Methods for quantifying potential bias in epidemiological studies

Ian Douglas
Professor of Pharmacoepidemiology

Disclosure

- Financial and other relationships over the last 12 months
  - Grant support for the LSHTM EHR group from GSK and AstraZeneca
  - Shares in GSK

Content

Some thoughts about QBA application in epidemiology

Some examples of methods applied to confounding, misclassification and selection bias

Not exhaustive, hopefully motivating!

Thanks to Jeremy Brown for some of the content

Quantitative Bias Analysis

Older than you might think

Less used than you might hope - a lot of qualitative bias discussion

"…blah blah… bias towards the null"

When applied, not always used well or interpreted correctly

Several options to choose from

Broadly tackling

- Confounding
- Misclassification
- Selection Bias

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Broadly tackling

Confounding	40%
Misclassification	57%
Selection Bias	17%

Petersen et al, International Journal of Epidemiology, 2021, 1–23 doi: 10.1093/ije/dyab061

QBA for confounding

We generally acknowledge confounding adjustment unlikely perfect

QBA can help in two main ways

1. Propose characteristics of a confounder and see how data for it would have impacted on results
2. What confounding would be needed to negate a result? Or to hide a true association (just as important)?

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QBA for confounding – bias adjustment

Imagine we did a study and got a risk ratio for the association between exposure E and outcome Y

$$RR_{EY}^{obs}$$

We suppose this may be affected by residual confounding, and we know something about one or more potential confounders. We can adjust for this using the following equation

$$RR_{EY}^{adj} = RR_{EY}^{obs} / \frac{1+(RR_{UY}-1)P(U=1|X=1)}{1+(RR_{UY}-1)P(U=1|X=0)}$$

$P(U=1\|X=1)$	*Prevalence of unmeasured confounder among exposed*
$P(U=1\|X=0)$	*Prevalence of unmeasured confounder among unexposed*
RR_{UY}	*Risk ratio between unmeasured confounder and outcome*

QBA for confounding – bias adjustment

Important questions

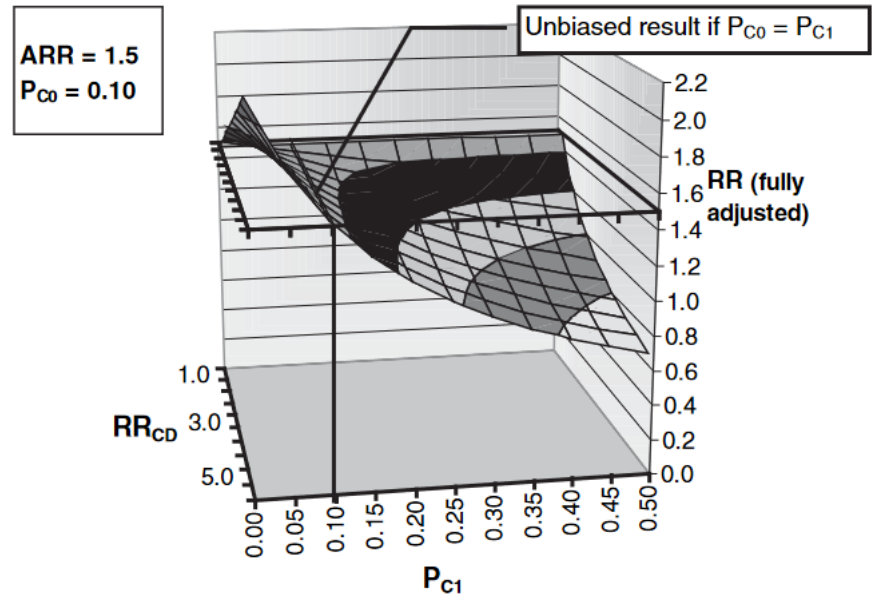
- Do we have definitive values for prevalence of confounder in exposed/unexposed? Association with the outcome?
- Are we happy with a single "go" at making this adjustment for bias?

