ARTICLE

The efficacy of methylxanthines as adjunct to standard of care in improving outcomes among chronic obstructive pulmonary disease patients at high risk for and in acute exacerbation: A systematic review and meta-analysis of randomized and non-randomized studies

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ABSTRACT

Methylxanthines has established recommendations among stable COPD patients as third line bronchodilator to beta-agonist and anti-cholinergics. However, data on its recommendation as an adjunct in exacerbation and its utility in preventing exacerbation among high risk patients remain scarce and conflicting. A systematic review and meta-analysis was performed on all randomized and non-randomized control trials determining association between the addition of methylxanthines to standard of care in improving outcomes in 1) high risk patients 2) patients in exacerbation. Two reviewers independently studied and reviewed the articles for quality. The following data extracted from the studies included: incidence of COPD exacerbation in one year, exacerbation requiring hospitalization, breathlessness score/quality of life score and inflammatory indices. A total of 7 studies were included in the final study. Pooled analysis of data showed that methylxanthines were associated with lower risk of exacerbations requiring hospitalization after 1 year of treatment (RR 0.79, [95% CI 0.71, 0.89]) and improved anti-inflammatory response by increasing histone deacetylase (HDAC) activity. However, it did not show statistical difference on the incidence of COPD exacerbation after 1 year (RR 0.94, [95% CI 0.86, 1.02]) nor improvement in breathlessness score/quality of life

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KEYWORDS

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score. Looking at adverse events, methylxanthines were not associated with an increased risk (RR 2.69, CI 0.29, 26.9 I^2 65%) of palpitations and regurgitation. The systematic review and meta-analysis showed that methylxanthines have utility in increasing HDAC and decreasing hospital related admissions due to exacerbation without additional adverse events. However, it does not decrease risk of exacerbation, self-reported symptom score and quality of life.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease due to persistent and progressive airflow limitation affecting almost 12 percent of adults over the age of 30 (Singh et al. 2019). It is a worldwide global problem and is the fourth most common cause of death among adults (Lozano et al. 2012), (Nahers and Loncar 2006).

An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy. It can be precipitated by multiple factors, the most common of which remain respiratory infections (Adeloye et al. 2015). Current recommendations (Grade 1B and 1A recommendations) for the treatment of COPD in exacerbation include short acting beta-adrenergic agonists (SABA) with short acting anticholinergic agent as an alternative or in combination with SABA and systemic corticosteroids (Singh et al. 2019).

Guidelines have already established both pharmacologic and non-pharmacologic management of the symptoms among patients with COPD. Pharmacologic management includes using bronchodilators and corticosteroids while non-pharmacologic management includes smoking cessation, vaccination and pulmonary rehabilitation.

Methylxanthines as a drug class, has generally been considered a third line bronchodilator after beta agonists and anti-cholinergics among patients with chronic COPD (Singh et al. 2019). The clinical indication of theophylline in stable COPD mainly lies on its ability to improve functional impairment – mainly dyspnea, exercise capacity, respiratory mechanics and respiratory muscle strength (Wegner et al. 2015). However, data for the use of methylxanthines as adjunct to the standard of care among COPD patients in acute exacerbation remain conflicting.

A study in 2008 by Barr and his colleagues evaluated the utility of methylxanthines versus placebo in decreasing hospitalization, relapse, length of hospital stay and improving FEV1 and self-rated symptoms. The result of this meta-analysis showed the absence of statistical benefit of methylxanthines versus placebo with increased side effects associated with its administration. The study concluded against using methlyxanthines for COPD in acute exacerbation.

