**Occupational Contribution to Chronic Bronchitis and COPD; an ATS/ERS task force update.**

**Long Version 10 Milano, ERS**

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**Methods**

Relevant publications from 2001 onwards were identified by a recent systematic review (Fishwick *et al*, using MEDLINE, EMBASE, Emcare and the British Nursing Index). This review was designed to develop a standard of care for clinicians, occupational health professionals, employers and employees for the identification and management of occupational COPD. In addition, the outputs of five other systematic reviews (Blanc 2007, Eisner 2010, Mazitova 2010, Omland 2014, Alif 2016) were used to supplement the included papers from 2001. It should be noted that the latter only reviewed papers that described the findings of studies where occupational exposure had been attributed using a job exposure matrix (JEM).

To cover the additional period between 2014 and 2016 following that covered by the main reviews, an identical search strategy adopted by Fishwick *et al* was adopted to ensure completeness.

Given the large number of potentially relevant papers, published data were only included from studies that were population based, rather than studying specific workplaces or occupational groupings, and either calculated a population attributable fraction (PAF) for Chronic Bronchitis (CB) and / or for Chronic obstructive Pulmonary Disease (COPD), or data were available to allow this calculation to be carried out. Where necessary, further information and original raw data was sourced from the authors, in order to allow calculation of a PAF. If this was required, this was noted in the relevant results table.

Additionally, where varying definitions of COPD were used, that based on a lower limit of normal (LLN) for physiology measures was used preferentially. Similarly, where lung function was used to define COPD, it has been made clear in the relevant results table where bronchodilators were used; if this information was available.

PAF estimates were deemed statistically significant if either (i) their confidence limit did not include zero, or (ii) the associated 95% confidence limit of the odds ratio (OR) (or relative risk (RR)) did not include unity.

**Results**

The six reviews identified 33 papers for inclusion. The additional literature search from 2014 to 2016 identified a further 11 papers for inclusion (two for CB and 9 for COPD). Of the 44 papers in total, 32 were included in the COPD table, and 13 in the chronic bronchitis (CB) table.

Table 1 summarises the 32 studies included for COPD. These were heterogeneous. For example, studies dealt with both never smoking and mixed smoking populations, used varying definitions of COPD, and also employing differing physiology assessment protocols both with and without bronchodilator.

Limiting the analysis to only the 24 statistically significant COPD studies, the median PAF for occupational contribution to the burden of COPD was 21.1% (range 4% to 65.3%). If all 32 studies were considered irrespective of significance, the median PAF was identified to be 16.2% (range 0% to 65.3%). Three studies assessed the PAFs (respectively 18.3, 48 and 53%) specifically in non-smokers [Lee 2015, Wurtz 2015 and Toren 2014]. Similarly, only two studies calculated separate PAFs for each gender. The significant of these two identified a PAF of 18.7% for males and 8% for females [Hutchins 2017].

There were only 7 studies that clearly used post bronchodilator lung function as an outcome. If only these were considered, a median PAF of 9% was identified, with a range between 4 and 65.3%.

Table 2 summaries the 13 studies included for CB. Again, these studies were heterogeneous. Certain considered the occupational contribution to CB as the main research question, whereas others dealt with both COPD and CB and are thus included in both Tables 1 and 2. Five of the 13 studies specifically made mention of the use of a JEM to attribute occupational exposures.

Limiting the analysis to only the 10 significant CB studies, the median PAF for occupational contribution to the burden of CB was 15.5% (range 4% to 56.8%). If all studies were considered irrespective of significance, the median PAF was identified to be 15% (range 0.19% to 56.8%). Only one study assessed the PAF (12%, not significant) in non-smokers [Zock 2001]. Similarly, only one study identified a difference between genders and CB PAF values, with a higher PAF for males (18% versus 2.8%).

Other papers felt to be of importance, but not included in the main CB and COPD tables, were identified. Harber *et al* described an accelerated annual decline in FEV1 in males with early COPD exposed specifically to fume. This longitudinal study estimated that each year of fume exposure was associated with a 0.25% predicted reduction in post-bronchodilator FEV1. These effects were not seen in females, and no exposure response effects were seen for dust. Equally, Blanc *et a*l have confirmed a global association between COPD and occupation exposures. Using an ecological approach from 90 sex-specific strata, and the prevalence of occupational exposure and ever-smoking, the prevalence of occupational exposures predicted COPD prevalence (with a 0.8% increase in COPD prevalence per 10% increase in occupational exposure prevalence).

**Conclusions**

This review has considered both the development of CB and COPD in the context of workplace exposures, focussing on available evidence since the last ATS consensus statement (Balmes 2003). It has specifically identified a number of relevant population based studies that both uphold and strengthen the conclusion of the original consensus; that at least 15% of both CB and COPD burdens could be attributed to harmful inhaled occupational exposures. The heterogeneous nature of the included studies makes comment on association at sub-group levels more difficult. Nevertheless, the relatively large number of studies, estimating PAF values across many countries and in differing demographic, cultural and work sector populations did permit comment about certain sub-group risks.

Data from non-smoking populations are particularly compelling as a strength of this paper and support further associations between such exposures and the burden of COPD. Furthermore, seven studies were identified where it was clear that lung function estimates had been made post bronchodilator; these studies contributed to a median PAF of 9%, slightly lower than those identified for all studies. Only two studies explicitly stated PAF values between genders. One of these, based on the most recent assessment of the UK Biobank data, identified a greater PAF in males.

