

# Measures of ‘exposure needed for one additional patient to be harmed’ in population-based case-control studies

Jesper Hallas<sup>1,2\*</sup>, Rene Depont Christensen<sup>1,3</sup>, Til Stürmer<sup>4</sup> and Anton Pottegård<sup>1,2</sup>

<sup>1</sup>Clinical Pharmacology, IST, University of Southern Denmark, Odense, Denmark

<sup>2</sup>Department of Clinical Chemistry and Pharmacology, Odense University Hospital, Odense, Denmark

<sup>3</sup>Research Unit of General Practice, University of Southern Denmark, Odense, Denmark

<sup>4</sup>Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, CB # 7435, Chapel Hill, NC, 27599-7435, USA

## ABSTRACT

**Purpose** The magnitude of risk for adverse drug reactions may be communicated by a measure of ‘exposure needed for one additional patient to be harmed’ (ENH). We present four ENH measures, based on four different counterfactual contrasts, as illustrated by the known effects of NSAID use on peptic ulcer bleeding.

**Methods** The four measures were basic ENH (estimating the excess risk when treating the entire source population versus treating no one), age-restricted ENH (the entire source population above, e.g. 50 years old treated versus no one above 50 years old treated), standardised ENH (a population of similar age and gender distribution as those actually treated versus same subjects not treated) and naturalistic ENH (those actually treated versus same subjects not treated).

Data were derived from a case-control dataset on NSAIDs and severe peptic ulcer bleeding, collected in Funen County in 1995–2006. We incorporated prescription and census data to account for the source population’s drug use.

**Results** Estimates of basic, age-restricted, standardised and naturalistic ENH were 619 person-years (py) (95% confidence interval (CI): 558–684), 223 py (CI: 201–246), 131 py (CI: 118–144) and 162 py (CI: 151–173). The age-restricted ENH showed strong dependence on the chosen age limit.

**Conclusion** The differing counterfactual contrasts underlying the ENH result in widely different estimates. These differences reflect the clinical and epidemiological aspects of NSAID-related peptic ulcer bleeding. The ultimate choice of ENH measure will depend on epidemiological or clinical considerations and on availability of data. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—case-control study; risk communication; NSAIDs; pharmacoepidemiology

Received 18 September 2013; Revised 07 March 2014; Accepted 3 April 2014

## INTRODUCTION

It is widely agreed that epidemiologists should communicate their research findings to the public.<sup>1</sup> However, it is not always easy to communicate quantitative measures of harmful drug effects. Relative risk measures are difficult to interpret in terms of the magnitude of risk,<sup>2</sup> and physicians and lay people may falsely equate strong associations or high levels of statistical significance with clinical importance.<sup>3</sup>

The number needed to treat (NNT) has been generally adopted as a means to communicate beneficial drug effects observed in randomised trials. Its

popularity is based on the belief that the NNT conveys drug effects to physicians and their patients in a single, easily understood measure.<sup>4</sup> The NNT for one additional patient to be harmed (NNTH) has been suggested as a variant to express harmful drug effects in randomised clinical trials (RCTs)<sup>5</sup> and in observational studies.<sup>6</sup> Surprisingly, there is very little literature on NNTH in observational studies, and there is no consensus on how it should be calculated.

Bjerre and LeLorier<sup>6</sup> suggested that an NNTH-like measure could be derived from case-control studies by

$$NNTH = \frac{1}{(OR - 1) \cdot UER} \quad (1)$$

where untreated event rate (UER) is the event rate among untreated subjects and OR is the odds ratio

\*Correspondence to: J. Hallas, Clinical Pharmacology, IST, JB Winsløvsvej 19, 2 5000 Odense C, Denmark. E-mail: jhallas@health.sdu.dk

associating treatment with the particular adverse event. The thinking is similar to the NNTH concept from trials;  $OR - 1$  in the denominator is the 'excess relative risk', which, multiplied by the baseline rate of events among the untreated, yields the rate difference between treated and untreated. Often, the UER can be found in the same publication as the OR, otherwise external sources may be used.<sup>6</sup>

