Mortality Statistics in Asthma

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Ed. Note: Sentences that are **bolded** are of major importance in underwriting asthma and in discussion of cases in the Pulmonary Workshop.

Asthma is a disease characterized by recurring, reversible airways obstruction due to underlying inflammation and bronchial hyperresponsiveness. Asthma is one of the most common chronic noncommunicable lung diseases, affecting an estimated 260 million people globally, and is associated with significant morbidity and mortality.

- Vos T, Lim S, Abbafati C, et al. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396(10258): 1204-1222. doi.org:/10.1016/S0140-6736(20)30925-9

Asthma with usually mild or infrequent symptoms (50-75% of patients with asthma) contributes to 30% to 40% of exacerbations leading to emergency care; asthma-related death may occur in persons with asthma that is usually mild.

- Dusser d, Montani D, Chanez P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. *Allergy* 2007; 62(6): 591-604. doi.org/10.1111/j.1398-9995.2007.01394.x

GINA (Global Initiative for Asthma) is a collaboration of the National Institutes of Health, National Heart, Lung and Blood Institute (NHLBI), and World Health Organization. In 2019, GINA recommended *against* the use of monotherapy with short-acting beta-agonists (SABAs). They now believe there is no distinction between mild-intermittent and mild-persistent asthma, and inhaled corticosteroid (ICS)-containing therapies are recommended for both. ICS-formoterol is recommended as the preferred reliever inhaler for these entities. For treatment of moderate asthma, GINA recommends ICS-formoterol maintenance *and* reliever therapy. *See end of monograph for further information regarding therapies for asthma.*

- Gray SE, Cifu AS, et al. JAMA Clinical Guidelines Synopsis: Therapy for Mild to Moderate Asthma. *JAMA* August 9, 2022;328(6):575-576 doi.org/10.1001/jama.2022.12258

Overall asthma mortality has been declining over the past two decades. As the U.S. population ages, there are more elderly patients older than 65 years who have asthma. Asthma mortality is highest in this population even after adjusting for other age-related comorbidities.

- Zein JG, Udeh BL, et al. Impact of age and sex on outcomes and hospital cost of acute asthma in the United States, 2011-2012. *PLoS One* 2016;11:e0157301 doi.org/10.1371/journal.pone.0157301

Differences in asthma severity have also been observed in women and black patients. **Women have more severe asthma, higher hospitalization rates, and higher mortality rates.**

- Kynyk JA, Mastronarde JG, McCallister JW. Asthma, the sex difference. *Curr Opin Pulm Med* 2011;17:6-11 https://doi.org/10.1097/MCP.0b013e3283410038

Black patients with asthma have poorer asthma control, more emergency room visits, and more treatment failures.

- Haselkort T, Lee JH, et al. TENOR Study Group. Racial disparities in asthma-related health outcomes in severe or difficult-to-treat asthma. *Ass Allergy Asthma Immunol* 2008;101;256-263 https://doi.org/10.1016/S1081-1206(10)60490-5
- Wechsler ME, Castro M, et al. Impact of race on asthma treatment failures in the asthma clinical research network. *Am J Respir Crit Care Med* 2011;184:1247-1253 https://doi.org/10.1164/rccm201103-0514OC

Pathophysiology of Severe Asthma:
Chronic severe asthma includes two subtypes based on the amount of **Type 2 (T2) inflammation**:

- **T2-high** inflammation asthma
- and **T2-low** inflammation asthma.

Persons with T2-high inflammation asthma have elevated airway and systemic eosinophilia, elevated fractional exhaled nitric oxide (FeNO), and respond better to glucocorticoids. They also have other signs of type 2 inflammation, such as increased numbers of airway mast cells (MCs) and sputum basophils and are often seen in association with severe sinus disease and nasal polyposis. In addition to high dose inhaled glucocorticoids plus a second controller (eg, long-acting beta agonist, leukotriene modifier, or theophylline), T2 high patients may need treatment with biologics, as follows:

- Anti-immunoglobulin IgE – omalizumab
- Anti-interleukin IL5 agents – mepolizeumab, benralizumab, reslizumab
- Anti-IL-4 subunit alpha – dupilumab
- Anti-thymic stromal lymphopoietin (TSLP) – tezepelumab

[Note to underwriters: for applicants with eosinophils ≥300/μl, investigate for non-asthma causes including Strongyloides (often asymptomatic). For applicants with hypereosinophilia (e.g. ≥1500/μl, consider EGPA (eosinophilic granulomatosis with polyangiitis)]

Persons with type 2-low inflammation asthma *do not have airway or systemic eosinophilia* and respond more poorly to glucocorticosteroids. They may be treated tezepelumab, although their response is not as good as persons with eosinophilic asthma.

Several studies have identified an **increased prevalence of asthma among obese individuals** compared with those of normal weight. In a Dutch cohort, the prevalence of obesity (body mass index ≥30 kg/m^2) among a cohort with severe asthma was 21 percent.

- Van Veen IH, Brinke A, Stark P, et al. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. J *Allergy* 2008; 63: 570-574 doi.org/10.1111/j.1398-9995.2007.01597x

In a similar cohort in the United Kingdom, the prevalence of obesity was 48 percent.

- Gibeon D, Batuwita K, Osmond M, et al. Obesity-associated severe asthma represents a distinct clinical phenotype: analysis of the British Thoracic Society Difficult Asthma Registry Patient cohort according to BMI. *Chest* 2013; 143: 406-416 doi.org/10.1378/chest.12-0872

The risk of obesity-associated asthma is higher for women than men and among nonatopic individuals than atopic. Asthma associated with obesity is often more difficult to control and less likely to respond to traditional asthma therapy. There appears to be a particular phenotype of obese asthma associated with metabolic syndrome and elevated blood IL-6 levels.

- Peters M, McGrath K, Hawkins G, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med* 2016: 4:574 doi.org/10.1016/S2213-2600(16)30048-0

Clinical studies have demonstrated various degrees of associations of asthma, asthma-associated medications, allergic rhinitis and even atopic dermatitis and anaphylaxis with cardiovascular disease (CVD), including coronary heart diseases (CHD), aortic diseases, peripheral arterial diseases (PAD), pulmonary embolism, pulmonary hypertension, right ventricular (RV) dysfunctions, atrial fibrillation, cardiac hypertrophy, and even systemic hypertension.

Asthma mortality statistics:

These mortality statistics do not apply to childhood asthma that *completely remits* by their teens. That being said, severe early childhood bronchitis manifested by recurrent protracted wet cough have a 3-fold increased risk pneumonia, a 4.5-fold increased risk of current asthma, and a 6.4-fold increased risk for developing adult-onset asthma (but not bronchitis) by age 53, according to a recent study.

