Title Page

Title: Non-randomised studies of interventions: a systematic review of methodological conduct and reporting

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Abbreviations:

NRSIs	Non randomised studies for interventions
RCT	Randomised controlled trial
RoB	Risk of bias
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
NIHR	National Institute for Health Research
BRC	Biomedical Research Centre

Abstract

Objective: Evaluate the methodological conduct, reporting, and risk of bias of non-randomised studies of interventions (NRSIs) published by UK National Institute for Health Research Biomedical Research Centres (NIHR-BRCs).

Study design and setting: We conducted a systematic review, searching the Medline and Web of Science databases between 2012-2018, for NRSIs funded by NIHR-BRCs. Eligible studies were published between April 2012 and December 2017. We selected a contemporary subset of NRSIs published in 2017. We extracted study design, methods for overcoming confounding bias from non-randomisation, analysis methods, and items for assessing risk of bias. Risk of bias was the primary outcome, assessed using Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I).

Results: Fifty-two NSRI publications were included, of which over half were cohort studies and 29% before-and-after studies. 77% analysed non-purposefully-collected data. All had serious or critical risk of bias. Regression adjustment was most commonly used to address confounding bias (50%). Few (12%) studies accounted for missing data and 42% reported different numbers of outcomes in their methods and results.

Conclusion: Most reviewed NRSIs had serious or critical risk of bias. Although NRSIs can evaluate treatment effects when appropriately conducted, this review shows that their design, analysis, and reporting require more consideration.

Keywords:

Systematic Review; Methodology; Non-randomised; Observational; Reporting

1. Introduction

Non-randomised studies of interventions (NRSIs) are often used to estimate comparable intervention effects when randomised controlled trials (RCTs) are unfeasible or unethical (2-4). NRSIs have risen in popularity with the increasing availability of data, including routinely collected data sources (5). They are increasingly included in systematic reviews and used to inform clinical and policy decisions about implementing interventions when few RCTs are available (6-10). However, as NRSIs cannot fully account for their lack of randomisation, biased estimates of intervention effects can result. Including NRSIs in systematic reviews requires special consideration of their risk of bias (11-14).

NRSIs can overestimate intervention effects (15, 16), with one Health Technology Assessment finding overestimates of on average 17%, compared with RCT estimates (1). Although this bias was lower in studies with prospective design and statistical adjustment for confounders, NRSIs are also affected by bias from other sources, such as selection and immortal time bias. The extent to which NRSIs are at risk of bias, use prospective study designs and statistical adjustments, and are affected by other sources of bias is currently unknown.

At the time of writing, the National Institute for Health Research (NIHR) Biomedical Research Centres (BRCs) are in their third round of funding (2017-2022). This initiative supports partnerships between National Health Service (NHS) organisations and universities in England to accelerate research translation from early experimental research to clinical studies, for patients' benefit (17, 18). However, this accelerated research environment requires caution to ensure research quality is not compromised, which could bias findings and contribute to research waste (19).

We conducted a systematic review to evaluate the methodological quality, reporting, and risk of bias of NRSIs funded by NIHR-BRCs during their second round of funding (2012-2017). We aimed to describe and critically appraise the methods used to design, conduct, and analyse NRSIs; evaluate their risk of bias; and evaluate their reporting quality.

1. Materials and methods

1.1 Protocol registration and reporting standards

The study protocol was registered on the Open Science Framework (20). This paper is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (21).

1.2 Information sources

We searched the Medline (OVID) and Web of Science Core Collection databases on 4 April 2018 to identify studies funded by NIHR-BRCs and published 2012-2018. The Web of Science search (Supplementary Table 1) used terms such as 'NIHR' and 'BRC' in the funding agency field and BRC-related terms in the organisation-enhanced field to identify studies. We used the Medline (OVID) database to capture additional publications and those 'in process' by searching for relevant 'NIHR' and 'BRC' terms in the institution- and investigator-affiliation fields.

1.3 Eligibility criteria

NRSIs fully or partially funded by an NIHR-BRC and published from 1 April 2012 to 31 December 2017 were eligible. NRSIs were defined as quantitative studies estimating a treatment, intervention, or policy effect that did not use randomisation to allocate study participants to comparison groups. This definition is in line with previous research (1, 22).

1.3.1 *Inclusion criteria*

Studies were eligible for inclusion if they were:

- Testing any healthcare intervention, treatment, or policy
- Reporting a comparative treatment or intervention effect estimate between groups
- Primary research
- In humans
- Published in English
- Using one of the following non-randomised study designs (described in Box 1)
    - Before-and-after
    - Non-randomised controlled trial
    - Cohort
    - Case-control
    - Cross-sectional
    - Time-series or case-series analysis
    - Concurrently or historically controlled trial
- Fully or partially funded by second-round NIHR-BRC funding (2012-2017). Supplementary Table 2 lists funded NIHR-BRCs
- Published 1 April 2012 to 31 December 2017

1.3.2 *Exclusion criteria*

We excluded the following article and study types:

- Quasi- and pseudo-randomisation

- Protocols, reviews, and commentaries
- Dose-finding studies
- Intervention devices for diagnostics
- Single-arm trials
- Diagnostic and prognostic accuracy studies
- In-vitro and in-vivo studies
- Pilot, feasibility, and exploratory studies
- Non-interventional case-series studies

We also excluded studies funded by NIHR Biomedical Research Units or outside the second NIHR-BRC funding round. Studies by the Barts, Sheffield, Leeds, Leicester, Birmingham, Bristol, Nottingham, and Manchester BRCs were excluded as they were first funded in the third NIHR-BRC funding round (2017-2022).

Box 1. Description of included study designs

Non-randomised controlled trial:

A clinical trial in which the intervention is not randomly allocated. Allocation mechanisms can include clinician preference/judgement, time, and location.

Before-and-after study:

Participants are observed before and after the intervention is given. Participants act as their own control before the intervention, compared with observations made after the intervention has been implemented.

Cohort study:

A defined group of participants, some of whom receive the intervention and some who do not, are followed over time. Comparisons are made based on subsequent observed health outcomes.

Cross-sectional study:

Participants are surveyed at a particular point in time to collect information on their past or present use of the intervention and their present health outcome.

Case-control study:

Compares prior exposure to the intervention in participants known to have the health outcome (cases) to those who do not (controls). Cases and controls are from the same population.

Time-series study:

Uses observations taken at multiple time points before and after the intervention. The intervention is assessed by its effect on underlying time trends.

Case-series (self-controlled) study:

All participants are cases and each acts as their own control. The observation time for each participant is divided into 'control' and 'risk' periods, where the risk period is defined as the time during or after the intervention is implemented. Comparisons are made between control and risk periods.

Concurrently or historically controlled trials:

Participants who receive the intervention are compared to similar participants recruited simultaneously to the intervention group (concurrently controlled) or similar participants from the past who do not receive the intervention (historically controlled)

1.4 Study selection

To capture up-to-date reporting practice and methodological conduct in NRSIs, we selected a subset of contemporary studies published from 1 January 2017 to 31 December 2017. Publications from the literature search were imported into Endnote Citation Manager and de-duplicated, then screened using the Rayyan web application (23).