Whilst certain studies did address the severity of COPD *post hoc*, there were insufficient data to develop a definitive view about the nature and severity of COPD in the context of occupational exposures.

Similarly, other considerations about underlying populations may influence the findings of each study, including the proportion of any population that consists of younger workers (who may not yet have been expected to develop CB or COPD) and also the ability of the study designs to adequately consider additive or multiplicative effects of tobacco smoking. This review is not able to contribute further here.

The findings of this review have significant biological plausibility, summarised previously in some detail by others (including Eisner 2010, who discussed occupational risk factors in the context of many other airway influences). Chronic Bronchitis is generally regarded as a combination of excess mucus production, hypersecretion and mucociliary dysfunction resulting from persisting airway inflammation (Kim). Whilst cigarette smoke and infections are the most common historically regarded classical causes, many individual occupational exposures are long recognised as potentially causative by their direct action on the airway (Morgan, Blanc).

In relation to COPD, there are specific exposures that are recognised to cause lung damage consistent with that seen in COPD. For example, cadmium fume is associated with the development of emphysema in animals (Kirschvink), and has also been linked to reduced lung function (Davison). Similarly, respirable crystalline silica (RCS), coal and welding fume have all been shown to be pro-inflammatory and thus capable of causing airway damage with repeated exposures (Rom, Castranova). Additionally, RCS exposure (Hnizdo 1991, Hnizdo 2003 ) and coal (Cockcroft) have been associated with human evidence, and endotoxin with animal (Shapiro) evidence, of airways disease. In reality, even within these specific examples, other influences will be operational that dictate the harm produced. For example, data support an interaction between dust exposure and α1 antitrypsin deficiency for causing lung function abnormalities (Piitulainen, Mayer).

In terms of future work in this area, the COPDGene study is beginning to unravel associations between occupational exposures and the appearances of relevant radiology, with particular focus on the presence of gas trapping and emphysema [Marchetti 2014, van Koeverden 2015]. Similarly, data from the Spiromix and COPDGene studies will undoubtedly assist the further understanding of the differential role of established and perhaps new risk factors for COPD. The Spiromix study is currently investigating the effects of occupational exposures on COPD severity, stratified by gender, noting that such exposures do influence COPD exacerbation severity when stratified by gender [Paulin 2015].

In summary, the overall findings of this current work confirm that recent published evidence supports the association between harmful inhaled workplace agents and the development of both CB and COPD. Workplace interventions designed to reduce these harmful exposures will reduce the overall population burdens of these two chronic and disabling conditions.

**References**

Alif SM1, Dharmage SC1,2, Bowatte G1, Karahalios A3, Benke G4, Dennekamp M4, Mehta AJ5, Miedinger D6,7, Künzli N8,7, Probst-Hensch N8,7, Matheson MC1,2. Occupational exposure and risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Expert Rev Respir Med. 2016 Aug;10(8):861-72. doi: 10.1080/17476348.2016.1190274. Epub 2016 Jul 1.

Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. PLoS One. 2015 Sep 3;10(9):e0136065.

Axelsson M1,2, Ekerljung L3, Eriksson J3,4, Hagstad S3,5, Rönmark E5,6, Lötvall J3, Lundbäck B3,5. Chronic bronchitis in West Sweden - a matter of smoking and social class. Eur Clin Respir J. 2016 Jul 13;3:30319. doi: 10.3402/ecrj.v3.30319. eCollection 2016.

Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Toren K, Viegi G; Environmental and Occupational Health Assembly, American Thoracic Society.Blanc PD, Torén K. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med. 2003 Mar 1;167(5):787-97.

Bang KM1, Syamlal G, Mazurek JM, Wassell JT. Chronic obstructive pulmonary disease prevalence among nonsmokers by occupation in the United States. J Occup Environ Med. 2013 Sep;55(9):1021-6. doi: 10.1097/JOM.0b013e31829baa97.

Bang KM1, Syamlal G, Mazurek JM. Prevalence of chronic obstructive pulmonary disease in the U.S. working population: an analysis of data from the 1997-2004 National Health Interview Survey. COPD. 2009 Oct;6(5):380-7.

Bergdahl IA1, Torén K, Eriksson K, Hedlund U, Nilsson T, Flodin R, Järvholm B. Increased mortality in COPD among construction workers exposed to inorganic dust. Eur Respir J. 2004 Mar;23(3):402-6.

Blanc PD, Torén K. COPD and occupation: resetting the agenda. Occup Environ Med. 2016 Jun;73(6):357-8. doi: 10.1136/oemed-2015-103300.

Blanc PD, Torén K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. Int J Tuberc Lung Dis. 2007 Mar;11(3):251-7.

Blanc PD1, Eisner MD, Earnest G, Trupin L, Balmes JR, Yelin EH, Gregorich SE, Katz PP. Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. J Occup Environ Med. 2009b Jul;51(7):804-10.

Blanc PD1, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, Sidney S, Eisner MD. Occupational exposures and the risk of COPD: dusty trades revisited. Thorax. 2009a Jan;64(1):6-12.

