THEORY AND APPLICATION OF ATTRIBUTABLE RISK ESTIMATION IN CROSS–SECTIONAL STUDIES

Olaf Gefeller

Department of Medical Statistics, Georg–August–University of Göttingen

The question of public health importance of an exposure for a particular disease is addressed by the concept of attributable risk. The four main types of attributable risk definitions in the literature are reviewed in this paper. Special attention is paid to the estimation problem in cross–sectional studies in which the potential prevalence–incidence bias needs adequate consideration. The extension to the multivariable case to adjust for confounding and effect–modification is sketched in the paper. A practical illustration of definitions and methods is given using data of the Luebeck Blood Pressure Study, a cross–sectional study in the field of cardiovascular disease epidemiology.

1. INTRODUCTION

Many measures of association to describe the relationship between two variables have been proposed in the literature. In various fields of statistical application like psychology, sociology, biology, or epidemiology different measures have come into fashion, because of their specific, application–orientated interpretation. In the epidemiologic context the relative risk and as its approximation the odds ratio play a dominating role. But there are other features of the relation between a disease variable and an exposure characteristic which are of interest in epidemiologic studies. Therefore another type of measures of the disease–exposure association, which has been referred to as attributable risk, is discussed in this paper.

Relative risk is defined as the relative increase (or decrease) of the disease probability among exposed subjects compared to unexposed. It may be thought of as indicating the strength of the physiologic effects of the exposure to the disease under study. On the other hand, this measure does not take into account the proportion of individuals exposed to the risk factor in the population, and so it is quite possible to identify a risk factor with a high relative risk, but which is not an important public health problem, because very few individuals are exposed to it. There are many examples of this type in the field of occupational epidemiology [1].

The paper is organized as follows: in chapter 2 the four definitions of attributable risk are reviewed. The confusion in terminology and algebraic formulation relating to this concept is discussed in chapter 3. The estimation of attributable risk in the situation of a 2x2–table from cross–sectional data is considered in chapter 4. Special attention is paid to the prevalence–incidence problem in cross–sectional studies. The extension of the simple 2x2–table situation to the multivariable case to adjust for confounding and effect–modification in the estimation of attributable risks is covered in chapter 5. Data of the Luebeck Blood Pressure Study are used in chapter 6 as a practical illustration of definitions and methods. Finally in chapter 7 conclusions concerning the application of this concept are discussed.

2. DEFINITIONS OF ATTRIBUTABLE RISKS

Consider a population that is classified into groups according to a dichotomous disease variable D and some dichotomous exposure characteristic E. Let $P(D \mid E)$, $P(D \mid \bar{E})$, $P(D)$ represent the incidence (or prevalence) of disease among the exposed, the unexposed, and the entire population, respectively. There are four main types of attributable risk definitions in the literature:

$$RD := P(D \mid E) - P(D \mid \bar{E}) \tag{1}$$

Berkson [2] proposed this simple difference of the conditional disease probabilities among the exposed and unexposed to measure the risk due to the exposure on an absolute scale. This 'risk difference' has often been referred to as attributable risk, even in a number of widely used epidemiologic textbooks [3–6].

$$PRD := P(E) \cdot \left[P(D \mid E) - P(D \mid \bar{E}) \right] = P(D) - P(D \mid \bar{E}) \tag{2}$$

This measure introduced by MacMahon and Pugh [3] multiplies the risk difference by the exposure prevalence to quantify the absolute exposure impact on the disease load in the population. The formula is equivalent to the difference of the disease probability in the entire population and the conditional one among the unexposed. Usually this measure is called 'population risk difference', 'population attributable risk', or 'population excess risk'.

$$AR := \frac{P(D) - P(D \mid \bar{E})}{P(D)} \tag{3}$$

The third attributable risk definition can originally be found in a paper by Levin in 1953 [7]. It is the oldest definition associated with the term 'attributable risk' in this list. The ratio of probabilities can be interpreted as the proportion of cases of

disease due to the exposure among all cases of disease in the population.

$$ARE := \frac{P(D|E) - P(D|\bar{E})}{P(D|E)} = \frac{RR - 1}{RR} \tag{4}$$

For the sake of completeness, the last measure, the attributable risk among the exposed, introduced by Cole and MacMahon[8] has to be mentioned. It very similar to (3), but it restricts its attention to the exposed part of the diseaded population. It can be rewritten as a function of the relative risk.

These four definitions seem to be very different at first glance, but in fact they are closely related to each other. All four definitions of attributable risk focus on the exposure–specific disease probability, but all under different conditions. The intrinsic relationship of these measures to each other is discussed in [9].