However, post 2008, numerous studies (Cosio et al. 2019), (Fort et al. 2010), (Fexer et al. 2014), (Devereux et al. 2018) continued to evaluate the efficacy of methlyxanthines for COPD as an adjunct to treatment with inhaled corticosteroids to improve outcomes among patients in acute exacerbation with newer studies evaluating its utility in preventing exacerbation in high risk patients. These studies had mixed recommendations regarding the utility of methylxanthines for COPD with the following indications. With conflicting data, this systematic and meta-analysis was conducted on all available evidence to determine if adjunct methlyxanthines to corticosteroids 1) improve outcomes among patients in acute exacerbation and 2) prevent exacerbation in high risk patients.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as reference in the conduct and development of this systematic review and meta-analysis. Studies were retrieved from a pool of aggregated data and did not necessitate ethics approval. All references and authors were acknowledged and identified properly.

Search Strategy and Study Selection

A comprehensive literature search of all available evidence was performed on PubMed, COCHRANE and Google Scholar to search for relevant articles showing the effect of additional methylxanthines to standard of care with two main endpoints: 1) assess improvement in outcomes among patients in acute exacerbation and 2) assess exacerbation prevention among high risk patients. To include all potential relevant articles, the authors decided to included methylxanthines as a drug class rather than limiting search to a specific drug. The following search terms were used: “chronic obstructive lung disease”, “exacerbation”, “methylxanthines”, “glucocorticoids” and “standard of treatment”. MeSH terms were used and publications in the English language were retrieved for review.

Eligibility Criteria

Eligibility for inclusion was as follows: (1) enrolled COPD patients, including patients in exacerbation in the ER and/or patients at high risk for exacerbation; (2) used methylxanthines including theophylline, aminophylline, and doxofylline as adjunct to corticosteroids in preventing and/or treating exacerbation; (3) measured COPD exacerbation, incidence of hospitalization and/or length of hospital stay, self-reported breathlessness or FEV1 as outcome. Studies including (1) stable COPD patients, (2) COPD patients who were asymptomatic or classified as mild, and (3) populations which included both asthma and COPD, were excluded from the study.

Data Extraction and Quality Assessment

After articles were screened based on the inclusion and exclusion criteria, the authors independently reviewed all eligible full-text articles independently. Eligibility of each study was determined by consensus and divergences were resolved via discussion.

The Cochrane Data Extraction Template was used for data extraction of the following: characteristics of the studies (first author, year of publication, study design), patient characteristics, number of patients enrolled/sample size, inclusion and exclusion criteria for patients of each study, interventions, and outcomes. The Newcastle-Ottawa Scale (0-9) was used for non-randomized control trials, while risk of bias for randomized studies was done using the Cochrane Collaboration tool. Quality assessment was independently done by two reviewers. Treatment effects were estimated by calculating the Mantel-Haenszel-weighted risk ratio (RR) using a random-effects model of data analysis available with RevMan 5.4.

Table 1: Characteristics of Included Studies

Study	Size (n)	Design	Population	Exposure (vs. Control)	Outcomes
Duffy et al (2005)	n = 80	Prospective RCT	1. Non-acidotic COPDIAE 2. FEV1 <70% 3. Age 40-80 yo with at least 20 pack year smoking	IV aminophylline vs placebo	• Change in FEV1 in first 5 days • pH and paCO2 x 2 hours after intervention • Mean length of hospital stay • Breathlessness score • Side effects between exposure vs. control • Hospitalization and/or mortality after discharge in 6 weeks
Blais et al (2007)	N = 3040	Retrospective cohort	1. COPD patients	Theophylline vs. Theophylline with ICS vs LABA vs LABA with ICS	• Prevention of moderate to severe exacerbations
Cosio et al (2009)	N = 35	RCT	1. COPDIAE 2. FEV1 <70% 3. Smoking history of at least 15 years	Low dose oral theophylline (100 mg BID)	• HDAC, NF-kb, TAS, TNFa, IL6 and IL8 pre-treatment and 3 mos post discharge
Ford et al (2010)	N = 30	RCT	1. Smoking history of at least 20 years 2. COPDIAE	Theophylline + inhaled ICS vs theophylline	• Lung function • Quality of life • Inflammatory indices in induced sputum
Fexer et al (2014)	N = 2,992	Retrospective cohort	1. COPD patients on theophylline for at least 6 mos	Theophylline vs placebo	• First time to exacerbation and hospitalization
Devereux et al (2018)	N = 1567	RCT	1. FEV <70% using inhaled ICS 2. Given theophylline prospectively (200 mg OD or BID) x 1 year	Theophylline vs Placebo	• COPD exacerbation requiring antibiotics, oral ICS • Hospital admissions • Quality of life scoring • FEV1 • Adverse events
Chen et al (2023)	N = 155	RCT	1. COPD patients	Doxofylline vs Placebo	• COPD exacerbation • FEV1 • Adverse events

