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Treatment Effects in Randomized and Nonrandomized Studies of Pharmacological Interventions
A Meta-Analysis

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Abstract

IMPORTANCE Randomized clinical trials (RCTs) are widely regarded as the methodological benchmark for assessing clinical efficacy and safety of health interventions. There is growing interest in using nonrandomized studies to assess efficacy and safety of new drugs.

OBJECTIVE To determine how treatment effects for the same drug compare when evaluated in nonrandomized vs randomized studies.

DATA SOURCES Meta-analyses published between 2009 and 2018 were identified in MEDLINE via PubMed and the Cochrane Database of Systematic Reviews. Data analysis was conducted from October 2019 to July 2024.

STUDY SELECTION Meta-analyses of pharmacological interventions were eligible for inclusion if both randomized and nonrandomized studies contributed to a single meta-analytic estimate.

DATA EXTRACTION AND SYNTHESIS For this meta-analysis using a meta-epidemiological framework, separate summary effect size estimates were calculated for nonrandomized and randomized studies within each meta-analysis using a random-effects model and then these estimates were compared. The reporting of this study followed the Guidelines for Reporting Meta-Epidemiological Methodology Research and relevant portions of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.

MAIN OUTCOME AND MEASURES The primary outcome was discrepancies in treatment effects obtained from nonrandomized and randomized studies, as measured by the proportion of meta-analyses where the 2 study types disagreed about the direction or magnitude of effect, disagreed beyond chance about the effect size estimate, and the summary ratio of odds ratios (ROR) obtained from nonrandomized vs randomized studies combined across all meta-analyses.

RESULTS A total of 346 meta-analyses with 2746 studies were included. Statistical conclusions about drug benefits and harms were different for 130 of 346 meta-analyses (37.6%) when focusing solely on either nonrandomized or randomized studies. Disagreements were beyond chance for 54 meta-analyses (15.6%). Across all meta-analyses, there was no strong evidence of consistent differences in treatment effects obtained from nonrandomized vs randomized studies (summary ROR, 0.95; 95% credible interval [CrI], 0.89-1.02). Compared with experimental nonrandomized studies, randomized studies produced on average a 19% smaller treatment effect (ROR, 0.81; 95% CrI, 0.68-0.97). There was increased heterogeneity in effect size estimates obtained from nonrandomized compared with randomized studies.

(continued)

Key Points

Question How do treatment effects for drugs compare when obtained from nonrandomized vs randomized studies?

Findings In this meta-analysis of 2746 primary studies in 346 meta-analyses using a meta-epidemiological framework, there was no strong evidence of systematic overestimation or underestimation of treatment effects. However, disagreements between nonrandomized and randomized studies were beyond chance in 15.6% of meta-analyses, and the 2 study types led to different statistical conclusions about the therapeutic effect of drug interventions in 37.6% of meta-analyses.

Meaning These findings suggest that relying on nonrandomized studies as substitutes for randomized clinical trials may introduce additional uncertainty about the therapeutic effects of new drugs.

+ Supplemental content

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In this meta-analysis of treatment effects of pharmacological interventions obtained from randomized and nonrandomized studies, there was no overall difference in effect size estimates between study types on average, but nonrandomized studies both overestimated and underestimated treatment effects observed in randomized studies and introduced additional uncertainty. These findings suggest that relying on nonrandomized studies as substitutes for RCTs may introduce additional uncertainty about the therapeutic effects of new drugs.

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Introduction

Randomized clinical trials (RCTs), in which participants are randomly assigned to treatments, are widely regarded as the methodological benchmark for assessing the clinical efficacy and safety of drugs.[1,2] When designed, conducted, analyzed, and reported adequately, RCTs minimize bias and can therefore provide regulatory bodies, payers, clinicians, and patients with robust evidence on what treatments work. In contrast with RCTs, treatment assignment in nonrandomized studies (NRSs) is influenced by the patient, the clinician, or the setting. Despite their higher generalizability, NRSs are more susceptible to bias due to confounding and to selection bias.[3] Consequently, discrepancies may emerge between the results of RCTs and NRSs.

The internal validity of NRSs has recently attracted renewed interest due to a growing enthusiasm for using NRSs when making decisions about new drugs. Drug regulatory agencies and health technology assessment bodies in the US and Europe are actively exploring the feasibility and validity of utilizing NRSs, including data collected outside of clinical trials (ie, observational data).[4-7] While NRSs have traditionally been used as a complement to RCTs, there is interest in potentially substituting or replacing RCTs with well-conducted NRSs.[8]

Previous research[9-18] has examined the comparability of treatment effect size estimates between RCTs and NRSs, yielding varied findings. However, the most recent comprehensive review,[12] encompassing 45 clinical questions and 408 individual studies, was published more than 20 years ago. Most published studies focused on selected therapeutic areas, limiting the generalizability of their findings. Most recently, replication studies for highly selected clinical questions with good data availability have identified a general alignment between RCTs and their nonrandomized emulations, although disagreements in results were observed in approximately one-quarter of the cases.[19] A comprehensive review of potential discrepancies between treatment effects of RCTs and NRSs is needed. In this study, our primary objective was to assess and compare treatment effects of the same drug when evaluated in NRSs vs RCTs.