One reviewer (PD) screened the titles and abstracts of the identified publications against the eligibility criteria. Two independent reviewers (PD and HL) then screened the full article text to further assess eligibility. A third reviewer (GSC) resolved disagreements. Reviewers were not blinded to the study authors, institutions, or BRCs.

1.1 Data extraction

Data were extracted on the primary outcome or, if not specified, the first intervention comparison and outcome measure in the study methods. Data were extracted using a standardised form informed by reporting guidelines for that study design and/or analysis. For example, the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement was used to assess observational studies and a modified STROBE statement to assess propensity-score analyses (24, 25).

The data extraction form was pilot-tested on five publications and amended as needed (PD and HL). Data were extracted using REDCap (26): NIHR-BRC, disease area, study design, participants, interventions, comparators, outcome, allocation mechanism for non-randomised trials, whether cohort studies were prospective or retrospective, methods accounting for confounding, blinding, sample size, and items for assessing risk of bias.

Cohort studies were considered prospective if participants were sampled based on the intervention they received and followed up for their outcome. This included studies where participants who had or had not received the intervention of interest were selected, recruited, and followed up. It also included studies that used existing observational data available when the study started, sampled participants who had or had not received the intervention of interest, and followed them up.

Cohort studies were considered retrospective if participants were sampled based on the outcome, which could be in addition to sampling on the intervention. This included studies that excluded participants due to missing outcome information (27, 28).

Two independent reviewers (PD and HL) performed a double data extraction for each publication, including any published supplementary information. Study authors were contacted for further information and clarification if needed. A third reviewer (GSC) resolved disagreements.

1.5 Analysis

The primary outcome was risk of bias, assessed using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool (22). Studies were ranked as low, moderate, serious, or critical risk of bias in seven domains:

1. Bias due to confounding
2. Bias in selecting participants
3. Bias in classifying interventions
4. Bias due to deviating from the intended interventions
5. Bias due to missing data
6. Bias in measuring outcomes
7. Bias in selecting which results to report

Domains were rated ‘no information’ if there was insufficient information available. Following ROBINS-I guidance, the overall risk of bias was derived from the seven domains. A study was considered at low risk of bias if it was ranked low for all domains; at moderate risk of bias if it was ranked low or moderate for all domains; at serious risk of bias if it was ranked serious in at least one domain; and at critical risk of bias if it was ranked critical in at least one domain.

Risk of bias, methodological conduct, and reporting results were summarised using descriptive statistics, graphs, and a narrative synthesis. The analysis was conducted across all NIHR-BRCs and by study design.

Analyses were conducted using Stata version 15 (29).

2. Results

We identified 1877 research papers published between 1 January 2017 and 31 December 2017. 1825 publications were excluded during screening, primarily due to the study design (n=1701), publication type (n=89), and funding (n=22). We reviewed and extracted information from 52 studies. Figure 1 shows the selection process.

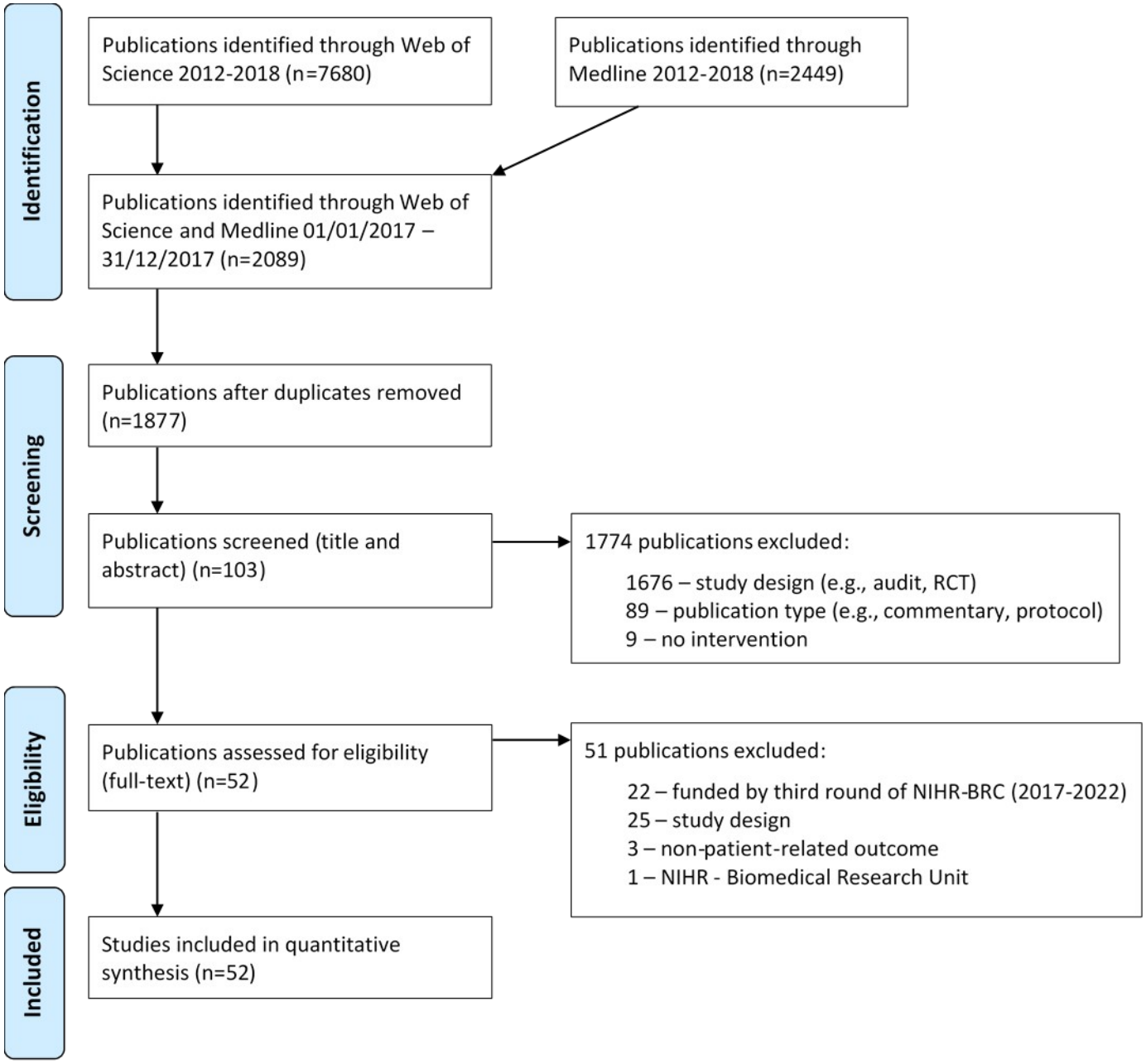

Figure 1. PRISMA flow diagram showing the selection of included studies.

2.1 General study characteristics

Table 1 summarises the characteristics of the included studies. We included twenty-nine cohort studies (56%), fifteen before-and-after studies (29%), four non-randomised controlled trials (8%), two cross-sectional studies, one time-series analysis, and one case-series analysis.