- Perret J, Wurzel D, Walters E, et. al., Childhood 'bronchitis' and respiratory outcomes in middle-age: a prospective cohort study from age 7 to 53 years. *BMJ Open Respiratory Research* Jun 2022, 9 (1) e001212 doi.org/10.1136/bmjresp-2022-001212

In the past decade, the prevalence of asthma has increased 8.6% in children and 7.4% in adults. **Asthma in adulthood is associated with increased risk of premature death and cardiovascular disease (CVD).** Links between asthma and CVD begin emerging as early as the 1970s. Patients with asthma, along with chronic obstructive pulmonary disease (COPD) and interstitial lung disease, have a higher incidence of CVD (such as acute myocardial infarction (AMI) and ischemic stroke) possibly due to chronic activation of pro-inflammatory cytokines, resulting in systemic and vascular inflammation.

These two diseases share a common etiology underlined by chronic systemic inflammation. Age and overweight or obesity commonly contribute to the risk of CVD and severe asthma. The mechanisms by which obesity contributes to asthma or CVD involve elevated systemic inflammation. Obese persons with high plasma cytokine interleukin (IL)-6 levels show more severe asthma than those with low IL-6 levels. Systemic inflammation in obese persons includes high plasma IL-6, IL-1, tumor necrosis factor (TNF) and leptin levels. For example, IL-6 influences naïve T cell differentiation into type 17 helper T (T_H17) cells and indirectly affects cardiac and lung functions via T_H-17. Such inflammatory mediators can drive CVD and may originate from adipocytes and activated inflammatory cells. These molecules also activate lung vascular endothelial cells, airway fibroblasts, smooth muscle cells (SMCs), tracheobronchial epithelial cells and inflammatory cells and the analogous cell types in the myocardium and vasculature.

Although adult asthma patients have an increased risk of all-cause mortality, only a small number of asthma patients die directly from the asthma itself.

- Lemmetyinen R, Karjalainen J, Nuy S, et al. Higher mortality of adults with asthma: a 15-year follow-up of a population-based cohort. *Allergy* 2018; 73: 1479-1488. doi.org:10.1111/all.13431

Thus, an increased risk of death in asthma patients is mainly due to comorbidities.

Zhang et. al. summarized the findings from 30 cohort studies comprising 4,157,823 participants, including:

- A large health check-up program of 446,346 adults from Taiwan
- A study of 94,079 individuals from the Copenhagen General Population Study
- A US National Health and Nutrition Study cross-sectional study of 16,941 individuals between 1999 and 2006
- A study of 37,015 individuals from the same survey between 2001 and 2014
- A retrospective cohort of 203,595 asthmatic patients and 203,595 reference individuals from the Kaiser Permanente Northern California healthcare plan
- A prospective population-based cohort of 3,612 patients from the Framingham Offspring Study
- And the Wisconsin Sleep Cohort of 1,269 patients

With the following findings:

1. Chronic adult asthma patients have **increased CVD (cardiovascular disease) mortality** compared to people without asthma (RR = 1.25, 95% CI = 1.14-1.38). Asthma patients also had **increased risk of all-cause mortality** (RR = 1.38, 95% CI = 1.07-1.77). In subgroup analysis **male asthma patients** had a mild higher risk of CVD mortality compared to people without asthma (RR = 1.19, CI 1.00-1.41, p=0.05). **Female asthma patients** had a more significant higher risk of CVD mortality compared to people without asthma (RR = 1.39, CI 1.20-1.61, p>0.00001).

2. In **male asthma patients**, risk of **all-cause mortality** increased compared to people without asthma, although this difference was not significant (RR = 1.52, 95% CI 0.88-2.62, p=0.13). **In female patients**, risk of **all-cause mortality** increased significantly compared to females without asthma (RR – 1.90, 95% CI 1.20-3.00, p-0.006).

3. **Early-onset asthma** (asthma onset ≤ age 18) ***with asthma persisting into adulthood*** had an increased **risk of CVD** compared to people without asthma (RR = 1.26, 95% CI 1.01-1.55, p=0.12), whereas **late-onset asthma** patients (age >40) had a more significantly increased **risk of CVD** compared to people without asthma (RR = 1.39, 95% CI 1.17-1.66, p=0.0002).

In conclusion, female asthma patients had a higher risk of CVD morbidity and all-cause mortality than male asthma patients, and late-onset asthma patients had a higher risk of CVD morbidity than early-onset asthma patients.

- Zhang B, Li, Z-F, An, Z et al. Association Between Asthma and All-Cause Mortality and Cardiovascular Disease Morbidity and Mortality: A Meta-Analysis of Cohort Studies. *Front Cardiovasc Med* 17 March 2022 doi.org/10.3389/fcvm.2022.861798

The gender difference may be associated with sex hormone. Some studies found that estrogen can cause low levels of systemic inflammation by modulating the release of proinflammatory cytokines and regulating the production of leukotrienes. In contrast, androgen may have anti-inflammation effects and protect against airway inflammation.

- Onufrak S, Abramson J, Austin H, et al. Relation of adult-onset asthma to coronary heart disease and stroke. *Am J Cardiol* 2008; 101: 1247-1252 doi.org/10.1016/j.amjcard.2007.12.024

Adult-onset asthma or use of asthmatic medications were also associated with CVD, CHD, cerebrovascular (CBV) disease, heart failure, all-cause mortality and increased CVD incidence before and after adjusting of established cardiovascular risk factors.

- Pollevick M, Xu K, Mhango G, et al. The Relationship Between Asthma and Cardiovascular Disease. *Chest* 2021; 159: 1338-1345 doi.org/10.1016/j.chest.2020.11.053
    - Unadjusted analyses revealed that asthma was associated with increased CVD incidence (hazard ratio, 1.40; 95% CI, 1.17-1.68).
    - Cox regression also showed an adjusted association between asthma and CVD incidence (hazard ratio, 1.28; 95% CI, 1.07-1.54) after controlling for established cardiovascular risk factors

Asthma or history of asthma has been associated with CVD and hypertension and high risk of acute myocardial infarction (AMI):

- Carter P, Lagan J, et al. Association of Cardiovascular disease with Respiratory Disease. *J Am Coll Cardiol* 2019; 73:2166-2173 doi.org:10.1016/j.jacc.2018.11.063
- Cepelis A, Brumpton B, et al. Asthma, asthma control and risk of acute myocardial infarction: HUNT study: *Eur J Epidemiol* 2019: 34; 965-977 doi.org:10.1007/s10654-019-00562-x
- Bang DW, Chung-Il W, et al. Asthma status and risk of incident myocardial infarction: a population-based case-control study. *J Allergy Clin Immunol Prac* 2016; 4: 917-923 doi.org:10.1016/j.jaiip.2016.02.018
    - Adjusted odds ratio [OR] 1.68, 95% CI: 1.06-2.66 adjusting for risk factors for MI and comorbid conditions excluding chronic obstructive lung disease
    - While inactive or resolved asthma did not increase the risk of MI, individuals with actively treated asthma had a higher odds of MI, compared to those without asthma – adjusted OR: 3.18; 95% CI: 1.57-6.44 without controlling for COPD

In a study with a mean follow-up of 5.7 years, 3584 admissions for coronary heart disease and 1590 admissions for heart failure were studied for concomitant asthma, COPD, and asthma-COPD overlap (ACO Syndrome). Compared with no respiratory disease:

- the highest risks of *coronary heart disease* were observed in ACO with late-onset asthma and an FEV1 < 50%p, HR = 2.2 (95% CI 1.6-3.0)
- the risk of *CHF* was seen with HR = 2.9 (95% CI 2.0-4.3)
- In COPD with FEV1 > 50%p, the HRs were 1.3 (95% CI 1.2-1.5) for coronary heart disease and 1.9 (95% CI 1.6-2.3) for heart failure.
    - Ingebrigsten T, Marott J, Vestbo J, et al. Coronary heart disease and heart failure in asthma, COPD, and asthma-COPD (ACO) overlap. *BMJ Open Respir Res* 2020; 7 (1) :e000470; doi.org:10.1136/bmjresp-2019-000470

In a 4607 person population-based study of adults with asthma, the risk of acute myocardial infarction and ischemic stroke increased significantly after asthma exacerbation.