Methods

The study protocol for this meta-analysis using a meta-epidemiological framework was registered on PROSPERO (CRD42018062204). The reporting of this study followed the Guidelines for Reporting Meta-Epidemiological Methodology Research by Murad et al[20] and relevant portions of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.[21]

Identification of Clinical Questions

We identified clinical questions for which meta-analyses including at least 1 RCT and 1 NRS were conducted to obtain estimates of the effectiveness of pharmacological treatments as defined in the participants, interventions, comparators, and outcomes (PICO) framework. Clinical questions with

potentially eligible meta-analyses were identified through 3 sources: (1) a database search in MEDLINE (via PubMed) for existing meta-epidemiological studies comparing RCTs with NRSs, (2) a database search in MEDLINE (via PubMed) for systematic reviews including both RCTs and NRSs, and (3) a review of all systematic reviews indexed in the Cochrane Database of Systematic Reviews that included both RCTs and NRSs. We only included records published from 2009 to 2018 to cover clinical questions from the last decade (our original plan was to cover 2000-2018). Details of the database searches are available in eAppendix 1 in Supplement 1.

We included only clinical questions where RCTs and NRS contributed to a single meta-analytic estimate, following the within–meta-analyses approach for meta-epidemiological studies.[22] We therefore capitalized on the subject matter expertise of researchers conducting meta-analysis in their area of interest and who judged RCTs and NRSs to be sufficiently similar to each with other with respect to study participants, intervention, comparator, and outcome to provide evidence on a drug's benefits or harms. Systematic reviews where RCTs and NRS were meta-analyzed separately were excluded.

Potential source systematic reviews containing such meta-analyses, as identified through database searches, were screened at the title and abstract level independently by 2 reviewers (M.S.K. and a research assistant). Conflicting decisions were resolved by consensus. Full texts of remaining records were screened by 1 reviewer (M.N. or M.S.K.), after double screening of a 10% sample of records showed almost perfect agreement ($\kappa = 0.85$).

For each included source systematic review, we selected 1 meta-analysis for data extraction. We extracted data for the meta-analysis of the primary outcome. In cases where the meta-analysis of the primary outcome did not include both RCTs and NRSs, we extracted the next most prominently presented outcome with the highest number of contributing RCTs and NRSs. We identified possible double-counting of original studies included in the identified meta-analyses on the basis of unique identifiers.[23] While original studies were eligible to contribute to several meta-analyses (eg, meta-analyses of the same intervention but measuring different outcomes), within each meta-analysis, only unique individual studies were included.

Data Extraction

Meta-analysis–level and study-level information were extracted from source systematic reviews using a prespecified spreadsheet by a single researcher (M.N.). We used a guidebook with instructions for each item and data extraction was checked by a second researcher (M.S.K.) for approximately 10% of meta-analyses. Where possible, we used prespecified categories for study design characteristics (eAppendix 2 in Supplement 1).

We based the categorization of study designs on typologies used in previous meta-epidemiological reviews.[13,24] We distinguished between RCTs and NRSs, where the former was defined by the use of a random sequence to allocate study participants to intervention and control groups, and the latter by the absence of such a random sequence. We relied on the assessment made by the authors of the source reviews whether a study should be categorized as an RCT or NRS.

For NRSs, we further distinguished between experimental and observational designs, a categorization also applied by others.[13,25-27] Experimental NRSs are studies in which the investigator has some control over study conditions, including the allocation of participants into treatment and control groups (eg, clinical trials where the allocation mechanism falls short of true randomization or where allocation is by patient or physician preference). Observational NRSs lack the experimental intention of experimental NRSs, exploiting natural variation in the use of interventions to evaluate patient outcomes.

Statistical Analysis

Main Analysis

All effect size estimates were converted into log odds ratios (ORs) and coded so that an OR less than 1 indicated a beneficial effect of the drug under investigation. For meta-analyses reporting

continuous outcomes, we first converted these into standardized mean differences (SMDs)[28] and then to ORs.[29] For meta-analyses with active comparators, we identified which drug was considered experimental through the descriptions provided by the authors of the source review or through web searches in cases where this could not be determined with certainty from the source review.

