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Research Article

Detection and Management of Confounding Variables in Prevention of Blindness Research: A Methodological Approach with Age and Sex as Models

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Abstract

Introduction: Confounding is a common type of bias in which a third variable may distort the assessment of a potential risk factor on the outcome of interest. Confounding is further classified into positive, negative and extreme negative confounding. Several methods are quite common in the management of confounding, of which: stratification using Mantel Haenszel common OR\ (MH) and binary logistic regression. The prevalence of low vision and blindness remains relatively high in developing countries, despite global efforts for prevention and intervention. In order to make the best use of the limited available resources for prevention and elimination in these poorer countries, it is essential to accurately detect the association between avoidable causes and blindness. There is a need to explore the accuracy, utilization and variation between both methods.

Methods: Data from two different blindness surveys (Menoufiya 1999, and Menia 2002) were abstracted and managed. Crude Odds ratios were calculated for the prevalence of blindness in both surveys. Two major causes of blindness (cataract and trachomatous corneal opacity) were implied in the analysis as potential risk factors. The estimated prevalence was adjusted for age and sex using Mantel Haenszel stratification and binary logistic regression methods separately. Adjusted odds ratios were compared to evaluate the variation.

Results: In Menia data, the unadjusted prevalence of blindness using crude odds ratio was 7.54, which was reduced to 3.63 with Mantel Haenszel adjustment and to 3.93 using logistic regression adjustment for age. Adjusting for sex, the OR was not much reduced using both methods (7.5 and 7.48), respectively while adjusting for both age and sex it was compromised to 3.83. Moreover, using Menoufiya data, the crude OR was 10.09, which was reduced adjusting for age with MH method to 7.53 and to 7.64 using regression analysis. In terms of sex, the OR was not much changed in both methods (OR: 10.16) for both. Adjusting for both confounders, the OR was compromised to 7.62.

Conclusion: Prevention of blindness requires accurate assessment of the magnitude and the associated risk factors. Confounders may distort this assessment and hence, yield biased results. Accounting for confounding is quite crucial to avoid resource wasting. Mantel Haenzel method can be used to manage the effect of a single variable, while regression models are more preferred in case of multiple confounders.

Introduction

Confounding is a situation in which a non-causal association between a given exposure and an outcome is observed as a result of the influence of a third variable (the confounder) [1]. Such cofounder must be related to both the putative risk factor(s) and the outcome of interest. Meanwhile, it should not be in the exposure–outcome pathway. Consequently, the association between the exposure and the outcome can be: induced, strengthened, weakened, or eliminated via the confounder's effect which may differ between the exposed and unexposed groups. Moreover, confounding is more likely to occur in observational studies than in experimental studies where the latter is one of the confounding-control approaches. According to its effect, confounding is further classified into: 1) Positive confounding; in which the confounder exaggerates the association (usually occurs in direct relationships); 2) Negative confounding; in which the confounder results in attenuation of the association (usually occurs in inverse relationships); 3) Extreme negative confounding; in which, the confounder over attenuates the association (resulting in totally reversed direction of the association).

A potential confounder is often suspected and detected through previous knowledge (experience / literature) and then confirmed through statistical testing. Therefore, when both crude and adjusted analyses are markedly varied, then adjustment for potential confounders is quite necessary. Although there is a debate about the

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threshold of such variation, it is highly recommended that adjustment is necessary when there is a more than 10 % difference [2].

Several methods of adjustment for confounding are available and applicable during different study phases. For example: at the design phase, some precautions may include: (1) increasing the sample size; (2) restricting the study population to those who are unexposed to the targeted confounder; (3) matching between cases and controls; and (4) randomization. Alternatively, the control for confounders in the analysis phase is usually conducted when the potential confounders were not controlled for, or couldn't be accounted for during the design phase. Meanwhile, controlling for potential confounders in the analysis phase is also dependent on the measure of association. For example, in cross sectional surveys where odds ratios or prevalence ratios can be alternatively used, the adjustment method would also vary [3]. At this stage, a potential confounder is usually tested to estimate the value of its induced bias in the study results. In this scenario, two main mathematical approaches can be implemented to control for the identified confounder; stratified analysis method and statistical modeling (multivariate analysis) [4-5].

