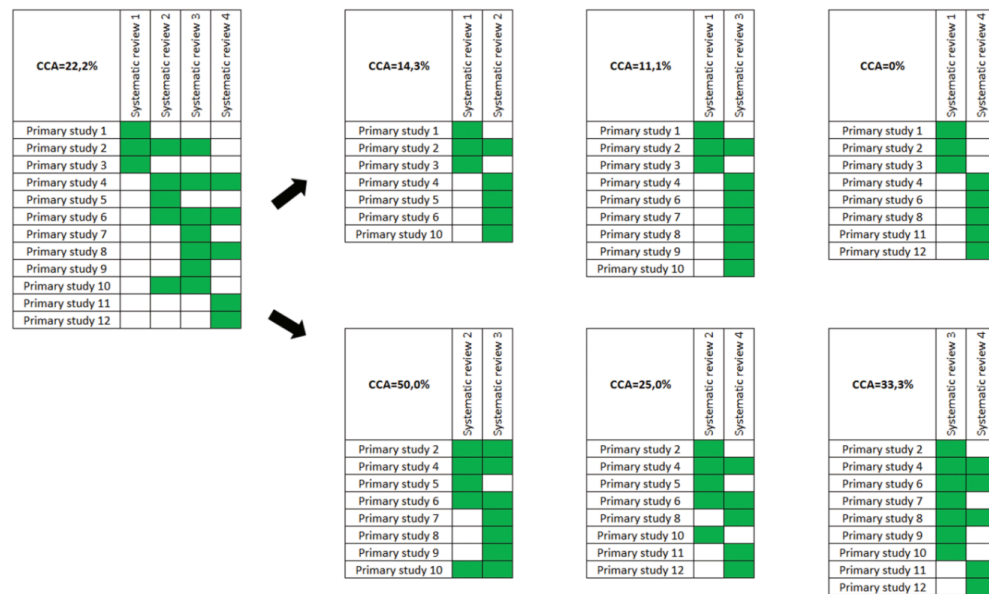


FIGURE 2 Rationale of GROOVE. The tool calculates the corrected covered area (CCA) for the overall matrix, and it also calculates the CCA for each possible pair of reviews. In this example, it is possible to find a specific pair of reviews (1 and 4) that have no overlap (CCA = 0.0%), in a context of very high overall overlap (overall CCA = 22.2%). The tool provides the result of the CCA for each possible pair of reviews, but does not visually display the specific matrices [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2753.2022.05001.x)]

Despite being appropriate, both of the described methods have limitations. First, a matrix of evidence becomes harder to interpret as the included body of evidence increases,¹¹ since it depends on a visual impression that becomes more difficult to capture when the sheet of studies and reviews is very extensive. On the other hand, CCA provides an assessment for a whole matrix of evidence. It is possible for two or more specific SRs to be highly overlapped among each other in a low overall CCA scenario, as well as not being overlapped in a high overall CCA scenario. In this article, we present a new tool to address these limitations.

3 | INTRODUCING GROOVE: GRAPHICAL REPRESENTATION OF OVERLAP FOR OVERVIEWS

In order to assess in a simpler and more comprehensive way the overlap of primary studies among SRs included in an overview, we developed the GROOVE (Graphical Representation of Overlap for OVERviews) tool. This tool is an Excel-based file which automatically calculates the overall

CCA for a whole matrix of evidence, and, at the same time, for each possible pair of SRs included in the overview. In other words, GROOVE calculates the CCA that a matrix would have if only two SRs were included into it, and repeats this process for every possible pair of SRs (Figure 2). This approach allows detecting highly overlapped pairs of SRs in a context of low-overall overlap, as well as non-overlapped pairs of SRs in a context of high-overall overlap, displaying these results into an easy-to-read figure.

GROOVE also provides an advanced optional new feature: the consideration of structural missingness (or structural zeros) when calculating the CCA. Structural missingness is operationally defined as an intersection in the matrix of evidence that cannot acquire a value other than “0.” For example, a SR published in 2015 cannot include a primary study published in 2018 (i.e., the value of this intersection cannot be other than “0”), therefore, this is a chronological structural missingness. Structural missingness is a topic not yet described in the assessment of overlap of primary studies among SRs, but we think this new feature could provide a complementary approach to overlap assessment. The GROOVE tool supports the inclusion of structural missingness at the moment of building

MATRIX OF EVIDENCE										
TOPIC: CALCIUM-BASED CARIES PREVENTIVE AGENTS										
Study ID	Reference	Systematic Reviews								
		Azarpazhooh 2008	Yengopal 2009	Teller 2013	Chen 2013	Li 2014	Raphael 2015	Li 2015	Abdullah 2016	Astvaldsdottir 2016
1	1. Iijima Y, Cai F, Shen P, Walker G, Reynolds C, Reynolds EC. Acid resistance of enamel subsurface lesions remineralized by a sugar-free chewing gum containing casein.	1	1							
2	2. Shen P, Cai F, Nowicki A, Vincent J, Reynolds EC. Remineralization of enamel subsurface lesions by sugar-free chewing gum containing casein phosphopeptide-amorphous calcium.	1	1							
3	3. Cai F, Shen P, Morgan MV, Reynolds EC. Remineralization of enamel subsurface lesions in situ by sugar-free lozenges containing casein phosphopeptide-amorphous calcium.	1	1							
4	4. Hay KD, Thomson WM. A clinical trial of the anticaries efficacy of casein derivatives complexed with calcium phosphate in patients with salivary gland dysfunction. Oral Surg.	1								
5	5. Ithagarun A, King NM, Yiu C, Dawes C. The effect of chewing gums containing calcium phosphates on the remineralization of artificial caries-like lesions in situ. Caries Res. 2005.	1	1							
6	6. Reynolds EC, Cai F, Shen P, Walker GD. Retention in plaque and remineralization of enamel lesions by various forms of calcium in a mouthrinse or sugar-free chewing gum. J.	1	1							
7	7. Walker G, Cai F, Shen P, Reynolds C, Ward B, Fone C, et al. Increased remineralization of tooth enamel by milk containing added casein phosphopeptide-amorphous calcium.	1	1							
8	8. Schirmeister JP, Seger RK, Altenburger MJ, Lussi A, Helling E. Effects of various forms of calcium added to chewing gum on initial enamel carious lesions in situ. Caries Res.	1								
9	9. Cai F, Manton DJ, Shen P, Walker GD, Cross KJ, Yuan Y, et al. Effect of addition of citric acid and casein phosphopeptide-amorphous calcium phosphate to a sugar-free chewing gum on	1	1							
10	10. Morgan MV, Adams GG, Bailey DL, Tsao CE, Fischman SL, Reynolds EC. The anticariogenic effect of sugar-free gum containing CPP-ACP nanocomplexes on approximal caries.		1	1		1				
11	11. Manton DJ, Walker GD, Cai F, Cochrane NJ, Shen P, Reynolds EC. Remineralization of enamel subsurface lesions in situ by the use of three commercially available sugar-free		1	1						
12	12. Reynolds EC, Cai F, Cochrane NJ, Shen P, Walker GD, Morgan MV, et al. Fluoride and casein phosphopeptide-amorphous calcium phosphate. J Dent Res. 2008 Apr;87(4):344-8.		1							
13	13. Andersson A, Skold-Larsson K, Hallgren A, Petersson LG, Twetman S. Effect of a dental cream containing amorphous cream phosphate complexes on white spot lesion regression.		1	1	1	1				1
14	14. Du M, Cheng N, Tai B, Jiang H, Li J, Bian Z. Randomized controlled trial on fluoride varnish application for treatment of white spot lesion after fixed orthodontic treatment.	X	X	1	1				1	
15	15. Zantner C, Martus P, Kiehlbassa AM. Clinical monitoring of the effect of fluorides on long-existing white spot lesions. Acta Odontol Scand. 2006 Apr;64(2):115-22.			1						1
16	16. Blesbroek AR, Faller RV, Bartizek RD, Court UK, McCranahan SF. Reversal of incipient and radioeraphic caries through the use of sodium and stannous fluoride dentifrices in a		1							

FIGURE 3 Example of GROOVE's matrix of evidence filled for a previously published overview.¹⁹ Green cells marked with a "1" represent a primary study included in a SR, while the black cells marked with an "X" represent a structural zero. The image has been cropped [Colour figure can be viewed at wileyonlinelibrary.com]

the matrix and when calculating the results, although this is an optional feature intended to calculate the proportion over the real denominator.

3.1 | How to use GROOVE?

GROOVE is a downloadable tool developed in Excel. It has four sheets:

- "0. Start here": It explains briefly what GROOVE is, how to use the tool and the optional advanced usage considering structural missingness.
- "1. Matrix": This is the only sheet that the user directly manipulates when entering data. It provides an empty matrix of evidence, supporting up to 70 SRs and 1000 unique primary studies. The user must fill the SRs ID in the columns (light blue cells starting from C5), and the primary study ID in the rows (light red cells starting from A6). Afterwards, the user must mark with a "1" each intersection in the matrix representing a primary study included in its respective SR. There is also space for annotating the topic of the matrix and the reference of the primary studies, although this does

not have any influence on the final results. If the user wants to consider structural missingness, an "X" must be annotated in all the intersections that are considered structural zeros. Figure 3 shows an example of GROOVE's matrix of evidence fulfilled for a previously published overview.¹⁹

- "2.1 GROOVE - colour version": Once the user enters all the information in the "1. Matrix" sheet, the tool will provide the results of the overlap analysis in this sheet. The results provided in this sheet are colour-blind friendly.²⁰
- "2.2 GROOVE - greyscale version": This tool is identical to the "2.1 GROOVE - colour version", except it provides the results in greyscale.

3.2 | What results does GROOVE achieve?

All the results will be provided in the "2.1 GROOVE - colour version" and the "2.2 GROOVE - greyscale version" sheets. The results are calculated automatically as the matrix is filled, and are included in three sections within these sheets:

FIGURE 4 Overall results as displayed by the GROOVE tool. These results include the components of the CCA formula, the calculation of the CCA, the calculation of CCA adjusted by structural zeros, and the absolute number of overlapped and non-overlapped primary studies. This example was elaborated using the data from a previously published overview.¹⁹ The image has been cropped [Colour figure can be viewed at wileyonlinelibrary.com]

Overall results		
Number of columns (number of reviews)	c	10
Number of rows (number of index publications)	r	72
Number of included primary studies (including double counting)	N	115
Covered area	$N/(rc)$	15,97%
Corrected covered area	$(N-r)/(rc-r)$	6,64%
Interpretation of overlap	Moderate overlap	
Structural Zeros	X	84
Corrected covered area (adjusting by structural zeros)	$(N-r)/(rc-r-X)$	7,62%
N° of non-overlapped primary studies	In 1 SR	46
	In 2 SRs	19
	In 3 SRs	2
	In 4 SRs	2
	In 5 SRs	1
	In 6 SRs	2
	In 7 SRs	0
	In 8 SRs	0
	In 9 SRs	0
Number of overlapped primary studies		

- “Overall results”: This section provides the overall overlap assessment for the whole matrix of evidence. The tool summarises the number of reviews, index publications and primary studies (including double counting) included in the matrix. With this data, it calculates the covered area, the CCA, and provides the interpretation of the overall overlap assessment, being slight if the CCA is <5%, moderate if it is ≥5% and < 10%, high if it is ≥10% and < 15%, and very high if CCA is ≥15%. If structural missingness was considered when filling the matrix, the tool will also provide a CCA adjusted by structural zeros. If structural missingness was not considered when filling the matrix, these results will be equal to the CCA not adjusted by structural missingness. The tool also indicates the number of unique primary studies (i.e., included in only one SR), as well as the absolute number of primary studies included in two or more SRs (Figure 4).
- “Graphical Representation of Overlap for OVERviews (GROOVE)”: This graphical representation gives the

name to our tool. The tool provides a calculation of a CCA for each possible pair of SRs or “nodes”, displaying these results in a figure resembling a leaning triangle (Figure 5). Each node shows the CCA for two specific SRs. In other words, it shows what the result of the CCA would be if, instead of the whole matrix, we considered a matrix including only those two specific SRs. The figure also highlights with different colours each node according to their interpretation: In the “2.1 GROOVE - colour version”, the nodes are white if CCA is low, bluish green if it is moderate, yellow if it is high, and vermillion if it is very high. All these colours are colour-blind friendly.²¹ The “2.2 GROOVE - greyscale version” displays the same results, with white being used for nodes with low CCA, light grey for nodes with moderate CCA, dark grey for nodes with high CCA, and black for nodes with very high CCA. The thresholds for this interpretation are the same as the ones mentioned previously. This figure also displays the total number of nodes that have low, moderate, high or very high overlap.

Graphical Representation of Overlap for OVERviews (GROOVE)

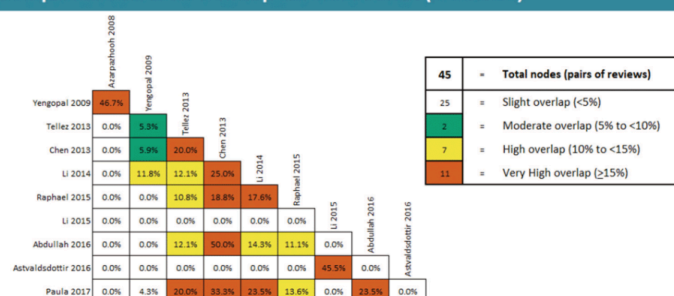


FIGURE 5 Graphical representation of the results as presented by the GROOVE tool (colour version). The intersections or nodes in this figure represent every possible pair of SRs. For each node, the tool calculates the CCA for that specific pair of SRs. The results are highlighted in colours. The tool also provides the total number of nodes with slight, moderate, high and very high overlap. This example was elaborated using the data from a previously published overview¹⁹ [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/jmi.12157)]

- “Graphical Representation of Overlap for OVERviews (GROOVE) - Considering Structural Missingness”: If the user considered structural missingness when making the matrix (that is, if he/she annotated any “X” in the matrix), this figure will show the results of the assessments of CCA for each node, but with the CCA formula adjusted by structural missingness. This figure has the same visual interface as the one mentioned above. If no “X” were annotated in the matrix, the results will be the same as those shown in the GROOVE not considering structural missingness.

3.3 | How does GROOVE calculate these results?

The results are calculated based on numerous but simple formulas in hidden columns and rows. In the “2.X GROOVE” sheets, there are four figures with the same leaning triangle structure as the GROOVE. For each possible node, these figures calculate the following:

- Total number of studies (including duplicates, “N”): The first of the hidden leaning triangle figures calculates the total number of studies for each node. To do this, the “1. Matrix” sheet sums all the “1” included in each column. The result for each intersection represents the sum of the results of the two corresponding columns.
- Total number of overlapped primary studies: In this hidden leaning triangle, the tool calculates the number of overlapped primary studies for each node. To do this, the “1. Matrix” sheet sums all the “1” included in

each row for each possible pair of SRs. If the result of the sum is “2” for any pair of SRs, this means that the primary study is overlapped. Then, the tool counts all the “2” in the respective columns. This count represents the total number of overlapped primary studies for a specific node.

- Total number of rows (index publications, “r”): In this hidden leaning triangle, the tool calculates the number of rows which there would be in a matrix with two specific SRs. This is directly done by subtracting the total number of overlapped primary studies to the total number of studies (“N”).
- Total number of structural missingness (“X”): In this hidden leaning triangle, the tool calculates the number of structural zeros or “X” in the matrix for each node. To do this, the “1. Matrix” sheet counts, for each possible pair of reviews, all the rows where one SR includes the study (that is, an intersection with a “1”) and the other states a structural zero (that is, an intersection with an “X”). The leaning triangle copies the count of cases where this happens.

With this information, GROOVE (and GROOVE adjusted by structural missingness) has all the necessary data to calculate the detailed CCA. There is no need to calculate the number of rows (“r”), as the assessment is presented for each pair of SRs, therefore, “r” is equal to 2.

4 | DISCUSSION

In this article, we present a new tool for assessing overlap of primary studies among SRs. GROOVE is a simple and

easy-to-use tool which might be valuable for authors of overviews, allowing them to perform a comprehensive analysis of the overlap. Besides the calculation of overall CCA, GROOVE provides a new graphical representation of the overlap among each pair of possible SRs. Other graphical and visual approaches have been reviewed in detail by Bougioukas et al.¹⁷ However, due to the complex and heterogeneous nature of possible findings when an overview is conducted, static figures, tables or graphs would not be enough. In this context, GROOVE provides dynamic and customizable features to apply the tool to different scenarios, allowing data exploration and management. For instance, GROOVE enables the analysis of overlap for specific outcomes by creating matrices containing only the SRs and their primary studies focusing on those outcomes,¹³ and it could certainly help for discussing the results. Indeed, adjusting a given matrix to a specific clinical question within an overview by including only primary studies and SRs meeting that specific criteria (which involves deleting certain rows and columns in the matrix), could be useful to avoid underestimation of overlap in certain scenarios.

We also propose a modification to the CCA formula by incorporating structural missingness. The consideration of structural missingness in the generation of a matrix of evidence may provide a complementary approach to the overlap assessment. Structural missing data refers to data that is missing for a logical reason and that should not exist. For example, if authors incorporate chronological structural missingness in their matrices (i.e., considering as structural zeros all primary studies published after the conduction of a specific SR), they could logically and explicitly explain the reason why some primary studies are not included in certain SRs. Also, if the CCA for a certain pair of SRs is 100% when considering chronological structural zeros, but below 100% when not considering it, authors could choose to analyse only the most recent SR for that node, since it probably provides all the useful data by itself. Structural missingness based on a chronological criteria is probably the most useful example of this feature, but overview authors may eventually consider other types of structural missingness. For example, if a SR considers only studies published in English, and a primary study written in Spanish is incorporated into the matrix, it could be considered as a language structural missingness for that specific SR. The use of this feature is optional in the tool and still needs to be studied, but it might be advantageous for many reviewers and authors.

The development of GROOVE raises some other future challenges. First, there is guidance regarding which steps to take in the development of an overview once the CCA is calculated, but none about how to explicitly build the

matrix of evidence from which the CCA is calculated.¹³ For example, authors could consider each row as a particular reference or as a publication thread (i.e., a group of references related to the same study or findings). This lack of clear guidance could lead to an inconsistent assessment of overlap among different authors. Second, the thresholds for considering the CCA as slight, moderate, high or very high are based on the original author recommendations, but the impact of this classification has not yet been assessed.¹⁸ We are confident that GROOVE will contribute to address these future challenges, as well as to improve the development of overviews.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The tool presented in this paper is freely available at <http://doi.org/10.17605/OSF.IO/U2MS4> and <https://es.cochrane.org/es/groovetool>

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Article 2: “A methodological review finds mismatch between overall and pairwise overlap analysis in a sample of overviews”

Main results

The results of the second study were published in an article titled “A methodological review finds mismatch between overall and pairwise overlap analysis in a sample of overviews” [145]. Drawing on the experience gained from developing GROOVE, this work provides an empirical basis for the theoretical concern raised in the first study: that overall and pairwise overlap analyses may lead to different interpretations—which reflects that overlap is a complex, layered phenomenon that is still not sufficiently addressed.

The initial search strategy in this meta-epidemiological review yielded a total of 629 records, of which 89 finally met the eligibility criteria. From these, we analysed a random sample of 30 overviews, that in total comprised 345 systematic reviews and 4,851 unique primary studies.

We found that almost a third of the overview authors did not explicitly address overlap ($n=11$, 36.7%). Among those who did, most used a visual representation of overlap ($n=11$, 36.7%) or discussed it as a limitation ($n=10$, 33.3%). Only four overviews quantified overlap, with only two (6.7%) using the CCA formula.

We created a *de novo* matrix of evidence for each of the included overviews, and described the overall and pairwise CCA overlap assessments using the GROOVE tool. The median overall CCA was 6.7% (interpreted as moderate overlap according to predefined thresholds). The pairwise analysis included a total of 3,138 CCA calculations for the set of 30 analysed overviews (median of 40.5 possible pairs of systematic reviews per overview). Around half (52.8%) of the possible pairs of systematic reviews within the analysed overviews had a slight overlap, and 28.3% had a very high overlap. Among the 30 analysed overviews, we found eight cases with overall slight or moderate overlap but with a significant proportion (>20%) of very high overlap in specific pairs of systematic reviews. Two

overviews had a scenario with very high overall overlap but with a significant proportion (>20%) of pairs of systematic reviews with slight overlap.

