Leiden University
Medical Center

Real-world evidence using routinely collected health data

when is the evidence convincing?

Rolf H.H. Groenwold

10 January 2023

Clinical

Demographics, EHR Data, Lab Test Results, Diagnoses, Procedures, Pathology/ Histology Data, Radiology Images, Microbiology Data, Provider Notes, Admission/ Discharge and Progress Reports, Performance Status

Medication

Medication Orders, Administration (Dose, Route, NDC/RxNorm codes), Concomitant Therapies, Point of Sale Data, (Prescription & OTC) Prescription Refill, Allergies

Claims

Medical Claims, Prescription Drug Claims, Other Drug and Treatment Use Data

Molecular Profiling

Genomic and Genetic Testing Data (SNPs/Panels), Multi-Omics Data (Proteomics, Transcriptomics , Metabonomics, Lipidomics), Other Biomarker Status

Family History

Historical Data on Health Conditions and Allergies Relating to Patient and Extended Family, Smoking Status, Alcohol Use

Mobile Health

Fitness Trackers, Wearable Devices, Other Health Apps Measuring Activity and Body Function

Environmental

Climate Factors, Pollutants, Infections, Lifestyle Factors (diets, stress), Other Environmental and Occupational Sources

Patient Reported

Patient Reported Outcomes, Surveys, Diaries (diets, habits), Personal Health Records, Adverse Event Reporting, Quality of Life Measures

Social Media

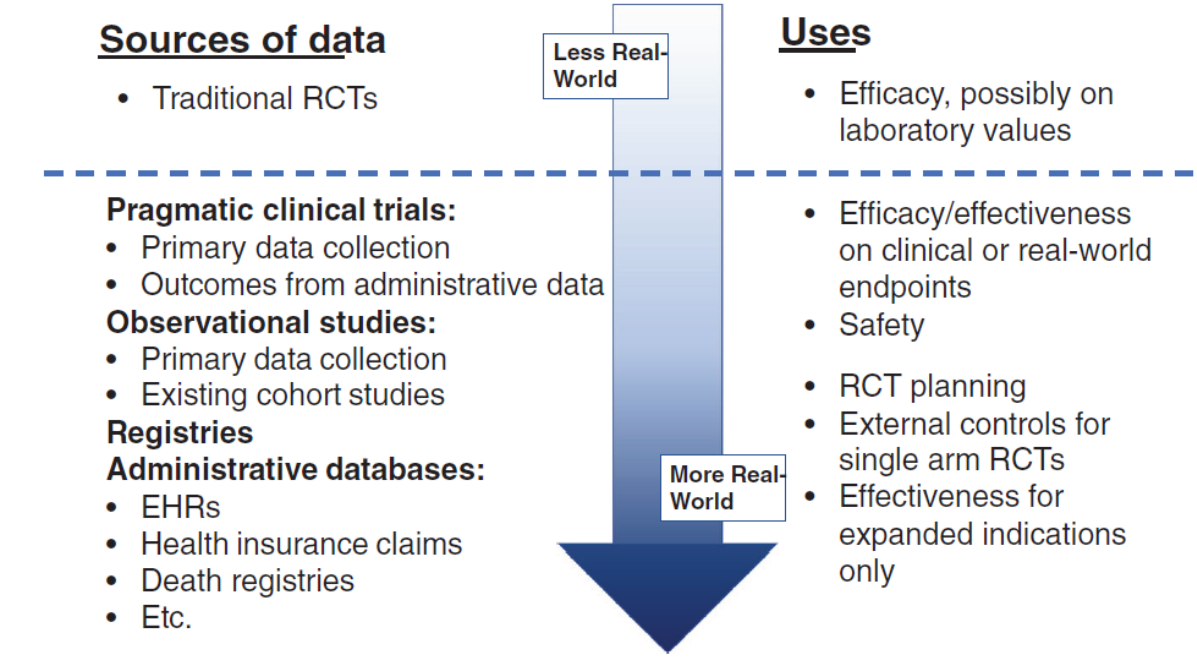
Patient Communities, Twitter, Facebook, Blogs

Literature

Disease Burden, Clinical Characteristics, Prevalence/Incidence, Rates of Treatment, Resource Use and Costs, Disease Control, Quality of Life Measures

