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Bottleneck analysis: Simple prediction of the precision of a planned case–control or cohort study based on healthcare registers

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Abstract

Purpose: In pharmacoepidemiological studies, the precision of effect estimates usually depends on the lowest number in the underlying two by two table. We denote this the "bottleneck count" (BNC). We describe how to translate the BNC into an achievable precision and provide empirical examples.

Methods: First, we derive a theoretical prediction of the precision in a study where only the BNC determines precision. As an illustration, we calculated the expected precision of a null-effect study on retinoids and peptic ulcer bleeding, expressed as the upper/lower confidence limit ratio (ULCLR). Finally, we reviewed 126 effect estimates from the literature, analyzing the relationship between the predicted and achieved precision.

Results: The log–log transformed ULCLR was shown to be a simple linear function of log(BNC). The expected annual number of retinoid-users experiencing a peptic ulcer bleeding was 9.8, yielding an estimated ULCLR for a 1-year study of 3.84. The literature review showed an inverse linear relationship between the logarithmic BNC and the log–log transformed ULCLR, which was largely independent of study design, effect measure and category of BNC. Achieved precision deviated little from predictions but was usually lower than predicted, particularly with low BNC.

Conclusion: The precision of a study can be predicted simply and with good accuracy from the BNC, which is useful for determining whether a study is worth pursuing or not.

KEYWORDS
case–control studies, cohort studies, pharmacoepidemiological databases, statistical precision

1 | BACKGROUND

Assessing the magnitude of a dataset required to perform a pharmacoepidemiological study is an integral part of study planning. In a traditional power-calculation, assumptions about prevalence of treatment and strength of association leads to a sample size required to fulfill a prespecified desired probability of achieving statistical significance.[1] While this has become the default approach for randomized trials, there is a growing consensus that significance testing should be abandoned for observational studies,[2,3] and assessing the ability to produce a statistically significant results thus seems somewhat inconsistent in such observational studies. Second, in the setting of pharmacoepidemiological studies based on healthcare registers, the size of the data material is often given, with little or no possibility of increasing the data material according to the results of a power calculation. The question is rarely "how many do I need to recruit," but more often "what can I achieve with what I have." Third, pharmacoepidemiological studies often aim to refute poorly founded suspicions of adverse drug effects, that is, to demonstrate a null association as precisely as possible rather than to achieve statistical significance.

The study has not been presented elsewhere.

Therefore, the quantity of interest is not the statistical power but the expected precision, for example, quantified as the width of the confidence interval of the effect estimate. Predicting statistical precision and statistical power are sometimes used interchangeably. However, while power (likelihood of achieving a statistically significant result) is a function of effect size and precision, precision is unrelated to effect size.

Under most circumstances, the achieved precision depends strongly on the lowest number in the underlying 2 by 2 table. Accordingly, we term the smallest number the "bottleneck count" (BNC) and an endeavor to estimate it a "bottleneck analysis." The outcome of such a bottleneck analysis is an indication of whether a planned study is worth pursuing or should be abandoned on the basis of insufficient precision.

In a given source population, it is usually possible to sample more untreated (with or without outcomes) than treated in a cohort study, at least if the proportion of treated is not too high (<33%). Thereby the untreated:treated ratio can be elevated above 1:1. In a conventional case–control study using risk-set or incidence density sampling, it is nearly always possible to sample more controls (treated or not) than cases. It is, however, rarely possible to increase the number of treated having an outcome by changing the sampling strategy. Hence, treated subjects with the outcome are usually the limiting parameter for the achievable statistical precision in an efficiently designed study.

In this paper, we demonstrate how one can assess the achievable precision of a planned pharmacoepidemiological study by estimating the BNC under the null hypothesis. In addition, we review a number of published pharmacoepidemiologic cause-effect studies and establish the relationship between the precision estimated from the BNC and the actually achieved precision.

KEY POINTS

- The statistical precision of a planned observational study can be predicted from the lowest number in the basic 2×2 table of exposure and outcomes, the bottleneck count.
- This bottleneck count can often be calculated from publicly available data on exposure and outcome.
- An empiric review demonstrated good agreement between achieved precision and predicted precision based on bottleneck count.