The included studies most commonly dealt with transplantation (n=7; 13%), visual assessment and imaging (n=7; 13%), and mental health (n=6; 12%). Most assessed drug therapy (n=22; 42%) and surgery (n=17; 33%) interventions. Six of the studies assessing surgery interventions were on transplantations. Interventions were often compared to 'no intervention' (n=24; 46%), other drug therapies (n=8; 15%), and surgery (n=12; 23%). Most of the studies were based in the UK (n=41; 79%) and set in tertiary care (n=27; 52%).

Table 1. Characteristics of the included studies.

Study characteristics		**n**	**%**
Clinical area	Cancer	5	9.62
	Cardiovascular disease	5	9.62
	Gastroenterology and hepatology	3	5.77
	Immunity, infection, and inflammation	4	7.69
	Mental health	6	11.54
	Metabolism, endocrinology, and bone	1	1.92
	Neonatal medicine	2	3.85
	Neuroimaging	1	1.92
	Neuroscience	2	3.85
	Nutrition, lifestyle, and healthy ageing	1	1.92
	Obesity, diabetes, endocrinology, and metabolism	1	1.92
	Renal medicine and transplantation	1	1.92
	Respiratory	3	5.77
	Rheumatology	2	3.85
	Surgery and technology	1	1.92
	Transplantation	7	13.46
	Visual assessment and imaging	7	13.46
Intervention type	Drug	22	42.31
	Drug and surgery	1	1.92
	Electrotherapy	2	3.85
	Non-invasive treatment	4	7.69
	Public health intervention	3	5.77
	Radiation	2	3.85
	Screening	1	1.92
	Surgery	17	32.69
Comparator type	Drug	8	15.38
	Drug and surgery	2	3.85
	Electrotherapy	1	1.92
	No intervention	24	46.15
	Radiation	1	1.92
	Screening	2	3.85

	Surgery	12	23.08
	Usual care	2	3.85
Study design	Non-randomised trial	4	7.69
	Before-and-after	15	28.85
	Cohort	29	55.77
	Time-series	1	1.92
	Case-series	1	1.92
	Cross-sectional	2	3.85
Country	UK only	41	78.85
	Single European country	5	9.62
	Single East Asian country	2	3.85
	Multiple international countries	4	7.69
Setting	Primary care	6	11.54
	Secondary care	18	34.62
	Tertiary care	27	51.92
	Other – public health campaign	1	1.92

2.2 Risk of bias

Figure 2 summarises the risk of bias ratings and a full description of the risk of bias assessment is given in Supplementary Table 3. No study was at low or moderate risk of bias. More studies were at critical (n=28; 54%) than serious (n=24; 46%) risk of bias.

Cohort studies had the smallest proportion of studies at critical risk of bias: 34% (n=10/29) versus 87% of before-and-after studies (n=13/15) and 75% of non-randomised trials (n=3/4). Fewer prospective cohort studies were at critical risk of bias (n=5/18; 28%) than retrospective cohort studies (n=5/11; 45%). Only 28% (n=7/25) of studies that adjusted for confounders were at critical risk of bias, compared with 80% (n=20/25) of those that only presented an unadjusted analysis.

Confounding bias was the largest contributor to the overall risk of bias (Figure 2), with over half of the studies (n=28; 54%) at critical risk with inherently uncontrollable confounding. For most studies, there was insufficient information to assess the risk of bias for missing data (n=33; 63%), selective reporting (n=49; 94%) and deviations from the intended intervention (n=25; 48%).

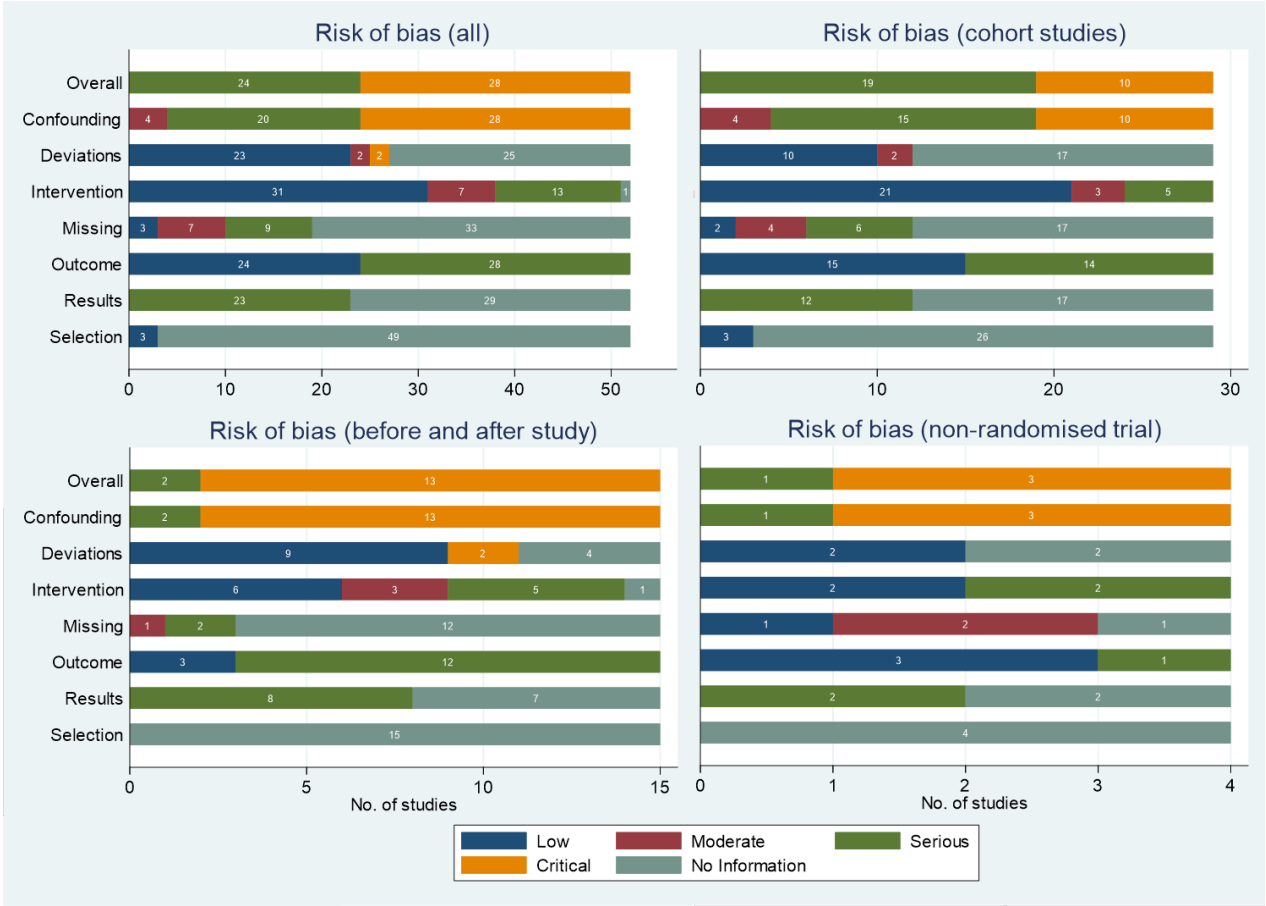

Figure 2. Bar charts showing the risk of bias ratings for each domain and the overall score, for (top left) all studies (n=52), (top right) cohort studies (n=29), (bottom left) before-and-after studies (n=15), and (bottom right) non-randomised trials (n=4). 'Overall' indicates the overall risk of bias; 'confounding' indicates bias due to confounding; 'deviations' indicates bias due to deviating from the intended interventions; 'intervention' indicates bias in classifying interventions; 'missing' indicates bias due to missing data; 'outcome' indicates bias in measuring outcomes; 'results' indicates bias in selecting which results to report; 'selection' indicates bias in selecting participants.

