SUPPLEMENTAL DIGITAL CONTENT FOR

Quantitative bias analysis for collaborative science

Jennifer Weuve, Sharon K. Sagiv, and Matthew P. Fox
Epidemiology • Volume 29, Number 5, September 2018
https://www.ncbi.nlm.nih.gov/pubmed/29923865

We used the study by Forns and colleagues[1] to outline how quantitative bias analysis (QBA) can be applied to collaborative science projects. Our objective was to quantify the conditions necessary to yield the observed cohort-specific effect estimates in scenarios when: [1] air pollution has no effect on attention-deficit/hyperactivity disorder (ADHD) risk, or [2] air pollution increases the risk of ADHD. We examined three classes of bias—differential misclassification, differential selection, and uncontrolled confounding. Where possible we used the reported data and based our assumptions on putative mechanisms of bias specific to the subject matter.

Differential misclassification

We explored the extent to which differential misclassification of ADHD could yield the observed findings from a true odds ratio (OR) that is either null (consistent with no effect of NO_2), or at least 1.2 (consistent with an adverse effect of NO_2 exposure). For each cohort, we used the crude OR reported by Forns *et al*. comparing children above versus below the median NO_2 exposure, along with counts of incident ADHD, to estimate the cell counts of a classic 2x2 contingency table (see supplemental spreadsheet). We then generated examples of exposure-level ADHD instrument sensitivities and specificities that could have resulted in the observed OR under two scenarios (true OR=1, and true OR$\geq$1.2). We first assigned both exposure groups the ADHD sensitivities and specificities cited by Forns *et al*. in eTable 19 of their report (step 1). These sensitivities and specificities were unique to the ADHD instruments used in each cohort. We then allowed the ADHD sensitivity in the high-NO_2 group to diverge from the ADHD sensitivity in the low-NO_2 group, and the ADHD specificity in the high-NO_2 group to diverge from the ADHD specificity low-NO_2 group (step 2). We widened these divergences until the misclassification parameters were consistent with a bias-adjusted OR of [1] 1 or [2] at least 1.2. As noted by Forns *et al*., the cited misclassification parameters for some studies resulted in negative cell counts in step 1. In those situations, we identified misclassification parameters as close as possible to the reported ones that generated positive cell counts. The results from these analyses are shown in eTable 1.

Differential selection

We also explored the potential impact of differential selection. Under the scenarios in which the [1] the true OR=1.0 and [2] the true OR≈1.2, we quantified the conditions[2] for each cohort in which selection bias could result in the observed cohort-specific OR. Again, we contrasted ADHD risks among children with above-median versus below-median NO_2 exposure. First, we computed the "selection OR," i.e., $OR_{selection} = OR_{observed}/OR_{expected\ true}$. The $OR_{selection}$ is equivalent to the OR computed using the joint exposure- and outcome-specific probabilities of selection into the analyzed study sample, i.e., [Pr(selection|ADHD, high exposure)×Pr(selection|no ADHD, low exposure)]/ [Pr(selection|ADHD, low exposure)×Pr(selection|no ADHD, high exposure)]. When $OR_{selection} = 1.0$, no selection bias is present, whereas when $OR_{selection} > 1$, there is upward bias, and when $OR_{selection} < 1$, there is downward bias. Numerous combinations of selection

probabilities can generate a given $OR_{selection}$. For each cohort, we produced examples of such probability combinations for each true OR scenario. We constrained our selection to probabilities that would, when applied to the underlying cohort, be consistent with the cohort's reported overall selection proportion (eTable 2 in the report by Forns *et al*.[1]). Where possible, we gave preference to combinations of selection probabilities that reflected lower participation among children with ADHD and high exposure. The results from these analyses are shown in eTable 2 in this appendix. Using the ABCD cohort as an example, under the scenario in which the true OR is 1, the $OR_{selection}$ required to generate the observed OR of 0.72 is also 0.72. Under the scenario in which the true OR is 1.2, the required $OR_{selection}$ is 0.60. eTable 2 shows examples of selection probabilities corresponding to these selection ORs.

Uncontrolled Confounding

The third bias we evaluated was uncontrolled confounding. Although confounding is often the work of several factors, we treated that collection as a single dichotomous confounder. Furthermore, when that confounder was related to air pollution exposure, we assumed that those relations were monotonic.[3] For confounding to bias a truly null or adverse relation downward, the confounder must be related to higher exposure and lower ADHD risk, or vice versa.

