# ORIGINAL RESEARCH PAPER

**Medicine**

## STUDY OF SERUM MAGNESIUM IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

**KEY WORDS:**

| Dr. Bency K.Thomas | Senior Resident, Department of Pulmonary Medicine, Sri Manakula Vinayagar Medical College and Research Centre, Puducherry |
| --- | --- |
| Dr. Mathanraj S | Assistant Professor, Department of Pulmonary Medicine, Aarupadai Veedu Medical College and Hospital, Puducherry |

**ABSTRACT**

**Background** : Chronic obstructive airway disease (COPD), which is an important public health challenge, is the fourth leading cause of death in the world today. The present study was to assess serum magnesium, as a biomarker in patients with COPD, to focus on the characterization of the individuals based on the severity and appropriate management of the patients.

**Objectives** : The different objectives of this study was to compare the serum magnesium levels among stable COPD, COPD exacerbation and asymptomatic healthy smokers; and to determine serum magnesium levels with severity of airway obstruction.

**Method** : Spirometry was performed and serum magnesium levels were assessed in 126 subjects (42 stable COPD, 44 COPD exacerbation and 40 asymptomatic smokers).

**Results** : Low magnesium levels were observed among both stable COPD and exacerbation COPD group of patients when compared to healthy smokers.

**Conclusion** : It can be concluded that serum magnesium gives an indirect clue to know the disease stability of the COPD patients.

## INTRODUCTION

Chronic obstructive airway disease (COPD), which is an important public health challenge, is the fourth leading cause of death in the world today.[1] It is one of the leading causes of death worldwide and becomes an economic and social burden that is substantial and rising.[2-4]

According to the Disability Adjusted Life Year (DALY), COPD, which was once ranking twelfth in leading cause of DALY's lost to the world, is estimated to become the seventh leading loss by the year 2030.[4,5]

Pathologically , COPD can be divided into :-
1. Emphysema, where there is destruction of the gas – exchanging surfaces of the lung ( alveoli ) causing irreversible enlargement of airspaces and loss of lung elasticity, and
2. Chronic Bronchitis, where there is the presence of cough and sputum production for atleast three months in each of the two consecutive years.[6]

The Global Initiative for Obstructive Lung Disease (GOLD) emphasizes on the Spirometry, which is required to make the diagnosis of COPD in a clinical context, where the presence of a post bronchodilator $FEV_1$/ FVC is less than 0.70.[7] In addition to it, there are certain key indicators that GOLD lays down especially in a patient who is above forty years of age. It should be noted that these indicators are not diagnostic themselves, but the presence of such key indicators increases the probability of COPD.

These key indicators include,
(I) dyspnea that is characterstically worse with exercise and which is persistent.
(ii) Chronic cough that is intermittent and which may be non – productive is another indicator.
(iii) Chronic sputum production .
(iv) A history of exposure to risk factors like tobacco smoke ( that includes popular local preparations also ) or smoke from home cooking and heating fuels or occupational dusts and chemicals.
(v) And finally whether the patient has a family history of COPD.[7]

The present study was to assess serum magnesium, as a biomarker in patients with COPD, to focus on the characterization of the individuals based on the severity and appropriate management of the patients.

Magnesium, which is one of the major intracellular cation, is an important co-factor for various enzymes, transporters and nucleic acids that are essential for normal cellular function, replication and energy metabolism.[8]

Low magnesium levels is associated with increased airway hyperreactivity and decreased muscle strength. It also plays a role in airway smooth muscle relaxation and bronchodilation, stabilization of mast cells, neurohumoral mediator release, various immune responses, muscarinic actions and mucociliary clearance.[9,10]

## OBJECTIVES

The different objectives in this study were:-
1. To study the level of serum magnesium in patients with stable COPD, COPD exacerbations and asymptomatic smokers.
2. To compare the levels of serum magnesium with severity of airway obstruction.

## REVIEW OF LITERATURE

Chronic Obstructive Pulmonary Disease (COPD) has become an important public health challenge which is in the same time preventable and treatable. A major cause of chronic morbidity and mortality throughout the world, many people suffer from COPD for years and die prematurely from it or due to its complications.