The Bjerre and LeLorier method has deservedly been widely recognised, but it is not without problems. The counterfactual contrast underlying the method may be criticised for not being realistic. In the example of the link between NSAIDs and upper gastrointestinal bleeding (UGB), their UER was an incidence rate estimate based on an entire population.<sup>7</sup> Thereby, the derived NNTH can be interpreted as the number of UGB that would occur if the entire source population had been treated with NSAIDs, as compared with the situation where none in the source population had been treated. While this approach usually makes sense in the setting of an RCT, such a hypothetical scenario would give little guidance to clinical practice outside the RCT. For example, NSAIDs are rarely used in children, and the risk of NSAID-induced UGB in young persons is very low.<sup>8</sup> By using the entire source population's baseline risk for UGB in Equation 1, the NNTH estimate becomes inflated, indicating that NSAIDs would be safer than they actually are in clinical practice. For the patient categories who actually receive the drugs, the risk would be much higher, and the NNTH should correspondingly be lower.

The purpose of this paper was to further develop the concept behind NNTH and present some alternatives to the simple NNTH method described previously. We use data from an actual case-control dataset on serious peptic ulcer bleeding, combined with census data and data from a regional prescription database.

## METHODS

### Setting

We used a data set that has previously been used to study the association between selective serotonin reuptake inhibitors and serious peptic ulcer bleeding.<sup>9</sup> In brief, it is a matched case-control material based on all cases of serious UGB in Funen County, Denmark, from August 1995 through July 2006. The cases were identified by manual review of 12 607 discharge summaries. Controls were selected in a ratio of 10:1 by a risk-set sampling, matching on birth year and gender to the individual cases. All controls were assigned an index date similar to their corresponding cases.

Funen County is covered by a prescription database, Odense University Pharmacoepidemiological Database (OPED),<sup>10</sup> which allowed us to account for the cases' and controls' treatment, to describe the source population's drug use in detail and to estimate the UER. The OPED is derived from a health plan that offers prescription reimbursement for all citizens of Funen County, irrespective of income.

The original study from which the data were drawn was approved by the Danish Data Protection Agency. Approval from an ethics board was not required, according to Danish law.

### *Measures of exposure needed for one additional person to be harmed*

For this study, we defined treatment to NSAIDs by the redeeming of an NSAID prescription 90 days or less before the index date. For the sake of simplicity, we shall not consider NSAIDs bought over the counter (accounting for 21% of all NSAID use in our setting<sup>11</sup>), and the analysis shall not account for confounders other than age, gender and calendar time, which are all handled by using the matched data technique. In addition, we shall assume a uniform OR across all age groups and both genders. We will comment on these assumptions in the Discussion section.

It should also be clear whether the measuring unit is actually a count of persons followed for a defined period of time. Usually, the UER would have the form of an incidence density. As a simple matter of having consistent units in Equation 1, the NNTH measure should thus be in the form of an amount of treated person-time required to cause one additional outcome, not a count of treated persons. We therefore chose treated person-time instead of counts of treated persons as our measuring unit. The term employed will be 'exposure needed for one additional person to be harmed' or ENH.

Four methods of calculating the ENH are compared:

*Basic ENH method.* This approach is identical to the method used by Bjerre and LeLorier, except that it employs treated person-time as its unit. The UER was derived from the same source population as was used in establishing the case-control material, as described previously. The entire source population was used, and the counterfactual contrast underlying the basic ENH is what would have happened if the entire source population were treated versus if no one were treated.

*Age-restricted ENH method.* The counterfactual contrast underlying the basic ENH method is clinically

misleading, as it incorporates young subjects and children who are unlikely to be treated and to experience the adverse outcome and who would dilute the ENH towards unrealistically high values for older adults. This can be partly remedied by applying an age restriction on the basic ENH method, that is, confining the analysis to persons above a certain age limit. For the analysis of age-restricted ENH, we use Equation 1 but included only persons above an age limit of 50 years old, thus applying this limit both to the cases and the source population. A similar approach was used by our group in a study of anti-thrombotics and UGB.<sup>12</sup> The age-restricted ENH is equivalent to the counterfactual contrast of treating all the source population's subjects above the age of 50 years old versus treating no one above the age of 50 years old. To describe its sensitivity towards the age limit, we calculated the age-restricted ENH, while varying the limit between 20 and 80 years old in successive steps of 5 years.

