





RESEARCH MAP:

Health risks associated with the use of electronic cigarettes: an interactive research map

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Responsible	Camilla Stoltenberg, Director-General
Authors	Rune Becher, Norwegian Institute of Public Health. Project leader
	Håkon Valen, Norwegian Institute of Public health
	Gunn E. Vist, Norwegian Institute of Public health
	Bendik C. Brinchmann, Norwegian Institute of Public health
	Jørn A. Holme, Norwegian Institute of Public health
	Tom K. Grimsrud, Cancer Registry of Norway
	Ida-Kristin Ørjasæter Elvsaas, Norwegian Institute of Public health
	Vigdis Underland, Norwegian Institute of Public health
	Miriam Bakkeli, Norwegian Institute of Public health
	Jan Alexander, Norwegian Institute of Public health

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Key messages

We have systematically surveyed and created an interactive research map of existing literature on health risks associated with use of e-cigarettes. We included 1482 publications in the report. Since several of these may have reported to have more than one study design, such as both a publication with a human study and an animal experiment, the number of study designs included are in total 1760. Respiratory, cardiovascular as well as other adverse events (outcome not given under other code) were the health outcomes most often reported.

Very few human studies were published the first years after the introduction of e-cigarettes in 2007, but from 2013 there was an increase. Case reports and case series led the way, followed by cross-sectional studies. We identified 41 randomised controlled trials (RCT). This study design is the most rigorous way of determining if a cause-effect relation exists between intervention (here use of e-cigarettes) and outcome. Only one of the RCTs had a follow-up time of six months or more. Among the other 105 studies with a control group, only six had a follow-up time of more than 2 years. Thus, any adverse impact of e-cigarette use on health which may take long time to develop, may remain undetected.

Overall, the interactive research map gives a visual presentation of the broad variety of health consequences linked to the use of e-cigarettes and may be used to identify potential human health risks and possible research gaps. Identification of the latter can be useful for the discussion of focus of future research The map shows what research is available, it does not assess the quality of the studies or size or severity of the health risk from using e-cigarettes.

Title:

Health risks associated with the use of electronic cigarettes: an interactive research map

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Peer reviewers: Elisabeth Kvaavik Department Director Alcohol, tobacco and drugs NIPH

Gunnar Sæbø Senior scientist Alcohol, tobacco and drugs NIPH

Johan Øvrevik Director of Research / Chief Scientist NIPH

Hovedbudskap

Vi har på en systematisk og vitenskapelig måte undersøkt og laget et interaktivt forskningskart over eksisterende litteratur om helserisiko knyttet til bruk av e-sigaretter. Vi inkluderte 1482 publikasjoner. Siden flere av disse kan ha rapportert fra mer enn et studiedesign, for eksempel både resultater fra studier med mennesker og dyreforsøk, er antall studiedesign inkludert i alt 1760. Effekter på luftveier og lunge, hjerte- og kar-systemet samt andre utfall (ikke angitt i annen kode) var det som oftest ble rapportert.

Svært få studier på mennesker ble publisert årene etter introduksjonen av e-sigaretter i 2007, men fra 2013 var det en økning. Innledningsvis var kasus-rapporter etterfulgt av tverrsnittstudier de vanligste studietypene. Vi identifiserte 41 randomiserte kontrollerte studier (RCT). Dette studiedesignet er den «strengeste» metoden for å påvise en årsakssammenheng mellom intervensjon (her bruk av e-sigaretter) og utfall. Bare en av RCT-ene hadde en oppfølgingstid på seks måneder eller mer. Av de 105 andre studiene med kontrollgruppe var det bare seks studier med oppfølgingstid lenger på over 2 år. I hvilken grad e-sigaretter kan forårsake helseskader som utvikles etter lengre tids bruk er dermed uavklart.

Det interaktive forskningskartet gir en visuell oversikt over områder med mange, noen eller ikke-eksisterende vitenskapelig dokumentasjon. De identifiserte kunnskapshullene kan indikere hvor fremtidig forskning bør settes inn.

Forskningskartet synliggjør hvilken forskning som finnes, det viser ikke kvaliteten på studiene, størrelsen eller alvorlighetsgraden på helserisikoen ved bruk av elektroniske sigaretter.

Tittel:

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Fagfeller:

Elisabeth Kvaavik Avdelingsdirektør Rusmidler og tobakk Folkehelseinstituttet

Gunnar Sæbø Seniorforsker Rusmidler og tobakk

Johan Øvrevik Forskningssjef Folkehelseinstituttet

Preface

In 2020, the Ministry of Health and Care Services requested the Norwegian Institute of Public Health (NIPH) to update and expand the report «Health risks from the use of e-cigarettes» published by the NIPH in 2015 (NIPH, 2015). The mandate for the assignment of a new report on health risks associated with the use of e-cigarettes was given in June 2020.

Since the report from NIPH in 2015, new products with changes in design and content have been introduced, and the scientific literature on health effects of e-cigarettes has increased significantly. This implies a need for updated information. The Ministry gave the NIPH a two-part assignment:

The first part of the assignment was to perform a systematic literature search and subsequently prepare an interactive map of research on health effects of e-cigarette use or exposure. This research map should include all studies (in vitro, in vivo, clinical, epidemiological, etc.) classified by type of publication and topic of the research. Areas where research is lacking or insufficient should be identified. The systematic literature search should be restricted to studies addressing health effects and not include other e-cigarette related issues such as harm reduction and "gateway" (here the possibility that use of e-cigarettes leads to use of other tobacco or nicotine containing products) or the use of e-cigarettes in smoking cessation.

In agreement with the established policy of leading scientific journals, research funded by or otherwise linked to the tobacco industry should not be included. Otherwise, NIPH was free to organize the work with the interactive map, as found appropriate, including consultation with any external expertise.

The present report with linked interactive research map is the result of the first part of the assignment. The report including its interactive research map provides an orientation on available research and knowledge gaps on the potential health effects from e-cigarettes.

The report and the interactive map will be an important base for the second part of the assignement; the preparation of a systematic review over selected possible health consequences of e-cigarettes use and exposure.

Project leader

Rune Becher, Norwegian Institute of Public health

Working group

Håkon Valen, Norwegian Institute of Public health Gunn E. Vist, Norwegian Institute of Public health Bendik C. Brinchmann, Norwegian Institute of Public health Jørn A. Holme, Norwegian Institute of Public health Tom K. Grimsrud, Cancer Registry of Norway Ida-Kristin Ørjasæter Elvsaas, Norwegian Institute of Public health Vigdis Underland, Norwegian Institute of Public health Miriam Bakkeli, Norwegian Institute of Public health Jan Alexander, Norwegian Institute of Public health

We thank Johan Øvrevik, Gunnar Sæbø and Elisabeth Kvaavik who have commented and provided input to the report.

Conflict of interest

None of the contributing authors and reviewers have declared any conflict of interest.

The Norwegian Institute of Public Health is responsible for the content of this report.

Johan Øvrevik Director of Research / Chief Scientist Project responsible Rune Becher Senior scientist Project leader

Introduction

E-cigarettes

Electronic cigarettes (e-cigarettes) are electronic devices, essentially consisting of a cartridge filled with a liquid (e-cigarette liquid), an evaporator unit/heating element associated with a battery, all together connected to a mouthpiece. When heated, the e-cigarette liquid will form an aerosol (vapour) meant to be inhaled. Other terms such as ENDS (electronic nicotine delivery system) and NVP (nicotine vaping products) are also used.

E-cigarettes were developed and patented in China in 2003, subsequently modified and launched on the American market in 2006. They can be disposable, rechargeable with a cartridge, or manually refillable with e-cigarette liquid. First-generation e-cigarettes were often cigarette imitations. Later, more advanced products have appeared. Some shaped like a pen, while others come with systems that may carry larger amounts of e-liquid than earlier models. Third generation e-cigarettes consists of a diverse range of products often termed "vaping" products. Their design often has even less resemblance to cigarettes, as the cartridge may be square or rectangular and they may have options for customizing and conversion. These products are often referred to as "mods", since the users can modifythe device or build their own version (NASEM, 2018).

The e-cigarette liquid may contain nicotine or be nicotine free. The e-liquid usually contains a mixture of propylene glycol (PG), vegetable glycerine (VG), and various flavourings. The available number of these flavours/combination of flavours is exceedingly high.

The harmful potential of nicotine has been documented from studies in cell cultures, animals and, although less, in humans (US Surgeon General, 2014). For other constituents identified in e-liquids, such as PG/VG and flavours, the potential health risks have been evaluated following oral intake and are thus generally regarded as safe. However, the health risks associated with *inhalation* of these constituents have been less evaluated. Moreover, the heating process can lead to chemical decomposition of these constituents and the formation of new compounds of altered toxicity (pyrolysis). Other constituents found in aerosols including metals and silicate particles may add to the toxicity of the inhaled vapour (SCHEER, 2020).

Numerous *in-vitro-* and animal studies have been performed to elucidate the potential health consequences these inhalable constituents confer. Several of these studies

report cellular effects associated with potential impact on airways, inflammation, impairment of cardiovascular function and toxicity. In addition, some of the compounds identified in aerosol from e-liquid are known or potential carcinogens.

There is also an increasing number of studies adressing adverse impacts of e-cigarettes on human health, related to e-cigarette- or vaping use-associated lung injury (EVALI), ingestion by infants as well as explosions/burns. However, the composition of the inhaled vapour is affected by the e-cigarette device and e-liquid as well as the vaping pattern which all affect the dose of toxicants the user is exposed to. Any adverse outcomes will also depend on user specific (genetic) and environmental factors linked to the each vaper that may predispose for possible health effects (NASEM, 2018; SCHEER 2020). Thus, a more precise evaluation of the health risks linked to ecigarettes use is complicated due to the large variation of products on the marked and the heterogeneity of users (e.g. time of use, age of user, comorbidity). Furthermore, the potential long-term effects of e-cigarette use have so far only been scarcely investigated. It should also be noted that e-cigarettes may be used for vaping other liquids or compounds that may be illegal or produced for other purposes, and thus not provided commercially from the e-cigarette producer. However, this latter is beyond the scope of this report.

The need for an interactive research map

The previous report on health risks associated with the use of e-cigarettes from NIPH was published in 2015. In addition, the report "Public Health Consequences of E-Cigarettes" from the National Academies of Sciences, Engineering, and Medicine (NASEM) was published in 2018, with a literature search dated as of August, 2017 (NASEM, 2018). The European report from SCHEER published in April 2021 was based on a literature search dated as of April 2019 (SCHEER, 2020). This latter report did not include a clear description of the methods used for inclusion and evaluation of the scientific literature; and health consequences were only fully described for cardiovascular diseases. The rapid development and modification of e-cigarettes and e-liquids leading to diversification of the inhaled aerosols and habits, combined with a continuous stream of new research publications makes it relevant to update the literature search on this field to detect new data of importance for the assessment of health risks related to e-cigarette use.

The interactive map gives an overview over available research on health consequences from the use and exposure to e-cigarettes. The interactive map gives a visual overview of the amount and type of available research and allows the users to select themes and subgroups of special interest.

In addition to showing what research is available the map also shows where there are research gaps.

Aims

The aim of this work was to systematically search, identify and categorize published research linked to human health risks associated with the use of e-cigarettes and to present our findings in interactive maps which can be used for extracting references on self selected categories such as study design, age of participants in the studies and type of health consequences. In addition to human studies, the map includes relevant invitro- and animal studies.

Method

We have prepared this interactive research map in accordance with our pre-published protocol (<u>https://www.fhi.no/cristin-prosjekter/aktiv/health-risks-associated-with-the-use-of-electronic-cigarettes---a-protocol-/</u>) and the Campbell Collaboration's framework for evidence and gap maps (<u>https://campbellcollaboration.org/evidence-gap-maps.html</u>).

Problem statement

Since the introduction of e-cigarettes on the market, a development and diversification of both the e-cigarette and e-liquids has followed. The amount of scientific literature on health effects of e-cigarettes is increasing steeply. Thus, there is a need for updated overview of the available scientific information on health consequences of e-cigarettes to be able to contribute to evidence based advices and regulations regarding ecigarettes.

Inclusion criteria

We used the following inclusion criteria:

Populations:	No restrictions: all human-, animal- and in-vitro studies
Measures:	All types of electronic cigarettes and additives
Comparison:	No restrictions: smoking, snuff or no use of tobacco product
	allowed as comparison
Outcomes:	All health outcomes as a result of the use of electronic cigarettes
Study design:	No restriction
Publlcation year:	No restriction
Language:	Danish, English, Norwegian, Swedish

Exclusion criteria:

- Research funded by or otherwise linked to the tobacco industry
- Harm reduction publications without evidence of health outcomes
- Studies that only describe or discuss the pattern of use of tobacco products
- Primarily addiction focused research
- Discussion papers without primary data or secondary analysis

Literature search

Research librarian Miriam Bakkeli prepared, in collaboration with the project group, the search strategy. The strategy was peer reviewed by another research librarian before she conducted the searches. The following databases were searched:

- Ovid MEDLINE
- Embase
- PsycInfo
- Web of Science
- Cochrane Database of Systematic Reviews

The full search strategy in shown in Appendix 1.

Selection of studies

Two authors from the working group (RB, HV, BCB, JAH, GEV, TKG, JA and IKØE) read through and assessed each of the references identified in the literature searches. Relevant references were selected on the basis of our inclusion criteria. The selection was stepwise, first on the basis of title and summary/abstract, and then full-text versions of the publications. Any disagreements were resolved through discussion or contact with another researcher in the team. We used the software EPPI Reviewer 4.

Data collection and presentation

All categories were divided into subcategories, and the suggestions in the protocol were piloted and improved. Our final set of categories are presented in the code book in Appendix 2. EPPI Reviewer 4 software was used to code the included studies. At least two authors (RB, HV, BCB, JAH, GEV, and TKG) categorized each selected publication independently of each other. Disagreements were resolved by discussion.

Assessment of the risk of systematic biases and confidence in the results

Our research map provides an overview of the scope and type of research on the health effects of electronic cigarettes. This work does not include assessment of the risk of systematic biases in the included studies, analysis or assessment of confidence in the effect estimates.

We have deviated from the protocol by assessing the quality of the included systematic reviews using AMSTAR 2 (Shea et al., 2017). VU and GEV made these assessments independently, disagreements were solved by discussion.

Codebook

The development of a codebook was part of the project (Appendix 2). The purpose of the codebook was to give the project staff a common understanding of how the codes should be used. The codebook specifies which main and sub-categories are to be included in the research map's axes, filters and segments, with definitions and examples.

The project group at FHI first made a proposal for a codebook based on categories used in relevant publications that were already known to the group. A reference group consisting of the project's external experts reviewed and provided input to the proposal. The project group completed the codebook based on the input, and piloted it on a selection of systematic overviews.

Preparation of the interactive map

This NIPH report presents the different categories of the interactive research in tables and text describing the existence of available research. We extracted information from studies and sorted this into the various categories using frequency and cross table functions in EPPI-Reviewer.

The interactive research maps are available as html files which may be uploaded and freely available on a website. The maps show an interactive matrix that illustrates the landscape of evidence on health consequences from use of electronic cigarettes.

Results

Results from the literature search

Our literature searches in the databases Ovid MEDLINE, Embase, PsycInfo and Web of Science were conducted in December 2020, the literature search in Cochrane was conducted in February 2021. After removal of duplicates, we were left with 9969 references to be assessed on title and abstract against our inclusion criteria (Figure 1).

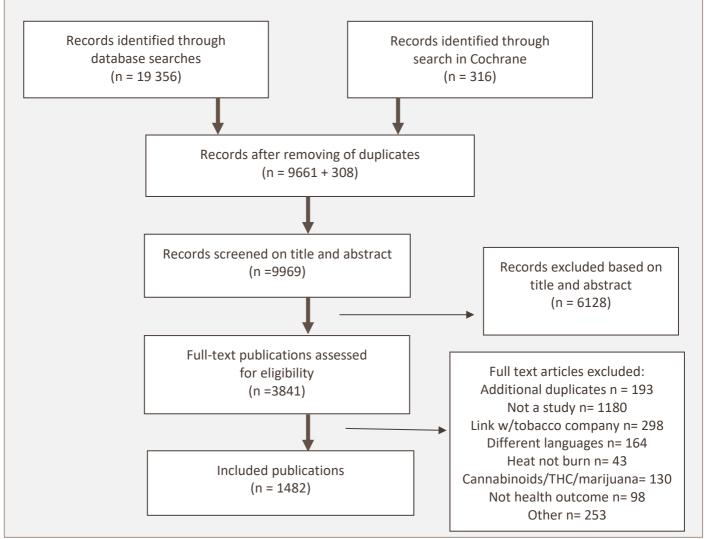


Figure 1. PRISMA flow diagram of the results of the literature search

Each of the 9969 identified references were assessed on title and abstract according to our inclusion criteria by two authors independently of each other. Disagreements were solved by a third reviewer. The 3841 references that were considered potentially relevant were assessed in full text, again according to the same inclusion criteria and by two people independently of each other. We did, however, code some references based only on abstract due to unavailable full texts.

Excluded studies

The reasons for exclusions are shown in figure 1. The most common reason for exclusion was that the publications did not actually present a study or systematic review, most of these 1180 excluded publications were commentaries, editorials and review articles without a literature search. The second most common reason for exclusion was that the publication was either sponsored by or written by authors with links to a tobacco company, which applied to 298 publications. There were still 193 duplicates unidentified before the full text assessment. One hundred and thirty publications reported either a study with the use of electronic cigarettes in combination with cannabinoids/THC/marijuana or on the health consequences or cases with adverse events resulting from such use. These studies and case reports where all the participants/cases had been using cannabinoids/THC/marijuana were excluded. Other studies or case reports involving one or more participants/cases who did not use these substances were included in the map.

Included studies

We included 1482 publications in the report, references are presented in Appendix 3. Since several of these may have one or more study design, such as a publication with both a human study and an animal experiment, the number of study designs included was in total 1760. Figure 2 shows that airway and pulmonary, cardiovascular and vascular as well as other adverse events were the health outcomes most often reported.

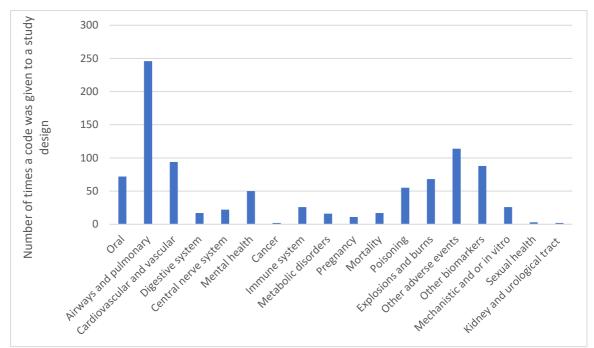


Figure 2. Proportion of health consequences studied in studies involving humans.

Since the invention of the electronic cigarette in 2003, there has been a rapid increase in publication of studies and case reports pertaining to the use of electronic cigarettes. The time distribution of publications is presented in Figure 3.

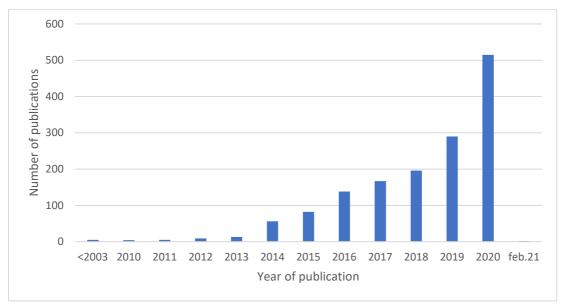


Figure 3. Time distribution of publications regarding health consequences of use of electronic cigarettes.

We show the distribution of study designs regarding the use of electronic cigarettes or their components and the reports of health consequences from its use in figure 4. We note that there are few human experimental studies regarding the health effects of use of electronic cigarettes.

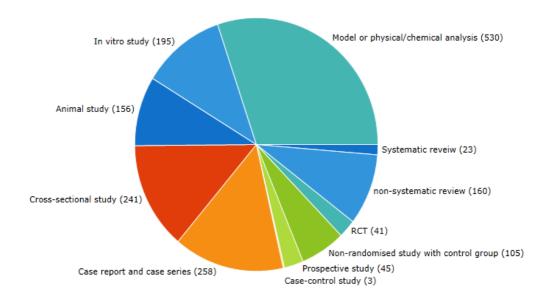


Figure 4. Study designs used to investigate the consequences of use of electronic cigarettes

Characteristics of the included studies: Systematic reviews

We identified 183 reviews with a literature search. However, only 23 of them had both a literature search and an assessment of the risk of bias (the internal validity) of the included studies. These 23 were included as systematic reviews and health consequences in humans were assessed in 15 of these. Three of the 23 studies assessed animal and in vitro/mechanistic data. The time trend for publication of systematic reviews and non-systematic reviews (with literature search) is shown in Figure 5.

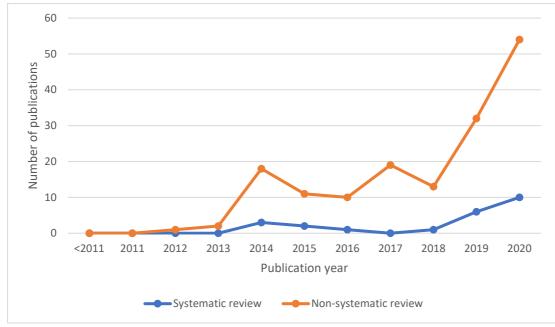


Figure 5. Time distribution of publications of systematic and non-systematic reviews regarding health consequences of use of electronic cigarettes

Critical appraisal of systematic reviews

We used the AMSTAR 2 critical appraisal tool (Shea et al 2017) to assess the quality of the included systematic reviews of health consequences. The 16 questions used for the AMSTAR 2 appraisal were:

- 1. Did the research questions and inclusion criteria for the review include the components of PICO (Population, Intervention/exposure, Comparison, Outcome)?
- 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
- 3. Did the review authors explain their selection of the study designs for inclusion in the review?
- 4. Did the review authors use a comprehensive literature search strategy?
- 5. Did the review authors perform study selection in duplicate?
- 6. Did the review authors perform data extraction in duplicate?
- 7. Did the review authors provide a list of excluded studies and justify the exclusions?
- 8. Did the review authors describe the included studies in adequate detail?
- 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

- 10. Did the review authors report on the sources of funding for the studies included in the review?
- 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
- 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
- 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
- 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
- 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
- 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Each question was answered yes (Y), probably yes (PY), probably no (PN), no (N) or not applicable (NA). Question #9 is answered twice, first for RCT and then for observational studies. Two authors critically appraised each systematic review independently before they compared and discussed.

Our full AMSTAR 2 assessments of the 18 included systematic reviews pertaining to health consequences in humans of use of electronic cigarettes are presented in Appendix 4. An overview of our assessments is presented in Table 1. Only four of these reviews obtained a High quality score (H), nine were of Moderate quality (M) and four of Low quality (L), one scored Critically Low (CL).

In Table 2 the systematic reviews are presented according to which health consequences that were assessed in the review, marked as dark green in the box. Reviews are listed so that the one with the most recent literature search is presented first. It is clear from the table that the following health consequences measured in human studies had not been summarised in a systematic review by the time of our search (February 2021):

- Digestive system
- Central nerve system
- Cancer
- Immune system
- Metabolic disorders
- Mortality
- Explosions and burns
- Other biomarkers
- Kidney and urological tract

D (Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Qua-
Reference																	lity
Becker et al 2021	Y	РҮ	Y	РҮ	Y	Y	РҮ	РҮ	N PY	N	NM	NM	N	N	NM	Y	L
Claire et al 2020	Y	Y	Y	Y	Y	Y	РҮ	Y	Y NA	Y	Y	Y	Y	Y	NA	Y	Н
Drovandi et al 2020	Y	N	Y	РҮ	Y	Y	РҮ	Y	PY NA	Y	Y	N	N	N	N	Y	М
Figueredo et al 2020	Y	РҮ	Y	РҮ	Y	Y	РҮ	Y	Y Y	N	Y	N	Y	Y	NA	Y	Н
Franck et al 2014	Y	N	Y	РҮ	N	Y	РҮ	Y	Y N	N	NM	NM	Y	Y	NM	Y	М
Goniewicz et al 2020	Y	N	Y	PY	Y	Y	РҮ	РҮ	NA Y	Y	NM	NM	Y	Y	NM	Y	М
Gualanao et al 2015	Y	N	Y	PY	N	N	РҮ	РҮ	PY Y	Y	NM	NM	N	Y	NM	N	М
Hartmann- B et al 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y NA	Y	Y	Y	Y	Y	Y	Y	Н
Holliday et al 2019	Y	РҮ	Y	РҮ	Y	Y	Y	Y	PY PY	Y	NM	NM	Y	N	NM	Y	М
Kennedy et al 2019	Y	N	Y	РҮ	N	N	РҮ	Y	Y Y	Y	NM	NM	Y	Y	NM	Y	М
Kwon et al 2019	Y	N	N	РҮ	N	Y	РҮ	Y	NA PY	N	NM	NM	N	Y	NM	Y	L
Liu et al 2018	Y	N	Y	РҮ	N	Y	РҮ	РҮ	Y Y	N	Y	N	N	N	NA	Y	М
Ralho et al 2019	Y	РҮ	Y	РҮ	Y	N	РҮ	РҮ	NA Y	N	NM	NM	Y	N	NM	Y	М
Riley et al 2016	Y	N	Y	PY	Y	N	N	Y	PY PY	Y	NM	NM	N	N	NM	Y	L
Scarpino et al 2020	Y	N	Y	РҮ	N	Y	N	РҮ	NA PY	N	NM	NM	Y	NA	NM	Y	М
Skotsimara et al 2019	Y	N	N	N	Y	Y	N	N	NA Y	N	N	N	N	N	N	Y	CL
Wang et al 2019	Y	N	Y	РҮ	N	N	РҮ	РҮ	NA PY	N	NM	NM	Y	Y	NM	Y	L
Zhao et al 2016	Y	Y	Y	PY	Y	Y	РҮ	РҮ	NA Y	N	Y	Y	Y	Y	Y	Y	Н

Table 1. AMSTAR 2 critical assessment of systematic reviews on the health consequences of use of electronic cigarettes

Table 2. Systematic reviews with the health consequences addressed in the review, newest search presented first.

		1 111 56.																
Reference Search date	Oral	Airways and pulmonary	Cardiovascular and vascular	Digestive system	Central nerve system	Mental health	Cancer	Immune system	Metabolic disorders	Pregnancy	Mortality	Poisoning	Explosions and burns	Other adverse events	Other biomarkers	Mechanistic and or in vitro	Sexual health	Kidney and urological tract
Goniewicz et al																		
2020																		
Sep 2020																		
Scarpino et al 2020																		
May 2020																		
Becker et al 2020																		
Mar 2020																		
Figueredo et al 2020																		
Mar 2020																		
Hartmann-Boyce et																		
al 2020 Jan 2020																		
Drovandi et al																		
2019																		
Aug 2019																		
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Jun 2015																		
Gualano et al 2015																		
Apr 2014																		
Franck et al 2014																		
Sep 2013																		
Animal studies, in v	itro an	d or me	chanis	tic														
Wang et al 2019																		
Nov 2018																		
Zhao et al 2020																		
Nov 2018																		
Holliday et al 2019																		_
Oct 2018																		
Physical and or che	mical a	nalysis																
Miller et al 2020, Aug 2020																		
	Ward et al 2020, May 2020																	
Fernandez et al 2015		15																
Brown and C 2014, O	ct 2013	;																
Burstyn 2014, Jul 201	13																	

Oral health consequences: 2 systematic reviews, the newest search date was March 2020 Airways and pulmonary health consequences: 4 systematic reviews, the newest search date was September 2020 Cardiovascular and vascular: 5 systematic reviews, the newest search date was September 2020

Mental health consequences: 2 systematic reviews, the newest search date was March 2020

Pregnancy: 1 systematic review, search date was May 2019

Poisoning: 1 systematic review, search date was May 2020

Other adverse events: 6 systematic reviews, the newest search date was January 2020 Sexual health: 1 systematic review, search date was June 2015

Characteristics of the included studies: Human studies

Very few human studies were published the first ten years after the e-cigarette entered the market, but from 2013 there was an increase in publications. Figure 6 indicates that the publication of case reports and case series led the way, followed by cross-sectional studies. The number of case-control studies has remained low.

