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SVSRK Bharadwaj
Sr. Manager, Sigma Research and Consulting, New Delhi, India

KVR Subrahamanyam
Director, Sigma Research and Consulting, New Delhi, India

UV Somayajulu
Sigma Research and Consulting, New Delhi, India

CP Prakasam
Former Professor, International Institute for Population Sciences, Mumbai, Maharashtra, India

Corresponding Author:
CP Prakasam
Former Professor, International Institute for Population Sciences, Mumbai, Maharashtra, India

Influence of confounding factors in determining the risk of chronic lung disease among the elderly: Application of the mantel-haenszel test

SVSRK Bharadwaj, KVR Subrahamanyam, UV Somayajulu and CP Prakasam

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Abstract
In epidemiological studies, the cause-and-effect relationship is commonly measured using the odds ratio (OR), which reflects the odds of an outcome occurring versus not occurring. However, the crude odds ratio is specific to individual strata and does not account for the influence of confounding variables. The Mantel-Haenszel (MH) test, an extension of the chi-square test, estimates the adjusted odds ratio by accounting for such confounders.
This study attempts to assess the influence of confounding factors on the risk of chronic lung disease (CLD) among the elderly, using data from the Study on Global AGEing and Adult Health (SAGE), India, Wave 3. Data were collected from individuals aged 50 years and above who reported being diagnosed with hypertension (HT), diabetes (DI), and asthma (AS), considered as possible risk factors for CLD (defined as "ever diagnosed with chronic lung disease"). Tobacco use ("ever smoked or used smokeless tobacco," SMOKE) and alcohol consumption ("ever consumed alcohol," AL) were treated as confounding variables.
In addition to the chi-square test, which assesses associations and crude odds ratios, the MH test was applied to estimate adjusted odds ratios and evaluate the magnitude of confounding. Since smoking and alcohol use vary by age and sex, the analysis was stratified by the age group (AGE) and sex (SEX). Analysis revealed that.

Keywords: Mantel-Haenszel (MH) test, odds ratio, chronic lung disease, risk ratio, risk difference

Introduction
Cause and effect relation in epidemiological studies measured through odds ratio. Odds ratio is the ratio between cause and effect for a selected stratum in 2x2 contingence table. One of the limitations of odds ratio is that it is not "collapsable" to measure 2x2xk stratums adjusted odds ratio, where k is the number of confounders (Birch, (1964) [2]. That is overall odds ratio is not equal to weighted average of stratum specific odds ratio. The crude odds ratio is specific to individual strata and does not account for the influence of confounding factors. The Mantel-Haenszel (MH) (1959) [8] test, which is an extension of the chi-square test, estimates the adjusted odds ratio by accounting for such confounders.
Pearson's Chi-square test and Fisher's exact test suggests association between two variables and gives odds ratio without the influence of third (confounding) variable (Lawal Bayo 2003) [7]. To measure the influence of confounders on cause-effect, Cochran (1954) [3] proposed a test, which is an extension of Pearson's chi-square with an assumption that each 2x2 table data consists of independent binomials (Adejumo and Adetunji (2013) [1]. Mantel and Haenszel (MH) (1959) [8] proposed similar test statistics using hypergeometric assumption. That is in 2x2 table the cell counts in each table (strata) have hypergeometric distribution. The results of MH test give adjusted odds ratio which measures the influence of confounding variables on cause and effect (Daniel et. al., 2000, Greenland & Robins 1985) [4, 5].

The magnitude of confounding is determined by comparing the crude OR with the adjusted OR estimated by the MH test (Robins et.al., 1986) [9]. A substantial difference between the two indicates a strong influence of the confounder on the observed association. With this concept in view present study aims to assess the influence of confounding factors on the risk of chronic lung disease (CLD) among elderly, using the data from the *Study on Global AGEing and Adult Health* (SAGE), India wave 3, and applying the Mantel-Haenszel test.

Data and Methodology

To find out the prevalence and influencing risk factors of Chronic Lung disease (CLD), data were collected from SAGE India, wave 3. SAGE is a collaborative project of World Health Organisation (WHO) [11], Geneva, covering adults aged 50 years and older from nationally representative samples in China, Ghana, India, Mexico, Russian Federation and South Africa.

For the present study, data were derived from a sample of 6719 elderly (aged ≥50 years) from SAGE India Wave 3 (2019-2020), conducted by International Institute for Population Sciences (IIPS), Mumbai in collaboration with the WHO (Sekher, T, V., *et al*., 2024) [10]. Detailed information on the survey design, instruments used and reports can be assessed from IIPS website (IIPS) [6]. From this survey, elderly who have reported "Ever diagnosed hypertension" (HT), "Ever diagnosed diabetes" (DI), and "ever diagnosed asthma" (AS), as risk factors influencing "Ever diagnosed chronic lung disease" (CLD), has been collected. Other factors such as "ever used tobacco products" (TOB), "ever consumed alcohol" (AL), Age (AGE) and sex (SEX) of elderly considered as confounding factors.