In descriptive analyses, we first plotted the summary estimates for NRSs and RCTs conducted for the same clinical question and reported the number of meta-analyses for which the NRS and RCT effect size estimates, respectively, were more favorable. Within each meta-analysis, we calculated the summary estimates and 95% CIs of NRSs and RCTs, respectively, using a random-effects Hartung-Knapp-Sidik-Jonkman meta-analysis model to take into account between-study heterogeneity.[30,31]

We reported 4 measures of discrepancy. First, we reported the frequency of substantial disagreement, operationalized as the summary OR obtained from one type of study being twice as favorable as the other (ie, OR obtained from one study type was at most one-half the OR obtained from the other study type).[12] We also considered alternative cutoff values (differences in summary OR by 50% and 10%). Second, we reported the frequency of discrepancies in the summary logOR being beyond what would be expected by chance alone at the 5% significance level.[12] We compared the summary logORs for the NRS and RCT for each meta-analysis using the equation:

$$\log_{ROR} = \log(OR_{NRS}) - \log(OR_{RCT}),$$

where ROR is the ratio of odds ratios, and then computed a 95% CI using standard error (SE) of logROR using the equation:

$$SE(\log_{ROR}) = \sqrt{SE(OR_{NRS})^2 + SE(OR_{RCT})^2}$$

and compared these CIs with the null value of logROR = 0. Third, we reported the frequency of meta-analyses for which the summary estimates of NRSs and RCTs, respectively, led to different statistical conclusions. A different statistical conclusion was considered to be reached if one study type produced a meta-analytic result with 95% CI excluding an OR of 1 in a particular direction and the other study type did not. Contradictory treatment effects were considered to occur when a 95% CI for the meta-analytic OR for NRSs was entirely less than 1 while that for the meta-analytic OR for an RCTs was entirely greater than 1, or vice versa. This analysis did not account for differences in sample sizes between the 2 study types. Fourth, in the main, prespecified analysis, we quantified discrepancies between NRSs and RCTs through a 2-stage meta-analysis to obtain RORs for treatment effects obtained from NRSs vs RCTs.[32] The analysis was implemented in a bayesian framework, with noninformative prior distributions for the discrepancy of treatment effects between NRS and RCTs.[33] We also quantified the variation of discrepant treatment effects between NRS and RCT results across meta-analyses using the between–meta-analysis SD in discrepancies (φ) and the variation of discrepancies across studies within meta-analyses using the between-study SD in discrepancies (κ).[34,35] These measures indicate variation in effect size estimates obtained from different study designs; higher values indicate a wider spread in the magnitude of discrepancies between the 2 study types across meta-analyses (φ) and across individual studies within meta-analyses (κ).

Other measures for assessing discrepancies in treatment effects exist, such as correlation and concordance coefficients and the absolute ROR.[10,12,14,15,17,34,36-38] We focused on measures that we deemed important from a clinical or regulatory decision-making perspective (ie, that provide estimates of both absolute and relative discrepancies, potential differences in statistical conclusions drawn, and direction of deviation).

Analyses were implemented in Stata version 13.1 (StataCorp) and WinBUGS version 1.4.3 (Imperial College and Medical Research Council). Analysis was conducted from October 2019 to July 2024.