2 | METHODS AND RESULTS

We first review how the BNC is related to the standard error of odds ratios and relative risks, when they are estimated from 2×2 tables. We then give an example of how the established relationship can be used to assess the precision of a planned registry-based study on the association between systemic retinoids and upper gastrointestinal bleeding (UGIB) (an assumed null association), based on published or publicly available data on treatment and outcomes in Denmark. Finally, we review cause-effect studies published in *Pharmacoepidemiology and Drug Safety* in 2015–2018 in order to identify the BNC and compare predicted and achieved precision.

2.1 | Precision of planned case–control study on the association between use of systemic retinoids and upper gastrointestinal bleeding

According to Cornfield,[4] an approximate confidence interval for the crude odds ratio in a 2×2 table (whether it is from a case–control or a simple cohort study) can be calculated from observing that the log(OR) has a standard error given by:

$$\mathrm{se}(\log(\mathrm{OR})) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}, \quad (1)$$

where a, b, c, and d are obtained from a conventional 2×2 table of number of individuals classified according to the binary treatment and the binary outcome:

		Outcome	
		+	–
Treatment	+	a	b
	–	c	d

Based on the estimated standard error the confidence limits are then computed on the log-scale using the standard normal approximation and finally back-transformed to the original odds ratio scale.

As is evident from Cornfield's equation, the precision depends on the figures a, b, c and d, and if just one of them is small compared to the others, then that smaller count will largely determine the size of the standard error. If, for example, a = 5 and b, c and d are all equal to 100, then the standard error is $\sqrt{0.23} = 0.48$, which is very close to the square root of a in itself, that is, $\sqrt{1/a} = \sqrt{0.2} = 0.45$. When the difference in magnitude between a vs the remaining cells increases, this approximation by $\sqrt{1/a}$ improves.

When a 2×2 table is instead analyzed by computation of a relative risk, its standard error on the log-scale is similar:

$$\mathrm{se}(\log(\mathrm{RR})) = \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}. \quad (2)$$

In the example above with a = 5 and with b, c and d all equal to 100, this standard error becomes $\sqrt{0.20} = 0.44$, which is even closer to the value of $\sqrt{1/a} = 0.45$. For both standard errors, their values come closer to $\sqrt{1/a}$ with larger values b, c and d.

TABLE 1 Assessment of precision in a hypothetical study on the association between systemic retinoids and upper gastrointestinal bleeding

Sex	Age group	Count of retinoid users	Incidence rate of upper gastrointestinal bleeding (/1000 person years)	Expected count of treated outcomes during 1 year
F	0–4	0	0.00	0.00
M	0–4	0	0.00	0.00
F	5–9	<5	0.00	0.00
M	5–9	<5	0.00	0.00
F	10–14	592	0.00	0.00
M	10–14	396	0.00	0.00
F	15–19	2587	0.00	0.00
M	15–19	3093	0.00	0.00
F	20–24	2500	0.26	0.64
M	20–24	1313	0.24	0.32
F	25–29	1542	0.06	0.09
M	25–29	515	0.63	0.32
F	30–34	713	0.11	0.08
M	30–34	277	1.03	0.29
F	35–39	540	0.51	0.27
M	35–39	173	0.96	0.17
F	40–44	461	1.51	0.70
M	40–44	153	3.00	0.46
F	45–49	277	1.40	0.39
M	45–49	138	2.80	0.39
F	50–54	111	2.81	0.31
M	50–54	109	5.07	0.55
F	55–59	54	3.63	0.20
M	55–59	96	7.52	0.72
F	60–64	24	4.46	0.11
M	60–64	50	10.37	0.52
F	65–69	23	8.13	0.19
M	65–69	71	13.69	0.97
F	70–74	17	12.96	0.22
M	70–74	38	21.82	0.83
F	75–79	12	19.87	0.24
M	75–79	16	29.86	0.48
F	80–84	0	28.18	0.00
M	80–84	8	41.83	0.33
F	85–89	0	42.66	0.00
M	85–89	0	52.40	0.00
F	90–94	0	29.51	0.00
M	90–94	0	70.74	0.00
F	95–99	0	38.17	0.00
M	95–99	0	101.48	0.00
SUM				9.77

Note: The data on count of users were from MEDSTAT.dk for the calendar year 2016.