*Standardised ENH method.* Any fixed limit used in the age-restricted ENH method is bound to be a compromise. With the limit of 50 years old, there are a few bleeding cases excluded, and the ENH estimates are based on persons who are not too unlikely to experience an adverse outcome and not too unlikely to be treated. On the other hand, the probability that a person in his early 50s will experience an NSAID-induced UGB is still low, and the inclusion of 50-year olds might also to some extent dilute the ENH towards unrealistically high values. As a solution, we propose an age-standardised and gender-standardised ENH. To do so, we created a reference population with an age and gender distribution similar to the distribution observed in prevalent NSAID users in our source population. We then calculated their expected crude UER by direct standardisation using the age-specific and gender-specific incidence rate of UGB among subjects untreated with NSAIDs. This UER estimate was then used as input for Equation 1. Age was categorised in 5-year bands.

The standardised ENH addresses the counterfactual contrast of what would happen if we treated a population with an age and gender distribution similar to the population that is actually treated versus not treating this population. Other characteristics are not taken into account. If, for example, NSAIDs are channelled to low-risk individuals within a given age, the standardised ENH would overestimate the risk for those who are actually treated.

*Naturalistic ENH method.* The naturalistic ENH is the reciprocal of the estimated excess rate among the exposed. All ENH measures express a ratio between an amount of exposure and the number of events that can be ascribed to that exposure. Both of these elements can be estimated separately for the treated. We thus calculated the naturalistic ENH as the entire cumulative NSAID exposure in the source population ( $PT_{exp}$ ), divided by the estimated number of bleeding cases caused by the NSAID exposure. The latter can be calculated as the number of treated cases,  $n_{exp}$ , multiplied by the attributable proportion among the treated, which again can be calculated as  $OR/(OR - 1)$ .<sup>13</sup> Thus,

$$\text{Naturalistic ENH} = \frac{PT_{exp}}{\left(\frac{OR-1}{OR}\right) \cdot n_{exp}} \quad (2)$$

This ENH measure calculates the ratio between cumulative exposure and the number of cases caused by the exposure, as the NSAIDs are actually used in the source population, that is, given the factual distribution between short-term and long-term exposure, between men and women, between high-risk and low-risk individuals, etc. The naturalistic ENH thus addresses the counterfactual contrast of what would happen if we treated the ones who actually received the treatment versus those who did not receive treatment, with their age and gender distribution and other characteristics taken into account. One important caveat is whether we can use a uniform OR for men, women, young, old, high-risk or low-risk individuals, etc. We address this limitation in the Discussion section.

#### *Statistical analysis*

We estimated the OR associating NSAIDs with UGB using conditional logistic regression with current NSAID use as the only independent variable. We extracted all NSAID prescriptions for the Funen County population for the period April 1995–July 2006 and used these to characterise the source population's NSAID use. We defined the treatment period for each prescription similarly to the treatment definition used for cases and controls, that is, assigning a period of 90 days to each prescription, starting on the date of dispensing. The treatment period was continued if a new prescription was redeemed before 90 days had passed. Census data for the Funen County were retrieved from Statistics Denmark.<sup>14</sup> These three data sources, OPED prescription data, census data and the case-control data set for UGB, allowed us to determine the cumulative age-specific and gender-specific

NSAID treatment in our source population and to estimate the crude and age-specific and gender-specific UER. In the standardisation procedures, age was categorized in 5-year bands.

Confidence intervals for ENH were calculated by two different approaches. For the basic ENH, age-restricted ENH and standardised ENH, it was assumed that the all-dominant source of variation was in the estimate of the OR because estimates of UER and age-specific and gender-specific user prevalence were invariably based on much larger numbers of observations. Hence, confidence intervals for basic ENH, age-restricted ENH and standardised ENH were calculated simply by substituting the OR with the lower and upper limit of the confidence interval for the OR.

For the naturalistic ENH,  $n_{exp}$  might show the same degree of variation as the OR, particularly if the numbers of controls and untreated cases were much larger than the number of treated cases. This pattern was actually observed. Also, the  $n_{exp}$  and the OR are mutually dependent. We therefore chose to calculate the confidence interval for naturalistic ENH using bootstraps.<sup>15</sup>

All analyses were performed using Stata version 11 (StataCorp, College Station, Texas 77845, USA).

## RESULTS

Out of the 3652 cases of UGB, 1213 (33%) were treated with NSAIDs, compared with 3887 (11%) of

the 36 502 controls. The OR, calculated by conditional logistic regression, was 4.28 (CI 3.97–4.64).