Blanc PD, Menezes AM, Plana E, Mannino DM, Hallal PC, Torén K, et al. Occupational exposures and COPD: An ecological analysis of international data. Eur Respir J. 2009 Feb;33(2):298–304. http://dx.doi.org/10.1183/09031936.00118808.

Boggia B1, Farinaro E, Grieco L, Lucariello A, Carbone U. Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of Southern Italy. J Occup Environ Med. 2008 Mar;50(3):366-70. doi: 10.1097/JOM.0b013e318162f601.

Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). persistent asthma syndrome after high level irritant exposures. Chest 1985;88:376-84.

Castranova V, Vallyathan V. Silicosis and coal workers' pneumoconiosis. Environ Health Perspect 2000;108:675-84.

Cockcroft A, Seal RM, Wagner JC, Lyons JP, Ryder R, Andersson N. Post-mortem study of emphysema in coalworkers and non-coalworkers. Lancet. 1982 Sep 11;2(8298):600–3.

Darby AC1, Waterhouse JC, Stevens V, Billings CG, Billings CG, Burton CM, Young C, Wight J, Blanc PD, Fishwick D. Chronic obstructive pulmonary disease among residents of an historically industrialised area. Thorax. 2012 Oct;67(10):901-7. doi: 10.1136/thoraxjnl-2011-200543. Epub 2012 Jun 28.

Davison AG, Fayers PM, Taylor AJ, Venables KM, Darbyshire J, Pickering CA, Chettle DR, Franklin D, Guthrie CJ, Scott MC, et al. Cadmium fume inhalation and emphysema. Lancet. 1988 Mar 26;1(8587):663-7.

de Jong K1, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM; LifeLines Cohort study. Pesticides and other occupational exposures are associated with airway obstruction: the LifeLines cohort study. Occup Environ Med. 2014 Feb;71(2):88-96. doi: 10.1136/oemed-2013-101639. Epub 2013 Oct 10.

de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, et al. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax. 2004 Feb;59(2):120–5.

de Meer G1, Kerkhof M, Kromhout H, Schouten JP, Heederik D. Interaction of atopy and smoking on respiratory effects of occupational dust exposure: a general population-based study. Environ Health. 2004 Jun 2;3(1):6.

Fishwick D, Sen D, Barber C, Bradshaw L, Robinson E, Sumner J; COPD Standard Collaboration Group. Occupational chronic obstructive pulmonary disease: a standard of care. Occup Med (Lond). 2015 Jun;65(4):270-82.

Hanania NA1, Celli BR, Donohue JF, Martin UJ. Bronchodilator reversibility in COPD. Chest. 2011 Oct;140(4):1055-63. doi: 10.1378/chest.10-2974.

Hansell A1, Ghosh RE, Poole S, Zock JP, Weatherall M, Vermeulen R, Kromhout H, Travers J, Beasley R. Occupational risk factors for chronic respiratory disease in a New Zealand population using lifetime occupational history. J Occup Environ Med. 2014 Mar;56(3):270-80. doi: 10.1097/01.jom.0000438382.33221.dc.

Harber P, Tashkin DP, Simmons M, Crawford L, Hnizdo E, Connett J; Lung Health Study Group. Effect of occupational exposures on decline of lung function in early chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007 Nov 15;176(10):994-1000. Epub 2007 Jul 12.

Hnizdo E, Sluis-Cremer GK, Abramowitz JA. Emphysema type in relation to silica dust exposure in South African gold miners. Am Rev Respir Dis. 1991 Jun;143(6):1241–7.

Hnizdo E, Vallyathan V. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. Occup Environ Med. 2003 Apr;60(4):237-43.

Hnizdo E1, Sullivan PA, Bang KM, Wagner G. Airflow obstruction attributable to work in industry and occupation among U.S. race/ethnic groups: a study of NHANES III data. Am J Ind Med. 2004 Aug;46(2):126-35.

Hnizdo E1, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2002 Oct 15;156(8):738-46.

Holm M, Kim JL, Lillienberg L, Storaas T, Jögi R, Svanes C, Schlünssen V, Forsberg B, Gíslason T, Janson C, Torén K; RHINE Study Group, Northern Europe. Incidence and prevalence of chronic bronchitis: impact of smoking and welding. The RHINE study.

Hutchins S. EPICOH abstract 2017.

Int J Tuberc Lung Dis. 2012 Apr;16(4):553-7. doi: 10.5588/ijtld.11.0288.

Idolor LF1, DE Guia TS, Francisco NA, Roa CC, Ayuyao FG, Tady CZ, Tan DT, Banal-Yang S, Balanag VM Jr, Reyes MT, Dantes RB. Burden of obstructive lung disease in a rural setting in the Philippines. Respirology. 2011 Oct;16(7):1111-8. doi: 10.1111/j.1440-1843.2011.02027.x.

Jaén A1, Zock JP, Kogevinas M, Ferrer A, Marín A. Occupation, smoking, and chronic obstructive respiratory disorders: a cross sectional study in an industrial area of Catalonia, Spain. Environ Health. 2006 Feb 14;5:2.

Kainu A1, Rouhos A, Sovijärvi A, Lindqvist A, Sarna S, Lundbäck B. COPD in Helsinki, Finland: socioeconomic status based on occupation has an important impact on prevalence. Scand J Public Health. 2013 Aug;41(6):570-8. doi: 10.1177/1403494813484554. Epub 2013 Apr 18.