The above derivation shows how we can link the BNC a to the uncertainty estimate of an odds ratio or a relative risk when we do not adjust for covariates. In almost all applications, the formulas above show that the precision predicted from the BNC will be an optimal precision for the unadjusted association. This is always the case for the OR, but is also true for the RR, whenever there are fewer patients

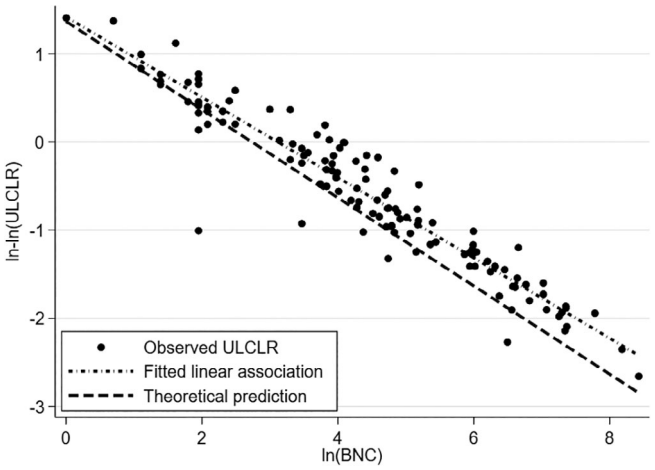

FIGURE 1 Empirical relationship between bottleneck count (BNC) and observed upper/lower confidence limit ratio (ULCLR) in 126 effect estimates from 57 publications in *Pharmacoepidemiology and Drug Safety*, 2015–2018

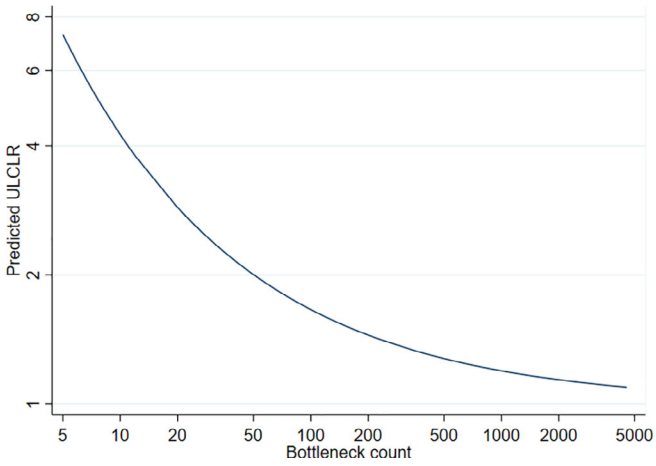

FIGURE 2 Relationship between the predicted ULCLR and the bottleneck count (BNC) in the simple empirical model with the BNC as the only predictor [Colour figure can be viewed at wileyonlinelibrary.com]

experiencing the outcome than not. When the odds ratio or relative risk is estimated with adjustment for covariates, there is no universal closed form expression for the standard as it is estimated based on optimizing the log-likelihood by numerical iteration. It is however known that for logistic regression the precision of the adjusted OR is lower than for the crude OR,[5] whereas there is no general rule for binary regression with a log-link (estimation of RR) or Cox-regression.[5]

As a measure of statistical precision in all analyses, we use the upper/lower confidence limit ratio (ULCLR) of the effect estimate (whether it is odds ratio, hazard ratio, incidence rate ratio or relative risk). This is equivalent to considering the magnitude of the standard error on the log scale for these relative measures. Following our derivation above, we assumed that the highest achievable precision (i.e., the lowest ULCLR) for a planned study would be equivalent to the ULCLR of an observed count of a, which corresponds to the likelihood-based standard error of a rate based on a events.