The age-specific and gender-specific point prevalence of NSAID use in the source population is shown in Figure 1. These were calculated as averages for the entire study period. Figure 2 shows the age-specific and gender-specific incidence rates of UGB among persons untreated with NSAIDs, also as averages for the entire study period.

The cumulative NSAID treatment during the entire study period was 263 661 person-years (py), and the total amount of follow-up in the source population was 5 216 918 py. Thereby, the cumulative amount of follow-up untreated with NSAIDs was 4 953 257 py, which gave rise to 2439 untreated cases and a UER of 4.9 per 10 000 py.

When restricting to subjects aged 50 years old or more, we found a cumulative NSAID treatment of 150 798 py and a total follow-up of 1 757 746 py. The corresponding follow-up untreated with NSAIDs was 1 606 948, giving rise to 2196 untreated cases and a UER of 13.7 per 10 000 py.

We present the results from the four different ENH methods in Table 1. Estimates of basic, age-restricted, standardised and naturalistic ENH were 619 py (CI: 558–684), 223 py (CI: 201–246), 131 py (CI: 118–144) and 162 py (CI: 151–173) respectively.

The age-restricted ENH showed a strong dependence on the chosen age limit (Figure 3), varying between 464 py for a limit of 20 years old to 75 py for a limit of 80 years old.

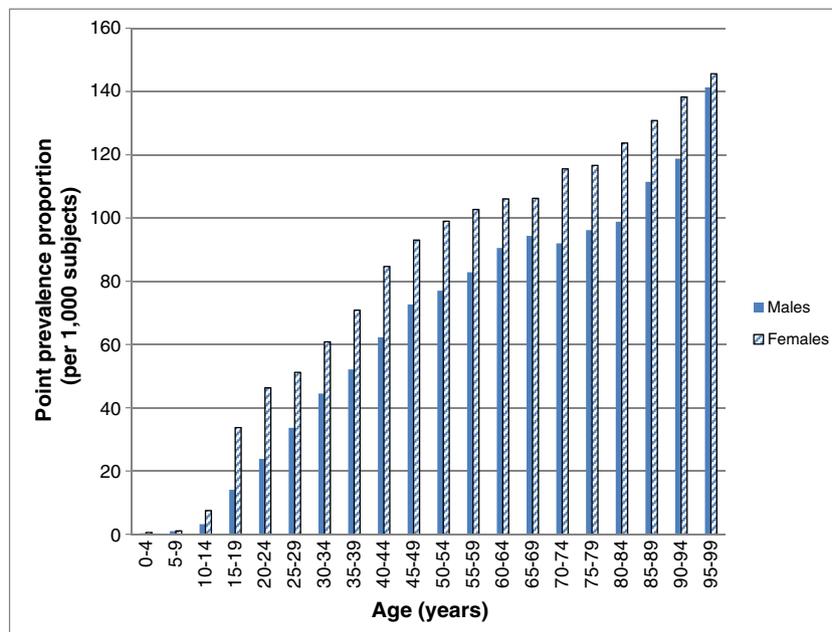


Figure 1. Age-specific and gender-specific point prevalence proportion of NSAID use for the Funen County. Average over the study period of 1995–2006

MEASURES OF ENH

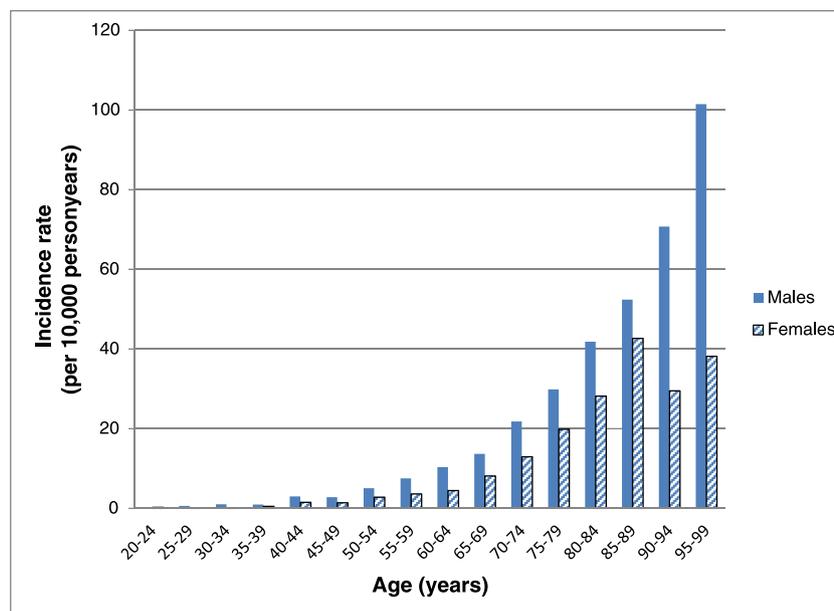


Figure 2. Age-specific and gender-specific incidence rate of serious upper gastrointestinal bleeding among subjects not treated with NSAIDs