Kim H, Herbert R, Landrigan P, Markowitz SB, Moline JM, Savitz DA, Todd AC, Udasin IG, Wisnivesky JP. Increased rates of asthma among World Trade Center disaster responders. Am J Ind Med. 2012 Jan;55(1):44-53.

Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013 Feb 1;187(3):228-37.

Kirschvink N, Vincke G, Fiévez L, Onclinx C, Wirth D, Belleflamme M, Louis R, Cataldo D, Peck MJ, Gustin P. Repeated cadmium nebulizations induce pulmonary MMP-2 and MMP-9 production and emphysema in rats. Toxicology. 2005 Jul 1;211(1-2):36-48. Epub 2005 Mar 29.

Lam KB1, Yin P, Jiang CQ, Zhang WS, Adab P, Miller MR, Thomas GN, Ayres JG, Lam TH, Cheng KK. Past dust and GAS/FUME exposure and COPD in Chinese: the Guangzhou Biobank Cohort Study. Respir Med. 2012 Oct;106(10):1421-8. doi: 10.1016/j.rmed.2012.05.009. Epub 2012 Jul 12.

Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, Studnicka M, Bateman E, Anto JM, Burney P, Mannino DM, Buist SA; BOLD Collaborative Research Group. COPD in never smokers: results from the population-based burden of obstructive lung disease study. Chest. 2011 Apr;139(4):752-63. doi: 10.1378/chest.10-1253. Epub 2010 Sep 30.

Lamprecht B1, Schirnhofer L, Kaiser B, Studnicka M, Buist AS. Farming and the prevalence of non-reversible airways obstruction: results from a population-based study. Am J Ind Med. 2007 Jun;50(6):421-6.

Lange P1, Parner J, Prescott E, Vestbo J. Chronic bronchitis in an elderly population. Age Ageing. 2003 Nov;32(6):636-42.

Lee SJ, Kim SW, Kong KA, Ryu YJ, Lee JH, Chang JH. Risk factors for chronic obstructive pulmonary disease among never-smokers in Korea. Int J Chron Obstruct Pulmon Dis. 2015 Mar 5;10:497-506.

LeVan TD1, Koh WP, Lee HP, Koh D, Yu MC, London SJ. Vapor, dust, and smoke exposure in relation to adult-onset asthma and chronic respiratory symptoms: the Singapore Chinese Health Study. Am J Epidemiol. 2006 Jun 15;163(12):1118-28. Epub 2006 May 17.

Lindberg A1, Jonsson AC, Rönmark E, Lundgren R, Larsson LG, Lundbäck B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest. 2005 May;127(5):1544-52.

Mak GK1, Gould MK, Kuschner WG. Occupational inhalant exposure and respiratory disorders among never-smokers referred to a hospital pulmonary function laboratory. Am J Med Sci. 2001 Sep;322(3):121-6.

Marchetti N1, Garshick E, Kinney GL, McKenzie A, Stinson D, Lutz SM, Lynch DA, Criner GJ, Silverman EK, Crapo JD; COPDGene Investigators. Association between occupational exposure and lung function, respiratory symptoms, and high-resolution computed tomography imaging in COPDGene. Am J Respir Crit Care Med. 2014 Oct 1;190(7):756-62. doi: 10.1164/rccm.201403-0493OC.

Matheson MC1, Benke G, Raven J, Sim MR, Kromhout H, Vermeulen R, Johns DP, Walters EH, Abramson MJ. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Thorax. 2005 Aug;60(8):645-51.

Mayer AS, Stoller JK, Bucher Bartelson B, James Ruttenber A, Sandhaus RA, Newman LS. Occupational exposure risks in individuals with PI\*Z alpha(1)-antitrypsin deficiency. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):553–8.

Mazitova NN1, Saveliev AA, Berheeva ZM, Amirov NKh. COPD and occupation: a retrospective cohort study of industrial workers. Arh Hig Rada Toksikol. 2012 Sep;63(3):345-56. doi: 10.2478/10004-1254-63-2012-2178.

Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux PO, Curjuric I, Kromhout H, Rochat T, Rothe T, Russi EW, Schikowski T, Schindler C, Schwartz J, Turk A, Vermeulen R, Probst-Hensch N, Künzli N; SAPALDIA Team. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. Am J Respir Crit Care Med. 2012 Jun 15;185(12):1292-300. doi: 10.1164/rccm.201110-1917OC. Epub 2012 Apr 6.

Melville AM1, Pless-Mulloli T, Afolabi OA, Stenton SC. COPD prevalence and its association with occupational exposures in a general population. Eur Respir J. 2010 Sep;36(3):488-93. doi: 10.1183/09031936.00038309. Epub 2010 Jan 28.

Montnémery P, Bengtsson P, Elliot A, Lindholm LH, Nyberg P, Löfdahl CG. Prevalence of obstructive lung diseases and respiratory symptoms in relation to living environment and socio-economic group. Respir Med. 2001 Sep;95(9):744-52.

Morgan WK. Industrial bronchitis. Br J Ind Med. 1978 Nov; 35(4): 285–291.

Obaseki DO, et. al. Chronic Airflow Obstruction in a Black African Population: Results of BOLD Study, Ile-Ife, Nigeria. COPD. 2016 Feb; 13:42-9.