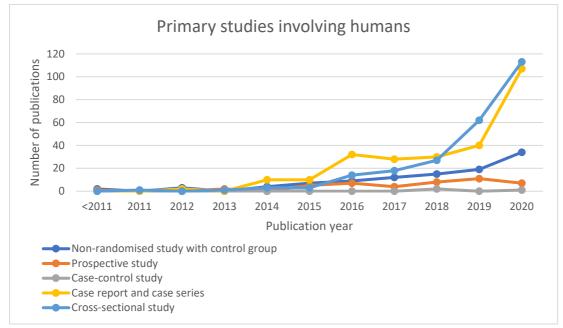


Figure 6. Time distribution of publications of human studies regarding health consequences of use of electronic cigarettes

In the following we present some more information about each of the different human study types:

Randomised controlled trials (RCTs)

We identified 41 randomised controlled trials involving the use of electronic cigarettes. In figure 7, the RCTs are presented according to the areas of health consequences covered by the trials. The numbers add up to more than 41 because some trials assessed several different outcome categories. Exposure characterisation and assessment and or physical or chemical analysis was the aim in 5 of the randomised trials, providing no explicit measure of health consequences.

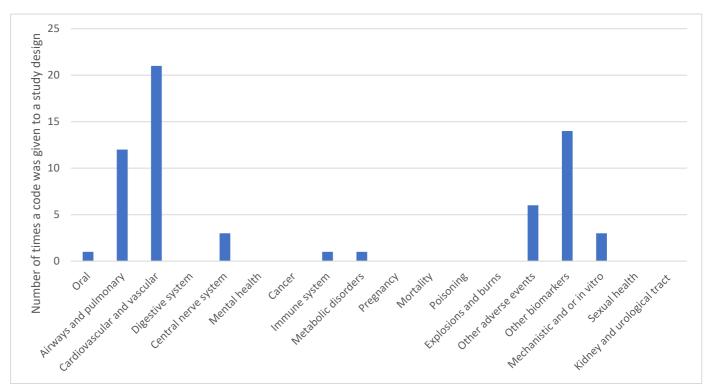


Figure 7. Health consequences addressed in the randomised controlled trials

Participants in these 41 RCTs were adolescents and young adults 16-24 years (27 trials) and adults > 25 years (33 trials). Two trials did not provide the age of the participants. These age groups were not exclusive, as several of the trials included participants from more than one age group.

Only one of the RCTs had a follow-up time of six months or more, which was an 8-week study with a follow-up telephone call at six months (Lee et al 2018). The other 40 RCTs had a follow-up time of < 6 months.

We coded publications involving humans according to what the use of e-cigarettes was compared with (figure 8). Multiple comparisons could be performed for each of the studies. Typically the use of e-cigarettes could be compared to an unexposed control group or to tobacco smoking. In addition we coded when comparisons were performed for different contents of e-liquid used, such as with or without nicotine as well as with or without flavours.

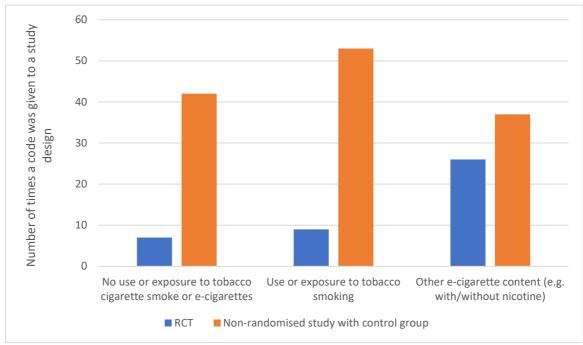


Figure 8. Shows the proportion between the different comparisons, exposures for randomised controlled trials and non-randomised studies with a control group

Non-randomised studies with a control group

We identified 105 non-randomised controlled studies involving the use of electronic cigarettes. In figure 9, these studies are presented according to the relevant areas of health consequences measured. The numbers add up to more than 105 because some studies measured several different health outcome categories.

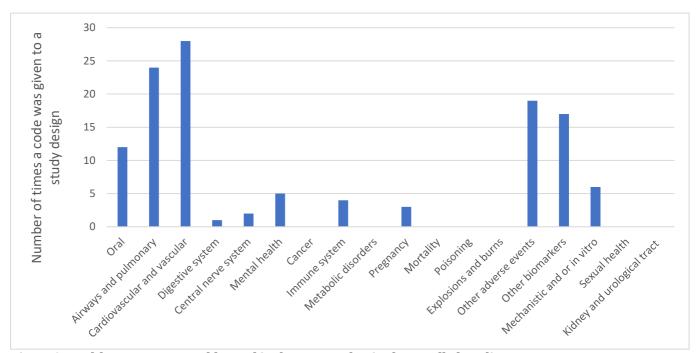


Figure 9. Health consequences addressed in the non-randomised controlled studies

Exposure characterisation and assessment and/or physical or chemical analysis was the aim in 34 of the non-randomised controlled studies, these studies did not measure health consequences and were therefore not included in the present report and interactive maps.

Participant characteristics in these 105 non-randomised controlled studies are shown in figure 10. Adolescents and young adults 16-24 years (69 studies) and adults > 25 years (85 studies) were well represented. Thirteen studies did not provide the age of the participants. These age groups were not exclusive, as many of the trials included participants from more than one age group.

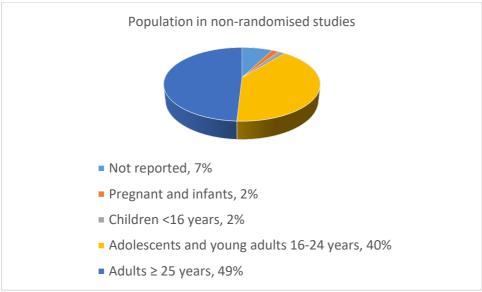


Figure 10. Participant characteristics for the non-randomised controlled studies

Only six of the 105 non-randomised controlled studies on use of electronic cigarettes had a follow-up time of more than two years. One study investigated changes in chronic obstructive pulmonary disease (COPD) progression over a six-year period (Bowler et al 2017). Two studies had a four-year follow-up, one reported on the participants' perceived stress (Leventhal et al 2017) and one reported on the participants' self-reported health (Bhatta et al 2020). Three studies had a three-year follow-up, one reported on the development of gum disease (Atuegwu et al 2019), one on respiratory disease (Xie et al 2020) and one on depressive symptoms (Marsden et al 2019). Follow-up time in non-randomised controlled studies on use of electronic cigarettes are shown in Figure 11.

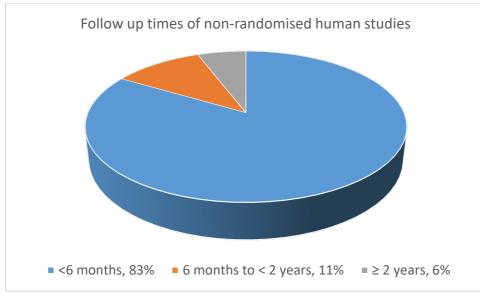


Figure 11. Follow-up time of the non-randomised controlled studies

Prospective studies

We have coded human studies with a prospective design which did not fit into any of the above categories (RCT or non-randomised controlled study) into this group. The majority of these studies are before and after studies without a control group. The health consequences measured in the 45 prospective studies are shown in figure 12.

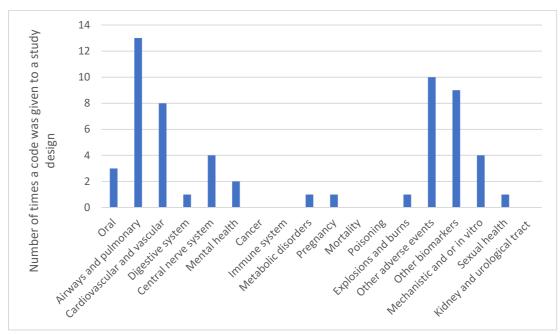


Figure 12. Health consequences addressed in prospective studies

Exposure characterisation and assessment and/or physical or chemical analysis was the aim in 16 of the prospective studies, and these studies did not measure health consequences.

The distribution of the participants' age is shown in Figure 13. The majority of participants were adults \geq 25 years, followed by adolescents and young adults of 16 to 24 years old. Six studies did not report the age of their participants.

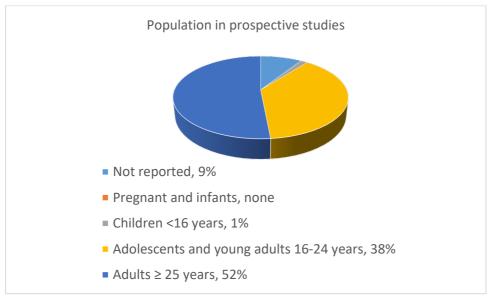


Figure 13. Participant characteristics for the prospective studies

Follow-up time for the prospective studies were under six months for 36 of the 45 studies (figure 14). One prospective study, assessing the impact of e-cigarette use on female fecundability, had a follow-up time maximum of three years (Harlow et al 2020).

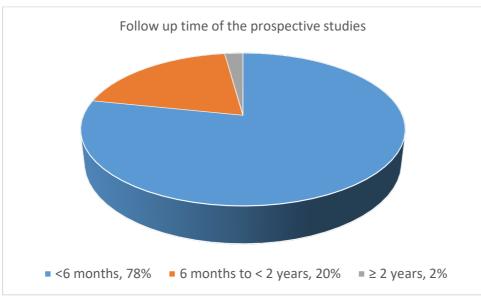


Figure 14. Follow-up time of the prospective studies

Case-control studies

Our searches identified three case-control studies. One studied oral mucosal lesions in 45 users of electronic cigarettes and 45 former smokers (Bardellini et al 2018). The

other studied infant neurobehaviour one month after birth and where mother used either electronic cigarettes (10 infants), mother smoked (29 infants) or where mother did not use tobacco products (44 infants) during pregnancy (Froggatt et al 2020). The third case-control study looked at nicotine replacement where the use of ENDS was an alternative to smoking for patients undergoing plastic surgery (Michaels et al 2018).

Case report and case series

We found 258 case reports and case series pertaining to the use of electronic cigarettes. The health consequences reported on are shown in Figure 15. The numbers add up to more than 258 because some studies measured several different health outcome categories.

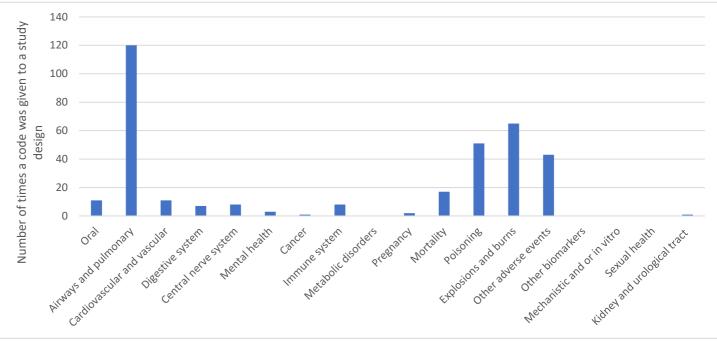


Figure 15. Health consequences addressed in case reports and case series

We see a predominance of case reports and case series reporting on consequences for the airways and pulmonary system (figure 15). Many case reports and case series addressed explosions and burns, poisoning and other adverse events.

The distribution of the patients and participants age are shown in Figure 16. Fourteen percent of the case reports and case series addressed children under 16 years of age. The majority of participants were adults \geq 25 years (43%) and adolescents and young adults of 16 to 24 years old (33%). Twenty studies did not report the age of their participants.

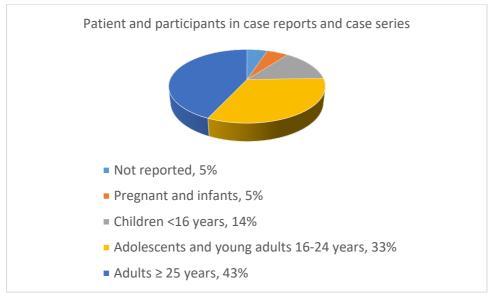


Figure 16. Patient and participant characteristics for the case series and case reports

Cross-sectional studies

We found 241 cross-sectional studies that include people who use electronic cigarettes. The health consequences reported on are shown in figure 17.

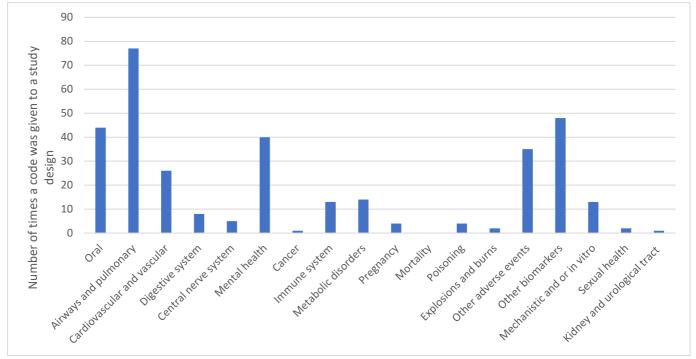


Figure 17. Health consequences addressed in cross-sectional studies

One of only two human studies addressing cancer and use of electronic cigarettes was a cross-sectional study. In a U.S survey, adults who experienced homelessness were asked about chronic health conditions (Leavens et al 2020). The other publication was a case report of one young person with eye cancer (Shields et al 2020). The age distribution of individuals in the cross-sectional studies is shown in figure 18.

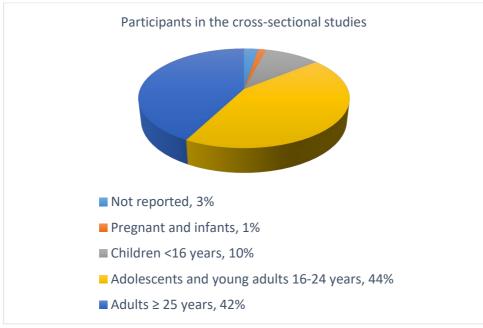


Figure 18. Participants in cross sectional-studies

Animal studies

We identified 156 animal studies involving the exposure to e-liquid/e-liquid constituents or aerosol from e-cigarettes or aerolized nicotine. The health consequences measured in animal studies are presented in figure 19.

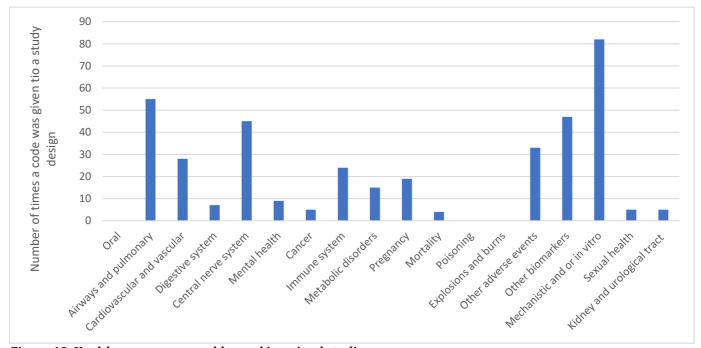


Figure 19. Health consequences addressed in animal studies

Interactive research map

We have in a systematic and scientific way mapped the existing research on potential health consequences from e-cigarettes. The interactive research maps give a systematic and visual overview by providing graphical presentations of areas with many, some or non-existent scientific documentation.

The identified research gaps further indicate where future research may be useful. This interactive research map visualise the available research but it does not assess the size of the health risk associated with electronic cigarettes.

The interactive research maps are available as html files which may be uploaded and freely available on a website. These maps should be useful for evidence synthesis and the production of systematic reviews as well as for prioritising new research.

We have made 5 evidence and gap maps about research on electronic cigarettes:

Health consequences of e-cigarettes, studies involving humans

Health consequences of e-cigarettes, prospective studies involving humans

Health consequences of e-cigarettes, case reports and case series

<u>Health consequences of e-cigarettes, follow up time for prospective studies involving humans</u>

Health consequences associated with e-cigarettes, follow up time for animal studies

We classify the studies involving humans in four study groups: randomised controlled study, non-randomised controlled study, prospective study, case-controls.

The interactive map enables the user to click anywhere in a bubble to access a list of all studies addressing that particular population and topic.

Figure 20 shows an example of such an interactive map, whereas figure 21 shows an example of how the references look like when clicking on a bubble. The referenc list may be easily exported to a users own library.

		Health concequences												
		Oral	«	Airways and pulmonary	«	Cardiovascular 《 and vascular	Digestive system≪	Central nerve 🧹 system	Mental health 《	Cancer 🔍	Immune system ≪	Metabolic disorders	K Pregnancy	«
Publication type human	RCT 🖄		•	•		•		•			•	•		
	Non- randomised study with control group		•	•		•	•	•	•		•		•	
	Prospective study		•	•		•	•	•	•			•	•	
	Case- control study		•										•	
	Case report and case series		•			•	•	•	•	•	•		•	
	Cross- 🔊					•	•	•	•	•	•	•	•	

Figure 20. Image of the interactive research map showing health consequences in columns and study design in rows. The size of the bubbles indicates the number of studies in each square.

Filters	Hide H	leaders 🖸 Ful th concequences	X 21 Records		All ~	Filter	Download Listed References			
	Oral	Airway pulmor	Clear Filters	Sort by: Title 🗸	Acute	Effects of Electro	nic Cigarette			
Publication RCT	*		Health concequences	Acute Effects of Electronic Cigare		tion on the Vascul	0			
		•	Oral			Conducting Airways				
			Airways and pulmo	Acute Effects of Heat-Not-Burn, El	· · · · ·					
			Cardiovascular an	Biondi-Zoccai G ; Sciarretta S ; Bulle	The use of electronic cigarettes has increased exponentially since its introduction onto the global market					
	omised y with		Digestive system	2019						
		•	Central nerve system	Acute and chronic sympathomim	in 2006.	in 2006. However, short- and long-term health effects				
			Mental health	Arastoo S ; Haptonstall K P; Choroo 2020	remain largely unknown due to the novelty of this product.					
			Cancer	Acute effects of electronic cigaret		The present study examines the acute effects of e-				
		•	Immune system	Gonzalez J E; Cooke W H; 2020	÷		ith and without nicotine, on ion in healthy volunteers.			
			Metabolic disorders		Sevente	een healthy subjects in	haled electronic cigarette			
			Pregnancy	Acute inhalation of vaporized nico Cooke W H; Pokhrel A ; Dowling C ;	aerosol with and without nicotine on two separate					
		•	Mortality	Mortality 2015	occasio	occasions in a double-blinded crossover fashion. Blood				
			Poisoning Altered lung biology of healthy he			pressure, heart rate, and arterial stiffness measured by				
				Staudt M R; Salit J ; Kaner R J; Holl		ave velocity and pulse				
			Explosions and burns	2018	assesse	ed at baseline, and the	n at 0 h, 2 h, and 4 h			
					fallouin	a aunaaura Dunamia /	aniramater and importan			

Figure 21. An image showing the information provided when you click on a bubble.

Discussion

Main findings of this interactive research map on health consequences from e-cigarette use

We have systematically surveyed and created an inter-active research map of existing literature on health risks associated with use of e-cigarettes. Our literature searches were conducted in December 2020 (in Cochrane in February 2021). After removal of duplicates, we had 9969 references. These references were assessed on title and abstract according to our inclusion criteria by two authors independently of each other. The 3841 references that were considered potentially relevant were assessed in full text, again according to the same inclusion criteria and by two people independently of each other. After exclusion, a total of 1482 publications related to health consequences of the use of electronic cigarettes were included.

There were many reviews, however, only 23 of them were systematic reviews, fifteen of them were on health consequences in humans who use electronic cigarettes. Health consequences summarised in these systematic reviews covered oral, airways and pulmonary health, cardiovascular and vascular health, mental health, pregnancy, poisoning, other adverse events and sexual health.

Randomized controlled trial (RCT) studies are the most rigorous study design for determining if a causality between intervention (here use of e-cigarettes) and outcome. However, among the 41 RCTs, only one study had a follow-up of six months. Among the other 105 studies with a control group, only six had a follow-up time of more than 2 years. Thus, any (adverse) impact of e-cigarette use on health which may take an extended time to develop may so far pass undetected.

Due to the recognised health hazards associated with tobacco use, it would be in general unethical to randomise people without any experience with tobacco use or with use of electronic cigarettes. Hence, it is no surprise that there was no long-term randomised human studies on the health consequences associated with the use of electronic cigarettes.

Among the health consequences reported in the included human studies, respiratory and cardiovascular outcomes and other adverse events (outcome not given under other code), were most frequently assessed. For case-reports and case-series studies, after respiratory outcomes, the second and third highest numbers of adverse outcomes were injuries caused by explosions and burns, and by poisoning. Many of the studes on poisoning episodes assess ingestion of nicotin-containing e-liquid by children.

In addition there are numerous animal and *in vitro* studies examining the effect of exposure to e-liquid/constituents of e-liquid and/or their aerosols available. Such studies may be use to support or refute if the use of electronic cigarettes confer a risk for specific adverse health outcomes, or to detect potential health risk which are difficult to reveal in present human studies

Evidence gaps

The interactive research map visualizes identified knowledge gaps.

There are few publications, and hence, little available documentation regarding effects of e-cigarette use on the digestive system, the central nervous system, mental health, cancer, immune system, metabolic disorder, pregnancy, mortality, sexual health, kidney and urinary tract. Research and surveillance regarding these outcomes may therefore be needed before any conclusion regarding potential health impact from the use of e-cigarettes is reached.

The majority of available epidemiological studies investigating an association between adverse health outcomes and the use of e-cigarettes have focused on health consequences related to respiratory and cardiovascular health. Few studies have long follow-up time, thus any adverse health consequences of e-cigarette use which may take an extended time to develop, may so far gone undetected.

With regard to animal and *in vitro* studies, there are still need for supportive studies for assiciations/lack of associations seen in epidemiological studies. There is in particular a strong need for information further elucidating any potential risk for adverse health outcomes which takes long time to develop in humans.

Strengths and limitations of this research map

The strength of the map is that it provides an overview over current knowledge and identifies knowledge gaps by a systematic and transparent approach. The systematic mapping of an area of research is a steppingstone for conducting new research. The map provides easy access to relevant studies to summarize evidence in a systematic review.

On the other hand, the map does not assess the quality of the studies nor the size or severity of the health risks.

It is always a limitation with any summarising documents that they may be outdated as soon as new literature is published. This also goes for our interactive map on research

on the use of electronic cigarettes, as our literature searches were conducted in December 2020 and February 2021.

Another limitation of interactive research maps is that they are based on categorisation systems that can be difficult to use consistently. The aim of each category/code is to be as specific as possible, but not all data extracted from the different publications will always fit with one code precisely. An example is that several of the publications included in the present maps have study designs that are difficult to categories precisely to one code, as overlaps may occur between study designs.

Conclusion

The codes most often in the included human studies were related to respiratory and cardiovascular health, along with adverse events not associated with a specific organ or disease type.

Few human studies were published during the first years after the introduction of the e-cigarettes in 2007, with an increasing rate from 2013, and a steep increase in publications the last few years. Case reports and case series led the way, followed by cross-sectional studies.

As for all new products put on the market, there are few long-term human studies available to detect adverse effects that may develop over years and decades. However, numerous *in-vitro-* and animal studies were identified in our search. These may be useful for assessing human health risk.

A common reason for exclusion was that the publication was either sponsored by or written by authors with links to tobacco industry, this applied to 298 publications.

The present interactive research map gives a visual presentation of the broad variety of health consequences linked to the use of e-cigarettes and may be used to identify potential human health risks and possible research gaps.

The interactive research map does not assess the size or severity of the health risks from use of e-cigarettes. Identification of research gaps can be useful for discussion of where future research should focus.

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Appendix 1: Search strategy

For this interactive research map the aim was to get an overview of all relevant reseach regarding the use of e-cigarettes and health consequences. Hence all health consequences were relevant and the search was not restricted on outcomes.