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REVIEW ARTICLE

A methodological review finds mismatch between overall and pairwise overlap analysis in a sample of overviews

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Abstract

Objectives: Overlap of primary studies is a key methodological challenge for overviews. There are limited reports of methods used to address overlap, and there is no detailed assessment of the corrected covered area (CCA) of a representative sample of overviews. To describe the approaches used to address overlap, and to estimate the overall and pairwise CCA.

Methods: We searched PubMed for overviews published in 2018. Two authors conducted the screening process. We described the strategy used for assessing overlap, and calculated overall and pairwise CCA for each overview.

Results: We analyzed a random sample of 30 out of 89 eligible articles. Eleven did not address the overlap. Of the remainder, most frequent strategies were visual assessment and discussion of overlap as a limitation. Median overall CCA among the included overviews was 6.7%. The pairwise analysis showed that 52.8% of SR pairs had slight overlap, while 28.3% had very high overlap.

Conclusion: Reported strategies for addressing overlap vary considerably among overview authors. The pairwise approach for assessing the CCA revealed highly overlapped pairs of SRs in overviews with overall slight overlap and vice versa. We encourage authors to complement the overall CCA assessment with a pairwise approach. © 2023 Elsevier Inc. All rights reserved.

Keywords: Overview; Overlap; Corrected covered area; Systematic reviews as topic; Meta-reviews; Overview of reviews; Review of reviews; Umbrella reviews; Methods

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1. Introduction

The increasing quantity of health articles over the last few decades has led to further development of methodological designs for research synthesis, including overviews of systematic reviews (SRs) [1–3]. Overviews, broadly defined as a synthesis of SRs derived from a systematic search, aim to present and describe the current body of evidence regarding a specific question or to address new or different questions, to facilitate decision-making in clinical and public health contexts [4–7]. The development of overviews has brought new methodological challenges, among which one of the most important is the overlap of primary studies among SRs [5,8].

Overlap of primary studies can be defined as the multiple counting of one or more primary studies included in two or more SRs, which in turn are included in the same overview [9]. If not addressed properly, the same data from a

What is new?**Key findings**

- Only 63% of overview authors report a method to address overlap of primary studies, using mainly a visual assessment or consideration in their discussion section.
- The median corrected covered area for the assessed overviews showed a moderate overlap, but there were overviews with slight overall overlap that had highly overlapped specific pairs of systematic reviews.

What this adds to what is known?

- Our assessment using the corrected covered area formula revealed heterogeneous findings among the assessed overviews, both in an overall and a pairwise assessment.
- It is possible to have a mismatch between the overall overlap assessment and a pairwise assessment.

What is the implication, what should change now?

- A pairwise approach to the overlap assessment (such as the proposed by the GROOVE tool) may be adopted as a methodological standard for future overviews, complementary to the overall overlap assessment.

single overlapped primary study across multiple SRs may be analyzed multiple times by overview authors, giving it too much influence and statistical weight [5]. This may bias the results toward the direction of the result of the most overlapped primary studies across the included SRs.

Identifying, measuring, and dealing with overlap has been a key methodological challenge in the development of overviews, and several authors have provided guidance about how to incorporate overlap assessments into the development process of an overview [6,10–20]. One of the most accepted approaches for assessing overlap is the calculation of the corrected covered area (CCA), a simple formula derived from a matrix of evidence that estimates overlap degree as a percentage [17,21]. Recently, it has been proposed that the CCA should be calculated not only for the whole matrix, but also for every possible pair of SRs included in an overview [21–23].

Despite being recommended, not all overview authors use this approach for addressing overlap. Moreover, some authors may not report any method for managing overlap. On the other hand, no detailed assessment of the degree of overlap of a representative random sample of published overviews, using the CCA formula for whole matrices but also for every possible pair of SRs, has been made so far. The aim of this research is to describe the approaches for

addressing overlap reported by authors of overviews, and to assess the degree of overlap, both overall and by pairs of SRs, using the CCA formula.

2. Methods

This methodological review analyses a random sample of overviews of SRs, adhering to adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) reporting standards [24]. First, we described the approaches reported by overview authors to address (or not) overlap of primary studies among SRs. Then, regardless of the methods described, we obtained the list of all the included SRs of each overview, and listed every included primary study within each of those SRs. With this information, we created the matrix of evidence for each included overview, and conducted our own analysis of the overlap degree with the CCA formula, using an overall and pairwise approach.

2.1. Eligibility criteria

We considered for inclusion any overview that met the following criteria [5].

- Published during 2018.
- Provided an explicit search strategy, including at least one electronic database and reporting the list of terms included in the search strategy.
- Focused on answering intervention or therapy questions and with a primary objective focused on effectiveness.
- Included SRs (defined as a research synthesis design using a structured search strategy to identify and include only primary studies) [25].
- Provided an explicit list of the included SRs.

We considered the following as exclusion criteria.

- Overviews using specific methods for qualitative evidence synthesis or mixed methods [26].
- Overviews published in a language other than English or Spanish.
- Overviews including any research design other than SRs.

2.2. Search methods

We searched MEDLINE (accessed via PubMed) using a previously validated search strategy for retrieving overviews (Appendix 1) [27]. We limited our results to articles published in 2018. We did not apply any other limits to our search.

2.3. Selection of the studies

Two independent authors (JB, NM) conducted a pilot screening with 30 references, and, after calibration,

screened the retrieved references by title and abstract first, and then by full text. We solved discrepancies by consensus. For the screening process, we used the software Rayyan [28].

2.4. Data extraction and analysis

From all the articles fulfilling the eligibility criteria, we took a random sample of 30 overviews to be analyzed. One author (JB) extracted data regarding the approach used by authors to address overlap from the methods, results, discussion, and conclusion sections of the included overviews, and classified it according to a predefined framework using a previously piloted data extraction sheet [11]. A second author (NM, IP or LV) cross-checked this process, and discrepancies were solved by consensus. We classified the strategies for addressing overlap as follows [11].

- Uses a tool or decision rule in case of overlap (for example, extracts and analyzes data only from the SR with best-quality assessment in case of overlapping SRs).
- Undertakes a visual representation of overlap (e.g., evidence matrix or Venn's diagrams).
- Quantifies overlap without using the CCA formula (e.g., describes the total number of primary studies overlapped among SRs).
- Quantifies overlap using the CCA formula.
- Considers overlap as an overview limitation.
- Ignores or does not specify any method to handle overlap.

For each included overview we quantified the overlap using the CCA formula. One author (JB) built an evidence matrix considering the SRs included in each overview, and the primary studies included in each one of these SRs. A second author (NM, IP or LV) cross-checked this process. To obtain the CCA calculations, we used the “Graphical Representation of Overlap for OVERviews” (GROOVE) tool [23]. Besides calculating an overall CCA for the whole matrix, this tool calculates the CCA for every “node” (or possible pair of SRs within the matrix), visually summarizing these results in a figure.

To interpret the results, we considered overlap as slight or low if the CCA was less than 5%, moderate if the CCA was 5% or greater but less than 10%, high if the CCA was 10% or greater but less than 15%, and very high if the CCA was 15% or greater, in accordance with previously published thresholds [17]. If the overview included an SR containing no primary studies, or if an SR did not specify which primary studies it included, the SR was neither incorporated into the evidence matrix nor included in the calculation of the CCA. We present the results of overall CCA and the CCA calculated by nodes, as well as the number of nodes with low, moderate, high and, very high overlap.

2.5. Statistical analysis

We described categorical variables by using percentages and absolute frequencies, ordinal, and quantitative variables without normal distribution using the median and interquartile range (IQR), and quantitative variables with normal distribution using the mean and their respective standard deviation (SD). Given that this study is the first of its kind, we considered it as a pilot, and as such we did not plan to perform statistical inference. For the statistical analysis we used Microsoft Excel® software and the R-based statistical package Jamovi [29].

3. Results

3.1. Search results

Our search strategy yielded a total of 629 references. After removing 15 duplicates, we excluded 468 references based on title and abstract screening. We then sought and assessed the remaining 146 reports for full text screening, of which we excluded 57 for the following reasons: Different study design ($n = 28$); different scope ($n = 19$); lack of explicit search strategy ($n = 4$); lack of explicit list of included SRs ($n = 3$); qualitative or mixed-methods overviews ($n = 2$); and different language ($n = 1$). Appendix 2 provides the list of excluded studies, with reasons. A total of 89 articles were finally eligible for inclusion. Appendix 3 provides the full list of eligible studies. Of these 89 articles, we selected a random sample of 30 overviews to be analyzed [30–59]. Figure 1 provides a PRISMA flow diagram summarizing the screening process.

The 30 analyzed overviews included a total of 345 SRs, comprising a total of 4,851 unique primary studies, of which 766 were overlapped in at least two SRs within a single overview.

3.2. Strategies reported by overview authors for addressing overlap

Among the analyzed overviews, 11 (36.7%) [30,31,35,37,41–44,51,58,59] did not report any method to handle overlap. Among the 19 (63.3%) overviews that stated at least one method, 11 (36.7%) [33,34,39,40,45–47,52,54,56,57] used a visual representation, 10 (33.3%) [36,45,47–50,52,53,55,56] discussed overlap as a limitation of their studies, six (20.0%) [32,38,39,53,54,57] used a decision rule derived from the presence of overlap, two (6.7%) [45,56] quantified overlap using the CCA formula and another two (6.7%) [47,50] quantified overlap without using the CCA formula. A total of nine (30.0%) [39,45,47,50,52–54,56,57] overviews used two or more strategies to address overlap.

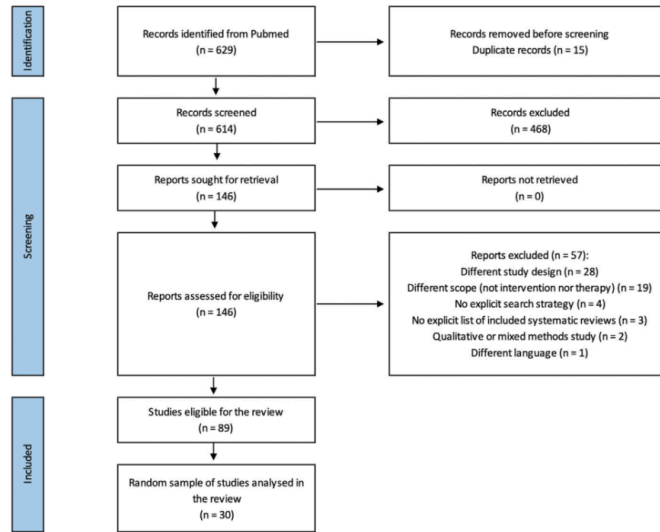


Fig. 1. PRISMA flow diagram.

3.3. Assessment of overall and pairwise CCA for the included overviews

We calculated the CCA for each of the 30 included overviews, regardless of their approach for addressing overlap. The median overall CCA was 6.7% (IQR: 15.3%). Regarding the interpretation of the overall CCA, 10 (33.3%) of the analyzed overviews had a slight overall overlap, eight (26.7%) a moderate overall overlap, three (10.0%) a high overall overlap, and nine (30.0%) a very high overall overlap.

The pairwise CCA analyses comprised a total of 3,138 nodes (or pairs of SRs), with a median of 40.5 (IQR: 29.7) nodes per overview. Considering the set of all possible nodes within an overview as unit of analysis, a median of 52.8% (IQR: 73.7%) nodes had a slight overlap per overview, 4.1% (IQR: 10.7%) a moderate overlap, 2.2% (IQR: 10.5%) a high overlap, and 28.3% (IQR: 51.6%) a very high overlap. Eight (26.7%) of the included overviews had at least 80% of the analyzed nodes with slight overlap whereas six (20.0%) had at least 80% of the nodes with very high overlap. Table 1 summarizes both the overall and pairwise assessment of overlap, and Figure 2 summarizes the analysis of overall and pairwise overlap. Appendix 4 provides the detailed visual assessment of overlap for each analyzed overview, as reported by the GROOVE tool [23].

4. Discussion

Of the 30 analyzed overviews, only 19 described at least one strategy for addressing overlap of primary studies among the included SRs, among which only two used the CCA formula. By looking thoroughly at the elaboration process of overviews, the Methods for Overviews of Reviews (MOoR) framework provides a structured classification of methods for conducting overviews (including specification of the purpose, objectives and scope; eligibility criteria; search methods; data extraction methods; assessment of risk of bias; certainty of evidence; synthesis, presentation and summary of findings; and interpretation and conclusions), and proposes major granularity for classifying strategies to cope with overlap [10,11]. In this sense, we observed that 20% of the overviews used decision rules derived from the presence of overlap (which is encompassed across the “eligibility,” “data extraction,” and “assessment of risk of bias” steps, detailed in MOoR). The rest of the overviews appealed to the use of visual representation (36.7%), discussion of overlap as a limitation (33.3%), and the quantification of overlap (6.7% using the CCA formula, and 6.7% through another method of quantification); which are considered into “synthesis and presentation of the findings”, according to the MOoR framework. These findings as a whole may be explained due to the paucity of summarized

Table 1. Summary of overall and pairwise CCA for each overview

Study ID	Overall assessment			Pairwise assessment			
	Overall CCA	Interpretation	Total nodes	Nodes with slight overlap (%)	Nodes with moderate overlap (%)	Nodes with high overlap (%)	Nodes with very high overlap (%)
Bijle 2018	6.64%	Moderate	45	25 (55.6%)	2 (4.4%)	7 (15.6%)	11 (24.4%)
Bonovas 2018	17.98%	Very high	45	11 (24.4%)	5 (11.1%)	8 (17.8%)	21 (46.7%)
Carr 2018	0.14%	Slight	435	430 (98.9%)	2 (0.5%)	2 (0.5%)	1 (0.2%)
Chen SY 2018	24.69%	Very high	45	20 (44.4%)	0 (0.0%)	0 (0.0%)	25 (55.6%)
Chen X 2018	15.82%	Very high	28	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (100%)
Cheng 2018	6.55%	Moderate	45	36 (80.0%)	0 (0.0%)	1 (2.2%)	8 (17.8%)
Churuangsuk 2018	9.53%	Moderate	66	13 (19.7%)	11 (16.7%)	9 (13.6%)	33 (50.0%)
Costa 2018	0.52%	Slight	190	182 (95.8%)	7 (3.7%)	1 (0.5%)	0 (0.0%)
Dyer 2018	1.36%	Slight	105	100 (95.2%)	2 (1.9%)	0 (0.0%)	3 (2.9%)
Grassi 2018	30.89%	Very high	45	0 (0.0%)	0 (0.0%)	0 (0.0%)	45 (100%)
Häuser 2018	1.75%	Slight	45	33 (73.3%)	4 (8.9%)	4 (8.9%)	4 (8.9%)
Jadczak 2018	4.94%	Slight	21	13 (61.9%)	3 (14.3%)	2 (9.5%)	3 (14.3%)
Kim 2018	21.82%	Very high	15	0 (0.0%)	1 (6.7%)	2 (13.3%)	12 (80.0%)
Latorraca 2018	0.00%	Slight	28	28 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lee P 2018	8.74%	Moderate	6	3 (50.0%)	0 (0.0%)	2 (33.3%)	1 (16.7%)
Marin-Puyalto 2018	6.79%	Moderate	136	33 (24.3%)	25 (18.4%)	17 (12.5%)	61 (44.9%)
Matsui 2018	29.17%	Very high	21	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (100%)
McMahon 2018	6.39%	Moderate	45	32 (71.1%)	5 (11.1%)	1 (2.2%)	7 (15.6%)
Nadeem 2018	12.82%	High	21	0 (0.0%)	4 (19.0%)	6 (28.6%)	11 (52.4%)
Ng 2018	3.30%	Slight	55	41 (74.5%)	1 (1.8%)	5 (9.1%)	8 (14.5%)
Prothero 2018	6.18%	Moderate	28	16 (57.1%)	3 (10.7%)	0 (0.0%)	9 (32.1%)
Riera 2018	0.05%	Slight	91	91 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Schussel 2018	37.23%	Very high	10	0 (0.0%)	1 (10.0%)	1 (10.0%)	8 (80.0%)
Solmi 2018	0.21%	Slight	1,431	1,414 (98.8%)	10 (0.7%)	2 (0.1%)	5 (0.3%)
Suttle 2018	13.33%	High	6	3 (50.0%)	1 (16.7%)	0 (0.0%)	2 (33.3%)
Tan 2018	11.01%	High	36	9 (25.0%)	3 (8.3%)	1 (2.8%)	23 (63.9%)
Visser 2018	0.52%	Slight	28	27 (96.4%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Webster 2018	38.69%	Very high	28	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (100%)
Xie 2018	26.60%	Very high	28	0 (0.0%)	3 (10.7%)	3 (10.7%)	22 (78.6%)
Zhang 2018	6.58%	Moderate	10	6 (60.0%)	1 (10.0%)	1 (10.0%)	2 (20.0%)

guidance about specific methods for conducting overviews available before 2018. The MOoR framework was published in November 2017 [10] and October 2018 [11], so it is unlikely that authors of the overviews included in our review had fully incorporated this guidance. The recently published Preferred Reporting Items for Overviews of Reviews (PRIOR) statement [60] is expected to standardize the reporting of this type of research in the future.

In their original article describing the CCA calculation, Pieper et al. found that almost half of the overviews did not mention overlap [17]. Bajpai et al. described that almost 40% of non-Cochrane overviews published during 2015–2017 did not mention overlap, while almost 30% mentioned it without describing any strategy to deal with it [61].

Lunny et al. found that, over the same period, only 30% of the overviews reported a method to handle overlap, but none of them described a statistical approach to measure it [62]. Sachse et al. reported that only 22% of overviews investigating adverse events of pharmacological interventions reported a strategy to face overlap [63]. Our analysis using a sample of overviews published during 2018 showed that only 63% of overviews reported a method to address overlap, and few of them assessed it quantitatively. All these results show that discussion by overview authors of strategies to address overlap is still scarce and not exhaustive enough. We hope that the inclusion of the overlap assessment in the Cochrane handbook of SRs and in the recently developed PRIOR statement will help to minimize these issues [5,60].

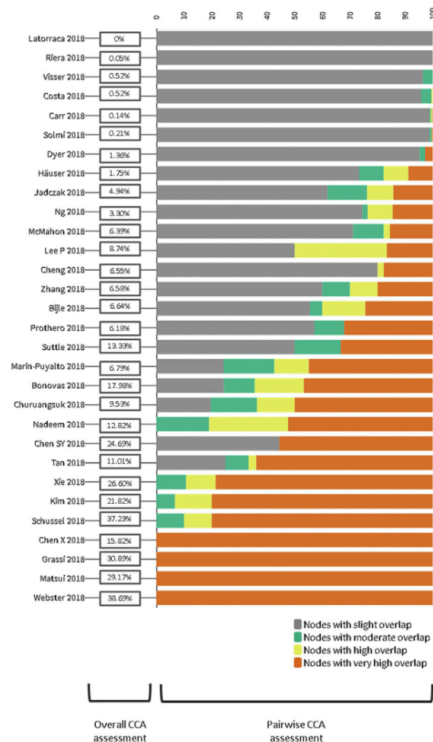


Fig. 2. Overall overlap assessment and pairwise overlap assessment, with distribution of nodes according to overlap interpretation.

Pieper et al. reported a median CCA of 4.0% among overviews published between 2009 and 2011 [17]. Pollock et al. described CCAs ranging from 3.3% to 14.9% in a sample of overviews published between 2010 and 2016, highlighting challenges that may also influence the CCA calculation in overviews, such as authors' decisions about eligibility. Kho et al. found more variability in CCA calculation when assessing it at an outcome-level, with CCA ranging from 0% to 71.4% [64]. Our assessed body of evidence had an overall moderate median overlap according to the CCA formula (6.7%), but GROOVE's pairwise approach showed that it is possible for an overview with an overall slight or moderate overlap to have a significant proportion of nodes with very high overlap [30,36,41,45,47,49,50,58], and vice-versa [31,33]. Our experience using the GROOVE approach has helped us to elucidate that the overlap assessment in overviews has different complexity layers, which the sole use of an overall CCA may not reveal. These findings imply that it may be necessary to adopt a detailed and complementary pairwise analysis as a methodological standard for overlap analyses

within overviews, whether at an overview-level or an outcome-level [22,23,65,66]. An inadequate overlap assessment within an overview may lead to overestimation of findings from the subset of primary studies most repeatedly included among the SRs [5]. Since overviews may be used by clinicians, decision-makers or patients, it is of paramount importance for overview authors to conduct the overlap assessment properly and thoroughly for avoiding both a biased analysis and presentation of the results, and a misinterpretation of the findings within their conclusions (spin bias).