2.3 Study design

2.3.1 *Study design features*

Eighteen cohort studies (62%) were prospective. Eleven cohort studies (38%) used matching, of which six matched based on specified covariates, four based on propensity scores, and one based on nearest neighbour.

Three of the four non-randomised trials used a parallel design, one of which was multi-centre. Two studies allocated the intervention based on clinician judgement. One study was blinded. None of the non-randomised trials reported changing any element of their design after starting the trial.

2.3.2 *Sample size*

Two studies reported sample size calculations. The median total sample size across all studies was 888 [range: 12-190618] participants. Forty studies (77%) did not use purposefully collected data. Cohort studies had a higher median sample size (1884, [range: 89-190618]) than other study designs (Table 2).

Table 2. Sample sizes for all participants and the intervention and comparator arms in the cohort, before-and-after, non-randomised trial, and cross-sectional study designs.

Study design	N	n (%) use non-purposefully data	Median total sample size [range]	Median intervention sample size [range]	Median control sample size [range]
All study designs	51*	44 (77%)	888 [12-190618]	393 [12-25583]	467 [11-189002]
Cohort study	29	26 (90%)	1884 [86-190618]	401 [21-25583]	544 [29-189002]
Before-and-after study**	15	8 (53%)	90 [24-16571]	-	-
NR trial	4	3 (75%)	398.5 [12-7839]	235.5 [12-1795]	163.5 [11-6044]
Study design	**n**	**n (%) use non-purposefully data**	**Mean total sample size (SD)**	**Mean intervention sample size (SD)**	**Mean control sample size (SD)**
Cross-sectional	2	1 (50%)	617 (667.5)	54 (31.1)	537.5 (672.5)

*sample size was not reported for the time series analysis

**no intervention and comparator median sample size is given for the before-and-after study design as it is the same as the total.

2.3.3 *Analytical methods*

Forty-six studies (n=46/52; 88%) descriptively compared the baseline characteristics of the intervention groups. Six studies did not assess this. Twenty-three (44%) studies tested for baseline differences using a median of ten independent sample statistical tests [range: 4-36]. Three studies also tested for baseline differences in their matched cohorts.

Twenty-five studies (48%) compared the intervention and control arms with an unadjusted analysis. Forty-five studies (87%) did not account for missing data in the analysis (Table 3). Three of the six studies that did account for missing data carried the last case forward. The rest used best/worst case scenarios, simple imputation of the median, or multiple imputation.

Thirty-one studies (60%) performed additional analyses, including subgroup (n=18/31; 35%), sensitivity (n=7/31; 13%), or both (n=6/31; 12%) analyses. Ten studies stratified participants based on severity of a pre-existing condition in a subgroup analysis (e.g., diabetes/no diabetes). Sensitivity analyses included assessing the sensitivity of missing data (n=2) and matching methodology (n=3).

2.3.4 *Accounting for lack of randomisation*

Excluding the case-series and time-series studies, thirty studies (n=30/50; 60%) addressed confounding bias due to non-randomisation. The most common methods were regression adjustment (n=25/50; 50%) and matching (n=11/50; 22%). Seven studies used propensity-score methods, of which four used the propensity score for 1:1 matching, one for weighting, and one for covariate adjustment. One study conducted a marginal structural model with inverse probability weighting. None used instrumental variables to address the lack of randomisation.

No studies reported how missing data were handled in propensity-score analyses, although one reported using list-wise deletion. Propensity-score matching reduced the median total sample size from 608 participants [range: 145-11772] to 442 participants [range: 58-5814].

2.4 Reporting

Twelve studies (23%) explained why an RCT was not feasible and/or why a non-randomised study design was chosen. Seven studies wanted to study the intervention in the 'real world'. Three studies used a non-randomised design due to a rare outcome that would have required an impractically

large sample size, and one study reported investigating a long term out. One study deemed randomisation inappropriate as treatment modality was determined by the clinician and patient preference at their institution.

Twenty-four studies (46%) did not report the degree and pattern of missing data (Table 3). Of the 28 studies that mentioned missing data (54%), seven (25%) reported missing data for baseline variables and conducted a complete-case analysis. One of these seven also reported the missingness of the data.

Missing data was most commonly handled (61%) by list-wise deletion, excluding participants with incomplete data, and conducting a complete-case analysis, without reporting missing data at baseline.

Loss to follow was mentioned in 13/50 (26%) applicable studies (excluding the time series study and a before-and-after study of a public health intervention) and was unclear for 5/50 (10%) of studies. The median loss to follow-up rate was 3.4% [range: 0%-45.5%].

Table 3. Reporting and analysis methods for missing data

Missing data	**n (%)**
Not reported	24 (46.2)
Reported	28 (53.8)
Missing data excluded*	17 (60.7)
Incomplete excluded	14
Complete-case analysis	3
Missing data included*	11 (39.3)
Not reported for baseline characteristics	4
Reported for baseline characteristics	7
Accounted for in the analysis*	6 (21.4)
Last case carried forward	3
Simple (median) imputation	1
Best/worst case scenario	1
Multiple imputation	1

*denominator is studies that reported missing data (n=28)

No study reported pre-registration or a protocol. Twenty-seven studies specified a primary outcome measure (51.9%), of which one specified the time point of interest. Twenty-two studies (42%) reported different numbers of outcomes in the methods and results, of which sixteen (73%) reported results for more outcome measures than introduced in the methods. The two largest discrepancies were forty-four and fifty-seven more outcome measures in the results than in the methods. Forty studies (77%) reported an intervention effect estimate, but nine of these (23%) did not report a measure of uncertainty.

3. Discussion

3.1 Summary of results

Our systematic review evaluated the risk of bias, methodological conduct, and reporting of NRSIs. All of the included NRSIs were at serious or critical risk of bias, largely attributable to inadequately accounting for confounding bias. Most studies had poor methodological conduct and reporting and did not explain why they had conducted an NRSI instead of an RCT.

Before-and-after studies had the highest proportion of studies at critical risk of confounding bias. Though before-and-after studies are prospective studies and account time-unvarying confounding by design (participants are followed up over time and act as their own control), we found they did not consider or control for time-varying confounding.