- Raita Y, Camargo C, et al. Risk of acute myocardial infarction and ischemic stroke in patients with asthma exacerbation: a population-based, self-controlled case series study. *J Allergy Clin. Immunol. Pract:* 2020; 8: 188-194 doi.org:10.1016/j.jaip.2019.06.043

Therapies in Asthma:

- In patients *with cardiovascular diseases*, use of Beta2-2 agonists may have adverse risk not seen with use of anticholinergic agents.
- Oral or IV corticosteroids may be harmful to the heart, but inhaled corticosteroids are not. Inhaled corticosteroids, however, may be related to osteoporosis, increased fracture risk, and pneumonia.
- Insulin may promote lung tissue remodeling and worsen lung function by stimulating airway small muscle cell proliferation and collagen release.
- Leukotriene modifiers and antibodies against IgE and interleukin-5 for asthma can benefit patients with CV risk factors
- Overuse of albuterol is associated with excess risk for severe asthma exacerbations. Global Initiative for Asthma (GINA) guidelines recommend avoiding albuterol for all patients and using inhaled corticosteroids (ICS)/formoterol as a rescue inhaler. Although the National Asthma Education and Prevention Program (NAEPP) guidelines have not gone that far, they do recommend using as-needed ICS/albuterol for mild asthma (note: such a combined inhaler is not in the U.S. Formulary). In a multinational trial, more than 3100 adolescents and adults with uncontrolled moderate-to-severe asthma were randomized to high-dose albuterol/budesonide (180/160 μg) versus albuterol alone (180 μg) alone as rescue inhaler while continuing their current ICS or ICS/LABA therapy. After 24 weeks, severe exacerbations requiring systemic steroids for rescue were significantly less common in the albuterol/budesonide group than in the albuterol group (annualized rate, 0.45 vs. 0.59).
    - Papi A, Chipps B, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. *N Engl J Med* 2022; 386:2071-2083 doi.org:10.1056/NEJMoz2203163
    - Chipps B, Albers F, Reilly L, et al. Efficacy and safety of as-needed albuterol/budesonide versus albuterol in adults and children aged ≥ years with moderate-to-severe asthma: rationale and design of the randomized, double-blind active-controlled MANDALA study. *BMJ Open Respiratory Research* Dec 2021, 8 (1) e001077 doi.org:10.1136/bmjresp-2021-001077

- A meta-analysis of asthma treatment studies has shown the preponderance of evidence favoring the efficacy of SMART (single maintenance and reliever therapy) – most commonly the combination of budesonide and formoterol – as most effective in reducing asthma exacerbations compared to the prior standard of using inhaled corticosteroid maintenance and short-acting β-1-agonist (SABA) rescue therapy.
    - Imam, SF, Zafar S, and Oppenheimer J. SMART in treatment of asthma exacerbations. *Ann Allergy, Asthma & Immunology* July 29, 2022. doi.org/10.1016/j.anai.2022.07.024

- Persons with biologic treatments did *not* have higher rates of SARS-CoV-2 infection than the general population, and the use of biologics for severe asthma did not seem related to adverse outcomes from severe COVID-19. However, in general, COVID-infected persons with asthma do appear to be at higher risk for hospitalizations.
    - Papaioannov A, Fouka E, Tzanakis N,, et. al. SARS-CoV-2 Infection in Severe Asthma Patients Treated with Biologics. *J Allergy and Clin Immun* June 22, 2022. doi.org/10.1016/j.jaip.2022.05.041

Chronic Obstructive Pulmonary Disease (COPD)

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My summary of COPD begins with what I think most medical directors will be interested in: the morbidity and mortality associated with COPD. ***Bolded statements with ***** *are of particular reference to the case presentations (and I believe are of particular underwriting significance). I have then summarized what most of you already know about COPD (and you can skip over that quickly), but I will ask that you pay particular attention to the part of this document* ***(Pulmonary Function Tests)*** *dealing with* ***spirometry (page 11)****. It is my opinion that all underwriters and medical directors understand the three basic measurements of spirometry (FVC, FEV1, and FEF25-75) as well as the significance of the FEV1/FVC ratio, in establishing an applicant as having an obstructive or restrictive impairment.*

The global prevalence of chronic obstructive pulmonary disease (COPD) has increased markedly in recent decades. It is estimated that between 300 and 400 million people globally live with COPD, with particular concern in low- and middle-income countries due to increasing rates of smoking, household- and ambient air pollution (*see my separate document on air pollution*) and other exposures, coupled with large and ageing populations. Furthermore, the ongoing COVID-19 pandemic highlighted COPD as a condition that predisposes to increased risk of hospitalization and death.

- Adeloye et al. Research priorities to address the global burden of chronic obstructive pulmonary disease (COPD) in the next decade. *J Global Health* Oct 9,2021. https://doi.org: 10.7189/jogh.11.15003
- GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017; 5: 691-706. https://doi.org: 10.1016/S2213-2600(17)30293-X

COPD is the fourth-ranked cause of death in the U.S., killing more than 120,000 individuals each year and 3 million deaths around the world. It affects more than 5% of the U.S. population and may be associated with significant morbidity and mortality. From an underwriting standpoint, it is estimated that there are almost as many persons with *undiagnosed* COPD as those carrying this diagnosis. It has been found that most persons seeing a physician for the first time for symptoms of COPD on spirometry are found to have late-moderate to early-severe disease as measured by GOLD spirometry criteria.

