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The Mantel-Haenszel procedure. 50 years of the statistical method for confounders control

Alice Mannocci

Epidemiological and Biostatistics Unit, Institute of Hygiene, Catholic University of the Sacred Heart, Rome, Italy; Clinical Medicine and Public Health Unit, Sapienza University of Rome, Italy

Correspondence to: Alice Mannocci, Epidemiological and Biostatistics Unit, Institute of Hygiene, Catholic University of the Sacred Heart, Largo F. Vito 1, 00168 Rome, Italy

Nathan Mantel (1919-2002)

William M Haenszel (1910-1998)

The Mantel Haenszel procedure represents a simple and useful tool to obtain estimates of association, adjusted for the effect of one or more confounders.

Nathan Mantel (1919-2002) was a biostatistician. In 1947 he was hired as a member of a new biometry group at the National Cancer Institute (NCI) in the National Institute of Health (NIH), Maryland, and in this time he collaborated with William M Haenszel (1910-1998). Haenszel, who was a sociologist, mathematician and statistician, had been working on interpreting the case-control studies of the connection between smoking and lung cancer, requested Mantel's assistance on how to analyze the retrospective data. In the 1959 they published the "Statistical aspects of the analysis of data from retrospective studies of disease" on the Journal of the National Cancer Institute [1]. In this paper Mantel and Haenszel present for the first time what is known as the Mantel-Haenszel procedure, which provides a summary estimate of exposure effect stratified by multiple sources (i.e. different studies) or *confounding factors* (such as age and gender), show Box 1, which is a weighted average of the odds ratios across various data.

When an analysis has been stratified on the basis of one or more variables, each of the subgroups-specific disease-exposure odds ratios may be regarded as representing the effect of the study exposure on the risk of disease when the joint effect of the stratification variables has been held constant. In the event that the odds ratios are relatively constant across subgroup, being consistently elevated or reduced, one way combine them to form a summary estimate. One refers to the summary estimate as having been "adjusted" for the effects of those variables used in the stratification.The Mantel-Haenszel's method published in 1959, is a procedure to estimate a summary of odds ratio series. It's remarkably easy to apply and requires no iterative calculation [2].

The Mantel-Haenszel method allows the researcher to obtain an estimate of the odds ratio (OR_{MH}), across the strata of the variables (confounders), it is:

$$OR_{MH} = \sum_{i=1}^{k} \frac{a_i d_i}{n_i} \Bigg/ \sum_{i=1}^{k} \frac{b_i c_i}{n_i} \quad \text{(formula 1)}$$

where:

- i-th subgroup is:

	Cases	Controls	Total
Exposure			
Yes	a_i	b_i	m_{1i}
No	c_i	d_i	m_{2i}
	n_{1i}	n_{2i}	n_i

Box 1. Confounding term and example.

The *confounding* term refers to the effect of an extraneous variable that wholly or partially accounts for the apparent effect of the study exposure, or that masks an underlying true association. Thus, an apparent association between an exposure and disease may actually be due to another variable [7].

A confounding factor, therefore, must have an effect and must be imbalanced between the exposure groups to be compared. In essence, these conditions imply that a confounding factor must have two association:

- A confounder must be associated with the disease
- A confounder must be associated with exposure.

There is also third requirement. A confounder must not be an effect of the exposure [8].

To further clarify this concept consider the following example. Suppose you need to investigate a postulated casual connection between alcohol consumption and myocardial infarction (MI). Smoking is known to be a cause of MI, and alcohol intake and smoking are known to be correlated. Suppose that alcohol consumption in fact is not a cause of MI. By virtue of its association with smoking, however, alcohol intake would be found to be associated, apparently increasing the risk of this disease. One might even find an apparent dose response between alcohol and MI due to heavy drinkers being heavy smokers. To disentangle the effect of smoking from the effect (if any) of alcohol, using stratification: one could stratify subjects (both cases and controls) into a smoking group and non-smoking group. Within each subgroup, one could look for an association between alcohol consumption and MI. Insofar as cases and controls are similar with respect to smoking habits within subgroups, a subgroup-specific association between alcohol and MI cannot be explained in terms of differenced in smoking habits [9].

- *k* represents the number of subgroups defined on the base of the stratification variable.

It's a consistent estimate of OR, i.e., even in presence of few data or zero counts in some cells, a real number for OR_{MH} is obtained.

Another observation that the OR_{MH} is equivalent to OR when k=1, i.e., in absence of confounders.

The Mantel-Haenszel estimate, OR_{MH}, can be considered as a weighted average of the subgroup-specific odds ratios, provided that none of the values of b_i or c_i, are equal to zero.

If the weights for the i-th subgroup, w_i ,is

$$w_i = \frac{b_i c_i}{n_i} \quad \text{(formula 2)}$$

The substitution of the formula 2 in the equation formula 1 gives:

$$OR_{MH} = \sum_{i=1}^{k} OR_i w_i \Big/ \sum_{i=1}^{k} w_i \quad \text{(formula 3)}$$

An example of the Mantel Haenszel procedure in Box 2.

In fact both Mantel and Haenszel indicated their disbelief in the constancy of the odds ratio. By contrast, the odds ratio estimates derived by Woolf (1955), Grat (1962-1970), Birch (1964) and Goodman (1969) were based on the assumption of a constant odds ratio across the subgroup's 2x2 tables [3].

The procedure of Mantel and Haenszel represents one of the more commonly used techniques due to its relative simplicity of computation with respect to other estimates. It is a potential method for studying differential item functioning in any two groups examined [4], because it makes meaningful comparisons of item performance for different groups, by comparing examinees of similar proficiency levels, instead of comparing overall group performance on an item [5]. After the their article and the publication of the Mantel-Haenszel formulae in the Journal of the Cancer Institute, an important group of formulas for pooled analyses (pooled risk difference, pooled risk ratio, pooled incidence rate difference) was derived for obtaining unconfounded estimates of effect across a set of strata [6] .

Box 2. Hypothetical data: relationship of alcohol consumption to myocardial infarction [10].

A. Association between Myocardial Infarction (MI) and recent use of oral contraceptives (ignoring age)

	Cases of MI	Control	Total
Alcohol			
Yes	29	135	164
No	205	1607	1812
Total	234	1742	**1976**

$$OR = (a \cdot d) / (b \cdot c) = (29 \cdot 1607) / (135 \cdot 205) = 1.6$$

B. Association between Myocardial Infarction (MI) and alcohol consumption (age strata):

25-29 years

	Cases of MI	Control	Total
Alcohol			
Yes	4	62	66
No	2	224	226
Total	6	286	**292**

OR=7.2

30-34 years

	Cases of MI	Control	Total
Alcohol			
Yes	9	33	42
No	12	390	402
Total	21	423	**444**

OR=8.9

35-39 years

	Cases of MI	Control	Total
Alcohol			
Yes	4	26	30
No	33	330	363
Total	37	356	**393**

OR=1.5

40-44 years

	Cases of MI	Control	Total
Alcohol			
Yes	6	9	15
No	65	362	427
Total	71	371	**442**

OR= 3.7

45-49 years

	Cases of MI	Control
Alcohol		
Yes	6	5
No	93	301

OR=3.9

$$OR_{MH} = \frac{\sum_i a_i d_i / n_i}{\sum_i b_i c_i / n_i} = \frac{(4 \cdot 224/292) + (9 \cdot 390/444) + \ldots}{(2 \cdot 62/292) + (12 \cdot 33/444) + \ldots} = \frac{23.71}{5.97} = 3.97$$

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