Analysis has been carried out in three stages. Initially the association between CLD and all selected risk and confounding factors has been tested by applying Chi-Square test (χ^2) and significant factors with CLD has been considered for further analysis. Results are listed in (Table 1). To understand the influence of risk factors and confounding variables on CLD, MH test has been applied to derive adjusted odds ratio and magnitude of confounders estimated (Table 2). Final stage, by introducing confounders one by one through cause factor and effect (CLD) variable, relative risk (Table 3) and risk difference (Table 4) has been calculated.

Mantel and Haenszel (MH) test

Mantel-Haenszel (MH) test is used to estimate the risk ratios or odds ratios by analysing 2 × 2 x k contingency table with k confounders. The MH test works by stratifying data into homogeneous subgroups (strata) based on the confounder. Within each stratum, a 2×2 table is constructed to calculate the stratum-specific odds ratios. These individual estimates are then combined using a weighted average, where the weights depend on the number of observations in each stratum. The MH adjusted odds ratio gives a more accurate estimate of the association by controlling for those third variables. The method assumes that the odds ratio is homogeneous across all strata, meaning the true effect does not vary between subgroups. MH test is:

$$\widehat{OR}_{MH} = \frac{\sum_{i=1}^{k}\left(\frac{a_i d_i}{n_i}\right)}{\sum_{i=1}^{k}\left(\frac{b_i c_i}{n_i}\right)}$$

Where a, b, c, d represents cell frequency in 2x 2 table and ni is the sum of row total and column total, where i= 1, k strata. Magnitude of confounding factor calculated as:

$$\text{Magnitude of confounding} = \frac{(\text{Crude OR} - \text{Adjusted OR})}{\text{Crude OR}} \text{ ---- } (1)$$

In this study by applying MH (1959) test for common odds ratio and adjusted odds ratio by confounder has been derived for the data set collected from SAGE India, wave 3. Results are given in Table 2. For analysis of data STATA 16 (64 bit) has been used.

Results

To identify the significant association of risk factors influencing CLD, Pearson's chi-square test has been applied and the results are given in Table 1. Among the set of eight factors, only three factors show significant association with CLD. Elderly who had reported "ever had asthma" are significantly associated (χ^2 =249.4, p<.0001) with risk of reporting CLD than their counter part. Similarly, HT (4.35, p<.05) and SEX (8.44, p<.01) showed significant association with CLD. Among the significant risk factors, odds ratio (11.04) and relative risk (9.64) of AS with CLD was very high reveals that risk of elderly reporting "ever had asthma" found to be 11 times higher risk of reporting CLD then their counterpart. Considering AS - as significant cause factor on CLD, and HT and SEX as confounders, odds ratios, adjusted odds ratio has been estimated by applying MH test.

Crude odds ratio and Mantel-Haenszel (MH) adjusted odds ratio for the relationship between Asthma (AS) and chronic lung disease (CLD) among elderly aged 50 and above and magnitude of confounder is given in Table 2. The crude odds ratio (OR) for the AS--CLD is 11.04 and upon adjusting for potential confounder, the odds ratios slightly decrease from 10.721 to 10.218, indicating the presence of confounding effect.

When HT is adjusted, the OR drops to 10.721 with CI of 7.416-15.499. The magnitude of confounding is 2.85, suggests moderate confounding. Adjustment for SEX results in an OR of 10.519, with a 95% CI of 7.279 - 15.200 and the magnitude of confounding increases to 4.68, indicating stronger confounding by SEX.

When both SEX and HT are controlled together, the adjusted OR further reduces to 10.218 (CI: 7.059-14.792) and the combined magnitude of confounding from SEX and HT is 7.41, the highest among all adjustment by MH test, implies that both are significant confounders (Table 2).

Table 1: Testing the significance of association between Chronic lung disease (CLD) and the confounding factors by Pearson Chi-square test: SAGE India, wave 3

Chronic Lung Disease (CLD)								
		Yes	No	Total	Pearson Chi-square	Asymp. Sig. (2-sided)	odds ratio	Relative risk
1	2	3	4	5	6	7	8	9
Age group (AGE)	50-70 years	103	5106	5209	1.284	.257	0.803	0.807
	70+	37	1473	1510				
Sex (SEX)	Male	81	2993	3074	8.443	.004	1.645	1.628

	Female	59	3586	3645				
Hypertension (HT)	Yes	54	1998	2052	4.347	.037	1.440	1.428
	No	86	4581	4667				
Diabetes (DI)	Yes	21	815	836	0.859	.364	1.248	1.242
	No	119	5764	5883				
Asthma (AS)	Yes	48	297	345	249.436	.000	11.036	9.639
	No	92	6282	6374				
Alcohol (AOL)	Yes	20	698	718	1.941	.164	1.404	1.393
	No	120	5881	6001				
Smokeless (SML)	Yes	62	2685	2747	0.685	.408	1.153	1.149
	No	78	3894	3972				
Sig(2-sided)								

The adjusted results by MH test strengthen the causal inference between AS and CLD accounting for SEX and HT and the relationship remains strong even after controlling for confounders.