The Global Burden of Disease Study (GBDS) had projected that COPD, which ranked sixth as a cause of death in 1990, has come up with a new estimate that it will be the fourth leading cause of death by 2030.[4]

Half a million people in India die every year due to COPD, which is more than those who die due to COPD in U.S.A and Europe. COPD is in fact the leading cause of death in Maharashtra, causing more deaths than those due to Ischaemic Heart Disease, Stroke and Diabetes Mellitus all put together, according to the report published by the Maharashtra State Health Resources Centre. A nationwide prevalence studies regarding Asthma and COPD was conducted in 16 centers across India by the Indian Council of Medical Research. The study which was conducted in sample of 242,575 subjects, a prevalence of 3.49 % was reported. ( 4.29 % in males and 2.7 % in females ).[11,12]

By far the strongest risk factors for airflow obstruction are smoking and exposure to environmental tobacco smoke[13], but many areas of the world with high mortality rates from 'COPD' still have low consumption of tobacco[14]. The distribution of death from COPD in the UK is not the same as that of lung cancer, the disease most strongly associated with tobacco consumption, but is more closely associated with low social status[15] and poverty[16]. Burney et al demonstrated that there is a high prevalence of restriction associated with poverty which could explain the high COPD mortality in poor countries.[17]

Magnesium is the second most abundant intracellular cation and the fourth most abundant cation in the body. It plays an essential physiological role in a number of functions of the body.

This role is achieved through two important properties of magnesium:
(I)   the ability to form chelates with important intracellular anionic-ligands, especially ATP, and
(ii)  its ability to compete with calcium for binding sites on proteins and membranes.[10]

Hypomagnesaemia may result from one or more of the following mechanisms: redistribution, reduced intake, reduced intestinal absorption, increased gastrointestinal loss and increased renal loss.[8,18]

The exact role of magnesium in respiratory homeostasis is not clear. Hypomagnesemia is associated with increased airway hyperreactivity and decreased muscle strength.[19,20] It also plays a role in relaxation of smooth muscles of airways and bronchodilation, stabilization of mast cells, neurohumoral mediator release, various immune responses, muscarinic actions and mucociliary clearance.[21-24] The cause of lower serum magnesium remains unclear.

While therapies for COPD such as beta agonists, steroids, and diuretics can all theoretically lower serum magnesium levels studies have shown conflicting results.

Bhatt SP and colleagues, from a study conducted in St. Luke's Hospital, USA, observed that serum magnesium is an independent predictor of frequent readmissions for acute exacerbations of COPD.[9]

Jeswani G et al, concluded from a study conducted in 150 COPD patients, that serum magnesium is an independent predictor of COPD exacerbations and there exists a negative correlation between hypomagnesemia and frequency and duration of hospitalization.[10]

In a study conducted by JP Singh, Sahil Kohli and colleagues, they observed that hypomagnesemia in patients presenting with COPD have advanced disease, prolonged hospital stay and need mechanical ventilation more often.[25]

Thus, serum magnesium may have a role in assessing the disease stability in COPD patients, but the relationship between serum magnesium and COPD disease flares outcome has not been thoroughly explored. Standard guidelines have not yet recommended the implication of serum magnesium on COPD.

## MATERIALS AND METHODS
The study titled, "STUDY OF SERUM MAGNESIUM IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE" was carried out in the Department of Pulmonary Medicine, Sri Manakula Vinayagar Medical College and Hospital, Puducherry.

**STUDY DESIGN :** Cross Sectional Study.

**SAMPLE SIZE AND DURATION OF STUDY :** Considering a sensitivity of 70% and specificity of 86%, with alpha error of 0.05 (freecal software), based on a previous study[26], a sample size of 126 was obtained. The study was conducted for a period of 1 year starting from the date of getting approval from the Ethics Committee.

## Serum magnesium determination
After getting an informed written consent from each patient enrolled in the study, 2 ml of their venous blood was collected between 9a.m and 4p.m of each day, and serum magnesium was assessed using

## AGAPPE CHEMCHEK™.
This kit is intended for in vitro quantitative determination of magnesium in serum or plasma. It is based on the principle that magnesium will react with xylidyl Blue, one of its reagents to form a colored compound in alkaline solution, and the intensity of the color formed will be proportional to the magnesium in the sample.

## SAMPLING :
**INCLUSION CRITERIA :** The patients who are presented to the Chest OPD and diagnosed by spirometry were considered for the present study. Patients who were having typical symptoms of chronic cough with or without expectoration with shortness of breath on exertion were included in the study after confirming the diagnosis by $FEV_1$ / FVC < 70% and post bronchodilator $FEV_1$ < 70% on spirometry as per the GOLD guideline.