Subgroup and Sensitivity Analyses

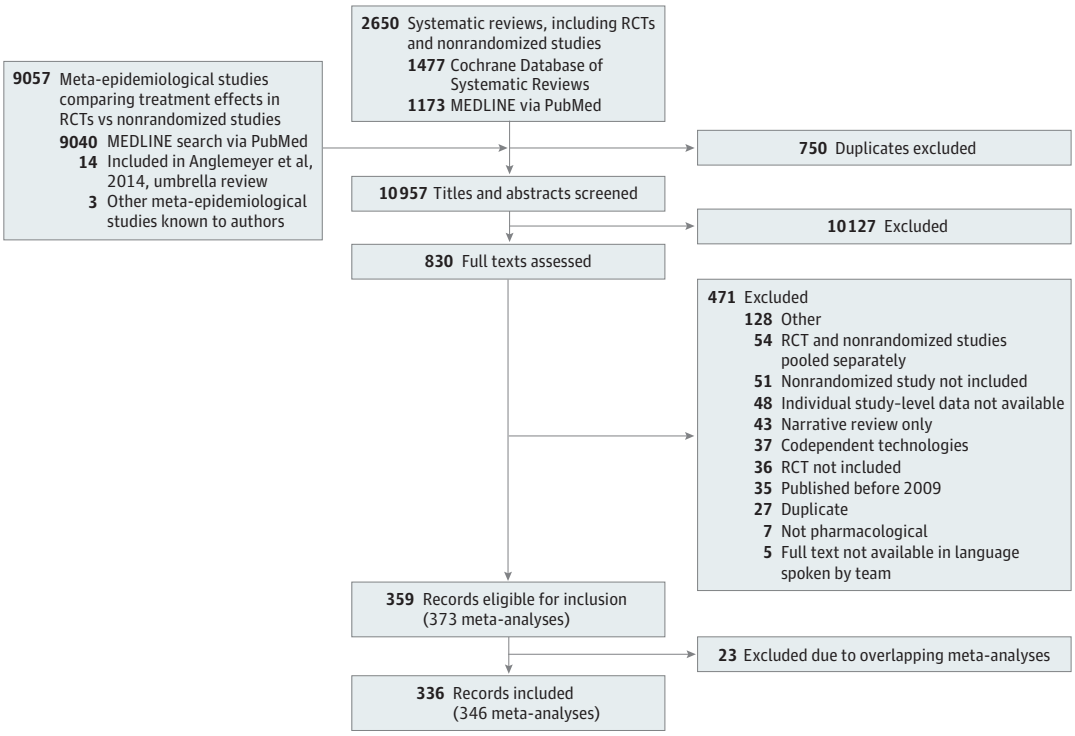
Subgroup analyses were conducted for prespecified characteristics at the meta-analysis level and study level. Additional subgroup analysis to explore heterogeneity in the discrepancy in treatment effects in RCTs vs NRSs was conducted by data source of NRSs, type of control in NRSs, therapeutic area, how well matched RCTs and NRSs included in a meta-analysis were, and methodological quality of source meta-analyses. Study-level characteristics were often not reported in detail in source meta-analyses, resulting in small sample sizes for most subgroups. We therefore only report the results of subgroup analyses for selected characteristics (details in eAppendix 3 in Supplement 1). In a post hoc sensitivity analysis, we restricted our sample to meta-analyses where NRSs were published before the first RCT.

Results

A total of 10 957 records were screened at the title and abstract level, and 830 were reviewed in full, resulting in a total of 336[14,39-373] included records (**Figure 1**). These 336 records contributed 346 unique meta-analyses (2 meta-epidemiological studies[14,174] contributed more than 1 meta-analysis), with 2746 contributing individual studies (median [range] 3 [1-92] RCTs with a median [range] 100 [5-235 600] participants and median [range] 2 [1-44] NRSs with a median [range] 195 [6-2 145 593] participants per meta-analysis). Characteristics of included meta-analyses are presented in eTable 1 in Supplement 1 and summarized in the **Table**.

Discrepancies between treatment effects are displayed in **Figure 2**, which shows the effect size estimates obtained from RCTs and NRSs for all 346 meta-analyses. NRSs gave a more favorable effect (ie, a lower summary OR) for 186 meta-analyses (53.8%), and RCTs gave a more favorable effect for 158 meta-analyses (45.7%). Results for all measures of discrepancy are summarized in the eTable 2 in Supplement 1. For 121 meta-analyses (35.0%), the OR obtained from one study type was twice as

Figure 1. Flowchart of Selection of Meta-Analyses for Meta-Epidemiological Study



RCT indicates randomized clinical trial.

large or more (or one-half the OR or less) than the other, including 65 (18.8% of all meta-analyses) where NRSs indicated a substantially more beneficial effect and 56 (16.2%) where RCTs indicated a substantially more beneficial effect (Figure 2). Disagreement between study types was beyond chance for 54 meta-analyses (15.6%), including 30 (8.7%) where the OR obtained from NRSs was more beneficial, and 24 (6.9%) where the OR obtained from RCTs was more beneficial. In a subgroup analysis that only included experimental NRSs, the OR from one study type was twice as favorable as the other for 55 meta-analyses (45.1% of all meta-analyses including experimental NRSs), including 36 (29.5%) where the OR obtained from experimental NRSs was one-half the OR of RCTs or less. Disagreement between study types was beyond chance for 31 meta-analyses (25.4%) with

Table. Characteristics of Meta-Analyses Including Both Nonrandomized and Randomized Studies