RESULTS AND DISCUSSION

Study Selection

An electronic search was done, which resulted in 74 studies. After initial review of the abstract and titles, 66 were excluded due to the following: included stable COPD patients, a heterogenous population of both COPD and bronchial asthma patient, non-English articles and abstract only publications. One study was found to have a duplicate which resulted in 7 studies included in the meta-analysis. The studies included for meta-analysis all involved COPD patients receiving methylxanthines (aminophylline, theophylline, doxofylline).

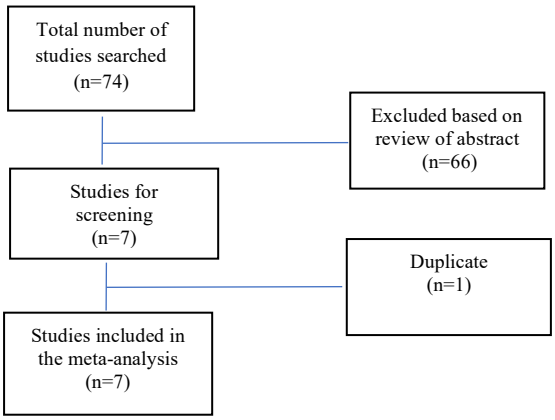

Figure 1: Flow Diagram of Study Selection

Study Characteristics

The characteristics of the studies included are summarized in table 1. The studies included were RCTS (4), and retrospective cohort (2). The outcomes varied, but the majority measured the efficacy of theophylline in decreasing exacerbation of COPD, its effect on lung function in terms of change in FEV1, and its impact on the length of hospital stay. Two studies measured the anti-inflammatory effect of theophylline through reduction of HDAC and one measured the reduction of sputum eosinophils post treatment.

COPD Exacerbation

Pooled analysis of data showed that the addition of methylxanthines (theophylline) showed no significant difference in the incidence of COPD exacerbations after 1 year (RR 0.94; 95% CI 0.86, 1.02; I^2 99%). However, the two studies showed significant heterogeneity.

COPD exacerbation requiring hospital admission

A fixed-effects meta-analysis showed that methylxanthines (theophylline) was associated with lower risk of COPD exacerbations requiring hospitalization after 1 year of treatment (RR 0.79; 95% CI 0.71, 0.89; I^2 95%). Exclusion of the study by Blais in 2007 removes the heterogeneity (RR 0.72 95% CI 0.65, 0.81; I^2 0%).

Breathlessness score / Quality of life score

Three studies reported symptom scores and quality of life (Duffy 2005, Ford 2010, Devereux 2018). Different scales were used by each study (Borg score, mMRC dyspnea score, and SAS-CRQ) and are summarized in Table 4. Addition of methylxanthine-derivatives had no significant difference in improving symptom scores or quality of life.

Inflammatory indices (HDAC)

Two studies measured histone deacetylase activity (Cosio 2009, Ford 2010). The addition of theophylline significantly increased HDAC activities (Table 5).