Search librarian:	Miriam Bakkeli	
Reviewer:	Astrid Nøstberg	
Database: Web of	science, Date:	18. 12.2020
Duplication control in	Before: 19356	
EndNote:	After: 9661	
Number of hits:	6308	

1 6,308

TOPIC: (("electronic cigarette\$" or "e-cigarette\$" or "ecigarette\$" or "eCIG*" or "e-CIG*" or "electronic nicotine delivery system\$" or "electronic nicotine delivery device\$" or "nicotin* vapor*" or "nicotin* vapour*" or "vaporised nicotin*" or "vaporized nicotin*" or "vapourised nicotin*" or "vapourized nicotin*" or "e-hookah\$" or "Electronic Hookah\$" or "Hookah Pen\$"))

AND

DOCUMENT TYPES: (Article OR Book OR Book Chapter OR Correction OR Early Access OR Editorial Material OR Letter OR Proceedings Paper OR Reprint OR Review)

Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=1987-2020

ARTICLE (4,552)	LETTER (485)	PROCEEDINGS PAPER (33)
REPRINT (3)	EDITORIAL MA	TERIAL (696)
EARLY ACCESS (147)	BOOK CHAPTE	R (14)
DATA PAPER (1)	REVIEW (502)	CORRECTION (70)

Database:Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-In-
dexed Citations, Daily and Versions(R) <1946 to December 15, 2020>Date17.12.2020, Number of hits:7526

#	Searches	Re-
		sults
1	Electronic Nicotine Delivery Systems/ or ("Electronic Cigarette?" or "E-Cigarette?"	7114
	or "E Cigarette?" or "E-Cig?" or "E Cig?" or "ecigarette\$" or "eCIG*" or "Elec-	
	tronic Nicotine Delivery System?" or "Electronic Nicotine Delivery De-	
	vice?").tw,kf.	
2	("nicotin* vapor*" or "nicotin* vapour*" or "vapori#ed nicotin*" or "vapouri#ed	94
	nicotin*").tw,kf.	
3	("e-hookah?" or "e hookah?" or "Electronic Hookah?" or "Hookah Pen?").tw,kf.	26
4	Vaping/ or (Vape? or vaping).tw,kf.	2626
5	or/1-4	7526
6	from 5 keep 1-1999	1999
7	from 5 keep 2000-3999	2000
8	from 5 keep 4000-5999	2000
9	from 5 keep 6000-7526	1527

Database: Embase <1974 to 2020 December 15>

Dato: 17.12.2020, **Number of hits**: 5522

#	Searches	Results
1	electronic cigarette/ or ("Electronic Cigarette?" or "E-Cigarette?" or "E Cigarette?"	8919
	or "E-Cig?" or "E Cig?" or "ecigarette\$" or "eCIG*" or "Electronic Nicotine Deliv-	
	ery System?" or "Electronic Nicotine Delivery Device?").tw,kw.	
2	("nicotin* vapor*" or "nicotin* vapour*" or "vapori#ed nicotin*" or "vapouri#ed	127
	nicotin*").tw,kw.	
3	("e-hookah?" or "e hookah?" or "Electronic Hookah?" or "Hookah Pen?").tw,kw.	32
4	vaping/ or (Vape? or vaping).tw,kw.	3220
5	or/1-4	9493
6	conference abstract.pt.	393734
		2
7	5 not 6	8131
8	limit 7 to embase	5522
9	from 8 keep 1-999	999
10	from 8 keep 1000-1999	1000
11	from 8 keep 2000-2999	1000
12	from 8 keep 3000-3999	1000
13	from 8 keep 4000-4999	1000
14	from 8 keep 5000-5522	523

Duplication control in	Import to EndNote 316
EndNote:	After: 308

Database:	Cochrane Library Issue 2 of 12, February	2021
Dato:	08. februar 2021, Number of hits:	316

ID	Search	Hits
#1	[mh ^"Electronic Nicotine Delivery Systems"]	137
	((Electronic NEXT Cigarette?) or (E NEXT Cigarette?) or (E NEXT Cig?) or (ecigarette?) or (eCIG*)	
	or (Electronic NEXT Nicotine NEXT Delivery NEXT System?) or (Electronic NEXT Nicotine NEXT	
#2	Delivery NEXT Device?)):ti,ab	678
	((nicotin* NEXT vapor*) or (nicotin* NEXT vapour*) or (vapori?ed NEXT nicotin*) or (vapouri?ed	
#3	NEXT nicotin*)):ti,ab	20
#4	((e NEXT hookah?) or (Electronic NEXT Hookah?) or (Hookah NEXT Pen?)):ti,ab	4
#5	[mh ^"Vaping"]	45
#6	((Vape?) or "vaping"):ti,ab	156
#7	{OR #1-#6}	745*

Appendix 2: Code book

Code book for interactive research maps on health consequences associated with the use of electronic cigarettes

Publication type	Comments
Systematic reviews (including HTA)	With search and quality
	assessment of included studies
Non-systematic review	Literature search but not quality
	assessment
	No other codes needed
Randomised Controlled Trials (RCT)	
Non-randomised controlled study	
Prospective study	
Case-control study	
Case report and case series	Follow up is "single time event"
Cross sectional study	Follow up is "no follow up"
Animal study	
In vitro study	
Model or physical/chemical analysis	
Other	
Publication year	
<2003	
2003	
2004	
2005	
2006	
2007	
2008	
2009	
2010	
2011	
2012	
2013	
2014	
2015	
2016	
2017	
2018	
2019	
2020	
Population/experimental model	Population and Pattern of prod uct use only for human studies
Human - not reported	
Pregnant and infants	

Children < 16 years	
Adolescents and young adults 16-24 years	
Adults > 25	
Follow-up time	
Single time event	
< 6 months	
6 months to <2 years	
≥2 years	
No follow up	
Pattern of e-cigarette use or exposure	e
e-cigarette use only	
E-cigarette use (history of other tobacco products not specified)	
Concurrent use of other tobacco product(s)	
e-cigarette second hand exposure	
No previous use of tobacco	
Previous tobacco use	
Not reported	
Other	
E-cigarette use or exposure compared with	
No use or exposure to tobacco cigarette smoke or e-cigarettes	
Use or exposure to tobacco smoking	
Other e-cigarette content (e.g. with/without nicotine)	
Exposure characterisation and assessment (includin	g liquid content)
Liquid content - with nicotine	
Liquid content- with nicotine salts	
Liquid content - without nicotine	
Liquid content - Others additions like flavour, vit E acetate, etc	
Device temperature reported	
External dose: nicotine content, puffing frequency, etc	
Internal dose: Substances levels from vaping measured in blood/urine	
Not given or not reported	
Not given or not reported Other	
Other	
Other Health consequences	
Other	
Other Health consequences Oral	
Other Health consequences	
Other Health consequences Oral Airways and pulmonary	
Other Health consequences Oral	
Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular	
Other Health consequences Oral Airways and pulmonary	
Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular Digestive system	
Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular	
Other Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular Digestive system Central nerve system	
Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular Digestive system	
Other Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular Digestive system Central nerve system Mental health	
Other Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular Digestive system Central nerve system	
Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular Digestive system Central nerve system Mental health Cancer Other	
Other Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular Digestive system Central nerve system Mental health	
Other Health consequences Oral Airways and pulmonary Cardiovascular & vascular Digestive system Central nerve system Mental health Cancer Other	

Pregnancy	
Mortality	
Poisoning	
Explosions and burns	
Other adverse events	Such as poisoning and burns/ explosions
Other biomarkers	
Mechanistic and/or in vitro	
Sexual health	
Kidney and urological tract	

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Appendix 4: AMSTAR 2 assessments

AMS	ΓAR 2 checklist, critical questions				
	Becker et al 2021				
1. Di	d the research questions and inclusion	ı criteri	a for the review include the components	of PIC	C O ?
For Y		Optio	nal (recommended)		
Х	Population		Timeframe for follow up	х	Yes
Х	Intervention		•		No
	Comparator group				
Х	Outcome				
2. Di	d the report of the review contain an o	explicit	statement that the review methods were	establ	lished prior to the
cond	uct of the review and did the report ju	ustify ar	ny significant deviations from the protoco	ol?	
For P	artial Yes: The authors state that they	For Y	es: As for partial yes, plus the protocol		
had a	written protocol or guide that in-	shoul	d be registered and should also have spec-		
clude	d ALL the following:	ified:			
Х	review question(s)	х	a meta-analysis/ synthesis plan, if ap-		Yes
			propriate, and		
Х	a search strategy		a plan for investigating causes of heter- ogeneity	х	Partial Yes
Х	inclusion/exclusion criteria		<u> </u>	1	No
х	a risk of bias assessment				
3. Di	d the review authors explain their sel	ection o	f the study designs for inclusion in the re	view?	,
	es, the review should satisfy ONE of th			х	Yes
	Explanation for including only RCTs		C C		No
	OR Explanation for including only N				
	OR Explanation for including both R		1 NRSI		
4. Di	d the review authors use a comprehen			<u> </u>	
	artial Yes (all the following):		es, should also have (all the following):	1	Yes
Х	searched at least 2 databases (rele-		searched the reference lists / bibliog-	x	Partial Yes
	vant to research question)		raphies of included studies		
Х	provided key word and/or search		searched trial/study registries		No
	strategy	-			
Х	justified publication restrictions		included/consulted content experts in		
	(e.g. language)	-	the field	_	
			where relevant, searched for grey litera-		
			ture	-	
		х	conducted search within 24 months of		
5 D'	d the new outbour fame of the		completion of the review		
	d the review authors perform study so	election	in auplicate?		
	Yes, either ONE of the following:	1		1	
Х	at least two reviewers independently	-	-	х	Yes
	achieved consensus on which studies	to inclu	ae	<u> </u>	

	OR two reviewers selected a sample of eligible studies and achieved good agreer				No
	(at least 80 percent), with the remaind	ted by one reviewer.			
6. Dic	the review authors perform data ext	in duplicate?	1	1	
For Y	es, either ONE of the following:				
х		nsus on	which data to extract from included stud-	х	Yes
			1 (1' '11 / 1' 1 1' 1 1		N -
		-	ble of eligible studies and achieved good		No
7 D:	agreement (at least 80 percent), with t the review authors provide a list of e			1	
	artial Yes:		es, must also have:	r –	
		FOR Y	Justified the exclusion from the review		v
х	provided a list of all potentially rel- evant studies that were read in full-				Yes
	text form but excluded from the re-		of each potentially relevant study	х	Partial Yes
	view				No
8. Dic	the review authors describe the inclu	uded sti	udies in adequate detail?		
	artial Yes (ALL the following):		es, should also have ALL the following:		
Х	described populations		described population in detail		Yes
X	described interventions		described intervention in detail (includ-	x	Partially Yes
			ing doses where relevant)	~	rununy res
Х	described comparators		described comparator in detail (includ-		No
			ing doses where relevant)		110
Х	described outcomes	x			<u> </u>
			described study's setting		
х	described research designs				
9. Dic	the review authors use a satisfactory	techni	que for assessing the risk of bias (RoB) in	ı indiv	vidual studies that
were	included in the review?				
RCTS	3				
For Pa from	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
x	unconcealed allocation, and		allocation sequence that was not truly		Yes
л	unconceated anocation, and		random, and		Partial Yes
	lack of blinding of patients and as-	x	selection of the reported result from	x	No
	sessors when assessing outcomes		among multiple measurements or anal-		Includes only
	(unnecessary for objective out-		yses of a specified outcome		NRSI
	comes such as all-cause mortality)				INKSI
NRSI		1			
	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from				┨┌───	
х	from confounding, and	х	methods used to ascertain exposures		Yes
v	from selection bias		and outcomes, and selection of the reported result from	x	Partial Yes
х			among multiple measurements or anal-		No
			yses of a specified outcome		Includes only
10 P					RCT
10. D For Y		urces o	f funding for the studies included in the	review	16
For Y		C 1'			37
	-	-	for individual studies included in the re-		Yes
		ers look	ted for this information but it was not re-	х	No
11 If	ported by study authors also qualifies			tistics	l combination of
	mate-analysis was norfarmed did the	rouis	authors use annronriate methods tor sta		
	meta-analysis was performed did the	review	authors use appropriate methods for sta	usuca	II combination of
result	s?	review	authors use appropriate methods for sta	usuca	in combination of
	s?	review	authors use appropriate methods for sta		

AND they used an appropriate weighted technique to combine study results and ad-		No
AND they used an appropriate weighted technique to combine study results and ad- justed for heterogeneity if present.		110
AND investigated the causes of any heterogeneity	x	No meta-analysis conducted
For NRSI		conducted
For Yes		
		Vee
The authors justified combining the data in a meta-analysis		Yes
AND they used an appropriate weighted technique to combine study results, adjusting		No
for heterogeneity if present		
AND they statistically combined effect estimates from NRSI that were adjusted for	х	No meta-analysis
confounding, rather than combining raw data, or justified combining raw data when		conducted
adjusted effect estimates were not available		
AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review		
12. If meta-analysis was performed, did the review authors assess the potential impact of I on the results of the meta-analysis or other evidence synthesis?	RoB in	individual studies
For Yes		
included only low risk of bias RCTs	1	Yes
OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-	1	No
thors performed analyses to investigate possible impact of RoB on summary estimates	x	No meta-analysis
of effect.		conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discus	sing t	
review?	,sing t	ine results of the
For Yes		
For Yes included only low risk of bias RCTs		Yes
For Yes included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	x	Yes No
 included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here 		No
 included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here the results of the review? 		No
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes		No eneity observed in
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here results of the review? For Yes There was no significant heterogeneity in the results	eterog	No eneity observed in Yes
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any high results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of		No eneity observed in
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the results	eterog	No eneity observed in Yes
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	eterog	No eneity observed in Yes No
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate	eterog	No eneity observed in Yes No
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any hether results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review?	eterog	No eneity observed in Yes No
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any hether results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review?	eterog	No eneity observed in Yes No igation of publica-
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes	eterog	No eneity observed in Yes No igation of publica- Yes
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any hethe results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review?	eterog	No eneity observed in Yes No Yes No Yes No
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	x invest	No eneity observed in Yes No igation of publica- Yes No No meta-analysi conducted
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	x invest	No eneity observed in Yes No igation of publica- Yes No No meta-analysi conducted
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heteresults of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes	x invest	No eneity observed in Yes No igation of publica- Yes No No meta-analysi conducted
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any hete results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes Image: Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including an for conducting the review?	x invest	No eneity observed in Yes No igation of publica- Yes No No meta-analysi conducted
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any h the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including an for conducting the review? For Yes	x invest	No eneity observed in Yes No igation of publica- Yes No No meta-analysi conducted
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any h the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including an for conducting the review? For Yes x	x y func	No eneity observed in Yes No igation of publica- Yes No Yes No No meta-analysi conducted ling they received
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any hteresults of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes	x y func	No eneity observed in Yes No igation of publica- igation of publica- Yes No No meta-analysi conducted ling they received Yes
included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any h the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including an for conducting the review? For Yes x The authors reported no competing interests OR	x y func	No eneity observed in Yes No igation of publica- igation of publica- Yes No No meta-analysi conducted ling they received Yes

AMSTAR 2 checklist, critical questions
REF: Claire et al 2020
1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Y	les	Optio	nal (recommended)		
Х	Population	1	Timeframe for follow up	х	Yes
Х	Intervention		*		No
Х	Comparator group	_			
х	Outcome	-			
2. Di	d the report of the review contain an e	explicit	statement that the review methods were	e estab	lished prior to the
cond	uct of the review and did the report ju	ıstify ar	y significant deviations from the proto	col?	
For F	Partial Yes:	For Y	es:		
The a	authors state that they had a written	As for	r partial yes, plus the protocol should be		
proto	col or guide that included ALL the	registe	ered and should also have specified:		
follo	wing:				
Х	review question(s)	х	a meta-analysis/ synthesis plan, if ap- propriate, and	х	Yes
х	a search strategy	х	a plan for investigating causes of het- erogeneity		Partial Yes
х	inclusion/exclusion criteria				No
х	a risk of bias assessment	1		-	1
		ection of	f the study designs for inclusion in the r	eview?	•
	Ves, the review should satisfy ONE of th			x	Yes
x	Explanation for including only RCTs		<u> </u>		No
	OR Explanation for including only N				
	OR Explanation for including both R		INRSI		
4. Di	d the review authors use a comprehen				
	Partial Yes (all the following):		es, should also have (all the following):	x	Yes
x	searched at least 2 databases (rele-	S	searched the reference lists / bibliog-	A	Partial Yes
л	vant to research question)	3	raphies of included studies		Tartial Tes
x	provided key word and/or search	х	searched trial/study registries		No
л	strategy	л	searched than study registries		NO
x	justified publication restrictions	x	included/consulted content experts in		
л	(e.g. language)	л	the field		
	(e.g. miguage)	x	where relevant, searched for grey lit-		
		Λ	erature		
		x	conducted search within 24 months of		
		л	completion of the review		
5 Di	d the review authors perform study se	election	-		
	(es, either ONE of the following:		in aupitate.		
x	at least two reviewers independently a	agreed o	n selection of eligible studies and	x	Yes
л	achieved consensus on which studies	-	-	^	105
			le studies and achieved good agreement		No
	(at least 80 percent), with the remained				
6. Di	d the review authors perform data ext		-	I	1
	Yes, either ONE of the following:				
x	at least two reviewers achieved conse	ensus on	which data to extract from included	х	Yes
	studies				
		n a samr	ble of eligible studies and achieved good		No
	agreement (at least 80 percent), with	-			
7. Di	d the review authors provide a list of		-	L	
	Partial Yes:		es, must also have:		
x	provided a list of all potentially rel-		Justified the exclusion from the re-		Yes
	evant studies that were read in full-		view of each potentially relevant	x	Partial Yes
	text form but excluded from the re-		study	A	No
	view		Stady	Chart	-
					9 excluded, but
				only	6 are listed in the

				Table	e of excluded stud-
				ies	
8. Did	the review authors describe the incl	uded st	udies in adequate detail?		
For Pa	artial Yes (ALL the following):	For Y	es, should also have ALL the following:		
Х	described populations	Х	described population in detail	х	Yes
Х	described interventions	Х	described intervention in detail (in-		Partially Yes
			cluding doses where relevant)		
Х	described comparators	Х	described comparator in detail (in-		No
			cluding doses where relevant)		
х	described outcomes	х			
			described study's setting		
v	described research designs	x	timeframe for follow-up	_	
X 9 Did			que for assessing the risk of bias (RoB)	in indi	vidual studios that
	included in the review?	y techni	que for assessing the risk of blas (Rob)	in mu	ividual studies that
RCTs					
	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from		1011			
х	unconcealed allocation, and	x	allocation sequence that was not truly	x	Yes
			random, and		Partial Yes
Х	lack of blinding of patients and as-	х	selection of the reported result from		No
	sessors when assessing outcomes		among multiple measurements or		Includes only
	(unnecessary for objective out-		analyses of a specified outcome		NRSI
	comes such as all-cause mortality)				
NRSI			•		
For Pa	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from					
	from confounding, and		methods used to ascertain exposures		Yes
			and outcomes, and		Partial Yes
	from selection bias		selection of the reported result from		No
			among multiple measurements or	х	Includes only
			analyses of a specified outcome		RCT
		ources o	f funding for the studies included in th	e reviev	w?
For Y					
х	-	-	for individual studies included in the	х	Yes
			oked for this information but it was not		No
	reported by study authors also qualifi				
		e review	authors use appropriate methods for s	tatistic	al combination of
result					
RCTs For Y					
		lata in a	moto onalizaia		Yes
X	The authors justified combining the d		-	х	
х	justed for heterogeneity if present.	ted tech	nique to combine study results and ad-		No
v	AND investigated the causes of any h	eteroge	neity		No meta-analysis
х	The investigated the causes of any i	leteroge	nety		conducted
For N	RSI			1	conducted
For Y					
1011	The authors justified combining the d	lata in a	meta-analysis		Yes
	· ·		nique to combine study results, adjust-		No
	ing for heterogeneity if present				

	AND they statistically combined effect estimates from NRSI that were adjusted for		No meta-analysis
	confounding, rather than combining raw data, or justified combining raw data when		conducted
	adjusted effect estimates were not available		
	AND they reported separate summary estimates for RCTs and NRSI separately when		
	both were included in the review		
12. If	meta-analysis was performed, did the review authors assess the potential impact of	RoB in	n individual studies
on th	e results of the meta-analysis or other evidence synthesis?		
For Y	es		
Х	included only low risk of bias RCTs	х	Yes
	OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No
	thors performed analyses to investigate possible impact of RoB on summary esti-		No meta-analysis
	mates of effect.		conducted
13. D	id the review authors account for RoB in individual studies when interpreting/ discu	ussing	the results of the
revie	w?		
For Y	es		
х	included only low risk of bias RCTs	х	Yes
х	OR, if RCTs with moderate or high RoB, or NRSI were included the review pro-		No
	vided a discussion of the likely impact of RoB on the results		
14. D	id the review authors provide a satisfactory explanation for, and discussion of, any	hetero	geneity observed in
the re	esults of the review?		
For Y	es		
	There was no significant heterogeneity in the results	х	Yes
х	OR if heterogeneity was present the authors performed an investigation of sources of		No
	any heterogeneity in the results and discussed the impact of this on the results of the		
	review		
15. If	they performed quantitative synthesis did the review authors carry out an adequat	e inves	tigation of publica-
tion b	vias (small study bias) and discuss its likely impact on the results of the review?		
For Y	es		
NA	performed graphical or statistical tests for publication bias and discussed the likeli-	NR	Yes
no	hood and magnitude of impact of publication bias		No
MA			No meta-analysis
w>1			conducted
0			
stud			
ies			
16. D	id the review authors report any potential sources of conflict of interest, including a	ny fun	ding they received
for co	onducting the review?		
For Y	es		
-	The authors reported no competing interests OR	х	Yes
Х		T	No
X X	The authors described their funding sources and how they managed potential con-		No
	The authors described their funding sources and how they managed potential con- flicts of interest		NO
х			NO

AMS	AMSTAR 2 checklist, critical questions							
REF:	REF: Drovandi et al 2020							
1. Did the research questions and inclusion criteria for the review include the components of PICO?								
For Y	/es	Optional (recommended)						
Х	Population	Timeframe for foll	low up	Х	Yes			
Х	Intervention				No			
Х	Comparator group							
х	Outcome							

	-	-	statement that the review methods were o		ished prior to the
		istify an	y significant deviations from the protoco	ol?	
For Pa	artial Yes:	For Y	es:		
	uthors state that they had a written		partial yes, plus the protocol should be		
_	ol or guide that included ALL the	registe	ered and should also have specified:		
follow	•				1
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes
			propriate, and		
	a search strategy		a plan for investigating causes of heter-		Partial Yes
	inclusion/exclusion criteria		ogeneity	v	No
	a risk of bias assessment			Х	NO
3 Did		etion of	f the study designs for inclusion in the rev	viow?	
	es, the review should satisfy ONE of th			x	Yes
x	Explanation for including only RCTs	c lollow	ing.	^	No
	OR Explanation for including only N	DCI			NO
	OR Explanation for including both R		NRSI		
4 Did	the review authors use a comprehen				
	artial Yes (all the following):		es, should also have (all the following):	r	Yes
x	searched at least 2 databases (rele-	x	searched the reference lists / bibliog-	x	Partial Yes
л	vant to research question)	Λ	raphies of included studies	Λ	Tartial 105
х	provided key word and/or search		searched trial/study registries		No
А	strategy		searched that study registrics		110
х	justified publication restrictions		included/consulted content experts in		
	(e.g. language)		the field		
			where relevant, searched for grey litera-		
			ture		
		х	conducted search within 24 months of		
			completion of the review		
5. Did	the review authors perform study se	election	in duplicate?		
For Y	es, either ONE of the following:				
х	at least two reviewers independently	agreed o	n selection of eligible studies and	х	Yes
	achieved consensus on which studies				
			le studies and achieved good agreement		No
	(at least 80 percent), with the remained		-		
	the review authors perform data ext	traction	in duplicate?		
For Y	es, either ONE of the following:			r —	
х	at least two reviewers achieved conse ies	nsus on	which data to extract from included stud-	х	Yes
	OR two reviewers extracted data from	n a samp	le of eligible studies and achieved good		No
	agreement (at least 80 percent), with				
	the review authors provide a list of				
For Pa	artial Yes:	For Y	es, must also have:		
х	provided a list of all potentially rel-		Justified the exclusion from the review		Yes
	evant studies that were read in full-		of each potentially relevant study	х	Partial Yes
	text form but excluded from the re-				No
0.54	view	<u> </u>			
-	the review authors describe the incl		=	r —	
	artial Yes (ALL the following):		es, should also have ALL the following:		
Х	described populations	Х	described population in detail	х	Yes
х	described interventions	х	described intervention in detail (includ-		Partially Yes
	described commercians	v	ing doses where relevant)		No
х	described comparators	х	described comparator in detail (includ- ing doses where relevant)		No
1		1	ing uoses where relevant)	1	

x	described outcomes	x	E		
л	described outcomes	л	described study's setting		
х	described research designs	х	timeframe for follow-up		
9. Di	d the review authors use a satisfactor	y techn	ique for assessing the risk of bias (RoB) i	n indiv	vidual studies that
were	included in the review?				
RCT	\$				
For P	artial Yes, must have assessed RoB	For Y	Yes, must also have assessed RoB from:		
from					
Х	unconcealed allocation, and		allocation sequence that was not truly		Yes
			random, and	х	Partial Yes
Х	lack of blinding of patients and as-		selection of the reported result from		No
	sessors when assessing outcomes		among multiple measurements or anal-		Includes only
	(unnecessary for objective out-		yses of a specified outcome		NRSI
	comes such as all-cause mortality)				
NRS	Í				
For P	artial Yes, must have assessed RoB	For Y	Yes, must also have assessed RoB from:		
from					
	from confounding, and		methods used to ascertain exposures		Yes
			and outcomes, and		Partial Yes
	from selection bias		selection of the reported result from		No
			among multiple measurements or anal-	х	Includes only
			yses of a specified outcome		RCT
10. D	oid the review authors report on the s	ources	of funding for the studies included in the	review	?
For Y	/es			But	included them an-
				ywa	y due to very little
					-tobacco-company
					nsored research
х	Must have reported on the sources of	f fundin	g for individual studies included in the re-	X	Yes
	_		ked for this information but it was not re-		No
	ported by study authors also qualifies	s			
11. If	f meta-analysis was performed did th	e reviev	v authors use appropriate methods for sta	atistica	l combination of
resul	ts?				
RCT	5				
For Y	/es				
х	The authors justified combining the o	data in a	a meta-analysis	х	Yes
х			nnique to combine study results and ad-		No
	justed for heterogeneity if present.		- •		
	AND investigated the causes of any	heterog	eneity	1	No meta-analysis
		2			conducted
For I	NRSI				1
For Y	/es				
	The authors justified combining the o	data in a	a meta-analysis		Yes
			hnique to combine study results, adjusting		No
	for heterogeneity if present				
		ect estin	nates from NRSI that were adjusted for		No meta-analysis
			a, or justified combining raw data when		conducted
	adjusted effect estimates were not av		-		
	-		ates for RCTs and NRSI separately when		
	both were included in the review	-			
12. If		ie revie	w authors assess the potential impact of F	RoB in	individual studies
	e results of the meta-analysis or othe				
For Y					
	included only low risk of bias RCTs			1	Yes
	· ·			1	I

	OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-	х	No
	thors performed analyses to investigate possible impact of RoB on summary estimates		No meta-analysis
	of effect.		conducted
13. Di	d the review authors account for RoB in individual studies when interpreting/ discuss	sing t	he results of the
reviev	v?		
For Ye	es		
	included only low risk of bias RCTs		Yes
	OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a	х	No
	discussion of the likely impact of RoB on the results		
14. Di	d the review authors provide a satisfactory explanation for, and discussion of, any he	terog	eneity observed in
the re	sults of the review?		
For Y	es		
	There was no significant heterogeneity in the results		Yes
	OR if heterogeneity was present the authors performed an investigation of sources of	х	No
	any heterogeneity in the results and discussed the impact of this on the results of the re-		
	view		
15. If	they performed quantitative synthesis did the review authors carry out an adequate i	nvest	igation of publica-
tion b	ias (small study bias) and discuss its likely impact on the results of the review?		
For Y	es		
	performed graphical or statistical tests for publication bias and discussed the likelihood		Yes
	and magnitude of impact of publication bias	х	No
			No meta-analysis
			conducted
16. Di	d the review authors report any potential sources of conflict of interest, including any	fund	ling they received
for co	nducting the review?		
For Ye	es		
х	The authors reported no competing interests OR	х	Yes
	The authors described their funding sources and how they managed potential conflicts		No
	of interest		
Your	overall assessment of the risk of bias of this systematic review		
Mode	rate		

AMS	TAR 2 checklist, <mark>critical questions</mark>				
REF:	Figueredo et al 2020				
1. Di	id the research questions and inclusion	on criter	a for the review include the components	of PI	C O ?
For	Yes	Optio	onal (recommended)		
х	Population		Timeframe for follow up	х	Yes
х	Intervention				No
Х	Comparator group				
х	Outcome				
2. Di	id the report of the review contain an	explicit	statement that the review methods were	estab	lished prior to the
cond	luct of the review and did the report	justify a	ny significant deviations from the protoco	ol?	
For I	Partial Yes:	For Y	es:		
The	authors state that they had a written	As for partial yes, plus the protocol should be			
proto	ocol or guide that included ALL the	regist	ered and should also have specified:		
follo	wing:				
х	review question(s)	х	a meta-analysis/ synthesis plan, if ap- propriate, and		Yes
х	a search strategy		a plan for investigating causes of heter-	х	Partial Yes
			ogeneity		
х	inclusion/exclusion criteria				No
х	a risk of bias assessment				