Table 1. The exposure needed for one additional patient to be harmed (ENH) for the link between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and upper gastrointestinal bleeding

Model	Counterfactual contrast	Input	ENH value (95%CI)
Basic ENH	Entire source population treated versus no one treated	UER OR	619 (558–684)
Age-restricted ENH	Entire source population above 50 years old treated versus no one above 50 treated	Age-restricted UER OR	223 (201–246)
Standardised ENH	Population of similar age and gender distribution as those actually treated versus same population not treated	OR of age-specific and gender-specific NSAID user prevalence and age-specific and gender-specific UER	131 (118–144)
Naturalistic ENH	Those actually treated versus same persons not treated	OR of cumulative NSAID treatment for source population and number of treated cases	162 (151–173)

Illustrated by four different models.

UER, untreated event rate; OR, odds ratio; CI, confidence interval.

DISCUSSION

The four models for ENH presented in this paper produce different estimates, which can be explained by their different counterfactual contrasts. As expected, the highest ENH was found for the basic ENH, as it estimates the contrast between treating versus not treating the entire source population, including a vast contingency of low-risk subjects with low prevalence of use. The finding of a standardised ENH that is slightly lower than the naturalistic ENH suggests that factors other than age and gender are taken into account when prescribing NSAIDs and that—for a given age and gender—they are to some extent channelled to persons at a lower than average risk of the outcome.

From a conceptual viewpoint, the naturalistic ENH may appear as the most appealing. The age-restricted

or age-standardised ENH may take age and gender into account, but other characteristics, such as relative contraindications to NSAIDs, may be difficult to include. These factors are accounted for by the naturalistic ENH, even without measuring them. In fact, even age and gender may be ignored when calculating the naturalistic ENH, if a uniform OR can be assumed. Then, why offer four models for ENH? Clinical considerations may be relevant for the choice of the model. In the NSAID–UGB scenario, there is a very low risk in young NSAID users.<sup>18</sup> It might therefore be considered misleading to include young NSAID users in the ENH estimate, and an age-restricted ENH could be considered the model of choice. The data available in a given setting may not allow a calculation of the age-restricted, age-standardised or naturalistic ENH. Even the basic ENH may be difficult to

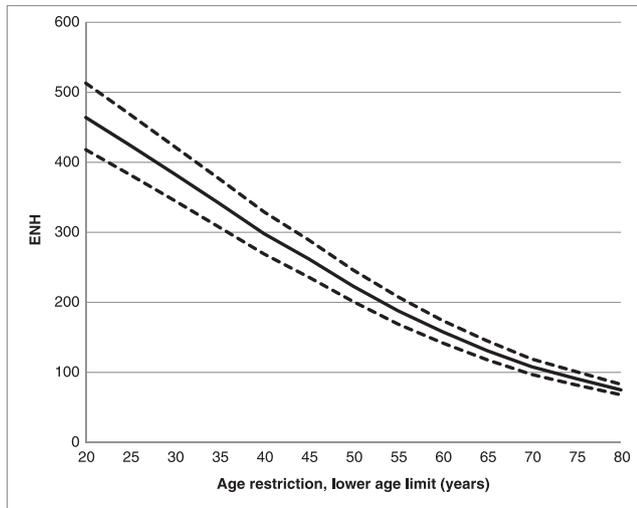


Figure 3. Dependence on the age limit for the age-restricted exposure needed for one additional patient to be harmed (ENH)

estimate in some situations. Particularly, estimating the untreated event rate may be problematic, if the user prevalence is high but unknown. Thus, in practice, it will often be necessary to select the method on the basis of availability of data rather than the ideal counterfactual contrast. In this context, it is noteworthy that only the basic ENH can realistically be applied to data retrieved by literature search, as in the examples provided by Bjerre and LeLorier.<sup>6</sup> The basic ENH can thus be viewed as a potential ‘reader’s tool’, while the other three are ‘researcher’s tools’.