Risk ratio (RR) which gives the ratio of the risk of reporting CLD who are exposed to AS compared with the risk of CLD in the non-exposed (no AS). Risk difference (RD) gives the difference in the risk of reporting CLD with the cause.

Table 2: Crude and adjusted odds ratio and Magnitude of confounders to estimate cause and effect of Chronic lung disease among elderly: SAGE India Wave 3

Cause and effect with confounding factors	Crude odds ratio	Confidence interval		Adjusted odds by MH test*	Confidence interval		Magnitude of confounder
		LL	UL		UL	LL	
AS--CLD	11.036	7.639	15.943				
HT--AS--CLD				10.721	7.416	15.499	2.8543
SEX--AS--CLD				10.519	7.279	15.200	4.6847
SEX--HT--AS--CLD				10.218	7.059	14.792	7.4121
*Mantel-Haenszel test (MH)							

The table 3 presents the Risk Ratio (RR) and Risk difference. The estimates RR for the association between Asthma (AS) and Chronic Lung Disease (CLD), while adjusting for potential confounders such as Hypertension (HT) and Sex (SEX), using the Mantel-Haenszel method is listed in Table 3. The unadjusted model (AS--CLD) shows a high-risk ratio of 9.639, indicating that individuals with asthma are over nine times more likely to have chronic lung disease compared to those without asthma and with significant at 95% confidence interval (CI), suggesting a statistically significant association.
After adjusting for hypertension (HT--AS--CLD), the risk ratio slightly decreases to (9.368), showing that HT may have a modest confounding effect. Similarly, adjustment for sex (SEX--AS--CLD) results in a risk ratio of 9.204, indicating a slight reduction in the strength of association.

When both sex and hypertension are considered simultaneously (SEX--HT--AS--CLD), the risk ratio further reduces to 8.879 (CI: 6.396-12.327), suggesting a combined confounding effect of both factors. Although the adjusted risk ratios remain high, the progressive decline across the models highlights the importance of controlling for confounders to obtain more accurate estimates of disease risk.
These findings emphasize that asthma significantly increases the risk of developing chronic lung disease among the elderly, even after accounting for other influencing factors. The results in table 3 shows that risk difference remains same when HT or SEX is added to AS-CLD but slight increase in RD when SEX and HT together introduced in the model reveals that asthma influences greatly chronic lung diseases and SEX and HT as confounders in this study.

Table 3: Estimation of risk ratio and Risk difference by Mantel and Haenszel test by confounding factors Sex (SEX), Hypertension (HT) influencing Chronic Lung disease (CLD) through Asthma (AS): SAGE India, Wave 3

Model	Risk Ratio	95% Conf. Intervals		Risk Difference	95% Conf. Int	
		LL	UP		LL	UP
AS--CLD	9.639	6.918	13.431	0.125	0.081	0.161
HT--AS--CLD	9.368	6.727	13.045	0.125	0.088	0.162
SEX--AS--CLD	9.204	6.618	12.8	0.125	0.088	0.162
SEX--HT--AS--CLD	8.879	6.396	12.327	0.127	0.089	0.165

Conclusion

The Mantel-Haenszel test was applied to estimate the adjusted odds ratio and magnitude of confounding by factors such as sex and hypertension to assess the relation between asthma (AS) and chronic lung disease (CLD) among elderly. Adjusted odds ratio indicates that risk of CLD with asthma among elderly is approximately eleven times higher than those reported without asthma. After adjusting for potential confounders, sex and hypertension by applying MH test, the odds ratios slightly decrease from 11.04 to 10.72 with HT as confounder and 10.22 with sex as confounder.

The combined effect of the confounders (sex and hypertension) in the model (SEX-HT-AS-CLD) showed a confounding magnitude of approximately 74%, whereas hypertension alone contributed only 2.8% to the confounding effect in the AS-CLD relationship. This suggests that elderly individuals with asthma are at a substantially higher risk of developing chronic lung disease, indicating a strong direct effect of asthma on CLD. Additionally, both sex and hypertension were found to be significant confounders in this relationship.
The calculated risk ratios and risk differences, derived using the MH test, further confirm that asthma significantly elevates

the risk of chronic lung disease among the elderly, even after accounting for the effects of confounding variables.

To reduce the asthma leading to risk of chronic lung disease, it is necessary to promote use of clean cooking fuels at household level with proper ventilation in home. Educate families on avoiding indoor smoking and burning incense/camphor excessively which produce excessive smoke. At the community level strategies should be adopted to reduce air pollution.

STATA commands

1. **Adjusted odds ratio:** Mhodds CLD AS, by (SEX HT)
2. **Risk Ratio (Relative risk):** cs CLD AS, by (SEX HT) pool **rr**
3. **Risk difference:** cs CLD AS, by (SEX HT**) rd** estandard

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