3. Di	d the review authors explain their seld	ection of	f the study designs for inclusion in the rev	view?	
For Y	Yes, the review should satisfy ONE of th	e follow	ring:	х	Yes
	Explanation for including only RCTs				No
	OR Explanation for including only N	RSI			
х	OR Explanation for including both R	CTs and	NRSI		
4. Di	d the review authors use a comprehen			1	
	Partial Yes (all the following):		es, should also have (all the following):		Yes
х	searched at least 2 databases (rele-		searched the reference lists / bibliog-	х	Partial Yes
	vant to research question)		raphies of included studies		
х	provided key word and/or search		searched trial/study registries		No
	strategy				
х	justified publication restrictions		included/consulted content experts in		•
	(e.g. language)		the field		
	•		where relevant, searched for grey litera-		
			ture		
		х	conducted search within 24 months of		
			completion of the review		
	d the review authors perform study se	election	in duplicate?		
For Y	Yes, either ONE of the following:				
Х	at least two reviewers independently	-	-	х	Yes
	achieved consensus on which studies	to inclu	de		
			le studies and achieved good agreement		No
	(at least 80 percent), with the remained	der selec	ted by one reviewer.		
6. Di	d the review authors perform data ex	traction	in duplicate?		
For Y	Yes, either ONE of the following:				
х	at least two reviewers achieved conse	ensus on	which data to extract from included stud-	х	Yes
	ies				
	OR two reviewers extracted data from	n a samp	ble of eligible studies and achieved good		No
	agreement (at least 80 percent), with				
	d the review authors provide a list of				
For F	Partial Yes:	For Y	es, must also have:		
х	provided a list of all potentially rel-		Justified the exclusion from the review		Yes
	evant studies that were read in full-		of each potentially relevant study	х	Partial Yes
	text form but excluded from the re-				No
	view				
	d the review authors describe the incl		-		
For F	Partial Yes (ALL the following):	For Y	es, should also have ALL the following:		
х	described populations	х	described population in detail	х	Yes
х	described interventions	х	described intervention in detail (includ-		Partially Yes
			ing doses where relevant)		
х	described comparators	х	described comparator in detail (includ-		No
			ing doses where relevant)		
х	described outcomes	х			
			described study's setting		
X	described research designs	na	timeframe for follow-up	l	
		y techni	que for assessing the risk of bias (RoB) in	ı indi	vidual studies that
	included in the review?				
RCT				1	
For F	Partial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
C					
from					
from x	unconcealed allocation, and	х	allocation sequence that was not truly random, and	х	Yes

lock of blinding of nationts and as	v	salaction of the reported regult from	TT -	Partial Yes
	X	-		
-				No
		yses of a specified outcome		Includes only
				NRSI
	D D		r –	
artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from confounding and	v	methods used to accertain exposures	v	Yes
from comounding, and	^	-	X	Partial Yes
from selection bias	v		┨┝──	No
nom selection blas	л	_		-
		- · · ·		Includes only RCT
id the review authors report on the s		· ·		
	burces o	in funding for the studies included in the l	eviev	N :
	funding	for individual studies included in the re		Yes
-	-	-		No
		ted for this information but it was not re-	х	NO
		authors use appropriate methods for sta	tistic	al combination of
		authors use appropriate methods for sta	usuc	
The authors justified combining the c	lata in a	meta-analysis		Yes
-				No
		1		
	neteroge	neity	na	No meta-analysis
	U	2		conducted
NRSI				
/es				
The authors justified combining the data in a meta-analysis				Yes
				No
for heterogeneity if present				
AND they statistically combined effe	ect estim	ates from NRSI that were adjusted for		No meta-analysis
confounding, rather than combining	raw data	, or justified combining raw data when		conducted
adjusted effect estimates were not av	ailable			
AND they reported separate summar	y estima	tes for RCTs and NRSI separately when		
both were included in the review				
f meta-analysis was performed, did th	e reviev	v authors assess the potential impact of R	oB in	individual studies
-	r eviden	ce synthesis?		
			wei	ighted
included only low risk of bias RCTs				Yes
-			х	No
	ite possi	ble impact of RoB on summary estimates		No meta-analysis
				conducted
	B in ind	ividual studies when interpreting/ discuss	sing t	he results of the
			1	
-			Х	Yes,
-		-		No
			<u> </u>	
-	actory of	explanation for, and discussion of, any he	terog	eneity observed in
			1	
	, • .1	1.	<u> </u>	
I nere was no significant heterogenei	ty in the	results	Х	Yes confounding
	Yes Must have reported on the sources of view. Note: Reporting that the review ported by study authors also qualifies Imeta-analysis was performed did the ts? Imeta-analysis was performed did the ts? S Yes The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any I VRSI Yes The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summare both were included in the review f meta-analysis was performed, did there results of the meta-analysis or othere Yes included only low risk of bias RCTs OR, if the pooled estimate was based thors performed analyses to investiga of effect. Vid the review authors account for Row? Yes included only low risk of bias RCTs OR, if RCTs with moderate or high F discussion of the likely impact of Ro vid the review authors provide a satisfeesults of the review?	sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) I artial Yes, must have assessed RoB For Y from confounding, and x from selection bias x id the review authors report on the sources of res Must have reported on the sources of funding view. Note: Reporting that the reviewers lood ported by study authors also qualifies f meta-analysis was performed did the review ts? review res The authors justified combining the data in a AND they used an appropriate weighted tech justed for heterogeneity if present. AND investigated the causes of any heteroge VRSI 'es The authors justified combining the data in a AND they used an appropriate weighted tech for heterogeneity if present AND investigated the causes of any heteroge VRSI 'es The authors justified combining the data in a AND they used an appropriate weighted tech for heterogeneity if present AND they statistically combined effect estim confounding, rather than combining raw data adjusted effect estimates were not available AND they reported separate summary estima both were included in the review 'meta-analysis was performed, did the review 'meta-analysis was performed, did the review 'meta-analysis was performed, did the review	sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) among multiple measurements or anal- yses of a specified outcome artial Yes, must have assessed RoB For Yes, must also have assessed RoB from: from confounding, and x methods used to ascertain exposures and outcomes, and from selection bias x selection of the reported result from among multiple measurements or anal- yses of a specified outcome id the review authors report on the sources of funding for the studies included in the re- view. Note: Reporting that the reviewers looked for this information but it was not re- ported by study authors also qualifies reta-analysis was performed did the review authors use appropriate methods for states? Seccess /cs The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results and ad- justed of heterogeneity if present. AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present. AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present. AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available AND they statistically combined effect estimates for RCTs and NRSI se	sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) among multiple measurements or anal- yes of a specified outcome artial Yes, must have assessed RoB For Yes, must also have assessed RoB from: from confounding, and x methods used to ascertain exposures and outcomes, and from selection bias x selection of the reported result from among multiple measurements or anal- yes of a specified outcome id the review authors report on the sources of funding for individual studies included in the review (res meta-analysis Must have reported on the sources of funding for individual studies included in the re- view. Note: Reporting that the reviewers looked for this information but it was not re- ported by study authors also qualifies meta-analysis The authors justified combining the data in a meta-analysis AND AND they used an appropriate weighted technique to combine study results and ad- justed for heterogeneity if present. ma AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present. ma AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present. x AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data, when adjusted effect estimates were not available AND they reported separate summary estimates for RCTs and NRSI separately w

х	OR if heterogeneity was present the authors performed an investigation of sources of		No
	any heterogeneity in the results and discussed the impact of this on the results of the re-		
	view		
15. If	they performed quantitative synthesis did the review authors carry out an adequate i	nvest	igation of publica-
tion b	ias (small study bias) and discuss its likely impact on the results of the review?		
For Y	es	Тоо	few studies to
		mał	ke sense of funnel
		plot	S
	performed graphical or statistical tests for publication bias and discussed the likelihood	na	Yes
	and magnitude of impact of publication bias		No
			No meta-analysis
			conducted
16. Di	d the review authors report any potential sources of conflict of interest, including any	fund	ing they received
for co	nducting the review?		
For Y	es		
х	The authors reported no competing interests OR	х	Yes
	The authors described their funding sources and how they managed potential conflicts		No
	of interest		
Your	overall assessment of the risk of bias of this systematic review		
High			

AMS	FAR 2 checklist, <mark>critical questions</mark>					
REF:	Franck et al 2014					
1. Di	d the research questions and inclusior	ı criteri	a for the review include the components	of PIC	C O ?	
For Y	Zes	Optio	nal (recommended)			
х	Population		Timeframe for follow up	х	Yes	
х	Intervention				No	
Х	Comparator group	1				
Х	Outcome	1				
2. Di	d the report of the review contain an o	explicit	statement that the review methods were	establ	lished prior to the	
cond	uct of the review and did the report ju	ustify an	y significant deviations from the protoco	ol?		
For P	artial Yes:	For Y	es:			
	uthors state that they had a written		partial yes, plus the protocol should be			
•	col or guide that included ALL the	registe	ered and should also have specified:			
follo			-			
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes	
			propriate, and			
	a search strategy		a plan for investigating causes of heter-		Partial Yes	
			ogeneity			
	inclusion/exclusion criteria			Х	No	
	a risk of bias assessment					
			f the study designs for inclusion in the re	view?	•	
For Y	ves, the review should satisfy ONE of th		ing:	х	Yes	
	Explanation for including only RCTs				No	
	OR Explanation for including only N					
х	OR Explanation for including both R	CTs and	NRSI			
4. Di	d the review authors use a comprehen					
For P	artial Yes (all the following):	For Y	es, should also have (all the following):		Yes	
х	searched at least 2 databases (rele-		searched the reference lists / bibliog-	х	Partial Yes	
	vant to research question)		raphies of included studies			
х	provided key word and/or search		searched trial/study registries		No	
	strategy					

		т —		1	
х	justified publication restrictions		included/consulted content experts in		
	(e.g. language)		the field		
		х	where relevant, searched for grey litera-		
			ture conducted search within 24 months of		
		х			
5 D'			completion of the review		
	d the review authors perform study s	election	in duplicate?		
For Y	es, either ONE of the following:			r –	
	at least two reviewers independently	e	e		Yes
	achieved consensus on which studies				N
			le studies and achieved good agreement	х	No
(D)	(at least 80 percent), with the remain				
	d the review authors perform data ex	traction	in duplicate?		
	es, either ONE of the following:			x	
х	at least two reviewers achieved consensus on which data to extract from included stu-				Yes
	ies				
		ble of eligible studies and achieved good		No	
	agreement (at least 80 percent), with				
	d the review authors provide a list of			r	
For Pa	artial Yes:	For Y	es, must also have:		
Х	provided a list of all potentially rel-		Justified the exclusion from the review		Yes
	evant studies that were read in full-		of each potentially relevant study	х	Partial Yes
	text form but excluded from the re-				No
	view				
	d the review authors describe the incl		-		
For Pa	artial Yes (ALL the following):	For Y	es, should also have ALL the following:		
х	described populations	х	described population in detail	х	Yes
х	described interventions	х	described intervention in detail (includ-		Partially Yes
			ing doses where relevant)		
х	described comparators		described comparator in detail (includ-		No
			ing doses where relevant)		
х	described outcomes	х			
			described study's setting		
	1 1 1 1 1				
X	described research designs	X	timeframe for follow-up		
	d the review authors use a satisfactor	v techni	que for assessing the risk of bias (RoB) ir	i indiv	vidual studies that
were		,	• • • • • • •		
DOT	included in the review?	y teenin		- mur	
RCT	included in the review? s				
For Pa	included in the review?		es, must also have assessed RoB from:		
For Pa from	included in the review? s artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
For Pa	included in the review? s		es, must also have assessed RoB from: allocation sequence that was not truly	x	Yes
For Pa from x	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and	For Y	es, must also have assessed RoB from: allocation sequence that was not truly random, and		Partial Yes
For Pa from	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as-	For Y	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from		Partial Yes No
For Pa from x	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes	For Y	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal-		Partial Yes No Includes only
For Pa from x	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out-	For Y	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from		Partial Yes No
For Pa from x x	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)	For Y	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal-		Partial Yes No Includes only
For Pa from x x NRSI	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)	For Y X X	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome		Partial Yes No Includes only NRSI
For Pa from x x NRSI For Pa	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)	For Y X X	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal-	All 1	Partial Yes No Includes only NRSI non-RCT assessed
For Pa from x x NRSI	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) I artial Yes, must have assessed RoB	For Y X X	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from:	All 1	Partial Yes No Includes only NRSI non-RCT assessed oor quality
For Pa from x x NRSI For Pa	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)	For Y X X	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from: methods used to ascertain exposures	All 1	Partial Yes No Includes only NRSI non-RCT assessed poor quality Yes
For Pa from x x NRSI For Pa	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) I artial Yes, must have assessed RoB from confounding, and	For Y X X	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and	All 1	Partial Yes No Includes only NRSI non-RCT assessed oor quality
For Pa from x x NRSI For Pa	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) I artial Yes, must have assessed RoB	For Y X X	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from	All 1	Partial Yes No Includes only NRSI non-RCT assessed poor quality Yes
For Pa from x x NRSI For Pa from	included in the review? s artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) I artial Yes, must have assessed RoB from confounding, and	For Y X X	es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and	All 1 as p	Partial Yes No Includes only NRSI non-RCT assessed oor quality Yes Partial Yes

10. Did the rev	iew authors report on the sources of funding for the studies included in the r	eview	v?				
For Yes							
Must ha	ve reported on the sources of funding for individual studies included in the re-		Yes				
	ote: Reporting that the reviewers looked for this information but it was not re-	х	No				
-	y study authors also qualifies						
11. If meta-ana results?	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?						
RCTs							
For Yes							
The auth	nors justified combining the data in a meta-analysis		Yes				
	ey used an appropriate weighted technique to combine study results and ad-		No				
	or heterogeneity if present.						
AND in	vestigated the causes of any heterogeneity	х	No meta-analysis				
			conducted				
For NRSI							
For Yes							
The auth	nors justified combining the data in a meta-analysis		Yes				
AND th	ey used an appropriate weighted technique to combine study results, adjusting		No				
for heter	ogeneity if present						
AND th	ey statistically combined effect estimates from NRSI that were adjusted for	х	No meta-analysis				
confoun	ding, rather than combining raw data, or justified combining raw data when		conducted				
-	effect estimates were not available						
AND th	ey reported separate summary estimates for RCTs and NRSI separately when						
	re included in the review						
	lysis was performed, did the review authors assess the potential impact of R	oB in	individual studies				
	f the meta-analysis or other evidence synthesis?						
For Yes							
	l only low risk of bias RCTs		Yes				
	ne pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No				
	rformed analyses to investigate possible impact of RoB on summary estimates	х	No meta-analysis				
of effect	•		conducted				
	iew authors account for RoB in individual studies when interpreting/ discuss	sing tl	he results of the				
review?		-					
For Yes			1				
	l only low risk of bias RCTs	х	Yes				
	CTs with moderate or high RoB, or NRSI were included the review provided a		No				
	on of the likely impact of RoB on the results						
	iew authors provide a satisfactory explanation for, and discussion of, any he	teroge	eneity observed in				
the results of th	ie review?						
For Yes			[
	as no significant heterogeneity in the results	Х	Yes				
	terogeneity was present the authors performed an investigation of sources of		No				
-	rogeneity in the results and discussed the impact of this on the results of the re-						
view							
	ormed quantitative synthesis did the review authors carry out an adequate i	nvesti	igation of publica-				
	study bias) and discuss its likely impact on the results of the review?	1					
For Yes			37				
-	ed graphical or statistical tests for publication bias and discussed the likelihood		Yes				
and mag	nitude of impact of publication bias	<u> </u>	No				
		х	No meta-analysis				
1(D'12			conducted				
	iew authors report any potential sources of conflict of interest, including any the review?	Tund	ing they received				
for conducting	the review?	<u> </u>					
For Yes							

х	The authors reported no competing interests OR	х	Yes			
	The authors described their funding sources and how they managed potential conflicts		No			
	of interest					
Your overall assessment of the risk of bias of this systematic review						
Moderate						

AMS	ΓAR 2 checklist, <mark>critical questions</mark>				
	Goniewicz et al 2020				
	-		a for the review include the components	of PIC	C O ?
For Y		Optio	nal (recommended)		
х	Population		Timeframe for follow up	х	Yes
х	Intervention				No
Х	Comparator group				
х	Outcome				
	-	-	statement that the review methods were (y significant deviations from the protoco		lished prior to the
	artial Yes:	For Y			
The a	uthors state that they had a written	As for	partial yes, plus the protocol should be		
proto	col or guide that included ALL the	registe	ered and should also have specified:		
follov	ving:				
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes
			propriate, and		
	a search strategy		a plan for investigating causes of heter- ogeneity		Partial Yes
	inclusion/exclusion criteria			х	No
	a risk of bias assessment				1
3. Di	d the review authors explain their sel	ection of	f the study designs for inclusion in the rev	view?	
For Yes, the review should satisfy ONE of the following:					Yes
	Explanation for including only RCTs				No
х	OR Explanation for including only N				
	OR Explanation for including both R		NRSI		
4. Di	d the review authors use a comprehe			1	
	artial Yes (all the following):		es, should also have (all the following):	1	Yes
x	searched at least 2 databases (rele-		searched the reference lists / bibliog-	x	Partial Yes
	vant to research question)		raphies of included studies		
х	provided key word and/or search strategy		searched trial/study registries		No
х	justified publication restrictions (e.g. language)		included/consulted content experts in the field		1
			where relevant, searched for grey litera- ture		
		х	conducted search within 24 months of completion of the review		
5. Di	d the review authors perform study s	election			
For Y	es, either ONE of the following:				
х	at least two reviewers independently achieved consensus on which studies	-	-	х	Yes
			le studies and achieved good agreement		No
	(at least 80 percent), with the remain	-			
6. Di	d the review authors perform data ex				1
	es, either ONE of the following:		-		
х	-	ensus on	which data to extract from included stud-	x	Yes

	OR two reviewers extracted data from	n a samı	ble of eligible studies and achieved good		No
	agreement (at least 80 percent), with	-			110
7. Did	the review authors provide a list of	exclude	d studies and justify the exclusions?		
For Pa	artial Yes:	For Y	es, must also have:		
х	provided a list of all potentially rel- evant studies that were read in full- text form but excluded from the re- view		Justified the exclusion from the review of each potentially relevant study	x	Yes Partial Yes No
8. Did	I the review authors describe the incl	uded st	udies in adequate detail?		
	artial Yes (ALL the following):		es, should also have ALL the following:		
х	described populations	х	described population in detail		Yes
Х	described interventions		described intervention in detail (includ- ing doses where relevant)	х	Partially Yes
Х	described comparators		described comparator in detail (includ- ing doses where relevant)		No
Х	described outcomes		described study's setting		
x	described research designs		timeframe for follow-up		
9. Did	e	y techni	que for assessing the risk of bias (RoB) i	n indi	vidual studies that
	included in the review?				
RCTs	5				
For Pa from	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
	unconcealed allocation, and		allocation sequence that was not truly random, and		Yes Partial Yes
	lack of blinding of patients and as-		selection of the reported result from		No
	sessors when assessing outcomes (unnecessary for objective out-		among multiple measurements or anal- yses of a specified outcome	x	Includes only NRSI
NDCI	comes such as all-cause mortality)				
NRSI		E V		1	
for Pa from	artial Yes, must have assessed RoB	FOF Y	es, must also have assessed RoB from:		
Х	from confounding, and	х	methods used to ascertain exposures	x	Yes
			and outcomes, and		Partial Yes
х	from selection bias	NA	selection of the reported result from		No
			among multiple measurements or anal- yses of a specified outcome		Includes only RCT
		ources o	f funding for the studies included in the	reviev	v?
For Y					
х	view. Note: Reporting that the review	ers lool	tor individual studies included in the re- teed for this information but it was not re-	x	Yes No
			authors use appropriate methods for sta	atistic	al combination of
result RCTs					
For Y					
	The authors justified combining the d	lata in c	meta_analveis		Yes
LOL L	T The authors fusitified combining the o		-		
FUF Y			nume to compline study results and ad-	1	No
ror Y	AND they used an appropriate weigh	ted tech	inque to comonie study results and ad-		
	AND they used an appropriate weigh justed for heterogeneity if present.				Nomé
For Y	AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any h			x	No meta-analysis conducted

	The authors justified combining the data in a meta-analysis		Yes
	AND they used an appropriate weighted technique to combine study results, adjusting		No
	for heterogeneity if present		
	AND they statistically combined effect estimates from NRSI that were adjusted for	х	No meta-analysis
	confounding, rather than combining raw data, or justified combining raw data when		conducted
	adjusted effect estimates were not available		
	AND they reported separate summary estimates for RCTs and NRSI separately when		
	both were included in the review		
12. If	meta-analysis was performed, did the review authors assess the potential impact of R	oB in	individual studies
on the	e results of the meta-analysis or other evidence synthesis?		
For Y	es		
	included only low risk of bias RCTs		Yes
	OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No
	thors performed analyses to investigate possible impact of RoB on summary estimates	х	No meta-analysis
	of effect.		conducted
13. D	id the review authors account for RoB in individual studies when interpreting/ discuss	ing tl	ne results of the
review	v?		
For Y	es		
	included only low risk of bias RCTs	х	Yes
х	OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a		No
	discussion of the likely impact of RoB on the results		
4. Did	l the review authors provide a satisfactory explanation for, and discussion of, any hete	erogei	eity observed in
the re	sults of the review?		
For Y	es		
х	There was no significant heterogeneity in the results	х	Yes
	OR if heterogeneity was present the authors performed an investigation of sources of		No
	any heterogeneity in the results and discussed the impact of this on the results of the re-		
	view		
	they performed quantitative synthesis did the review authors carry out an adequate i	nvesti	gation of publica-
tion b	ias (small study bias) and discuss its likely impact on the results of the review?		
For Y	es		
	performed graphical or statistical tests for publication bias and discussed the likelihood		Yes
	and magnitude of impact of publication bias		No
		х	No meta-analysis
			conducted
16. D	id the review authors report any potential sources of conflict of interest, including any	fund	ing they received
for co	nducting the review?		
For Y	es		
х	The authors reported no competing interests OR	х	Yes
	The authors described their funding sources and how they managed potential conflicts		No
	The authors described their funding sources and now they managed potential conflicts		110
	of interest		110
Your			

AMSTAR 2 checklist, critical questions								
REF: Gualanao et al 2015								
1. Did the research questions and inclusion criteria for the review include the components of PICO?								
For Yes		Optional (recommended)						
х	Population		Timeframe for follow up	х	Yes			
х	Intervention				No			
х	Comparator group							
х	Outcome							

2. Did	the report of the review contain an e	explicit s	statement that the review methods were o	establ	ished prior to the
condu	ict of the review and did the report ju	istify an	y significant deviations from the protoco	ol?	
For Pa	artial Yes:	For Y	es:		
	uthors state that they had a written	As for partial yes, plus the protocol should be			
-	ol or guide that included ALL the	registe	ered and should also have specified:		
follow					1
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes
			propriate, and		
	a search strategy		a plan for investigating causes of heter-		Partial Yes
	inclusion/exclusion criteria		ogeneity	x	No
	a risk of bias assessment	-		х	NO
3 Did		etion of	f the study designs for inclusion in the rev	view?	
	es, the review should satisfy ONE of th			x	Yes
101 1	Explanation for including only RCTs	c lollow	ing.	л	No
	OR Explanation for including only N	RSI			110
x	OR Explanation for including both R		NRSI		
	the review authors use a comprehen				
	artial Yes (all the following):		es, should also have (all the following):	1	Yes
x	searched at least 2 databases (rele-	1011	searched the reference lists / bibliog-	x	Partial Yes
А	vant to research question)		raphies of included studies	Α	i ui uu i co
x	provided key word and/or search	x	searched trial/study registries		No
	strategy				
х	justified publication restrictions		included/consulted content experts in		I
	(e.g. language)		the field		
			where relevant, searched for grey litera-		
			ture		
		х	conducted search within 24 months of		
			completion of the review		
5. Did	the review authors perform study se	lection	in duplicate?		
For Y	es, either ONE of the following:				
	at least two reviewers independently	-	-		Yes
	achieved consensus on which studies				
	_		le studies and achieved good agreement	х	No
	(at least 80 percent), with the remained		-		
	the review authors perform data ext	raction	in duplicate?		
For Y	es, either ONE of the following:				
	at least two reviewers achieved conse ies	nsus on	which data to extract from included stud-		Yes
	OR two reviewers extracted data from	n a samp	le of eligible studies and achieved good	х	No
	agreement (at least 80 percent), with		-		
7. Did	the review authors provide a list of a				
For Pa	artial Yes:	For Y	es, must also have:		
	provided a list of all potentially rel-	х	Justified the exclusion from the review		Yes
	evant studies that were read in full-		of each potentially relevant study	х	Partial Yes
	text form but excluded from the re-				No
0.54	view	Ļ			
	the review authors describe the inclusion of the inclusio			<u> </u>	
	artial Yes (ALL the following):	For Y	es, should also have ALL the following:		
Х	described populations		described population in detail		Yes
х	described interventions	х	described intervention in detail (includ-	х	Partially Yes
v	described comparators	v	ing doses where relevant) described comparator in detail (includ-		No
х	described comparators	х	ing doses where relevant)		
1		1	ing doses where relevant)	1	1

х	described outcomes	х			
			described study's setting		
X	described research designs		timeframe for follow-up		••••
		y techni	que for assessing the risk of bias (RoB) in	n indi	vidual studies that
	included in the review?				
RCT		E V		1	
for P	artial Yes, must have assessed RoB	FOR Y	es, must also have assessed RoB from:		
	unconcealed allocation, and	x	allocation sequence that was not truly		Yes
Х	unconceased anocation, and	X	random, and		Partial Yes
х	lack of blinding of patients and as-	-	selection of the reported result from	X	
л	sessors when assessing outcomes		among multiple measurements or anal-		No
	(unnecessary for objective out-		yses of a specified outcome		Includes only
	comes such as all-cause mortality)		yses of a specified outcome		NRSI
NRSI					
	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:	1	
from	,		,	1	
x	from confounding, and	x	methods used to ascertain exposures	х	Yes
			and outcomes, and		Partial Yes
х	from selection bias	x	selection of the reported result from	1├	No
			among multiple measurements or anal-		Includes only
			yses of a specified outcome		RCT
10. D	id the review authors report on the s	ources o	f funding for the studies included in the	reviev	w?
For Y			8	1	
Х		f funding	g for individual studies included in the re-	x	Yes
	-	-	xed for this information but it was not re-		No
	ported by study authors also qualifies				-
11. If			authors use appropriate methods for sta	tistic	al combination of
result	ts?				
RCTs					
For Y	es				
	The authors justified combining the	data in a	meta-analysis		Yes
	AND they used an appropriate weigh	nted tech	nique to combine study results and ad-		No
	justed for heterogeneity if present.				
	AND investigated the causes of any	heteroge	neity	х	No meta-analysis
					conducted
For N	VRSI				
For Y					
	The authors justified combining the data in a meta-analysis				Yes
	AND they used an appropriate weighted technique to combine study results, adjusting				No
	for heterogeneity if present				
	AND they statistically combined effect estimates from NRSI that were adjusted for				No meta-analysis
	confounding, rather than combining raw data, or justified combining raw data when				conducted
	adjusted effect estimates were not av			<u> </u>	
	AND they reported separate summary estimates for RCTs and NRSI separately when				
	both were included in the review				
12 If			v authors assess the potential impact of R	loB in	n individual studies
	e results of the meta-analysis or othe	r eviden	ce synthesis?	1	
on th				1	
	es				
on th	es included only low risk of bias RCTs				Yes
on th	es included only low risk of bias RCTs OR, if the pooled estimate was based	l on RCT	Is and/or NRSI at variable RoB, the au-		No
on th	es included only low risk of bias RCTs OR, if the pooled estimate was based	l on RCT	I's and/or NRSI at variable RoB, the auble impact of RoB on summary estimates	x	

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the						
review?						
For Yes						
included only low risk of bias RCTs			Yes			
OR, if RCTs with moderate or high RoB, or NRSI w	ere included the review provided a	х	No			
discussion of the likely impact of RoB on the results						
	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in					
the results of the review?						
For Yes						
x There was no significant heterogeneity in the results		х	Yes			
OR if heterogeneity was present the authors performed	-		No			
any heterogeneity in the results and discussed the imp	pact of this on the results of the re-					
view						
15. If they performed quantitative synthesis did the revie	• •	ivesti	igation of publica-			
tion bias (small study bias) and discuss its likely impact on the results of the review?						
For Yes						
performed graphical or statistical tests for publication		Yes				
and magnitude of impact of publication bias			No			
		х	No meta-analysis			
			conducted			
16. Did the review authors report any potential sources of conflict of interest, including any funding they received						
for conducting the review?						
For Yes						
The authors reported no competing interests OR			Yes			
The authors described their funding sources and how	they managed potential conflicts	Х	No			
of interest						
Your overall assessment of the risk of bias of this systematic review						
Moderate						

AMS	TAR 2 checklist, <mark>critical questions</mark>				
REF	HartmannBoyce et al 2020				
1. D	id the research questions and inclusion	on criter	ia for the review include the components	of PI	C O ?
For Yes Optional (recommended)					
х	Population	х	Timeframe for follow up	х	Yes
х	Intervention				No
х	Comparator group				•
х	Outcome				
2. D	id the report of the review contain an	explicit	statement that the review methods were	estab	lished prior to the
cond	luct of the review and did the report	justify a	ny significant deviations from the protoco	ol?	
For Partial Yes: For Yes:					
The authors state that they had a written		As fo	As for partial yes, plus the protocol should be		
protocol or guide that included ALL the		registered and should also have specified:			
follo	wing:				
Х	review question(s)	х	a meta-analysis/ synthesis plan, if ap-	х	Yes
			propriate, and		
х	a search strategy	х	a plan for investigating causes of heter- ogeneity		Partial Yes
Х	inclusion/exclusion criteria				No
Х	a risk of bias assessment				•
3. D	d the review authors explain their se	lection o	f the study designs for inclusion in the re	view?	,
For Yes, the review should satisfy ONE of the following:			х	Yes	
	Explanation for including only RCTs				No