In our study, we used the thresholds originally proposed by Pieper et al. for classifying overlap as slight, moderate, high or very high [17]. These categories have not been metaepidemiologically studied, and their implications have not been yet described. We would expect matrices with fewer primary studies to have a greater probability of having a slight or very high overlap—since a slight overlap includes the possibility of 0% overlap, and very high overlap is larger than the other categories (15% to 100%). Indeed, it is mathematically impossible for a certain pair of SRs with fewer than seven unique primary studies to have a moderate (5% to <10%) or high (10% to <15%) overlap (since a matrix with two SRs and six primary studies could only acquire a CCA value of multiples of $\frac{1}{6}$ and, therefore, the minimum value would be 0% and the next possible value would be 16.6%). This may explain why the pairwise assessment in some cases differs from the overall CCA assessment. In rough terms, we found that a third of the analyzed overviews had a slight overall overlap, a third had moderate or high overall overlap, and a third had an overall very high overall overlap; nevertheless, CCA quantification by nodes may show considerable heterogeneity when compared to the overall CCA measurement for the respective overviews.

A possible limitation of our review is the lack of sample size calculation, but we think that the amount of included overviews (representing more than a third of the total eligible studies) is sufficient to draw valid conclusions. Also, although not having a preregistered protocol, we did follow prespecified methods to conduct this research. We applied narrow eligibility criteria for the selection of studies, including only overviews focusing on effectiveness and excluding those using specific methods for qualitative evidence synthesis, which may limit the external validity of these results to other types of overviews (either qualitative overviews, or overviews focusing on diagnostic accuracy). Nevertheless, our findings may be applicable to the vast majority of published overviews, since currently they are focused on effectiveness using a quantitative approach. The restriction by language in our eligibility criteria is another limitation, but only one article was excluded on this basis, and it is unlikely that this decision could significantly affect our conclusions. We did not assess the included overviews' scope (i.e., classifying the overviews as narrow or broad, depending on the consideration of the same or different

populations, interventions and comparisons) [67]. Arguably, the scope of the overview may be a factor associated with the expected CCA, however, this may not always be the case. Even among overviews with very narrow questions, it is possible to find, indeed, scenarios with an expectable high overall and pairwise overlap [68], but also scenarios showing the mismatch between the overall and pairwise approach, with high overall CCA and several nodes of the pairwise approach with low CCA [69–71], and vice versa [72]. Other factors such as the amount of evidence included (regardless of the scope), chronological structural missingness (i.e., the publication of a relevant primary study after the publication of an SR), and the inherent search methods of each included review may also determine the overlap degree. Even more, CCA assessments of the same body of evidence may differ between authors. In our review, Marin-Puyalto et al. [45] and Webster et al. [56] reported a CCA of 16.8% and 54% respectively, whereas our overall CCA calculations for these two overviews were significantly lower (6.8% and 38.7%). These differences may be due to authors' decisions about how to construct the matrix. A possible explanation could be that, for constructing the matrices of evidence in our review, we considered all the primary studies included in each SR. Other authors may consider only certain primary studies that, for example, provide data for specific meta-analyses. Further studies need to address all these issues thoroughly, but currently, the overall CCA assessment complemented with a pairwise approach constitutes an appropriate and easy starting point for conducting a detailed measure of overlap.

Our review has several strengths, such as the use of a validated search filter for overviews, the identification of the whole set of overviews, the random sampling, and the comprehensive description of strategies used by overview authors to handle overlap using previously proposed frameworks. We think that our assessment of the CCA using both overall and pairwise approaches provide new insights for future improvements in the interpretation of overview findings.

To our knowledge, this is the first published overlap assessment of a representative sample of overviews using a pairwise approach. We also provide a detailed assessment of each overview, with the respective evidence matrix and GROOVE visualization (Appendix 4). Our findings demonstrate that it is possible to have a mismatch between an overall CCA assessment and a pairwise detailed approach, which emphasizes the importance of conducting an exhaustive and appropriate overlap analysis when doing an overview. Our study shows that there are still important challenges regarding reporting and usage of strategies to handle overlap of primary studies among SRs within overviews.

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Supplementary data

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Article 3: “Impact of matrix-construction assumptions on quantitative overlap assessment in overviews: A meta-research study”

Main results

As shown in the second article, important nuances and relationships within the evidence base may be obscured when overlap is described solely through an overall metric. Pairwise analysis provides an additional layer of insight into overlap patterns. However, because the CCA metric is inherently derived from a matrix of evidence, its value may be highly sensitive to the assumptions authors make when constructing that matrix. This third article, titled “Impact of matrix-construction assumptions on quantitative overlap assessment in overviews: A meta-research study,” defines these assumptions and examines their impact on CCA-based overlap assessments [146].

In this review, the initial search strategy retrieved 690 references. After title and abstract screening, we assessed 362 full texts, of which we finally included 193 overviews.

The overviews included a median of 15 systematic reviews (interquartile range: 10 to 27). Most (n=129, 66.8%) had an overall broad scope, due to broad consideration of population and/or interventions. The majority used a reporting guideline tailored for systematic reviews (n=117, 60.6%), with 53 (27.5%) not mentioning a reporting guideline, and only 23 (11.9%) using a reporting guideline specific for overviews.

Compared to our previous study, we found a higher proportion of overviews not mentioning overlap within their methods, results or discussion sections (n=85, 44.0%). Among those who mentioned it, most incorporated overlap during the ‘synthesis and presentation and summary of findings’ step (n=61, 31.6%).

After explicitly proposing and defining different assumptions that may be taken to construct a matrix, we selected seven overviews for further analysis of CCA under different matrix-construction scenarios. Four of these had a narrow scope and three a broad scope. The number of included systematic reviews of these overviews ranged from five to 51.

The maximum potential influence of scenario selection on CCA varied from 1.2% to 13.5% for overall CCA, and 0.0% to 15.7% for pairwise CCA. The largest sources of variation arose from the level of analysis, scope adjustments, and structural missingness adjustments. Adjustments related to publication threads had only a negligible effect on CCA in our sample, probably due to authors solving publication-thread issues prior to reporting their results (e.g., including only one reference whenever multiple were available).

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RESEARCH ARTICLE

Impact of matrix-construction assumptions on quantitative overlap assessment in overviews: A meta-research study

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Abstract

Overlap of primary studies among multiple systematic reviews (SRs) is a major challenge when conducting overviews. The corrected covered area (CCA) is a metric computed from a matrix of evidence that quantifies overlap. Therefore, the assumptions used to generate the matrix may significantly affect the CCA. We aim to explore how these varying assumptions influence CCA calculations. We searched two databases for intervention-focused overviews published during 2023. Two reviewers conducted study selection and data extraction. We extracted overview characteristics and methods to handle overlap. For seven sampled overviews, we calculated overall and pairwise CCA across 16 scenarios, representing four matrix-construction assumptions. Of 193 included overviews, only 23 (11.9%) adhered to an overview-specific reporting guideline (e.g. PRIOR). Eighty-five (44.0%) did not address overlap; 14 (7.3%) only mentioned it in the discussion; and 94 (48.7%) incorporated it into methods or results (38 using CCA). Among the seven sampled overviews, CCA values varied depending on matrix-construction assumptions, ranging from 1.2% to 13.5% with the overall method and 0.0% to 15.7% with the pairwise method. CCA values may vary depending on the assumptions made during matrix construction, including scope, treatment of structural missingness, and handling of publication threads. This variability calls into question the uncritical use of current CCA thresholds and underscores the need for overview authors to report both overall and pairwise CCA calculations. Our preliminary guidance for transparently reporting matrix-construction assumptions may improve the accuracy and reproducibility of CCA assessments.

  This article was awarded Open Data and Open Materials badges for transparent practices. See the Data availability statement for details.

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Highlights**What is already known?**

- Overlap of primary studies is a major methodological challenge when conducting overviews of systematic reviews (SRs).
- The corrected covered area (CCA) quantifies the percentage of overlap based on a matrix of evidence—a structured table that lists primary studies and indicates which ones are included in each SR.
- This measure is useful for understanding whether multiple SRs are providing largely the same information or if they offer unique contributions to the overall body of evidence.

What is new?

- We are the first to empirically demonstrate how key methodological choices—such as scope definitions, handling of structural missingness, and publication-thread adjustments—can alter CCA values across multiple overview scenarios.
- Drawing on our scenario analyses, we propose the field's first transparent protocol for constructing evidence matrices and reporting both overall and pairwise CCA, thereby enabling reproducible overlap assessments.
- By highlighting the unexplored methodological basis of existing CCA cut-offs (<5%, 5–10%, 10–15%, ≥15%), we provide the initial empirical foundation for refining these thresholds and guiding more robust methodological decisions in overviews.

Potential impact for RSM readers

- We demonstrate for the first time how critical decisions in evidence-matrix construction (scope, structural missingness, publication threads) quantitatively alter CCA values, encouraging methodologists to scrutinise and document these choices.
- We provide actionable advice for handling multiple publications ('publication threads') and structural missingness, strengthening the rigor and trustworthiness of overlap assessments in overviews.
- We highlight the complementary value of reporting both overall and pairwise CCA metrics to capture the full overlap phenomenon, preventing misleading interpretations driven by aggregate measures alone.
- We challenge the arbitrary nature of existing CCA cut-offs (<5% slight, 5–10% moderate, 10–15% high, ≥15% very high) and lay the groundwork for methodological validation.
- We introduce a clear protocol for transparently reporting matrix construction by explicating methodological assumptions for both overall and pairwise CCA calculations, enhancing reproducibility and comparability across overview studies.

1. Introduction

Overviews are a form of evidence synthesis that uses systematic reviews (SRs) as their unit of search, inclusion and analysis.¹ Because each SR is based on a set of primary studies, an overview that includes multiple SRs on the same research question is likely to have identical or partially overlapping primary studies. This redundancy, known as 'overlap of primary studies', poses a significant challenge when conducting overviews.^{1–8} Primary study overlap may bias the overview findings by disproportionately amplifying the influence of specific studies. Moreover, overlap leads to artificially precise estimates due to the repeated inclusion of identical effect estimates derived from the same primary studies.¹ When multiple SRs include the same primary studies, each duplicated study contributes its effect estimate more than once to the overall synthesis. Because meta-analytic methods weight studies by the inverse of their variance, these repeated entries artificially inflate the apparent sample size and reduce the estimated variance. As a result, confidence intervals around the pooled effect become narrower—not because the evidence is actually stronger or more consistent, but simply because identical data points have been counted multiple times. This misrepresents the degree of precision, increasing the risk of overconfident conclusions and potentially misleading decision-makers about the true estimates of effects.

There is no clear consensus on how to manage primary study overlap (hereafter referred to as overlap). Several authors do not consider overlap when conducting overviews or simply acknowledge it as a potential limitation in their discussion.^{2,5,9–12} By failing to formally assess and adjust for overlap, their syntheses remain vulnerable to bias and can produce misleading conclusions. Others propose addressing overlap by making eligibility or analytical decisions based on the presence of potential overlap—for instance, analysing only one SR (e.g. the most recent, the most comprehensive, or the highest quality) when multiple SRs share a common primary study.^{3,4} However, this approach risks losing valuable information provided by the primary studies included in the reviews that are excluded or not analysed. Moreover, there is no universally accepted guidance for choosing among multiple SRs, and the most appropriate choice often depends on the body of evidence of the specific clinical specialty or the particular public health concern being addressed.^{13,14}

Some authors have proposed meta-analysing data directly from the primary studies, instead of pooled data from the SRs.¹² With this approach, the potential for bias or distorted imprecision derived from overlap is solved, but it raises the question of why conducting an overview in the first place, and not a SR directly. Beyond simply providing a descriptive or statistical summary of the primary studies included in SRs, a critical role of overviews is to comprehensively display, analyse, and discuss the available evidence syntheses, in an effort to facilitate comparisons across them by explaining their possible differences and similarities, as well as strengths and limitations. Beyond these challenges, overviews also offer important advantages. They provide a comprehensive map of existing evidence syntheses, making it possible to identify where reviews converge or diverge in their conclusions, reveal methodological differences that may explain discordant findings, and highlight both duplication and research gaps. The unique contribution of overviews lies in critically analysing and comparing the body of SRs, rather than statistically combining their results, which may be particularly valuable for decision-makers and guideline developers. Therefore, assessing overlap is essential—not only to decide whether to pool primary study data, but to ensure that the interpretive comparisons provided by overviews reflect the actual evidence base rather than artefacts of duplication.

Another approach to address overlap is to include all the available SRs and explicitly describe its magnitude. Visual representations can be used, such as Venn or Euler diagrams, node-link graphs, bar plots, and upset plots.¹⁵ Among overlap-mapping methods, the evidence matrix is most commonly used.¹ An evidence matrix (or citation matrix) is a simple two-dimensional table: one axis lists the SRs and the other lists the primary studies, and each cell is filled in to show when a given study appears in a particular SR.² While this clear visualisation works well for small numbers of reviews, it rapidly becomes unwieldy and hard to interpret as more SRs and studies are added.

The corrected covered area (CCA) is a quantitative approach to describe overlap, based on a matrix of evidence.^{2,16} CCA is a quantitative measure of how much primary-study overlap exists across a set of SRs, expressed as a percentage. It is calculated by comparing the total number of ‘occurrences’ of primary studies (i.e., the sum of all studies counted in every SR) with the number of unique primary studies and the number of SRs included. Conceptually, CCA answers the question: ‘Of all the study entries in my overview, what proportion are duplicates?’ A higher CCA indicates more repeated studies and therefore greater overlap.

To interpret CCA, researchers have adopted the following (albeit arbitrary) thresholds²:

- <5%: slight overlap
- 5–10%: moderate overlap
- 10–15%: high overlap
- >15%: very high overlap

These cut-offs have been used by some authors as practical guidance when planning or conducting overviews, helping teams decide whether overlap is trivial or whether it must be formally addressed to avoid bias.

Because these percentage thresholds were chosen arbitrarily and have not been subjected to meta-epidemiological validation, we still lack empirical evidence on how varying degrees of overlap bias

overview results. Standardising the matrix assumptions for CCA calculations may guide researchers on how to interpret overlap in quantitative synthesis—whether using predefined thresholds or considering CCA as a broad indicator of overlap—helping to determine whether an overview could definitively answer a clinical question.

Therefore, it is essential to establish a clear method for building an evidence matrix before measuring overlap with the CCA. Constructing an evidence matrix involves several methodological assumptions, including how rows and columns are defined (e.g. whether each row represents an individual reference or the set of references related to a primary study), how CCA calculations are performed (overall or pairwise CCA), and how the unit of analysis is determined (overview-level or outcome-level).¹⁷ So far, no study has assessed the impact of these assumptions. Our research aims to examine how varying assumptions in constructing matrices of evidence influence CCA calculations when assessing primary study overlap in overviews.

2. Methods

We conducted a methodological review, reporting our publication based on relevant items in the ‘Preferred Reporting Items for Systematic reviews and Meta-Analyses’ (PRISMA) guidelines.^{18,19} The protocol for this study was prospectively registered.¹⁷

2.1. Eligibility criteria

We included overviews, defined as any type of evidence synthesis in which the unit of searching, inclusion, and analysis is SRs.¹ We only considered overviews focused on health interventions of any type published in peer-reviewed journals that explicitly listed the references of the included SRs. We excluded other types of evidence syntheses (such as individual SRs and broad literature reviews including both SRs and primary studies), as well as overviews with a non-intervention focus (e.g. diagnostic, prognosis).

2.2. Search methods and selection of studies

We searched MEDLINE via PubMed and the Cochrane Database of Systematic Reviews using previously validated filters for retrieving overviews ([Appendix 1](#)).²⁰ We limited our search to articles published between January 1, 2023, and April 1, 2023. We set the lower chronological limit considering that the latest version of the ‘Cochrane Handbook for Systematic Reviews of Interventions’, which introduced guidance for conducting overviews, was first published in 2019, and the ‘Preferred Reporting Items for Overviews of Reviews’ (PRIOR) statement was released in 2022.^{1,21}

Two authors (among JB, NM, MV, JV, RGP, and IPC) conducted the selection process, determining eligibility first by title and abstract, and then by full-text assessment. Discrepancies were solved through discussion and consensus.

2.3. Data extraction and analysis

Data extraction was conducted in two steps. First, one author (JB) extracted the study characteristics for all the identified overviews, and a second author (MV, JV) cross-checked them. The variables included:

- Year of publication.
- Reporting guideline used, classified as overview-specific (i.e. those stating overlap of primary studies within their reporting statements, such as PRIOR) or non-overview specific (i.e. those developed for other types of evidence syntheses, such as PRISMA).
- Main outcome.
- Number of included SRs.

- Methods to address overlap, according to the ‘Methods for Overviews of Reviews’ (MOoR) framework (further detailed in [Appendix 2](#)), which may be done:
 - In the ‘eligibility criteria’ step (by including reviews are selected based on pre-specified criteria, excluding those without unique primary studies, or including all the reviews).
 - In the ‘data extraction’ step (by extracting data from all reviews, or only from selected ones according to prespecified criteria).
 - In the ‘risk of bias assessment’ step (by selecting reviews according to their risk of bias).
 - In the ‘synthesis and presentation and summary of findings’ step (by selecting reviews according to prespecified criteria, or using methods to visualise or quantify overlap).
- Scope classification is defined as either:²²
 - Narrow: covering a single population and a single intervention or comparison (e.g. ‘*Clinical Efficacy of Platelet Derivatives in Periodontal Tissue Regeneration*’).²³
 - Broad: covering multiple populations or multiple interventions (e.g. ‘*Non-pharmacological interventions for self-management of fatigue in adults*’).²⁴
 - Borderline cases, such as overviews including multiple drugs within a single treatment class (e.g. ‘*Chemotherapy and targeted therapy for advanced biliary tract cancers*’), were classified as narrow if the interventions were conceptually similar and addressed a single clinical question (see [Appendix 3](#) for the full list of overviews and their classifications)²⁵

We summarised these data descriptively in tables. As a post hoc analysis, we compared the association between using a reporting guideline tailored for overview methodology (i.e. a guideline mentioning overlap specifically in their reporting criteria, such as PRIOR²¹ or PRIO-harms²⁶) and whether the authors considered overlap within the identified overviews.

After summarising these data, we selected a purposive sample of overviews to create matrices of evidence. For this, we considered overviews that had different scopes (broad and narrow), and with a heterogeneous number of included SRs. The sample did not consider overviews that solved the overlap during the eligibility criteria step (i.e. excluded SRs based on overlap), as overlap is not expected to appear in those cases. One author (JB, FB) created the matrices of evidence for each overview, and a second author (NM) cross-checked for accuracy. The initial matrix considered all the SRs included in the overview, as well as all the references of the primary studies within those SRs.

For each overview, we tested different assumptions that authors may have considered when constructing matrices of evidence.^{2,16,27–40} These assumptions include factors related to the level of analysis (overview-level versus outcome-level) and how the matrix was constructed (adjustments for scope, publication threads, and structural missingness), as defined in [Table 1](#). By considering all possible combinations of these assumptions, we created a total of 16 matrices per overview. These scenarios are detailed in [Table 2](#).

Once we constructed a matrix for each scenario, we calculated the overall and pairwise CCA using the ‘Graphical Representation of Overlap for OVERviews’ (GROOVE) tool.¹⁶ We present the results of both assessments in boxplots for each scenario and overview. We calculated the difference between the maximum and minimum CCA values across the different scenarios to estimate the potential impact of different assumptions on the CCA value.