Omland O, Würtz ET, Aasen TB, Blanc P, Brisman JB, Miller MR, Pedersen OF, Schlünssen V, Sigsgaard T, Ulrik CS, Viskum S. Occupational chronic obstructive pulmonary disease: a systematic literature review. Scand J Work Environ Health. 2014 Jan;40(1):19-35.

Pallasaho P1, Kainu A, Sovijärvi A, Lindqvist A, Piirilä PL. Combined effect of smoking and occupational exposure to dusts, gases or fumes on the incidence of COPD. COPD. 2014 Feb;11(1):88-95. doi: 10.3109/15412555.2013.830095. Epub 2013 Oct 10.

Paulin LM, Diette GB, Blanc PD, Putcha N, Eisner MD, Kanner RE, Belli AJ, Christenson S, Tashkin DP, Han M, Barr RG, Hansel NN; SPIROMICS Research Group. Occupational exposures are associated with worse morbidity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015 Mar 1;191(5):557-65.

Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001 Apr;163(5):1256-76.

Pérez-Rial S1, Girón-Martínez Á1, Peces-Barba G2. Animal models of chronic obstructive pulmonary disease. Arch Bronconeumol. 2015 Mar;51(3):121-7. doi: 10.1016/j.arbres.2014.06.016. Epub 2014 Sep 5.

Piitulainen E, Tornling G, Eriksson S. Effect of age and occupational exposure to airway irritants on lung function in non-smoking individuals with alpha 1-antitrypsin deficiency (PiZZ). Thorax. 1997 Mar;52(3):244–8.

Rom WN. Relationship of inflammatory cell cytokines to disease severity in individuals with occupational inorganic dust exposure. Am J Ind Med 1991;19:15-27.

Scholes S1, Moody A1, Mindell JS1. Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales. BMJ Open. 2014 Jul 23;4(7):e005685. doi: 10.1136/bmjopen-2014-005685.

Shapiro SD. Animal models for COPD. Chest. 2000 May;117(5 Suppl 1):223S–7S.

Sheikh M. Alifa SM et. al. Occupational exposure and risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Expert Rev Respir Med 2016; 10: 861 -72.

Suadicani P1, Hein HO, Meyer HW, Gyntelberg F. Exposure to cold and draught, alcohol consumption, and the NS-phenotype are associated with chronic bronchitis: an epidemiological investigation of 3387 men aged 53-75 years: the Copenhagen Male Study. Occup Environ Med. 2001 Mar;58(3):160-4.

Sunyer J1, Zock JP, Kromhout H, Garcia-Esteban R, Radon K, Jarvis D, Toren K, Künzli N, Norbäck D, d'Errico A, Urrutia I, Payo F, Olivieri M, Villani S, Van Sprundel M, Antó JM, Kogevinas M; Occupational Group of the European Community Respiratory Health Survey. Lung function decline, chronic bronchitis, and occupational exposures in young adults. Am J Respir Crit Care Med. 2005 Nov 1;172(9):1139-45. Epub 2005 Jul 22.

Torén K, Järvholm B. Effect of occupational exposure to vapors, gases, dusts, and fumes on COPD mortality risk among Swedish construction workers: a longitudinal cohort study. Chest. 2014 May;145(5):992-7.

Trupin L1, Earnest G, San Pedro M, Balmes JR, Eisner MD, Yelin E, Katz PP, Blanc PD. The occupational burden of chronic obstructive pulmonary disease. Eur Respir J. 2003 Sep;22(3):462-9.

van Koeverden I, Blanc PD, Bowler RP, Arjomandi M. COPDGene Study Cohort – COPD Risk. J Chronic Obstr Pulm Dis [2015;12:182-9]

Weinmann S, Vollmer WM, Breen V, Heumann M, Hnizdo E, Villnave J, Doney B, Graziani M, McBurnie MA, Buist AS. COPD and occupational exposures: a case-control study. J Occup Environ Med. 2008 May;50(5):561-9. doi: 10.1097/JOM.0b013e3181651556. abstract only

Würtz ET1, Schlünssen V2, Malling TH1, Hansen JG3, Omland Ø4. Occupational COPD among Danish never-smokers: a population-based study. Occup Environ Med. 2015a Jun;72(6):456-9.

Würtz ET1, Schlünssen V, Malling TH, Hansen JG, Omland Ø. Occupational Chronic Obstructive Pulmonary Disease in a Danish Population-Based Study. COPD. 2015b Aug;12(4):435-43.

Xu F1, Yin X, Zhang M, Shen H, Lu L, Xu Y. Prevalence of physician-diagnosed COPD and its association with smoking among urban and rural residents in regional mainland China. Chest. 2005 Oct;128(4):2818-23.

Zhong N1, Wang C, Yao W, Chen P, Kang J, Huang S, Chen B, Wang C, Ni D, Zhou Y, Liu S, Wang X, Wang D, Lu J, Zheng J, Ran P. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. Am J Respir Crit Care Med. 2007 Oct 15;176(8):753-60. Epub 2007 Jun 15.

Zock JP1, Sunyer J, Kogevinas M, Kromhout H, Burney P, Antó JM. Occupation, chronic bronchitis, and lung function in young adults. An international study. Am J Respir Crit Care Med. 2001 Jun;163(7):1572-7.