In never-smokers, airway lumen at chest CT images was smaller in women than men. ****In ever-smokers, worsening of lumen size impacted respiratory outcomes more in women than men. With the prevalence of COPD in women fast approaching that in men, women experience greater symptom burden and mortality**.**

- Bhatt SP, Bodduluri S, Nakhmani S, et al. Sex Differences in Airways at Chest CT: Results from the COPDGene Cohort. *Radiology* Aug 2022. doi.org/10.1148/radiol.212985

A key feature of COPD is an accelerated rate of decline in forced expiratory volume in the 1st second (FEV1 – best expressed clinically as FEV1 % predicted). Changes in FEV1 after administration of a bronchodilator over a 3-year period were studied in 2163 persons. The mean (±SE) rate of change in FEV1 was a decline of 33±2 ml per year, but with significant variation among persons studied. Thirty-eight percent of persons had an estimated decline in FEV1 of more than 40 ml per year. ****The rate of decline was greater in current smokers, persons with emphysema compared to those without emphysema, and persons with some bronchodilator reversibility (Asthma-COPD overlap, or ACO) compared to those without reversibility**.**

- Vestbo et al. Changes in Forced Expiratory Volume in 1 second over time in COPD. *N Engl J Med* 2011; 365: 1184-1192. doi.org/10.1056/NEJMoa1105482

Although FEV1 is often used to grade the severity of COPD, persons with COPD have systemic manifestations that are not reflected by the FEV1. In an evaluation of 207 persons with COPD, four factors predicted the risk of death in this cohort: the body-mass index (**B**), the degree of airflow obstruction (**O**) and dyspnea (**D**), and exercise capacity (**E**) measured by the six-minute-walk test. These variables were used to construct the **BODE Index**, a multidimensional 10-point scale in which higher scores indicate a higher risk of death. This index was prospectively validated in a cohort of 625 persons, with death from any cause and from respiratory causes as the outcome variables. Persons with higher BODE scores were at higher risk for death; the hazard ratio for death from any cause per one-point increase in the BODE score was 1.32 (95% CI, 1.26-1.42; P<0.001), and the hazard ratio for death from respiratory causes was 1.62 (95% CI, 1.48-1.77; P<0.001). The C statistic for the ability of the BODE Index to predict the risk of death was larger than that for the FEV1 (0.74 vs. 0.65).

COMPUTATION OF THE BODE INDEX

Variable	1	2	3	4
B-BMI	>21	<21		
O-FEV1%p	≥65	64-50	49-34	<34
D-Distance walked in 6 min (m)	≥350	349-250	249-150	<150
E-MMBC Dyspnea Scale	0-1	2	3	4

- Bartolome et al. The Body-Mass Index, Airflow Obstruction Dyspnea, and Exercise capacity Index in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2004; 350(10): 1005-1012. doi.org/10.1056/NEJMoa02132
- Quartararo, Paul. *J Insur Med* 2008; 40: 20-25
    - "We do not need to add up the 'BODE points' as if we are doing clinical research, but we do need to search the attending physician's statement for each of these characteristics, and then piece them together into a global view of the applicant. If the proposed insured is losing weight, has a reduced FEV1%p, is dyspneic, and is unable to exert himself, then our job is easy." – Paul Quartararo MD – Medical Director New York Life, Co-Presenter 2022 Pulmonary Workshop

As noted above, decreasing body mass is associated with increasing mortality. The fat-free mass index (FFMI) can identify a subgroup of persons with an increased mortality despite a normal BMI, and the FFMI is a better predictor of disease severity than is BMI alone. Persons with COPD who are obese have more of the phenotype of chronic bronchitis – "blue bloaters", while emphysema patients are typically more underweight – "pink puffers". Potentially related to these observations is the observation that obese persons with emphysema often have low muscle mass contributing to worse lung function, exercise tolerance, and muscle strength compared to emphysema persons with comparable BMI and normal muscle mass.

- Machado, F, Spruit M, et al. Frequency and functional translation of low muscle mass in overweight and obese patients with COPD. *Respir Res* 2021;22: 93 **doi.org/10.1186/s129310-21-01689-w**

Structural, mechanical effects of obesity on lung function are known. Accumulation of fat in the mediastinum and abdominal and thoracic cavities causes reduction in lung volume, in functional residual capacity (see" lung volumes" at end of this document), and in the compliance of the lungs and chest wall.

Yet obesity is more than a state of increased BMI. What we've begun to understand is that its impact on the lungs and respiratory health is much more complicated than just a mechanical problem. With obesity, adipose tissue changes not only in quantity but in function, producing proinflammatory cytokines and hormones – such as tumor necrosis factor-alpha (TNF-alpha), leptin, and interleukin-6 –

that can have direct deleterious effects on the lung. Associations between lung disease and the metabolic and other disturbances of obesity are most established in asthma research and have taken hold in the realm of sleep-disordered breathing. But as the prevalence of obesity continues to grow, its role in other lung diseases such as chronic obstructive pulmonary disease and, most recently, pulmonary arterial hypertension (PAH), is gaining more attention in academia.

- Peters, et al. Beyond BMI: Obesity and Lung Disease. *CHEST* 2017; 153: 702-709. doi.org/10.1016/j.chest.2017.07.010
- Dixon A, Peters U. The effect of obesity on lung function. *Exper Rev Respir Med* 2018; 12: 755-67 doi.org/10.1080/1746348.2018.1506331

A major red flag for mortality in COPD is **hypercapnic respiratory failure**, signaled by the progressive rise in an individual's *arterial* carbon dioxide levels and decrease in arterial pH. This condition is commonly referred to as "chronic hypercapnic respiratory failure" and is usually seen with very low FEV1 levels and carries a significant risk for death within 5 years. If bloodwork is available, the serum bicarbonate will be elevated (to try an compensate for the [respiratory] acidosis) and on arterial blood gases (ABGs) the pCO2 will be elevated and the pH decreased. **Pulmonary arterial hypertension (PAH)** is often co-existing in this population and compounds the morbidity and mortality of this population.

COPD itself is an independent risk factor for lung cancer and increases the risk of lung cancer by 6 to 13-fold relative to individuals without COPD. The association of emphysema with lung cancer is stronger than the association of chronic bronchitis with airflow limitation and lung cancer.

****Airway hyperresponsiveness** (defined as a post-bronchodilator improvement of FEV1 by ≥ 12% but not improving back to normal as might be seen in asthmatics) **affects approximately 25% of persons with COPD** (Asthma-COPD overlap, now known as **ACO Syndrome**) and **is associated with more rapid decline in lung function and mortality**.** Combined data from two large studies (5938 total participants) found that airway hyperresponsiveness was associated with greater respiratory mortality (HR 2.38, 95% CI, 1.38-4.11).

- Tkacova et al. Airway hyperresponsiveness in chronic obstructive pulmonary disease: A marker of asthma-chronic obstructive pulmonary disease overlap (ACO) syndrome? *J Allergy Clin Immunol*. 2016; 138:1571-1579. doi.org/10.1016/jaci.2016.04.022

In a meta-analysis of 18 studies (418,251 patients) looking for significant predictors of mortality in COPD within a 3-24 month span, previous hospitalization for acute exacerbation (HR 1.97; 95% CI 1.32-2.95), hospital readmission within 30 days (HR 5.01; 95% CI 2.16-11063), cardiovascular comorbidity (HR 1.89; 95% CI 1.2501.59), age (HR 1.74; 95% CI 1.3801.59), male sex (HR 1.68, 95% CI 1.38-1.59), and long-term oxygen therapy (HR 1.74; 95% CI 1.10-2.73) were reported.