Characteristic	Meta-analyses, No. (%) (N =346)
Comparator	
Active	94 (27.2)
Placebo or no treatment	226 (65.3)
Both active and placebo-controlled studies	26 (7.5)
Outcome type[a]	
Mortality	59 (17.1)
Other objective outcome	158 (45.7)
Subjective outcome	126 (36.4)
Different types of outcomes	3 (0.9)
Therapeutic area by WHO ATC first level categorization	
Anti-infective for systemic use	66 (19.1)
Blood and blood forming organs	64 (18.5)
Cardiovascular system	45 (13.0)
Antineoplastic and immuno-modulating agents	43 (12.4)
Nervous system	27 (7.8)
Alimentary tract and metabolism	23 (6.6)
Systemic hormonal preparations	19 (5.5)
Genito-urinary system and sex hormones	14 (4.0)
Other categories combined	45 (13.0)
Risk of bias across NRSs in a meta-analysis[b]	
Low median risk of bias	96 (27.7)
Moderate median risk of bias	61 (17.6)
High median risk of bias	123 (35.5)
No risk of bias information	66 (19.1)
Risk of bias across RCTs in a meta-analysis[b]	
Low median risk of bias	90 (26.0)
Moderate median risk of bias	95 (27.5)
High median risk of bias	103 (29.8)
No risk of bias information	58 (16.8)
Median publication year of studies included in a meta-analyses	
Before 2000	56 (16.2)
2000-2009	131 (37.9)
2010 and later	159 (46.0)
Matching quality of RCTs and NRSs in a meta-analysis[c]	
High (score of 10-12 of 12)	111 (32.1)
Moderate (score of 7-9 of 12)	166 (48.0)
Low (score of 4-6 of 12)	69 (19.9)
Timing of evidence generation	
NRS published before first RCT	146 (42.2)
First RCT published before NRS	169 (48.8)
First NRS and first RCT published in the same year	31 (9.0)

Abbreviations: NRS, nonrandomized study; RCT, randomized clinical trial; WHO ATC, World Health Organization Anatomical Therapeutic Chemical classification system.

[a] Outcomes were categorized according to the extent to which their assessment could be influenced by investigators' judgment.[374] For composite outcomes, we used the most subjective component.

[b] The proportion of meta-analyses for which the median of the risk of bias scores of NRSs or RCTs included in that meta-analysis was low, moderate, or high. Risk of bias assessments were extracted from source meta-analyses and standardized as low, moderate, or high.

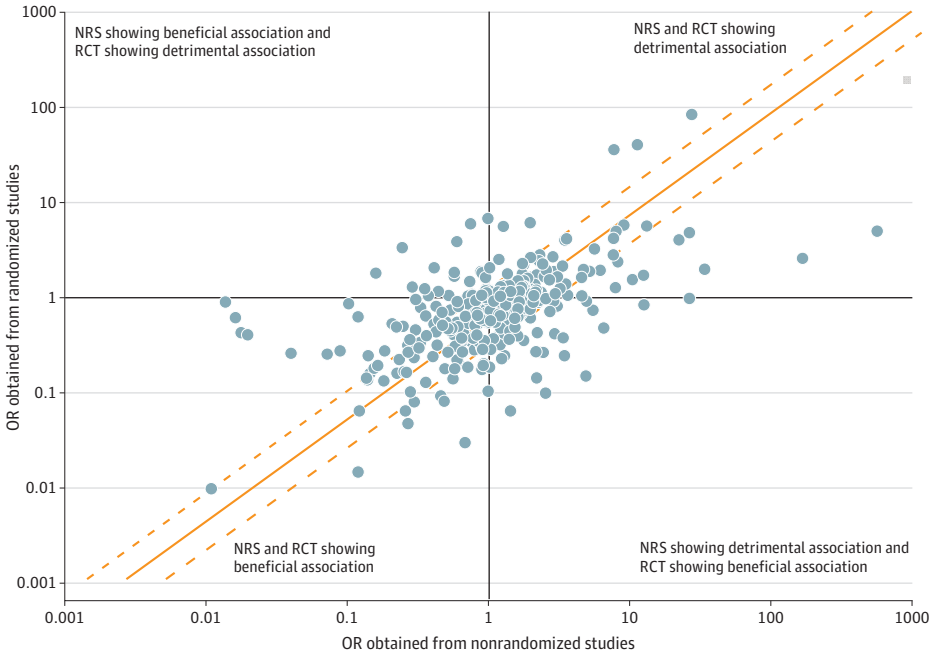
[c] The proportion of meta-analyses for which the quality of the matching between NRSs and RCTs included in the meta-analysis was deemed high, moderate, or low according to how closely aligned each of the 4 PICO components (participants, intervention, comparator, outcome) were between NRSs and RCTs. A score from 1 to 3 was assigned for each of the 4 PICO components according to how well NRSs and RCTs included in the same meta-analysis were matched.

experimental NRS. The subgroup analysis for observational studies showed lower frequencies of discrepancies (eTable 2 in Supplement 1).

RCTs and NRSs led to different statistical conclusions about the therapeutic benefit of pharmacological interventions in 130 meta-analyses (37.6%) and 216 (62.4%) reached the same statistical conclusion, based on comparing 95% CIs around the OR from either study type with a null effect (**Figure 3**). In 69 meta-analyses (19.9%), NRSs showed a favorable effect while evidence obtained from RCTs was inconclusive and in 33 meta-analyses (9.5%), RCTs showed a favorable effect while the NRS evidence was inconclusive. Contradictory treatment effects were observed in 4 meta-analyses (1.2%).