3. TERMINOLOGY

There is a considerable confusion in terminology and algebraic definitions relating to the concept of attributable risk in the epidemiologic literature. In an excellent article by Greenland and Robins [10] the following passage can be found "While the concept is known by many names..., we would think this variety would cause no problem as long as the conceptual and algebraic formulation were unambiguous. Unfortunately,...distinct concepts have been variously identified as the attributable fraction (risk), although these concepts have usually not been distinguished in the literature." That sheds a light upon the situation. In another part of the same article they state "The number of terms for AR is perhaps the largest of any concept in epidemiology." An own literature review supports their opinion. In epidemiologic journals and textbooks I have found sixteen different terms used for Levin's attributable risk as defined in (3). They are listed in table I.

Tab. I: Terms used synonymously for AR in the epidemiologic literature.

• attributable risk	• assigned share
• attributable fraction	• associated mortality ratio
• attributable proportion	• population attributable risk
• attributable risk ratio	• population attributable fraction
• attributable risk percentage	• population proportional attributable risk
• etiologic fraction	• population attributable risk percent
• excess fraction	• population attributable rate
• probability of causation	• population attributable different percent

4. ESTIMATION OF ATTRIBUTABLE RISK IN CROSS–SECTIONAL STUDIES

The statistical consideration of attributable risk estimation in the situation of a 2x2–table from cross–sectional data is simple. The sampling model in this situation is represented by a multinomial distribution with five parameters (the sample size and the four cell probabilities). The maximum likelihood estimator of the attributable risk defined in (3) – which is consistent and asymptotically normal in this situation – and its asymptotic variance can be easily derived. It is:

$$\widehat{AR} = \frac{ad - bc}{(a+c)\cdot(c+d)}$$

$$\widehat{Var}\widehat{AR} = \frac{cN\cdot\left(ad\cdot(N-c)+bc^2\right)}{(a+c)^3\cdot(c+d)^3}$$

where a denotes the number of exposed cases, b the number of exposed non–cases, c the number of unexposed cases, d the number of unexposed non–cases, and N the total number of subjects, respectively.

More problematic is the cross–sectional study design itself. There are many limitations of the cross–sectional study design, but for the purpose of this paper I want to focus on the prevalence–incidence problem. Prevalence and incidence are very different measures of disease frequency. Incidence relates to the new occurrences of cases within a specific time interval in a population, whereas prevalence measures the existing proportion of cases at a fixed point in time in a population. In cross–sectional studies only the prevalence can be studied. But the prevalence depends on the number of new occurrences and the duration of the disease. The duration of the disease relates to the case–fatality and the recovery–rate. As a consequence the prevalence involves factors which are irrelevant when studying the causes of disease, and which can distort the analysis. If we have only prevalence data to study the association between a disease and potential risk factors, at least the following assumptions have to be fulfilled:

- the occurrence of disease does not lead to a change of the exposure status
- the exposure is not a 'prognostic factor', i.e., the duration of disease is independent of the exposure status.
- the exposure information is relevant for the disease under study (adequate time frame).

In general, a great deal of a priori information is needed for an analysis based on cross–sectional data to conduct a reasonable study.

5. EXTENSION TO THE MULTIVARIABLE CASE

The reduction to a simple 2x2–table of disease and exposure is often an unrealistic approach to estimate the potential exposure impact on the disease load in the population. Therefore, the 2x2–table situation has to be extended to the multivariable case to adjust for confounding and effect–modification. This extension leads to the situation of a 2x2xK–table where the third dimension is represented by a stratum variable C with K levels, which could be one observed variable or a construct of the combination of two or more variables. The distributional assumption in the situation of a cross–sectional study and post–sampling stratification is that of one multinomial distribution with 4K+1 parameters (sample size and 4K cell probabilities). Two different models should be distinguished: *(i)* the homogeneity model, *(ii)* the interaction model. In the homogeneity model C acts as a pure confounding variable, i.e., the relative risks in the strata are all equal but different from the crude relative risk in the collapsed 2x2–table. In the interaction model C acts as an effect–modifying variable, i.e., the relative risks differ between the strata.

Different strategies to adjust for confounding and effect–modification in the estimation of attributable risks have been proposed in the literature [11–18]. These strategies can be categorized into three types. Type I estimators employ a weighting procedure of the stratum–specific attributable risk estimates. Type II estimators use the functional relationship of relative and attributable risk to adjust attributable risk via adjustment of the relative risk. The type III estimator adapts Miettinen's factorization idea in the context of relative risk adjustment [19] to attributable risk adjustment. A formal presentation and a detailed discussion of these estimators are given elsewhere [20]. A simulation study was conducted to investigate the finite properties of these adjusted attributable risk estimators under the unrestricted multinomial sampling model of the cross–sectional study design. The simulation study demonstrated that the maximum likelihood estimator will be the best overall choice under this sampling model. It was practically unbiased in all situations. Other adjusted attributable risk estimators depended heavily on the underlying structure of the multinomial model. Details of design and results are provided in [21].