	OR Explanation for including only N	RSI			
х	OR Explanation for including both R	CTs and	INRSI		
4. Di	d the review authors use a comprehe	asive lite	erature search strategy?		
	Partial Yes (all the following):		es, should also have (all the following):	х	Yes
х	searched at least 2 databases (rele-	х	searched the reference lists / bibliog-		Partial Yes
	vant to research question)		raphies of included studies		
х	provided key word and/or search strategy	х	searched trial/study registries		No
х	justified publication restrictions (e.g. language)	x	included/consulted content experts in the field		1
			where relevant, searched for grey litera- ture		
		х	conducted search within 24 months of completion of the review		
5. Di	d the review authors perform study s	election	in duplicate?		
	es, either ONE of the following:		-		
х	at least two reviewers independently	agreed c	on selection of eligible studies and	х	Yes
	achieved consensus on which studies	-	-		
			le studies and achieved good agreement	1	No
	(at least 80 percent), with the remain	-			
6. Di	d the review authors perform data ex			1	J
	Yes, either ONE of the following:				
x			which data to extract from included stud-	x	Yes
	OR two reviewers extracted data from	n a sam	ble of eligible studies and achieved good		No
	agreement (at least 80 percent), with	-			
7. Di	d the review authors provide a list of		-	1	
	Partial Yes:		es, must also have:	1	
x	provided a list of all potentially rel-	x	Justified the exclusion from the review	x	Yes
	evant studies that were read in full-		of each potentially relevant study		Partial Yes
	text form but excluded from the re-				No
	view				
8. Di	d the review authors describe the incl	uded st	udies in adequate detail?		
	Partial Yes (ALL the following):		es, should also have ALL the following:		
x	described populations		described population in detail	х	Yes
x	described interventions	x	described intervention in detail (includ-		Partially Yes
			ing doses where relevant)		
х	described comparators	х	described comparator in detail (includ-		No
	1		ing doses where relevant)		
x	described outcomes	x	described study's setting		1
		┥───	timeframe for follow-up	-	
	described research designs	х	_		
9. Di	d the review authors use a satisfactor		que for assessing the risk of bias (RoB) in	ı indi	vidual studies that
9. Di were	d the review authors use a satisfactor included in the review?		_	ı indiv	vidual studies that
9. Di were RCT	d the review authors use a satisfactor included in the review? s	y techni	que for assessing the risk of bias (RoB) in	ı indiv	vidual studies that
9. Di were RCT For P	d the review authors use a satisfactor included in the review? s Partial Yes, must have assessed RoB	y techni	_	n indiv	vidual studies that
9. Di were RCT For P from	d the review authors use a satisfactor included in the review? s Partial Yes, must have assessed RoB	y techni	que for assessing the risk of bias (RoB) in	n indiv	vidual studies that
9. Di were RCT For P from	d the review authors use a satisfactor included in the review? s Partial Yes, must have assessed RoB	y techni For Y	que for assessing the risk of bias (RoB) in es, must also have assessed RoB from:		
9. Di were RCT For P from x	d the review authors use a satisfactor included in the review? s Partial Yes, must have assessed RoB	y techni For Y	que for assessing the risk of bias (RoB) in es, must also have assessed RoB from: allocation sequence that was not truly		Yes
9. Di were RCT For P from x	d the review authors use a satisfactor included in the review? s Partial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes	y techni For Y x	que for assessing the risk of bias (RoB) in in es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal-		Yes Partial Yes
were RCT	d the review authors use a satisfactor included in the review? s Partial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as-	y techni For Y x	que for assessing the risk of bias (RoB) in es, must also have assessed RoB from: allocation sequence that was not truly random, and selection of the reported result from		Yes Partial Yes No

NRSI								
For Partial Yes, must have assessed RoB For Yes, must also have assessed RoB from:								
from								
	from confounding, and	methods used to ascertain exposures		Yes				
		and outcomes, and		Partial Yes				
	from selection bias	selection of the reported result from		No				
		among multiple measurements or anal-	х	Includes only				
		yses of a specified outcome		RCT				
10. Di	d the review authors report on the s	ources of funding for the studies included in the r	review	/?				
For Y	es							
х	Must have reported on the sources of	х	Yes					
	view. Note: Reporting that the review		No					
	ported by study authors also qualifie							
		e review authors use appropriate methods for sta	tistica	al combination of				
result	s?							
RCTs								
For Y								
Х	The authors justified combining the		х	Yes				
х		nted technique to combine study results and ad-		No				
	justed for heterogeneity if present.							
х	AND investigated the causes of any	heterogeneity		No meta-analysis				
				conducted				
For N								
For Y								
	The authors justified combining the		Yes					
	AND they used an appropriate weigh		No					
	for heterogeneity if present							
	AND they statistically combined effe	х	No meta-analysis					
	confounding, rather than combining		conducted					
	adjusted effect estimates were not av AND they reported separate summar	-						
	both were included in the review							
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?								
For Y	•		Γ					
x	included only low risk of bias RCTs		x	Yes				
		l on RCTs and/or NRSI at variable RoB, the au-		No				
		ate possible impact of RoB on summary estimates	-	No meta-analysis				
	of effect.	1 1 5		conducted				
13. Di	d the review authors account for Ro	B in individual studies when interpreting/ discuss	sing tl					
reviev		r s g min						
For Y								
х	included only low risk of bias RCTs		х	Yes				
	OR, if RCTs with moderate or high	RoB, or NRSI were included the review provided a		No				
	discussion of the likely impact of Ro	B on the results						
14. Di	d the review authors provide a satis	factory explanation for, and discussion of, any he	terog	eneity observed in				
the results of the review?								
For Y	es							
	There was no significant heterogener	ity in the results	х	Yes				
х	OR if heterogeneity was present the	authors performed an investigation of sources of		No				
	any heterogeneity in the results and o	discussed the impact of this on the results of the re-						
	view							
		sis did the review authors carry out an adequate i	nvest	igation of publica-				
tion bias (small study bias) and discuss its likely impact on the results of the review?								

For Y	/es		
Х	performed graphical or statistical tests for publication bias and discussed the likelihood	х	Yes
	and magnitude of impact of publication bias		No
			No meta-analysis conducted
16. D	id the review authors report any potential sources of conflict of interest, including any	y fun	ding they received
for c	onducting the review?		
For Y	<i>l</i> es		
Х	The authors reported no competing interests OR	х	Yes
	The authors described their funding sources and how they managed potential conflicts		No
	of interest		
Your	overall assessment of the risk of bias of this systematic review		·
High			

. Did	the research questions and inclusion	n criter	ia for the review include the components	of PIC	CO?
For Y	es	Optio	onal (recommended)		
х	Population		Timeframe for follow up	х	Yes
Х	Intervention		•		No
х	Comparator group				
х	Outcome				
2. Did	the report of the review contain an	explicit	t statement that the review methods were	establ	lished prior to t
condu	ict of the review and did the report j	ustify a	ny significant deviations from the protoco	ol?	
For Pa	artial Yes:	For Y	Yes:		
The a	uthors state that they had a written	As fo	or partial yes, plus the protocol should be		
protoc	col or guide that included ALL the	regis	tered and should also have specified:		
follow	_				
х	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes
			propriate, and		
х	a search strategy		a plan for investigating causes of heter-	х	Partial Yes
			ogeneity		
х	inclusion/exclusion criteria				No
х	a risk of bias assessment				
	-		of the study designs for inclusion in the re-	view?	
For Y	es, the review should satisfy ONE of th		wing:	х	Yes
	Explanation for including only RCTs				No
	OR Explanation for including only N	RSI			
х	OR Explanation for including both R	CTs an	d NRSI		
4. Did	the review authors use a comprehe	nsive lit	terature search strategy?		
For Pa	artial Yes (all the following):	For Y	Yes, should also have (all the following):		Yes
х	searched at least 2 databases (rele-	Х	searched the reference lists / bibliog-	х	Partial Yes
	vant to research question)		raphies of included studies		
Х	provided key word and/or search		searched trial/study registries		No
	strategy				
х	justified publication restrictions		included/consulted content experts in		
	(e.g. language)		the field		
			where relevant, searched for grey litera-		
			ture		
		х	conducted search within 24 months of		
			completion of the review		

					-			
х	at least two reviewers independently	х	Yes					
	achieved consensus on which studies							
	OR two reviewers selected a sample of		No					
	(at least 80 percent), with the remained							
	6. Did the review authors perform data extraction in duplicate?							
	For Yes, either ONE of the following:							
х	at least two reviewers achieved conse ies	х	Yes					
		-	ble of eligible studies and achieved good		No			
	agreement (at least 80 percent), with		-					
	the review authors provide a list of a		· ·	1				
	artial Yes:		es, must also have:	 	1			
х	provided a list of all potentially rel-	х	Justified the exclusion from the review	х	Yes			
	evant studies that were read in full-		of each potentially relevant study		Partial Yes			
	text form but excluded from the re-				No			
	view			sup	plementary			
	I the review authors describe the incl							
For Pa	artial Yes (ALL the following):	For Y	es, should also have ALL the following:		1			
х	described populations	Х	described population in detail	х	Yes			
х	described interventions	х	described intervention in detail (includ- ing doses where relevant)		Partially Yes			
х	described comparators	х	described comparator in detail (includ-		No			
	-		ing doses where relevant)					
х	described outcomes	х	described study's setting					
х	described research designs	х	timeframe for follow-up	-				
9. Dic	_	y techni	que for assessing the risk of bias (RoB) in	ı indiv	vidual studies that			
	included in the review?							
RCT	5							
For Pa from	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:					
x	unconcealed allocation, and		allocation sequence that was not truly		Yes			
л	unconceated anocation, and		random, and	x	Partial Yes			
х	lack of blinding of patients and as-		selection of the reported result from		No			
	sessors when assessing outcomes		among multiple measurements or anal-		Includes only			
	(unnecessary for objective out-		yses of a specified outcome		NRSI			
	comes such as all-cause mortality)				1.1.01			
NRSI	[1				
For Pa	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:					
from								
х	from confounding, and	х	methods used to ascertain exposures		Yes			
v	from selection bias		and outcomes, and selection of the reported result from	x	Partial Yes			
х	Hom selection bias		among multiple measurements or anal-		No			
			yses of a specified outcome		Includes only RCT			
10. D	id the review authors report on the so	urces o	f funding for the studies included in the	review	?			
For Y								
х	Marthan was at 1 and a summer of	funding	for individual studies included in the re-	x	Yes			
	Must have reported on the sources of							
	-	-	ted for this information but it was not re-		No			
	-	ers look	ted for this information but it was not re-		No			
11. If	view. Note: Reporting that the review ported by study authors also qualifies	ers look	authors use appropriate methods for sta					
11. If result RCTs	view. Note: Reporting that the review ported by study authors also qualifies meta-analysis was performed did the ts?	ers look						

For Yes		
The authors justified combining the data in a meta-analysis		Yes
AND they used an appropriate weighted technique to combine study results and ad-		No
justed for heterogeneity if present.		110
AND investigated the causes of any heterogeneity	х	No meta-analysis
For NRSI		conducted
For Yes		
The authors justified combining the data in a meta-analysis		Yes
AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present		No
AND they statistically combined effect estimates from NRSI that were adjusted for		No moto onolygia
confounding, rather than combining raw data, or justified combining raw data when	Х	No meta-analysis conducted
adjusted effect estimates were not available		conducted
AND they reported separate summary estimates for RCTs and NRSI separately when		
both were included in the review		
12. If meta-analysis was performed, did the review authors assess the potential impact of F	PoR ir	individual studios
on the results of the meta-analysis or other evidence synthesis?	ID II	i muividuai studies
For Yes	T	
included only low risk of bias RCTs		Yes
OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No
thors performed analyses to investigate possible impact of RoB on summary estimates		-
of effect.	Х	No meta-analysis conducted
12 Did the verying outhous account for DoD in individual studies when intermeding discus	aina 4	he weenly of the
• •	sing t	he results of the
review?	sing t	he results of the
review? For Yes		
review? For Yes included only low risk of bias RCTs	sing t	Yes
x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a		
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	x	Yes No
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here	x	Yes No
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here the results of the review?	x	Yes No
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here the results of the review? For Yes	x	Yes No geneity observed in
review? For Yes included only low risk of bias RCTs X OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here the results of the review? For Yes There was no significant heterogeneity in the results	x x	Yes No eneity observed in Yes
review? For Yes included only low risk of bias RCTs X OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of	x	Yes No geneity observed in
review? For Yes Included only low risk of bias RCTs X OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re-	x x	Yes No eneity observed in Yes
review? For Yes included only low risk of bias RCTs X OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	eterog	Yes No geneity observed in Yes No
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate	eterog	Yes No geneity observed in Yes No
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review?	eterog	Yes No geneity observed in Yes No
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review?	eterog	Yes No Yes No tigation of publica-
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood	eterog	Yes No eneity observed in Yes No tigation of publica-
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review?		Yes No encity observed in Yes No tigation of publica-
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any hete results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood	eterog	Yes No Yes No tigation of publica- Yes No No No meta-analysis
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heteresults of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	x x invest	Yes No Yes No Yes No tigation of publica- Yes No No meta-analysis conducted
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any hete results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes Image: Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including an	x x invest	Yes No Yes No Yes No tigation of publica- Yes No No meta-analysis conducted
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heteresults of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias I6. Did the review authors report any potential sources of conflict of interest, including an for conducting the review?	x x invest	Yes No Yes No tigation of publica- Yes No No meta-analysi conducted
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heteresults of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes Image: Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias It herewise authors report any potential sources of conflict of interest, including an for conducting the review?	x x x x x x x x x x x x y fund	Yes No Yes No tigation of publica- Yes No No meta-analysi conducted ding they received
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heteresults of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes Image: Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias Ib. Did the review authors report any potential sources of conflict of interest, including an for conducting the review? For Yes x The authors reported no competing interests OR	x x invest	Yes No Yes No Yes No tigation of publica- Yes No No meta-analysi conducted ding they received Yes
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heter results of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including an for conducting the review? For Yes x The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts	x x x x x x x x x x x x y fund	Yes No Yes No tigation of publica- Yes No tigation of publica- igation of publica-
review? For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heteresults of the review? For Yes There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes Image: Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias Ib. Did the review authors report any potential sources of conflict of interest, including an for conducting the review? For Yes x The authors reported no competing interests OR	x x x x x x x x x x x x y fund	Yes No Yes No Yes No tigation of publica- Yes No No meta-analysis conducted ding they received Yes

AMST	AR 2 checklist, <mark>critical questions</mark>						
REF: H	Kennedy et al 2019						
1. Did the research questions and inclusion criteria for the review include the components of PICO?							
For Ye	es	Option	nal (recommended)				
Х	Population		Timeframe for follow up	х	Yes		
Х	Intervention				No		
Х	Comparator group				•		
Х	Outcome						
2. Did	2. Did the report of the review contain an explicit statement that the review methods were established prior to the						
condu	ict of the review and did the report ju	istify an	y significant deviations from the protoco	1?			
For Pa	artial Yes:	For Y	es:				
	thors state that they had a written		partial yes, plus the protocol should be				
_	ol or guide that included ALL the	registe	ered and should also have specified:				
follow	-						
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes		
			propriate, and				
	a search strategy		a plan for investigating causes of heter-		Partial Yes		
			ogeneity				
	inclusion/exclusion criteria			Х	No		
	a risk of bias assessment						
	-		the study designs for inclusion in the rev	view?	1		
For Y	es, the review should satisfy ONE of th	e follow	ing:	х	Yes		
	Explanation for including only RCTs				No		
OR Explanation for including only NRSI							
x OR Explanation for including both RCTs and NRSI							
4. Did the review authors use a comprehensive literature search strategy?							
For Pa	artial Yes (all the following):	For Y	es, should also have (all the following):		Yes		
х	searched at least 2 databases (rele-	х	searched the reference lists / bibliog-	х	Partial Yes		
	vant to research question)		raphies of included studies				
х	provided key word and/or search		searched trial/study registries		No		
	strategy						
х	justified publication restrictions		included/consulted content experts in				
	(e.g. language)	-	the field				
			where relevant, searched for grey litera-				
			ture				
		х	conducted search within 24 months of				
			completion of the review				
	the review authors perform study se	lection	in duplicate?				
For Y	es, either ONE of the following:	1					
	at least two reviewers independently a	-	-		Yes		
	achieved consensus on which studies		le studies and achieved good agreement		N -		
	(at least 80 percent), with the remained			х	No		
6 Did	the review authors perform data ext						
	es, either ONE of the following:	raction	in duplicate:				
FOI TO		naua on	which data to extract from included stud-		Yes		
	ies	lisus oli	which data to extract nom mended stud-		165		
	OR two reviewers extracted data from	n a samp	le of eligible studies and achieved good	х	No		
	agreement (at least 80 percent), with	the rema	inder extracted by one reviewer.				
7. Did	the review authors provide a list of e	exclude	l studies and justify the exclusions?				
For Pa	artial Yes:	For Y	es, must also have:				
	provided a list of all potentially rel-	х	Justified the exclusion from the review		Yes		
	evant studies that were read in full-		of each potentially relevant study	x	Partial Yes		

	text form but excluded from the re-				No
	view				
8. Did	the review authors describe the inclu	uded stu	Idies in adequate detail?		
	rtial Yes (ALL the following):		es, should also have ALL the following:		
х	described populations	х	described population in detail	х	Yes
х	described interventions	x	described intervention in detail (includ-		Partially Yes
			ing doses where relevant)		,
х	described comparators	X	described comparator in detail (includ-		No
			ing doses where relevant)		
х	described outcomes	х	described study's setting		
x	described research designs		timeframe for follow-up	-	
		, toobni	que for assessing the risk of bias (RoB) in	indi	vidual studios that
	ncluded in the review?		que for assessing the risk of blas (Rob) in	mui	vidual studies that
RCTs					
	rtial Yes, must have assessed RoB	For V	es, must also have assessed RoB from:		
from	intar res, must have assessed Rob	10110	es, must also have assessed Rob nom.		
x	unconcealed allocation, and	x	allocation sequence that was not truly	x	Yes
Λ	unconceated unocation, and	^	random, and	~	Partial Yes
х	lack of blinding of patients and as-	x	selection of the reported result from	-	No
~	sessors when assessing outcomes	A	among multiple measurements or anal-		Includes only
	(unnecessary for objective out-		yses of a specified outcome		NRSI
	comes such as all-cause mortality)		5 -		INKSI
NRSI					
	rtial Yes, must have assessed RoB	For Ye	es, must also have assessed RoB from:		
from	,				
х	from confounding, and	х	methods used to ascertain exposures	x	Yes
			and outcomes, and		Partial Yes
х	from selection bias	х	selection of the reported result from		No
			among multiple measurements or anal-		Includes only
			yses of a specified outcome		RCT
10. Di	d the review authors report on the so	urces of	f funding for the studies included in the r	eviev	w?
For Ye	es				
Х	Must have reported on the sources of	funding	for individual studies included in the re-	х	Yes
	view. Note: Reporting that the review	ers look	ed for this information but it was not re-		No
	ported by study authors also qualifies				
11. If	meta-analysis was performed did the	review	authors use appropriate methods for sta	tistic	al combination of
result	s?				
RCTs					
For Ye					
	The authors justified combining the d		-		Yes
		ted techi	nique to combine study results and ad-		No
	justed for heterogeneity if present.				
	AND investigated the causes of any h	eterogei	neity	х	No meta-analysis
					conducted
For N				1	1
For Ye					
	The authors justified combining the d		-		Yes
		ted techi	nique to combine study results, adjusting		No
	for heterogeneity if present				
			ates from NRSI that were adjusted for	х	No meta-analysis
			or justified combining raw data when		conducted
	adjusted effect estimates were not ava	ulable			

	AND they reported separate summary estimates for RCTs and NRSI separately when		
	both were included in the review		
12. If	meta-analysis was performed, did the review authors assess the potential impact of R	oB in	individual studies
on the	e results of the meta-analysis or other evidence synthesis?		
For Y	25		
	included only low risk of bias RCTs		Yes
	OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No
	thors performed analyses to investigate possible impact of RoB on summary estimates	х	No meta-analysis
	of effect.		conducted
13. Di	d the review authors account for RoB in individual studies when interpreting/ discuss	sing t	he results of the
reviev	v?		
For Y	ĉs		
	included only low risk of bias RCTs	х	Yes
х	OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a		No
	discussion of the likely impact of RoB on the results		
14. Di	d the review authors provide a satisfactory explanation for, and discussion of, any he	terog	eneity observed in
	sults of the review?		
For Y	ĉs		
	There was no significant heterogeneity in the results	х	Yes
Х	OR if heterogeneity was present the authors performed an investigation of sources of		No
	any heterogeneity in the results and discussed the impact of this on the results of the re-		
	view		
15. If	they performed quantitative synthesis did the review authors carry out an adequate i	nvest	igation of publica-
tion b	ias (small study bias) and discuss its likely impact on the results of the review?		
For Y	es		
	performed graphical or statistical tests for publication bias and discussed the likelihood		Yes
	and magnitude of impact of publication bias		No
		х	No meta-analysis
			conducted
16. Di	d the review authors report any potential sources of conflict of interest, including any	func	ling they received
for co	nducting the review?		
For Y	es		
	The authors reported no competing interests OR		Yes
	The authors described their funding sources and how they managed potential conflicts	х	No
	of interest		
Your	overall assessment of the risk of bias of this systematic review		•
Mode	rate		

AMSTAR 2 checklist, critical questions									
REF: Kwon et al 2019									
1. Did	1. Did the research questions and inclusion criteria for the review include the components of PICO?								
For Ye	es								
х	Population	Timeframe for follow up	х	Yes					
х	Intervention			No					
na	Comparator group			·					
Х	Outcome								
2. Did	the report of the review contain an e	explicit statement that the review methods were	estab	lished prior to the					
condu	ict of the review and did the report ju	ustify any significant deviations from the protoco	ol?						
For Pa	artial Yes:	For Yes:							
The au	thors state that they had a written	As for partial yes, plus the protocol should be							
protoc	ol or guide that included ALL the	registered and should also have specified:							
follow	ving:								

	review question(s)		a meta-analysis/ synthesis plan, if ap- propriate, and		Yes
	a search strategy		a plan for investigating causes of heter- ogeneity		Partial Yes
	inclusion/exclusion criteria		-8	х	No
	a risk of bias assessment	-			-
3. Die		ection o	f the study designs for inclusion in the re	view?	
	es, the review should satisfy ONE of the				Yes
	Explanation for including only RCTs		, mg.	x	No
	OR Explanation for including only N			л	110
	OR Explanation for including both R		ANDSI		
D:	d the review authors use a compreher				
		-		1	Voc
	artial Yes (all the following):	-	es, should also have (all the following):		Yes
K	searched at least 2 databases (rele- vant to research question)	х	searched the reference lists / bibliog- raphies of included studies	х	Partial Yes
¢	provided key word and/or search strategy	x	searched trial/study registries		No
ĸ	justified publication restrictions (e.g. language)	1	included/consulted content experts in the field		1
	(0.5. milguige)		where relevant, searched for grey litera-	_	
			ture		
		х	conducted search within 24 months of	1	
			completion of the review		
5. Die	d the review authors perform study s	election	in duplicate?	1	
	es, either ONE of the following:		-		
K	at least two reviewers independently	agreed o	on selection of eligible studies and		Yes
	achieved consensus on which studies	-	-		
			ble studies and achieved good agreement	х	No
	(at least 80 percent), with the remained	-			-
6. Die	d the review authors perform data ex		-	1	
	es, either ONE of the following:		*		
		ensus on	which data to extract from included stud-	х	Yes
	ies				One + check
	OR two reviewers extracted data from	n a sam	ple of eligible studies and achieved good		No
	agreement (at least 80 percent), with				
7. Die	d the review authors provide a list of		-		
	artial Yes:		es, must also have:		
K	provided a list of all potentially rel-	1011	Justified the exclusion from the review	l r	Yes
7	evant studies that were read in full-		of each potentially relevant study		Partial Yes
	text form but excluded from the re-		of each potentially relevant study	x	
	view				No
יים צ	d the review authors describe the incl	udad et	 udies in adequate detail?	I	
	artial Yes (ALL the following):		fes, should also have ALL the following:		
	described populations		described population in detail	v	Yes
x	described populations described interventions	X		Х	
K	described interventions	х	described intervention in detail (includ-		Partially Yes
			ing doses where relevant)		N
ıa	described comparators	na	described comparator in detail (includ- ing doses where relevant)		No
	described outcomes	х	described study's setting		
x	described outcomes		described study's setting		
x	described research designs	x	timeframe for follow-up		