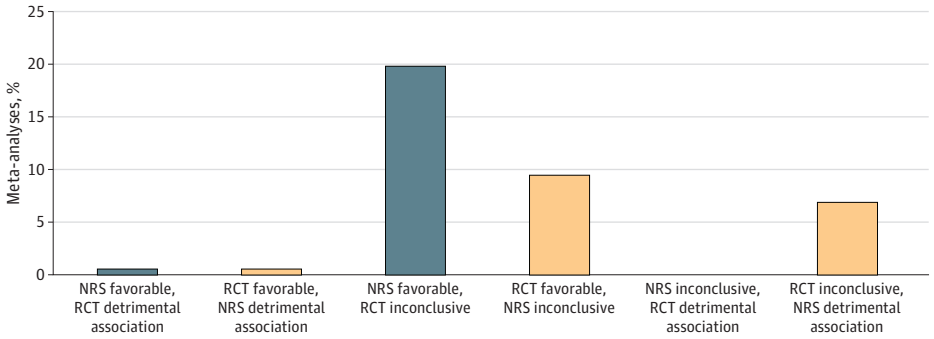
In the main analysis, there was no evidence of a difference between effect size estimates obtained from NRSs vs RCTs on average when combining discrepancies across all 346 meta-analyses (ROR, 0.95; 95% credible interval [CrI], 0.89-1.02) (**Figure 4**). In subgroup analyses, effect size

Figure 2. Agreement of Summary Effect Size Estimates Obtained From Randomized and Nonrandomized Studies for 346 Clinical Questions



Each circle shows the summary odds ratio (OR) obtained from a meta-analysis of randomized clinical trials (RCTs; vertical axis) and nonrandomized studies (NRSs; horizontal axis) for 1 clinical question. An OR less than 1 indicates a beneficial effect. The solid orange line indicates perfect agreement (exact same summary OR obtained from randomized and nonrandomized studies) and the dashed orange lines indicate substantial disagreement (OR obtained from randomized studies is at most one-half of the OR obtained from nonrandomized studies, or vice versa). Results for alternative cutoff values for substantial disagreement are provided in eTable 2 in Supplement 1. Circles in the upper left quadrant show meta-analyses where NRS evidence indicates a beneficial effect (summary OR <1) and RCT evidence a detrimental effect (summary OR >1), and circles in the bottom right quadrant show meta-analyses where NRS evidence indicates a detrimental effect (summary OR >1) and RCT evidence a beneficial effect (summary OR <1). Circles in the upper right quadrant show meta-analyses where both NRS and RCT evidence indicate a detrimental effect; circles above the solid orange line indicate a larger detrimental effect size in RCTs and circles below the solid orange line indicate a larger detrimental effect size in NRSs. Circles in the bottom left quadrant show meta-analyses where both NRS and RCT evidence indicate a beneficial effect; circles above the solid orange line indicate a larger beneficial effect size in NRS and circles below the solid orange line indicate a larger beneficial effect size in RCTs.

Figure 3. Discrepancies in Statistical Conclusions About Therapeutic Benefit of Pharmacological Interventions Based on Evidence Obtained From Nonrandomized Studies (NRSs) or Randomized Clinical Trials (RCTs)



The figure shows proportions of meta-analyses based on the statistical conclusions about the existence of a therapeutic benefit drawn from NRS or RCT evidence. A favorable or detrimental effect was deemed to exist if the 95% CI of the summary odds ratio did not include 1. Evidence was considered inconclusive if the 95% CI of the summary odds ratio included 1.

estimates obtained from experimental NRSs were more favorable compared with RCTs (ROR, 0.81; 95% CrI, 0.68-0.97), overestimating RCT estimates by 19%, while no difference was observed between observational NRS and RCTs (ROR, 0.98; 95% CrI, 0.87-1.06).

Variation in the discrepancy of treatment effects was present between studies within meta-analyses (κ = 0.22) and between meta-analyses (φ = 0.26). Variation between meta-analyses was reduced for meta-analyses measuring mortality (φ = 0.11) compared with other objective outcomes (φ = 0.34) or subjective outcomes (φ = 0.28). There were no systematic differences in between-meta-analysis variation (φ) or within-meta-analysis variation (κ) for the other characteristics at meta-analysis level.

Study-level data regarding analytical methods and data sources used in NRSs were only available for a subset of meta-analyses. Between-meta-analysis variation (φ) and within-meta-analysis variation (κ) were reduced for studies using propensity score methods compared with other analytical methods (eFigure in Supplement 1).