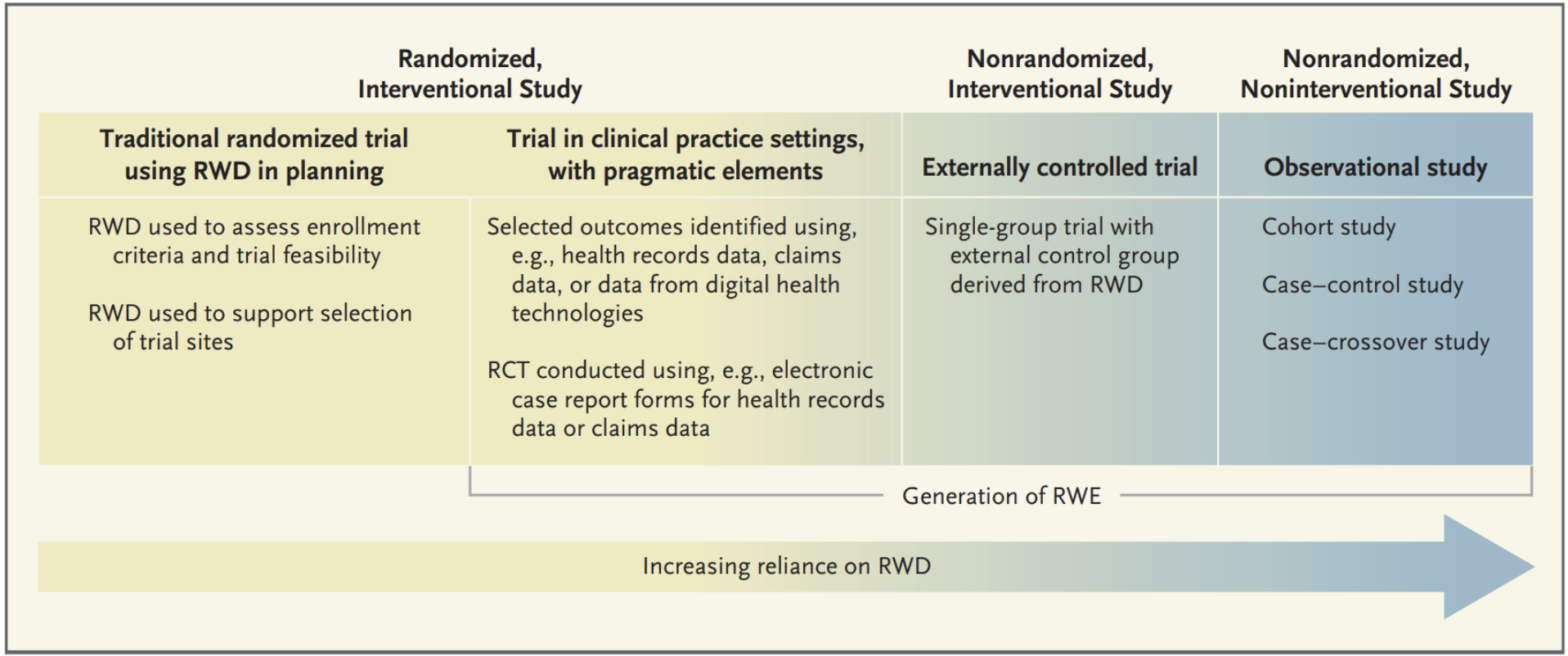
Institute	Year	RWD	RWE
GetReal	2017	It is an umbrella term for data regarding the effects of **health interventions** (e.g., safety, effectiveness, resource use, etc.) that are **not collected in the context of highly controlled RCTs** and is assumed to provide data that are applicable to the real-life use and users of drug treatments, including data on relative effectiveness.	Real-world evidence is the evidence derived from the **analysis and/or synthesis of real-world data**.
FDA	2018	Data relating to patient **health status** and/or the **delivery of health care** routinely collected from a variety of sources	Clinical evidence about the usage and potential benefits or risks of a medical product derived from **analysis of real-world data**.
EMA	2019	Routinely collected data relating to a **patient's health status** or the **delivery of health care** from a variety of sources **other than traditional clinical trials**.	Information derived from **analysis of real-world data**.
NICE	2022	Data relating to **patient health** or **experience** or **care delivery** collected **outside the context of a highly controlled clinical trial**. Real-world data can be routinely collected during the delivery of health or social care. It can also be collected prospectively, to address 1 or more specific research questions.	Evidence generated from the **analysis of real-world data**. This includes studies using real-world data to form an external control to a clinical trial.

FIGURE 1 Data sources and corresponding uses across the spectrum of real-world evidence. Each real-world data source may be more or less real-world, depending on the specifics of how it is used. EHR, electronic health records; RCTs, randomized controlled trials [Colour figure can be viewed at wileyonlinelibrary.com]