To quantify the conditions under which confounding could result in the observed ADHD OR, for two underlying scenarios (when the true OR per 10-$\mu g/m^3$ increment in NO_2 is 1.0, and when the true OR is 1.2), we computed the "E-value" for each cohort.[4] The E-value pertains to the confounder-exposure and the confounder-outcome associations. In particular, the E-value is the minimum of these two associations (on the risk ratio [RR] scale for our application), from which it would be possible for the true OR to be estimated as the observed OR. We computed E-values using the adjusted and weighted ORs reported by Forns and colleagues (figure 2 in their report),[1] so that the resulting E-value referred to confounding *above and beyond* that which any of these previously applied adjustments corrected. Note that unlike the ORs in our QBAs for differential misclassification and selection, the ORs in the confounding QBA correspond to NO_2 modeled as a continuous variable, i.e., OR per 10-$\mu g/m^3$ increment in NO_2 exposure. To accommodate the different modeling scales of the confounder-exposure (continuous) and confounder-ADHD (dichotomous) associations, we characterized the confounder-exposure association as the RR of the confounder per 10-$\mu g/m^3$ increment in NO_2 exposure, rather than the difference in mean NO_2 exposure in the presence versus the absence of the confounder.

The results from these analyses are shown in eTable 3. Observed ORs closer to 1.0 had smaller E-values under the null scenario, indicating that less extreme associations of a confounder with exposure and AHDH would be required to fully explain the findings.

eTable 1. Quantitative analysis of bias from misclassification of ADHD status that varies by NO_2 exposure.

	ADHD measure			Hypothetical sensitivity of ADHD measure[b]		Hypothetical specificity of ADHD measure[b]		ADHD odds ratio, high versus low NO_2 exposure (reference)	
Cohort study[a]	Measure	Published sensitivity	Published specificity	among high-exposed	among low-exposed	among high-exposed	among low-exposed	Unadjusted[c]	Misclassification-adjusted[c]
CATTS[d]	A-TAC	0.91	0.73	0.93	0.87	0.96	0.95	0.93	1.00
				0.91	0.91	0.92	0.91	0.93	1.54
DNBC	SDQ	0.49	0.96	0.49	0.49	0.96	0.95	0.89	0.99
				0.49	0.49	0.97	0.95	0.89	1.21
ABCD	SDQ	0.49	0.96	0.49	0.49	0.98	0.95	0.72	0.99
				0.49	0.49	0.98	0.94	0.72	1.22
Generation R[d]	CBCL½-5	0.77	0.73	0.94	0.68	0.96	0.95	0.91	1.00
				0.77	0.77	0.95	0.94	0.91	6.18
GINI/LISA-Wesel	SDQ	0.49	0.96	0.51	0.49	0.95	0.96	1.11	1.00
				0.49	0.49	0.96	0.95	1.11	1.31
GINI/LISA-Munich	SDQ	0.49	0.96	0.49	0.49	0.96	0.94	0.86	1.00
				0.49	0.49	0.97	0.93	0.86	1.30
EDEN-Nancy	SDQ	0.49	0.96	0.49	0.50	0.97	0.93	0.75	1.00
				0.49	0.49	0.97	0.91	0.75	1.28
EDEN-Poitiers	SDQ	0.49	0.96	0.49	0.49	0.97	0.95	0.94	1.01
				0.49	0.49	0.98	0.93	0.94	1.20
GASPII[d]	CBCL½-5	0.77	0.73	0.77	0.76	0.88	0.96	1.84	1.00
				0.77	0.77	0.92	0.91	1.84	6.80
INMA-Gipuzkoa[d]	DSM-IV	0.86	0.89	0.91	0.92	0.96	0.94	0.72	1.00
				0.91	0.91	0.97	0.94	0.72	1.67
INMA-Sabadell[d]	DSM-IV	0.86	0.89	0.90	0.83	0.96	0.95	0.95	1.00
				0.86	0.86	0.91	0.90	0.95	2.22
INMA-Valencia[d]	DSM-IV	0.86	0.89	0.84	0.88	0.91	0.88	0.76	1.00
				0.86	0.86	0.91	0.87	0.76	1.63
INMA-Granada	DSM-IV	0.86	0.89	0.86	0.85	0.90	0.88	0.90	1.01
				0.86	0.86	0.91	0.87	0.90	1.33

[a] In the order presented in the paper by Forns et al. 2018.