Most studies did not include sufficient information to assess bias due to missing data and participant selection. Studies that analysed complete cases used inadequate methodology and reporting for participant selection and statistical analyses. No study mentioned pre-registration or a published protocol, and there were large differences between the numbers of outcomes reported in the methods and results, indicating many post-hoc analyses. These issues point to a high risk of selective reporting.

Cohort and before-and-after studies were the most common study designs and often used routinely collected data. Sample size was rarely reported. As most of the studies used data that had not been purposefully collected for that study, it is likely that sample sizes were based on convenience sampling. It was unclear whether studies were powered to detect meaningful intervention effects based on thresholds such as a minimally clinically important difference.

3.2 Literature

Our findings support the existing evidence that many NRSIs exhibit very high risk of bias. A recent systematic review of vitamin D supplements that included RCTs and NRSIs found that five of the seven included NRSIs had serious or critical risk of bias. The primary source of bias was also confounding (10). Another systematic review found high risk of bias due to design in all included NRSIs. They categorised these studies as having small or large flaws based on prospective design, endpoint blinding, reporting missing data, and adequate confounder control. 63% of studies were found to have large flaws (9).

Regression adjustment and propensity-score analyses can be used to remove confounding bias (1, 15, 30). However, residual confounding should be considered as these methods cannot ensure that bias has been eliminated. We found a higher proportion of prospectively designed studies and studies that performed adjusted analyses to address confounding bias, compared to other reviews (9, 10). However, most studies in this review did not blind outcome assessment, probably because they used data that had not been purposefully collected for that study, affecting selection bias.

We found a greater proportion of studies not reporting missing data than previous reviews (9, 10), affecting bias due to missing data. Poor reporting of NRSIs has been previously highlighted. Peinemann et al. found that NRSIs did not adequately report all investigated study aspects, including baseline data, potential confounding, and missing data (31).

3.3 Limitations

We used the ROBINS-I tool to assess the risk of bias in NRSIs, as recommended by the Cochrane Scientific Committee. We were limited by our lack of expert clinical knowledge in all of the clinical areas represented by the included studies. This may have affected our assessment of the risk of confounding bias. We used the presence of confounder adjustment to evaluate the risk of confounding bias, but could not assess whether the confounders used in the adjusted analyses were appropriate for the clinical question. If inappropriate confounders were used, our estimates of the risks of confounding and overall bias may have been conservative compared with the actual risks.

There is a small risk that we may have missed eligible papers in our review. However, we searched two major databases for health research publications that allow funding information to be included in the search strategy. As we selected a contemporary subset of publications from our overall search, and given findings from previous literature, it is unlikely that additional studies would change the review conclusions.

3.4 Future research

Well-conducted NRSIs can provide useful estimates of the effects of health interventions when an RCT is not ethical or feasible. However, NRSIs can only provide meaningful, robust estimates of treatment effects when sources of bias can be mitigated. Recent advances such as the 'target trial emulation' framework can help researchers achieve less biased estimates of treatment effects by explicitly specifying a hypothetical target trial and emulating its critical elements in an observational study (5, 32, 33). This approach has been shown to prevent common biases in NRSIs such as immortal time bias (34). As NRSIs rely on identifying and adjusting for a sufficient set of confounders, directed acyclic graphs should help researchers select a necessary set of confounding variables and be explicit about omitted confounders. As residual confounding is a challenging limitation for NRSIs (35, 36), sensitivity analyses and metrics such as the e-value could help readers judge the degree of robustness in NRSIs (37).

3.5 Conclusion

Most of the reviewed NRSIs were at serious or critical risk of bias, largely due to confounding. Although NRSIs have the potential to evaluate treatment effects when appropriately conducted, we found that more consideration is needed when designing and analysing these studies. In particular, data sources and whether purposeful data collection is needed should be considered to help reduce bias.

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5. Supplementary Tables

Supplementary Table 1: Web of Science search strategy

Database & platform: Web of Science Core Collection (Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI)

Date range: Timespan=2012-2018

Search date: 4 April 2018

#1 FO=(nihr OR "national institute for health research" OR "national institute of health research" OR "nat inst hlth res" OR "natl inst hlth res" OR "natl inst healthcare res")

#2 FO=(brc OR "biomedical research centre" OR "biomedical research center" OR "biomed res ctr")

#3 #1 AND #2

#4 OG=((BIOMED RES CTR AND University of Cambridge) OR (CAMBRIDGE BIOMED CTR AND University of Cambridge) OR (CAMBRIDGE BIOMED RES CTR AND University of Cambridge) OR (NIHR CAMBRIDGE BIOMED RES CTR AND University of Cambridge))

#5 OG=((BIOMED RES CTR OPHTHALMOL AND University College London) OR (COMPREHENS BIOMED RES CTR UCLH UCL AND University College London) OR (JOINT UCL UCLH COMPREHENS BIOMED RES CTR AND University College London) OR (JOINT UCLH UCL COMPREHENS BIOMED RES CTR AND University College London) OR (MOORFIELDS EYE HOSP BIOMED RES CTR AND University College London) OR (MOORFIELDS EYE HOSP BIOMED RES CTR OPHTHALMOL AND University College London) OR (MOORFIELDS EYE HOSP NIHR BIOMED RES CTR AND University College London) OR (NIHR BIOMED RES CTR OPHTHALMOL AND University College London) OR (UCH UCL COMPREHENS BIOMED CTR AND University College London) OR (UCH UCL COMPREHENS BIOMED RES CTR AND University College London) OR (UCH UCL NIHR COMPREHENS BIOMED RES CTR AND University College London) OR (UCL COMPREHENS BIOMED RES CTR AND University College London) OR (UCL INST OPHTHALMOL BIOMED RES CTR AND University College London) OR (UCL INST OPHTHALMOL NIHR BIOMED RES CTR AND University College London) OR (UCL MOORFIELDS EYE HOSP BIOMED RES CTR OPHTHALMOL AND University College London) OR (UCL WOLFSON INST BIOMED RES AND University College London) OR (UCLH UCL BIOMED RES CTR AND University College London) OR (UCLH UCL COMPREHENS BIOMED CTR AND University College London) OR (UCLH UCL COMPREHENS BIOMED RES CTR AND University College London) OR (UCLH UCL JOINT COMPREHENS BIOMED RES CTR AND University College London) OR (WOLFSON INST BIOMED RES AND University College London))

#6 OG=((BIOMED RES CTR MENTAL HLTH AND Kings College London) OR (KINGS COLL LONDON BIOMED RES CTR AND Kings College London) OR (NIHR AND Kings College London) OR (NIHR BIOMED CTR MENTAL HLTH AND Kings College London) OR (NIHR BIOMED RES CTR MENTAL HLTH AND Kings College London) OR (NIHR BIOMED RES CTR MENTAL HLTH S LONDON AND Kings College London) OR (NIHR GSTFT KCL COMPREHENS BIOMED RES CTR AND Kings College London) OR (NIHR SPECIALIST BIOMED RES CTR MENTAL HLTH AND Kings College London) OR (NIHR SPECIALIST BIOMED RES CTR MENTAL HLTH S LOND AND Kings College London) OR (RES BIOMED RES CTR MENTAL HLTH AND Kings College London))