Table 1; COPD studies summarised

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| --- | --- | --- | --- | --- |
| **Author and date** | **OR (95% CI).**  **PAF for COPD;** significant (SIG, not significant (NS) | **Numbers of cases, non-cases, participants where available** | **Definition of COPD** | **Exposure**  **Stratified by** |
| Hutchings 2016 | 11.5% overall (1.3%-36.3%), SIG  18.7% for males  8.0% for females | Proportion of population exposed;  25.5% for males  10.8% for females | Pre BD | Self-reported  JEM |
| Paulin 2015 | OR 1.44 (1.04-1.97)  12.0%, SIGa | 721 cases  354 non cases | Post BD | JEM |
| Lee 2015 | 2.6 (1.3-5.3)  18.3%, never smokers, SIGb | 39 cases in manual labour, 131 in occupational subgroup | Pre BD | Job title |
| Würtz 2015a | 3.7, (1.4-10.0)  48.0%, never smokers, SIGc | 23 cases  1463 non cases | Pre BD | Self-reported  Expert judgement |
| Würtz 2015b | 1.38 (0.99-1.93)  12.3%, NSd | 2330 non exposed, 1351 high exposure, 279 cases in all groups of exposure | Pre BD | Self-reported  Expert-judgement |
| Toren 2014 | RR 1.3 (1.2-1.5)  24.0% for all workers, SIG  RR 2.1 (1.2-3.8)  53% for never smoking workers, SIGe | 1085 deaths from COPD | Other (death certification from COPD) | JEM |
| Hansell 2014 | 1.07 (0.64 – 1.81)  4.3%, NSf | 83 cases, 665 non cases | Pre BD | JEM |
| De Jong 2014 | 1.41 (1.16-1.7)  6.4%, SIGg | 1176 cases, 6690 non cases | Pre BD | JEM |
| Pallasaho 2014 | OR=2.1 (1.5-3.0)  23.6%, SIGh | 140 cases  4162 non cases | Self-reported | Self-reported  Job Title |
| Scholes 2014 | OR 1.61 (1.13-2.31).  9.4%, SIGi | 7879 participants, 2.8% were cases | Pre BD | Self-reported |
| Mehta 2012 | OR -  23%, NS for LLN stage II+ COPDj | 520 GOLD 1 cases, 57 GOLD 2+ cases, 3321 non cases | Pre BD | JEM |
| Mazitova 2012 | OR 5.9 (3.6-9.8)  65.3%, SIGk | 1375 participants, 105 cases | Post BD | Self-reported  Exposure information |
| Lam 2012 | OR -  10.4%, NSl | 396 cases, 6819 non cases | Pre BD | Self-reported |
| Darby 2012 | OR 3.9 (2.7-5.8)  58.7% (45.6% to 68.7), SIGm | 216 cases, 1754 participants | Pre BD | Self-reported |
| Govender 2011 | OR 5.9 (2.6 to 13.2)  25%, SIG | 110 cases, 102 non cases | Doctor diagnosed | JEM |
| Idolor 2011 | OR 1.16 (0.79-1.69)  5.3%, NSn | 141 cases, 518 non cases | Post BD | Self-reported |
| Melville 2010 | 39.6%o | 15% of males and 7% of females (10% overall) were cases, 845 participants | Post BD | Self-reported |
| Blanc 2009a | OR 2.1 (1.6-2.8)  31.0%, SIG | 742 cases, 302 non cases | Pre BD | Self-reported  JEM |
| Blanc 2009 | OR 2.5, (1.9 to 3.4)  32.0%, SIG | 233 cases, 1709 non cases | Self-reported | Self-reported  JEM |
| Bang 2009 | 12.2% (12.1-12.5), SIGp | 5134 COPD cases, 122490 non-COPD | Self-reported | JEM |
| Zhong 2007 | OR 1.2 (1.0-1.4)  4.0%, SIGq | 838 cases, 9973 non cases | Post BD | Self-reported |
| Lamprecht 2007 | OR 1.8, (1.2–2.8)?  7.7%, SIGr | 304 cases, 954 non-cases [119 GOLD II or higher cases] | Post BD | Self-reported |
| Jaén 2006 | 1.2 (0.7-2.2)  9.0%, NSs | 26 males (10.4%) and 10 females (4.1%) cases | Post BD | Self-reported |
| Lindberg 2005 | 1.8 (0.8-4.0)  15.0%, NS | 127/982 (GOLD); 83/1026 (BTS) | Pre BD | Job Title |
| Matheson 2005 | OR 2.7 (1.4-5.2)  37%, SIGt | 226 mild airways obstruction, 83 moderate, 42 with study defined COPD. | Pre BD | Self-reported  JEM |
| Sunyer 2005 | Males OR 1.01 (0.3-4.1)  Females OR 1.1 (0.2-8.8)  Males 0%, NS  Females 1%, NS | Males : 221/2981 (among them 61 new cases in the follow-up); Females 148/3131 (among them 52 new cases in the follow-up) | Pre BD | JEM |
| De Marco 2004 | OR 1.47 (1.31-1.65)  17.4, SIGu | 1751 cases, 12567 non cases | Pre BD | Self-reported |
| Bergdahl 2004 | OR 1.1 (1.03-1.2)  11.0%, SIG | 523 cases, 200212 non cases | Death Certification | JEM |
| Hnizdo 2004 | 22.2% (9.1-33.4), SIG | 911 cases, 9152 participants | Pre BD | Self-reported |
| Trupin 2003 | 2.0 (1.6-2.5)  20.0%, SIG | 377 cases, 1555 non cases | Self-reported | Self-reported |
| Hnizdo 2002 | OR 1.4 (1.0-2.0)  15.0%, SIG | 693 cases, 9130 non cases | Pre BD | JEM |
| Mak 2001 | OR 1.8 (1.1-2.9)  30%, SIG | 67 cases | Pre BD | Self-reported |