RCT	5				
For P	artial Yes, must have assessed RoB	For Yes, must also hav	re assessed RoB from:		
from					
	unconcealed allocation, and		ence that was not truly		Yes
		random, and			Partial Yes
	lack of blinding of patients and as-		e reported result from		No
	sessors when assessing outcomes		e measurements or anal-	х	Includes only
	(unnecessary for objective out-	yses of a specif	fied outcome		NRSI
	comes such as all-cause mortality)				
NRS				1	
	artial Yes, must have assessed RoB	For Yes, must also hav	e assessed RoB from:		
from					1
х	from confounding, and		to ascertain exposures		Yes
		and outcomes,		х	Partial Yes
Х	from selection bias		e reported result from		No
			e measurements or anal-		Includes only
		yses of a specif	fied outcome		RCT
10. D	id the review authors report on the s	urces of funding for the	e studies included in the	review	v?
For Y					
	Must have reported on the sources of	e			Yes
	view. Note: Reporting that the review	ers looked for this inform	nation but it was not re-	х	No
	ported by study authors also qualifier				
11. If	meta-analysis was performed did th	review authors use app	propriate methods for sta	atistic	al combination of
resul	ts?				
RCTs					
RUIS					
		ta in a meta-analysis			Yes
	es		study results and ad-		Yes No
For Y	es The authors justified combining the e		study results and ad-		
	The authors justified combining the of AND they used an appropriate weight	ed technique to combine	e study results and ad-	x	No
	The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present.	ed technique to combine	study results and ad-	x	
For Y	The authors justified combining the operation of the authors justified combining the operation of the authors is a set of the authors in the authors is a set of the author authors and a set of the authors of any set of the authors of any set of the authors of any set of the authors are also as a set of the author authors are also as a set of the author authors are also as a set of the author authors are also as a set of the author and a set of the author and a set of the author authors are also as a set of the author and a set of the author and a set of the author author are also as a set of the author and a set of the author and a set of the author and a set of the author are also as a set of the author and a set of the author are also as a set of the aut	ed technique to combine	e study results and ad-	X	No No meta-analysis
For Y	The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any ERSI	ed technique to combine	study results and ad-	x	No No meta-analysis
For Y	The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any ERSI	ed technique to combine eterogeneity	study results and ad-	x	No No meta-analysis
For Y	The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any set of any set of any set of a set of	ed technique to combine eterogeneity nta in a meta-analysis	·	X	No meta-analysis conducted
For Y	es The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any RSI es The authors justified combining the of	ed technique to combine eterogeneity nta in a meta-analysis	·	X	No meta-analysis conducted Yes
For Y	res The authors justified combining the organization AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any set VRSI res The authors justified combining the organization AND they used an appropriate weigh	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine	e study results, adjusting		No meta-analysis conducted Yes
For Y	res The authors justified combining the organization AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any structure WRSI res The authors justified combining the organization AND they used an appropriate weigh for heterogeneity if present	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine t estimates from NRSI t	e study results, adjusting hat were adjusted for		No meta-analysis conducted Yes No
For Y	es The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any RSI es The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com	e study results, adjusting hat were adjusted for		No No meta-analysis conducted Yes No No meta-analysis
For Y	es The authors justified combining the organization of the second seco	ed technique to combine eterogeneity ata in a meta-analysis ed technique to combine it estimates from NRSI t w data, or justified com ilable	e study results, adjusting hat were adjusted for bining raw data when		No No meta-analysis conducted Yes No No meta-analysis
For Y	es The authors justified combining the operation of the second	ed technique to combine eterogeneity ata in a meta-analysis ed technique to combine it estimates from NRSI t w data, or justified com ilable	e study results, adjusting hat were adjusted for bining raw data when		No No meta-analysis conducted Yes No No meta-analysis
For Y For N For Y	res The authors justified combining the oral AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any analysis AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar	ed technique to combine eterogeneity ta in a meta-analysis ed technique to combine t estimates from NRSI t w data, or justified com ilable estimates for RCTs and	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when	x	No meta-analysis conducted Yes No No meta-analysis conducted
For Y For M For Y 12. If	res The authors justified combining the oral AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any and the causes and th	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when	x	No meta-analysis conducted Yes No No meta-analysis conducted
For Y For M For Y 12. If on th	es The authors justified combining the orgeneity if present. AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any structure VRSI es The authors justified combining the orgeneity if present AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review Theta-analysis was performed, did theta eresults of the meta-analysis or othe	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when	x	No meta-analysis conducted Yes No No meta-analysis conducted
For Y For M For Y 12. If on th	es The authors justified combining the orgeneity if present. AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any structure VRSI es The authors justified combining the orgeneity if present AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review Theta-analysis was performed, did theta eresults of the meta-analysis or othe	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when	x	No meta-analysis conducted Yes No No meta-analysis conducted
For Y For M For Y 12. If on th	es The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any set of the causes of the causes of the causes of any set of the causes of the ca	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine tt estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess evidence synthesis?	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when the potential impact of F	x	No meta-analysis conducted Yes No No meta-analysis conducted individual studies
For Y For M For Y 12. If on th	es The authors justified combining the oral AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any and the causes of the meta-analysis or othe fees	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess evidence synthesis?	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when the potential impact of R the variable RoB, the au-	x	No meta-analysis conducted Yes No No meta-analysis conducted individual studies Yes No
For Y For Y For Y 12. If on th	es The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any WRSI res The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review results of the meta-analysis or othe fes included only low risk of bias RCTs OR, if the pooled estimate was based	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess evidence synthesis?	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when the potential impact of R the variable RoB, the au-	x x toB in	No meta-analysis conducted Yes No No meta-analysis conducted individual studies Yes No
For Y For M For Y 12. If on th For Y	es The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any set of the causes of the causes of the causes of any set of the causes of the ca	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess evidence synthesis? on RCTs and/or NRSI at e possible impact of RoI	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when the potential impact of F t variable RoB, the au- B on summary estimates	x x	No meta-analysis conducted Yes No No meta-analysis conducted individual studies Yes No No meta-analysis conducted
For Y For M For Y 12. If on th For Y 13. D	es The authors justified combining the oral AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any analysis of the authors justified combining the oral AND they used an appropriate weigh for heterogeneity if present. AND they used an appropriate weigh for heterogeneity if present. AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review. meta-analysis was performed, did the results of the meta-analysis or othe fes included only low risk of bias RCTs OR, if the pooled estimate was based thors performed analyses to investigate of effect. id the review authors account for Ro	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess evidence synthesis? on RCTs and/or NRSI at e possible impact of RoI	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when the potential impact of F t variable RoB, the au- B on summary estimates	x x	No meta-analysis conducted Yes No No meta-analysis conducted individual studies Yes No No meta-analysis conducted
For Y For Y For Y 12. If on th For Y 13. D revie	es The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any set of the authors justified combining the of AND they used an appropriate weigh for heterogeneity if present. AND they used an appropriate weigh for heterogeneity if present. AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review meta-analysis was performed, did the results of the meta-analysis or othe fees included only low risk of bias RCTs OR, if the pooled estimate was based thors performed analyses to investiga of effect. id the review authors account for Row	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess evidence synthesis? on RCTs and/or NRSI at e possible impact of RoI	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when the potential impact of F t variable RoB, the au- B on summary estimates	x x	No meta-analysis conducted Yes No No meta-analysis conducted individual studies Yes No No meta-analysis conducted
For Y For M For Y 12. If on th For Y	es The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any investigated causes of any investingated causes of any investingated causes of a	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess evidence synthesis? on RCTs and/or NRSI at e possible impact of RoI	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when the potential impact of F t variable RoB, the au- B on summary estimates	x x	No No meta-analysis conducted Yes No No meta-analysis conducted individual studies Yes No individual studies Yes No No meta-analysis conducted he results of the
For Y For M For Y 12. If on th For Y 13. D revie	es The authors justified combining the of AND they used an appropriate weigh justed for heterogeneity if present. AND investigated the causes of any set of the authors justified combining the of AND they used an appropriate weigh for heterogeneity if present. AND they used an appropriate weigh for heterogeneity if present. AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review meta-analysis was performed, did the results of the meta-analysis or othe fees included only low risk of bias RCTs OR, if the pooled estimate was based thors performed analyses to investiga of effect. id the review authors account for Row	ed technique to combine eterogeneity nta in a meta-analysis ed technique to combine et estimates from NRSI t w data, or justified com ilable estimates for RCTs and review authors assess evidence synthesis? on RCTs and/or NRSI at e possible impact of RoI in individual studies w	e study results, adjusting hat were adjusted for bining raw data when NRSI separately when the potential impact of F t variable RoB, the au- B on summary estimates vhen interpreting/ discus	x x	No meta-analysis conducted Yes No No meta-analysis conducted individual studies Yes No No meta-analysis conducted

For Y	<i>l</i> es		
Х	There was no significant heterogeneity in the results	х	Yes
	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view		No
	f they performed quantitative synthesis did the review authors carry out an adequate i bias (small study bias) and discuss its likely impact on the results of the review?	nvest	igation of publica-
For Y	les		
	performed graphical or statistical tests for publication bias and discussed the likelihood		Yes
	and magnitude of impact of publication bias		No
		х	No meta-analysi conducted
16. I	d the review authors report any potential sources of conflict of interest, including any	, fund	ling they received
for c	onducting the review?		
For Y	<i>l</i> 'es		
х	The authors reported no competing interests OR	х	Yes
	The authors described their funding sources and how they managed potential conflicts		No
	of interest	1	1

AMST	AR 2 checklist, <mark>critical questions</mark>						
REF: I	iu et al 2018						
1. Did the research questions and inclusion criteria for the review include the components of PICO?							
For Ye	25						
х	Population		Timeframe for follow up	х	Yes		
х	Intervention				No		
х	Comparator group						
х	Outcome						
	-	-	statement that the review methods were		ished prior to the		
			ny significant deviations from the protoco	ol?			
For Pa	artial Yes:	For Y	•••				
The authors state that they had a written As for partial yes, plus the protocol should be							
protocol or guide that included ALL the registered and should also have specified:							
following:					r		
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes		
			propriate, and				
	a search strategy		a plan for investigating causes of heter-		Partial Yes		
			ogeneity				
	inclusion/exclusion criteria			х	No		
	a risk of bias assessment						
	-		f the study designs for inclusion in the re	view?			
For Y	es, the review should satisfy ONE of the	e follow	ving:	х	Yes		
	Explanation for including only RCTs				No		
	OR Explanation for including only NRSI						
х	OR Explanation for including both R	CTs and	INRSI				
4. Did	the review authors use a comprehen	sive lite	erature search strategy?				
For Pa	rtial Yes (all the following):	For Y	es, should also have (all the following):		Yes		
х	searched at least 2 databases (rele-		searched the reference lists / bibliog-	х	Partial Yes		
	vant to research question)		raphies of included studies				

x	provided key word and/or search		searched trial/study registries		No
	strategy				
х	justified publication restrictions (e.g. language)		included/consulted content experts in the field		
			where relevant, searched for grey litera- ture		
		х	conducted search within 24 months of		
			completion of the review		
	d the review authors perform study s	election	in duplicate?		
For Y	es, either ONE of the following:			1	1
	at least two reviewers independently	-	-		Yes
	achieved consensus on which studies				
	-	-	le studies and achieved good agreement	х	No
(D'	(at least 80 percent), with the remain				
	the review authors perform data ex	traction	in duplicate?		
	Yes, either ONE of the following:			1_	V
Х		ensus on	which data to extract from included stud-	х	Yes
	ies			<u> </u>	Ne
		-	ble of eligible studies and achieved good		No
7 D.	agreement (at least 80 percent), with		-		
	d the review authors provide a list of	-		1	
	artial Yes:	For Y	es, must also have:	<u> </u>	
х	provided a list of all potentially rel-		Justified the exclusion from the review		Yes
	evant studies that were read in full-		of each potentially relevant study	x	Partial Yes
	text form but excluded from the re-				No
0 D'	view	1.1.4	1		
	d the review authors describe the incl		-	1	
	artial Yes (ALL the following):	For Y	es, should also have ALL the following:		
Х	described populations		described population in detail		Yes
Х	described interventions	х	described intervention in detail (includ-	х	Partially Yes
			ing doses where relevant)		N
Х	described comparators		described comparator in detail (includ-		No
			ing doses where relevant)	-	
х	described outcomes		described study's setting		
х	described research designs		timeframe for follow-up		
9. Dic	l the review authors use a satisfactor	y techni	que for assessing the risk of bias (RoB) in	n indi	vidual studies that
were	included in the review?				
RCT	8				
For P from	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
	unconcealed allocation, and	x	allocation sequence that was not truly	x	Yes
X	and another another and		random, and		Partial Yes
х			· · ·	- 1	105
x x	lack of blinding of patients and as-	х	selection of the reported result from		No
	lack of blinding of patients and as- sessors when assessing outcomes	х	selection of the reported result from among multiple measurements or anal-		No Includes only
	sessors when assessing outcomes	x	among multiple measurements or anal-		Includes only
	sessors when assessing outcomes (unnecessary for objective out-	x	-		-
	sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)	x	among multiple measurements or anal-		Includes only
x NRSI	sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)		among multiple measurements or anal- yses of a specified outcome		Includes only
x NRSI For P	sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)		among multiple measurements or anal-		Includes only
x NRSI	sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)		among multiple measurements or anal- yses of a specified outcome		Includes only

х	from selection bias	х	selection of the reported result from		Partial Yes
			among multiple measurements or anal-		No
			yses of a specified outcome		Includes only
					RCT
10. Di	d the review authors report on the so	ources o	f funding for the studies included in the r	eview	
For Ye	-				
		funding	for individual studies included in the re-		Yes
	-	-	ed for this information but it was not re-	x	No
	ported by study authors also qualifies				
11. If			authors use appropriate methods for sta	tistica	al combination of
result					
RCTs					
For Ye	es				
Х	The authors justified combining the d	ata in a	meta-analysis	х	Yes
х	AND they used an appropriate weight	ted tech	nique to combine study results and ad-		No
	justed for heterogeneity if present.				
Х	AND investigated the causes of any h	eteroge	neity		No meta-analysis
					conducted
For N	RSI				
For Ye	es				
Х	The authors justified combining the d	ata in a	meta-analysis		Yes
х	AND they used an appropriate weight	ted tech	nique to combine study results, adjusting	х	No
	for heterogeneity if present				
х	AND they statistically combined effect	ct estim	ates from NRSI that were adjusted for		No meta-analysis
	confounding, rather than combining rather	aw data	, or justified combining raw data when		conducted
	adjusted effect estimates were not ava	ilable			
		v estimat	tes for RCTs and NRSI separately when		Pooled data from
	both were included in the review				RCTs and sur-
					veys in meta
					analyses
			v authors assess the potential impact of R	oB in	individual studies
	e results of the meta-analysis or other	eviden	ce synthesis?		
For Ye					
	included only low risk of bias RCTs				Yes
	-		's and/or NRSI at variable RoB, the au-	х	No
		te possil	ble impact of RoB on summary estimates		No meta-analysis
10.51	of effect.				conducted
		3 in ind	ividual studies when interpreting/ discuss	sing the	he results of the
review				1	
For Ye				-	Vac
	included only low risk of bias RCTs	- D N			Yes
	discussion of the likely impact of Rol		NRSI were included the review provided a	х	No
14 D:				torrog	anaity abcomyod in
	a the review authors provide a saush	actory e	explanation for, and discussion of, any he	terog	enerty observed in
For Ye				1	
101 10	There was no significant heterogeneit	w in the	regulto		Yes
)))))))))))))))))))))))))))))))))))))))	-	performed an investigation of sources of	v	No
		-	the impact of this on the results of the re-	х	110
	view	13043500	the impact of this on the results of the re-		
15. If		is did th	e review authors carry out an adequate i	nvest	igation of nublica-
	ias (small study bias) and discuss its l				Sector of Publica
For Ye		incig in		Too	few studies
				na	Yes
				114	100

	performed graphical or statistical tests for publication bias and discussed the likelihood		No
	and magnitude of impact of publication bias		No meta-analysis
			conducted
16. Di	d the review authors report any potential sources of conflict of interest, including any	y func	ling they received
for co	nducting the review?		
For Y	es		
Х	The authors reported no competing interests OR	х	Yes
	The authors described their funding sources and how they managed potential conflicts		No
	of interest		
Your	overall assessment of the risk of bias of this systematic review		
Mode	rate		

AMSTAR 2 checklist, critical questions				
REF: Miller et al 2021				
1. Did the research questions and inclusion	n criteri	a for the review include the components	of PIC	CO?
For Yes	Optio	nal (recommended)		
x Population		Timeframe for follow up	х	Yes
x Intervention				No
na Comparator group				•
x Outcome				
2. Did the report of the review contain an	explicit	statement that the review methods were	establ	lished prior to the
conduct of the review and did the report j	ustify ar	y significant deviations from the protoco	ol?	
For Partial Yes:	For Y	es:		
The authors state that they had a written	As for	partial yes, plus the protocol should be		
protocol or guide that included ALL the	registe	ered and should also have specified:		
following:				
review question(s)		a meta-analysis/ synthesis plan, if ap- propriate, and		Yes
a search strategy		a plan for investigating causes of heter- ogeneity		Partial Yes
inclusion/exclusion criteria			x	No
a risk of bias assessment				
3. Did the review authors explain their sel	ection of	f the study designs for inclusion in the re	view?	
For Yes, the review should satisfy ONE of the				Yes
Explanation for including only RCTs	5		х	No
OR Explanation for including only N	IRSI			
OR Explanation for including both R	CTs and	NRSI		
4. Did the review authors use a comprehen	nsive lite	erature search strategy?	1	
For Partial Yes (all the following):		es, should also have (all the following):		Yes
x searched at least 2 databases (rele-		searched the reference lists / bibliog-	x	Partial Yes
vant to research question)		raphies of included studies		
x provided key word and/or search strategy		searched trial/study registries		No
x justified publication restrictions		included/consulted content experts in		
(e.g. language)		the field		
		where relevant, searched for grey litera-	-	
		ture		
	х	conducted search within 24 months of	1	
		completion of the review		
5. Did the review authors perform study s	election	-		
For Yes, either ONE of the following:				

	at least two reviewers independently a	-	-		Yes
	achieved consensus on which studies				
	-	-	le studies and achieved good agreement	х	No
	(at least 80 percent), with the remaind		-		
	the review authors perform data ext	traction	in duplicate?		
For Y	es, either ONE of the following:				X
	at least two reviewers achieved conse	nsus on	which data to extract from included stud-	х	Yes
		n a samp	le of eligible studies and achieved good		No
	agreement (at least 80 percent), with t	the rema	inder extracted by one reviewer.		
7. Did	the review authors provide a list of e	exclude	d studies and justify the exclusions?		
For Pa	artial Yes:	For Y	es, must also have:		
Х	provided a list of all potentially rel-	х	Justified the exclusion from the review	х	Yes
	evant studies that were read in full-		of each potentially relevant study		Partial Yes
	text form but excluded from the re-				No
	view				
8. Did	the review authors describe the inclu	uded stu	idies in adequate detail?		
For Pa	artial Yes (ALL the following):	For Y	es, should also have ALL the following:		
Х	described populations		described population in detail		Yes
Х	described interventions		described intervention in detail (includ-	х	Partially Yes
			ing doses where relevant)		
na	described comparators		described comparator in detail (includ-		No
			ing doses where relevant)		
Х	described outcomes				
			described study's setting		
				_	
Х	described research designs		timeframe for follow-up		
		y techni	que for assessing the risk of bias (RoB) in	ı indiv	idual studies that
were	included in the review?				
DOT.					
RCTs		E V		1	
		For Y	es, must also have assessed RoB from:		
For Pa	artial Yes, must have assessed RoB	For Y			Yes
For Pa		For Y	es, must also have assessed RoB from: allocation sequence that was not truly random, and		
For Pa	artial Yes, must have assessed RoB	For Y	allocation sequence that was not truly		Partial Yes
For Pa	artial Yes, must have assessed RoB unconcealed allocation, and	For Y	allocation sequence that was not truly random, and		Partial Yes No
For Pa	artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as-	For Y	allocation sequence that was not truly random, and selection of the reported result from		Partial Yes
For Pa	artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes	For Y	allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal-		Partial Yes No Includes only
For Pa	artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)	For Y	allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal-	x	Partial Yes No Includes only
For Pa from	artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)		allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal-		Partial Yes No Includes only
For Pa from	unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)		allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome		Partial Yes No Includes only
For Pa from NRSI For Pa	unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality)		allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome		Partial Yes No Includes only
For Pa from NRSI For Pa from	artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) artial Yes, must have assessed RoB		allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from:		Partial Yes No Includes only NRSI
For Pa from NRSI For Pa from	artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) artial Yes, must have assessed RoB		allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from: methods used to ascertain exposures		Partial Yes No Includes only NRSI Yes
For Pa from NRSI For Pa from x	artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) artial Yes, must have assessed RoB from confounding, and		allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and		Partial Yes No Includes only NRSI Yes Partial Yes
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For Pa from NRSI For Pa from X X	artial Yes, must have assessed RoB unconcealed allocation, and lack of blinding of patients and as- sessors when assessing outcomes (unnecessary for objective out- comes such as all-cause mortality) artial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the so es Must have reported on the sources of	For Y	allocation sequence that was not truly random, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the re -		Partial Yes No Includes only NRSI Yes Partial Yes No Includes only RCT Yes
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For Yes		
The authors justified combining the data in a meta-analysis		Yes
AND they used an appropriate weighted technique to combine study results and ad-	-	No
justed for heterogeneity if present.		110
AND investigated the causes of any heterogeneity	x	No meta-analysis conducted
For NRSI		conducted
For Yes	1	1
The authors justified combining the data in a meta-analysis		Yes
AND they used an appropriate weighted technique to combine study results, adjusting		No
for heterogeneity if present		NO
AND they statistically combined effect estimates from NRSI that were adjusted for	x	No meta-analysis
confounding, rather than combining raw data, or justified combining raw data when	л	conducted
adjusted effect estimates were not available		conducted
AND they reported separate summary estimates for RCTs and NRSI separately when		
both were included in the review		
12. If meta-analysis was performed, did the review authors assess the potential impact of R	oB in	individual studies
on the results of the meta-analysis or other evidence synthesis?		
For Yes		
included only low risk of bias RCTs		Yes
OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No
thors performed analyses to investigate possible impact of RoB on summary estimates	x	No meta-analysis
of effect.		conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discus	sing t	he results of the
review?	8	
	x	Yes
For Yes included only low risk of bias RCTs		
For Yes included only low risk of bias RCTs		Yes
For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	x	Yes No
For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any here	x	Yes No
For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review?	x	Yes No
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For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results x OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate it tion bias (small study bias) and discuss its likely impact on the results of the review?	x terog	Yes No eneity observed in Yes No
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For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results x OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate it tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes gerformed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including and the review authors report any potential sources of conflict of interest, including and the review of conflict of interest, including and the review of conflict of interest, including and content of conflict of conflict of interest, including and content of conflict of interest, including and content of conflict of content of con	x x x x x x x x x	Yes No encity observed in Yes No igation of publica- Yes No No meta-analysi conducted
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For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results x OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate i tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including any for conducting the review? For Yes	x x x x x x x x x	Yes No eneity observed in Yes No igation of publica- Yes No No meta-analysi conducted
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For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results x OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate i tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes Image: Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias 16. Did the review authors report any potential sources of conflict of interest, including any for conducting the review?	x x x x x x x x x x y fund	Yes No eneity observed in Yes No igation of publica- igation of publica- igation of publica- ing they received
For Yes included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 14. Did the review authors provide a satisfactory explanation for, and discussion of, any he the results of the review? For Yes There was no significant heterogeneity in the results x OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review 15. If they performed quantitative synthesis did the review authors carry out an adequate it tion bias (small study bias) and discuss its likely impact on the results of the review? For Yes	x x x x x x x x x x y fund	Yes No encity observed in Yes No igation of publica- Yes No No meta-analysi conducted ling they received Yes

AMS	TAR 2 checklist, critical questions				
	Ralho et al 2019				
1. Die	l the research questions and inclusion	n criteria	a for the review include the components	of PIC	C O ?
For Y	es	Optio	nal (recommended)		
х	Population		Timeframe for follow up	х	Yes
х	Intervention				No
х	Comparator group				
X	Outcome				
	-	-	statement that the review methods were		ished prior to the
			y significant deviations from the protoco	ol?	
	artial Yes:	For Y			
	uthors state that they had a written		partial yes, plus the protocol should be		
	col or guide that included ALL the	registe	ered and should also have specified:		
ollov					
ĸ	review question(s)		a meta-analysis/ synthesis plan, if ap-	1	Yes
	a secure atrategy		propriate, and		Partial Yes
C	a search strategy		a plan for investigating causes of heter-	х	Parual Yes
ζ	inclusion/exclusion criteria		ogeneity	1	No
<u> </u>	a risk of bias assessment	-			NU
-		oction of	f the study designs for inclusion in the re	viow?	
	es, the review should satisfy ONE of th			x x	Yes
01 1	Explanation for including only RCTs		ing.	л	No
:	OR Explanation for including only N				NO
	OR Explanation for including both R		NRSI		
l Di	the review authors use a comprehen				
	artial Yes (all the following):		es, should also have (all the following):	1	Yes
<u> </u>	searched at least 2 databases (rele-	x	searched the reference lists / bibliog-	x	Partial Yes
•	vant to research question)	~	raphies of included studies	'n	i ui tiui i co
K	provided key word and/or search	x	searched trial/study registries		No
	strategy				-
K	justified publication restrictions		included/consulted content experts in		
	(e.g. language)		the field		
			where relevant, searched for grey litera-		
			ture		
		х	conducted search within 24 months of		
			completion of the review		
	I the review authors perform study so	election	in duplicate?		
For Y	es, either ONE of the following:				
[at least two reviewers independently	e	6	х	Yes
	achieved consensus on which studies			<u> </u>	
		•	le studies and achieved good agreement	1	No
· • ·	(at least 80 percent), with the remained			1	
	the review authors perform data ex	traction	in duplicate?		
or Y	es, either ONE of the following:			1	
	ies		which data to extract from included stud-		Yes
			le of eligible studies and achieved good	х	No
	agreement (at least 80 percent), with				
	I the review authors provide a list of				
For P	artial Yes:	For Y	es, must also have:		
K	provided a list of all potentially rel-		Justified the exclusion from the review		Yes
	evant studies that were read in full-		of each potentially relevant study	х	Partial Yes

	text form but excluded from the re-				No
	view				110
8. Did	the review authors describe the inclu	l uded sti	idies in adequate detail?	1	
	urtial Yes (ALL the following):		es, should also have ALL the following:		
x	described populations	X	described population in detail		Yes
x	described populations	x	described intervention in detail (includ-	х	Partially Yes
л	described interventions	^	ing doses where relevant)	~	rartially res
х	described comparators	x	described comparator in detail (includ-		No
л	deserved comparators	Λ	ing doses where relevant)		NO
х	described outcomes				
л	described outcomes		described study's setting		
х	described research designs	х	timeframe for follow-up		
9. Did	the review authors use a satisfactory	/ technie	que for assessing the risk of bias (RoB) in	ı indi	vidual studies that
	ncluded in the review?				
RCTs					
For Pa	urtial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from	,		,		
	unconcealed allocation, and		allocation sequence that was not truly		Yes
			random, and		Partial Yes
	lack of blinding of patients and as-	1	selection of the reported result from		No
	sessors when assessing outcomes		among multiple measurements or anal-	x	Includes only
	(unnecessary for objective out-		yses of a specified outcome	•	NRSI
	comes such as all-cause mortality)		5		INKSI
NRSI	······································				
	rtial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from		1011			
x	from confounding, and	x	methods used to ascertain exposures	x	Yes
	nom como anang, ana		and outcomes, and	-	Partial Yes
х	from selection bias	x	selection of the reported result from		No
~		~	among multiple measurements or anal-		Includes only
			yses of a specified outcome		RCT
10 Di	d the review authors report on the so	urces o	f funding for the studies included in the i	revie	
For Ye		urces o	i funding for the studies included in the	evie	w .
101 10		C 1'	for individual studies included in the re-		Yes
	-	-	ed for this information but it was not re-		
	ported by study authors also qualifies		ed for this information but it was not re-	х	No
11 If			authors use appropriate methods for sta	tistio	al combination of
result		leview	authors use appropriate methods for sta	usuc	al complitation of
RCTs	· ·				
For Ye	20			1	
101 10	The authors justified combining the d	ata in a	mate englyzia		Yes
			nique to combine study results and ad-		No
	justed for heterogeneity if present.	led lech	nique to combine study results and ad-		NO
		- 4			No moto on lossio
	AND investigated the causes of any h	leterogei	letty	х	No meta-analysis conducted
For M	Dei				conducted
For N					1
For Ye		ata :-	moto enclusia		Vee
	The authors justified combining the d		-	<u> </u>	Yes
		ted tech	nique to combine study results, adjusting		No
	for heterogeneity if present			<u> </u>	
			ates from NRSI that were adjusted for	х	No meta-analysis
			or justified combining raw data when		conducted
	adjusted effect estimates were not ava	ulable		1	

	AND they reported separate summary estimates for RCTs and NRSI separately when		
	both were included in the review		
12. If	meta-analysis was performed, did the review authors assess the potential impact of R	oB in	individual studies
on the	e results of the meta-analysis or other evidence synthesis?		
For Y	es		
	included only low risk of bias RCTs		Yes
	OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No
	thors performed analyses to investigate possible impact of RoB on summary estimates	х	No meta-analysis
	of effect.		conducted
13. Di	d the review authors account for RoB in individual studies when interpreting/ discuss	sing t	he results of the
review	v?		
For Y	-		
	included only low risk of bias RCTs	х	Yes
Х	OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a		No
	discussion of the likely impact of RoB on the results		
14. Di	d the review authors provide a satisfactory explanation for, and discussion of, any he	terog	eneity observed in
	sults of the review?		
For Y	es		
FOI I			
FOI 1	There was no significant heterogeneity in the results		Yes
	OR if heterogeneity was present the authors performed an investigation of sources of	x	Yes No
	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re-	x	
	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view		No
15. If	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i		No
15. If tion b	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review?		No
15. If	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es		No igation of publica-
15. If tion b	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood		No igation of publica- Yes
15. If tion b	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es		No igation of publica- Yes No
15. If tion b	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood		No igation of publica- Yes No
15. If tion b For Y	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	nvest x	No igation of publica- Yes No No meta-analysis conducted
15. If tion b For Y 16. D	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any	nvest x	No igation of publica- Yes No No meta-analysis conducted
15. If tion b For Y 16. Di for co	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	nvest x	No igation of publica- Yes No No meta-analysis conducted
15. If tion b For Y 16. Di	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any nducting the review? es	nvest x	No igation of publica- Yes No No meta-analysis conducted
15. If tion b For Y 16. Di for co	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	nvest x	No igation of publica- Yes No No meta-analysis conducted
15. If tion b For Y 16. Di for co For Y	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any nducting the review? es The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts	nvest x y func	No igation of publica- Yes No No meta-analysic conducted ling they received
15. If tion b For Y 16. Di for co For Y x	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any nducting the review? es The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts of interest	nvest x y func	No igation of publica- Yes No No meta-analysis conducted ling they received Yes
15. If tion b For Y 16. Di for co For Y x	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re- view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any nducting the review? es The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts	nvest x y func	No igation of publica- Yes No No meta-analysis conducted ling they received Yes