Researchers are quite often not aware of the need to control for confounders. Meanwhile, the process of detection and management of confounders may require specific knowledge and skills [6]. In a study in 2002, Mullner M et al. reviewed 537 original articles published in 34 different medical journals in January 1998, and found out that only 169 (31.5%) articles controlled for confounders while very few of them mentioned the methods they used. Thus, only a few authors have provided adequate evidence of correct controlling, although most of those authors were affiliated to reputable statistics, epidemiology, or public health departments [7].

Low vision and blindness have a significant negative socioeconomic impact on both individual and community levels. According to the WHO guidelines, low vision is defined as: visual acuity (VA) < 6 / 18, severe low vision as: VA < 6/60 and blindness as: visual acuity < 3/60 in the better eye. Worldwide – as per the last formal WHO assessment - an estimated 160 (2.6 %) million people are visually impaired, of them 124 million (2 %) have low vision and 36 million (0.6 %) are blind [8]. These figures are recently estimated to be dramatically increased to 32.4 million blind and 191 million visually impaired [9-10]. Moreover, approximately 90 % of blindness occurs in developing countries, namely: Africa, Middle East, and Asia. The main documented causes of low vision and blindness are uncorrected refractive errors (43%), unoperated cataract (33%) and glaucoma [11]. Out of the total burden of blindness, 80 % is avoidable, either curative (cataract, glaucoma, and corneal opacity) or preventable (trachoma, and onchocerciasis). Of particular interest in this study are reports of the prevalence of low vision and blindness in the Eastern Mediterranean Region (EMR) of WHO classification (Morocco – Pakistan). This region has the highest prevalence of visual impairment and blindness. Epidemiological studies are considered as the first formative step to develop both preventive and intervention programs. Accurate estimates of the exact prevalence and effect size of different risk factors are quite crucial in program development. confounders may inadvertently reverse the arrangement of priorities and hence results in wasting of – the usually - very limited health resources.

Researchers in the prevention of blindness field, usually control for confounders during the analysis phase using the two mentioned common mathematical approaches (stratification and modeling), specifically; Mantel Haenszel common OR\, and binary logistic regression analysis. There is still uncertainty about assumptions, situations, variation, advantages and disadvantages of using either of these methods. There is also uncertainty about the consistency of results derived from both methods.

Two large community based surveys were conducted in Egypt by Al Noor Foundation in collaboration with Pfizer© pharmaceutical Inc., NY, USA and the International Trachoma Initiative (ITI), GA, USA in two different governorates (Menoufiya (Lower Egypt; 1999), and (Menia (Upper Egypt; 2002), with total sample sizes of 6000, and 4500 inhabitants, respectively. Both surveys were aiming to assess the prevalence and causes of blindness [12-13].

Methods

Data from Menoufiya (1999) and Menia (2002) surveys were extracted and stored in a new database specifically designed using Microsoft Access 2010®. A new coding system was applied to the original data sets of the two mentioned surveys to suit the analysis coping with purpose of the current study. A subset of the examined adults in the age 40 years and above with available visual acuity were abstracted which yielded 2325 and 2028 inhabitants in Menoufiya and Menia surveys respectively. A person was considered blind if his/her presenting visual acuity in the better eye was < 3/60. Two common causes of avoidable blindness were selected for the analysis, namely: cataract and Trachomatous Corneal Opacity (TCO). To facilitate the analysis, a new variable was constructed to indicate the presence or absence of avoidable blindness. A person was considered to have avoidable blindness if he/she had bilateral cataract and / or bilateral trachomatous corneal opacity. The reason for using bilateral affection was to ensure that vision loss is attributed to the specifically selected major cause. Age was transformed from a continuous to a categorical variable (in decades) which are: (40 – 49), (50 – 59), (60 – 69), and (70 +). The latest category (70 +) was used as reference. The sex variable was entered as a dichotomous variable with men as the reference group.

Crude odds ratios were calculated using avoidable causes of blindness (cataract and / or TCO) as the main exposure and vision loss (identified as visual acuity in the better eye < 3/60) as an outcome. Mantel Haenszel common (pooled) odds ratios were calculated across categories of age and sex separately in each data set (controlling for age and sex) and then compared to the previously calculated crude odds ratios [14-15]. Calculation procedures were conducted as follows:

(A) Crude OR = (a * d) / (b * c).

(B) Mantel Haenszel common OR\ = $\Sigma^{k}_{i=1} [(a_i * d_i) / n_i] / \Sigma^{k}_{i=1} [(b_i * c_i) / n_i]$

Table 1: Exposure versus outcome in assessment of the potential association using crude and adjusted odds ratios.