- Owusuaa C, Dikland S, et al. *BMC Pulmonary Medicine* 2022; 22:125. doi.org/10.1186/s12890-022-01911-5

Relationship between COPD and CVD

Cardiovascular diseases (CVDs) are arguably the most important comorbidities in COPD, and their presence is associated with increased all-cause and CVD-related mortality. ****Indeed, the typical COPD patient is just as likely to die from a cardiovascular disease as they are from a respiratory one***.** While smoking remains an important shared risk factor for both diseases, it is becoming more widely accepted that responses to smoking are not the sole reason for the observed association between COPD and CVD. Our perceptions of COPD as a disease have changed. No longer 'just a disease of the lungs', COPD is now described as the pulmonary component of systematic endothelial disease whereby a range of 'inflammageing' processes simultaneously affect multiple organs giving rise to a state multimorbidity, without any clear indication as to which disease came first.

- Morgan AD, Zakeri R, Quint, JK. Defining the relationship between COPD and CVD *Ther Adv Respir Dis* Jan 22, 2018; 12: 1-16 doi.org/10.1177/1753465817750524

A meta-analysis of observational studies supports more than a two-fold increase in the odds of having any CVD in persons with COPD relative to COPD-free patients [odds ratio (OR) = 2.46; 96% CI; 2.02-3.00; p<0.0001], and the ORs in the range 2-5 for ischemic heart disease, arrhythmias, heart failure, and diseases of the arterial circulation. Additionally, patients with COPD reported hypertension more often (OR 1.33, 95% CI 1.13-1.56; p-0.0007), diabetes (OR 1.36, 95% CI 1.21-1.53; p<0.0001) and ever smoking (OR 4.25, 95% CI 3.23-5.60; p<0.0001).

- Chen w, Thomas, J et al. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2015; 3: 631-639. doi.org/10.1016/S2213-2600(15)00241-6

A more recent meta-analysis reveals accumulating evidence suggesting a temporal association between COPD exacerbations and acute CV events, likely due to lung hyperinflation, increased hypoxemia and systemic inflammation. In a review of seven studies examining the risk of CV events 1-3 months after an exacerbation compared for no exacerbations, RR was 1.68 (95% CI, 1.19-2.38) for stroke, RR 2.43 (95% CI, 1.40-4.20) for acute myocardial infarction.

- Mullerova H, Marshall J, et. al. Association of COPD exacerbations and acute cardiovascular events: a systematic review and meta-analysis. *Ther Adv in Resp Dis* 2022;16L1-11. doi.org/10.1177/1753466622113647

Cardiovascular Disease (CVD), heart failure and cardiac arrhythmias are among the most commonly observed CVDs seen in persons with COPD. Estimates of the prevalence of ischemic heart disease in people with COPD vary from less than 28% to over 70%, depending on the characteristics of the study population. Heart failure prevalence estimates lie in the range 10-30%. Prevalence estimates for arrhythmias also exhibit a degree of variability depending on the clinical setting but are typically between 10-15%. Unadjusted rate ratio (RR) estimates of unspecified CVD among patients with COP compared with patients without COPD ranged from 2.1 to 5.0, with this association persisting after adjustment for shared risk factors in the majority of studies.

- Mullerva H, Agusti A, Erqou S, and Mapel D. Cardiovascular comorbidity in COPD: systematic literature review. *Chest* 2013; 144: 1163-1178. doi.org/10.1378/chest.12-2847

Stroke prevalence in community or primary care COPD populations is generally less than 10% but can be as high as 20% in hospital-based cohorts.

- Lahousse L, Tiemeier H, et al. Chronic obstructive pulmonary disease and cerebrovascular disease: a comprehensive review. *Respir Med* 2015; 109: 1371-1380 doi.org/10.1016/j.med.2015.07.014

Peripheral arterial disease (PAD) was found in 8.6% of COSYCONET study participants who had a diagnosis of COPD. PAD was associated with a clinically relevant reduction in functional capacity and health status.

- Houben-Wilke S, Jorres R, et al. Peripheral artery disease and its clinical relevance in patients with chronic obstructive pulmonary disease in the COPD and Systemic Consequences-Comorbidities Network Study. *Am J Respir Crit Care Med* 2017; 195: 189-197. doi.org/10.1164/rccm.201602-0354OC

Several studies have investigated whether CVDs are more prevalent in certain subtypes of COPD (i.e., emphysema, chronic bronchitis, asthma-COPD overlap (ACO Syndrome). What has emerged is that ****CVD comorbidity is not confined to those with more advanced airflow obstruction but occurs across the entire spectrum of COPD disease severity.**** There is some suggestion that the prevalence of CVDs (in particular IHD and PAD) may be higher in those with higher body mass index (BMI) and chronic bronchitis.

- Camiciottoli G, Bigazzi F, et al. Prevalence of comorbities according to predominant phenotype and severity of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2229-2236. doi.org/10.2147/COPD.S111724

Observational studies have also established the reverse association, namely that COPD is common in people presenting with various forms of CVD. In CHF, for example, the prevalence of COPD varies between 13% and 39%; in cases of atrial fibrillation, most estimates lie in the range of 10-15% with some studies reporting prevalence rates in excess of 20%.

- Bhatt SP and Dransfield MT. Chronic Obstructive pulmonary disease and cardiovascular disease. *Transl Res* 2013; 162: 237-251. doi.org/10/1016/j.trsl.2013.05.001

A study conducted by Franssen et al. found airflow limitation in 30.5% of patients attending 15 cardiovascular outpatient clinics in nine European countries (3,103 patients). Of these, 11.3% had mild, 15.8% had moderate and 3.4% had severe or very severe airflow obstruction. Significantly, more than 70% of those with airflow limitation had not previously had spirometry or been diagnosed with pulmonary disease.

- Franssen et al. Lung function abnormalities in smokers with ischemic heart disease. *Am J Respir Crit Care Med* 2016; 194: 568-576. doi.org/10.1164/rccm.201512-24800C

Attention has focused on acute events, namely myocardial infarction and stroke, for which an increased risk in COPD is now well established. It is generally accepted that **having a diagnosis of COPD approximately doubles the mortality risk of an MI** (clearly with smoking or history of smoking contributing to this association).

- Yin Li, Lensmar C, Ingelsson E, and Back, Magnus. Differential association of chronic obstructive disease with myocardial infarction and ischemic stroke in a nation-wide cohort. *Int J Cardiology* 2014: 140: 601-603 doi.org/10.1016/j.ijcard.2014.03.140
- Pujades-Rodriguez M, George J, Shah A, et al. Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1,937,360 people in England: lifetime risks and implications for risk prediction. *Int J Epidemiol* 2015; 44: 129-141 doi.org/10.1093/ije/dyu218

Evidence is accumulating that COPD is linked to increased risks for CVD outcomes other than MI and stroke. The indications are that the magnitude of the increased risk associated with COPD for outcomes such as heart failure, angina and cardiac arrhythmias, as well as diseases of the arterial circulation, is even greater than that for MI and stroke. Curkendall et al estimated an age-adjusted risk ratio for heart failure of 4.5 (95% CI:2.8-6.2) in a Canadian cohort, while Agarwal et al. in their longitudinal study of a United States cohort of patients aged 45-64 years found that the incidence of heart failure increased with decreasing FEV1, even after adjustment for age, smoking, and other cardiovascular risk factors.