Because existing CCA cut-offs are arbitrary, we did not intend to adopt strict thresholds to determine the importance of change. Our narrative labels describe the magnitude of variation across scenarios (e.g. as ‘minimal’, ‘moderate’ or ‘marked’) based on the absolute observed change in CCA for that overview, with the intention of providing readers with contextual information. To improve transparency and repeatability, we explicitly report the exact change in CCA values for every overview, in every scenario. With the intent of improving clarity in the text, we have used the following operational (non-normative) categories for the absolute change in CCA across scenarios: minimal, if the change in CCA is equal or below 5%; moderate, if above 5% and below 10%; and marked if equal or above 10%. These categories are reported only as descriptive aids and do not imply formal benchmarks.

Table 1. Important overlap definitions.

Concept		Definition	Further considerations
General concepts	Matrix of evidence ²	A grid that maps the SRs against their respective primary studies.	A matrix of evidence (also called a citation matrix) is a two-dimensional table used to quantify overlap among systematic reviews (SRs) when computing the Corrected Covered Area (CCA). In this matrix, rows represent individual SRs included in an overview, columns represent all unique primary studies cited across those SRs, and cells contain a mark (often '1' for presence, '0' for absence) indicating whether a given primary study appears in a particular SR.
	Corrected covered area (CCA) ²	A metric that quantifies the degree of overlap of primary studies across different SRs, expressed as a percentage.	CCA is calculated using data from a matrix of evidence, as follows: $CCA = \frac{N-r}{rc-r}$ Where: <i>c</i> : the total number of included systematic reviews (columns). <i>r</i> : the total number of unique index publications (rows). <i>N</i> : the total number of primary studies (including duplicates of the same primary study across reviews). A higher CCA represents a higher degree of overlap.
Unit of analysis for the overlap assessment	Overview-level overlap assessment ²	The construction of one matrix for the whole overview, considering all the included SRs.	This approach treats the entire overview as the unit of analysis. The CCA is derived from one matrix for the whole overview.
	Outcome-level overlap assessment ^{36–39}	The construction of one matrix per outcome, considering only the SRs providing data for the specific outcome.	This approach treats each outcome within the overview as the unit of analysis. A CCA is derived from multiple matrices (one matrix for each outcome).

(Continued)

Table 1. Continued.

Concept		Definition	Further considerations
Assumptions for creating a matrix of evidence and calculating CCA	Scope adjustment ⁴⁰	The consideration—and inclusion in the matrix—only of the primary studies that provide useful data for a given outcome within an overview.	Some SRs within an overview may contain primary studies that do not provide valuable data for the overview. • We will consider a matrix as non-adjusted by scope if it includes all the primary studies within the SRs, irrespective of whether they provide useful data for the overview. • We will consider a matrix as adjusted by scope if it includes only the primary studies providing data for at least one outcome of interest.
	Publication-thread adjustment ^{27–35}	The consideration of each set of references related to a single primary study as a unique row in a matrix of evidence, instead of multiple rows.	When a single research project gives rise to several journal articles—such as an initial protocol paper, one report on outcome A, another on outcome B, and perhaps a long-term follow-up—this is known as multiple publications (or sometimes ‘salami slicing’). Although each paper appears distinct, they all stem from the same underlying study and patient cohort. As such, data from the same primary study may be split and published in multiple publications. • We will consider a matrix as non-adjusted by publication-thread (‘studification’) if each row represents a unique reference (in which case the same study could be represented by multiple rows). • We will consider a matrix as adjusted by publication-thread if each row of the matrix represents a set of references related to the same primary study.

(Continued)

Table 1. Continued.

Concept		Definition	Further considerations
	Structural missingness adjustment ^{16,37,38}	The exclusion of primary studies that cannot be included in the SRs due to methodological constraints for purposes of CCA calculation.	Some intersections in a matrix of evidence may be blank for valid reasons, which is referred to as 'structural missingness'. For this study, publication timing will be considered as the only valid and unequivocal methodological constraint (e.g., a primary study published in 2024 cannot be included in an SR published in 2021). In practical terms, structural missingness adjusts the original CCA formula by subtracting the number of intersections considered as structurally missed from the denominator. This modified CCA formula is: $CCA_{adj-sm} = \frac{N-r}{rc-r-X}$ Where X is the number of intersections considered as structural missingness. • We will consider a CCA calculation as non-adjusted by structural missingness if it uses the original CCA formula. • We will consider a CCA calculation as adjusted by structural missingness if it uses this modified CCA formula.
CCA calculation approach	Overall CCA calculation ²	The calculation of a unique CCA value for a given matrix of evidence.	The overall CCA calculation considers every SR and primary study within the matrix of evidence.
	Pairwise CCA calculation ^{11,16}	The calculation of multiple CCA values for a given matrix of evidence, each representing the specific overlap for every possible pair of SRs.	The pairwise CCA calculation considers the theoretical construction of a matrix of evidence for each possible pair of SRs. Each of those matrices contains only the primary studies relevant to that specific pair of reviews. Since this approach provides multiple CCA values, the results are summarised using box plots, displaying the medians and interquartile ranges for the calculated CCAs across different pairs of SRs.

CCA: corrected covered area; SR: systematic review.

Table 2. Different scenarios planned for overlap analysis through CCA.

Scenario number ^a	Level of analysis	Scope adjustment ^b	Publication thread adjustment	Structural missingness adjustment
1	Overview	✗	✗	✗
2	Overview	✓	✗	✗
3	Overview	✗	✓	✗
4	Overview	✗	✗	✓
5	Overview	✓	✓	✗
6	Overview	✓	✗	✓
7	Overview	✗	✓	✓
8	Overview	✓	✓	✓
9	Outcome	✗	✗	✗
10	Outcome	✓	✗	✗
11	Outcome	✗	✓	✗
12	Outcome	✗	✗	✓
13	Outcome	✓	✓	✗
14	Outcome	✓	✗	✓
15	Outcome	✗	✓	✓
16	Outcome	✓	✓	✓

Note: ✓: adjusted; ✗: non-adjusted; CCA: corrected covered area.

^a We conducted overall and pairwise CCA calculations for each scenario.

^b Scope adjustment considers a matrix including only the reviews relevant to the main outcome of the review.

3. Results

3.1. Search results

Our search strategy yielded a total of 690 references. After removing duplicates, we screened 685 records by title and abstract, excluding 323. A total of 362 reports were retrieved, of which we excluded 169 due to the following reasons: non-intervention focus ($n = 137$), not being an overview ($n = 30$), no explicit list of included reviews ($n = 1$), and preprint not published in a peer-reviewed journal ($n = 1$). [Appendix 3](#) provides the list of excluded studies, with reasons. Ultimately, 193 studies met our eligibility criteria. [Figure 1](#) summarises the selection process.

3.2. Description of the identified overviews

The 193 identified overviews included a median of 15 SRs (IQR: 10–27, range 0–101), with most classified as having a broad scope ($n = 129$, 66.8%). Most overviews ($n = 117$, 60.6%) used a reporting guideline not specific to overviews (e.g. PRISMA), with only 23 (11.9%) using an overview-specific reporting guideline (e.g. PRIOR). A significant proportion ($n = 85$, 44.0%) did not mention overlap in their manuscript, while 14 (7.3%) addressed it only in the discussion section. A total of 94 (48.7%) overviews incorporated overlap within their methods or results sections, mainly in the ‘Synthesis and presentation and summary of findings’ step ($n = 61$, 31.6%). There was no statistically significant association between the guideline used and the consideration of overlap ($p = 0.104$). The main characteristics of the identified overviews are summarised in [Table 3](#) and detailed in [Appendix 4](#).

3.3. CCA assessment under different assumptions

We selected a sample of seven overviews to test the quantitative assessment of overlap using the CCA under different matrix assumptions.^{41–46} Four of these overviews had a narrow scope,^{43–46} and three

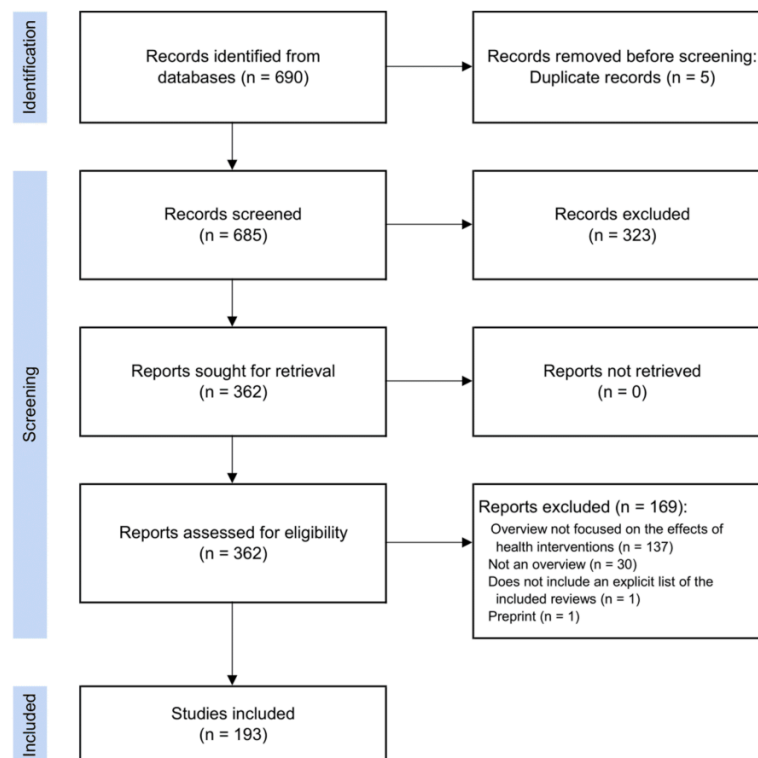


Figure 1. PRISMA flow chart summarising the selection process.

had a broad scope.^{41,42,47} The number of included SRs in each overview ranged from five⁴¹ to 51.⁴⁶ Appendix 5 provides further details about the seven sampled overviews.

We constructed 16 matrices for each overview, according to the scenarios outlined in Table 2. Figure 2 visually summarises the overall and pairwise CCA assessments for each overview and scenario. As expected, scenario 1 usually shows the lowest CCA values, whereas scenario 16 shows the highest CCA values.

In our sample, the potential impact on the overall CCA approach (i.e. the difference between the maximum and minimum value) ranged from 1.2%⁴³ to 13.5%.⁴⁷ The potential impact of the pairwise approach ranged from 0.0%^{43,45,46} to 15.7%.⁴¹ Appendix 6 details the range between minimum and maximum CCA values for each overview and scenario.

4. Discussion

Among the 193 overviews of SRs of health interventions identified in this methodological review, almost half (44.0%) did not mention overlap, and a few (7.3%) mentioned it only in the discussion. Nearly half (48.7%) of the overviews explicitly accounted for overlap within the methods or results, and in those studies, it was most often addressed in the synthesis and summary of findings step. Most had a broad scope (66.8%), and only 11.9% used an overview-specific reporting guideline when submitting their manuscript for publication. This limited adoption of overview-specific reporting guidelines (e.g. PRIOR) alongside the reliance on SR-specific guidelines (e.g. PRISMA) may be partly explained

Table 3. Summary of the main characteristics of the included overviews.

Characteristics	Total overviews (n = 193)
Median included SRs (IQR)	15 (10–27)
Scope of the population	
Narrow	138 (71.5%)
Broad	55 (28.5%)
Scope of the interventions or comparisons	
Narrow	93 (48.2%)
Broad	100 (51.8%)
Overall scope^a	
Narrow	64 (33.2%)
Broad	129 (66.8%)
Reporting guideline used	
Not reported	53 (27.5%)
SR-specific	117 (60.6%)
PRISMA	114 (59.1%)
PRISMA-ScR	2 (1.0%)
MOOSE	1 (0.5%)
Overview-specific	23 (11.9%)
PRIOR	17 (8.8%)
PRIO-harms	6 (3.1%)
Overlap mention	
No mention of overlap	85 (44.0%)
Methods or results section	94 (48.7%)
Discussion section	14 (7.3%)
Specific steps in which overlap was addressed^b	
‘Eligibility criteria’ step	10 (5.2%)
‘Data extraction’ step	2 (1.0%)
‘Assessment of risk of bias’ step	0 (0.0%)
‘Synthesis and presentation and summary of findings’ step	61 (31.6%)
More than one step	19 (9.8%)
Not specified	2 (1.0%)

IQR: Interquartile range; MOOSE: ‘Meta-analysis Of Observational Studies in Epidemiology’; PRIO-harms: ‘Preferred Reporting Items for Overviews of systematic reviews including harms’; PRIOR: ‘Preferred Reporting Items for Overviews of Reviews’; PRISMA: ‘Preferred Reporting Items for Systematic reviews and Meta-Analyses’; PRISMA-ScR: ‘PRISMA Extension for Scoping Reviews’; SR: Systematic review.

^a Overall scope was considered ‘narrow’ if both the population and the intervention were narrow; otherwise, it was considered ‘broad’.

^b According to the MOOR framework (Appendix 2), and considering only those overviews that mention overlap in their methods or results section. Percentages are calculated considering the total number of included overviews (n = 193) as the denominator.

by the recency of these tools, with PRIOR—widely considered the most recommended guideline for overviews of health interventions—being published in August 2022.²¹

We conducted a detailed *de novo* CCA assessment for a subset of seven overviews, using 16 predefined scenarios. These scenarios represented different assumptions depending on the level of analysis—overview level (scenarios 1–8) and outcome level (scenarios 9–16)—and three methodological assumptions, namely scope, publication-thread, and structural missingness. For each scenario, we calculated both overall and pairwise CCA. As expected, matrices adjusted with these three assumptions usually exhibited higher CCA values, as the adjustments removed ‘noise’ (i.e. blank intersections). For example, a matrix adjusted by scope deleted the rows of the primary studies that did not contribute data for an overview outcome, and it is more likely for these specific primary studies to be included only in one (or few) SRs within the overview.

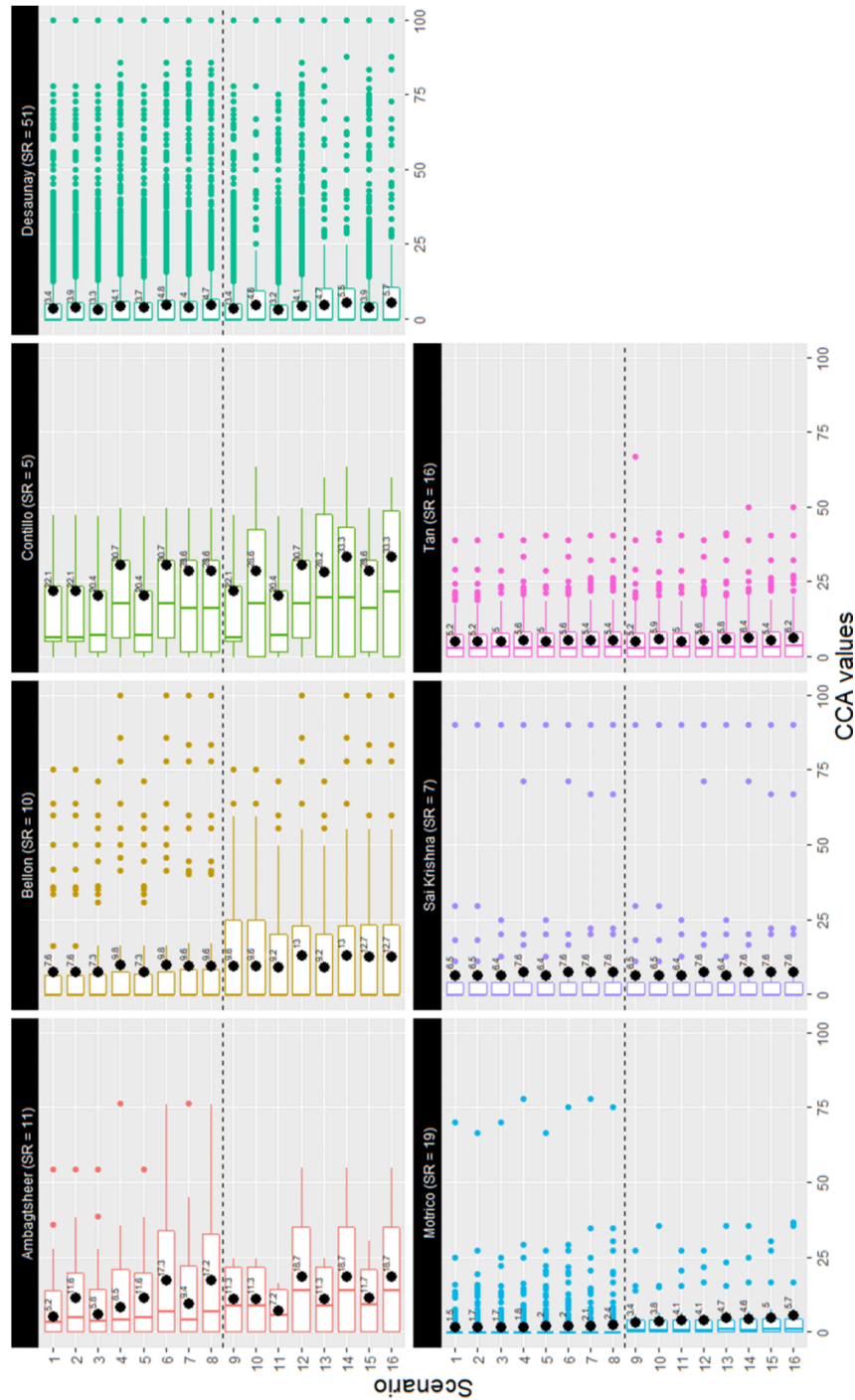


Figure 2. Box plots showing overall and pairwise CCA values for each overview, according to predefined scenarios. This figure summarises the overall and pairwise CCA for each scenario per overview. Each facet presents the result for a specific overview, with each overview author's name (and the number of included SRs in the overview) in the header. The X-axis contains the CCA value, expressed as a percentage. The Y-axis contains each one of the predefined scenarios (see Table 2). The black dots and the value on the right of each dot indicate the overall CCA. The box plot represents a summary of the pairwise CCA values. The dashed line in each facet separates the overview-level scenarios (1–8) from the outcome-level scenarios (9–16). CCA: corrected covered area; SR: systematic review.

We found that the maximum potential impact of selecting different scenarios on CCA ranged from 1.2% to 13.5% for overall CCA, and 0.0% to 15.7% for pairwise CCA. Level of analysis, scope adjustment, and structural missingness adjustment had the greatest impact on these variations, whereas publication-thread adjustments had little effect on CCA in our sample. Despite these general ideas, it is worth discussing specific aspects identified for each overview.

Of the sampled overviews, Ambagtsheer and Contillo showed the greatest variability of CCA depending on different adjustment scenarios.^{38,44} In Contillo's overview—which included the fewest references per SR (mean = 5.2)—the unadjusted scenario produced an overall CCA of 22.1%. Adjusting for structural missingness caused the largest shifts in CCA values, whereas scope adjustment (scenario 2) left the overall CCA unchanged from the unadjusted value, and publication-thread adjustment (scenario 3) yielded only minimal differences. Moreover, this overview consistently exhibited a higher overall CCA than its median pairwise CCA, underscoring the importance of using both overall and pairwise measures to accurately describe overlap in overviews.¹¹

Ambagtsheer's overview similarly highlights how scenario choice can influence CCA interpretation, though with markedly different results.⁴⁴ This analysis has the highest reference density of all sampled overviews (mean = 22.2 references per SR) yet yields a much lower unadjusted overall CCA of just 5.2%. Unlike in Contillo's overview, Ambagtsheer's CCA values were driven chiefly by scope adjustments: when recalculated under scenario 2 (scope adjusted), the CCA increased by 6.4% compared with the non-adjusted scenario 1, a moderate change. Interestingly, when we limit the analysis to the outcome-level scope, adjustments have minimal impact—the overall CCA stays at 11.3% under both scenarios 9 and 10. In contrast, accounting for structural missingness moderately increases overlap, raising the CCA from 11.3% (scenario 9) to 18.7% (scenario 12). Because outcome-level analyses include only reviews with data on that outcome, changing the review scope does little to alter overlap, whereas filling in missing structural links reveals considerable additional duplication. Since outcome-level analysis includes only reviews with data on the specific outcome, scope adjustments are unlikely to significantly affect CCA. On the other hand, structural missingness adjustments may be an important factor explaining the variability of the CCA, reflecting a major problem related to the inclusion of outdated SRs in overviews, which may compromise the comparability of different SRs analysing the same phenomenon.⁴⁵

The overview by Tan showed minimal variations in overall CCA (1.4%) and median pairwise CCA (0.6%) across scenarios.⁴¹ This overview included 16 SRs with a mean of 11.4 primary studies per review, but had a narrow scope. Indeed, according to our subjective assessment, we think this overview had the narrowest scope among those sampled, which could explain the stability of the CCA across different scenarios.