6. EXAMPLE: THE LUEBECK BLOOD PRESSURE STUDY

As a practical illustration of definitions and methods discussed in this paper data of the Luebeck Blood Pressure Study (LBS), a study in the field of cardiovascular disease epidemiology, are used. The LBS is a cross–sectional study on a systematic random sample of 3100 (2833 available) Luebeck citizens, aged 30 to

69 years, of whom 2359 took part in the study. Details of the study design and particular results have been published elsewhere [22–24]. The principal goal of the LBS was to provide data on the prevalence, awareness, treatment, and control of hypertension and on other cardiovascular risk factors in a urban middle–aged population. For the purpose of this illustration data on the relationship between hypertension (the disease variable) and obesity (the exposure variable) in men are selected. The crude 2x2–table is given in table II.

Tab. II: Data of Luebeck men aged 30–69 yrs on the relationship between hypertension and obesity (LBS 1984).

	hypertensive	not hypertensive	
obese	165	553	718
not obese	46	301	347
	211	854	1065

$$\widehat{RD} = 0.097$$
$$\widehat{PRD} = 0.065$$
$$\widehat{AR} = 0.331$$
$$\widehat{ARE} = 0.423$$

Using this data Berkson's risk difference *RD* can be calculated as 0.097, meaning that the hypertension probability is 0.097 higher among obese men compared to non–obese. In this example obesity is defined using the Body Mass Index and a cutpoint of 25 kg/m ^{2} as recommended by Bray [25]. Employing this exposure definition we yield a very high exposure prevalence (67.4%) in this population. As a consequence the population risk difference *PRD* is not much below the risk difference. 6.5% of the population suffer from hypertension due to obesity. Levin's attributable risk is computed as nearly one third, meaning that among all hypertensives one third can be attributed to obesity. The *ARE* value of 0.423 can be interpreted in the way that among all obese hypertensives 42.3% of the cases are attributable to the exposure 'obesity'.

These values are epidemiologically meaningless unless we consider the potentially confounding or effect–modifying effects of other variables. In this situation age is know to be a relevant confounder. After stratifying by age (in ten year age groups) different adjustment methods were employed. Table III summarizes the results of these methods.

Tab. III: Relationship between hypertension and obesity in 1065 Luebeck men aged 30–69 yrs.

Estimator	Point estimate	Asymptotic standard error	95% – CI (Logit–Version)
Type I:			
– case load	0.317	0.085	(0.177, 0.500)
– precision	0.318	0.083	(0.181, 0.496)
Type II:			
– Mantel–Haenszel	0.318	0.083	(0.181, 0.496)
– Tarone	0.318	0.083	(0.180, 0.496)
– OR–approximation	0.369	0.088	(0.217, 0.551)
Type III:	0.326	0.097	(0.169, 0.535)

The estimates are very similar with the exception of the type II estimator based on the odds ratio and the type III estimator. The former one is much too high, because the odds ratio constitutes a bad approximation to the relative risk in this situation. The type III estimator revealed bad properties under a variety of situations in the simulation study [21]. In this particular case its bias is only small.

7. DISCUSSION

In this paper the concept of attributable risk has been reviewed to contribute to a better understanding of these measures. When analysing epidemiologic data on the relationship between a disease and an exposure, it is unjustified to reduce the analysis to the calculation of relative risks. Attributable risk should in no way be regarded as a substitute for relative risk, but rather as an additional dimension of the health hazard appraisal. The identification of an exposure characteristic with a high relative risk may yield important clues to the mechanism of the disease development. But this would be of little interest to health administrators planning preventive strategies for the disease, if the same exposure were found only rarely in the population. This question of public health importance is addressed by the concept of attributable risk.

Special attention has to be paid to the cross–sectional study design. Under special circumstances prevalence data obtained in a cross–sectional study can form a solid basis for an analysis of the disease–exposure association, but usually these assumptions are not fulfilled. In practical applications one should carefully scrutinize the medical background of the association under study and what prevalence data can tell about it.

The multifactorial approach to adjust for confounding and effect–modification in the estimation of attributable risk is often more realistic than the reduction to a simple 2x2–table of disease and exposure. Therefore, one should routinely incorporate these adjustment methods when estimating attributable risk. The resulting estimate may reveal an interesting feature of the association under study.

ACKNOWLEDGEMENT

The author gratefully acknowledge the support of Prof. Dr. S. Schach. The "Arbeitsgruppe Epidemiologie" at the GSF–Medis Institute and especially Prof. Dr. U. Keil kindly made the data of the Luebeck Blood Pressure Study available to the author. Ms A. Pfahlberg and Ms A. Ochsmann deserve special thanks for their technical assistance in preparing the manuscript.