RCTs = randomized controlled trials; EHR = electronic health records

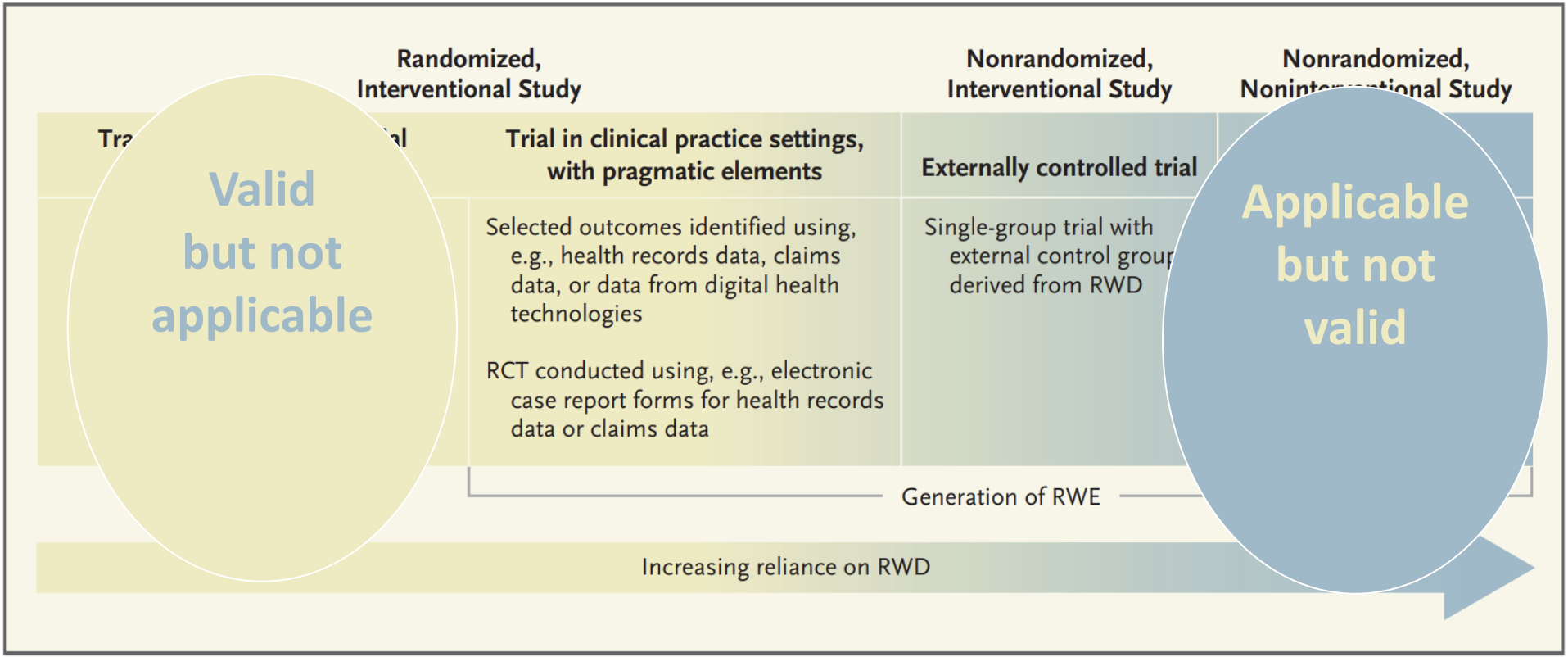
Franklin e.a., PDS 2021



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

Concato J, Corrigan-Curay J. Real-World Evidence - Where Are We Now? N Engl J Med. 2022 May 5;386(18):1680-1682. doi: 10.1056/NEJMp2200089. Epub 2022 Apr 30. PMID: 35485775.



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

Concato J, Corrigan-Curay J. Real-World Evidence - Where Are We Now? N Engl J Med. 2022 May 5;386(18):1680-1682. doi: 10.1056/NEJMp2200089. Epub 2022 Apr 30. PMID: 35485775.

Table 2 Signatures of RWE use of medicinal products that were subject to additional monitoring, classified as orphan medicines or received a conditional approval and the most common therapeutic areas included in the cohort of 111 medicinal products evaluated centrally by EMA in European Union in 2018–2019

	All products	Additional monitoring	Orphan medicine	Conditional approval	Anti-neoplastic and immunomodulating agents (oncology)	Anti-infectives for systemic use	Nervous system	Alimentary tract and metabolism	Blood and blood-forming organs
Number of MAAs	*n* = 111 (100.0%)	*n* = 86 (77.5%)	*n* = 26 (23.4%)	*n* = 9 (8.1%)	*n* = 30 (27.0%)	*n* = 17 (15.3%)	*n* = 16 (14.4%)	*n* = 14 (12.6%)	*n* = 10 (9.0%)
1. Discovery/epidemiology of disease									
RWE signature	98.2	98.9	96.2	88.9	100.0	94.1	100.0	92.9	100.0
RWE signature with data	33.3	32.6	42.3	55.5	56.7	23.5	12.5	28.6	30.0
2. Early development/comparison to current (clinical) practice									
RWE signature	35.1	33.7	65.3	44.4	33.3	41.2	31.3	50.0	40.0
RWE signature with data	0.9	0.0	3.8	0.0	0.0	0.0	0.0	7.1	0.0
3. Full development/clinical development									
RWE signature	48.6	43.0	50.0	55.6	50.0	64.7	37.0	50.0	60.0
RWE signature with data	8.1	7.0	11.5	0.0	13.3	11.8	0.0	7.1	10.0
4. Registration/market access/therapeutic benefit									
RWE signature	46.8	48.8	46.2	77.8	56.7	64.7	25.0	28.6	50.0
RWE signature with data	5.4	5.8	7.7	0.0	6.7	5.9	0.0	0.0	20.0
5. Lifecycle management/safety profile/clinical guidance									
RWE signature	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
RWE signature with data	81.1	81.4	100.0	88.9	96.7	64.7	75.0	78.6	80.0