#7 OG=((BIOMED RES CTR AGEING AGE RELATED DIS AND Newcastle University - UK) OR (NIHR BIOMED CTR AGEING LIVER THEME AND Newcastle University - UK) OR (NIHR BIOMED RES CTR AGEING AGE RELATED DIS AND Newcastle University - UK) OR (UK NIHR BIOMED RES CTR AGEING CARDIOVASC THEME AND Newcastle University - UK) OR (UK NIHR BIOMED RES CTR AGEING LIVER THEME AND Newcastle University - UK) OR (UK NIHR AND Newcastle University - UK))

#8 OG=((BIOMED RES CTR AND University of Oxford) OR (COMPREHENS BIOMED RES CTR AND University of Oxford) OR (INST HLTH RES BIOMED RES AND University of Oxford) OR (NATL INST HEALTHCARE RES OXFORD BIOMED RES CTR AND University of Oxford) OR (NATL INST HLTH RES NIHR AND University of Oxford) OR (NATL INST HLTH RES OXFORD AND University of Oxford) OR (NIHR AND University of Oxford) OR (NIHR BIOMED RES CTR AND University of Oxford) OR (NIHR OXFORD BIOMED RES AND University of Oxford) OR (NIHR OXFORD BIOMED RES CTR AND University of Oxford) OR (NIHR OXFORD COMPREHENS BIOMED RES CTR AND University of Oxford) OR (OXFORD BIOMED RES AND University of Oxford) OR (OXFORD BIOMED RES CTR AND University of Oxford) OR (OXFORD BIOMED RES CTR NIHR AND University of Oxford) OR (OXFORD NIHR BIOMED RES CTR AND University of Oxford) OR (OXFORD PARTNERSHIP COMPREHENS BIOMED RES CTR AND University of Oxford))

#9 OG=((BIOMED RES CTR MENTAL HLTH AND University of London) OR (BIOMED RES CTR OPHTHALMOL AND University of London) OR (COMPREHENS BIOMED RES CTR UCLH UCL AND University of London) OR (JOINT UCL UCLH COMPREHENS BIOMED RES CTR AND University of London) OR (JOINT UCLH UCL COMPREHENS BIOMED RES CTR AND University of London) OR (KINGS COLL LONDON BIOMED RES CTR AND University of London) OR (MOORFIELDS EYE HOSP BIOMED RES CTR AND University of London) OR (MOORFIELDS EYE HOSP BIOMED RES CTR OPHTHALMOL AND University of London) OR (MOORFIELDS EYE HOSP NIHR BIOMED RES CTR AND University of London) OR (NIHR BIOMED CTR MENTAL HLTH AND University of London) OR (NIHR BIOMED RES CTR MENTAL HLTH AND University of London) OR (NIHR BIOMED RES CTR MENTAL HLTH S LONDON AND University of London) OR (NIHR BIOMED RES CTR OPHTHALMOL AND University of London) OR (NIHR BMRC OPHTHALMOL AND University of London) OR (NIHR BRC MOORFIELDS EYE HOSP AND University of London) OR (NIHR GREAT ORMOND ST HOSP AND University of London) OR (NIHR GSTFT KCL COMPREHENS BIOMED RES CTR AND University of London) OR (NIHR SPECIALIST BIOMED RES CTR MENTAL HLTH AND University of London) OR (NIHR SPECIALIST BIOMED RES CTR MENTAL HLTH S LOND AND University of London) OR (RES BIOMED RES CTR MENTAL HLTH AND University of London) OR (UCH UCL COMPREHENS BIOMED CTR AND University of London) OR (UCH UCL COMPREHENS BIOMED RES CTR AND University of London) OR (UCH UCL NIHR COMPREHENS BIOMED RES CTR AND University of London) OR (UCL COMPREHENS BIOMED RES CTR AND University of London) OR (UCL INST OPHTHALMOL BIOMED RES CTR AND University of London) OR (UCL INST OPHTHALMOL NIHR BIOMED RES CTR AND University of London) OR (UCL MOORFIELDS EYE HOSP BIOMED RES CTR OPHTHALMOL AND University of London) OR (UCLH UCL BIOMED RES CTR AND University of London) OR (UCLH UCL COMPREHENS BIOMED CTR AND University of London) OR (UCLH UCL COMPREHENS BIOMED RES CTR AND University of London) OR (UCLH UCL JOINT COMPREHENS BIOMED RES CTR AND University of London))

#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 AD=("Biomed Engn" OR "Biomed Res Ctr" OR "BRC" OR "Biomedical Research Centre" OR "Inst Biomed Engn" OR "Biomedical Research Center")

#12 AD=("national institute for health research" OR "natl inst hlth res" OR "nat inst hlth res" OR "natl inst healthcare res" OR "national institute of health research" OR "nihr")

#13 OG=(University of Oxford OR University of Cambridge OR Newcastle University - UK OR University of Southampton OR Kings College London OR University of London OR University College London OR Imperial College London OR Institute of Cancer Research - UK)

#14 OG=(Great Ormond Street Hospital for Children NHS Foundation Trust OR Guy's & St Thomas' NHS Foundation Trust OR Moorfields Eye Hospital NHS Foundation Trust OR South London & Maudsley NHS Trust OR University Hospital Southampton NHS Foundation Trust OR University College London Hospitals NHS Foundation Trust)

#15 #11 AND #12

#16 #13 OR #14

#17 #15 AND #16

#18 #3 OR #10 OR #17

#19 WC= ("Dentistry, Oral Surgery & Medicine" or "Dermatology" or "Family Studies" or "Integrative & Complementary Medicine" or "Allergy" or "Anesthesiology" or "Audiology & Speech-Language Pathology" or "Behavioral Sciences" or "Cardiac & Cardiovascular Systems" or "Clinical Neurology" or "Critical Care Medicine" or "Emergency Medicine" or "Endocrinology & Metabolism" or "Gastroenterology & Hepatology" or "Genetics & Heredity" or "Geriatrics & Gerontology" or "Gerontology" or "Health Care Sciences & Services" or "Health Policy & Services" or "Hematology" or "Immunology" or "Infectious Diseases" or "Medical Informatics" or "Medicine, General & Internal" or "Medicine, Research & Experimental" or "Neuroimaging" or "Neurosciences" or "Nutrition & Dietetics" or "Obstetrics & Gynecology" or "Oncology" or "Ophthalmology" or "Optics" or "Orthopedics" or "Otorhinolaryngology" or "Pathology" or "Pediatrics" or "Peripheral Vascular Disease" or "Pharmacology & Pharmacy" or "Physiology" or "Primary Health Care" or "Psychiatry" or "Psychology" or "Psychology, Applied" or "Psychology, Clinical" or "Psychology, Social" or "Radiology, Nuclear Medicine & Medical Imaging" or "Respiratory System" or "Rheumatology" or "Statistics & Probability" or "Surgery" or "Transplantation" or "Tropical Medicine" or "Urology & Nephrology")