In the overviews by Bellon, Desaunay, Motrico, and Sai Krishna, changing the matrix-construction assumptions led to minimal changes in overall CCA in most cases ($\leq 5\%$), with Bellon's overview showing a moderate change of 5.7%.^{39,40,42,43} Yet in every case, the pairwise CCA stayed at 0.0% across all scenarios. This pattern shows that, although the total amount of duplicated study entries can vary slightly depending on how the matrix is built, virtually no individual SR-to-SR comparison actually shares any primary studies, so pairwise overlap remains zero. In the Desaunay panel of Figure 2, the median pairwise CCA stays at 0.0% across all scenarios, showing that most SR pairs share no primary studies. However, a handful of outliers reveal specific review pairs with markedly different overlap, highlighting how these few cases can disproportionately affect interpretation despite the generally low overall CCA.

The implications of overlap across SRs are context-dependent, subject to interpretation, and not inherently positive or negative. High overlap may introduce bias and distort the precision of the results by giving disproportionate influence to certain primary studies, and may be considered research waste, as redundant reviews consume resources without necessarily adding new knowledge. At the same time, overlap can represent legitimate scientific replication, and when overlapping reviews—despite using different methods or eligibility criteria—reach consistent conclusions, this may strengthen confidence in the robustness of findings for the interventions under study.⁴⁸ Conversely, low overlap coupled

with heterogeneous results may signal that conclusions are highly sensitive to differences in eligibility criteria or scope of the reviews, potentially reflecting a broad overview scope, thereby requiring cautious interpretation. Thus, overlap should be considered both as a methodological challenge and as a potentially informative feature of the evidence landscape.

Currently, creating evidence matrices is highly burdensome. Most SRs do not separate the citations of included primary studies from other references—instead, journals usually list all sources together (with the remarkable exception of Cochrane), making it very labour-intensive to identify which studies were actually analysed. Constructing a single matrix—including all different scenarios—required more than one week of full-time work, which limited our capacity to include more than seven overviews in the present sample. As far as we are aware, there is no metadata signalling which references corresponds to the included studies in a SR. Addressing this gap in the future could greatly facilitate the identification of primary studies and support meta-epidemiological research in evidence synthesis. In addition, we expect that explicitly considering and reporting the matrix-construction assumptions before starting will help authors define the most appropriate scenarios in advance, thereby reducing unnecessary work and increasing both efficiency and the clinical usefulness of the resulting matrices.

Another limitation is that authors often overlook publication-thread issues. Multiple papers reporting on the same primary study population pose a significant challenge in medical publishing, and to date, there is no universally accepted editorial solution.^{27,49–51} Some SR authors implicitly adjust for publication-thread by citing only one article per study, which may explain why publication-thread adjustments had no significant impact on CCA in our sample. Nevertheless, in settings where multiple references per study are common, this adjustment could substantially influence overlap estimates.

This is the first study exploring the different assumptions for constructing matrices of evidence on a quantitative overlap assessment. Our review highlights key challenges that persist in overview reporting and overlap assessment, including the limited reporting of overlap, underuse of overview-specific guidelines, inconsistent integration of overlap across methodological steps, and considerable variability in overlap estimates depending on analytical assumptions—several of which have also been noted in previous studies.^{5,10–12,52} This raises questions about the validity of existing CCA thresholds—low (<5%), moderate (5–10%), high (10–15%), and very high (≥15%)—used to describe overlap.^{2,16} We recommend applying these cut-offs with caution because (i) they were proposed arbitrarily and have not been tested in methodological studies to understand their impact; and (ii) as our review demonstrates, CCA values can vary depending on the assumptions made when constructing the evidence matrix. Therefore, any methodological recommendations based on CCA results should be refined and validated.³⁶ Our definitions serve as an initial guidance for improving the reporting of evidence matrix construction and, therefore, quantitative overlap assessment through CCA.

5. Conclusion

We offer preliminary guidance for transparently reporting evidence matrix construction, which will, in turn, enhance the accuracy and reproducibility of quantitative overlap assessments using CCA. In conclusion, our analysis reveals that the way an evidence matrix is constructed—through decisions about rows versus columns, scope definitions, structural missingness, and publication-thread handling—significantly alters CCA values. This variability undermines uncritical use of the current overlap thresholds (<5% low, 5–10% moderate, 10–15% high, ≥15% very high) without empirical validation. To strengthen overlap assessment, we must adopt a transparent, standardised framework that clearly documents matrix construction choices and reports both overall and pairwise CCA measures. By refining CCA protocols in this way, overview authors will be better equipped to synthesise evidence accurately, interpret redundancy appropriately, and make informed methodological decisions in support of robust, evidence-informed healthcare. It is also important to emphasise that CCA was not developed to define the presence or absence of overlap—since some degree of overlap is expectable among reviews with similar scope—but rather to provide an approximate, descriptive summary of its magnitude. While the formula makes it reproducible and robust across approaches, CCA should not

be interpreted as a test statistic with fixed thresholds or cut-offs of significance. Instead, it should be applied cautiously as a guide to understanding redundancy in the evidence base.

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All the supporting data related to this study are publicly available at <https://osf.io/hbf5j/>.⁵³

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Discussion

This thesis sought to explore practical solutions to describe the overlap phenomenon, focusing on its quantitative measurement and visualisation, aiming to ultimately enhance a deeper interpretation and improve the available methodological approaches.

Advancing overlap assessment in overviews

The studies presented in this thesis contribute to the methodological understanding of overlap in overviews by introducing and empirically evaluating the pairwise CCA approach as a complement to overall CCA [144,145], and exploring the underlying assumptions for its calculation [146].

While overall CCA provides a single estimate of overlap for an entire matrix of evidence [108], it may fail to detect highly overlapped or non-overlapped specific pairs of systematic reviews, particularly in large matrices [145]. Study 1 lays the foundation for a new approach to measure overlap—the pairwise approach—, questioning the reliance on a single metric for representing the whole overlap phenomenon in an overview. This approach was materialised through the creation of GROOVE, a practical, easy-to-use tool that automates both overall and pairwise CCA calculation and generates a visual representation of pairwise overlap [144]. This first study also introduces the concept of structural missingness into the overlap assessment, proposing an adjustment to the original formula to incorporate impossible intersections within the matrix, thereby offering a formalised method to address such scenarios. GROOVE outputs overall and pairwise CCA, both adjusted and unadjusted for structural missingness, and provides visual representations of pairwise CCA to facilitate its interpretation. In this way, it automates a previously manual process, while promoting a deeper assessment of overlap.

Study 2 empirically confirmed what the first study theoretically hypothesised: that scenarios with low overall CCA can still contain pairs of systematic reviews with

very high overlap, and conversely, high overall overlap may include pairs with little or no overlap [145]. These results highlight the added value of pairwise CCA for capturing the complexity of overlap patterns that remain undetected using only an overall metric.

While demonstrating that the overlap phenomenon requires a careful—and likely layered—description, both studies highlighted that calculating CCA values relies on assumptions in constructing evidence matrices—assumptions that were neither explicit nor formally defined. Building on this insight, the third study systematically defined and tested these assumptions to evaluate their impact on overall and pairwise CCA assessments [146]. Variations in unit of analysis (overview-level versus outcome-level), scope adjustments, and structural missingness adjustments produced important differences in CCA values, ranging up to 15.7%. This indicates that methodological choices may substantially alter overlap estimates. By contrast, publication-thread adjustments had minimal impact in the sampled overviews, likely due to pre-processing of same-thread references prior to reporting. These findings underscore that standardising matrix construction is critical to ensure comparability and reproducibility in overlap assessments. Explicit definitions of units of analysis, scope, structural missingness, and CCA calculation approach are essential to avoid ambiguity and to provide transparency in overview methods. Standardising matrix construction—and ultimately, CCA calculations—should be considered a mandatory step before further advancing methods for quantitative overlap assessments (e.g., proposing new CCA thresholds, if appropriate).

Integration with previous research

The methodological challenges posed by overlap in overviews of systematic reviews have been widely recognised within the evidence synthesis community. As the volume of systematic reviews grows, redundancy and heterogeneity across reviews increasingly complicate drawing conclusions from evidence syntheses [42,43,50]. Despite the recognition of overlap as a methodological issue, prior

approaches have often relied on purely qualitative descriptions or overall metrics, which may obscure nuanced patterns across individual review pairs.

However, omission of overlap assessment remains a frequent methodological shortcoming [111,147,148]. A recent cross-sectional study estimated that only 48% of the overviews address overlap, with 21% using the CCA as an overlap metric [111]. Another meta-epidemiological appraisal on vaccination overviews found that when overlap was assessed, the CCA was the most common approach (applied in 32% of the overviews assessed), yet it informed an explicit methodological decision—such as excluding a systematic review with substantial overlap—in only a minority of cases [147]. Overall, overlap continues to be inconsistently assessed in overviews, and among those that do address it, no standardised approach exists to integrate or interpret it.

Previous methodological research has considered the CCA as an overall measure of overlap, trying to provide practical guidance [103,149]. This has encouraged some overview authors to treat the overall CCA as a benchmark for making methodological decisions. However, the current lack of consensus leaves overview authors without clear guidance on how to manage different overlap scenarios [111]. Table 1 presents a set of representative examples selected to illustrate the current diversity of methodological implications considered by overview authors after evaluating overlap using CCA. The absence of clear guidance may be primarily attributed to the limited attention that methodological research has given to first describing the overlap phenomenon itself, which is the main focus of this thesis. By providing explicit definitions of the assumptions underlying the CCA calculation and proposing a complementary pairwise approach—both theoretically and practically, including an automated tool and empirical evaluation—, this thesis seeks to lay the groundwork for future methodological guidance on the implications of overlap for overview interpretation.

Table 1. Examples of implications and variability of CCA assessments in recent overviews.

Overview title	Overlap assessment	Implications derived from CCA assessment
<i>Risk factors for running-related injuries: An umbrella systematic review [150]</i>	- Calculated only overall CCA at an overview-level. - No matrix available. - No description of assumptions for creating the matrix.	- Only description of overlap as 'slight' (overall CCA = 4%). - No methodological decision derived from overlap assessment. No clear purpose of overlap calculation, beyond its description.
<i>Umbrella review of systematic reviews on the efficacy and safety of using mesh in the prevention of parastomal hernias [151]</i>	Used fixed, predetermined thresholds for interpreting overlap (slight 0-5%, moderate 6-10%, high 11-15%, very high $\geq 15\%$).	- Conducted meta-analysis of already pooled results (i.e., meta-meta-analysis) due to 'slight overlap' (overall CCA = 0.97%). - Quote from discussion: "(...) we pooled the effect estimates of each review instead of the individual patients. Moreover, we used the CCA index to assess the extent of overlap of the original studies included in each systematic review, which indicated a slight overlap between the systematic reviews included in the pooled analysis"
<i>Clinical and pharmacokinetic/dynamic outcomes of prolonged infusions of beta-lactam antimicrobials: An overview of systematic reviews [152]</i>	- Calculated overall and pairwise CCA at an overview-level and outcome-level. - Matrices and graphical representation of pairwise CCA available. - No description of assumptions for creating the matrix. - Used fixed, predetermined thresholds for interpreting overlap (slight 0-5%, moderate 6-10%, high 11-15%, very high $\geq 15\%$).	- Several interpretations of review findings enhanced by overlap assessment. - Quote from the outcome 'microbiologic cure': "Despite the overall moderate overlap, pairwise overlap assessment confirms that the review by Yu et al. included four primary studies not found in the other three reviews and has no overlap with either of the 3 reviews that did not find a microbiological cure benefit with prolonged infusions when compared with intermittent administration". - Authors describe the variation of CCA values depending on the outcome being assessed: "Overlap of primary studies and proportion of unique primary studies were highly variable depending on the outcome assessed, ranging from 4.8% to 13.2% and 36% to 78%". - Authors discuss each outcome considering overall and pairwise CCA. This approach seemed to better explain the similarities or discrepancies in the findings of each review. - Authors also reflect on the possible bias derived from overlap: "Although overlap, as measured by CCA, was generally moderate to high for each clinical outcome studied, percentage of unique references ranged from 38–78%. Thus, as is typical of overviews, our findings are more strongly impacted by primary studies found in multiple reviews than not".

<i>The efficacy of acupuncture for post-stroke dysphagia: an overview of systematic reviews and meta-analyses [153]</i>	• Calculated overall and pairwise CCA at an overview-level, using GROOVE. • Graphical representation of pairwise CCA available.	• No explicit methodological decision predefined depending on CCA value. • CCA only mentioned to explain the results broadly: <i>“The overall CCA was 2.86%, indicating a slight overlap among included reviews. This low level of redundancy indicates that the included SRs and MAs were largely independent, thereby minimizing the risk of inflated or biased conclusions resulting from duplicated primary studies”</i>.
<i>Acupuncture Therapy for Sciatica: An Overview of Systematic Reviews and Meta-Analysis [154]</i>	• Calculated overall and pairwise CCA at an overview-level, using GROOVE. • Description of total number of primary studies overlapped among systematic reviews. • Graphical representation of pairwise CCA available.	• Overlap solved by excluding repeated primary studies before meta-analysis: <i>“To avoid duplication caused by overlapping SRs/MAs, we excluded redundant RCTs before conducting a secondary meta-analysis aimed at comprehensively evaluating the efficacy of acupuncture for sciatica”</i>. • Overlap interpreted in the discussion: <i>“Regarding study overlap, the degree of redundancy among original RCTs across SRs/MAs was moderate. Overlap typically reflects similarities in search timeframe, strategy, and methodology. However, some SRs/MAs conducted during similar periods had minimal or no overlap in included studies—an unexpected finding that suggests possible deficiencies in search strategies, inconsistencies in inclusion criteria, or reliance on single-database searches. These issues may have led to the omission of relevant literature and warrant further investigation”</i>.
<i>Effectiveness of virtual reality for functional disorders in cerebral palsy: an overview of systematic reviews and meta-analyses [155]</i>	• Calculated overall CCA at an overview-level. • Matrix available.	• ‘High’ degree of overlap found (overall CCA = 13.5%). • Decision to narratively summarise the findings: <i>“As the aim of this study was to summarize outcome measures rather than perform quantitative synthesis, no statistical methods were applied to address overlapping studies.”</i> • Authors propose how to handle overlap in future overviews: <i>“To handle substantial overlap among primary studies in systematic reviews, a two-step selection method is recommended. All non-overlapping systematic reviews should be included first. For overlapping reviews, priority should be assigned to Cochrane reviews, followed by an assessment of publication date, methodological quality, and relevance to the research question”</i>.

The findings from Study 2 illustrate why such refinement is needed. Pairwise CCA revealed highly overlapping review pairs that remained undetected when relying solely on overall CCA [145]. This reflects a fundamental limitation of the overall measure: it can mask substantial heterogeneity in overlap patterns, including situations where specific pairs exhibit high overlap despite a low overall CCA, and vice versa. Study 3 further strengthens this perspective by demonstrating how variations in scope, unit of analysis, and structural missingness affect CCA calculations, offering explicit definitions for matrix construction assumptions.

The GROOVE tool developed in study 1 advances this field by automating both overall and pairwise CCA and offering heatmap visualisations. When combined with the empirical findings from studies 2 and 3, these developments underscore the need for careful and standardised approaches to measuring and reporting overlap in overviews of systematic reviews. Together, these contributions provide a deeper understanding of the overlap phenomenon. By linking explicit assumptions, empirical pairwise insights, and an automated visualisation tool, this thesis offers a preliminary framework that integrates quantitative assessment with a more nuanced interpretation of overlap in overviews. This builds on earlier research that has highlighted how redundancy and discordance across systematic reviews may lead to misinterpretation and research waste [54,56–58]. The conceptual consequences of overlap underscore the need for precise, reproducible methods that can illuminate underlying patterns of evidence synthesis.

To date, matrix-based approaches to overlap—including those presented in this thesis—have treated every intersection within the matrix as equal. Recent proposals have sought to refine this by weighting matrix intersections according to the square root of each study's sample size (weighted CCA) or to the total population of the indexed primary studies (sample size-based CCA), thereby modifying the CCA calculation [156,157]. While these weighted approaches add a potentially informative layer, they also raise several practical and conceptual challenges. First, a statistical-based approach overlooks qualitative findings, whose contribution is not tied to sample size and thus cannot be appropriately

represented through such weighting. In overviews containing both quantitative and qualitative syntheses, or qualitative-only reviews, this risks producing an inconsistent or inadequate assessment of overlap. Second, it depends on additional assumptions about the primary studies (e.g., intention-to-treat versus per-protocol analyses in randomised trials), which may not be consistently reported. Third, the implementation of such approaches is likely to be labour-intensive. The methods are not automated and would require additional efforts in data extraction, which many times—as authors acknowledge—may require resolving inconsistent reporting about sample size by assessing the primary studies directly. Even more, applying such weighting at the outcome-level would further increase workload and complexity. Finally, at a more conceptual level, these approaches prompt a reflection on the purpose of overlap assessment in the first place. The primary role of overlap evaluation is often explanatory rather than purely statistical. Rather than aiming to produce a single summary statistic, overlap assessment enhances the interpretation of heterogeneous findings among reviews, aids the exploration of redundancy versus appropriate replication, and provides an overall landscape of the evidence in different subgroups, among others. Weighted CCAs may serve as a complementary approach in highly specific contexts, but their adoption as a general methodological standard is unlikely to be appropriate at this stage.

Overall contributions and implications

Taken together, the findings of this thesis demonstrate that while CCA as a quantitative metric may allow a precise assessment of overlap, it also exposes broader conceptual challenges that overlap poses for overviews. This thesis provides comprehensive methodological advances by integrating three complementary contributions: the GROOVE tool, which automates overall and pairwise CCA calculations and provides visual representations of overlap; the explicit definitions of matrix construction assumptions proposed in study 3; and empirical evidence from studies 2 and 3 showing how overlap estimates vary depending on pairwise versus overall CCA and on matrix construction choices.

Specifically, the three studies collectively show that:

- GROOVE automates and standardises overlap assessment, reducing the workload and promoting reproducibility.
- Pairwise CCA complements overall CCA, capturing granular overlap patterns that overall metrics may obscure.
- Matrix construction assumptions may impact CCA calculations, emphasising the need for standardised reporting and methodological guidance.

These contributions enhance consistent quantification and reporting of overlap, facilitating its interpretation and reproducibility. In this sense, they establish a methodological foundation for standardisation, including explicit definitions of units of analysis, scope, structural missingness, and CCA calculation approaches. By integrating pairwise analysis, structural adjustments, and automated tools, this thesis advances the rigour, transparency, and interpretability of overviews, supporting authors and decision-makers in navigating complex bodies of synthesised evidence.

The practical contribution of this thesis is reflected by its bibliographic metrics. The first paper of this thesis compendium was recognised by Wiley as a top cited article for the journal 'Research Synthesis Methods' in the period 2022-2023, and is currently the fourth item contributing more to the journal's impact factor [144]. According to Google Scholar, since its publication in May 2022 and until November 2025, GROOVE has been cited 162 times, mostly by overview authors actively using the tool and approach. It has also prompted methodological discussions and software development [141,157–160]. We actively proposed the Cochrane Collaboration to consider the pairwise CCA assessment for their Handbook (appendix 2), and although it has not been officially incorporated, some recent Cochrane overviews have already included this approach as part of their methods [161,162]. All of this reflects the broad acceptance and contribution of this thesis methodological advancements for the conduction of overviews.