QBA for confounding – bias adjustment

Array- Based Approaches

Assumptions about the confounder(s) are probably subject to uncertainty

Specify a range of possible values and/or a probability distribution from which they can be drawn



Fixed
ARR = apparent or observed RR
P_{CO} = prevalence of unmeasured confounder in unexp

Variable
P_{C1} = prevalence of unmeasured confounder in exp
RR_{CD} = association between confounder and outcome

Schneeweiss et al, 2006 May 2006

Pharmacoepidemiology and Drug Safety 15(5):291 - 303

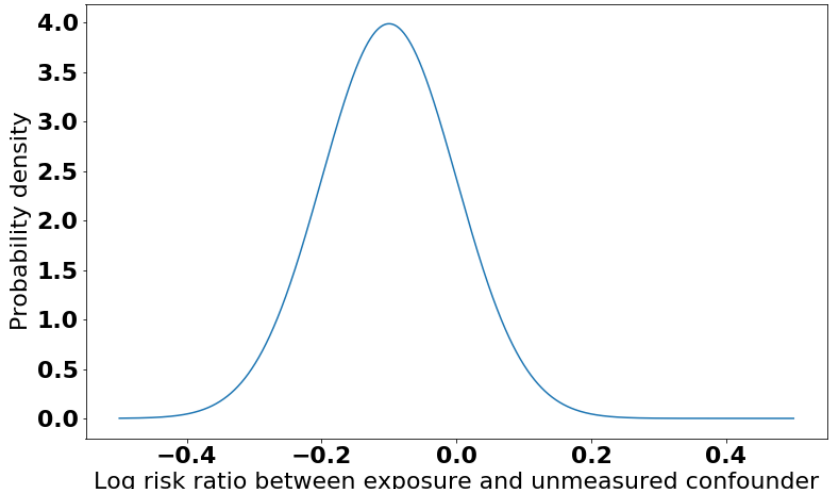
DOI:10.1002/pds.1200

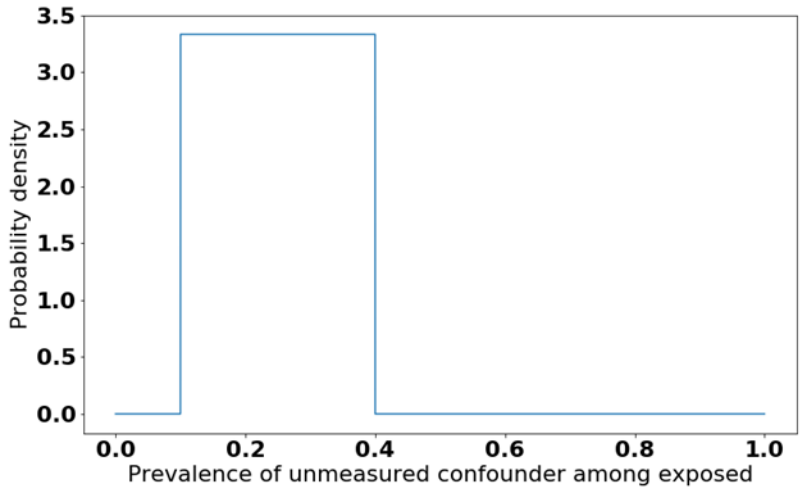
QBA for confounding – bias adjustment

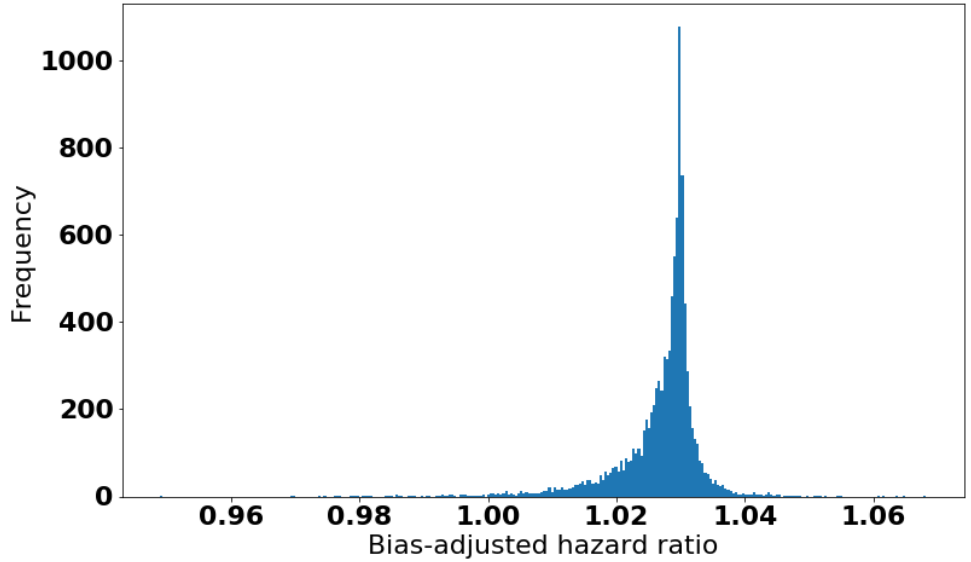
Probabilistic Approaches (thanks to Jeremy Brown for figures)