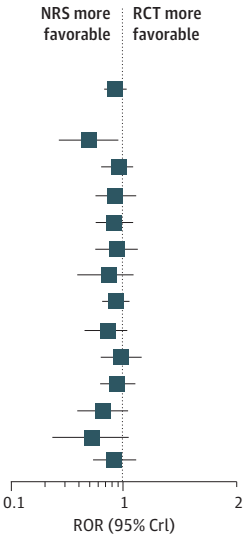
In 146 meta-analyses (42.2%), the first NRS was published before the first RCT. In this subset of meta-analyses, findings were consistent with the overall sample (eTable 2 in Supplement 1). In 53 of the 146 meta-analyses (36.3%), the summary OR was twice as favorable for one study type vs the other; in 31 meta-analyses (21.2%), the discrepancy in summary OR was beyond chance, while 50 (34.2%) reached different statistical conclusions and the ROR was 0.95 (95% CrI, 0.83-1.08) (Figure 4).

Discussion

This meta-analysis of 346 clinical questions using a meta-epidemiological framework did not uncover any systematic underestimation or overestimation of treatment effects in NRSs when compared with RCTs. However, this overall finding masks substantial variability in the observed differences between treatment effects derived from the 2 study types. A considerable number of meta-analyses exhibited discrepancies in effect size estimates, with some cases showing effect size estimates differing by a factor of 2 or more. Estimates of the variation in discrepancies show that decision-makers face uncertainty around both the direction and magnitude of potential disagreement between RCTs and NRSs; NRSs both overestimated and underestimated treatment effects observed in randomized studies.

Figure 4. Results of Meta–Meta-Analytic Comparison

Analysis	ROR (95% CrI)	φ	κ	MAs (studies), No. (No.)
Main analysis				
NRS vs RCT	0.95 (0.89-1.02)	0.26	0.22	346 (2924)
Subgroup analyses				
Experimental NRS vs RCT	0.81 (0.67-0.97)	0.33	0.34	122 (933)
Observational NRS vs RCT	0.98 (0.87-1.06)	0.26	0.22	227 (1943)
Mortality outcome	0.95 (0.84-1.08)	0.11	0.24	59 (474)
Other objective outcome	0.95 (0.85-1.06)	0.34	0.18	161 (1426)
Subjective outcome	0.97 (0.84-1.09)	0.28	0.28	126 (1008)
Active comparator	0.91 (0.76-1.07)	0.29	0.18	120 (853)
Placebo or no treatment	0.95 (0.88-1.04)	0.28	0.24	252 (2071)
Good match RCT-NRS	0.91 (0.79-1.03)	0.22	0.24	111 (842)
Moderate match RCT-NRS	0.98 (0.87-1.12)	0.41	0.14	166 (1264)
Low match RCT-NRS	0.96 (0.87-1.08)	0.17	0.24	69 (818)
Top journals only	0.88 (0.76-1.03)	0.33	0.13	118 (938)
Cochrane reviews only	0.83 (0.65-1.03)	0.41	0.19	78 (665)
NRS published before first RCT	0.95 (0.83-1.08)	0.42	0.17	146 (787)



The figure shows the ratio of odds ratios (ROR) comparing effect size estimates obtained from nonrandomized studies (NRSs) with effect size estimates obtained from randomized clinical trials (RCTs) and heterogeneity parameters (φ, between–meta-analysis heterogeneity; κ, increase in within–meta-analysis heterogeneity). Results are shown for all meta-analyses, followed by subgroup analyses by type of NRS, different types of outcomes, types of comparators, matching quality of RCTs and NRSs in the same meta-analysis, and high-quality publications. MA indicates meta-analyses.

Our study extends previous research investigating the comparability of treatment effects derived from RCTs and NRSs.[18] In particular, it provides findings across a broad range of therapeutic areas, reflecting how NRSs were designed and implemented for the clinical questions included and quantifies uncertainty associated with treatment effects derived from NRSs. Previous meta-epidemiological reviews yielded mixed results,[9-13] with varying factors such as outcome types,[24] study timing,[14] and analytical methods in NRSs contributing to discrepancies across reviews.[15,18,375,376] In our study, 37.6% of meta-analyses reached different statistical conclusions regarding the effectiveness of a drug depending on the type of study design considered, and 62.4% reached the same statistical conclusion. This finding broadly aligns with a recent study[19] that sought to emulate highly selected RCTs using administrative data, yielding concordant conclusions for 56% of emulated trials. Our approach was different from this study[19] and other observational studies[377] aiming to emulate RCTs by design using the target trial approach. By applying strict criteria to emulate RCTs, these observational studies aim to obtain the same estimand of effectiveness as the target trial. Other NRSs do not necessarily aim to replicate RCTs, and discrepancies in effect size estimates may reflect differences in study design, implementation, and populations. From a decision-maker's perspective, what matters is the availability of clinical evidence; in situations with uncertainty about the effectiveness of a treatment, NRSs of any design are likely to inform decision-making. Target trial emulation studies apply advanced methodological standards, but there are important data limitations to implement them.[378] While they are becoming more common,[379] they represent a small subset of all NRSs evaluating treatment effects. It is therefore important to understand how the body of evidence from NRSs overall compares with evidence obtained from RCTs.