Limitations and strengths

The studies conducted in the context of this thesis have some important limitations. First, GROOVE requires as input the construction of a matrix of evidence. This process is highly burdensome (as explicitly acknowledged in the third article of this compendium), and to our knowledge, there is still no computerised solution to automate it. GROOVE also has some limitations inherent to its implementation in Microsoft Excel. It currently supports up to 70 systematic reviews and 1,000 primary studies. Increasing these numbers would lead to a significantly slower performance of the software. Besides, GROOVE still relies on the originally defined thresholds of 5%, 10% and 15% CCA, which have already been challenged by our third study. Although GROOVE is probably sufficient for most overview authors in its current form, it is expected that for a minority this is not enough. An R package called 'ccaR' has been developed based on GROOVE's principles [158]. This package solves the problem of the amount of systematic reviews and primary studies supported, but it requires much more expertise to be used, and still carries the problem of the burdensome process of matrix construction.

The burdensome process of constructing evidence matrices also limited our capacity to analyse more overviews for the second and third study. Depending on its size, a single matrix of evidence may take several days or even weeks to be completed. This posed a major challenge in the conduct of the last two studies of this compendium, as it limited the total number sampled to analyse different CCA approaches (overall versus pairwise for study 2, and different assumptions for study 3), and therefore precluded us from making statistical inference. These initial, exploratory analyses, may have a double role of highlighting the need for automation of the matrix-construction process, while also providing the initial data for future advancements in methodological validation and guidance regarding overlap.

Beyond these limitations, this thesis has several strengths. First, GROOVE provides an easy-to-use tool to detailedly assess overlap. It enhances overlap

assessment, while saving time and resources for overview authors by automatically providing the absolute count of overlapped studies, and overall and pairwise CCA values, among other parameters. In second place, both the second and the third article of this thesis—which are methodological reviews—comply with appropriate reporting and methodological guidance. Third, beyond the CCA assessment itself, this thesis contributes to diagnosing how overview authors are dealing with overlap, highlighting the need to better account for this phenomenon. Although these findings were clearly presented in the second article, they were re-evaluated in the third article to examine trends in the consideration and implementation of overlap assessment by overview authors. In both articles, we also provide explicit discussions comparing these findings with other similar research. Fourth, the articles included in this thesis explicitly propose and define key concepts regarding overlap. The first article—which relies on the definition of CCA proposed by previous research [149]—proposes the concept of structural missingness as an additional layer of analysis. The second article explores the empirical difference of overall and pairwise assessments. The third article consolidates these proposals, by proposing other assumptions for creating and analysing evidence matrices and explicitly defining key concepts related to overlap assessment. Finally, the findings and overall reflections derived from this thesis have been widely disseminated in scientific congresses, conferences and other dissemination resources, as detailed in appendix 3.

Future developments

Although this thesis significantly advances methods for conducting overviews by focusing on overlap assessment, there is still substantial room for future development. There is an urgent need—not only for overviews but also for meta-epidemiological and bibliometric research—to create clear metadata regarding the citations in evidence syntheses. Currently, most journals provide an undifferentiated list of references for a given evidence synthesis, combining both general references and the included primary studies. Furthermore, there is no unified or automated system to clearly track publication threads across the published literature, and existing efforts largely rely on human efforts [52]. Having

a system of metadata with explicit citation networks effectively correlating the links between primary studies, systematic reviews and overviews could potentially automate the whole overlap assessment process—especially matrix construction—, which would largely alleviate the workload of overview authors.

As mentioned in the previous section, GROOVE (an Excel-based tool) and its counterpart ccaR (an R package) have some limitations. We are currently working on a new version of our tool called GROOVE-R, which we expect to be an important improvement. Although GROOVE-R is being developed in the R programming language, it aims to maintain the ease of use of the original, excel-based GROOVE tool. To do this, we are working on a shiny app, which will provide a web-accessible system for the tool. Besides, GROOVE-R will provide new features, such as the option to change (or omit) the thresholds, change colours, download the images in several formats, and explore uniqueness uniqueness of primary studies (i.e., the inclusion of data not repeated in any other SR), among others.

In addition to technological developments, there is an urgent need for methodological guidance. Since this thesis aimed to deepen the description of the overlap phenomenon, the next logical step is to generate recommendations on the methodological decisions to make once overlap has been thoroughly described. This may comprise several decisions, from the eligibility criteria and selection process to certainty of evidence assessments. However, perhaps the most important advance in the near future will be to clearly define the role of overviews within the evidence ecosystem.

Rethinking the role of overviews

Beyond its negative implications, overlap can serve as a lens through which to evaluate the broader landscape of evidence synthesis in a given field. Measuring and describing overlap—whether through pairwise CCA analyses or other systematic approaches—enables a critical appraisal of the proliferation and distribution of systematic reviews. Such assessment helps to clarify whether multiple reviews provide genuinely independent insights or represent redundant

efforts, offering a conceptual tool to gauge research efficiency and identify potential waste.

Traditionally, overviews have been conducted for several purposes: synthesising evidence from multiple reviews of different interventions for the same condition or population; comparing alternative approaches to the same intervention; assessing the same intervention across different populations or conditions; collating evidence on adverse effects; or examining variations in outcomes or time points within the same intervention [32]. Additionally, overviews may be used with a mapping intention, broadly exploring concepts or phenomena studied by the landscape of evidence syntheses [50,77,82,85,87]. Stakeholders and authors may also conduct overviews pragmatically to rapidly identify the available body of primary evidence by retrieving existing systematic reviews, updating their searches, and reanalysing primary study data [77,86,93,101,143,163–165]. In this way, overviews can serve as an efficient method to update existing systematic reviews. In summary, overviews currently serve three broad purposes: i) an analytical aim, by examining and comparing effect estimates across systematic reviews; ii) an exploratory aim, by mapping or exploring broader concepts in the body of evidence synthesis; and iii) an efficiency-related aim, by functioning as a rapid and resource-efficient synthesis approach.

However, alternative evidence syntheses approaches may provide more appropriate solutions for these objectives. Network meta-analyses can directly identify and assess primary studies, analyse their direct and indirect effects, and provide complete certainty of evidence assessments [166–168]. Scoping and mapping reviews may substitute the exploratory role of overviews by directly examining the primary study findings [24]. Living evidence synthesis aim to continuously update the searches and integrate new findings in real time [38,169], and although its implementation remains challenging, recent technological advances—particularly in the field of artificial intelligence—are expected to facilitate its widespread adoption in the near future [170–172].

In this context, it is imperative to revisit the role of overviews in the evidence ecosystem. Although computational advances may narrow the role of overviews

by enhancing a broader use of other types of evidence synthesis such as network meta-analyses or living systematic reviews, this thesis proposes that overviews are not primarily a substitute for statistical synthesis or a higher hierarchy type of evidence synthesis, but rather a methodological framework for mapping, contextualising, and interpreting complex bodies of synthesised evidence.

The process of prioritising a single systematic review when multiple are available—particularly in a decision-making context—is inherently complex. It requires weighing several dimensions, including methodological quality (e.g., completeness of reporting, risk of bias, and robustness of the search and synthesis methods), relevance to the specific decision contexts (e.g., alignment with the target population, interventions, comparators, and outcomes), and practical constraints faced by decision-makers (e.g., language barriers, time availability, and overall resources). Additional considerations may include the currency of the evidence, the degree of conceptual or scope alignment with the question at hand, the transparency of the review methods, and the assessment of potential conflicts of interests. This complexity explains why current recommendations on how to select the best type of evidence synthesis remain insufficient [73,74,173,174].

In this sense, overlap becomes a methodological advantage rather than a limitation. By highlighting areas of convergence and divergence across systematic reviews, overlap enables a more nuanced evaluation of each review scope, strengths, and weaknesses. Then, it allows to shift the critical question, from identifying the *best* systematic review to selecting an *appropriate* review for a specific purpose or decision context. Overviews are not necessarily designed to reanalyse quantitative data or qualitative findings; rather, their primary role should be to present the findings from the included systematic reviews and decide which review should be prioritised—or, alternatively, whether a new review is warranted. Overviews may achieve this by contrasting the review findings, and evaluating their scope, quality, relevance, and overlap. By mapping patterns of overlap across reviews, overviews can support informed decision-making by highlighting which evidence is most applicable to a given context, rather than attempting to generate a new pooled estimate or reinterpret primary findings directly. For

instance, one review may be methodologically robust yet narrow in scope, whereas another may offer broader applicability despite certain methodological limitations. Overlap analysis helps clarify these distinctions and guides decision-makers toward the evidence most relevant to their specific context.

Finally, overlap assessment may provide overviews with a meta-epidemiological role. Overlap consideration enriches the discussion on the spectrum between unnecessary duplication and valid scientific replication [175]. High overlap may indicate redundant efforts, prompting reflection on research prioritisation, yet it can also reflect deliberate replication that strengthens cumulative knowledge. By highlighting these distinctions, overlap assessment links methodological rigour with conceptual insight, reinforcing the role of overviews not only as tools for evidence synthesis but also as instruments for evaluating the broader research ecosystem.

Conclusion

This thesis critically evaluated and advanced methodologies to address the overlap of primary studies in overviews of systematic reviews, aiming to improve the quality and efficiency of the conduct of overviews. By examining current practices, developing new tools, and clarifying methodological assumptions, we provide a stronger foundation for assessing and interpreting overlap—a central issue in overview methodology.

The development of GROOVE operationalised both overall and pairwise CCA assessments, enabling authors to quantify overlap and uncover specific duplication patterns across review pairs.

The empirical evaluation of existing overviews revealed that many authors still neglect overlap, highlighting the need for stronger guidance and more consistent implementation. It also demonstrated that pairwise analysis offers additional insights by revealing localised patterns concealed by overall metrics.

This thesis systematically defined and tested assumptions for constructing evidence matrices and calculating CCA, clarifying conceptual and operational ambiguities. Building on this, we challenge the use of rigid CCA thresholds and support a more nuanced interpretation of overlap metrics—one that accounts for matrix construction decisions and the intended context of use for the overview.

Collectively, these contributions underscore the importance of routine and detailed overlap assessment. Conceptually, interpreting overlap strengthens the role of overviews in selecting the most appropriate reviews for each context and in distinguishing valid replication from research waste.

Glossary

This section provides operational definitions for the key terms used in this thesis.

- **Covered area (CA):** A quantitative measurement of the proportion of primary studies included across systematic reviews in a matrix of evidence, without accounting for multiple counts of the same study.
- **Corrected covered area (CCA):** A metric that quantifies the degree of overlap of primary studies across different SRs, expressed as a percentage. CCA is derived from a matrix of evidence, ranging from 0% (no overlap) to 100% (total overlap).
- **Evidence ecosystem:** Any conceptual theoretical framework that integrates the processes of evidence generation, synthesis, and translation.
- **Evidence synthesis:** A type of research that assesses the phenomenon of interest by considering other research as the unit of analysis, and not directly the subjects experiencing the phenomenon of interest. Also called “secondary research” or “secondary studies”.
- **GROOVE:** An acronym for the tool called “Graphical Representation of Overlap for OVERviews”, which provides automatic overall and pairwise CCA analyses, and a graphical display of these results, among other parameters.
- **Matrix of evidence:** A grid that maps the systematic reviews against their respective primary studies.
- **Meta-review:** See “overview”.

- **Outcome-level overlap assessment:** The consideration of each outcome as a unit of analysis for purposes of creating matrices of evidence and calculating CCA.
- **Overall CCA:** The calculation of a unique CCA value for a given matrix of evidence.
- **Overlap of primary studies:** The consideration of data from the same set of primary studies across two or more systematic reviews within a specific overview. This phenomenon may also be referred to as “overlapping systematic reviews”. For purposes of this thesis, this may be simply referred to as “overlap”.
- **Overview:** A specific type of evidence synthesis that considers systematic reviews as the unit of analysis, instead of primary studies. It may be also called “overview of reviews”, “umbrella reviews”, “meta-reviews”, “systematic review of systematic reviews”, among others.
- **Overview-level overlap assessment:** The consideration of the whole overview as the unit of analysis for purposes of creating matrices of evidence and calculating CCA.
- **Pairwise CCA:** The calculation of multiple CCA values for a given matrix of evidence, each representing the specific overlap for every possible pair of SRs.
- **Primary research:** See “primary study”.
- **Primary study:** A type of research that assesses the phenomenon of interest directly in the subjects of study at a sub-individual, individual or population level. It may be also called “primary research”.

- **Publication-thread adjustment:** The consideration of each set of references related to a single primary study as a unique row in a matrix of evidence, instead of multiple rows.
- **Scope adjustment:** The consideration—and inclusion in the matrix—only of the primary studies that provide useful data for a given outcome within an overview.
- **Secondary research:** See “evidence synthesis”.
- **Secondary study:** See “evidence synthesis”.
- **Structural missingness:** An intersection in a matrix of evidence that cannot acquire a value other than blank due to plausible reasons (e.g. chronological). It may be also called “structural zero”.
- **Structural missingness adjustment:** The exclusion of primary studies that cannot be included in the SRs due to methodological constraints for purposes of CCA calculation. In practical terms, it is a modification of the CCA formula, where the number of intersections considered as structurally missed are subtracted from the denominator.
- **Systematic methods:** Set of methodological standards used in the context of evidence synthesis that comprehends the explicit reporting of the research question, search sources, eligibility criteria, methods for selection of the studies, critical appraisal, and data analysis/synthesis of the included studies, in a predefined and transparent manner.
- **Systematic review:** A type of evidence synthesis that uses systematic methods to identify, select, assess and summarise all the relevant primary studies available to a specific research question.
- **Systematic review of systematic reviews:** See “overview”.

- **Umbrella review:** See “overview”.
- **Waste research:** Any type of research that assesses irrelevant questions, has inadequate design or methods, is non-accessible, or is reported in a biased or unusable manner.

Appendices

Appendix 1. Accompanying manuscripts for this doctoral thesis

Opinion or discussion papers authored by the doctoral candidate directly related to this thesis

Received: 8 June 2022 | Accepted: 3 July 2022
DOI: 10.1002/jrsm.1588

Check for updates

LETTER TO THE EDITOR

Research
Synthesis Methods WILEY

Response to: ‘Additional considerations and response to Graphical Representation of Overlap for OVERviews (GROOVE tool)’

We thank Thabet et al. for their interest in our proposed tool and methods for analysing the overlap of primary studies among systematic reviews. As they imply, we aimed to complement the overall assessment proposed by Pieper et al.¹ and the recommendations made by Hennessy et al.² using a pairwise approach of the corrected covered area (CCA), and incorporating a novel consideration for adjusting the CCA by structural missingness.³

As Thabet et al state, the overlap assessment using GROOVE methods could be more informative when conducted at an outcome level. An overlap assessment at the overview level (i.e., the whole set of systematic reviews included in an overview) may be helpful in getting a general idea about that specific body of evidence, yet an outcome-level assessment of overlap could be more reliable in terms of describing the body of evidence adjusted for the scope of a specific outcome. In other words, an outcome-level assessment allows removing both systematic reviews and primary studies that do not provide valuable data for a given outcome. Thus, it should be noted that an outcome-level assessment may result in a higher CCA than an overview-level assessment, so results should be interpreted upon a rationale based on the scope of the question that arranges the overview. Ultimately, this approach resembles the risk of bias assessment for systematic reviews: risk of bias assessment at a primary study level could deliver an element-by-element description of the body of evidence, but an assessment made at an outcome-level allows (among other factors) to estimate the certainty of evidence. In this sense, as the certainty of evidence estimation requires a series of assumptions to meet its final categories (i.e., high, moderate, low, or very low), CCA interpretation could also result from a well-established multidimensional framework additional to GROOVE, eventually.

The consideration of structural missingness when assessing overlap using the CCA formula is a novel concept proposed by our team. In our paper, we described the chronological criteria as a basic type of structural missingness—although not the only one. GROOVE could be considered a proof of concept approach regarding this idea since its utility and interpretation have not been

studied yet. Therefore, as stated by Thabet et al, we agree that the interpretation of CCA when considering structural missingness should be cautious.

In their letter, Thibaut et al have highlighted the implications of having, in a matrix of evidence, the primary studies included by only one systematic review in the overview, (i.e., unique primary studies). This could facilitate the interpretation of matrices, although the readability of this approach is increasingly difficult as the matrix becomes larger. Other types of structural missingness (e.g. based on search strategies or eligibility criteria of the systematic reviews) may explain why these unique primary studies have not been identified or included by the other systematic reviews.

On the other hand, a highly overlapped primary study (that is, a primary study included in all or most of the systematic reviews within an overview) may even serve as a proxy for updating the overview using a forward citation search strategy.⁴ Under the assumption that one or more primary studies have been easily identified by all or most of the systematic reviews, it could be expected that future systematic reviews with the same scope will probably also include those studies. Therefore, it could be hypothesised that a matrix of evidence might not only serve as a way for describing the current body of evidence and overlap, but it could also be a starting point for rapidly updating overviews, assuming that all relevant future systematic reviews will have a CCA >0% when incorporated to the current matrix of evidence. Even more, a GROOVE approach could track the continuous updating or development of new systematic reviews (from which structural missingness results) for specific outcomes over time.

Finally, we would like to thank the analysis conducted by Thibaut et al. We think the methodology proposed by GROOVE facilitates the overlap assessment and adds value to the interpretation of the results, at the same time that it gathers many other potential uses beyond the development of overviews themselves (rapid recommendations, meta-epidemiological studies, etc.). Likewise, we think that the iterative use of GROOVE will allow knowing its scope and limitations, which could lead to the

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conceptualisation of a comprehensive framework aiming to an adequate interpretation of CCA. Similarly, the cumulative experience gained from the application of GROOVE will feed the discussion about both the CCA thresholds and their mathematical formulation. We are aware that this topic still needs to be studied, but we hope our approach makes current overlap assessment easier and more accurate for overview authors.

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AUTHORS CONTRIBUTION

All authors made substantial contributions to the conception and design of this letter. JB drafted the article. NM and EM revised the article critically for important intellectual content. All authors provided approval for this letter to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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2. Hennessy EA, Johnson BT. Examining overlap of included studies in meta-reviews: guidance for using the corrected covered area index. *Res Synth Methods*. 2020;11(1):134-145. doi:10.1002/jrsm.1390
3. Pérez-Bracchiglione J, Meza N, Bangdiwala SI, et al. Graphical representation of overlap for OVERviews: GROOVE tool. *Res Synth Methods*. 2022;13(3):381-388. doi:10.1002/jrsm.1557
4. Haddaway NR, Grainger MJ, Gray CT. Citationchaser: a tool for transparent and efficient forward and backward citation chasing in systematic searching. *Res Synth Methods*. 2022;13(4):533-545. doi:10.1002/jrsm.1563

Relevant articles (authored or co-authored by the doctoral candidate) related to this thesis

Full reference: Vergara-Merino L, Meza N, Couve-Pérez C, Carrasco C, Ortiz-Muñoz L, Madrid E, Bohorquez-Blanco S, Pérez-Bracchiglione J. Maternal and perinatal outcomes related to COVID-19 and pregnancy: An overview of systematic reviews. *Acta Obstet Gynecol Scand*. 2021 Jul;100(7):1200-1218. doi: 10.1111/aogs.14118. Epub 2021 Apr 2. PMID: 33560530; PMCID: PMC8014248.