Specify known or plausible distribution of parameters to sample from

Present arising bias adjusted estimates as a histogram







QBA for Confounding Example

Population:	People with RA or SLE in England, via the OpenSAFELY platform
Exposure:	Ongoing hydroxychloroquine use
Outcome:	COVID-19 mortality
Result:	Hazard ratio = 1·03, 95% CI 0·80 to 1·33

Unmeasured confounding?

Biologic DMARD use

- known to be higher in hydroxychloroquine non-users (21%) than users (18%)
- Effect on COVID-19 mortality unknown. Assumed values between 0.8 and 1.2

Rentsch CT, DeVito NJ, MacKenna B, Morton CE et al. Lancet Rheumatol. 2021 Jan;3(1):e19-e27. doi: 10.1016/S2665-9913(20)30378-7.

QBA for Confounding Example

eTable 5. Bias-adjusted associations using a range of estimated prevalence of biologic DMARDs and associations with COVID-19 mortality

Prevalence of bDMARD among exposed	Prevalence of bDMARD among unexposed	Association between bDMARD and COVID-19 mortality			
		HR 0.80	HR 0.90	HR 1.10	HR 1.20
18%	21%	1.02 (0.79-1.32)	1.03 (0.79-1.32)	1.03 (0.80-1.33)	1.03 (0.80-1.34)
3%	30%	0.97 (0.75-1.26)	1.00 (0.78-1.29)	1.06 (0.82-1.36)	1.08 (0.84-1.40)
30%	3%	1.09 (0.84-1.40)	1.06 (0.82-1.36)	1.00 (0.78-1.29)	0.98 (0.76-1.26)

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; COVID-19, coronavirus disease 2019; HR, hazard ratio

Tested a range of scenarios. None would have led to a different conclusion

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QBA for confounding – Rule-out approach

What if there is no background data on the association between the confounder and the outcome, but we have some idea about prevalence?

Ask a slightly different question:

How strong would unmeasured confounding need to be to reduce an observed association to the null? Or to a different specified value?

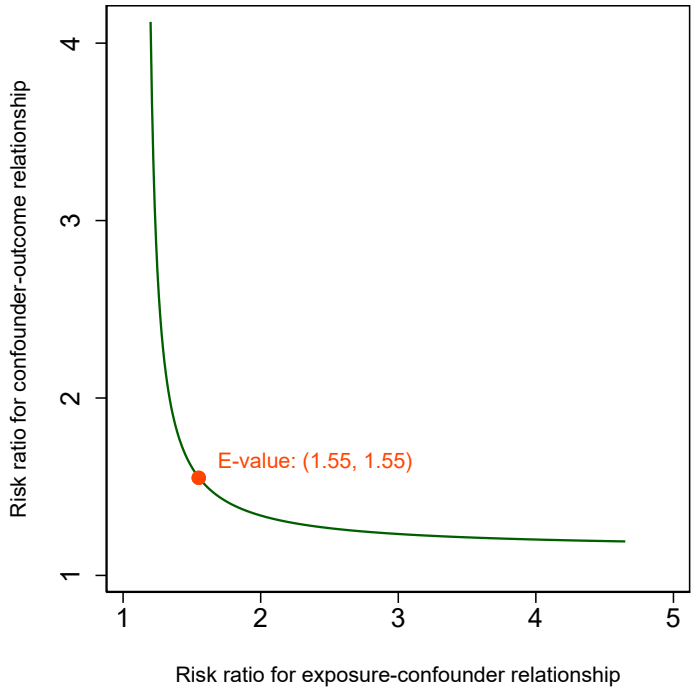
The earlier equation can be rearranged to find a value for the association between unmeasured confounder and the outcome to produce a bias adjusted RR of a specified magnitude