Figure 2: Methylxanthines and incidence of COPD exacerbations after 1 year

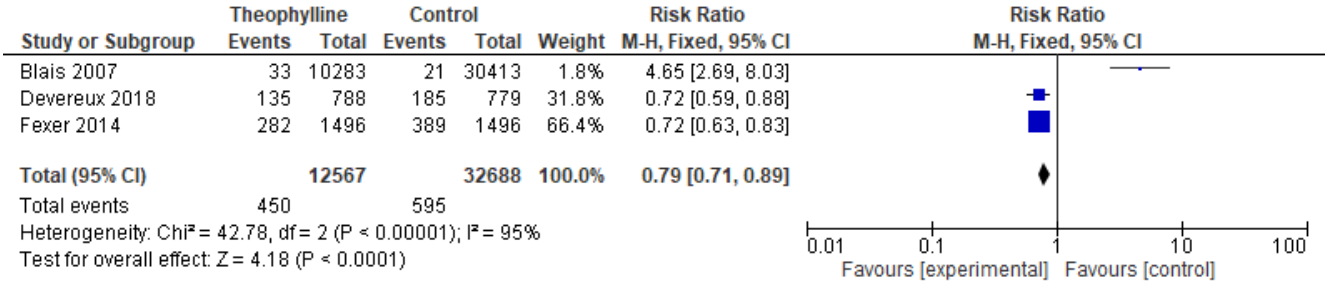

Figure 3: Methylxanthines and incidence of COPD exacerbations after 1 year requiring hospitalization

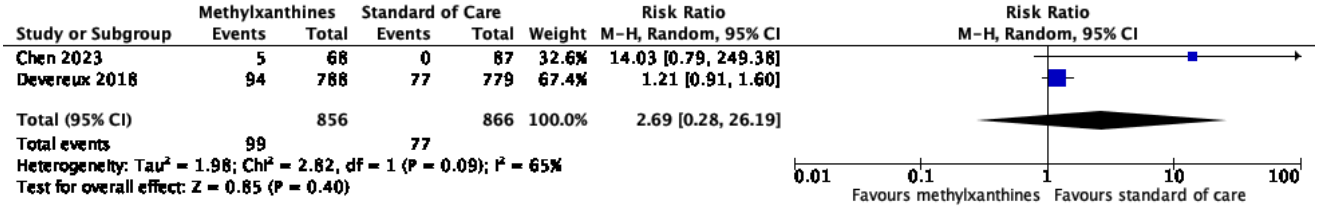

Figure 4: Methylxanthines and incidence of adverse events within the 1 year treatment period

Table 2: Newcastle-Ottawa Assessment of Study Quality

	Blais 2007	Fexer 2014
Selection		
Representativeness of exposed cohort	1	1
Selection of non-exposed cohort	1	1
Ascertainment of exposure	1	1
Demonstration that outcome of interest was not present at the start of study	1	1
Comparability		
Comparability of cohorts on the basis of the design or analysis controlled for confounders	1	1
Outcome		
Assessment of outcome	1	1
Was follow-up long enough for outcomes to occur	1	1
Adequacy of follow-up of cohorts	1	1
Total	8	8
Quality	Good	Good

Table 3: Assessment of Risk Bias for Randomized Control Trials

Study	Sequence Generation	Allocation Concealment	Blinding			Incomplete Outcome	Selective Outcome reporting	Over-all risk of bias
			Participant	Personnel	Outcome Assessor			
Duffy et al	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	Unclear
Cosio et al	Low	Low	Low	Low	Unclear	Low	Low	Low
Ford et al	Low	Low	Low	Low	Low	Low	Low	Low
Devereux et al	Low	Low	Low	Low	Low	Low	Low	Low

Table 4: Symptom Score/ Quality of Life

Study	Aminophylline/Theophylline	Placebo	p-value
Duffy 2005 *	2.6 (1.7 – 3.5)	2.4 (1.6 – 3.2)	Not significant
Ford 2010	SAS-CRQ 4.9	SAS-CRQ 4.8	Not significant
Devereux 2018 • mmRC 0 • mmRC 1	 38 of 772 (6%) 186 of 772 (29.5%)	 52 of 764 (8.5%) 158 of 764 (25.7%)	Not significant 0.31

* Fall in Borg score

Table 5: Histone Deacetylase Activity

Study	Theophylline	Placebo	p-value
Cosio 2009	34% (n=16)	9.6% (n=19)	0.02
Ford 2010	875 $\pm$ 70	95 $\pm$ 24	< 0.01

While the utility of methylxanthines (doxofylline, theophylline) in stable COPD has been established and recommendations of its use already in the GOLD guidelines, literature has been scarce regarding its utility in preventing and/or treating exacerbation.