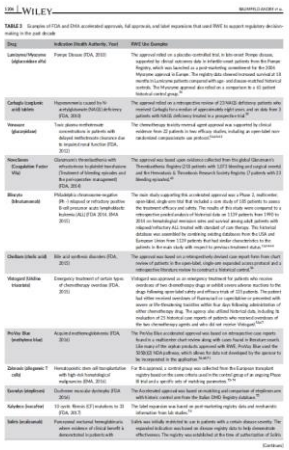
Eskola SM, Leufkens HGM, Bate A, De Bruin ML, Gardarsdottir H. Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018-2019. Clin Pharmacol Ther. 2022 Jan;111(1):310-320. doi: 10.1002/cpt.2462. Epub 2021 Nov 16. PMID: 34689334; PMCID: PMC9299055.

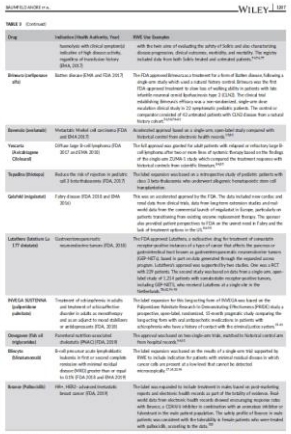
Regulatory experiences with RWE

"While RWE from observational studies is well accepted for satisfying postapproval safety monitoring requirements, it has not commonly been used to demonstrate drug effectiveness for regulatory purposes."

Positive examples mainly

- Rare diseases
- Single arm studies
- High unmet medical need
- (or combination thereof)





Nishioka e.a., Clin Pharmacol Ther 2022; Baumfeld Andre e.a., PDS 2020; De e.a., J Orthop Trauma, 2021; Burcu e.a. PDS 2020

Summary RWE in regulatory decision-making

- RWE used in regulatory decision-making: post market safety, post market effectiveness and rare orphan diseases
- Shift from large generic target populations to smaller populations (personalized medicine, rare diseases, complex/patient-specific therapies)
- Acknowledged that traditional RCTs may not be feasible
- Expectation of increased need for RWE to support regulatory decision-making

- "When collected using **reliable methodologies** and used in appropriate situations, RWE presents a faster, less expensive, and potentially more clinically meaningful alternative to RCTs for obtaining […] regulatory approvals."

Eichler e.a. Clin Pharmacol Ther. 2021
De e.a., J Orthop Trauma, 2021

Types of epidemiologic research

- Prevalence studies (*how many patients are there?*)
- Risk factor studies (*what causes disease X?*)
- Prognosis studies (*what is to be expected for this individual patient?*)
- Effectiveness studies (*how effective is this treatment?*)
- HTA studies (*how cost-effective is this treatment?*)

Types of epidemiologic research (with caveats)

- Prevalence studies (*how many patients are there?*)
  - misclassification
- Risk factor studies (*what causes disease X?*)
  - misclassification / (residual) confounding
- Prognosis studies (*what is to be expected for this individual patient?*)
  - misclassification
  - limited follow-up
- Effectiveness studies (*how effective is this treatment?*)
  - residual confounding
  - limited info on treatments
  - limited follow-up
- HTA studies (*how cost-effective is this treatment?*)
  - same as for effectiveness studies
  - limited info on health-care costs

Target trial emulation

- Eligibility criteria
- Treatment strategies
- Assignment procedure
- Outcome(s)
- Follow-up
- Causal contrast of interest
- Statistical methods

FAST FACTS

Target trial emulation: applying principles of randomised trials to observational studies

The randomised trial is the preferred study design for evaluating the effectiveness and safety of interventions. Yet such trials can be prohibitively expensive, unethical, or take too long. When it is not possible to carry out a randomised trial, observational data can be used to answer similar questions. Here, we describe the process of using observational data to emulate a target trial, which applies the study design principles of randomised trials to observational studies that aim to estimate the causal effect of an intervention. The target trial provides a formal framework to help avoid self-inflicted biases common to observational studies.

Anthony A Matthews,[1] Goodarz Danaei,[2] Nazrul Islam,[3,4] Tobias Kurth[5]

Matthews e.a. BMJ 2022

Target trial emulation for RWE

- Structured way of designing a study using RWD
- These studies could have many different objectives:
  - Efficacy (single arm studies)
  - Effectiveness
  - Post-marketing safety studies
  - Expanded indication (new/expanded label)

- While reliance on RWD is a continuum, target trial emulation seems valuable over the entire range of objectives

Efficacy vs. effectiveness

Efficacy: Does it work? (potentially)

Effectiveness: Does it help? (in daily practice)

Efficacy-effectiveness gap

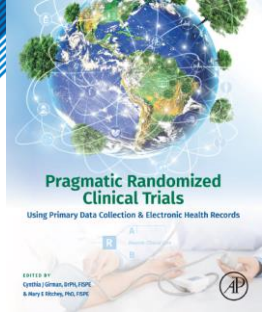


Table 2.1: Factors contributing to the efficacy-effectiveness gap.