#20 SU= ("Life Sciences & Biomedicine" or "Anesthesiology" or "Cardiovascular System & Cardiology" or "Critical Care Medicine" or "Dentistry, Oral Surgery & Medicine" or "Emergency Medicine" or "Endocrinology & Metabolism" or "Gastroenterology & Hepatology" or "General & Internal Medicine" or "Genetics & Heredity" or "Geriatrics & Gerontology" or "Health Care Sciences & Services" or "Hematology" or "Immunology" or "Infectious Diseases" or "Life Sciences Biomedicine Other Topics" or "Neurosciences & Neurology" or "Nutrition & Dietetics" or "Obstetrics & Gynecology" or "Oncology" or "Ophthalmology" or "Orthopedics" or "Otorhinolaryngology" or "Pathology" or "Pediatrics" or "Pharmacology & Pharmacy" or "Physiology" or "Psychiatry" or "Radiology, Nuclear Medicine & Medical Imaging" or "Rehabilitation" or "Research & Experimental Medicine" or "Respiratory System" or "Rheumatology" or "Substance Abuse" or "Surgery" or "Transplantation" or "Tropical Medicine" or "Urology & Nephrology" or "Psychology")

#21 #19 OR #20

#22 #18 AND #21

#23 TI=("in vitro" OR "in-vitro" OR "invitro" or "cell")

#24 TI=("in vivo" OR "in-vivo" OR "invivo" or "animal*" or "cell*" or "mice" or "mouse" or "inhibitor*" or "mutation*") OR TS=("in vivo" OR "in-vivo" OR "invivo" or "animal*" or "mice" or "mouse" or "inhibitor*" or "mutation*")

#25 TI=("protocol" or "rationale")

#26 TI=("feasibility" or "pilot")

#27 TI =("qualitative" or "mixed method*" or "mixed-method*" or "interview*" or "focus group" or "focus-group" or "explor*" or "view*" or "experience*" or "narrative" or "factor" or "factors" or "concept*")

#28 TI=("systematic" or "review" or "meta" or "narrative" or "synthesis")

#29 TI=("letter" or "reply" or "comment" or "editorial")

#30 TI=("guideline*" or "case study" or "case-study")

#31 TI=("dose-finding" or "dose finding" or "adaptive dose")

#32 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31

#33 #22 NOT #32

#34 #33 Refined by: [excluding] DOCUMENT TYPES: (EDITORIAL MATERIAL OR BOOK CHAPTER OR BIOGRAPHICAL ITEM OR REVIEW OR LETTER OR CORRECTION OR REPRINT OR MEETING ABSTRACT OR PROCEEDINGS PAPER OR NEWS ITEM OR RETRACTION) AND [excluding] LANGUAGES: (GERMAN OR ROMANIAN)

Supplementary Table 2: NIHR-BRCs funded during 2012-2017.

Host organisation/NHS trust	Academic partner/University (Department)	n (%)
Cambridge University Hospitals	University of Cambridge	6 (11.5%)
Great Ormond Street Hospital for Children NHS	University College London	2 (3.9%)
Guy's and St Thomas' NHS Foundation Trust	King's College London	4 (7.7%)
Imperial College Healthcare NHS Trust	Imperial College London	4 (7.7%)
Moorfields Eye Hospital NHS Foundation Trust	UCL Institute of Ophthalmology	7(13.5%)
Newcastle upon Tyne Hospitals NHS Foundation Trust	Newcastle University - Newcastle BRC in Ageing and Chronic Disease	1 (1.9%)
Oxford University Hospitals NHS Foundation Trust	University of Oxford	10 (19.2%)
The Royal Marsden NHS Foundation	The Institute of Cancer Research	1 (1.9%)
South London and Maudsley NHS Foundation Trust	King's College London	4 (7.7%)
University Hospital Southampton NHS Foundation Trust	University of Southampton	3 (5.8%)
University College London Hospitals NHS Foundation Trust	University College London	8 (15.4%)

Supplementary Table 3. Summary of ROBINS-I assessment for each included study.

Study Title	Design	Risk of bias							
		Confounding	Selecting participants	Classifying interventions	Deviating from the intended interventions	Missing data	Measuring outcomes	Selective reporting	Overall
Early Outcomes of the New UK Deceased Donor Kidney Fast-Track Offering Scheme (1)	NR trial	Serious	NI	Serious	Low	Moderate	Low	Serious	Serious
Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study (2)	NR trial	Critical	NI	Low	Low	NI	Serious	Serious	Critical
Comparison of microbubble presence in the right heart during mechanochemical and radiofrequency ablation for varicose veins (3)	NR trial	Critical	NI	Low	NI	Moderate	Low	NI	Critical
Brand-to-generic levetiracetam switch in patients with epilepsy in a routine clinical setting (4)	NR trial	Critical	NI	Serious	NI	Low	Low	NI	Critical
The impact of social marketing campaigns on reducing mental health stigma: Results from the 2009-2014 Time to Change programme (5)	Before-and-after	Serious	NI	Moderate	NI	NI	Serious	NI	Serious
Haemodynamic changes with paracetamol in critically-ill children (6)	Before-and-after	Serious	NI	Low	Low	NI	Serious	Serious	Serious
Long-Term Outcomes of Aflibercept Treatment for Neovascular Age-Related Macular Degeneration in a Clinical Setting (7)	Before-and-after	Critical	NI	Low	Low	Moderate	Serious	NI	Critical
Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice (8)	Before-and-after	Critical	NI	Low	Critical	NI	Serious	Serious	Critical
The impact of rifaximin-alpha on the hospital resource use associated with the management of patients with hepatic encephalopathy: a retrospective observational study (IMPRESS) (9)	Before-and-after	Critical	NI	Moderate	Low	NI	Serious	NI	Critical
The efficacy of a low-fat diet to manage the symptoms of bile acid malabsorption - outcomes	Before-and-after	Critical	NI	Low	Low	Serious	Serious	Serious	Critical

in patients previously treated for cancer (10)									
Multicenter Study of 6-Month Clinical Outcomes After Descemet Membrane Endothelial Keratoplasty (11)	Before-and-after	Critical	NI	Serious	NI	NI	Serious	Serious	Critical
Effects of a smoking ban on clozapine plasma concentrations in a nonsecure psychiatric unit (12)	Before-and-after	Critical	NI	NI	Low	NI	Low	NI	Critical
Effectiveness of percutaneous tibial nerve stimulation in managing refractory constipation (13)	Before-and-after	Critical	NI	Low	Low	NI	Serious	NI	Critical
Binocular Therapy for Childhood Amblyopia Improves Vision Without Breaking Interocular Suppression (14)	Before-and-after	Critical	NI	Serious	Low	NI	Serious	Serious	Critical
30-year trends in admission rates for encephalitis in children in England and effect of improved diagnostics and measles-mumps-rubella vaccination: a population-based observational study (15)	Before-and-after	Critical	NI	Low	NI	NI	Low	NI	Critical
Early Effect of Bariatric Surgery on Urogenital Function in Morbidly Obese Men (16)	Before-and-after	Critical	NI	Serious	Low	NI	Serious	Serious	Critical
Long-Term Results of Deep Brain Stimulation of the Anterior Cingulate Cortex for Neuropathic Pain (17)	Before-and-after	Critical	NI	Serious	Critical	Serious	Serious	Serious	Critical
The UK Diabetic Retinopathy Electronic Medical Record (UK DR EMR) Users Group, Report 2: real-world data for the impact of cataract surgery on diabetic macular oedema (18)	Before-and-after	Critical	NI	Serious	Low	NI	Serious	NI	Critical
Efficacy and safety of bimatoprost in glaucoma and ocular hypertension in non-responder patients (19)	Before-and-after	Critical	NI	Moderate	NI	NI	Low	Serious	Critical
National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer (20)	Cohort	Moderate	NI	Low	NI	Low	Serious	NI	Serious