The systematic review and meta-analysis aimed to determine if methylxanthines on top of standard treatment (with intravenous or inhaled corticosteroids) improve outcomes among COPD patients in exacerbation and prevented exacerbation among high risk patients. The study reviewed all available evidence since 2005 of its use in exacerbation – as treatment and to prevent exacerbation among high risk patients.

Based on the results of the study, the addition of methylxanthines, particularly theophylline to the standard of care for high risk patients in COPD did not decrease the risk of exacerbation. While Blais 2007 found a reduction in exacerbation among COPD patients with theophylline use, Fexer 2014 actually recommended against its use due to the statistically significant increased risk of harm (with a hazard ratio of 1.41 and a number needed to harm of 11). Potential confounders for the opposing results of the study were the 1) profile of the patients enrolled in each arm of the study – Fexer et al identified that patients with theophylline prescriptions tended to suffer from advanced COPD resulting in a potentially poorer outcome; 2) exposure to other treatments – Blais et al enrolled patients with multiple and variable treatment regimens which could potentially affect outcomes. As such, given these biases, the quality and type of study (retrospective cohort) and heterogeneity, the pooled analysis is statistically non-significant and clinically non-conclusive.

However, it is of interest that although the risk of exacerbation does not decrease with the use of theophylline compared to the control, there is a statistically significant association between the incidence of hospital-related admissions due to exacerbation with the theophylline group having reduced exacerbations requiring hospital admissions. This effect was most evident among the subgroup of patients who have had multiple admissions for exacerbation in the past.

Three studies (Ford et al. 2010), (Devereux et al. 2018), (Duffy et al. 2005) measured symptom score and quality of life. A pooling of data statistically was not possible due to the different scales available for each study. With varied breathlessness score/quality of life assessment, results were consistent that methylxanthines (aminophylline, theophylline) were not associated with improvement in subjective dyspnea. Although the study by Ford et al showed possible attenuation of airway inflammation in COPD with theophylline through demonstrating a decrease in sputum eosinophilia, all studies evaluated symptom improvement within a few days to weeks. Data on the correlation between laboratory improvement and clinical benefit may take more than a few weeks and as such observation period may be insufficient to demonstrate improvement.

Aside from hard outcomes, two studies (Cosio et al. 2009), (Ford et al. 2010) evaluated the histone deacetylase activity (HDAC). HDAC suppresses inflammatory gene expression, attenuating the progressive inflammation in the small airways and lung parenchyma of patients with COPD (Barnes 2009). In addition, HDAC increases the anti-inflammatory effect of glucocorticoids (Ford et al. 2010), (Barnes 2009). Both studies were able to document that theophylline increases HDAC activity and reduces inflammation when added to a standard of treatment for COPD in acute exacerbation.

Adverse Events

Two studies (Devereux et al. 2018), (Chen et al. 2023) included adverse events as outcomes of interest in the study. The study by Chen et al included doxofylline as the intervention, while the study by Devereux et al included theophylline. Pooled analysis showed that methylxanthines were not associated with an increase in adverse events (RR 2.69, CI 0.29, 26.9 I^2 65%). Specific adverse events measured on both studies were palpitations and gastroesophageal reflux. In addition, the study by Devereux also showed no significant difference in the symptom profile of adverse events between theophylline and placebo group (13.2% versus 14.0%, p-value 0.60).