## GOLD SPIROMETRIC CRITERIA FOR COPD SEVERITY:
In patients with $FEV_1 FVC < 0.70$:

| Stage | Characterstics |
|---|---|
| I. Mild COPD | $FEV_1 \geq 80$ % predicted. With or without presence of chronic symptoms (cough, sputum production). |
| II. Moderate COPD | 50 % $\leq FEV_1 <$ 80 % predicted. With or without presence of chronic symptoms (cough, sputum production). |
| III. Severe COPD | 30 % $\leq FEV_1 <$ 50 % predicted. With or without presence of chronic symptoms (cough, sputum production). |
| IV. Very severe COPD | $FEV_1 <$ 30 % predicted. |

## EXCLUSION CRITERIA :.
1)  COPD patients with coexisting Tuberculosis.
2)  Renal failure patients.
3)  Heart failure patients.
4)  Liver disease patients.
5)  Patients who are diagnosed with any malignancy.

The subjects who satisfies the above mentioned criteria, a thorough analysis on their TLC, DLC were done to rule out any co-existing infections. Random Blood sugar levels and ECG were done to rule out other co - morbidities and Myocardial infarction. Serum Urea and Creatinine levels were assessed to rule out any co – existing kidney diseases. Liver function tests were carried out to rule out liver diseases as serum magnesium is seen to be elevated in those conditions. A chest X – ray was done to further support the evidence of COPD. Sputum AFB and Grams stain was done to rule out any active Tuberculosis and other Lung infections. Finally a spirometry was performed to record and give the confirmation of COPD. Serum magnesium level was assessed finally in those subjects who satisfied the above tests.

## STATISTICAL ANALYSIS :
The data was entered and analysed with epi info software version 3.4.3. Proportions were calculated and ANOVO was used to compare magnesium levels among stable COPD, COPD exacerbation and healthy asymptomatic smokers. For the statistical analysis p <0.001 was considered significant.

## RESULTS:
In the present study that was conducted, of 126 subjects, all were males.

Majority of the patients were between 61 and 70 years of age (33.3%, n=42).
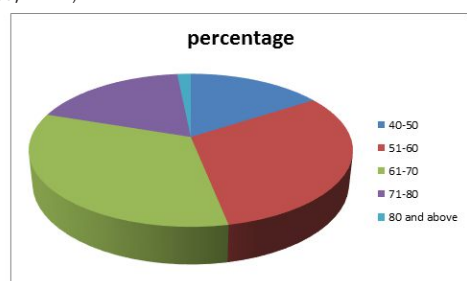


**Figure 1. Age population in the study**

**Table 1.**

| Age | | | Frequency | Percent |
|---|---|---|---|---|
| Valid | 40-50 | | 20 | 15.9 |
| | 51-60 | | 39 | 31.0 |
| | 61-70 | | 42 | 33.3 |
| | 71-80 | | 23 | 18.3 |
| | >80 | | 2 | 1.6 |
| | Total | | 126 | 100.0 |

Of the 126 study subjects, 33.3% (n=42) of people were stable COPD patients, 34.9% (n=44) were COPD exacerbation patients and the rest 31.7% (n=40) were asymptomatic people who smoked.
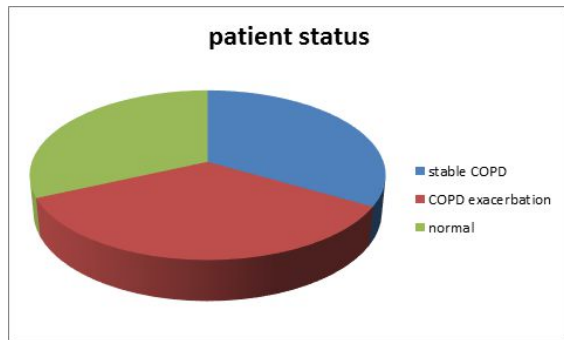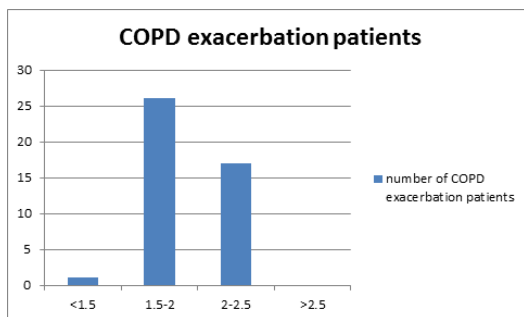