[b] Starting with the published sensitivity, we allowed the ADHD sensitivity in the high-exposed group to diverge from the ADHD sensitivity in the low-exposed group. We followed a similar procedure for the ADHD specificity in each exposure group. We widened these divergences until the misclassification parameters were consistent with a bias-adjusted OR of (1) 1 or (2) at least 1.2.

[c] Unadjusted OR: crude OR. Misclassification-adjusted OR: crude OR adjusted for the specified degrees of ADHD misclassification.

[d] Using the published sensitivity and specificity for this cohort's ADHD test resulted in negative cell counts. For this analysis, we identified misclassification parameters as close as possible to the reported ones that would generate positive cell counts.

Abbreviations. ADHD: attention-deficit/hyperactivity disorder; A-TAC, Autism-tics, Attention Deficit and Hyperactivity Disorders, and Other Comorbidities; CBCL½-5: Child Behavior Checklist for Toddlers; DSM_IV: Diagnostic and Statistical Manual of Mental Disorders IV; SDQ: Strengths and Difficulties Questionnaire.

eTable 2. Quantitative analysis of bias from differential selection.

			Selection pattern yielding unadjusted OR from a true OR of about 1.0					Selection pattern yielding unadjusted OR from a true OR of about 1.2				
Cohort study	Maximum retention[a]	Unadjusted OR[b]	Selection OR needed	Example selection proportions from original cohort[c]	High-exposed	Low-exposed	Selection-adjusted OR[b]	Selection OR needed	Example selection proportions from original cohort[c]	High-exposed	Low-exposed	Selection-adjusted OR[b]
CATTS												
	71%	0.93	0.93	ADHD	67%	72%	1.00	0.78	ADHD	73%	96%	1.19
				No ADHD	72%	72%			No ADHD	69%	71%	
DNBC												
	11%	0.89	0.89	ADHD	6%	8%	1.01	0.74	ADHD	5%	8%	1.21
				No ADHD	11%	13%			No ADHD	11%	13%	
ABCD												
	53%	0.72	0.72	ADHD	34%	47%	1.00	0.60	ADHD	29%	52%	1.20
				No ADHD	55%	55%			No ADHD	52%	56%	
Generation R												
	58%	0.91	0.91	ADHD	53%	58%	0.99	0.67	ADHD	44%	58%	1.20
				No ADHD	58%	58%			No ADHD	58%	58%	
GINI/LISA-Wesel												
	46%	1.11	1.11	ADHD	46%	46%	0.99	0.92	ADHD	40%	45%	1.21
				No ADHD	44%	49%			No ADHD	46%	48%	
GINI/LISA-Munich												
	46%	0.86	0.86	ADHD	46%	49%	1.00	0.72	ADHD	44%	55%	1.21
				No ADHD	48%	44%			No ADHD	48%	43%	
EDEN-Nancy												
	42%	0.75	0.75	ADHD	38%	46%	1.00	0.62	ADHD	36%	48%	1.20
				No ADHD	44%	40%			No ADHD	46%	38%	
EDEN-Poitiers												
	43%	0.94	0.94	ADHD	42%	47%	1.00	0.78	ADHD	30%	51%	1.20
				No ADHD	42%	44%			No ADHD	42%	43%	
GASPII												
	73%	1.84	1.84	ADHD	68%	40%	1.00	1.54	ADHD	64%	45%	1.20
				No ADHD	75%	81%			No ADHD	74%	80%	
INMA-Gipuzkoa												
	47%	0.72	0.72	ADHD	34%	48%	0.99	0.60	ADHD	28%	48%	1.19
				No ADHD	47%	48%			No ADHD	48%	49%	
INMA-Sabadell												
	64%	0.95	0.95	ADHD	59%	64%	1.00	0.79	ADHD	50%	64%	1.20
				No ADHD	63%	65%			No ADHD	65%	66%	
INMA-Valencia												
	52%	0.76	0.76	ADHD	38%	52%	1.01	0.64	ADHD	31%	51%	1.20
				No ADHD	52%	54%			No ADHD	54%	56%	
INMA-Granada												
	18%	0.90	0.90	ADHD	17%	19%	1.00	0.75	ADHD	15%	20%	1.20
				No ADHD	18%	18%			No ADHD	19%	19%	

[a] Maximum retention based on number of participants included in the analyses relative to participants in the cohort study. Does not account for recruitment response.

[b] Uncorrected OR: crude OR. Corrected OR: crude OR corrected for the specified selection probabilities.