Table 1 notes NOT for publication

a.12% PAF. The proportion of cases exposed is 283/(283+438) which is 0.3925. OR 1.44 (1.04–1.97).

b. PAR COPD 18.3%. 39 cases of COPD in manual labour, total of 131 cases in the occupational subgroup. Proportion of cases in manual labour 39/131=29.8%. OR for risk of COPD in manual labour=2.6 (1.3-5.3) (adjusted). PAR=29.8\*(1.6/2.6)=18.3% for manual labour. OR represents manual labour v those with a “lack of occupational exposure: managers or professionals, office work, service or sales”.

c. COPD; PAF (COPD LLN definition) 48% (30% to 65%) for VGDF. OR=3.69 (95% CI 1.36 to 10.04).

d. COPD; no information given to allow proportion of cases exposed to be calculated. VGDF category data as follows; No versus high exposure OR (adjusted) =1.38 (0.99-1.93). n=2330 no exposure, n=1351 high exposure. Proportion of population exposed=1351/3681=37%. PAR=p(RR-1)/(p(RR-1)+1)=0.37(0.38)/((0.37(0.38))=1)=12.3%.

e. COPD; 24% for all workers, 53% for never smokers. The fraction of COPD attributable to occupational exposure was estimated to be 0.24 among all workers (RR, 1.32, 1.18-1.47)) and 0.53 among never-smoking workers (RR, 2.11, 1.17-3.83).

f. COPD LLN (after contacting authors for additional information) as follows for ever/never VGDF exposed; ((OR-1)/OR)\*Pe (Pe=proportion of cases exposed) OR=1.07 (0.64 – 1.81) (55/83)\*(0.07/1.07)=4.3%

g. COPD; (“mild obstruction”). OR 1.41 (1.16 to 1.70) VGDF not exposed v VGDF high exposure. In non-exposed group, 917/6534 were cases. In high exposed group, 259/1332 were cases. Total cases in these two groups was 917+259=1176. Proportion of cases exposed=259/1176=22%. PAR=(0.41/1.41)\*22=6.4%.

h. 140 incident cases from 4302 followed up. 44.3% of the incident cases had self-reported occupational exposure ("dust, gases or fumes") in 2007. This equates to 62 individuals. Proportion of cases with self-reported exposures thus 62/140. Adjusted OR=2.140 (1.503-3.046) for COPD. PAR=(1.142/2.142)\*(62/140)=.53\*44.2=23.6%

i. COPD; (i) self-reported COPD from HSE study. Effect of routine job v professional 166 cases in referent and routine job groups, 108 of which are in routine job. 1.61 (1.13-2.31). PAR=((.61/1.61)\*108)/166. PAR=24.7%. (ii) PB advice; 503 with COPD defined by LLN and of those 195 (43%) are in the routine work (e.g., heavy exposure) category. The OR of 1.28 taken from the main paper and exposure fx 0f 0.43 among cases gives 0.28/1.28 x 0.43 = 9.4% PAR.

j. PAFs calculated by authors for two COPD endpoints and 4 exposure categories, and also for ever or never smokers. For ever smokers exposed to VGDF, PARs calculated as 24% for stage II+ GOLD COPD and 23% for LLN stage II+ COPD.

k. PAR 65.3% for "overall" occupational exposures, calculated by authors. Multiple other endpoints used to calculate PAR (low, medium, high VGDF, silica, etc..). This was based on OR 5.9 (3.6 to 9.8)

l. 10.4% (95% CI -0.9%, 19.5%) as calculated by the authors for any dust gas/fume exposure and COPD using LLN definition [9.1%. This was not calculated by the authors. COPD was associated with high exposure to dust or gas/fume (exposed: 87/1206 v non-exposed: 191/3853; adjusted odds ratio: 1.41; 95% confidence interval (CI) 1.06, 1.87). 278 cases, 87 of which were exposed=31.3%. PAR=0.41/1.41\*31.3=9.10%]

m. COPD; 20% for spirometry defined COPD GOLD 1 or greater. 58.7% for self-reported VGDF exposures, and 31% based on high risk JEM derived exposure category.

n. COPD; data used from Table 3 (univariate OR only quoted, thus unadjusted for other factors (adjusted models only contain duration of occupational exposures). Dusty job yes/no (by greater or less than 30 years of exposure), COPD yes/no. OR=1.16 (0.79-1.69). 141 cases, 53 of whom are exposed. Pe=53/141. PAR=(0.16/1.16)\*(53/141)=0.14\*0.38=5.3%

o. 39.6%; not calculated by authors and does not appear to contain enough data to derive a PAR. After contacting them directly; data as follows. 39.6%. (PAR%) of occupational exposures to COPD was: (417/839) x [(61 x 393)/(356 x 29) – 1] / [0.497 x (2.32 – 1) +1] = 39.6%.