**Figure 2. Patient classification for the study.**

**Table 2.**

| group | | Frequency | Percent |
|---|---|---|---|
| Valid | COPD exacerbation | 44 | 34.9 |
| | Normal Healthy smokers | 40 | 31.7 |
| | Stable COPD | 42 | 33.3 |
| | Total | 126 | 100.0 |

Among the 44 subjects who presented with exacerbation of COPD, 26 patients (59.1%) had their serum magnesium levels between 1.5 and 2 mg/dl.
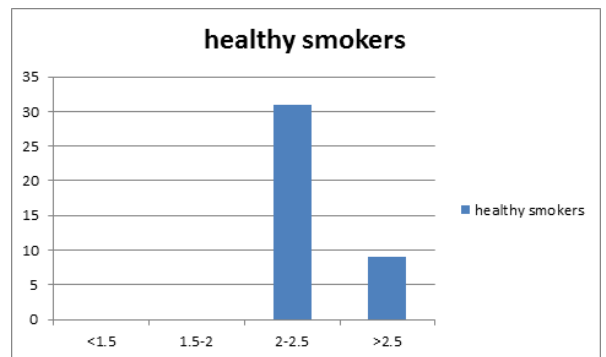


**Figure 3.**

66.7% (n=28) of the 42 stable COPD patients too had their magnesium levels ranging between 1.5 and 2 mg/dl.
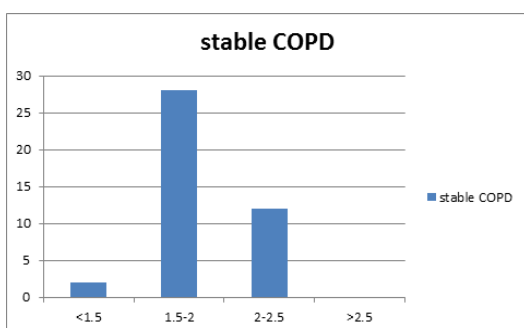


**Figure 4.**

Whereas 77.5% (n=31) subjects of the 40 healthy asymptomatic smokers had their serum magnesium levels between 2 to 2.5 mg/dl.
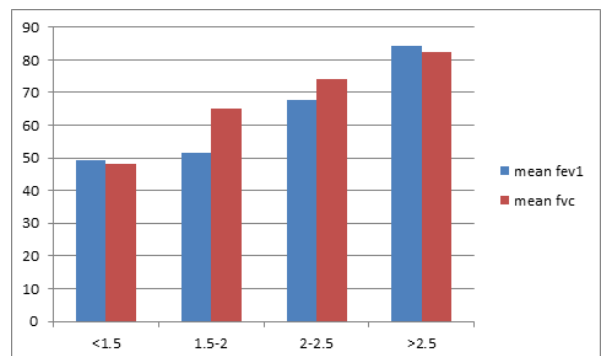


**Figure 5.**

**Table 3. serum magnesium levels in all groups of patients.**

| Crosstab | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Mg | | | | Total |
| | | | <1.5 | 1.5-2.0 | 2.0-2.5 | >2.5 | |
| group | COPD exacerbation | N | 1 | 26 | 17 | 0 | 44 |
| | | % | 2.3% | 59.1% | 38.6% | 0.0% | 100.0% |
| | Normal Healthy smokers | N | 0 | 0 | 31 | 9 | 40 |
| | | % | 0.0% | 0.0% | 77.5% | 22.5% | 100.0% |
| | Stable COPD | N | 2 | 28 | 12 | 0 | 42 |
| | | % | 4.8% | 66.7% | 28.6% | 0.0% | 100.0% |
| Total | | N | 3 | 54 | 60 | 9 | 126 |
| | | % | 2.4% | 42.9% | 47.6% | 7.1% | 100.0% |

It was observed that as FEV1 and FVC of the subjects had decreased there was a decrease in their serum magnesium levels that was directly proportional.
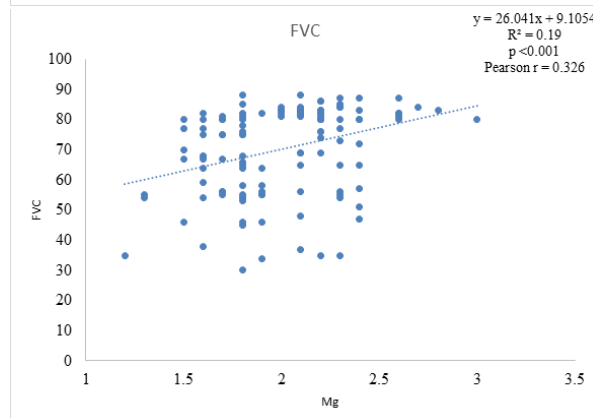