Factor	Examples
Extrinsic factor	Inappropriate storage of drugs
	Incomplete explanation of drug use
	Shortage of drugs
	Unfamiliarity with instructions
	Incorrect labeling of medication
	Inexperience of health professionals
	Non-adherence
	Supply chain disorder (e.g., due to natural disaster)
Intrinsic factor	Limited absorption (e.g., due to co-morbidity)
	Drug-drug or drug-gene interactions
	Reduced metabolism or clearance (e.g., due to co-morbidity)

This list is not exhaustive. Whether examples apply depends on the treatment that is being studied and the conditions under which it is investigated.

- Studies of efficacy and effectiveness target a different estimand

  → results need not be the same

  → comparisons of quantitative results not directly useful

JAMA Network | Open™

Invited Commentary | Oncology

Trial Emulation and Real-World Evidence

Rolf H. H. Groenwold, MD, PhD

Real-world studies

- Aim of real-world studies is *not* to repeat traditional RCTs (nor to confirm)
- Aim of real-world studies is to answer *different* questions or questions that are otherwise unanswerable

- Real-world evidence = complementary evidence

Real-world observational studies

1. Missing data (cave bias)
2. Measurement error (cave bias)
3. No randomisation!!! (cave confounding)

Are all biases missing data problems?

Chanelle J. Howe, PhD MHS MPH[a], **Lauren E. Cain, PhD ScM MHS**[b], and **Joseph W. Hogan, ScD MS**[c]

Missing data

- Many data sources are primarily set up to support healthcare processes (not to support research)
- Availability of information depends on usefulness and the need to register

GP file: Ms X.

- ❑ 26 years
- ❑ No recent visits to the practice
- ❑ Visits the practice for a fungal infection of toe nails
- ❑ For the rest, she seems completely healthy

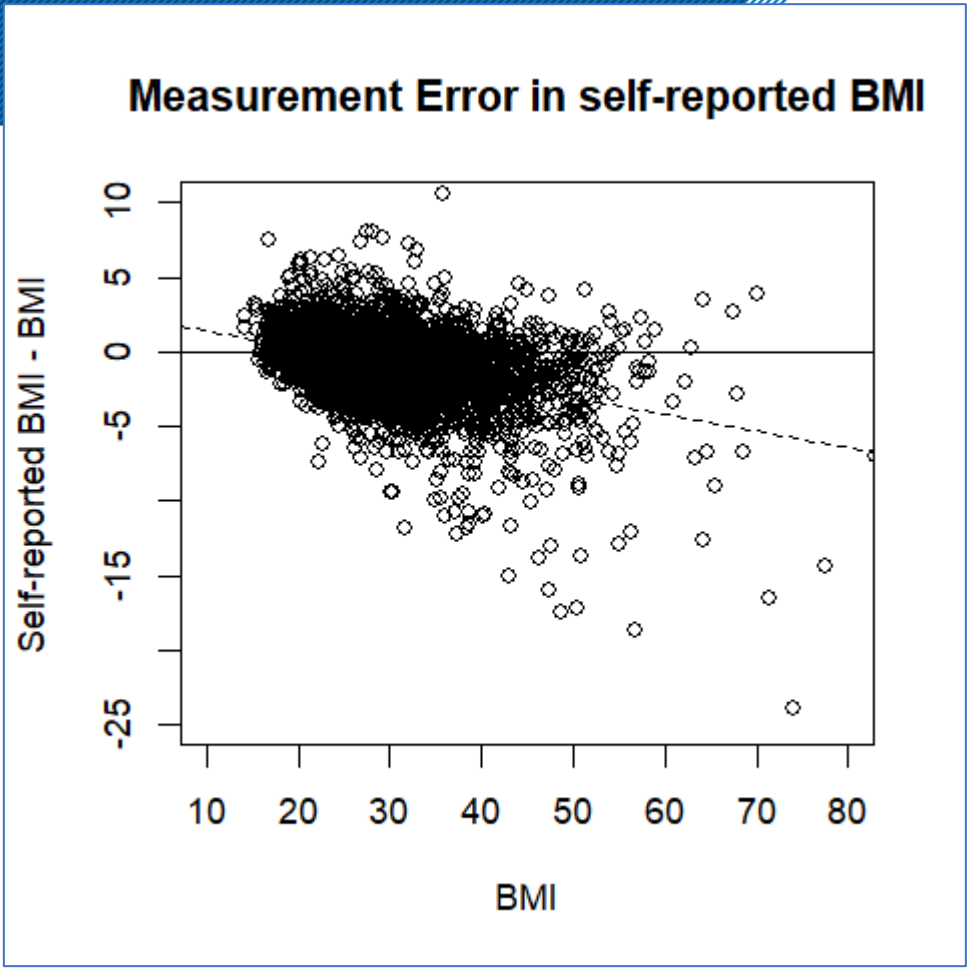
Measurement error

- Many data sources are primarily set up to support healthcare processes (not to support research)
- Quality of information depends on usefulness and the need to register

GP file: Ms X.