If the BNC is assumed to be the only factor contributing to the se (log(OR)) (Equation (1) above), then the expected confidence interval for the OR is given by

$$95\%\mathrm{CI}(\mathrm{OR}) = \left(\mathrm{OR}\cdot\exp\left(-\frac{1.96}{\sqrt{a}}\right);\mathrm{OR}\cdot\exp\left(\frac{1.96}{\sqrt{a}}\right)\right). \quad (3)$$

A similar expression would apply for the confidence interval of a relative risk, cf. Equation (2) above. When we divide the two limits to obtain the ULCLR, we find that it can be directly expressed as a linear function of the logarithmic BNC:

$$\log(\log(\mathrm{ULCLR}_{\mathrm{approx}})) = \log(2) + \log(1.96) - \frac{1}{2}\log(a). \quad (4)$$

2.2 | Example of using the BNC when planning a study

In our first application, we used this linear relationship (Equation (3)) to predict the ULCLR for a planned study on the association between systemic retinoids and upper GI bleeding, based on Danish registry data, assuming this to be a null association. To do so, we used two data sources; a published paper on the association between NSAIDs and upper gastrointestinal (GI) bleeding,[6] and www.medstat.dk,[7] a public data source on drug use in Denmark. From the paper by Hallas et al,[6] we retrieved data on the incidence rate of upper GI bleeding by sex and age in 5-year categories. From MEDSTAT, we retrieved the annual count of users of systemic retinoids use. MEDSTAT provides sex- and age-specific counts by either 1-year categories or certain age categories predefined by MEDSTAT. We transformed the MEDSTAT counts of users by sex and 1-year categories into sex and 5-year categories simply by summation of the counts for consecutive 1-year groups. We based all calculations on drug utilization data for the year 2016.

For a person categorized as having redeemed a prescription for systemic retinoids in 2016, we assumed that the person was a user for the entire year and calculated the person's 1-year cumulative risk of a having an upper GI bleeding using the incidence rates from Hallas et al.[6] The counts of users and the incidence rate of upper GI bleeding by sex and 5-year age categories are shown in Table 1, together with the expected count of treated subjects with outcomes in each age- and sex category. Based on these tabulations, we calculated the total expected number of treated outcomes for 2016 by summation across all sex- and age-categories.

TABLE 2 Linear regression of the log-transformed bottleneck count (BNC) and the corresponding log–log transformed observed ULCLR, adjusted for the type of association measure, study design and category of BNC in 126 effect estimates from 57 publications

Explanatory variable	Category	Simple model coefficient (95% confidence interval)	Full model coefficient (95% confidence interval)
log(BNC)		−0.46 (−0.48; −0.43)	−0.46 (−0.48; −0.44)
Study design	Cohort (Ref)	-	0.00 (Ref)
	Case–control	-	0.02 (−0.10; 0.14)
Type of BNC	Exposed without outcomes	-	0.28 (0.03; 0.53)
	Exposed with outcomes (Ref)	-	0.00 (Ref)
	Unexposed without outcomes	-	−0.29 (−0.50; −0.08)
	Unexposed with outcomes	-	0.09 (−0.02; 0.19)
Type of association measure	OR (Ref)	-	0.00 (Ref)
	Non OR	-	−0.15 (−0.27; −0.04)
Intercept		1.42 (1.30; 1.54)	1.51 (1.36; 1.65)

Note: The model had a root MSE of 0.244.

TABLE 3 Relationship between bottleneck count and predicted precision in a null result

	Theoretical optimum, prediction based on Equation (3)		Prediction based on simple empirical model in Table 2		
Bottleneck count	95% CI (null estimate)	ULCLR	95% CI (null estimate)	ULCLR	Relative increase in empirical ULCLR over theoretical optimum
5	(0.42; 2.40)	5.77	(0.37; 2.70)	7.27	1.26
10	(0.54; 1.86)	3.45	(0.49; 2.06)	4.25	1.23
20	(0.65; 1.55)	2.40	(0.59; 1.69)	2.87	1.20
50	(0.76; 1.32)	1.74	(0.71; 1.42)	2.00	1.15
100	(0.82; 1.22)	1.48	(0.78; 1.29)	1.66	1.12
200	(0.87; 1.15)	1.32	(0.83; 1.20)	1.45	1.10
500	(0.92; 1.09)	1.19	(0.89; 1.13)	1.28	1.07
1000	(0.94; 1.06)	1.13	(0.92; 1.09)	1.19	1.06

Note: ULCLR: ratio between upper and lower confidence limit.