**Figure 6. Levels of serum magnesium with mean FEV1 and FVC**

**Table 4. . Levels of serum magnesium with mean FEV1 and FVC**

| Statistics | | | | |
|---|---|---|---|---|
| Mg | | | FEV1_value | FVC_value |
| <1.5 | N | Valid | 3 | 3 |
| | | Missing | 0 | 0 |
| | Mean | | 49.2333 | 48.0000 |
| | Median | | 44.0000 | 54.0000 |
| | Mode | | 36.70a | 35.00a |
| | Std. Deviation | | 15.81339 | 11.26943 |
| 1.5-2.0 | N | Valid | 54 | 54 |
| | | Missing | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| | Mean | | 51.3926 | 65.2778 |
| | Median | | 48.8500 | 67.0000 |
| | Mode | | 43.00 | 75.00a |
| | Std. Deviation | | 15.91966 | 13.91133 |
| 2.0-2.5 | N | Valid | 60 | 60 |
| | | Missing | 0 | 0 |
| | Mean | | 67.7150 | 74.1000 |
| | Median | | 80.5000 | 81.0000 |
| | Mode | | 82.00 | 83.00 |
| | Std. Deviation | | 19.64855 | 13.91707 |
| >2.5 | N | Valid | 9 | 9 |
| | | Missing | 0 | 0 |
| | Mean | | 84.4667 | 82.3333 |
| | Median | | 83.4000 | 82.0000 |
| | Mode | | 83.20 | 82.00 |
| | Std. Deviation | | 1.87816 | 2.17945 |
| a. Multiple modes exist. The smallest value is shown | | | | |



FEV1

$y = 26.041x + 9.1054$
$R^2 = 0.19$
$p < 0.001$
Pearson r = 0.436



FVC

$y = 26.041x + 9.1054$
$R^2 = 0.19$
$p < 0.001$
Pearson r = 0.326
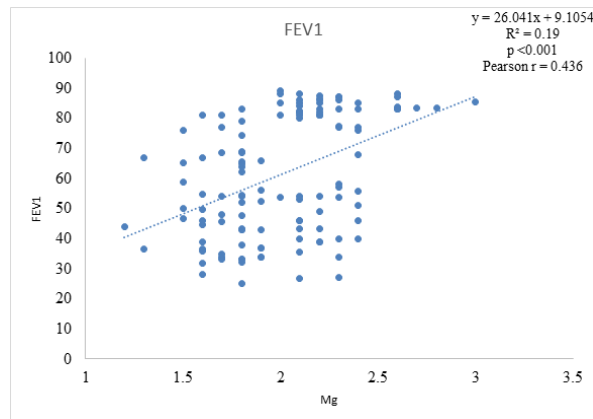
**ANOVA**

| | | Sum of Squares | df | Mean Square | F | Sig. P value |
|---|---|---|---|---|---|---|
| FEV1_value | Between Groups | 13032.748 | 3 | 4344.249 | 14.426 | .000 |
| | Within Groups | 36738.300 | 122 | 301.134 | | |
| | Total | 49771.049 | 125 | | | |
| FVC_value | Between Groups | 5023.481 | 3 | 1674.494 | 9.296 | .000 |
| | Within Groups | 21976.233 | 122 | 180.133 | | |
| | Total | 26999.714 | 125 | | | |

## DISCUSSION

COPD, which is a persistent and irreversible chronic airway inflammatory disorder is one of the leading causes of death worldwide and is projected to become the seventh leading cause of death by the year 2030.

Serum magnesium has been studied to be of vital importance to indirectly observe the exacerbation event in a COPD patient. It has become one of the observed value to assess the disease stability.

Magnesium is the second most abundant intracellular cation after potassium, being essential in a great number of enzymatic and metabolic processes. It is a co-factor of all enzymatic reactions that involve ATP and found in the membranes that maintain the electrical excitability of muscular and nervous cells. The normal level of magnesium in serum is 1.8-2.6 mg/dl.