- ❑ 26 years
- ❑ No recent visits to the practice
- ❑ Visits the practice for a fungal infection of toe nails
- ❑ For the rest, she seems completely healthy
- ❑ Body weight: 65 kg

Self-reported BMI (NHANES)



Confounding

- Usually, there is a reason why patients get a certain treatment (or switch, or stop)

- If that reason depends on the risk of developing the outcome ….

…. A direct comparison between groups of patients who received a different treatment is not valid.

Observational research

1. Missing data (cave bias)
2. Measurement error (cave bias)
3. No randomisation!!! (cave confounding)

For all these problems (statistical) solutions exist
Provided sufficient information is available
Assumptions dependent on data and research question

Quantitative bias analysis (QBA)

(or “sensitivity anlaysis”)

How *sensitive* are the results to violations of certain assumptions made in the design/analysis?

Focus of QBA likely to be different for

- Randomised trial
- Observational (non-randomised) study of medical treatment

Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly

- ❑ Large (>700k) US EHR database study
- ❑ Exposure: influenza vaccination vs. no vaccination
- ❑ Outcome: mortality during influenza season
- ❑ Confounders: age, sex, comorbidity, ..
- ❑ Odds ratio: 0.52 (95%CI 0.50-0.55)

Assumptions:

- ➢ No unmeasured confounding
- ➢ No selective drop-out
- ➢ No classification error

Nichol et al. *NEJM* 2007;357(14):1373-81

Table 1. Baseline Characteristics of the Study Subjects.*

Characteristic	Unvaccinated (N=298,623)	Vaccinated (N=415,249)
Age (yr)	73.6±6.9	73.9±6.3
Male sex (%)	41.7	44.4
Presence of one or more high-risk medical conditions (%)	45.6	55.6
Diabetes	11.0	14.4
Heart disease	22.7	26.8
Lung disease	15.2	19.2
Renal disease	2.0	2.3
Vasculitis or rheumatologic disease	1.4	1.9
Immune deficiency	1.0	1.2
Cancer	13.3	14.5
Dementia or stroke	4.7	3.4
No. of outpatient visits during baseline period	10.3±15.6	12.8±13.3
Hospitalization during baseline period (%)	13.3	14.5

(at least) Two possible questions

1. “What amount of unmeasured confounding is needed to explain the observed effect (OR 0.52)?”

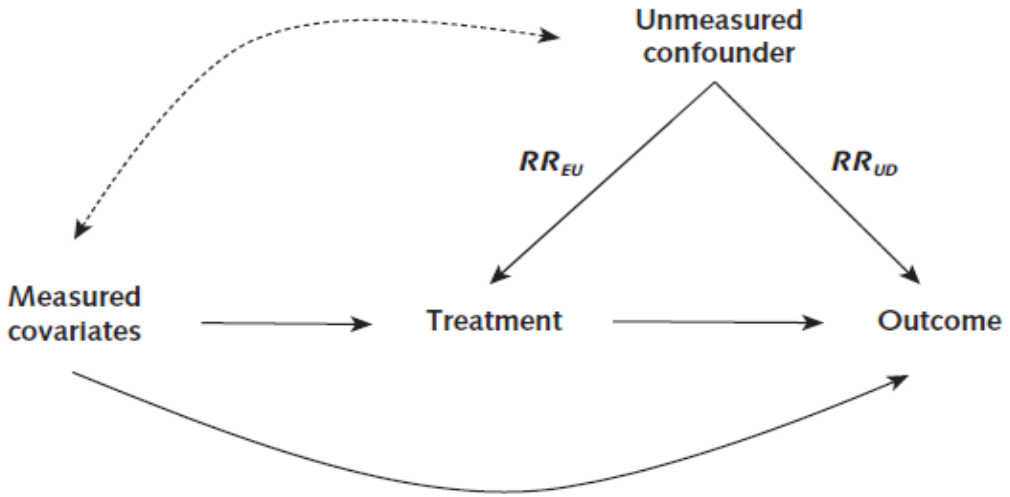
2. “What would be the impact of unmeasured confounding due to, say, smoking status?”