It may be argued that if, for example, the naturalistic ENH requires data on the entire source population’s drug use and outcomes, then why not use the same data to conduct a cohort study and estimate the ENH measures directly. There may, however, be reasons to prefer a population-based case-control approach over a cohort approach, even when all data are available. The population-based case-control approach is computationally very efficient and produces the same estimates as the cohort approach with little or no loss in precision.<sup>17,18</sup> For the naturalistic ENH, however, we need cohort data anyway. A cohort design could be used to estimate the treatment effect in the treated, including the naturalistic ENH, directly without the need for a uniform treatment effect assumption.<sup>19</sup>

### Limitations

For the sake of simplicity, we used a number of short cuts in our analysis. We used a uniform OR across all ages, we did not consider the time dependence of the OR, we did not adjust for confounders in the

calculation of the OR, and we used a fairly crude exposure definition. These limitations could all be easily remedied by extending the analysis, for example, by using adjusted ORs or by calculating age-specific ORs. For the NSAID–UGB association, using a uniform OR is not entirely inappropriate. The OR (or other relative measures) for this particular association is fairly stable across age groups,<sup>20,21</sup> even though the baseline risk varies by several orders of magnitude (Figure 2). The OR is also remarkably similar in high-risk and low-risk individuals.<sup>20</sup> With other drug–disease associations, a constant biological effect (on an absolute scale) would entail a decreasing relative effect with increasing baseline risk,<sup>22</sup> in which case a uniform OR would not be appropriate.

The clinical utility of the age-restricted ENH may be debated. A physician who is about to treat a given patient would know his/her exact age not just that the patient was above 50 years old. If the risk varies strongly with age, as is the case with the NSAID–UGB association, an age-stratified model might be more useful from a clinical perspective. The model could also include other well-known effect modifiers.

For NSAID-related UGB, it has been shown that the OR is time dependent with the highest relative risk being found during the first months of treatment. This could be handled by a time-dependent model, for example, calculating the naturalistic ENH for the first three months of treatment, for months 4–6, etc. It might also be extended by age categorisation. This would allow us to relax the assumption of uniform ORs. Obviously, the ENH model should reflect the complexity of the OR estimates. If the OR is calculated without specifying the time- or age dependence, then a time- and age-dependent ENH model would make little sense. Unfortunately, few studies are large enough to allow an extensive stratification, or the relevant effect modifiers may not be known.

Another limitation is that three of the models, the age-restricted, age-standardised and naturalistic ENH, all require data on the source population’s drug treatment. Not all settings can offer this. However, as the controls in a case-control study should represent the exposure attributes of the source population, the source population’s exposure might be modelled from data on the controls’ treatment, at least if the sampling fractions are known. Finally, one may question whether ENH is an easily understood measure of the drug’s toxicity. Research on interpretations of NNTs from clinical trials shows that lay people and prescribers are remarkably unresponsive, making the same therapeutic decision across a wide range of given NNT values.<sup>23,24</sup>

This suggests that the NNT is not as intuitive as we would like to believe. This may apply to the ENH as well, irrespective of the chosen method.

Measures of ENH should be used to better quantify and communicate risk for harm from pharmaco-epidemiologic studies. We propose the extension of existing ENH measures for case-control studies based on different causal contrasts. The naturalistic ENH based on the causal contrast of what would hypothetically have happened if everyone who actually received the treatment did not receive treatment might be most relevant in many settings.

## CONFLICT OF INTEREST

J.H. has participated in research projects funded by Novartis, Pfizer, Menarini, MSD, and Takeda with grants paid to the institution where he was employed. He has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers and from Takeda, Pfizer, Novartis and Menarini. T.S. has received investigator-initiated research funding and support as Principal Investigator (R01 AG023178) from the National Institute on Aging at the National Institutes of Health. T.S. also received research funding as Principal Investigator of the University of North Carolina Develop Evidence to Inform Decisions About Effectiveness centre from the Agency for Healthcare Research and Quality. T.S. does not accept personal compensation of any kind from any pharmaceutical company, although he has received salary support from the Center for Pharmaco-epidemiology and from unrestricted research grants from pharmaceutical companies (GlaxoSmithKline, Merck, Sanofi and Amgen) to his research department. R.C. and A.P. declare none.