Low magnesium levels is associated with increased airway hyperreactivity and decreased muscle strength. It also plays a role in relaxation of smooth muscles of airways and bronchodilation, stabilization of mast cells, neurohumoral mediator release, various immune responses, muscarinic actions and mucociliary clearance.

The present study was conducted to determine serum magnesium levels among stable COPD, exacerbation of COPD and normal healthy asymptomatic smokers. Another aim of this study was to assess the magnesium levels with severity of airway obstruction.

It was observed from the present study that the majority of stabe COPD patients and COPD exacerbation patients had their serum magnesium levels ranging from 1.5-2 mg/dl, whereas asymptomatic smokers had their serum magnesium levels in the normal range between 2 and 2.5 mg/dl.

It was also seen that their was a significant reduction in serum magnesium levels with the severity of airway obstruction.

## CONCLUSION

From the present study it was concluded that their is a low magnesium level seen among COPD individuals compared to normal healthy smokers and a significant reduction of magnesium levels with airway obstruction severity.

It could be implicated from this study that magnesium supplements could be administered among these patients in order to reduce the risk of frequent exacerbations and comorbidities.

**REFERENCES:**
1. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis,Management and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2015);xiv.
2. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis,Management and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2015);2.
3. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27:397-412.
4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
5. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis,Management and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2015);4.
6. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis,Management and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2015);6.
7. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis,Management and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2015);10-12.
8. Bringhurst FR DM, Krane SM, Kronenberg HM. Bone and Mineral Metabolism in Health and Disease. Longo DL FA, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012.
9. Bhatt SP., et al. Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of chronic obstructive pulmonary disease. Respir Med. 2008.
10. Jeswani G, Kumar J, Rathi A, et al. Serum magnesium as an important and independent predictor of acute exacerbation of COPD patients. Adv. Biores., Vol 5 (4) December 2014:157-163.
11. Salvi S, Agarwal A. India needs a National COPD Prevention and Control Programme. Supplement to JAPI 2012 Feb;60:5-6.
12. Health Status Maharashtra 2009: A report by the State Health Systems Resource Centre. 2010;20-21.
13. Hooper R, Burney P, Vollmer WM, et al. Risk factors for COPD spirometrically defined from the lower limit of normal in the BOLD project. Eur Respir J 2012;39:1343–53.
14. Salvi S, Barnes P. Chronic obstructive pulmonary disease in non-smokers. Lancet

2009;374:733–43.

15. Office of Population Censuses and Surveys. Occupational mortality: the Registrar General's decennial supplement for Great Britain, 1979–80, 1982–83, Great Britain. Office of Population Censuses and Surveys. London: H M Stationery Office, 1986.

16. Barker DJP, Osmond C. Childhood respiratory infection and adult chronic bronchitis in England and Wales. BMJ 1986;293:1271–5.

17. Burney P, Jithoo A, Kato B, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty—a BOLD analysis. Thorax 2013;0:1-9.

18. Williamson MA, Snyder LM, Wallach JB. Wallach's interpretation of diagnostic tests. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2011.

19. Dominguez LJ, Barbagallo M, Di Lorenzo G, et al. Bronchial reactivity and intracellular magnesium: a possible mechanism for the bronchodilating effects of magnesium in asthma. Clin Sci (London) 1998;95(2):137–42.

20. Dhingra S, Solven F, Wilson A, McCarthy DS. Hypomagnesemia and respiratory muscle power. Am Rev Respir Dis 1984;129(3):497–8.

21. Spivy WH, Skobelof EM, Levin RM. Effect of Mg chloride on rabbit bronchial smooth muscle. Ann Emerg Med 1990;19:1107–12.

22. Del Castillo J, Engbeak L. The nature of the neuromuscular block produced by Mg. J Physiol 1954;124:370–84.

23. Bois P. Effect of Mg deficiency on mast cells and urinary histamine in rats. Br J Exp Pathol 1963;44:151–5.

24. Alamoudi OS. Hypomagnesaemia in chronic, stable asthmatics: prevalence, correlation with severity and hospitalization. EurRespir J 2000;16(3):427–31.

25. Singh JP, Kohli S, Devi A. Serum Magnesium Level In COPD Patients Attending A Tertiary Hospital - A Cross Sectional Study. JK Science Vol. 14 No. 4, Oct -December 2012.

26. Aziz H, Blamoun A, Shubair M et al. Serum magnesium levels and acute exacerbation of chronic obstructive pulmonary disease. Annals of Clinical and Laboratory Science. 2005;35(4):424.