Investigators/readers can judge whether this is plausible/likely

QBA for confounding – Bounding Methods

E-values (VanderWeele & Ding 2017)

Relatively often used, relatively often misunderstood



Plot shows RR for EC and CY required to reduce an observed association to null

Here 1.55 is the minimum value that at least one of these parameters must take AND the value that if true for both, *may* reduce the observed RR to null. THIS IS THE E-VALUE

BUT If one is greater, the other could be smaller

Doesn't account for prevalence of the unmeasured confounder

Requires thinking about EC or CY to interpret

Single confounder only

QBA for confounding

Several methods and permutations

Require a range of inputs/assumptions

Bias adjustment formulae are preferable if there is prior knowledge about the unmeasured confounder

E-values are simple (single measure) but great caution needed for interpretation

QBA for misclassification

A great alternative to:

"…blah blah… bias towards the null"

Ideally study parameters are well measured and validated, but…

QBA for misclassification

How well do we measure what we need in a study?

- Exposure
- Outcome
- Confounders

QBA for misclassification

Simple Bias Analysis

Needs prior knowledge of sensitivity, specificity, PPV and NPV of the measure ***in the study setting or at least generalisable to it***

Easiest applied to crude aggregate data or stratified data

Best applied to simple situations e.g. prevalence estimates of a disease by exposure status

Gold Standard (Truth)

	Outcome +	Outcome -
Exp+	A	B
Exp-	C	D

Observed (subject to misclassification)

	Outcome +	Outcome -
Exp+	a	b
Exp-	c	d

QBA for misclassification

Bias corrected counts for prevalence:

	Outcome +
Exp+	A = [a – (a + c) (1-SP)] / [SE - (1-SP)]
Exp-	C = (a + c) – A

Se = sensitivity; Sp = specificity;

More complex methods exist

Probabilistic Bias Analysis samples bias parameters from a pre-specified distribution

Can be summary or individual record level

QBA for misclassification – correcting for outcome misclassification

Hall et al Pharmacoepidemiology and Drug Safety, 28 Aug 2020, 29(11):1450-1455
DOI: 10.1002/pds.5109

We often assume outcome measurement validity is the same in exposed and unexposed, but this is a strong assumption

$$RR = RR' \times (PPV_1/PPV_0) \times (Se_0/Se_1)$$

Online app to plug in numbers and obtain corrected RR

http://apps.p-95.com/ISPE/

QBA for selection bias

Motivating intuitive example from a non-database setting (Lash et al 2009)

Research question: Does living near a hazardous waste site increase the risk of leukaemia

Study design: Case control

QBA for selection bias

Research question: Does living near a hazardous waste site increase the risk of leukaemia

Study design: Case control

Cases: More likely to participate than invited controls (more interest in the question)

Exposed: More likely to participate if living near a hazardous waste site (more interest in the question)

If no true association, selection bias likely to induce one

QBA for selection bias – correction formula

Who was invited and who participated?

Calculate selection probabilities

- Easily determined by case/control status
- Not always by exposure status
- If not available, repeat for different plausible values

	Exposed	Unexposed
Case	S_{11}	S_{01}
Control	S_{10}	S_{00}

Corrected odds ratio = $OR_{obs} X (S_{10}S_{01}/S_{11}S_{00})$

QBA for selection bias – a pharmacoepidemiology example

Most of our studies use EHR data

Often nationally representative

Selection bias is unlikely?

Mostly true, but some exceptions e.g.

Early loss to FU and subsequent missed outcomes may be an issue in claims data, for example in studies of drugs and cancer risk

Maternal exposure and adverse neonatal outcomes

Pregnancy pharmacoepi selection bias example

Exposure: Lithium during 1st trimester of pregnancy

Outcome: Cardiac malformation

Result: Odds Ratio = 1.65 (1.02-1.68)

How would selection bias operate?