AMST	AR 2 checklist, critical questions			
REF: I	Riley et al 2016			
	-			
1. Did	the research questions and inclusion	n criteria for the review include the components	of PI	C O ?
For Y	es	Optional (recommended)		
х	Population	Timeframe for follow up	х	Yes
х	Intervention			No
х	Comparator group			·
х	Outcome			
2. Did	the report of the review contain an	explicit statement that the review methods were	estab	lished prior to the
condu	ict of the review and did the report j	ustify any significant deviations from the protoco	ol?	
For Pa	artial Yes:	For Yes:		
The au	uthors state that they had a written	As for partial yes, plus the protocol should be		
protoc	col or guide that included ALL the	registered and should also have specified:		
follow	ving:			

	review question(s)		a meta-analysis/ synthesis plan, if ap- propriate, and		Yes
	a search strategy		a plan for investigating causes of heter- ogeneity		Partial Yes
	inclusion/exclusion criteria			х	No
	a risk of bias assessment				
3. Dic	I the review authors explain their sele	ection of	f the study designs for inclusion in the re	view?	
	es, the review should satisfy ONE of th			Х	Yes
	Explanation for including only RCTs		5		No
	OR Explanation for including only N				-
x	OR Explanation for including both R		NRSI		
	the review authors use a comprehen			I	
	artial Yes (all the following):		es, should also have (all the following):	1	Yes
x	searched at least 2 databases (rele-	1011	searched the reference lists / bibliog-	x	Partial Yes
Λ	vant to research question)		raphies of included studies	л	raitiai ies
	provided key word and/or search		searched trial/study registries		No
X	strategy				NO
x	justified publication restrictions (e.g. language)		included/consulted content experts in the field		
			where relevant, searched for grey litera-	1	
			ture		
		x	conducted search within 24 months of		
		А	completion of the review		
5 Di	l the review authors perform study se	lection	-	1	
	es, either ONE of the following:		m suphence.		
x	at least two reviewers independently	agreed o	n selection of eligible studies and	х	Yes
Λ	achieved consensus on which studies	-	-	Λ	105
			le studies and achieved good agreement		No
	(at least 80 percent), with the remained				110
6 Di	the review authors perform data ext				
	es, either ONE of the following:	action	in dupicate.		
101 1		nelle on	which data to extract from included stud-		Yes
	ies	iisus oii	which data to extract from mended stud-		165
		a o comr	ble of eligible studies and achieved good	v	No
	agreement (at least 80 percent), with	-	0	х	NO
7 05	I the review authors provide a list of		-		
	artial Yes:		es, must also have:	1	
	provided a list of all potentially rel-	FOI 1	Justified the exclusion from the review		¥
	evant studies that were read in full-				Yes
	text form but excluded from the re-		of each potentially relevant study		Partial Yes
	view			X	No
<u>, n:</u>	1 the review authors describe the incl	udad at	udios in adagnata data:19	1	
	artial Yes (ALL the following):		es, should also have ALL the following:	1	
			-		Voc
x	described populations	х	described population in detail	х	Yes
x	described interventions	х	described intervention in detail (includ-		Partially Yes
			ing doses where relevant)		
ĸ	described comparators	х	described comparator in detail (includ-		No
			ing doses where relevant)		
¢	described outcomes	x	described study's setting		
		1		1	
x	described research designs	х	timeframe for follow-up		

RCT	8				
For P	Partial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from					
х	unconcealed allocation, and		allocation sequence that was not truly		Yes
			random, and	х	Partial Yes
х	lack of blinding of patients and as-		selection of the reported result from	1	No
	sessors when assessing outcomes		among multiple measurements or anal-		Includes only
	(unnecessary for objective out-		yses of a specified outcome		NRSI
	comes such as all-cause mortality)				
NRSI					
	Partial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from					
х	from confounding, and	х	methods used to ascertain exposures		Yes
	from selection bias		and outcomes, and	X	Partial Yes
Х	from selection bias		selection of the reported result from		No
			among multiple measurements or anal- yses of a specified outcome		Includes only
10 D				II.	RCT
		ources (of funding for the studies included in the r	eview	V C
For Y		cc. 1	- Contradiction 1 of 1 1 1 1 1 1		Vec
Х	-	-	g for individual studies included in the re-	х	Yes
			ked for this information but it was not re-		No
11 T4	ported by study authors also qualifie		, authors use annuarrists mothods for sta	tistics	al combination of
result		e review	v authors use appropriate methods for sta	tistica	al combination of
RCTs					
For Y					
FOF 1	The authors justified combining the	data in a	moto analyzia		Yes
			inique to combine study results and ad-		
	justed for heterogeneity if present.	neu tech	inique to combine study results and ad-		No
	AND investigated the causes of any	heteroge	meity	x	No meta-analysis
	The investigated the eauses of any	neteroge	herry	л	conducted
For N	NRSI				conducted
For Y					
	•	data in a	meta-analysis		Yes
	The authors justified combining the				Yes
	The authors justified combining the of AND they used an appropriate weight		meta-analysis nique to combine study results, adjusting		Yes No
	The authors justified combining the AND they used an appropriate weigh for heterogeneity if present	nted tech	nique to combine study results, adjusting	x	No
	The authors justified combining the AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effe	nted tech	nique to combine study results, adjusting nates from NRSI that were adjusted for	x	
	The authors justified combining the AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effe	nted tech ect estim raw data	nique to combine study results, adjusting	x	No No meta-analysis
	The authors justified combining the ofAND they used an appropriate weighfor heterogeneity if presentAND they statistically combined effectconfounding, rather than combiningadjusted effect estimates were not av	nted tech ect estim raw data ailable	nique to combine study results, adjusting nates from NRSI that were adjusted for	x	No No meta-analysis
	The authors justified combining the ofAND they used an appropriate weighfor heterogeneity if presentAND they statistically combined effectconfounding, rather than combiningadjusted effect estimates were not av	nted tech ect estim raw data ailable	nates from NRSI that were adjusted for a, or justified combining raw data when	x	No No meta-analysis
12. If	The authors justified combining the original appropriate weigh for heterogeneity if presentAND they statistically combined efference on founding, rather than combining adjusted effect estimates were not available AND they reported separate summare both were included in the review	nted tech ect estim raw data ailable y estima	nates from NRSI that were adjusted for a, or justified combining raw data when		No meta-analysis conducted
	The authors justified combining the original appropriate weigh for heterogeneity if presentAND they statistically combined efference on founding, rather than combining adjusted effect estimates were not available AND they reported separate summare both were included in the review	nted tech ect estim raw data ailable y estima ne review	nnique to combine study results, adjusting nates from NRSI that were adjusted for n, or justified combining raw data when ntes for RCTs and NRSI separately when w authors assess the potential impact of R		No meta-analysis conducted
	The authors justified combining the ofAND they used an appropriate weighfor heterogeneity if presentAND they statistically combined efforconfounding, rather than combiningadjusted effect estimates were not avAND they reported separate summarboth were included in the reviewf meta-analysis was performed, did theresults of the meta-analysis or othe	nted tech ect estim raw data ailable y estima ne review	nnique to combine study results, adjusting nates from NRSI that were adjusted for n, or justified combining raw data when ntes for RCTs and NRSI separately when w authors assess the potential impact of R		No meta-analysis conducted
on th	The authors justified combining the ofAND they used an appropriate weighfor heterogeneity if presentAND they statistically combined efforconfounding, rather than combiningadjusted effect estimates were not avAND they reported separate summarboth were included in the reviewf meta-analysis was performed, did theresults of the meta-analysis or othe	nted tech ect estim raw data ailable y estima ne review	nnique to combine study results, adjusting nates from NRSI that were adjusted for n, or justified combining raw data when ntes for RCTs and NRSI separately when w authors assess the potential impact of R		No meta-analysis conducted
on th	The authors justified combining the original operation of the second s	nted tech ect estim raw data ailable y estima ne review r eviden	nnique to combine study results, adjusting nates from NRSI that were adjusted for n, or justified combining raw data when ntes for RCTs and NRSI separately when w authors assess the potential impact of R		No meta-analysis conducted individual studies
on th	The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review F meta-analysis was performed, did the results of the meta-analysis or othe Yes included only low risk of bias RCTs OR, if the pooled estimate was based	nted tech ect estim raw data ailable y estima ne review r eviden	nnique to combine study results, adjusting nates from NRSI that were adjusted for a, or justified combining raw data when ates for RCTs and NRSI separately when w authors assess the potential impact of R ace synthesis?		No meta-analysis conducted individual studies
on th	The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review F meta-analysis was performed, did the results of the meta-analysis or othe Yes included only low risk of bias RCTs OR, if the pooled estimate was based	nted tech ect estim raw data ailable y estima ne review r eviden	nique to combine study results, adjusting nates from NRSI that were adjusted for n, or justified combining raw data when nates for RCTs and NRSI separately when w authors assess the potential impact of R nce synthesis? Ts and/or NRSI at variable RoB, the au-	oB in	No meta-analysis conducted individual studies Yes No
on th For Y	The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effor confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review f meta-analysis was performed, did the results of the meta-analysis or othe Yes included only low risk of bias RCTs OR, if the pooled estimate was based thors performed analyses to investigation of effect.	nted tech ect estim raw data ailable y estima ne review r eviden	nique to combine study results, adjusting nates from NRSI that were adjusted for n, or justified combining raw data when nates for RCTs and NRSI separately when w authors assess the potential impact of R nce synthesis? Ts and/or NRSI at variable RoB, the au-	oB in	No No meta-analysis conducted individual studies Yes No No meta-analysis conducted
on th For Y	The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effect confounding, rather than combining adjusted effect estimates were not ave AND they reported separate summar both were included in the review f meta-analysis was performed, did the results of the meta-analysis or other version of the pooled estimate was based thors performed analyses to investigation of effect. vid the review authors account for Ro	nted tech ect estim raw data ailable y estima ne review r eviden	anique to combine study results, adjusting nates from NRSI that were adjusted for a, or justified combining raw data when nates for RCTs and NRSI separately when wauthors assess the potential impact of R nee synthesis? Ts and/or NRSI at variable RoB, the au- ble impact of RoB on summary estimates	oB in	No No meta-analysis conducted individual studies Yes No No meta-analysis conducted
on th For Y 13. D	The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined efformed confounding, rather than combining adjusted effect estimates were not average of the adjusted effect estimates were not average both were included in the review AND they reported separate summare both were included in the review F meta-analysis was performed, did there results of the meta-analysis or other the results of the meta-analysis or other there included only low risk of bias RCTs. OR, if the pooled estimate was based thors performed analyses to investigate of effect. Vid the review authors account for Row?	nted tech ect estim raw data ailable y estima ne review r eviden	anique to combine study results, adjusting nates from NRSI that were adjusted for a, or justified combining raw data when nates for RCTs and NRSI separately when wauthors assess the potential impact of R nee synthesis? Ts and/or NRSI at variable RoB, the au- ble impact of RoB on summary estimates	oB in	No No meta-analysis conducted individual studies Yes No No meta-analysis conducted
on th For Y 13. D revie	The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined efformed confounding, rather than combining adjusted effect estimates were not average of the adjusted effect estimates were not average both were included in the review AND they reported separate summare both were included in the review F meta-analysis was performed, did there results of the meta-analysis or other the results of the meta-analysis or other there included only low risk of bias RCTs. OR, if the pooled estimate was based thors performed analyses to investigate of effect. Vid the review authors account for Row?	nted tech ect estim raw data ailable y estima ne review r eviden	anique to combine study results, adjusting nates from NRSI that were adjusted for a, or justified combining raw data when nates for RCTs and NRSI separately when wauthors assess the potential impact of R nee synthesis? Ts and/or NRSI at variable RoB, the au- ble impact of RoB on summary estimates	oB in	No No meta-analysis conducted individual studies Yes No No meta-analysis conducted
on th For Y 13. D revie	The authors justified combining the of AND they used an appropriate weigh for heterogeneity if present AND they statistically combined effor confounding, rather than combining adjusted effect estimates were not av AND they reported separate summar both were included in the review f meta-analysis was performed, did there results of the meta-analysis or othe Tes included only low risk of bias RCTs OR, if the pooled estimate was based thors performed analyses to investigation of effect. vid the review authors account for Row? Yes included only low risk of bias RCTs	nted tech ect estim raw data ailable y estima ne review r eviden l on RC ² ate possi B in ind	anique to combine study results, adjusting nates from NRSI that were adjusted for a, or justified combining raw data when nates for RCTs and NRSI separately when wauthors assess the potential impact of R nee synthesis? Ts and/or NRSI at variable RoB, the au- ble impact of RoB on summary estimates	oB in	No No meta-analysis conducted individual studies Yes No No meta-analysis conducted he results of the

For Y	7es		
	There was no significant heterogeneity in the results		Yes
	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	х	No
	If they performed quantitative synthesis did the review authors carry out an adequate i bias (small study bias) and discuss its likely impact on the results of the review?	nvest	igation of publica-
For Y	7es		
	performed graphical or statistical tests for publication bias and discussed the likelihood		Yes
	and magnitude of impact of publication bias		No
		х	No meta-analysi conducted
16. D	id the review authors report any potential sources of conflict of interest, including any	func	ling they received
for co	onducting the review?		
For Y	7es		
х	The authors reported no competing interests OR	х	Yes
	The authors described their funding sources and how they managed potential conflicts		No
			1

AMST	AR 2 checklist, <mark>critical questions</mark>				
REF: S	Scarpino et al 2020				
	•		a for the review include the components	of PIC	CO?
For Ye	es	Optio	nal (recommended)		
х	Population		Timeframe for follow up	х	Yes
х	Intervention				No
na	Comparator group				
х	Outcome				
2. Did	the report of the review contain an e	xplicit	statement that the review methods were	establ	ished prior to the
condu	ct of the review and did the report ju	stify an	y significant deviations from the protoco	ol?	
For Partial Yes: For Yes:					
The au	thors state that they had a written	As for	partial yes, plus the protocol should be		
protoc	ol or guide that included ALL the	registered and should also have specified:			
follow	ving:				
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes
			propriate, and		
	a search strategy		a plan for investigating causes of heter-		Partial Yes
			ogeneity		
	inclusion/exclusion criteria			х	No
	a risk of bias assessment				
3. Did	the review authors explain their sele	ction of	the study designs for inclusion in the rev	view?	
For Y	es, the review should satisfy ONE of the	e follow	ring:	х	Yes
	Explanation for including only RCTs				No
х	OR Explanation for including only N	RSI			
	OR Explanation for including both RO				
4. Did	the review authors use a comprehen	sive lite	rature search strategy?		
For Pa	artial Yes (all the following):	For Y	es, should also have (all the following):		Yes
х	searched at least 2 databases (rele-	х	searched the reference lists / bibliog-	х	Partial Yes
	vant to research question)		raphies of included studies		

	· · · · · · · · · ·	1	1 1. • 1/. 1 • . •	-	
х	provided key word and/or search strategy		searched trial/study registries		No
х	justified publication restrictions		included/consulted content experts in		
	(e.g. language)		the field		
			where relevant, searched for grey litera-		
			ture		
		х	conducted search within 24 months of		
			completion of the review		
	l the review authors perform study s	election	in duplicate?		
For Y	es, either ONE of the following:				
	at least two reviewers independently	•	5		Yes
	achieved consensus on which studies				
	OR two reviewers selected a sample	of eligib	le studies and achieved good agreement	х	No
	(at least 80 percent), with the remain	der selec	ted by one reviewer.		
6. Dic	I the review authors perform data ex	traction	in duplicate?		·
For Y	es, either ONE of the following:				
х	at least two reviewers achieved conse	ensus on	which data to extract from included stud-	х	Yes
	ies				
	OR two reviewers extracted data from	n a samp	ble of eligible studies and achieved good	1	No
	agreement (at least 80 percent), with	-			
7. Did	I the review authors provide a list of	exclude	d studies and justify the exclusions?		
	artial Yes:	-	es, must also have:		
	provided a list of all potentially rel-		Justified the exclusion from the review		Yes
	evant studies that were read in full-		of each potentially relevant study		Partial Yes
	text form but excluded from the re-			x	No
	view				NO
8. Dic	I the review authors describe the incl	uded str	udies in adequate detail?		
	artial Yes (ALL the following):		es, should also have ALL the following:		
x	described populations	1011	described population in detail		Yes
X	described interventions	x	described intervention in detail (includ-	x	Partially Yes
х	described interventions	X	ing doses where relevant)	х	Faltially les
na	described comparators	na	described comparator in detail (includ-		No
na	described comparators	na	ing doses where relevant)		INU
••	described outcomes				
х	described outcomes	х	described study's setting		
			y =y		
х	described research designs	na	timeframe for follow-up		
	÷		que for assessing the risk of bias (RoB) in	n indiv	vidual studies that
	included in the review?	y teenin	que for assessing the fish of blus (100) h	ii iiiui i	iuuui stuuies tiiut
RCT					
	artial Yes, must have assessed RoB	For V	es, must also have assessed RoB from:		
from		1011			
nom	unconcealed allocation, and		allocation sequence that was not truly	+	Yes
	unconceated anocation, and		random, and		
	lack of blinding of patients and as-		selection of the reported result from	┨┝──	Partial Yes
	sessors when assessing outcomes		among multiple measurements or anal-		No
	(unnecessary for objective out-		yses of a specified outcome	х	Includes only
	comes such as all-cause mortality)		yses of a specified outcome		NRSI
NRSI					
		E- 17	as must also have a D.D.C.	"0	a daamed C
for Pa from	artial Yes, must have assessed RoB	FORY	es, must also have assessed RoB from:		ses deemed of
					erate to low
nom					
nom				qua	lity were fur-

from confounding, and from selection bias		methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome	add sea tho poo	Iluated by two Iitional re- urchers, and ose deemed of or quality were cluded. » Yes Partial Yes No Includes only RCT
10. Did the review authors report on the s	sources o		eviev	
For Yes				
view. Note: Reporting that the revier ported by study authors also qualifie	wers look es	for individual studies included in the re- ed for this information but it was not re-	x	Yes No
11. If meta-analysis was performed did th results?	ie review	authors use appropriate methods for sta	tistic	al combination of
RCTs				
For Yes			1	
The authors justified combining the	data in a	meta-analysis		Yes
		nique to combine study results and ad-		No
justed for heterogeneity if present.				
AND investigated the causes of any	heterogen	neity	х	No meta-analysis
				conducted
For NRSI				1
For Yes				
The authors justified combining the	data in a	meta-analysis		Yes
		nique to combine study results, adjusting		No
for heterogeneity if present				
	raw data,	ates from NRSI that were adjusted for or justified combining raw data when	х	No meta-analysis conducted
AND they reported separate summar	ry estimat	tes for RCTs and NRSI separately when		
both were included in the review				
12. If meta-analysis was performed, did th		· ·	oB ir	individual studies
on the results of the meta-analysis or othe	er eviden	ce synthesis?		
For Yes				
included only low risk of bias RCTs				Yes
-		's and/or NRSI at variable RoB, the au-		No
of effect.		ble impact of RoB on summary estimates	x	No meta-analysis conducted
13. Did the review authors account for Romanian?	oB in indi	ividual studies when interpreting/ discuss	sing t	ne results of the
review? For Yes			<u> </u>	
			v	Yes
x included only low risk of bias RCTs		IPSI were included the review provided a	х	
discussion of the likely impact of Ro		NRSI were included the review provided a results		No
14. Did the review authors provide a satis			terec	eneity observed in
the results of the review?	nactory e	appranation for, and discussion of, any ne	terog	chefty observed in
For Yes			1	
There was no significant heterogene	its in the	results	na	Yes
There was no significant neterogene	ny m me	results	na	ies

	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re-		No
	view		
	they performed quantitative synthesis did the review authors carry out an adequate i	nvest	igation of publica-
tion b	ias (small study bias) and discuss its likely impact on the results of the review?		
For Y	es		
	performed graphical or statistical tests for publication bias and discussed the likelihood		Yes
	and magnitude of impact of publication bias		No
		х	No meta-analysis
			conducted
16. D	id the review authors report any potential sources of conflict of interest, including any	fund	ling they received
for co	nducting the review?		
For Y	es		
х	The authors reported no competing interests OR	х	Yes
	The authors described their funding sources and how they managed potential conflicts		No
	of interest		
Your	overall assessment of the risk of bias of this systematic review		
Mode	rate		

AMST	FAR 2 checklist, <mark>critical questions</mark>				
REF:	Skotsimara et al 2019				
1. Dic	the research questions and inclusion	criteri:	a for the review include the components	of PIC	C O ?
For Y	es	Optio	nal (recommended)		
Х	Population		Timeframe for follow up	х	Yes
Х	Intervention				No
Х	Comparator group				
х	Outcome				
2. Dic	the report of the review contain an e	explicit	statement that the review methods were	establ	lished prior to the
condu	uct of the review and did the report ju	istify an	y significant deviations from the protoco	ol?	
For Pa	artial Yes:	For Y	es:		
The a	uthors state that they had a written	As for	partial yes, plus the protocol should be		
-	col or guide that included ALL the	registe	ered and should also have specified:		
follov	-				
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes
			propriate, and		
	a search strategy		a plan for investigating causes of heter-		Partial Yes
			ogeneity		
	inclusion/exclusion criteria			х	No
	a risk of bias assessment				
	-		f the study designs for inclusion in the re-	view?	
For Y	es, the review should satisfy ONE of th		ving:		Yes
	Explanation for including only RCTs			х	No
	OR Explanation for including only N				
	OR Explanation for including both R				
4. Dio	I the review authors use a comprehen	sive lite	erature search strategy?		
For Pa	artial Yes (all the following):	For Y	es, should also have (all the following):		Yes
	searched at least 2 databases (rele-	х	searched the reference lists / bibliog-		Partial Yes
	vant to research question)		raphies of included studies		
х	provided key word and/or search		searched trial/study registries	х	No
	strategy				
	justified publication restrictions		included/consulted content experts in	1	
	(e.g. language)		the field		

			where relevant, searched for grey litera-		
			ture	-	
		-	conducted search within 24 months of		
			completion of the review		
	d the review authors perform study se <i>Y</i> es, either ONE of the following:	lection	in duplicate?		
	at least two reviewers independently		n solution of aligible studies and		Yes
х	achieved consensus on which studies	-	-	х	ies
			le studies and achieved good agreement		Ne
	-	-			No
<u>(n:</u>	(at least 80 percent), with the remained d the review authors perform data ext				
	Yes, either ONE of the following:	Taction	in duplicate:		
		naua on	which data to extract from included stud-	v	Yes
х	ies	insus on	which data to extract from included stud-	х	165
			ble of eligible studies and achieved good		No
	agreement (at least 80 percent), with				NO
7 D:	d the review authors provide a list of		-	1	
	a the review authors provide a list of a artial Yes:		es, must also have:		
1.01 P	•	101 1	Justified the exclusion from the review	 	Vac
	provided a list of all potentially rel- evant studies that were read in full-		of each potentially relevant study		Yes Dortial Vac
	text form but excluded from the re-		or each potentiany relevant study		Partial Yes
	view			X	No
8 Di	d the review authors describe the incl	uded et	l Idies in adequate detail?	1	
	Partial Yes (ALL the following):		es, should also have ALL the following:		
	described populations	101 1	described population in detail		Yes
x	described populations described interventions	<u> </u>	described intervention in detail (includ-		
х	described interventions	х	ing doses where relevant)		Partially Yes
	described commentant		described comparator in detail (includ-		No
х	described comparators		ing doses where relevant)	х	NO
••	described outcomes				
х	described outcomes		described study's setting		
	described research designs	-	timeframe for follow-up		
9. Di	-	y techni	que for assessing the risk of bias (RoB) in	n indiv	vidual studies tha
were	included in the review?				
RCT	s				
For P	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from					
	unconcealed allocation, and	1	allocation sequence that was not truly	1	Yes
			random, and		Partial Yes
	lack of blinding of patients and as-	1	selection of the reported result from	1⊣	No
	sessors when assessing outcomes		among multiple measurements or anal-	x	Includes only
	(unnecessary for objective out-		yses of a specified outcome	"	NRSI
	comes such as all-cause mortality)				L
NRS	I	<u>. </u>	·	-	
	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
For P					
For P from		1	methods used to ascertain exposures	x	Yes
	from confounding, and	Х	-	I	
from	from confounding, and	x	and outcomes, and		Partial Yes
from	from confounding, and from selection bias	x x	and outcomes, and selection of the reported result from	┨┣──	Partial Yes No
from x					No
from x			selection of the reported result from		

	Most have not stad and the second of the disc for individual stadies included in the se		Vee
	Must have reported on the sources of funding for individual studies included in the re-		Yes
	view. Note: Reporting that the reviewers looked for this information but it was not re-	х	No
	ported by study authors also qualifies		
	meta-analysis was performed did the review authors use appropriate methods for sta	tistica	al combination of
result	5?		
RCTs			
For Y	25		
	The authors justified combining the data in a meta-analysis		Yes
	AND they used an appropriate weighted technique to combine study results and ad-		No
	justed for heterogeneity if present.		
	AND investigated the causes of any heterogeneity	na	No meta-analysis
			conducted
For N	RSI- combined in analysis-cig vs tobacco and sham and		•
For Y	28		
Х	The authors justified combining the data in a meta-analysis		Yes
	AND they used an appropriate weighted technique to combine study results, adjusting	х	No
	for heterogeneity if present		
х	AND they statistically combined effect estimates from NRSI that were adjusted for		No meta-analysis
	confounding, rather than combining raw data, or justified combining raw data when		conducted
	adjusted effect estimates were not available		
х	AND they reported separate summary estimates for RCTs and NRSI separately when		
	both were included in the review		
12. If	meta-analysis was performed, did the review authors assess the potential impact of R	oB in	individual studies
	results of the meta-analysis or other evidence synthesis?		
For Y			
1011	included only low risk of bias RCTs		Yes
	OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-	Х	No
	thors performed analyses to investigate possible impact of RoB on summary estimates	л	No meta-analysis
	of effect.		conducted
12 D	d the review authors account for RoB in individual studies when interpreting/ discuss	ing t	
review		ing ti	ie results of the
For Y		1	
1011	included only low risk of bias RCTs		Yes
	OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a		No
	discussion of the likely impact of RoB on the results	Х	INO
14 D		torog	anaity absorved in
	d the review authors provide a satisfactory explanation for, and discussion of, any her sults of the review?	lerog	enerty observed in
For Y			
101 1	There was no significant heterogeneity in the results		Yes
	OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the re-	х	No
	any neterogeneity in the results and discussed the impact of this on the results of the re-		
15 16			
15.11	view		
4 1.	view they performed quantitative synthesis did the review authors carry out an adequate i	nvest	igation of publica-
	view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review?	nvest	igation of publica-
tion b For Y	view they performed quantitative synthesis did the review authors carry out an adequate it ias (small study bias) and discuss its likely impact on the results of the review?	nvest	
	view they performed quantitative synthesis did the review authors carry out an adequate it ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood	nvest	Yes
	view they performed quantitative synthesis did the review authors carry out an adequate it ias (small study bias) and discuss its likely impact on the results of the review?	nvest 	Yes No
	view they performed quantitative synthesis did the review authors carry out an adequate it ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood		Yes No No meta-analysis
For Y	view they performed quantitative synthesis did the review authors carry out an adequate it ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	X	Yes No No meta-analysis conducted
For Y 16. Di	view they performed quantitative synthesis did the review authors carry out an adequate it it (small study bias) and discuss its likely impact on the results of the review? ess performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any	X	Yes No No meta-analysis conducted
For Y 16. Di for co	view they performed quantitative synthesis did the review authors carry out an adequate it ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any nducting the review?	X	Yes No No meta-analysis conducted
For Y 16. Di	view they performed quantitative synthesis did the review authors carry out an adequate it ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any nducting the review?	X	Yes No No meta-analysis conducted

17	of interest	
	of interest	INO
	The authors described their funding sources and how they managed potential conflicts	No