## KEY POINTS

- The magnitude of a risk identified in a case-control study may be communicated by a measure of the amount of exposure that on the average would be required to produce one additional outcome.
- This measure can be constructed on the basis of different underlying contrafactual experiments, for example, treating the entire source population versus treating no one. Four of such measures are presented.
- The ultimate choice of the ENH measure will depend on clinical considerations and availability of data.

## ETHICS STATEMENT

The study was approved by the Danish Data Protection Agency. Approval from an ethics committee is not required for a pure register study according to Danish law (ref 16).

## ACKNOWLEDGEMENT

The project was funded by the University of Southern Denmark.

## REFERENCES

1. International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf* 2008; **17**: 200–208.
2. Sackett DL, Deeks JJ, Altman DG. Down with odds ratios!. *Evid Based Med* 1996; **1**: 164–166.
3. Gigerenzer G, Gaissmaier W, Kurz-Milcke E, Schwartz LM, Woloshin S. Helping doctors and patients to make sense of health statistics. *Psychol Sci Public Interest* 2007; **8**: 53–96.
4. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995; **310**: 452–454.
5. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998; **317**: 1309–1312.
6. Bjerre LM, LeLorier J. Expressing the magnitude of adverse effects in case-control studies: "the number of patients needed to be treated for one additional patient to be harmed". *BMJ* 2000; **320**: 503–506.
7. Carson JL, Strom BL, Soper KA, West SL, Morse ML. The association of non-steroidal antiinflammatory drugs with upper gastrointestinal tract bleeding. *Arch Intern Med* 1987; **147**: 85–88.
8. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Complicated and uncomplicated peptic ulcers in a Danish county 1993-2002: a population-based cohort study. *Am J Gastroenterol* 2006; **101**: 945–953.
9. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2009; **7**: 1314–1321.
10. Gaist D, Sørensen HT, Hallas J. The Danish prescription registers. *Dan Med Bull* 1997; **44**: 445–448.
11. www.medstat.dk [22 April 2014]
12. Hallas J, Dall M, Andries A, et al. Use of single and combined antithrombotic therapy and the risk of serious upper gastrointestinal bleeding. A nested case-control study. *BMJ* 2006; **333**: 726–730.
13. Rothman KJ. Epidemiology – an introduction. Oxford University Press: Oxford, England, 2002. p. 53.
14. www.dst.dk [22 April 2014]
15. Haukoos JS, Lewis RJ. Advanced Statistics: Bootstrapping Confidence Intervals for Statistics with "Difficult" Distributions. *Acad Emerg Med* 2005; **12**(4): 360–365.
16. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) Registers on Health and Social Issues: Structure, Access, Legislation, and Archiving. *Scand J Publ Health* 2011; **39**(Suppl 7): 12–16.
17. Essebagg V, Platt RW, Abrahamowicz M, Pilote L. Comparison of nested case control and survival analysis methodologies for analysis of time-dependent exposure. *BMC Med Res Methodol* 2005; 5–10.
18. Essebagg V, Genest J, Jr, Suissa S, Pilote L. The nested case-control study in cardiology. *Am Heart J* 2003; **146**: 581–590.
19. Stürmer T, Rothman KJ, Glynn RJ. Insights into Different Results from Different Causal Contrasts in the Presence of Effect-Measure Modification. *Pharmacoepidemiol Drug Saf* 2006; **15**: 698–709.
20. Hallas J, Lauritsen J, Villadsen HD, Gram LF. NSAID and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. *Scand J Gastroenterol* 1995; **30**: 438–444.
21. Hernández-Díaz S, Rodríguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000; **160**: 2093–2099.
22. Rothman KJ, Poole C. A strengthening programme for weak associations. *Int J Epidemiol* 1988; **17**: 955–959.
23. Christensen PM, Brosen K, Brixen K, Andersen M, Kristiansen IS. A randomized trial of laypersons' perception of the benefit of osteoporosis therapy: number needed to treat versus postponement of hip fracture. *Clin Ther* 2003 Oct; **25**(10): 2575–2585.
24. Halvorsen PA, Kristiansen IS. Decisions on drug therapies by numbers needed to treat: a randomized trial. *Arch Intern Med* 2005; **165**: 1140–1146.