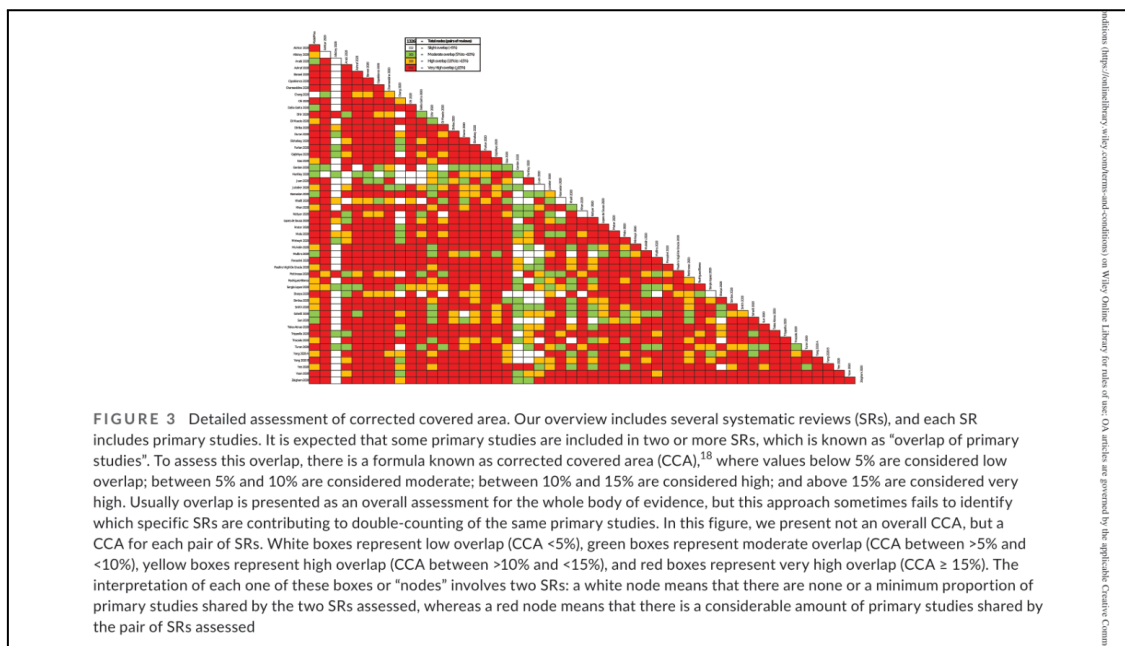
Relevance for this thesis: This is the first overview that describes the pairwise CCA approach and its graphical representation, using a preliminary version of the GROOVE tool [142].

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DOI: 10.1111/aogs.14118

SYSTEMATIC REVIEW

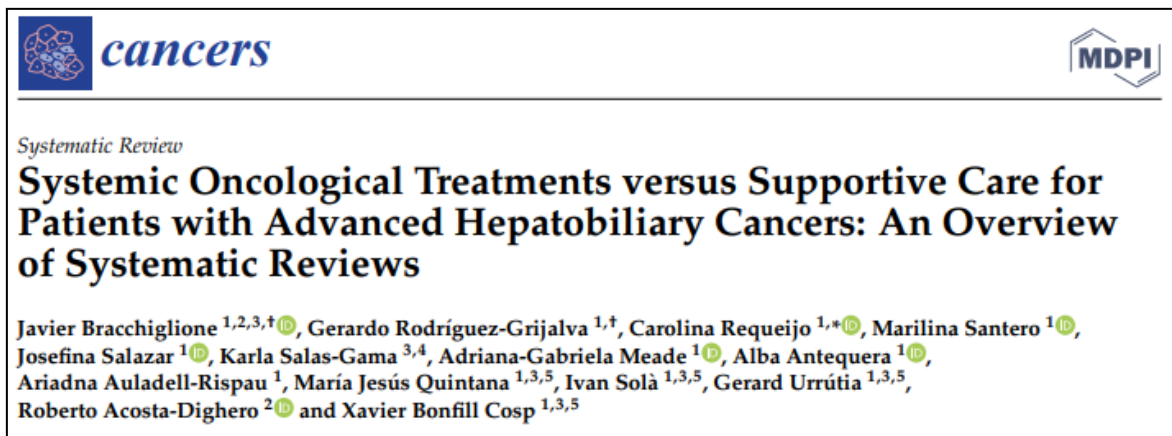
Maternal and perinatal outcomes related to COVID-19 and pregnancy: An overview of systematic reviews

Laura Vergara-Merino¹ | Nicolás Meza¹ | Constanza Couve-Pérez² |
Cynthia Carrasco¹ | Luis Ortiz-Muñoz³ | Eva Madrid¹ |
Sandra Bohorquez-Blanco⁴ | Javier Pérez-Bracchiglione¹



Full reference: Bracchiglione J, Rodríguez-Grijalva G, Requeijo C, Santero M, Salazar J, Salas-Gama K, Meade AG, Antequera A, Auladell-Rispau A, Quintana MJ, Solà I, Urrútia G, Acosta-Dighero R, Bonfill Cosp X. Systemic Oncological Treatments versus Supportive Care for Patients with Advanced Hepatobiliary Cancers: An Overview of Systematic Reviews. *Cancers* (Basel). 2023 Jan 26;15(3):766. doi: 10.3390/cancers15030766. PMID: 36765723; PMCID: PMC9913533.

Relevance for this thesis: First overview to show a matrix of evidence considering structural missingness, and GROOVE tool's full report output [143].



Primary Studies		Systematic Reviews																	
Study ID	Reference	Ling-lin 2011	Zhang 2012	Faruque 2014	Finn 2017	Abdel-Rahman 2018	Guo 2019	Huang 2019	Sonbol 2020	Zlogas 2021	Park 2021	Chen 2021	Meyers 2021	Haber 2021	Jiang 2021	Jacome 2021	Liu 2021	Sollimando 2022	Griffiths 2022
SHARP	Ulovet 2008	1	1	1	1		1	1	1		1			1				1	1
(-)	Cheng 2009	1	1	1	1		1	1	1		1			1				1	1
(-)	Sharma 2010					1									1				
(-)	Hsu 2012	X	X	X			1												
BRISK-PS	Ulovet 2013	X	X	X			1		1		1	1	1	1				1	1
(-)	Santoro 2013	X	X	X			1				1	1	1	1				1	1
(-)	Rimassa 2013	X	X	X			1	1											
(-)	Yen 2014	X	X	X									1						
EVOLVE-1	Zhu 2014	X	X	X							1	1	1	1				1	1
(-)	Ji 2014	X	X	X				1											
REACH	Zhu 2015	X	X	X			1		1		1	1	1	1				1	1
(-)	Kang 2015	X	X	X			1				1	1						1	1
(-)	Abou-Alfa 2016	X	X	X	X		1											1	
RESORCE	Bruix 2017	X	X	X	X		1		1		1	1	1	1				1	1
S-CUBE	Kudo 2017	X	X	X	X								1	1					
METIV-HCC	Rimassa 2018	X	X	X	X	X					1	1	1	1				1	1
(-)	Abou-Alfa 2018	X	X	X	X	X		X					1	1				1	
CELESTIAL	Abou-Alfa 2018b	X	X	X	X	X	1	X	1		1	1	1	1				1	1
REACH-2	Zhu 2019	X	X	X	X	X	X	1	1	1	1	1	1	1				1	1
KEYNOTE-240	Finn 2019	X	X	X	X	X	X	1	1	1	1	X	1	1		1		1	1
(-)	Li 2020	X	X	X	X	X	X	X	X		X	X	X			X			
JET-HCC	Kudo 2020	X	X	X	X	X	X	X	X		X	X	X	1		X		1	

Figure 2. Matrix of evidence. All the included SRs are listed in the columns. All the relevant primary studies (i.e., those reporting at least one outcome of interest for the studied interventions) are listed in the rows. ‘1’ represents a primary study included in a specific SR. ‘X’ represents chronological structural missingness, that is, a primary study that cannot possibly be included in a SR, given that its publication date was more recent than the search date of the SR.

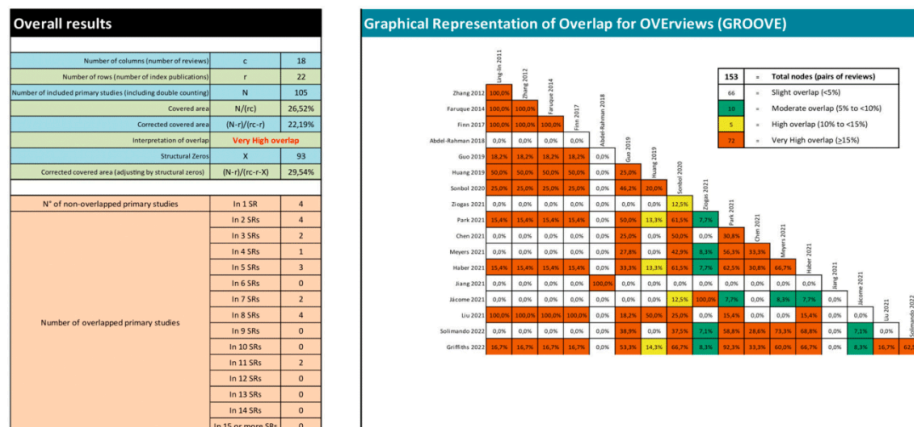


Figure 3. ‘Graphical representation of overlap’ (GROOVE) assessment for each possible pair of SRs. For purposes of pairwise analysis of CCA, we did not consider structural missingness.

Full reference: Cruzat B, Reveco-Guzmán K, Encina-Meneses M, Ortiz-Muñoz L, Bracchiglione J. Approaching the body of evidence: Key concepts of Overviews. *Medwave* [Internet]. 2023 Jun 6;23(5). Available from: <http://dx.doi.org/10.5867/medwave.2023.05.2704>

Relevance for this thesis: An article aimed for a broad audience that presents general overview concepts, with a discussion that introduces and contextualises CCA, GROOVE, and pairwise overlap assessment [80].

REVIEWS

Approaching the body of evidence: Key concepts of overviews

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Citation
Cruzat B, Reveco-Guzmán K, Encina-Meneses M, Ortiz-Muñoz L, Bracchiglione J. Approaching the body of evidence: Key concepts of overviews. *Medwave* 2023;23(5):e2704

Abstract

The increasing production of primary research and literature reviews in the last decades has made it necessary to develop a new methodological design to synthesize the evidence: the overviews. An overview is a type of evidence synthesis that uses systematic reviews as the unit of analysis, with the aim of extracting and analyzing the results for a new or broader research question, helping the shared decision-making processes. The aim of this article is to introduce the reader to this type of evidence summaries, highlighting the differences between overviews and other types of synthesis, the unique methodological aspects of overviews, and future challenges. This is the twelfth article from a collaborative methodological series of narrative reviews about biostatistics and clinical epidemiology.

Relevance for this thesis: First overview that assessed outcome-level overlap using GROOVE's pairwise approach and its graphical representation [135].



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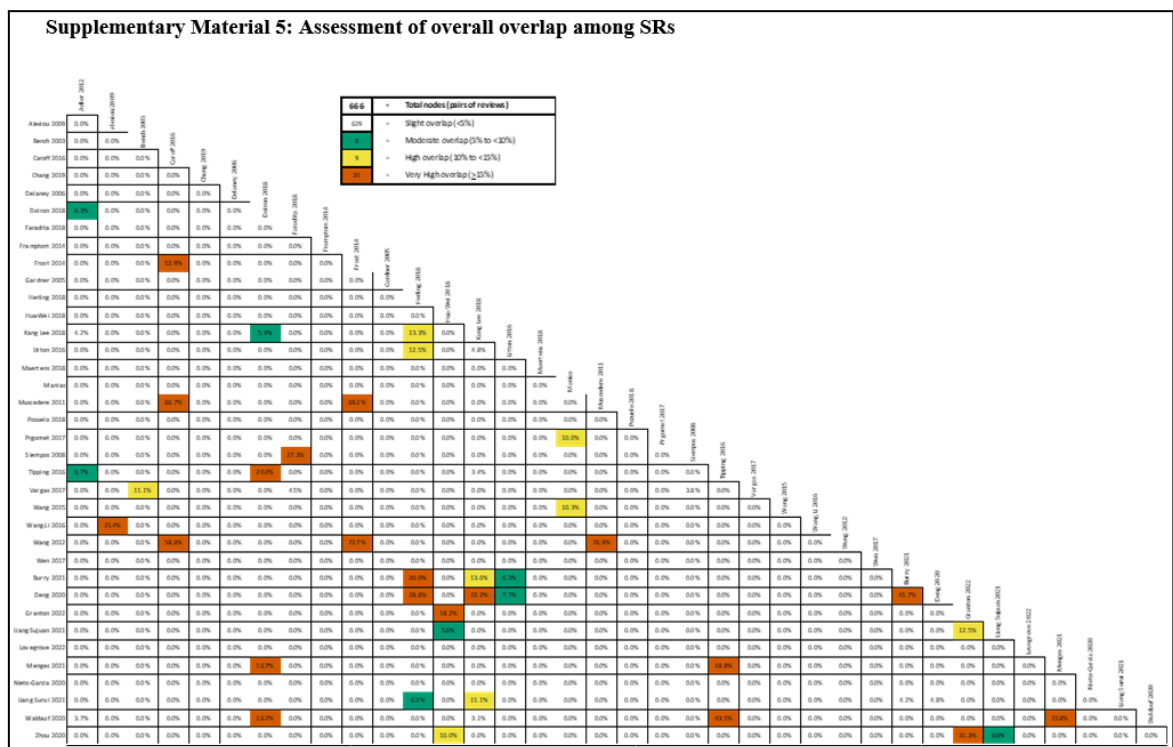
Australian Critical Care

journal homepage: www.elsevier.com/locate/aucc



Australian
Critical Care





Adverse event	Outcome	Comparison	Systematic reviews	Overlap assessment				
				CCA†	Detailed CCA by pairs of reviews			
2. Delirium	2.1 Incidence of delirium	2.1.1 Environmental intervention vs usual care	Burry 2021 Deng 2020 Herling 2018 Liang Surui 2021	10.3% High		Herling 2018 20.0%	Burry 2021 41.7%	Deng 2020 4.8%
					Burry 2021 28.6%			
					Deng 2020 6.3%			
					Liang Surui 2021 4.2%			
3. Reintubation	3.1 Rate of Reintubation	3.1.1 High-flow nasal cannula vs Conventional oxygen therapy	Granton 2022 Hua-Wei 2018 Liang Sujuan 2021 Zhou 2020	38.9% Very high		Hua-Wei 2018 50.0%	Granton 2022 16.7%	Liang Sujuan 2021 16.7%
		3.1.2 Noninvasive ventilation vs Conventional oxygen therapy	Granton 2022 Hua-Wei 2018 Liang Sujuan 2021 Zhou 2020	14.3% High		Hua-Wei 2018 33.3%	Granton 2022 0.0%	Liang Sujuan 2021 20.0%

Appendix 2. Proposal to the Cochrane Collaboration: Pairwise CCA approach for assessing overlap of primary studies in overviews

<https://methods.cochrane.org/cochrane-method-or-tool-interest-form>

Submitted May 18, 2023

Cochrane method or tool of interest form

Please complete and submit this "Method or Tool Interest Form". Submissions will be triaged by the Methods Executive and if applicable, will be escalated to the Scientific Committee. This form records essential information to enable consideration by either group. We will acknowledge receipt of submission. Following assessment of your submission you will receive notification on further action or their position. The Methods Implementation Manager will liaise with you if further information and supporting evidence is required.

Short title of method or method-related development

Pairwise approach using the corrected covered area formula to assess overlap of primary studies in overviews.

Name

Javier Bracchiglione

Person completing this form

Email

javier.bracchiglione@gmail.com

Main Cochrane Affiliation (if any)

Iberoamerican Cochrane Centre
Cochrane Chile

List all Cochrane groups and entities with which you are affiliated using separate rows.

Lead researchers submitting the proposal

Javier Bracchiglione
Nicolás Meza
Eva Madrid
Gerard Urrútia

Xavier Bonfill Cosp

List all lead researchers or developers, if known, using separate rows.

Confirm explicitly how, and in what context, you would like Cochrane to consider the method or tool

Overlap of primary studies among systematic reviews (SRs) included in an overview may be approached at different stages in the overview development process. As stated in section V.4.7 of the Cochrane Handbook, at a minimum authors should create a citation matrix to assess overlap, and may also calculate the 'corrected covered area' (CCA) to quantify its degree.

These approaches may be enough in certain cases, especially if the amount of included evidence is limited. However, as the identified body of evidence becomes larger, matrices of evidence become more difficult to interpret, and CCA calculation tends to be diluted. In this context, we propose complementing the overall CCA calculation using a pairwise approach (i.e. iterate the CCA calculation for each possible pair of included SRs, and not only for the whole matrix). We developed this approach and created a tool already published (GROOVE, see references below).

We think that overview authors may use this approach to enhance their analysis and interpretation of results. The pairwise approach allows to conduct a more detailed assessment of primary studies overlap, and may identify specific pairs of SRs highly overlapped in contexts of low overall CCA, or vice versa.

Briefly detail why you think Cochrane should consider the method or tool and how you envision it being used in Cochrane Reviews. Please state whether your proposal is to replace an existing method or if it is to be used in parallel with current methods. Please state if you are seeking Cochrane's approval, endorsement, mandate or other (<200 words).

Detail what contribution or communication you have had with the Cochrane Methods Group relevant to the method or tool

None

Briefly detail which Methods Groups you have been in contact with and describe the level of collaboration and any support for the development of your proposal, if any. A list of the Methods Groups can be found here (<200 words).

Aims and objectives

- To complement the overall CCA assessment of overlap of primary studies among SRs included in an overview, with a pairwise approach.

Briefly describe the aims and objectives of the method or development (<200 words).

Key features

We have thoroughly described our approach in the GROOVE (Graphical Representation of Overlap for OVERviews) paper. Starting from a matrix of evidence, GROOVE provides the overall CCA assessment and a pairwise CCA assessment, as well as the number of included primary studies and SRs included in the matrix, and the absolute number of overlapped and non-overlapped primary studies.

The GROOVE approach provides both an overall CCA and a pairwise CCA.

- The overall approach is the classical method of calculating the CCA for the whole matrix of evidence (already recommended in the Cochrane Handbook).
- The pairwise approach calculates a CCA for each possible pair of SRs included in the overview. In other words, it calculates the CCA that a matrix would have if only two SRs were included into it, and repeats this process for every possible pair of SRs.

The pairwise approach allows detecting highly overlapped pairs of SRs in a context of low-overall overlap, as well as non-overlapped pairs of SRs in a context of high-overall overlap. The results are displayed in an easy-to-read figure.

The tool also proposes a modification of the original formula based on the 'structural missingness' optional feature (defined as an intersection in the matrix of evidence that cannot acquire a value other than blank). However, this specific feature has not been empirically tested so far, so we think it is not ready to be recommended yet.

Briefly describe the key features of the method or development or methodological problem. Please state whether the method should be applied in standard Cochrane Reviews, specific types of reviews or whether more experimental (<300 words).

Implementation considerations

The GROOVE tool is publicly available as an Excel file. A GROOVE-based R package (ccaR) has also been developed. Overview authors may need to include additional figures to show the pairwise assessment. To be integrated in RevMan, first it will need to include an evidence matrix generator.

For the time, we think that the available tools may be enough for Cochrane overview authors. A recent Cochrane overview protocol has already cited GROOVE as part of its methods (<https://doi.org/10.1002/14651858.CD015044>)

Briefly highlight any potential implementation considerations you envision, including, but not limited to; developments to Cochrane systems or tools, e.g. RevMan functionality or integration; specific requirement for publications and how it's visualised; whether it generates large datasets, how these should be managed and whether they should be published; and requirements for training authors, editors and/or peer reviewers, etc.

Key supporting information, publication(s) and guidance document(s)

1. Pérez-Bracchiglione J, Niño de Guzmán E, Roqué Figuls M, Urrútia G. Graphical representation of overlap degree of primary studies in systematic reviews included in overviews. *Cochrane Colloquium*. 2019, Santiago, Chile. Available at <https://colloquium2019.cochrane.org/abstracts/graphical-representation-overlap-degree-primary-studies-systematic-reviews-included>
2. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: practical considerations for authors of overviews of reviews. *BMC Med Res Methodol*. 2021 Jul 7;21(1):140. doi: 10.1186/s12874-021-01269-y. PMID: 34233615; PMCID: PMC8265144.
3. Bougioukas KI, Vounzoulaki E, Mantsiou CD, Savvides ED, Karakosta C, Diakonidis T, Tsapas A, Haidich AB. Methods for depicting overlap in overviews of systematic reviews: An introduction to static tabular and graphical displays. *J Clin Epidemiol*. 2021 Apr;132:34-45. doi: 10.1016/j.jclinepi.2020.12.004. Epub 2020 Dec 9. PMID: 33309886.
4. Pérez-Bracchiglione J, Meza N, Bangdiwala SI, Niño de Guzmán E, Urrútia G, Bonfill X, Madrid E. Graphical Representation of Overlap for OVERviews: GROOVE tool. *Res Synth Methods* [Internet]. 2022 May;13(3):381-8. Available from: <http://dx.doi.org/10.1002/jrsm.1557>
5. Thabet P, Kanji S, Pieper D, Lunny C. Additional considerations and response to 'graphical representation of overlap for OVERviews (GROOVE tool)'. *Res Synth Methods*. 2022 Sep;13(5):548-551. doi: 10.1002/jrsm.1586. Epub 2022 Jul 27. PMID: 35798685.
6. Bracchiglione J, Meza N, Madrid E. Response to: "Additional considerations and response to Graphical Representation of Overlap for OVERviews (GROOVE tool)." *Res Synth Methods* [Internet]. 2022 Jul 7; Available from: <https://onlinelibrary.wiley.com/doi/10.1002/jrsm.1588>
7. Bracchiglione J, Meza N, Pérez-Carrasco I, Vergara-Merino L, Madrid E, Urrútia G, Bonfill X. A methodological review finds mismatch between overall and pairwise overlap analysis in a sample of overviews. *J Clin Epidemiol* [Internet]. 2023 May 8; Available from: <https://www.sciencedirect.com/science/article/pii/S0895435623001129>
8. Bougioukas KI, Diakonidis T, Mavromanoli AC, Haidich AB. ccaR: A package for assessing primary study overlap across systematic reviews in overviews. *Res Synth Methods*. 2023 May;14(3):443-454. doi: 10.1002/jrsm.1610. Epub 2022 Nov 20. PMID: 36369993.