CONCLUSION

The systematic review and meta-analysis showed that methylxanthines (theophylline, aminophylline) have utility in increasing HDAC and decreasing hospital related admissions due to exacerbation. However, it does not decrease risk of exacerbation, self reported symptom score, and quality of life. There was no associated risk of increased side effects with methylxanthine use. At present, due to the limitations in the available evidence, the authors recommend using methylxanthines for stable COPD and among patients at high risk for exacerbations as maintenance treatment, with increased monitoring, for possible side effects. In addition, further studies should be done to assess its utility given the statistically significant benefit in improving HDAC activity among COPD patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

CONTRIBUTION OF INDIVIDUAL AUTHORS

M.K. Zamora and D. Guevara were involved with the literature search, appraisal of articles, data collection and interpretation. J. Santiaguel was involved with the analysis of data and writing and drafting of thr manuscript. M.P. Jorge provided analysis of data and manuscript revision.

REFERENCES

Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, Nair H, Gasevic D, Sdridhar D, Campbell H, Yee Chan K, Sheikh A, Rudan I. Global and regional estimates of COPD prevalance: systemic review and meta-analysis. J Glob Health. 2015;5(2):020415.

Barnes PJ. Role of HDAC2 in the pathophysiology of COPD. Annu Rev Physiol. 2009;71:451-64.

Barr RG, Rowe BH and Camargo Jr CA. Methlyxanthines for exacerbations of chronic obstructive pulmonary disease: Meta-analysis of Randomized Trials. 2003;327:643.

Chen MF, He W, Huang DS, Jia H, Zhong ZS, Li N, Li SS, Xia SY. Effects of doxofylline as an adjuvant on severe exacerbation and long-term prognosis for COPD with different clinical subtypes. Clin Respir J. 2023 Sep;17(9):851-864.

Cosio BG, Iglesias A, Rios A, Noguera A, Sala E, Ito K, Barnes PJ, Agusti A. Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD. Thorax. 2009 May;64(5):424-9.

Cyr MC, Beauchesne MF, Lemière C, Blais L. Effect of theophylline on the rate of moderate to severe exacerbations among patients with chronic obstructive pulmonary disease. Br J Clin Pharmacol. 2008 Jan;65(1):40-50.

Devereux G, Cotton S, Fielding S, McMeekin N, Barnes PJ, Briggs A, Burns G, Chaudhuri R, Chrystyn H, Davies L, De Soyza A, Gompertz S, Haughney J, Innes K, Kaniewska J, Lee A, Morice A, Norrie J, Sullivan A, Wilson A, Price D. Effect of Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients With COPD: A Randomized Clinical Trial. JAMA. 2018 Oct 16;320(15):1548-1559.

Duffy N, Walker P, Diamantea F, Calverley PM, Davies L. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Thorax. 2005 Sep;60(9):713-7.

Fexer J, Donnachie E, Schneider A, Wagenpfeil S, Keller M, Hofmann F, Mehring M. The effects of theophylline on hospital admissions and exacerbations in COPD patients: audit data from the Bavarian disease management program. Dtsch Arztebl Int. 2014 Apr 25;111(17):293-300.

Ford PA, Durham AL, Russell RE, Gordon F, Adcock IM, Barnes PJ. Treatment effects of low-dose theophylline combined with an inhaled corticosteroid in COPD. Chest. 2010 Jun;137(6):1338-44.

Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2095-128. doi: 10.1016/S0140-6736(12)61728-0. Erratum in: Lancet. 2013 Feb 23;381(9867):628. AlMazroa, Mohammad A [added]; Memish, Ziad A [added]

Nahers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006 Nov;3(11):e442.

Singh D, Agusti A, Anzueto A, Barnes P, Bourbeau J, Celli B, Criner G, Frith P, Halpin D, Han M, Varela MV, Martinez F, Oca M, Papi A, Pavord I, Roche N, Sin D, Stockley R, Vestbo J, Wedicha N, Vogelmeir C. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J 2019; 53: 1900164.

Wegner RE, Jörres RA, Kirsten DK, Magnussen H. Factor analysis of exercise capacity, dyspnoea ratings and lung function in patients with severe COPD. Eur Respir J. 1994 Apr;7(4):725-9.