2.3 | Empirical evaluation of the BNC as predictor of achievable study precision

We examined how close studies published during 2015–2018 in *Pharmacoepidemiology and Drug Safety* came to realizing the optimally achievable precision as predicted from the reported BNC. Thus, for each of the selected papers, we computed the actually achieved ULCLR, and we recorded the BNC. Only papers testing a hypothesis regarding a clinical drug effect were included, and only main results for each paper were incorporated in the analysis. We also required that the paper allowed us to identify all counts included in the 2×2 table for the main results. The results are shown in Table S1.

Following the formula for the linear relationship (Equation (4)) we first computed the predicted ULCLR from the reported BNC, and we then log–log transformed the observed ULCLR for each study and plotted it against the logarithmic BNC together with the predicted ULCLR. We used linear regression to quantify the observed relationship and we compared the estimated linear association with the theoretical one derived in Equation (4).

In the analysis of the empirical association, we estimated the association between logarithmic BNC and log(log(ULCLR)) with and without adjustment for the type of association measure (odds ratio or other [hazard ratio, relative risk, relative prevalence]), study design (cohort or case–control study) and category of BNC (exposed

with outcome, unexposed with outcome, exposed without outcome or unexposed without outcome), We used a Bland–Altman approach[8] to investigate how the difference in log(log(ULCLR)) between predicted and observed value varied with the corresponding average of the two. To aid planning of future studies, we computed the theoretical prediction of ULCLR for typical sizes of the BNC and the corresponding 95% confidence limits for a null estimate of the association. For comparison, we computed the same measures from the simple model for the empirical association without adjustment.

3 | RESULTS

The age- and sex-specific incidence rate of UGIB and the age- and sex-specific 1-year count of retinoid users are presented in Table 1. As shown, retinoids are primarily used by the young and the incidence rate of UGIB rises steeply with age. The sum of age- and sex-specific BNCs for 1 year is 9.77, corresponding to a predicted ULCLR of 3.83 for 1 year of data, corresponding to a null estimate of 1.00 (CI: 0.48–1.84). For 5 and 10 years of data, assuming similar outcome and treatment frequencies, a predicted ULCLR of 1.79 and 1.50 is found, corresponding to null-results of 1.00 (CI: 0.74–1.32) and 1.00 (CI: 0.81–1.22), respectively.

The review of 126 estimates from 57 publications from PDS is shown in Table S1 and depicted graphically in Figure 1. The BNC was the treated outcomes in 84 analyses (67%), untreated outcomes in 32 analyses (25%) and others in 10 (8%).

As expected from the theoretical derivation, we found a linear association the log–log transformed observed ULCLR and the corresponding log-transformed BNC (Figure 1). The theoretical association predicted lower values of the ULCLR than the best fitting linear relation, reflecting that the theoretical association ignores the uncertainty stemming from sources other than the BNC. Eleven studies (8.7%) had an achieved precision, which was better than the predicted precision. The achieved ULCLR was in general estimated to be between 5.5% (BNC of 1) and 70% (BNC of 4559) higher than the ULCLR with theoretical optimal precision (Figure 2).

When we estimated the univariate relation between the observed log–log transformed observed ULCLR and the corresponding log-transformed BNC, we estimated a slope of −0.46 (−0.48; −0.43). After incorporating the type of association measure, type of study design and type of BNC, the slope was virtually unchanged, −0.46 (−0.48; −0.44) (Table 2), but the estimated residual variation decreased to a root mean square error of 0.244 versus 0.267 (8.6% reduction). We found that studies using OR in general had a lower precision (larger ULCLR), which is in agreement with the difference in the formulas for the se(log OR) and se(log RR) for 2 by 2 tables. A few estimates (n = 11, 8.7%) achieved a better precision than what was predicted from the BNC, and in particular one estimate appeared to be an outlier (Figure 1). These estimates have been marked with an asterisk in Table S1.