Ureteric complications in recipients of kidneys from donation after circulatory death donors (21)	Cohort	Serious	NI	Low	Low	Moderate	Serious	Serious	Serious
Does appropriate empiric antibiotic therapy modify intensive care unit-acquired Enterobacteriaceae bacteraemia mortality and discharge? (22)	Cohort	Serious	NI	Low	Moderate	NI	Low	NI	Serious
UK AMD/DR EMR REPORT IX: comparative effectiveness of predominantly as needed (PRN) ranibizumab versus continuous aflibercept in UK clinical practice (23)	Cohort	Serious	NI	Low	Low	NI	Serious	NI	Serious
Mortality and Self-Harm in Association With Clozapine in Treatment-Resistant Schizophrenia (24)	Cohort	Serious	NI	Low	Low	NI	Low	NI	Serious
Comparative Effectiveness of Step-up Therapies in Children with Asthma Prescribed Inhaled Corticosteroids: A Historical Cohort Study (25)	Cohort	Serious	NI	Low	NI	NI	Low	NI	Serious
Long-Acting beta-Agonist in Combination or Separate Inhaler as Step-Up Therapy for Children with Uncontrolled Asthma Receiving Inhaled Corticosteroids (26)	Cohort	Serious	NI	Low	Low	NI	Low	NI	Serious
Associations of Neuropsychiatric Symptoms and Antidepressant Prescription with Survival in Alzheimer's Disease (27)	Cohort	Serious	NI	Low	NI	NI	Low	NI	Serious
Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? (28)	Cohort	Serious	NI	Low	NI	NI	Serious	Serious	Serious
An analysis of the survival outcomes of simultaneous pancreas and kidney transplantation compared to live donor kidney transplantation in patients with type 1 diabetes: a UK Transplant Registry study (29)	Cohort	Serious	NI	Serious	NI	Moderate	Low	Serious	Serious
Multimodality treatment for esophageal adenocarcinoma: multi-center propensity-score matched study (30)	Cohort	Serious	NI	Low	NI	Moderate	Low	Serious	Serious

Risk of diabetes and dyslipidemia during clozapine and other antipsychotic drug treatment of schizophrenia in Iceland (31)	Cohort	Serious	NI	Low	Low	Serious	Low	NI	Serious
Survival Among Men at High Risk of Disseminated Prostate Cancer Receiving Initial Locally Directed Radical Treatment or Initial Androgen Deprivation Therapy (32)	Cohort	Serious	Low	Serious	NI	NI	Low	NI	Serious
UK National Registry Study of Kidney Donation After Circulatory Death for Pediatric Recipients (33)	Cohort	Serious	NI	Low	NI	Low	Low	NI	Serious
Transplantation of Kidneys From Donors With Acute Kidney Injury: Friend or Foe? (34)	Cohort	Serious	NI	Low	Low	Serious	Serious	NI	Serious
Bone mineral density in complete androgen insensitivity syndrome and the timing of gonadectomy (35)	Cohort	Serious	NI	Serious	Low	NI	Serious	Serious	Serious
Perinatal mortality associated with induction of labour versus expectant management in nulliparous women aged 35 years or over: An English national cohort study (36)	Cohort	Moderate	NI	Serious	NI	Moderate	Low	NI	Serious
Resource Utilization Among Glaucoma Patients in the UK Treated with Beta-Blocker and Non-Beta-Blocker Adjunctive Therapy: A Retrospective Cohort Analysis (37)	Cohort	Moderate	NI	Low	Moderate	NI	Serious	Serious	Serious
Mortality Among Men with Advanced Prostate Cancer Excluded from the ProtecT Trial (38)	Cohort	Moderate	NI	Low	Low	Serious	Low	Serious	Serious
Long-term outcome in biopsy-proven acute interstitial nephritis treated with steroids (39)	Cohort	Critical	NI	Moderate	NI	Serious	Low	Serious	Critical
Early performance-based and patientreported outcomes of a contemporary taper fit bone-conserving short stem femoral component in total hip arthroplasty (40)	Cohort	Critical	NI	Low	Low	NI	Serious	NI	Critical
Protective effect of antirheumatic drugs on dementia in rheumatoid arthritis patients (41)	Cohort	Critical	Low	Low	NI	NI	Serious	NI	Critical
Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring:	Cohort	Critical	NI	Low	Low	NI	Serious	NI	Critical

population based cohort study (42)									
Post-listing survival for highly sensitised patients on the UK kidney transplant waiting list: a matched cohort analysis (43)	Cohort	Critical	Low	Serious	NI	NI	Low	Serious	Critical
High frequency of antidrug antibodies and OPEN ACCESS association of random drug levels with efficacy in certolizumab pegol-treated patients with rheumatoid arthritis: results from the BRAGGSS cohort (44)	Cohort	Critical	NI	Low	NI	NI	Serious	NI	Critical
Robotic assisted laparoscopic radical prostatectomy following transrectal compared to transperineal prostate biopsy: surgical, oncological and functional outcomes (45)	Cohort	Critical	NI	Low	NI	Serious	Serious	NI	Critical
Right ventricular morphology and function following stage I palliation with a modified Blalock-Taussig shunt versus a right ventricle-to-pulmonary artery conduit (46)	Cohort	Critical	NI	Moderate	NI	NI	Low	Serious	Critical
Alemtuzumab dose adjusted for body weight is associated with earlier lymphocyte repletion and less infective episodes in the first year post renal transplantation - a retrospective study (47)	Cohort	Critical	NI	Moderate	NI	NI	Serious	Serious	Critical
Assessment of patient-reported outcome measures in pleural interventions (48)	Cohort	Critical	NI	Low	NI	Serious	Serious	Serious	Critical
Effect of adding a mobile health intervention to a multimodal antimicrobial stewardship programme across three teaching hospitals: an interrupted time series study (49)	Time series	Critical	NI	Low	Low	NI	Serious	NI	Critical
Influenza vaccination and risk of hospitalization in patients with heart failure: a self-controlled case series study (50)	Case series	Serious	NI	Serious	NI	NI	Low	NI	Serious
Maternal hyperglycemia in singleton pregnancies conceived by IVF may be modified by first-trimester BMI (51)	Cross-sectional	Serious	NI	Moderate	Low	Serious	Low	NI	Serious
Effect of topiramate and zonisamide on fMRI cognitive networks (52)	Cross-sectional	Critical	NI	Low	NI	NI	Low	Serious	Critical

6. References for supplementary files

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