		Outcome	
		Diseased	Not diseased
Exposure	Exposed	a	b
	Unexposed	c	d

Where $n_i = a_i + b_i + c_i + d_i$, and confidence intervals = exp.(log odds ± z_α * (S.E.).

Z_α = 1.96 for 95 % CI. and S.E. = $\sqrt{1 / [(a_i * d_i) / n_i] + 1/ [(b_i * c_i) / n_i]}$.

(C) Binary logistic regression analysis was conducted including and then excluding age and sex, with OR as the measure of association in the presence and absence of age and sex as potential confounders.

In this analysis the binary logistic regression model was considered as follows:

$Y = \alpha + \beta_1 X_1 + \beta_2 Z_1 + \beta_3 Z_2 + \text{Error};$

where Y is the primary outcome (blindness as previously defined), X_i variable denotes the presence of avoidable causes of blindness (bilateral cataract and / or bilateral TCO), and Z_1 & Z_2 variables are the two targeted potential confounders (age and sex respectively). Adjusted odds ratios calculated by both methods were then compared to evaluate the difference in estimation.

Results

The crude odds ratio in **Menia survey** was 7.54, which refers to the presence of a strong association between the avoidable causes of blindness and vision loss. In other words, a person with one or both of the avoidable causes of blindness (cataract and / or trachomatous corneal opacity) is 7.5 times more likely to get blindness. However, adjusting for age categories using Mantel Haenszel method, the pooled $OR^{\backslash}_{MH}$ was (3.63, [95% CI: 2.32 – 5.69]) which means that age is a strong (positive) confounder, i.e. magnifying the effect of the avoidable diseases. On the other hand, when controlling for sex in the same data, $OR^{\backslash}_{MH}$ was (7.5, [95% CI: 4.55 – 12.37]) with a slight decrease from the crude measure (7.54). This may be interpreted as: sex is not a potential confounder in the association between these avoidable causes and blindness.

Moreover, using the binary logistic regression model; with exclusion of age and sex, OR was (7.54, [95% CI: 5.85 – 9.73]) which is quite similar to that of the crude Odds ratio. However, when age was included in the model, OR was much reduced to a value of 3.93, [95% CI: 2.97 – 5.2], which reinforces the previous evidence from conduct of Mantel Haenszel $OR^{\backslash}$ identifying age as a positive confounder. Furthermore, when sex was entered into the model (controlling for sex) only a slight change in the odds ratio took place (7.48, [95% CI: 5.79 – 9.65]) which also confirms the previous interpretation that sex is probably not a potential confounder. Additionally, when both age and sex were included in the model, OR was (3.83, [CI: 2.89 – 5.07]), which compromises the two results, and indicates a much greater effect of age than sex.

Table 2: Summarizing results from Mantel Haenszel $OR^{\backslash}$ and binary logistic regression adjustments for age and sex as potential confounders.

Survey	Potential Confounder	Crude OR	Adjusted by Mantel Haenszel (OR, [95% CI])	Adjusted by Logistic Regression
Menia	Age	7.54	(3.63, [2.32 – 5.69])	(3.93, [2.97 – 5.2])
	Sex		(7.5, [4.55 – 12.37])	(7.48, [5.79 – 9.65])
	Both		-	(3.83, [2.89 – 5.07])
Menoufiya	Age	10.09	(7.53, [4.6 – 12.33]	(7.64, [5.91 – 9.88])
	Sex		(10.16, [6.08 – 16.99]	(10.16, [7.94 – 12.99])
	Both		-	(7.62, [5.89 – 9.87])

Using **Menoufiya Survey** data, the crude OR was 10.09 while Mantel Haenszel $OR^{\backslash}$ adjusted for age was (7.53, [95% CI: 4.6 – 12.33], which shows that age is probably a positive confounder that increases the effect size of the avoidable causes of blindness. When controlling for sex; $OR^{\backslash}_{MH}$ was (10.16, [95% CI: 6.08 – 16.99] which again tells us that sex is probably not a confounder in this association pathway.