p. COPD; 12.2% for industry and 17.4% for occupation stratifications. NEED FULL PAPER. Paper arrived 6.1.17. 12.2% has a limit of 12.1-12.5, and 17.4% has a limit of 17.1-17.6. Both thus significant.

q. 4% (calculated by DF). OR 1.2 (1.04-1.39), total cases 1668, total cases exposed 394 (dust/gases/fumes).

r. COPD; GOLD II or higher. 7.7%. Study largely related to assessment of farming exposures alone, not other high risk groups. Assume from paper that the PAR calculation relates to the OR 1.8; 95% CI 1.2–2.8?

s. COPD; 9% (calculated by PB). OR 1.2 (0.7-2.2). NEEDS CHECKING WITH PB’S ESTIMASTES FOR COPD AND CB

t. 37%, 8%, 27% in biological dusts, mineral dusts and gases/fumes exposed. OR 2.7 (1.4-5.2), 1.1 (0.6-2.3), 1.6 (0.8-3.2) respectively.

u. COPD; (not calculated by authors). OR (corrected) 1.47 (1.31-1.65) for GOLD 0. PAF%=(0.47/1.47)\*Pe. Pe=54.4% PAF%= 17.4

v. Hnizdo 2004 COPD (AO); 22.2%, (95% CI 9.1–33.4). Calculated by combining all occupational groups with OR for COPD>1. [23.4%, 49.6% in differing ethics groups.

Table 2; Chronic Bronchitis studies

|  |  |  |  |
| --- | --- | --- | --- |
| **Author and date** | **OR (95%CI).**  **PAF for chronic bronchitis; significant (SIG) or not significant (NS)** | **Numbers of cases, non-cases, participants where available** | **Exposure stratified by** |
| Axelsson 2016 | 1.4 (0.8-2.3)  8.6%, SIG a | 84 cases  1172 participants | Self-reported |
| Hansell A 2014 | 1.4 (0.8-2.3)  18.9%, NS b | 59 cases  27 non cases | JEM |
| Darby 2012 | 3.6 (1.9-6.9)  56.8%, SIG c | 70 cases, 55 of these exposed | Self-reported  JEM |
| Mazitova N 2012 | OR 1.0 (0.7-1.4)  0.19%, NS | 170 cases, 1375 participants | Self-reported |
| Holm M 2012 | OR -  10% (2.8% for females, 18% for males) | 866 cases, 15919 participants | Self-reported |
| LeVan TD 2006 | 1.3 (1.0-1.6)  6.0%, SIG | 417 cases  45104 non cases | Self-reported |
| Jaén A 2006 | 2.0 (1.1-3.7)  34.0%, SIG | 69 cases  576 participants | Self-reported |
| Sunyer J 2005 | 1.7 (1.2-2.5)  15.0% males, SIG  1.0 (0.4-2.1)  0.0% females, NS | 2.9% of females, 3.0% of males with CB | Self-reported  JEM |
| de Meer 2004 | OR 2.2 (1.2-4.2).  25.0%, SIG | 72 cases  1906 participants | Self-reported  JEM |
| Lange 2003 | 2.2 (1.7-2.7)  16.0%, SIG | 13.0% in females  18.6% in males | Self-reported |
| Montnemery P  2001 | 1.4 (1.1-1.7)  11.0%, SIG | 8469 participants  4.6% had CB | Self-reported |
| Zock JP  2001 | 1.7 (1.3-2.3)  24% for current smokers, SIG  1.8 (0.8-4.1)  26% ex-smokers, NS  1.3 (0.8-2.3)  12% never smokers, NS | 13,253 participants aged 20-44 years old  2.9% of never smokers, 3.3% of ex-smokers and 8.9% of current smokers had CB | JEM |
| Suadicani P  2001 | 2.2 (1.7-2.2)  4.0%, SIG | 485 cases  2846 non cases | Self-reported |

a. CB; data taken from Tables 1 and 4. 288 with exposure to dust, gases fumes, and 876 not exposed. No information about proportion of cases exposed. However, total number exposed and RR known. Assuming table 4 relates to the same data, OR for CB of exposed v not exposed is adjusted and = 1.38 (0.84-2.26). (1.8 for chronic sputum). PAR calculated using second formula as follows; PAR=(p(RR-1))/(p(RR-1)+1). p=288/(288+876)=0.25 PAR=(0.25\*0.38)/(0.25\*0.38)+1=8.6%.

b. After contacting authors; Pc x ((OR-1)/OR) where Pc is the proportion of cases exposed. OR=1.38 (0.84-2.28). (59/(59+27)) x (0.38/1.38) = 0.68 x 0.28 = 18.9% for CB symptoms (cough AND sputum at least 3 months of year), VGDF exposed v non-exposed.

c. Unpublished data from the Sheffield cohort. 70 cases of CB alone, compared to all others in the dataset. VGDF ever/never. OR adjusted for age, gender and smoking. OR=3.606 (1.898-6.852). 70 cases of CB, 55 of whom exposed. PAR%=2.606/3.606\*(55/70)=56.8%.