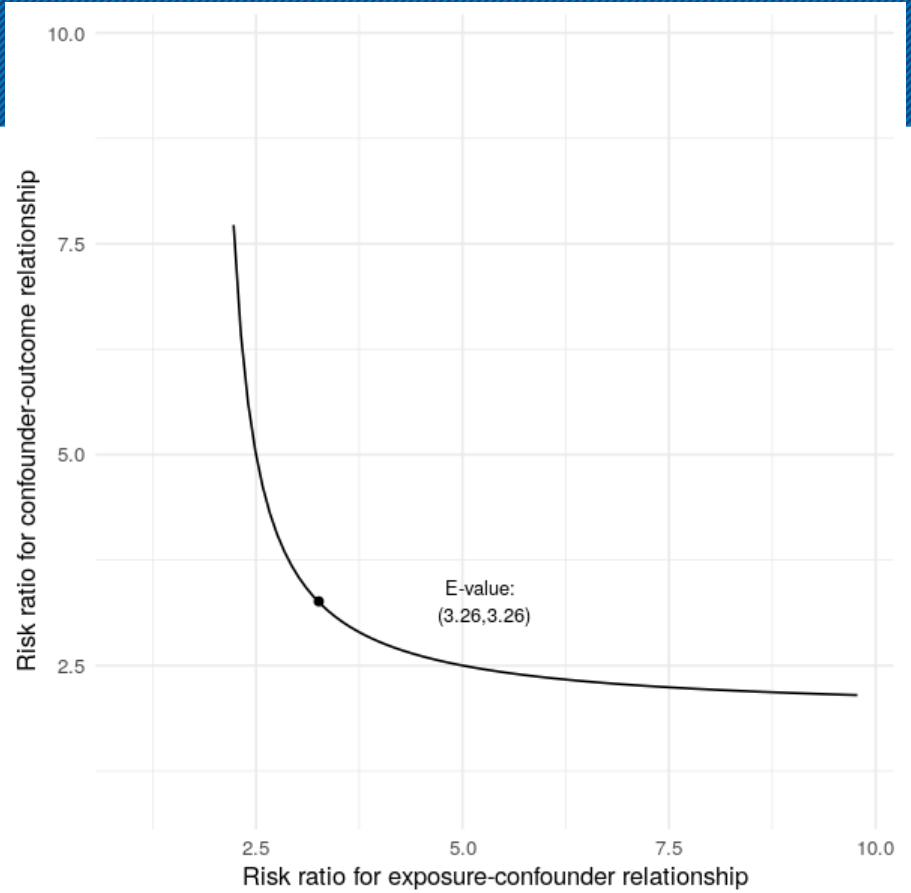
Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Sensitivity Analysis in Observational Research: Introducing the E-Value

Tyler J. VanderWeele, PhD, and Peng Ding, PhD

Figure 1. Unmeasured confounder of the treatment–outcome relationship.



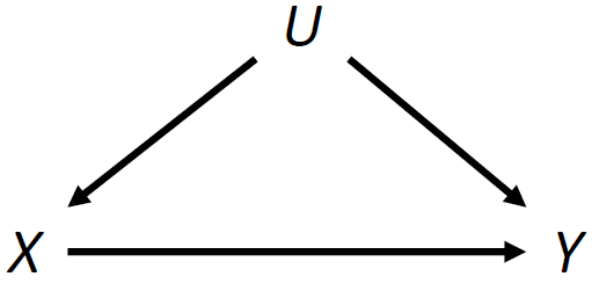


E-value = 3.26

Value of the joint minimum strength (RR) of confounder-exposure AND confounder-outcome relation to fully explain away the observed effect (OR = 0.52)

$$E_{value} = OR + \sqrt{\{OR(OR-1)\}}$$

https://www.evalue-calculator.com/evalue/

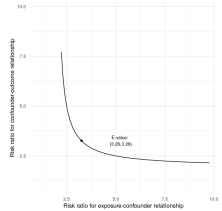


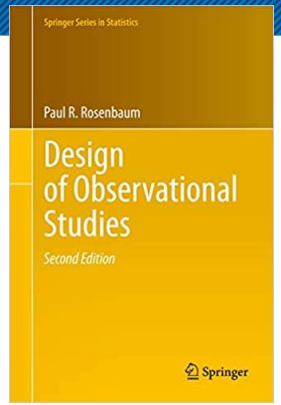
$$\text{bias}(\hat{\beta}_{yx}) = \frac{\beta_{xu}\beta_{yu}\sigma_u^2}{\beta_{xu}^2\sigma_u^2 + \sigma_x^2},$$

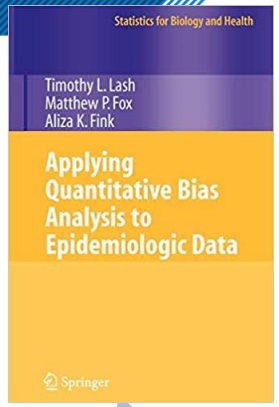
$$\text{bias}(\hat{\beta}_{yx}) = \frac{\beta_{xu}\beta_{yu}}{\beta_{xu}^2 + 1}.$$