Critically low

AMSTA	R 2 checklist, <mark>critical questions</mark>				
REF: Wa	ang et al 2019				
	he research questions and inclusion		a for the review include the components of	of PIC	CO?
For Yes		Option	nal (recommended)		
Х	Population		Timeframe for follow up	х	Yes
х	Intervention				No
Some	Comparator group				
х	Outcome				
			statement that the review methods were e		ished prior to the
			y significant deviations from the protoco	1?	
For Part		For Y			
	nors state that they had a written		partial yes, plus the protocol should be		
	or guide that included ALL the	registe	ered and should also have specified:		
followin	-				
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes
	1		propriate, and		
	a search strategy		a plan for investigating causes of heter-		Partial Yes
	inclusion/exclusion criteria		ogeneity		No
	a risk of bias assessment			Х	INU
2 D:44		ation of	f the study designs for inclusion in the rev		
	, the review should satisfy ONE of th				Yes
For Yes,	•		ing:	Х	
	Explanation for including only RCT				No
Х	OR Explanation for including only		INDO		
4 0114	OR Explanation for including both				
	he review authors use a comprehen			1	
	ial Yes (all the following):		es, should also have (all the following):		Yes
х	searched at least 2 databases (rel-	х	searched the reference lists / bibliog-	х	Partial Yes
	evant to research question)		raphies of included studies		N -
х	provided key word and/or search		searched trial/study registries		No
	strategy justified publication restrictions		included (computed content or name in		
х	(e.g. language)		included/consulted content experts in the field		
	(e.g. language)		where relevant, searched for grey litera-		
			ture		
		x	conducted search within 24 months of		
		л	completion of the review		
5. Did t	he review authors perform study se	lection			
	, either ONE of the following:				
	at least two reviewers independently	v agreed	on selection of eligible studies and		Yes
	achieved consensus on which studie				
	OR two reviewers selected a sample	e of elig	ible studies and achieved good agreement	х	No
	(at least 80 percent), with the remai				
6. Did t	he review authors perform data ext				ı
	, either ONE of the following:		-		
		sensus o	on which data to extract from included		Yes
	studies				

	OP two reviewers extracted data fr	012 0 501	nple of eligible studies and achieved good	x	No
	agreement (at least 80 percent), wit			X	INO
7. Did	the review authors provide a list of		-	1	
	urtial Yes:		es, must also have:		
х	provided a list of all potentially		Justified the exclusion from the review		Yes
	relevant studies that were read in		of each potentially relevant study	x	Partial Yes
	full-text form but excluded from				No
	the review				
8. Did	the review authors describe the incl	uded st	udies in adequate detail?		
For Pa	artial Yes (ALL the following):	For Y	es, should also have ALL the following:		
Х	described populations	*	described population in detail		Yes
Х	described interventions		described intervention in detail (includ-	х	Partially Yes
			ing doses where relevant)		
na	described comparators		described comparator in detail (includ-		No
	-		ing doses where relevant)		
х	described outcomes			Bet	tter for in vitro than
			described study's setting	in	vivo
Х	described research designs		timeframe for follow-up		
9. Did	the review authors use a satisfactory	y techni	que for assessing the risk of bias (RoB) in	n indi	ividual studies that
	included in the review?				
RCTs					
For Pa	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
from					
	unconcealed allocation, and		allocation sequence that was not truly		Yes
			random, and		Partial Yes
	lack of blinding of patients and		selection of the reported result from		No
	assessors when assessing out-		among multiple measurements or anal-	х	Includes only
			was of a supprised outcome		
	comes (unnecessary for objective		yses of a specified outcome		NRSI
	comes (unnecessary for objective outcomes such as all-cause mor-		yses of a specified outcome		NRSI
	outcomes such as all-cause mor- tality)				
	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity an		ngth of each study were determined base		a qualitative assess-
ment o	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity an of study objectives, animal models, co				a qualitative assess-
ment o	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity an		ngth of each study were determined base		a qualitative assess-
ment o limitat	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity an of study objectives, animal models, co	ell cultu	ngth of each study were determined base		a qualitative assess-
ment o limitat For Pa	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity an of study objectives, animal models, co tions were noted in the analysis."	ell cultu	ngth of each study were determined base re, depth of analysis, and experimental c		a qualitative assess-
ment o limitat For Pa	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity an of study objectives, animal models, co tions were noted in the analysis."	ell cultu	ngth of each study were determined base re, depth of analysis, and experimental c		a qualitative assess-
ment o limitat For Pa	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity and of study objectives, animal models, co tions were noted in the analysis." artial Yes, must have assessed RoB	ell cultu	ngth of each study were determined base ire, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and		a qualitative assess- s. Meaningful study Yes
ment o limitat For Pa	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity and of study objectives, animal models, co tions were noted in the analysis." artial Yes, must have assessed RoB	ell cultu	ngth of each study were determined base ire, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures	letail:	a qualitative assess- s. Meaningful study Yes
ment o limitat For Pa	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity and of study objectives, animal models, continued in the analysis." artial Yes, must have assessed RoB from confounding, and	ell cultu	ngth of each study were determined base ire, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and	letail:	a qualitative assess s. Meaningful study Yes Partial Yes
ment o limitat For Pa	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity and of study objectives, animal models, continued in the analysis." artial Yes, must have assessed RoB from confounding, and	ell cultu	ngth of each study were determined base are, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from	letail:	a qualitative assess- s. Meaningful study Yes Partial Yes No
ment o limitat For Pa from	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity and of study objectives, animal models, con- tions were noted in the analysis." artial Yes, must have assessed RoB from confounding, and from selection bias	ell cultu For Y	ngth of each study were determined base are, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal-		a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT
ment o limitat For Pa from 10. Di	outcomes such as all-cause mor- tality) - animal and in vitro- "The validity and of study objectives, animal models, co tions were noted in the analysis." artial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the so	ell cultu For Y	ngth of each study were determined base re, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome		a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT
ment o limitat For Pa from 10. Di	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." artial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the second es	For Y	ngth of each study were determined base re, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome		a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT
ment o limitat For Pa from	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." initial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the sources of Must have reported on the sources of t	ell cultu For Y	ngth of each study were determined base are, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the		a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT w?
ment o limitat For Pa from 10. Di	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." initial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the sources of Must have reported on the sources of t	ell cultu For Y Durces o of fundii viewers	ngth of each study were determined base re, depth of analysis, and experimental d es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the	letail:	a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT W? Yes
ment o limitat For Pa from 10. Di o For Ye	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." artial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the sources of review. Note: Reporting that the review reported by study authors also quality	ell cultu For Y Durces o of fundii viewers ifies	ngth of each study were determined base re, depth of analysis, and experimental d es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the	revie	a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT w? Yes No
ment of limitat For Pa from 10. Die For Ye	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." of study objectives, animal models, contions were noted in the analysis." artial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the sources of review. Note: Reporting that the review reported by study authors also qualitimeta-analysis was performed did the	ell cultu For Y Durces o of fundii viewers ifies	ngth of each study were determined base are, depth of analysis, and experimental d es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the ng for individual studies included in the looked for this information but it was not	revie	a qualitative assess s. Meaningful study Yes Partial Yes No Includes only RCT w? Yes No
ment of limitat For Pa from 10. Die For Ye 11. If t results	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." of study objectives, animal models, contions were noted in the analysis." artial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the sources of review. Note: Reporting that the review reported by study authors also qualitimeta-analysis was performed did the	ell cultu For Y Durces o of fundii viewers ifies	ngth of each study were determined base are, depth of analysis, and experimental d es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the ng for individual studies included in the looked for this information but it was not	revie	a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT w? Yes No
ment of limitat For Pa from 10. Did For Ye 11. If n results RCTs	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." utions were noted in the analysis." utions were noted in the analysis." utial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the sources of review. Note: Reporting that the review reported by study authors also qualities and the sources of review. Note: Reporting that the review reported by study authors also qualities analysis was performed did the sources of several	ell cultu For Y Durces o of fundii viewers ifies	ngth of each study were determined base are, depth of analysis, and experimental d es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the ng for individual studies included in the looked for this information but it was not	revie	a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT w? Yes No
ment of limitat For Pa from 10. Did For Ye 11. If n results RCTs	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." urtial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the sources of review. Note: Reporting that the review reported by study authors also quality meta-analysis was performed did the sources of set the sources of set the sources of the sources of review. Note: Reporting that the review reported by study authors also quality meta-analysis was performed did the set the set of the sources of set the set of the sources of set the sources of set the set of the sources	ell cultu For Y For Y ources o of fundin viewers ifies e review	ngth of each study were determined base re, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the ng for individual studies included in the looked for this information but it was not authors use appropriate methods for sta	revie	a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT w? Yes No cal combination of
ment of limitat For Pa from 10. Die For Ye 11. If t results	outcomes such as all-cause mortality) - animal and in vitro- "The validity and of study objectives, animal models, contions were noted in the analysis." artial Yes, must have assessed RoB from confounding, and from selection bias d the review authors report on the sources of review. Note: Reporting that the review reported by study authors also quality authors also quality and the authors justified combining the sources of the authors justified combining the sources of the authors is a statement of the authors is a stat	ell cultu For Y For Y ources o of fundii viewers ifies e review	ngth of each study were determined base re, depth of analysis, and experimental c es, must also have assessed RoB from: methods used to ascertain exposures and outcomes, and selection of the reported result from among multiple measurements or anal- yses of a specified outcome f funding for the studies included in the ng for individual studies included in the looked for this information but it was not authors use appropriate methods for sta	revie	a qualitative assess- s. Meaningful study Yes Partial Yes No Includes only RCT w? Yes No

	AND investigated the causes of any heterogeneity	х	No meta-analysis
			conducted
For NR	SI		•
For Yes			
	The authors justified combining the data in a meta-analysis		Yes
	AND they used an appropriate weighted technique to combine study results, adjust-		No
	ing for heterogeneity if present		
	AND they statistically combined effect estimates from NRSI that were adjusted for	х	No meta-analysis
	confounding, rather than combining raw data, or justified combining raw data when		conducted
	adjusted effect estimates were not available		
	AND they reported separate summary estimates for RCTs and NRSI separately when		
10 10	both were included in the review	D •	·
	neta-analysis was performed, did the review authors assess the potential impact of R	oB ir	i individual studies
	results of the meta-analysis or other evidence synthesis?	1	
For Yes			
	included only low risk of bias RCTs		Yes
	OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No
	thors performed analyses to investigate possible impact of RoB on summary esti- mates of effect.	х	No meta-analysis conducted
12 0.1			
15. Dia review?	the review authors account for RoB in individual studies when interpreting/ discuss	sing t	ne results of the
For Yes		1	
FOI TES	included only low risk of bias RCTs		Yes
	OR, if RCTs with moderate or high RoB, or NRSI were included the review pro-	х	No
Х	vided a discussion of the likely impact of RoB on the results		NO
14 Did	the review authors provide a satisfactory explanation for, and discussion of, any he	toroo	anaity absorved in
	ilts of the review?	terog	cherty observed in
For Yes			
101 100	There was no significant heterogeneity in the results	x	Yes
х	OR if heterogeneity was present the authors performed an investigation of sources of		No
	any heterogeneity in the results and discussed the impact of this on the results of the		
	review		
15. If tl	ey performed quantitative synthesis did the review authors carry out an adequate i	invest	tigation of publica-
tion b.	is (small study bias) and discuss its likely impact on the results of the review?		
uon Dia			
	performed graphical or statistical tests for publication bias and discussed the likeli-		Yes
			Yes No
	performed graphical or statistical tests for publication bias and discussed the likeli-	x	No
	performed graphical or statistical tests for publication bias and discussed the likeli-	x	
For Yes	performed graphical or statistical tests for publication bias and discussed the likeli-		No No meta-analysis conducted
For Yes	performed graphical or statistical tests for publication bias and discussed the likeli- hood and magnitude of impact of publication bias		No No meta-analysis conducted
For Yes	performed graphical or statistical tests for publication bias and discussed the likeli- hood and magnitude of impact of publication bias the review authors report any potential sources of conflict of interest, including any ducting the review?		No No meta-analysis conducted
For Yes 16. Did for con	performed graphical or statistical tests for publication bias and discussed the likeli- hood and magnitude of impact of publication bias the review authors report any potential sources of conflict of interest, including any ducting the review?		No No meta-analysi conducted
For Yes 16. Did for con For Yes	performed graphical or statistical tests for publication bias and discussed the likeli- hood and magnitude of impact of publication bias the review authors report any potential sources of conflict of interest, including any ducting the review?	y fun	No No meta-analysi conducted ding they received
For Yes 16. Did for con For Yes	performed graphical or statistical tests for publication bias and discussed the likeli- hood and magnitude of impact of publication bias the review authors report any potential sources of conflict of interest, including any ducting the review? The authors reported no competing interests OR	y fun	No No meta-analysi conducted ding they received Yes
For Yes 16. Did for con For Yes x	performed graphical or statistical tests for publication bias and discussed the likeli- hood and magnitude of impact of publication bias the review authors report any potential sources of conflict of interest, including any ducting the review? The authors reported no competing interests OR The authors described their funding sources and how they managed potential con-	y fun	No meta-analysis conducted ding they received Yes

AMSTAR 2 checklist, critical questions						
REF: Ward et al 2020						
1. Did the research questions and inclusion criteria for the review include the components of PICO?						
For Yes	Optional (recommended)					

na	Population		Timeframe for follow up	х	Yes		
Х	Intervention				No		
na	Comparator group						
Х	Outcome						
2. Did	the report of the review contain an e	explicit s	statement that the review methods were	establi	ished prior to the		
condu	ict of the review and did the report ju	istify an	y significant deviations from the protoco	ol?			
For Pa	artial Yes:	For Y	es:				
The au	uthors state that they had a written	As for	partial yes, plus the protocol should be				
protoc	ol or guide that included ALL the	registe	ered and should also have specified:				
follow	ving:						
	review question(s)		a meta-analysis/ synthesis plan, if ap-		Yes		
			propriate, and				
	a search strategy		a plan for investigating causes of heter- ogeneity		Partial Yes		
	inclusion/exclusion criteria			х	No		
	a risk of bias assessment			-			
3. Did	the review authors explain their sele	ction of	f the study designs for inclusion in the rev	view?			
	es, the review should satisfy ONE of the			x	Yes		
	Explanation for including only RCTs				No		
х	OR Explanation for including only N	RSI					
	OR Explanation for including both R		NRSI				
4. Did	the review authors use a comprehen			I			
	artial Yes (all the following):		es, should also have (all the following):	T	Yes		
x	searched at least 2 databases (rele-	1011	searched the reference lists / bibliog-	x	Partial Yes		
Α	vant to research question)		raphies of included studies	Α	r ar tiar res		
х	provided key word and/or search		searched trial/study registries		No		
	strategy		searchea anazonaa, regionneo				
х	justified publication restrictions		included/consulted content experts in				
	(e.g. language)		the field				
			where relevant, searched for grey litera-				
			ture				
		х	conducted search within 24 months of				
			completion of the review				
5. Did	the review authors perform study se	lection	in duplicate?				
For Y	es, either ONE of the following:						
	at least two reviewers independently a	agreed o	n selection of eligible studies and		Yes		
	achieved consensus on which studies	to inclu	de				
	OR two reviewers selected a sample of	le studies and achieved good agreement	х	No			
(at least 80 percent), with the remainder selected by one reviewer.							
6. Did	the review authors perform data ext	raction	in duplicate?				
For Y	es, either ONE of the following:						
	at least two reviewers achieved conse ies		Yes				
	OR two reviewers extracted data from	n a samp	le of eligible studies and achieved good	х	No		
	agreement (at least 80 percent), with the remainder extracted by one reviewer.						
7. Did the review authors provide a list of excluded studies and justify the exclusions?							
	artial Yes:		es, must also have:				
Х	provided a list of all potentially rel-		Justified the exclusion from the review		Yes		
	evant studies that were read in full-		of each potentially relevant study	x	Partial Yes		
	text form but excluded from the re-				No		
	view						
8. Did	the review authors describe the inclu	uded stu	idies in adequate detail?				
For Pa	artial Yes (ALL the following):	For Ye	es, should also have ALL the following:				
na	described populations		described population in detail		Yes		

х	described interventions	х	described intervention in detail (includ-		Partially Yes
			ing doses where relevant)		N
na	described comparators		described comparator in detail (includ- ing doses where relevant)	х	No
x	described outcomes	х	described study's setting		
	described research designs	х	timeframe for follow-up	1	
9. Did	I the review authors use a satisfactory	y techni	que for assessing the risk of bias (RoB) in	n indiv	vidual studies that
were	included in the review?				
RCTs	\$				
For Pa from	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:		
nom	unconcealed allocation, and		allocation sequence that was not truly		Yes
	unconceated anocation, and		random, and		Partial Yes
	lack of blinding of patients and as-		selection of the reported result from	-	
	sessors when assessing outcomes		among multiple measurements or anal-		No
	(unnecessary for objective out-		yses of a specified outcome	х	Includes only
	comes such as all-cause mortality)		yses of a specified butcome		NRSI
NRSI	- nonstandard question				
	artial Yes, must have assessed RoB	For V	es, must also have assessed RoB from:	Vori	ification of analysis
from					hods
	from confounding, and	х	methods used to ascertain exposures	х	Yes
			and outcomes, and		Partial Yes
	from selection bias	х	selection of the reported result from		No
			among multiple measurements or anal-		Includes only
			yses of a specified outcome		RCT
10. Di	id the review authors report on the so	ources o	f funding for the studies included in the	review	v?
For Y					
	-	-	for individual studies included in the re-		Yes
	view. Note: Reporting that the review	ers look	ed for this information but it was not re-	х	No
	ported by study authors also qualifies				
		review	authors use appropriate methods for sta	ntistica	al combination of
result					
RCTs					
For Y					
	The authors justified combining the d		-		Yes
		ted tech	nique to combine study results and ad-		No
	justed for heterogeneity if present.				
	AND investigated the causes of any h	eteroge	neity	х	No meta-analysis
					conducted
For N					
For Y					
	The authors justified combining the data in a meta-analysis				Yes
	AND they used an appropriate weighted technique to combine study results, adjusting				NT -
		ted tech	nique to combine study results, adjusting		No
	for heterogeneity if present				
	for heterogeneity if present AND they statistically combined effe	ct estim	ates from NRSI that were adjusted for	x	No meta-analysis
	for heterogeneity if present AND they statistically combined effe confounding, rather than combining r	ct estim aw data		x	
	for heterogeneity if present AND they statistically combined effer confounding, rather than combining r adjusted effect estimates were not available.	ct estim aw data ailable	ates from NRSI that were adjusted for , or justified combining raw data when	x	No meta-analysis
	for heterogeneity if present AND they statistically combined effe confounding, rather than combining r adjusted effect estimates were not ava AND they reported separate summary	ct estim aw data ailable	ates from NRSI that were adjusted for	x	No meta-analysis
10 10	for heterogeneity if present AND they statistically combined effe confounding, rather than combining r adjusted effect estimates were not ava AND they reported separate summary both were included in the review	ct estim aw data ailable / estima	ates from NRSI that were adjusted for , or justified combining raw data when tes for RCTs and NRSI separately when		No meta-analysis conducted
	for heterogeneity if present AND they statistically combined effe confounding, rather than combining r adjusted effect estimates were not ava AND they reported separate summary both were included in the review meta-analysis was performed, did th	ct estim aw data ailable / estima e reviev	ates from NRSI that were adjusted for , or justified combining raw data when tes for RCTs and NRSI separately when y authors assess the potential impact of R		No meta-analysis conducted
	for heterogeneity if present AND they statistically combined effe confounding, rather than combining r adjusted effect estimates were not ava AND they reported separate summary both were included in the review meta-analysis was performed, did th e results of the meta-analysis or other	ct estim aw data ailable / estima e reviev	ates from NRSI that were adjusted for , or justified combining raw data when tes for RCTs and NRSI separately when y authors assess the potential impact of R		No meta-analysis conducted

included only low risk of bias RCTs		Yes
OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the au-		No
thors performed analyses to investigate possible impact of RoB on summary estimates	х	No meta-analysis
of effect.		conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discuss	sing tl	ne results of the
review?		
For Yes		
included only low risk of bias RCTs	na	Yes
OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a		No
discussion of the likely impact of RoB on the results		
14. Did the review authors provide a satisfactory explanation for, and discussion of, any he	terog	eneity observed in
the results of the review?		
For Yes		
There was no significant heterogeneity in the results	na	Yes
OR if heterogeneity was present the authors performed an investigation of sources of		No
any heterogeneity in the results and discussed the impact of this on the results of the re-		
view		
15. If they performed quantitative synthesis did the review authors carry out an adequate i	nvest	igation of publica-
tion bias (small study bias) and discuss its likely impact on the results of the review?		
For Yes		
performed graphical or statistical tests for publication bias and discussed the likelihood		Yes
and magnitude of impact of publication bias		No
	х	No meta-analysis
		conducted
16. Did the review authors report any potential sources of conflict of interest, including any	fund	ing they received
for conducting the review?		
For Yes		
x The authors reported no competing interests OR	х	Yes
The authors described their funding sources and how they managed potential conflicts		No
of interest		
Your overall assessment of the risk of bias of this systematic review	•	
Moderate		

AMS	TAR 2 checklist, <mark>critical questions</mark>				
REF	: Zhao et al 2016				
1. D	id the research questions and inclusion	on criter	ia for the review include the components	of PI	CO?
For	Yes	Opti	onal (recommended)		
Х	Population		Timeframe for follow up	х	Yes
Х	Intervention		•		No
Х	Comparator group				
х	Outcome				
	•	•	statement that the review methods were ny significant deviations from the protoco		lished prior to the
For	Partial Yes:	For Y	Yes:		
The	authors state that they had a written	As fo	or partial yes, plus the protocol should be		
prote	ocol or guide that included ALL the	regis	tered and should also have specified:		
follo	wing:				
х	review question(s)	х	a meta-analysis/ synthesis plan, if ap- propriate, and	х	Yes
х	a search strategy	х	a plan for investigating causes of heter- ogeneity		Partial Yes
Х	inclusion/exclusion criteria				No
х	a risk of bias assessment				·

	-		the study designs for inclusion in the re-	view?				
For Y	es, the review should satisfy ONE of th	e follow	ring:	х	Yes			
	Explanation for including only RCTs				No			
Х	OR Explanation for including only N	RSI						
	OR Explanation for including both R	CTs and	NRSI					
4. Did	the review authors use a comprehen	sive lite	rature search strategy?	1				
For Pa	artial Yes (all the following):	For Y	es, should also have (all the following):		Yes			
х	searched at least 2 databases (rele-	х	searched the reference lists / bibliog-	х	Partial Yes			
	vant to research question)		raphies of included studies					
Х	provided key word and/or search		searched trial/study registries		No			
	strategy							
Х	justified publication restrictions		included/consulted content experts in					
	(e.g. language)		the field					
			where relevant, searched for grey litera-					
			ture					
		х	conducted search within 24 months of	1				
			completion of the review					
5. Did	the review authors perform study se	election	in duplicate?					
	es, either ONE of the following:							
х	at least two reviewers independently	agreed o	n selection of eligible studies and	х	Yes			
	achieved consensus on which studies	-	-					
	OR two reviewers selected a sample of	of eligib	le studies and achieved good agreement	1	No			
	(at least 80 percent), with the remained							
6. Did	the review authors perform data ext							
	es, either ONE of the following:							
x		nsus on	which data to extract from included stud-	х	Yes			
	Les							
	OR two reviewers extracted data from a sample of eligible studies and achieved good No							
	agreement (at least 80 percent), with	-						
7. Did	the review authors provide a list of			1				
	For Partial Yes: For Yes, must also have:							
x	provided a list of all potentially rel-	101 1	Justified the exclusion from the review	I T	Yes			
Α	evant studies that were read in full-		of each potentially relevant study	v	Partial Yes			
	text form but excluded from the re-		of each potentially following study	Х	No			
	view				NO			
8. Did	the review authors describe the inclu	l uded sti	l Idies in adequate detail?	1				
	artial Yes (ALL the following):		es, should also have ALL the following:					
	described populations	1011	described population in detail		Yes			
X	described interventions		described intervention in detail (includ-	v	Partially Yes			
х	described interventions		ing doses where relevant)	Х	ratually res			
v	described comparators		described comparator in detail (includ-		No			
х	described comparators		ing doses where relevant)		INU			
v	described outcomes	v	_					
х	described outcomes	х	described study's setting					
х	described research designs		timeframe for follow-up					
	-	l / techni/	que for assessing the risk of bias (RoB) in	 1 india	vidual studies that			
	included in the review?	teenno	que for assessing the risk of blas (ROB) II	mul	indai studies tilat			
RCTs								
		E or V	as must also have accessed D - D for m	1				
For Partial Yes, must have assessed RoB For Yes, must also have assessed RoB from:								
from	1 1 11 1		11					
	unconcealed allocation, and		allocation sequence that was not truly		Yes			
	1	1	random, and	1				

		1		rr—	D 117	
	lack of blinding of patients and as-		selection of the reported result from		Partial Yes	
	sessors when assessing outcomes		among multiple measurements or anal-		No	
	(unnecessary for objective out-		yses of a specified outcome	х	Includes only	
	comes such as all-cause mortality)				NRSI	
NRS				-		
	artial Yes, must have assessed RoB	For Y	es, must also have assessed RoB from:			
from						
х	from confounding, and	х	methods used to ascertain exposures	x	Yes	
	from selection bias		and outcomes, and		Partial Yes	
Х	from selection bias	х	selection of the reported result from among multiple measurements or anal-		No	
			yses of a specified outcome		Includes only	
10 5			-	Ц_	RCT	
		ources o	f funding for the studies included in the i	eview	/?	
For Y						
Х	-	-	for individual studies included in the re-		Yes	
			ted for this information but it was not re-	х	No	
11 14	ported by study authors also qualifies			4:-4:	l	
resul		e review	authors use appropriate methods for sta	tistica	al combination of	
RCTs						
For Y				r		
FOR Y					Yes	
	The authors justified combining the d					
		ted tech	nique to combine study results and ad-		No	
	justed for heterogeneity if present.					
	AND investigated the causes of any h	na	No meta-analysis			
F . N	unci		conducted			
For N For Y						
					Yes	
X	The authors justified combining the d		-	х		
Х	AND they used an appropriate weighted technique to combine study results, adjusting No					
x	for heterogeneity if present	ot estim	ates from NRSI that were adjusted for		No meta-analysis	
х			, or justified combining raw data when		conducted	
	adjusted effect estimates were not ava		, of Justified combining faw data when		conducted	
			tes for RCTs and NRSI separately when			
	both were included in the review	y counta	tes for RC15 and RR51 separatery when			
12. If		e reviev	v authors assess the potential impact of R	oB in	individual studies	
	e results of the meta-analysis or other					
For Y						
	included only low risk of bias RCTs			x	Yes	
х	-	on RCT	's and/or NRSI at variable RoB, the au-		No	
	-		ble impact of RoB on summary estimates		No meta-analysis	
	of effect.	-	- •		conducted	
13. D	id the review authors account for Ro	B in ind	ividual studies when interpreting/ discuss	sing th		
revie				5		
For Y	/es					
х	included only low risk of bias RCTs			х	Yes	
	OR, if RCTs with moderate or high F	RoB, or I	NRSI were included the review provided a		No	
	discussion of the likely impact of Rol		-			
14. D			explanation for, and discussion of, any he	terog	eneity observed in	
	esults of the review?	-		2		
For Y	7es					
	There was no significant heterogeneit	ty in the	results	х	Yes	

OR if heterogeneity was present the authors performed an investigation of sources of		No
any heterogeneity in the results and discussed the impact of this on the results of the re-		
view		
they performed quantitative synthesis did the review authors carry out an adequate i	invest	igation of publica-
ias (small study bias) and discuss its likely impact on the results of the review?		
25		
performed graphical or statistical tests for publication bias and discussed the likelihood	х	Yes
and magnitude of impact of publication bias		No
		No meta-analysis
		conducted
d the review authors report any potential sources of conflict of interest, including any	y func	ling they received
nducting the review?		
25		
The authors reported no competing interests OR	х	Yes
The authors described their funding sources and how they managed potential conflicts		No
of interest		
overall assessment of the risk of bias of this systematic review		-
	view they performed quantitative synthesis did the review authors carry out an adequate i ias (small study bias) and discuss its likely impact on the results of the review? es performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any nducting the review? es The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts of interest	view they performed quantitative synthesis did the review authors carry out an adequate invest ias (small study bias) and discuss its likely impact on the results of the review? ss performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias d the review authors report any potential sources of conflict of interest, including any funct nducting the review? ss The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts of interest



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