[c] Cell shading corresponds to the absolute difference between the cell-specific selection probabilty and the overall retained proportion. Darker shades represent larger differences:

- < 2.5 percentage points
- 2.5 to < 5 percentage points
- 5 to < 10 percentage points
- 10 to < 20 percentage points
- > 20 percentage points

Abbreviations. ADHD: attention-deficit/hyperactivity disorder. OR: odds ratio.

eTable 3. Cohort-specific E-values, the minimum strength of association, on the risk ratio (RR) scale, that the exposure (per 10 mg/m^3 NO_2) must have with an unmeasured dichotomous confounder, and that the confounder must have with ADHD, to fully account for the observed exposure-ADHD odds ratio (OR) when, in fact, the true OR is 1.0 or 1.2.

	Weighted and adjusted ADHD OR,	Scenario: true ADHD OR=1				Scenario: true ADHD OR=1.2			
			NO_2-confounder / confounder-ADHD				NO_2-confounder / confounder-ADHD		
Cohort study[a]	per 10 ug/m^3 NO_2	E-value	RRs that conform to the E-value[b]			E-value	RRs that conform to the E-value[b]		
INMA-Gipuzkoa	0.63	1.83	1.83 / 0.55	or	0.55 / 1.83	2.10	2.10 / 0.48	or	0.48 / 2.10
ABCD	0.84	1.70	1.70 / 0.59	or	0.59 / 1.70	2.25	2.25 / 0.44	or	0.44 / 2.25
EDEN-Nancy	0.87	1.56	1.56 / 0.64	or	0.64 / 1.56	2.10	2.10 / 0.48	or	0.48 / 2.10
Generation R	0.87	1.56	1.56 / 0.64	or	0.64 / 1.56	2.10	2.10 / 0.48	or	0.48 / 2.10
CATTS	0.90	1.46	1.46 / 0.68	or	0.68 / 1.46	2.00	2.00 / 0.50	or	0.50 / 2.00
DNBC	0.92	1.39	1.39 / 0.72	or	0.72 / 1.39	1.93	1.93 / 0.52	or	0.52 / 1.93
INMA-Valencia	0.94	1.21	1.21 / 0.83	or	0.83 / 1.21	1.51	1.51 / 0.66	or	0.66 / 1.51
GINI/LISA-Munich	1.01	1.08	1.08 / 1.08	or	0.93 / 0.93	1.40	1.40 / 0.71	or	0.71 / 1.40
INMA-Sabadell	1.06	1.20	1.20 / 1.20	or	0.83 / 0.83	1.32	1.32 / 0.76	or	0.76 / 1.32
GINI/LISA-Wesel	1.11	1.46	1.46 / 1.46	or	0.68 / 0.68	1.38	1.38 / 0.72	or	0.72 / 1.38
GASPII	1.19	1.67	1.67 / 1.67	or	0.60 / 0.60	1.10	1.10 / 0.91	or	0.91 / 1.10
INMA-Granada	1.22	1.74	1.74 / 1.74	or	0.57 / 0.57	1.15	1.15 / 1.15	or	0.87 / 0.87
EDEN-Poitiers	1.45	2.26	2.26 / 2.26	or	0.44 / 0.44	1.71	1.71 / 1.71	or	0.58 / 0.58

[a] In ascending order of observed OR.

[b] Set of exposure-confounder / confounder-ADHD RRs that conform to the E-value. There are two sets per E-value. E.g., Under the scenario in which the true OR=1, the E-value for the CATTS is 1.46. This corresponds to a exposure-confounder RR $\geq$ 1.46 and a confounder-ADHD RR $\leq$ 0.68, or a exposure-confounder RR $\leq$ 0.68 and a confounder-ADHD RR $\geq$ 1.46.

Abbreviations. ADHD: attention-deficit/hyperactivity disorder; OR: odds ratio; RR: risk ratio.

REFERENCES

1. Forns J, Sunyer J, García-Esteban R, et al. Air pollution exposure during pregnancy and childhood behavioral disorder symptoms in eight European cohort studies. *Epidemiology.* 2018;25:xxx.
2. Lash TL, Fox MP, Fink AK. Spreadsheets from Applying Quantitative Bias Analysis to Epidemiologic Data. 2014; https://sites.google.com/site/biasanalysis/, February 23, 2018.
3. VanderWeele TJ, Hernan MA, Robins JM. Causal directed acyclic graphs and the direction of unmeasured confounding bias. *Epidemiology.* 2008;19(5):720-728.
4. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.* 2017;167(4):268-274.