Groenwold et al. *Epidemiology* 2021

QBA continuum







Simple
Few assumptions
Unrealistic

Challenging
Many assumptions
More realistic

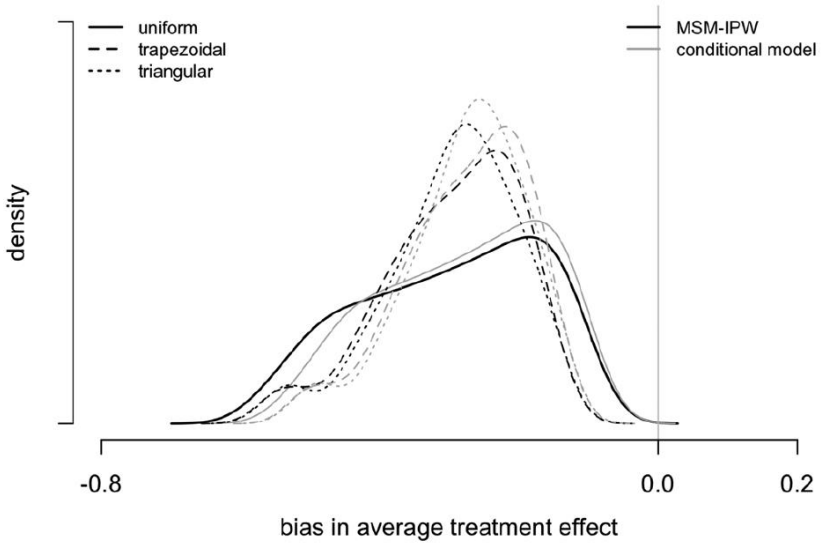
Probabilistic bias analysis

- Define range of values of bias parameters, including their (joint) probablility distribution
- Investigate various possible scenarios → distributions of results

Quantitative Bias Analysis for a Misclassified Confounder

A Comparison Between Marginal Structural Models and Conditional Models for Point Treatments

Linda Nab,[a] Rolf H. H. Groenwold,[a,b] Maarten van Smeden,[a] and Ruth H. Keogh[c]



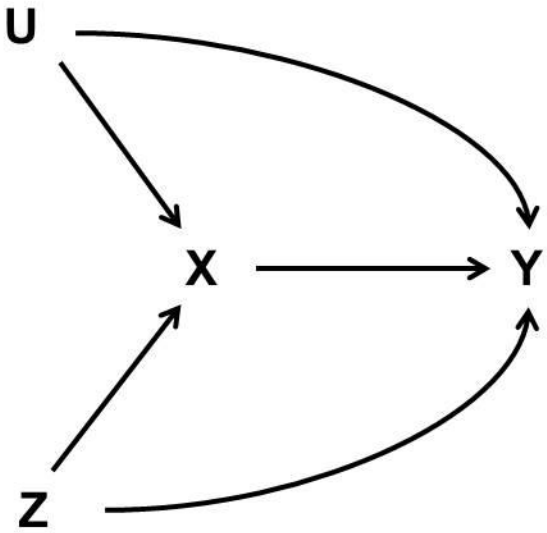
Nab et al. *Epidemiology* 2020;31:796-805

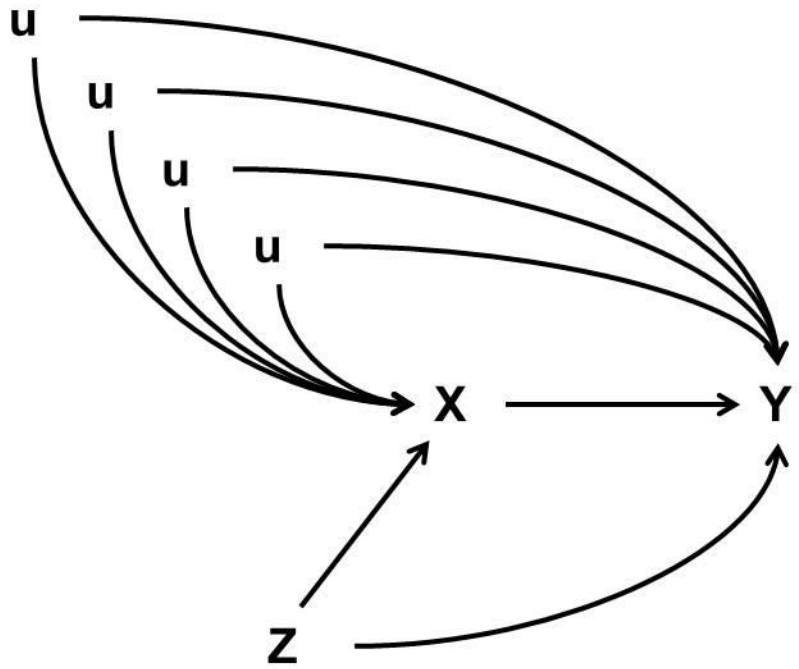
Known unknowns

Unknown unknowns

“There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.”

One or multiple unmeasured confounders?





Real World Evidence

1. Quality of real world evidence depends on research question and data quality

2. QBA helps to make discussions about validity more explicit

3. First, we have to get the basics right, before we look into
   - Subgroup effects
   - Predicting individualized treatment effects

Thank you

r.h.h.groenwold@lumc.nl

http://rolfgroenwold.nl