Since the estimated relationship is difficult to visualize intuitively, we present the consequences of the estimated relationship in Table 3 for selected BNCs. When we compared the predicted precision as measured by the ULCLR to the corresponding observed values, we found an improving agreement with increasing sample size (Table 3). For small BNCs of 5, the empirical ULCLR was estimated to be 26% larger than the theoretical optimal ULCLR of 5.77, decreasing to 6% for a BNC of 1000.

4 | DISCUSSION

We demonstrated how it is possible to obtain an estimate of the achievable precision in a planned observational study. Our review of published papers showed that in general the achieved precision was in good agreement with the prediction based on the BNC alone. Other authors have presented methods to predict precision, based on assumptions about treatment prevalence and expected ORs, often based on knowledge obtained from pilot studies.[9] Our approach is simpler and does not require available data beyond the population's drug treatment and incidence rates for the outcome.

There are a few assumptions that should be discussed. First, in the retinoid example we considered a subject treated for a whole year, if that person was observed as a user within a calendar year. Retinoids should be taken long-term. According to medstat.dk statistics, the crude 1-year prevalence of use was 2.90 per 1000 in 2018, which should be contrasted to a therapeutic intensity of 1.0 defined daily doses used per 1000 inhabitants per day.[6] These figures suggest that, on the average, a retinoid user is only treated for about one third of the time within a calendar year if we assume a daily intake of one defined daily dose. However, if there are good reasons to assume short-term use, our calculations can easily accommodate that, for example by lowering the prevalence figures.

Another assumption is that there are no other weighty sources of imprecision than the BNC. This usually requires a sampling ratio different from 1:1. If, for example, a simple 1:1 propensity score matching is employed in a cohort study and the HR is close to 1, then the untreated patients with an outcome will be as numerous as treated subjects with an outcome and will contribute as much to the imprecision. Under such circumstances, precision can be improved by including more untreated, for example, by using a matching ratio of 4:1. It is also conceivable that other aspects of the design and analysis could contribute to imprecision, for example by using multiple, correlated control samplings or using multivariable modeling. In such cases, there is no simple analytic expression for the standard error of the effect estimate. However, the good agreement between predicted and actual precision in our literature review suggests that our simple equation is both valid and optimal for most purposes.

For some drug-outcome associations, we might under- or overestimate the BNC from population data. In the retinoids—UGIB example, retinoids are mainly used by young women, and UGIB mainly occurs in older men. Failure to account for age and sex, that is, using crude utilization figures and incidence rates, would thus have led us to seriously overestimate the BNC. It is conceivable that our example might have other confounders which we could have incorporated in our bottleneck estimate if we had sufficiently detailed data on the

incidence rate of outcome and the prevalence of drug utilization in subgroups.

Our analysis or published papers showed a few estimates (n = 11, 8.7%) being more precise than what was predicted from the BNC, and a single outlier having substantially better precision. For estimates of relative risks, we showed in our thought experiment in Section 2 that it was possible to achieve a better precision than predicted by our theoretical equation. However, of the 11 such studies, only 5 used a hazard ratio or relative risk as their association measure. For the remaining 6 studies using odds ratios achieving superior precision, we currently cannot determine how, and we note that this conflicts with theoretical results.[5]

If the actual effect measure deviates substantially from the null value, then the achieved precision will deviate from the expected precision as well, since actual BNCs will differ from predictions. Effect measures below one will lead to an over-estimated precision, whereas values above one will lead to an under-estimated precision. If a certain effect measure is expected, it can easily be incorporated in the predictions, for example an incidence rate ratio of 2 will correspond to a doubling of the BNC of treated outcomes. Of note, this reservation is not relevant for the comparison between predicted and achieved precision in Table S1 and Figure 1, as this is based on the actual, observed BNCs and not predicted ones.

In conclusion, it is possible to estimate the precision-limiting count of subjects in a planned non-experimental study and to translate that into an optimal achievable precision. A review of estimates in the literature showed good agreement between predicted and observed precision. It should be noted, however, that these precision estimates require that the design is optimal and that only the BNC contributes substantially to imprecision.

ETHICS STATEMENT

According to Danish law, pure register-based studies do not require ethics board review.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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