- Curkendall S, DeLuise C, Jones J, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease: Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006; 16:63-70 doi.org/10.1016/j.annepidem.2005.04.008
- Agarwal S, Heiss G, Barr G et al. Airflow obstruction, lung function, and risk of incident heart failure: The Atherosclerosis Risk in Communities (ARIC) study. *Eur J Heart Fail* 2012; 14:414-422 doi.org/10.1093/eurjhf/hfs016

Although studies have on the whole failed to find convincing evidence that frequent exacerbators (defined as two or more exacerbations in one calendar year) are at greater risk for acute CVD outcomes (MI and Stroke) than people who rarely experience an exacerbation of their symptoms, the period immediately after an acute exacerbation of COPD (AECOPD) has been shown to be a period of high risk for such events.

- Portegies M, Lahousse L, Joos G, et al. Chronic obstructive pulmonary disease and the risk of stroke. The Rotterdam Study. *Am J Respir Crit Care Med* 2015; 193:251-258. doi.org/10.1164/rccm.201505-0962OC

A more rapid rate of decline in lung function (FEV1%p) has also been associated with an increased cardiovascular risk.

- Engstrom G, Hedblad B, Janzon L, et al. Respiratory decline in smokers and ex-smokers – an independent risk factor for cardiovascular disease and death. *J Cardiovasc Risk* 2000; 7:267-272 doi.org/10.1177/204748730000700404
- Tockman M, Pearson J, et al. Rapid decline in FEV1p. A new risk factor for coronary heart disease mortality. *Am J Respir Crit Care Med* 1995; 151:390-398. doi.org/10.1164/ajrccm.151.2.7842197

There are a number of mechanisms that provide a putative link between COPD and CVD and which may be driving CVD risks in COPD. The observation that arterial stiffness is more pronounced in patients with COPD compared in controls matched for age and smoking status has led to the hypothesis that COPD is associated with elastin degradation both in the lung (where it results in emphysema) and in the vasculature – systemic elastin degradation – where it results in increased arterial stiffness. Arterial stiffness is considered a surrogate indicator of coronary, cerebrovascular and PAD and is assessed by measuring aortic pulse wave velocity. This measure is strongly associated with cardiovascular mortality in the general population and is of potential interest as a predictive marker of CVD risk in COPD.

- Vivodtzev I, Tamisier R, et al. Arterial stiffness in COPD. *Chest* 2014; 145: 861-875 doi.org/10.1378/chest.13-1809

Patients with COPD are subject to sustained or intermittent hypoxia. Hypoxia is known to induce increased systemic inflammation, oxidative stress, foam cell production and up-regulation of cellular adhesion molecules in endothelial cells, which may contribute to progression of atherosclerosis. Chronic hypoxia also induces pulmonary vascular remodeling (intimal and medial thickening) and pulmonary artery endothelial dysfunction.

Therapies in COPD:

Evidence from many clinical trials suggests that inhaled COPD therapies do not pose a significant CVD risk, at least in persons free from cardiovascular comorbidities.

- Lahousse L, Verhamme K, et al. Cardiac effects of current treatments of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016; 4:149-164 doi.org/10.1016/S2213-2600(15)00518-4.

However, an impressive study from Canada (using UK Clinical Practice Research Datalink) of 180,567 ***new* asthmatic users** of β_2-agonists (SABA), inhaled corticosteroid (ICS), short-acting muscarinic agonists (SAMA) or long-acting muscarinic agonists (LAMA) were not associated with the risk of MACE (major adverse cardiovascular events) -- (SABA vs ICS: HR 1.29 [95% CI 0.96-1.73]; ICS/LABA vs ICS, HR 0.75 [95% CI 0.33-1.73]. In contrast, **among COPD patients**, new-use of long-acting beta-agonists (LABA) (HR, 2.38 [95% CI 1.04-5.47] and ICS/LABA (HR, 2.08 [95% CI 1.04-4.16] had an increased risk of MACE compared with SAMA users. Among patients with asthma-COPD overlap (ACO syndrome), new prescriptions for SABAs were associated with an increased risk of MACE compared with ICS (HR, 2.57 [95% CI 1.26-5.24]. The authors concluded that initiation of LABA, SABA, or ICS/LABA in COPD or SABA in asthma-COPD overlap was associated with increased risk of MACE, compared with ICS alone.

- Amegadzie, JE, Gamble, J-M et al. Association between inhaled β_2-agonists Initiation and Risk of Major Adverse Cardiovascular Events: A Population-based Nested Case-Control Study. *International J COPD* Dec 2022; 17:1205-1217 doi.org/10.2147;COPD.S358927

A concurring study found that cardiovascular risk (as measured by hospital admission or emergency room attendance for CVD) was increased in ***new*** long-acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA) users OR = 1.31 (CI 95% 1.12-1.52) and OR = 1.14 (CI 95% 1.01-1.28) respectively.

- Gershon A, Croxford R, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. *JAMA Intern Med* 2013; 173: 1175-1185 doi.org/10.100/jamainternmed.2013.1016

The SUMMIT trial, which included 16,000 people with moderate COPD at increased risk for or with a history of CVD, was designed to allow stratification to assess cardiac effects of LABA treatment in these groups. Interim results suggest that while use of a LABA either alone or in combination with inhaled corticosteroid may reduce the rate of FEV1p decline, the benefits of therapy appear to be confined to the respiratory system – **LABA therapy appears to have no beneficial effect on mortality or a composite CVD outcome.**

- Vestbo J, Anderson J, Brook R, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomized controlled trial. *Lancet* 2016; 387: 1817-1826

doi.org: 10.1016/S0140-6736(16)30069-1

- Calverley P, Anderson J, Brook R, et al. Fluticasone furoate, vilanterol and lung function decline in patients with moderate COPD and heightened cardiovascular risk. *Am J Respir Crit Care Med.* 2017. doi.org: 10.1164/rccm.201610-2086OC
- Brook R, Anderson J, Calverley P, et al. Cardiovascular outcomes with an inhaled beta2-agonist/corticosteroid in patients with COPD at high cardiovascular risk. *Heart* 2017; 103: 1536-1542 doi.org: 10.1136/heartjnl-2016-310897

Beta-blockers have long been avoided in persons with COPD for fear of worsening bronchospasm. However, in a meta-analysis of 15 retrospective studies involving patients with COPD, those who received beta-blockers had a 28% lower frequency of death and a 38% lower frequency of exacerbation than those who did not receive a beta-blocker.