We also provide novel evidence on how different types of study designs, analytical methods, and data used in NRSs perform when compared against RCTs. We found that effect size estimates obtained from experimental NRSs were systematically more favorable than those obtained from RCTs (overestimating RCT estimates by 19%). Experimental NRSs share important validity traits with RCTs, such as a controlled environment for administering the treatment and strict participant inclusion criteria. Nevertheless, the absence of random participant allocation in these studies can introduce bias through confounding. Experimental NRSs showed at least twice as favorable treatment effects as RCTs for 45.1% of meta-analyses.

Our study has important policy implications. NRSs are playing an increasingly important role in influencing decisions about the approval and reimbursement of new drugs.[380-383] Between 2015 and 2017, approximately 18% of new drugs gained approval in the US based on NRSs, up from just 6% between 1995 and 1997.[384] In draft guidance, the US Food and Drug Administration FDA names observational data as potentially suitable evidence for drug approval, replacing the previously used standard of 2 independent clinical studies.[385] It is therefore important to understand the benefits and risks of relying on NRSs for the evaluation of new drugs. While we found overall no systematic difference in treatment effects obtained from randomized and observational studies, there was considerable disagreement about therapeutic benefit (eTable 2 in Supplement 1).

Our study has implications for practice. Although RCTs are the mainstay of clinical practice guidelines, there are valid concerns about their cost and complexity.[386] RCTs may also be at high risk of bias due to problems with their design, conduct, analysis, and reporting.[387] Despite these concerns, our findings underline their importance because the conclusions about a drug's effect may differ when based on NRSs. In our study, the statistical conclusions about a drug's treatment effect were different for almost 4 in 10 clinical questions. In the past, medical reversals occurred because RCTs provided conclusive evidence about the benefits and harms of long-standing medical practices that were based on evidence obtained from NRSs.[388-392] Yet, there appears to be a limited effort to simplify the design and conduct of RCTs. As the push toward NRSs gains more traction, it could potentially impede the necessary progress required to improve the feasibility of RCTs.[393]

Limitations

This study has limitations. This is an observational study which limits causal interpretation of results.[22] We included 346 distinct clinical questions that were the subject of meta-analyses published from 2009 to 2018. While this represents, to our knowledge, the largest sample of clinical questions in a meta-epidemiological study comparing RCTs and NRSs, more recent clinical questions, in particular those relating to COVID-19,[17] were not included.

We included only meta-analyses where researchers combined both RCTs and NRSs in the same meta-analysis. While the 2 designs may not study the same estimand, the fact that they are pooled in the same meta-analysis suggests that the researchers considered them both to provide relevant evidence for decision-makers about whether the treatment is effective or harmful. It is therefore important to understand how their effect size estimates compare. The methodological decision to include meta-analyses where RCTs and NRSs were combined likely resulted in a sample more representative of clinical questions with overall limited levels of evidence (otherwise, only RCTs would be expected to be included in a meta-analysis). Including both study types in the same meta-analysis may also reflect limited methodological understanding of the authors of source meta-analyses, but our conclusions did not change when restricting our sample to meta-analyses conducted by Cochrane groups or those published in high-impact journals. Excluding clinical questions where researchers determined that there were substantial differences between the 2 study types—possibly due to observed differences in results—may have resulted in an underestimation of the true difference between treatment effects obtained from RCTs and NRSs.

Conclusions

In this meta-analysis using a meta-epidemiological framework, we found substantial disagreements between nonrandomized and randomized studies about the magnitude of effect and statistical conclusions about the therapeutic effect of pharmacological interventions for a large subset of clinical questions. While there was overall no systematic difference in effect size estimates obtained from NRSs vs RCTs, experimental NRSs studies produced 19% larger treatment effects compared with RCTs. Our findings suggest that caution is warranted when relying on NRSs as substitutes for RCTs.

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SUPPLEMENT 1.

eAppendix 1. Search Strategy
eAppendix 2. Extracted Data From Source Meta-Analyses
eAppendix 3. Subgroup Analyses
eReferences.
eTable 1. Characteristics of Included Meta-Analyses
eTable 2. Results for Measures of Discrepancy Between Nonrandomized Studies and RCTs
eFigure. Results From Additional Subgroup Analyses for Study-Level Characteristics

SUPPLEMENT 2.

Data Sharing Statement