If applicable, please list primary references. You can upload unpublished documents, such as proof of performance, details of testing or piloting, information on the acceptability of the method or tool, or other guidance using the link below.

Cochrane Methods_Submission #154: About your application

4 mensajes

Ingrid Arévalo-Rodríguez <iarevalo@cochrane.org>

16 de octubre de 2023, 10:01

Para: "javier.bracchiglione@gmail.com" <javier.bracchiglione@gmail.com>

CC: Gerard Urrutia <gurrutia@santpau.cat>

Dear Javier,

We hope this email finds you well. We are contacting you regarding your submission about a new methodological tool for developing Cochrane Overviews (enclosed in this message). Your application was assessed following the [procedure stated on our Methods Website](#), involving relevant members of the [Methods Executive](#) and our Methods Community. In this particular case, we also consulted authors of the *Cochrane Handbook for Systematic Reviews of Interventions*.

The assessment of primary study overlap is addressed in [Chapter V](#) of the *Cochrane Handbook for Systematic Reviews of Interventions*, suggesting a few methodologies as "minimum" measures to map the extent of overlap. We noticed that the chapter is open to other approaches not explicitly mentioned in the content, allowing authors to use other measures that would be helpful to address this issue with reasonable justification for why the method is appropriate in that case (we recommend including references that show it has been validated).

Since this approach is a new methodology that would be useful for Cochrane authors, chapter authors will consider this new methodology for the next content update of the *Cochrane Handbook for Systematic Reviews of Interventions*. Please note the current version of the *Handbook* (v6.4) has not introduced major scientific changes to this chapter, because the authors still consider the content to be accurate and valid. However, they are aware of new methodologies related to the development of overviews, and a new updated chapter will be under consideration in the near future.

Further implementation in RevMan might also be considered in due time; however, please be aware the implementation of tools and methods regarding overviews are not in the current roadmap for RevMan due to other priority developments. However, methods can be used outside RevMan in other software, with figures or other visual representations imported as needed.

We would like to thank you for your interest and help in keeping our methodologies up to date. We look forward to knowing more about your future endeavours in due time.

Kind regards,

Ingrid

Ingrid Arevalo-Rodriguez (MSc, PhD)

Methods Implementation Editor

Evidence Production and Methods Directorate

Cochrane Central Executive Team



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Appendix 3. Dissemination of findings related to this thesis

Invited conferences:

- “Overlap of primary studies in overviews.” Invited speaker, Therapeutics Initiative, The University of British Columbia. February 2024. Available at: <https://youtu.be/QDrbL3zxUrU?si=9zAh-eUwOxCHzxzy>
- “¿Qué hago con tanta evidencia? Haciendo un overview en la vida real” [“What to do with so much evidence? Conducting an overview in real life”]. III Cochrane Colombia Symposium, Bogotá, Colombia. October 2024.
- “Overviews.” XIX Annual Meeting of the Iberoamerican Cochrane Network / II International Congress of Evidence-Based Medicine, Quito, Ecuador. June 2023.
- “GROOVE: Graphical Representation of Overlap for OVERviews.” XVIII Annual Meeting of the Iberoamerican Cochrane Network, Barcelona, Spain. October 2022.

Blog entry:

- “Mirando el bosque más allá del árbol: ¿Qué son los overviews?” [“Looking at the forest beyond the tree: What are overviews?”]. *Estudiantes x la Mejor Evidencia*. June 2023. Available at: <https://exme.cochrane.org/blog/2023/04/06/mirando-el-bosque-mas-alla-del-arbol-que-son-los-overviews/>

Poster presentations at scientific congresses:

- “Overlap of primary studies on an overview of the effectiveness of pharmacological interventions for the prevention of adverse events.” Co-author. Global Evidence Summit, Prague, Czech Republic. September 2024. Available at: <https://abstracts.cochrane.org/2024-prague-global-evidence-summit/overlap-primary-studies-overview-effectiveness-pharmacological>

- “Mismatch between overall and pairwise overlap analysis in a sample of overviews: A methodological review.” First author. Cochrane Colloquium, London, UK. September 2023. Available at: <https://abstracts.cochrane.org/2023-london/mismatch-between-overall-and-pairwise-overlap-analysis-sample-overviews-methodological>
- “Overlapping of primary studies in a review of systematic reviews on interventions to prevent adverse events”. Co-author. Cochrane Colloquium. London, UK. September 2023. Available at: <https://abstracts.cochrane.org/2023-london/overlapping-primary-studies-review-systematic-reviews-interventions-prevent-adverse>

Oral presentation at scientific congresses:

- “Graphical representation of overlap degree of primary studies in systematic reviews included in overviews”. First author. Cochrane Colloquium. Santiago, Chile. October 2019. Available at: <https://abstracts.cochrane.org/2019-santiago/graphical-representation-overlap-degree-primary-studies-systematic-reviews-included>
- “*Solapamiento de estudios primarios en una revisión de revisiones sistemáticas sobre intervenciones para prevenir eventos adversos*” [“Overlap of primary studies in a review of systematic reviews about interventions to prevent adverse events”]. Co-author. XVIII annual meeting of the Iberoamerican Cochrane Network. Barcelona, Spain. October 2022.

Appendix 4. List of published articles by the author during the PhD period

This list includes only articles published in indexed, peer-reviewed journals, not considering the main articles of this thesis.

1. Whaley P, Alper B, Dehnbostel J, Alva-Diaz C, Antoniou S, Bognanni A, **Bracchiglione J**, Dalsbø TK, Grant S, Hunter J, Iorio A, Lagisz M, Lehmann H, Li S, Meerpohl J, Mokrane S, Monaco C, Neumann I, Pottier K, Sayfi S, Sekercioglu N, Singh J, Sousa-Pinto B, Tufte J, Vasanthan LT, Wang L, Xia J, Yao X, Schünemann H. GRADE concept paper 9: rationale and process for creating a GRADE Ontology. J Clin Epidemiol [Internet]. 2025 Aug 5;187:111921. Available from: <http://dx.doi.org/10.1016/j.jclinepi.2025.111921>
2. Franco JV, Guo Y, Varela LB, Aqra Z, Alhalahla M, Medina Rodriguez M, Salvador Oscco EL, Patiño Araujo B, Banda S, Escobar Liquitay CM, **Bracchiglione J**, Meza N, Madrid E. Tirzepatide for adults living with obesity. Cochrane Database Syst Rev [Internet]. 2025 Oct 30;10(10):CD016018. Available from: <http://dx.doi.org/10.1002/14651858.CD016018>
3. **Bracchiglione J**, Meza N, Franco JV, Escobar Liquitay CM, Novik A V, Ocará Vargas M, Lazcano G, Poloni D, Rinaldi Langlotz F, Roqué-Figuls M, Muñoz SR, Madrid E. Semaglutide for adults living with obesity. Cochrane Database Syst Rev [Internet]. 2025 Oct 30;10(10):CD015092. Available from: <http://dx.doi.org/10.1002/14651858.CD015092.pub2>
4. Meza N, **Bracchiglione J**, Escobar Liquitay CM, Madrid E, Varela LB, Guo Y, Urrutia G, Er S, Tiller S, Shokraee K, Alvarez Busco F, Solà I, Ocará Vargas M, Novik A V, Poloni D, Franco JV. Liraglutide for adults living with obesity. Cochrane Database Syst Rev [Internet]. 2025 Oct 30;10(10):CD016017. Available from: <http://dx.doi.org/10.1002/14651858.CD016017>
5. Venter C, Alonso-Coello P, Beltran J, **Bracchiglione J**, Fernandez-Saenz K, Riera P, Solà I, Arasi S, Berni Canani R, Fleischer D, Eguíluz-Gracia I, Meyer R, Roberts G, Roth-Walter F, Santos AF, Skypala I, Smith PK, Sokolowska M, Torres MJ, Vassilopoulou E, Walter J, O'Mahony L. Protocol: Scoping review of the association between complementary feeding, growth, and immune health in infants and toddlers-An EAACI guideline paper. Pediatr Allergy Immunol [Internet]. 2025 Aug;36(8):e70145. Available from: <http://dx.doi.org/10.1111/pai.70145>
6. Metzendorf MI, Aloosh M, Benton L, **Bracchiglione Pérez J**, Cumpston M, de'Donato FK, Laot S, Piggott T, Rahman KMSU, Stein AT. Integrating planetary health considerations into health guidelines: decision-making bodies must show leadership. BMJ Lead [Internet]. 2025 Jul 29; Available from: <http://dx.doi.org/10.1136/leader-2025-001277>
7. Salazar J, Moustgaard H, **Bracchiglione J**, Hróbjartsson A. Empirical evidence of observer bias in randomised clinical trials: updated and expanded analysis of trials with both blinded and non-blinded outcome assessors. J Clin Epidemiol [Internet]. 2025 Apr 19;111787. Available from: <http://dx.doi.org/10.1016/j.jclinepi.2025.111787>
8. Roura S, Alvarez G, Hohenschurz-Schmidt D, Solà I, Núñez-Cortés R, **Bracchiglione J**, Fernández-Jané C, Phalip J, Gich I, Sitjà-Rabert M, Urrutia G. Alignment between the research question, design and terminology is required in manual therapy trials - a methodological study. J Clin Epidemiol [Internet]. 2025 May 8;111817. Available from: <http://dx.doi.org/10.1016/j.jclinepi.2025.111817>
9. Bonfill Cosp X, Savall-Estève O, **Bracchiglione J**, Requeijo C, Santero M, Appropriateness of Systemic Oncological Treatments for Advanced Cancer (ASTAC-Study) Research Group. Mismatch between evidence and related clinical recommendations about the treatment of advanced esophageal cancer patients with anticancer drugs: A critical historical review. J Cancer Policy [Internet]. 2025 Mar 25;44(100580):100580. Available from: <http://dx.doi.org/10.1016/j.jcpo.2025.100580>
10. **Bracchiglione J**, Song Y, Meneses-Echávez JF, de Carvalho Gomes H, Albiger B, Solà I, Rigau D, Alonso-Coello P. Users' experience of frameworks to support evidence-informed decision-making in public health:

- a scoping review. *Euro Surveill* [Internet]. 2025 May;30(19). Available from: <http://dx.doi.org/10.2807/1560-7917.ES.2025.30.19.2400184>
11. Loyola G, Morales D, Leyton F, Alonso-Coello P, **Bracchiglione J**. Incorporating patients in the development of clinical practice guidelines. *Medwave* [Internet]. 2025 Jun 5;25(5):e3063. Available from: <http://dx.doi.org/10.5867/medwave.2025.05.3063>
 12. Song Y, **Bracchiglione J**, Meneses-Echávez JF, de Carvalho Gomes H, Albiger B, Solà I, Rigau D, Alonso-Coello P. Frameworks to support evidence-informed decision-making in public health and infectious disease prevention and control: a scoping review. *Euro Surveill* [Internet]. 2025 May;30(19). Available from: <http://dx.doi.org/10.2807/1560-7917.ES.2025.30.19.2400185>
 13. Díaz Menai S, Varela LB, Escobar Liquitay CM, Santero M, **Bracchiglione J**, Garegnani L. Short versus long drug regimens for Chagas disease. *Cochrane Database Syst Rev* [Internet]. 2025 May 9;5(5):CD016172. Available from: <http://dx.doi.org/10.1002/14651858.CD016172>
 14. Roura S, Alvarez G, Hohenschurz-Schmidt D, Solà I, Núñez-Cortés R, **Bracchiglione J**, Fernández-Jané C, Phalip J, Gich I, Sitjà-Rabert M, Urrútia G. A call for improving the internal validity and the reporting of manual therapy trials self-labelled as pragmatic: A methodological review. *Int J Osteopath Med* [Internet]. 2025 Mar;55(100754):100754. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1746068925000100>
 15. Meade A, Santero M, Savall-Esteve O, **Bracchiglione J**, Leache L, Selva A, Macías I, Cerdà P, Bonfill Cosp X. Immunotherapy or targeted therapy versus best supportive care for advanced gastric cancer: A systematic review and meta-analysis of randomized trials. *J Gastrointest Cancer* [Internet]. 2025 Mar 4;56(1):75. Available from: <http://dx.doi.org/10.1007/s12029-024-01155-y>
 16. Roura S, Alvarez G, Hohenschurz-Schmidt D, Solà I, Núñez-Cortés R, **Bracchiglione J**, C Fernández-Jané, Phalip J, Gich I, Sitjà-Rabert M, Urrútia G. Lack of pragmatic attitude of self-labelled pragmatic trials on manual therapy: a methodological review. *BMC Med Res Methodol* [Internet]. 2024 Nov 11;24(1):273. Available from: <http://dx.doi.org/10.1186/s12874-024-02393-1>
 17. Meza N, **Bracchiglione J**, Madrid E, Escobar Liquitay CM, Popova E, Salazar R, Urrútia G. Use of the patient-centered outcome Days Alive and Out of Hospital in clinical studies on perioperative care: a scoping review protocol. *F1000Res* [Internet]. 2024 Oct 10;13:1194. Available from: <https://f1000research.com/articles/13-1194/v1>
 18. Requeijo C, **Bracchiglione J**, Meza N, Ribera P, Güell E, Bonfill Cosp X, Appropriateness of Systemic Oncological Treatments for Advanced Cancer (ASTAC) Research Group. Anti-cancer drugs versus supportive care for advanced biliary tract cancers: a systematic review. *F1000Res* [Internet]. 2024 Jun 7;13:599. Available from: <https://f1000research.com/articles/13-599/v1>
 19. Santero M, Meade AG, Selva A, Savall-Esteve O, **Bracchiglione J**, Macías I, Leache L, Cerdà P, Bonfill Cosp X, Appropriateness of Systemic Oncological Treatments for Advanced Cancer (ASTAC-Study) Research Group. Utilising systematic reviews to assess potential overtreatment and claim for better evidence-based research: an analysis of anticancer drugs versus supportive care in advanced esophageal cancer. *Syst Rev* [Internet]. 2024 Jul 18;13(1):186. Available from: <http://dx.doi.org/10.1186/s13643-024-02594-1>
 20. Cabrera-Ubilla C, Nuñez-Galleguillos V, **Bracchiglione J**, Garnham R, Pérez I. Key factors in the choice of appropriate outcomes for clinical trials. *Medwave* [Internet]. 2024 May 15;24(4):e2790. Available from: <http://dx.doi.org/10.5867/medwave.2024.04.2790>
 21. Shang W, Hui X, Li M, Ren J, Huang X, Li J, Wang X, Wang Q, Ma Y, Madrid E, **Bracchiglione J**, Jiang L, Yang K, Yao L. Pharmacological treatments for adults with overweight and obesity without diabetes. *Cochrane Database Syst Rev* [Internet]. 2024 [cited 2024 Apr 19];(4). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015861/full>
 22. **Bracchiglione J**, Alonso-Coello P. Clinical practice guidelines today: Moving in the right direction. *Med Clin* [Internet]. 2024 Feb 19; Available from: <http://dx.doi.org/10.1016/j.medcli.2023.12.009>
 23. Requeijo C, **Bracchiglione J**, Meza N, Acosta-Dighero R, Salazar J, Santero M, Meade AG, Quintana MJ, Rodríguez-Grijalva G, Selva A, Solà I, Urrútia G, Bonfill Cosp X, Appropriateness of Systemic Oncological Treatments for Advanced Cancer (ASTAC) Research Group. Anticancer Drugs Compared to No Anticancer Drugs

- in Patients with Advanced Hepatobiliary Cancer: A Mapping Review and Evidence Gap Map. *Clin Epidemiol* [Internet]. 2023 Nov 10;15:1069–85. Available from: <http://dx.doi.org/10.2147/CLEP.S431498>
24. Niño-de-Guzman Quispe E, **Bracchiglione J**, Ballester M, Groene O, Heijmans M, Martínez García L, Noordman J, Orrego C, Rocha C, Suñol R, Alonso-Coello P. Patients' and informal caregivers' perspectives on self-management interventions for type 2 diabetes mellitus outcomes: a mixed-methods overview of 14 years of reviews. *Arch Public Health* [Internet]. 2023 Aug 4;81(1):140. Available from: <http://dx.doi.org/10.1186/s13690-023-01153-9>
 25. Escobar-Liquitay CM, Vergara-Merino L, Verdejo C, Kirmayr M, Schuller-Martínez B, Madrid E, Meza N, **Bracchiglione J**, Franco JVA. Methodological and users' surveys on the use of the LILACS database in Cochrane reviews identified desirable improvements to the database. *Health Info Libr J* [Internet]. 2023 Aug 13; Available from: <http://dx.doi.org/10.1111/hir.12505>
 26. Salazar J, **Bracchiglione J**, Savall-Estève O, Antequera A, Bottaro-Parra D, Gutiérrez-Valencia M, Martínez-Peralta S, Pericay C, Tibau A, Bonfill X, Appropriateness of Systemic Oncological Treatments for Advanced Cancer (ASTAC) Research Group. Treatment with anticancer drugs for advanced pancreatic cancer: a systematic review. *BMC Cancer* [Internet]. 2023 Aug 12;23(1):748. Available from: <http://dx.doi.org/10.1186/s12885-023-11207-4>
 27. Nino-de-Guzman E, **Bracchiglione J**, Vasquez-Mejia A, de Graaf G, Calderon CR, Alonso-Coello P. How do patients with Type 2 Diabetes Mellitus value the importance of outcomes? An overview of reviews. *Value Health* [Internet]. 2023 Jul 27; Available from: <http://dx.doi.org/10.1016/j.jval.2023.07.003>
 28. Marilina S, Adriana M, Anna S, Roberto AD, Nicolás M, Jesús QM, **Javier B**, Carolina R, Josefina S, Gerardo RG, Ivan S, Gerard U, Xavier BC, Appropriateness of Systemic Oncological Treatments for Advanced Cancer (ASTAC) Research Group. Comparative analysis of systemic oncological treatments and best supportive care for advanced gastrophageal cancer: A comprehensive scoping review and evidence map. *J Evid Based Med* [Internet]. 2023 Jun 12; Available from: <http://dx.doi.org/10.1111/jebm.12539>
 29. Cruzat B, Reveco-Guzmán K, Encina-Meneses M, Ortiz-Muñoz L, **Bracchiglione J**. Approaching the body of evidence: Key concepts of Overviews. *Medwave* [Internet]. 2023 Jun 6;23(5). Available from: <http://dx.doi.org/10.5867/medwave.2023.05.2704>
 30. Suzuki-Barrera K, Teramoto A, Sáez-Chandía J, Nakakuki K, Bracchiglione J. Oral Health Interventions in Natural Disasters: A Scoping Review. *Disaster Med Public Health Prep* [Internet]. 2023 May 9;17:e388. Available from: <http://dx.doi.org/10.1017/dmp.2023.62>
 31. **Bracchiglione J**, Song Y, Comas DR, Alonso-Coello P. Frameworks to support evidence-informed decision-making from a public health perspective [Internet]. 2023. Available from: <https://osf.io/9drm6>
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