- Du Q, Sun Y, Ding N, et al. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. PLoS One 2014;9(11):e113048-e113048 doi.org/10.1371/journal.pone.0113048

These results were questioned in the BLOCK COPD (Beta-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) trial, where patients with COPD without overt cardiovascular disease were given long-acting metoprolol vs. placebo. This study was stopped early because of the futility of achieving a salutary outcome for the primary end point. There was no between-group difference in the time until the first exacerbation or in the overall rate of exacerbation. However, among patients who received metoprolol, there was a greater risk of severe exacerbation (leading to hospitalization) and very severe exacerbation (leading to intubation and mechanical ventilation) in patients with more severe COPD. Although the FEV1 was similar in the two groups, there was a greater increase in a score for breathlessness in the metoprolol group, which suggests an adverse effect of the drug on COPD symptoms. This population contrasts with the patients in most observational studies that have shown positive effects of beta-blockers in patients with COPD who had an indication for treatment with a beta-blocker. The patients in the BLOCK COPD trial were also at higher risk for exacerbation and had at least one exacerbation during the preceding year severe enough to require ER visit or hospitalization. 40% of this population were also requiring long-term oxygen therapy. The results of this trial should not deter the use of beta-blockers in patients with COPD who have cardiovascular indications, with the caveat that the risk-benefit ratio should be considered in patients with very severe COPD at high risk for severe exacerbation.

- Dransfield M, Voelker H, et al. Metoprolol for the prevention of acute exacerbations of COPD. *N Engl J Medl* 2019; 381:2304-2314
doi.org: 10.1056/NEJMoa1908142
- MacNee W. Beta-Blockers in COPD – A Controversy Resolved? (Editorial) *N Engl J Med* 2019; 381: 2367-2368
doi.org: 10.1056/NEJMe1912664

BASICS OF COPD AND SPIROMETRY

(information mostly sourced from UpToDate – COPD)

The Global Initiative for Chronic Obstructive Lung disease (GOLD) defines COPD as follows: "COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality."

COPD has three major subtypes:

- **Chronic bronchitis** — a *clinical* diagnosis defined as a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough (eg, bronchiectasis) have been excluded. It may precede or follow development of airflow limitation. Current and former smokers have increased airway mucin concentration compared with never smokers.
- **Emphysema** — a *pathological* term that describes some of the structural changes sometimes associated with COPD. These changes include abnormal and permanent enlargement of the airspace's distal to the terminal bronchioles that is accompanied by destruction of the airspace walls, without fibrosis visible to the naked eye. Exclusion of obvious fibrosis is intended to distinguish the alveolar destruction due to emphysema from that due to the interstitial pneumonias. Subtypes of emphysema include:
    - **Proximal acinar** (also known as **centrilobular**) emphysema that refers to abnormal dilation or destruction of the respiratory bronchiole, the central portion of the acinus. This is seen in the lung apices associated with cigarette smoking (due to preferential distribution of initially inhaled air to the apices) and more diffusely in coal workers' pneumoconiosis.
    - **Panacinar** emphysema refers to enlargement or destruction of all parts of the acinus. Diffuse panacinar emphysema is most commonly associated with alpha-1-antitrypsin deficiency and is primarily seen in the lung bases corresponding to predominant blood flow to the lung bases (when patients are standing).
    - **Distal acinar** (also known as parastatal) emphysema is where the alveolar ducts are predominantly affected. Distal acinar emphysema may occur alone or in combination with proximal acinar and panacinar emphysema. When it occurs alone, the usual association is spontaneous pneumothorax in a young thin and usually tall adult.
- **Asthma** — "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment" (Global Initiative for Asthma — GINA).
    - ****Patients with asthma whose airflow obstruction is completely reversible are *not* considered to have COPD****.
    - ****Patients with asthma whose airflow obstruction does not remit completely with bronchodilators are considered to have Asthma with COPD, or ACO Syndrome****. The etiology and pathogenesis of the COPD in such patients may be different from that of patients with chronic bronchitis or emphysema.
    - The transition from asthma with complete reversibility either spontaneously or with inhalation of bronchodilators to asthma that fails to show reversibility back to normal is thought to reflect "remodeling", with a gradual change from an eosinophilic inflammatory cascade to a neutrophilic inflammatory cascade.
    - Chronic bronchitis and emphysema with airflow obstruction commonly occur together. Some of these patients may also an asthmatic component.
    - Individuals with asthma may develop a chronic productive cough and this is unofficially referred to as having "asthmatic bronchitis".

Smoking and inhalational exposure history:

- **Smoking history** — the amount and duration of smoking contribute to disease severity ***although it must be recognized that up to 20 percent of adults with COPD have no smoking history at all***. Smoking history is usually reflected as the number of packs of cigarettes per day multiplied by the number of years smoking — "pack-years". With enough smoking, almost all smokers will develop some measurably reduced lung function.
    - In one study, the single best variable for predicting which adults will have airflow obstruction on spirometry is a history of more than 40 pack-years of smoking (positive likelihood ratio (LR), 12 [95% CI, 2.7-50]).
    - However, other data suggest *smoking duration* may provide stronger risk estimates of COPD than the composite index of pack-years.
    - ****For the same amount of cigarette smoking, women have a higher risk of COPD than men**.**
    - Other types of tobacco smoke, such as from cigar, pipe, water-pipe, and hookah use also confer a risk. Water-pipe or hookah smoke appears to be as harmful or ever more harmful as smoking cigarettes.
- **Just a word about cigarette smoking and cancer**: In 2019, nearly 123,000 U.S. cancer deaths were from **cigarette smoking – 30% of all U.S. cancer deaths**. Cancers associated with smoking include cancers of the lung and bronchus, oral cavity, pharynx, esophagus, stomach, colon, liver and liver bile duct, pancreas, larynx, cervix, kidney, pelvis, bladder and acute myeloid leukemia.
- **History of fume and dust exposure** — the chronologically taken environmental/occupational history may disclose other important risk factors for COPD, such as exposure to fumes or organic or inorganic dusts. These exposures help to explain the 20 percent of individuals who die from COPD who never smoked.
    - Poorly ventilated fires used for cooking and heating, often fueled by coal or biomass such as wood and dry dung, may be one of the more common causes of COPD in women in developing countries; these fuels are used as the main source of energy in 80% of homes in India and sub-Saharan Africa.
    - People who live in large cities have a higher rate of COPD compared to people who live in rural areas.
    - *See additional document on WHO and EPIC studies of world pollution studies*
- **Genetic predisposition to COPD --** While studies have shown an overall "dose-response curve" for smoking and lung function, there appears to be a genetic predisposition to development of COPD in some individuals as some develop severe disease with fewer pack-years while others have minimal to no symptoms despite many pack-years of smoking. Alpha-1-antitrypsin deficiency is the most widely known genetic genotype causing Panacinar (panlobular) emphysema and, significantly, there is IV replacement therapy for this disease. Other genetic markers for development of COPD are evolving.

Symptoms and pattern of onset — the three cardinal symptoms of COPD are dyspnea, chronic cough, and sputum production. The most common early symptom is exertional dyspnea. Less common symptoms include wheezing and chest tightness.