REFERENCES

(1) Monson, R.R. (1980): Occupational epidemiology. CRC Press, Boca Raton.
(2) Berkson, J. (1958): Smoking and lung cancer. Some observations on two recent reports. JASA 53, 28–38.
(3) MacMahon, B. & Pugh, T.F. (1970): Epidemiology, principles and methods. Little, Brown & Co., Boston.
(4) Mausner, J.S. & Bahn, A.K. (1974): Epidemiology. W.B. Saunders Co., Philadelphia.
(5) Rothman, K.J. (1986): Modern epidemiology. Little, Brown & Co., Boston.
(6) Hennekens, C.H. & Buring, J.E. (1987): Epidemiology in medicine. Little, Brown & Co., Boston.
(7) Levin, M.L. (1953): The occurrence of lung cancer in man. Acta Unio Internationalis contra Cancrum 9, 531–541.
(8) Cole, P. & MacMahon, B. (1971): Attributable risk percent in case–control studies. Brit. J. prev. soc. Med. 25, 242–244.
(9) Gefeller, O. (1990): Definitions of attributable risk – Revisited. *Am. J. Epid.* (submitted).
(10) Greenland, S. & Robins, J.M. (1989): Conceptual problems in the definition and interpretation of attributable fractions. Am. J. Epid. 128, 1185–1197.
(11) Bruzzi, P., Green, S.B., Byar, D.P., Brinton, L.A., Schairer, C. (1985): Estimating the population attributable risk for multiple risk factors using case–control data. Am. J. Epid. 122, 904–914.
(12) Ejigou, A. (1979): Estimation of attributable risk in the presence of confounding. Biom. J. 21, 155–165.
(13) Greenland, S. (1984): Bias in methods for deriving standardized morbidity ratio and attributable fraction estimates. Stat. Med. 3, 131–141.
(14) Kuritz, S.J. & Landis, J.R. (1988): Summary attributable risk estimation from unmatched case–control data. Stat. Med. 7, 507–517.

(15) Miettinen, O.S. (1974): Proportion of disease caused or prevented by a given exposure, trait or intervention. Am. J. Epid. 99, 325–332.
(16) Walter, S.D. (1976): The estimation and interpretation of attributable risk in health research. Biometrics 32, 829–849.
(17) Walter, S.D. (1980): Prevention for multifactorial diseases. Am. J. Epid. 112, 409–416.
(18) Whittemore, A.S. (1982): Statistical methods for estimating attributable risk from retrospective data. Stat. Med. 1, 229–243.
(19) Miettinen, O.S. (1972): Components of the crude risk ratio. Am. J. Epid. 96, 168–172.
(20) Gefeller, O. (1991): Comparison of adjusted attributable risk estimators. *Stat. Med.* (in press).
(21) Gefeller, O. (1990): A simulation study on adjusted attributable risk estimators. Technical Report, University of Göttingen.
(22) Keil, U., Remmers, A., Chambless, L., Hense, H.W., Stieber, J., Lauck, A. (1986): Epidemiologie des Bluthochdruckes. Häufigkeit, Verteilung, Bekanntheits– und Behandlungsgrad der Hypertonie in der Hansestadt Luebeck. MMW 128, 424–429.
(23) Keil, U., Gefeller, O., Stieber, J. (1988): Rauchverhalten in Luebeck. Ergebnisse der Luebecker Blutdruckstudie. Fortschr. Med. 106, 563–567.
(24) Keil, U., Chambless, W., Remmers, A. (1989): Alcohol and blood pressure: Results from the Luebeck Blood Pressure Study. Prev. Med. 18, 1–10.
(25) Bray, G.A. (1978): Definition, measurement and classification of the syndrom of obesity. Int. J. Obesity 2, 99–112.

RIASSUNTO

Il problema dell'esposizione ad un fattore per una particolare malattia, importante dal punto di vista della sanità pubblica, è affrontato attraverso il concetto di rischio attribuibile. Vengono qui esaminate le quattro definizioni principali di rischio attribuibile presenti in letteratura. Una particolare attenzione è rivolta al problema della stima del rischio attribuibile negli studi trasversali, dove la potenziale distorsione nella stima della prevalenza e della incidenza rende necessarie opportune considerazioni. Nel lavoro, inoltre, si accenna all'estensione al caso multivariato dell'aggiustamento relativo ai fattori di confondimento e di modificazione dell'effetto.

Infine si presenta una applicazione delle definizioni di rischio attribuibile e dei metodi descritti ai dati dello studio sulla pressione sanguigna di Luebeck, uno studio trasversale di epidemiologia delle malattie cardiovascolari.