Only liveborn infants can be studied for the outcome

Not all pregnancies result in liveborn infants

Pregnancies ending without a liveborn infant could be affected by cardiac malformation

	Exposed	Unexposed
CM+	S_{11}	S_{01}
CM-	S_{10}	S_{00}

Patorno E, Huybrechts KF, Bateman BT, et al. *N Engl J Med* 2017;376:2245-54. doi:10.1056/NEJMoa1612222

Lithium and cardiac malformation

Specify termination probabilities for each of the four groups, e.g.

Unexposed with malformation	30%	→	$S_{01} = 0.7$
Exposed with malformation	35%	→	$S_{11} = 0.65$
Unexposed without malformation	20%	→	$S_{00} = 0.80$
Exposed without malformation	25%	→	$S_{10} = 0.75$

ORBiasAdj = 1.65 × ((0.7 × 0.75) ÷ (0.65 × 0.8)) = 1.67

Lithium and cardiac malformation

In practice more likely to specify a range of selection probabilities

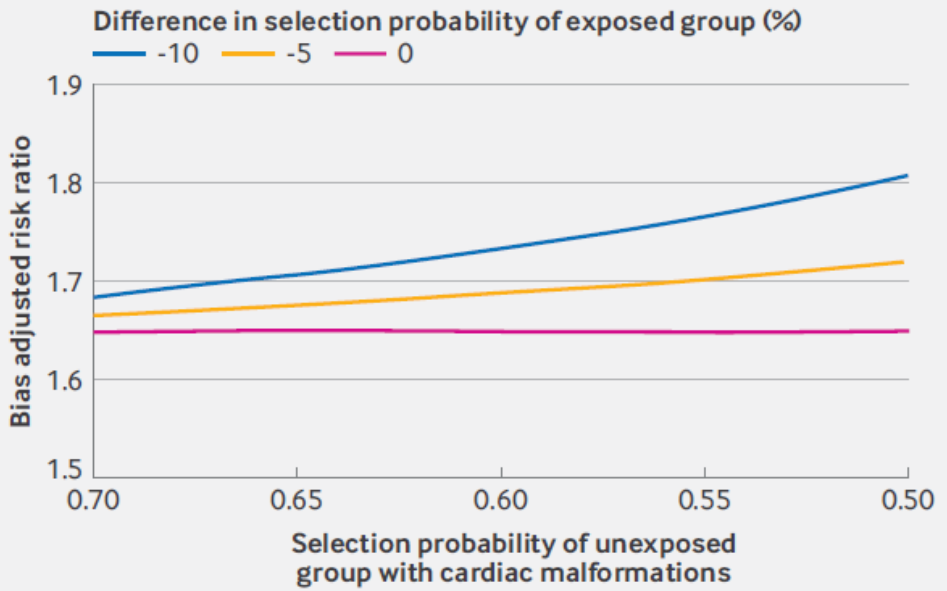


Fig 1 | Bias adjusted risk ratio for different assumed selection probabilities in cohort study investigating association between lithium use (relative to non-use) and cardiac malformations in liveborn infants. Redrawn and adapted from reference 32 with permission from Massachusetts Medical Society. Selection probability of the unexposed group without cardiac malformations was assumed to be 0.8 (ie, 20% probability of termination). Selection probabilities in the exposed group were defined relative to the unexposed group by outcome status (ie, −0%, −5%, and −10%)

Multiple Biases

Often concerned about >1 type of bias

Individual bias analyses may rule some out, but may not

How to quantify the impact of >1 potential bias?

Qualitative guessing or averaging based on the individual analyses may not be correct

Jointly accounting for each is possible, though not simple

See https://sites.google.com/site/biasanalysis/ for spreadsheets to aid (series of 2x2 tables)

Order of application matters. Lash et al advise application in reverse of the order in which they occurred within the data. Confounding occurs before misclassification.

Caveat – applies to crude estimates only, but likely to be useful re-magnitude and direction of bias

Summary

QBA much underused

Think about confounding, misclassification, selection bias

Many useful and free resources available

No need for "…blah blah… bias towards the null"

Refs

Petersen et al A systematic review of quantitative bias analysis applied to epidemiological research International Journal of Epidemiology, 2021, 1–23 doi: 10.1093/ije/dyab061

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