



Measures of “exposure needed for one additional patient to be harmed” in population-based case-control studies.

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Conflict of interest

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Background & Objectives

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). The ENH expresses the number of person years’ of exposure that on the average would be required to provoke one additional outcome, given the calculated ORs and other study output.

We present four ENH measures, based on four different counterfactual contrasts, as illustrated by the known association between NSAID use and peptic ulcer bleeding.

Methods

Data were derived from a case-control dataset on NSAID and severe peptic ulcer bleeding, collected in Funen County 1995-2006. We incorporated prescription and census data to account for the source population’s drug use and demography. Four measures of ENH were calculated:

- **Basic ENH** (the entire source population treated vs none treated)

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

Where UER is the incidence rate of the outcome among unexposed in the source population, and OR the odds ratio associating exposure with the outcome

- **Age-restricted ENH** (the entire source population above e.g., 50 vs none above 50 treated)
The equation is applied only to the source population and case material above 50 year of age
- **Standardised ENH** (a population of similar age- and gender distribution as those actually treated vs same subjects not treated)
The equation is applied to a standardized data set.
- **Naturalistic ENH** (those actually treated vs same subjects not treated).

$$\text{Naturalistic ENH} = \frac{\text{PT}_{\text{exp}}}{\left(\frac{\text{OR}-1}{\text{OR}}\right) \cdot n_{\text{exp}}}$$

Where PT_{exp} denotes the cumulative amount of exposed person-time in the source population and n_{exp} is the number of exposed cases in the data set.

Table 1

The exposure needed for one additional patient to be harmed (ENH) for the link between use of non-steroidal antiinflammatory drugs (NSAIDs) and upper gastrointestinal bleeding, illustrated by four different models.

Model	Counterfactual contrast	Input	ENH value, person-years (95% CI)
Basic ENH	Entire source population treated vs none treated	Untreated event rate Odds ratio	619 (558 - 684)
Age-restricted ENH	Entire source population above 50 years treated vs none above 50 treated	Age-restricted untreated event rate Odds ratio	223 (201 - 246)
Standardised ENH	Population of similar age- and gender distribution as those actually treated vs same persons not treated	Odds ratio Age- and gender specific NSAID user prevalence Age- and gender-specific untreated event rate	131 (118 - 144)
Naturalistic ENH	Those actually treated vs same persons not treated	Odds ratio Cumulative NSAID treatment for source population Number of treated cases	162 (151-173)

The input required to calculate each of these measures is shown in table 1.

Results

The four methods resulted in widely different ENH-values, ranging from 131 personyears of exposure to 619 personyears of exposure (Table 1). The value of the age-restricted ENH depended strongly on the chosen age-limit (Figure 1).

Conclusions and Discussion

The differing counterfactual contrasts underlying the ENH result in widely different estimates. These differences are best understood by considering the clinical aspects of NSAID-related peptic ulcer bleeding; strong age dependency of NSAID use, strong age dependency in the incidence rate of outcome, little age dependency of the odds ratio and channeling of NSAIDs to persons with high tolerance for a given age. The ultimate choice of ENH measure will depend on clinical or epidemiological considerations and on availability of data.

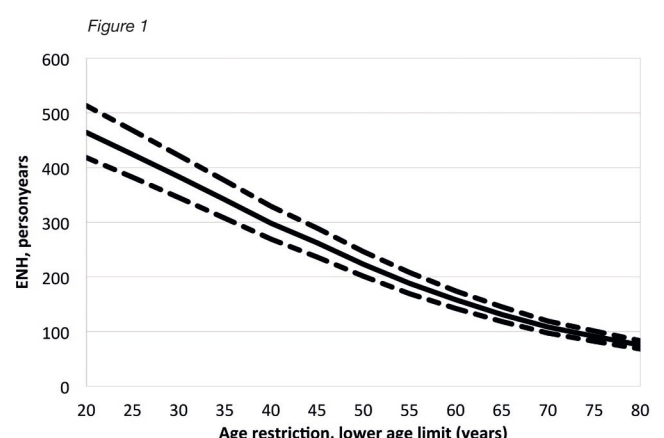


Figure 1: Age dependency of the lower limit in the age-restricted “Exposure needed for one additional patient to be harmed”