Meanwhile, conduct of binary logistic regression analysis to the same data set excluding age and sex, the OR was (10.09, [95% CI: 7.9 – 12.89]). However, controlling for age, the OR was much reduced to (7.64, [95% CI: 5.91 – 9.88]) while controlling for sex, the OR was (10.16, [95% CI: 7.94 – 12.99]). Moreover, controlling for both age and sex in the same time, the OR was (7.62, [95% CI: 5.89 – 9.87]) which is quite consistent with results from the Mantel Haenszel adjustment for the same survey data, and also shows much consistency with results from the other survey data.

Discussion

Research in prevention of blindness is usually aimed at reduction of the effect of potential risk factors (avoidable causes of blindness) [16]. Due to scarcity of resources, proper focus on highly effective risk factors is critical to any preventive and/or intervention program [17]. Therefore, accurate assessment of the association between avoidable risk factors as exposure and blindness as outcome is quite crucial. However, many confounders may distort this association and hence change the priorities of intervention programs. Moreover, suspicion and detection of a potential confounder may require previous knowledge about common causes and its causal association in prevention of blindness research [18]. Nevertheless, some researchers may not account for confounders, while others may report controlling for confounders without providing details on the methods they used [19]. Moreover, several types of confounding may require utilization of specific methods to manage its effect. Of these types: residual and indication confounders and tackling rare diseases [20-21]. Two methods are commonly used to adjust for confounding in health research; Mantel Haenszel common OR, and statistical modeling [22-23]. Criteria for selection of a certain method, advantages, disadvantage, and consistency of the results are not well utilized or documented in the blindness literature [23]. In this study, the aim was to compare results from both methods. Application of both methods to two different surveys' data provided consistent results. However, a major difference should be highlighted here that: although the Mantel Haenszel method provides accurate correction, it can be only used to control for one potential confounder each time via stratification technique [24]. On the other hand, statistical modeling (for example binary logistic regression) is strongly recommended in presence of multiple potential confounders. Table 3 compares and contrasts the advantages and disadvantages of the two methods.

Additionally, this table can be used also as a guideline for selection of the most appropriate method of control for confounders according to the type and nature of the available data and the number of suspect potential confounders.

Moreover, there is still a debate in the literature about using prevalence ratio in health surveys rather than odds ratios [25]. However, it is well established in the literature that the adjusted prevalence ratios are not much deviated from the estimated odds

Table 3: Comparing MH method with multivariate analysis:

Item of Comparison	Mantel Haenszel	Multivariate
Consistency and accuracy of results	Consistent and accurate	Consistent and accurate
Need for assumptions	Needs the necessary assumptions for weighting	Follows the model assumptions of linearity and proportionality
Simplicity of calculations	Can be done by calculators	Needs a statistical software
Accounting for effect modification	Can't account for effect modification, and if present may distort the results	Can account for effect modification in the same time by calculation of interaction terms
Control for more than one potential confounder	Can't control for more than one potential confounder	Can control for more than one potential confounder at the same time
Use of stratified variables	Essential	Can include variables with and without stratification, but preferred to do.
Test for significance	Needs a special test for significance	Test for significance is usually built in within the software packages
Use in publications	Less common and needs a special clarification	More common and well established in publications

ratios when using cluster sampling and when such clusters are relatively homogenous. In this case, it is anticipated that a minimal difference in the confidence intervals will be inferred from the estimated ones [25-26].

The advantages of being quite aware of potential confounders in health research – generally speaking - and specifically in preventive medicine are quite varied. The potentiality of bias, may reduce the opportunities for implementation of best practice and hence leads to a negative impact on both health institutions and the individuals who receive the service [27]. In prevention of blindness research, usually, a community based cross sectional survey would perceive a series of intervention programs to reduce the blindness's burden and increase the service uptake. Confounding and other types of bias may totally shift the findings of such services to a totally false direction, and hence result in wasting a lot of the usually scarce and hardly allocated resources for prevention programs, ending up with minimal impact on the community [27].

The current study discusses a single type of bias (confounding) although several other types may play an important role in prevention of blindness research. Meanwhile, the study focuses on two major methods of confounding management. Although those two types are the most commonly used methods, several other types can be utilized. There is a need for more methodological studies that discuss bias in terms of detection and management aspects.

In conclusion, prevention of blindness requires accurate assessment of the magnitude of the problem and detection of the associated risk factors to enable a concrete baseline for future interventions. Confounders may distort this assessment and hence produce biased results. Accounting for confounding is quite crucial to avoid resource wasting. In this regard, the Mantel Haenzel method can be used to manage the effect of single variable bias, while regression models are more preferred in case of multiple confounders.

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