- Approximately 62 percent of persons with moderate to severe COPD report variability in these symptoms over the course of the day or week-to-week. Mornings are typically the worse time of day.
- The majority of persons with COPD are overweight or obese. Weight loss, usually in emphysema, generally reflects more advanced disease and is associated with a worse prognosis.

- Comorbid diseases that may accompany COPD include lung cancer, bronchiectasis, cardiovascular disease, osteoporosis, metabolic syndrome, skeletal muscle weakness, anxiety, depression, and cognitive dysfunction.
- Finally, it is important to note that current and former smokers without spirometry evidence of airflow obstruction can have a substantial respiratory symptom and radiographic burden of disease. While such individuals are being actively investigated, the natural history of such individuals has not been fully studied and there is currently no evidence base to guide treatment and prognosis in such individuals.
- There are early reports of distal bronchial wall thickness in some users of **vaping** who report worsening shortness-of-breath (SOB)

Evaluation of COPD

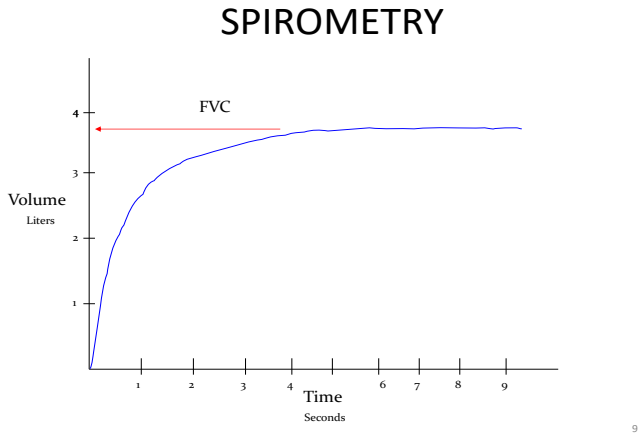
- There is no evidence to support the benefit of population-based screening of asymptomatic adults for COPD
    - US Preventive Services Task Force (USPSTF) reaffirms its recommendation against screening for chronic obstructive pulmonary disease 2022
        - Mangione et al. Screening for chronic obstructive pulmonary disease: US Preventive Services Task Force reaffirmation recommendation statement. *JAMA* 2022; 327:1806
        - Webber et al. Screening for chronic obstructive pulmonary disease: Updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2022; 327: 1812

but the Global Initiative for Chronic Obstructive Lung Disease (GOLD) does advocate active case finding among at risk individuals.

- No laboratory test is diagnostic for COPD, but certain tests are sometimes obtained to exclude other causes of dyspnea and comorbid diseases.
    - Assessment for anemia is an important step in the evaluation of dyspnea
    - Among stable COPD individuals with normal kidney function, an elevated serum bicarbonate may indirectly identify chronic hypercapnia. In the presence of chronic hypercapnia, the serum bicarbonate is typically increased due to a compensatory metabolic alkalosis. Abnormal results should be confirmed with arterial blood gas measurement.
    - Testing for alpha-2-antitrypsin (ATT) deficiency should be obtained in all symptomatic adults with persistent airflow obstruction on spirometry. Features that are particularly suggestive of ATT deficiency include emphysema in a young individual (eg, age < 45 years), emphysema in a nonsmoker or minimal smoker, emphysema characterized by predominantly basilar changes on chest radiograph or chest CT, a family history of emphysema, or a history of childhood liver disease.

Pulmonary Function Tests – PFTs, particularly spirometry, are the cornerstone of the diagnostic evaluation of patients with suspected COPD (and Asthma)

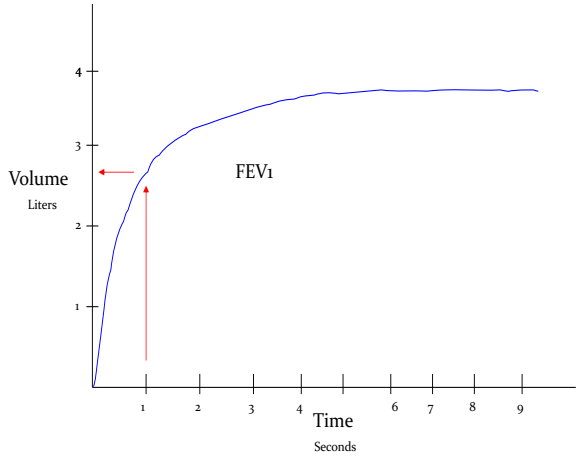
- **Spirometry** – when evaluating a patient for possible COPD, spirometry is performed with pre- and post-bronchodilator administration (e.g., inhalation of albuterol 400 mcg) to determine whether airflow limitation is present and whether it is partially or fully reversible.
    - American Thoracic Society (ATS) recommended **criteria for significant reversibility**:
        - An increase of 12% or greater in the FEV1 or FVC and at least by 200 ml following administration of inhaled beta2-agonist medication.
    - ****Airflow limitation that is irreversible or only partially reversible with bronchodilator is the characteristic physiologic feature of COPD. Complete reversibility signifies asthma. ****
    - The most important values measured during spirometry are:
        - the forced expiratory volume in one second (**FEV1**)
        - the forced vital capacity (**FVC**)
        - and the forced expiratory flow 25%-75% (**FEF_{25-75}**).
        - The ratio of **FEV1/FVC** is also reported.
    - There are percentages of normal for the FEV1, FVC, and FEF_{25-75} that are based on age, gender, height, and race. Note that weight is not included.
    - **Spirometric function is reported as % of predicted.**
    - **There is no percentage of normal for FEV1/FVC -> FEV1/FVC < 70% defines COPD, and FEV1/FVC > 80% is considered normal.**



The classic volume measurement of the “vital capacity” of the lungs by John Hutchinson in 1842 was marketed to London life insurance companies as a “predictor” of mortality.

Tiffeneau and Pinelli in 1947 added “time” using a water spirometer (best device at the time to minimize friction to airflow), allowing for the measurement of airflow as well as volumes.

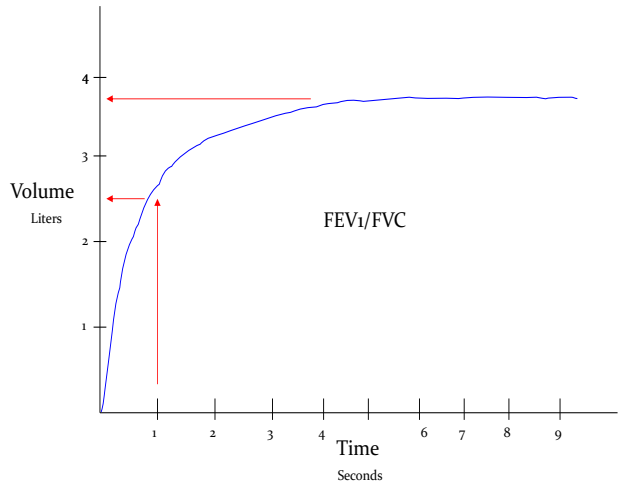
SPIROMETRY



8

Normally, 80% of the FVC comes out in the first second

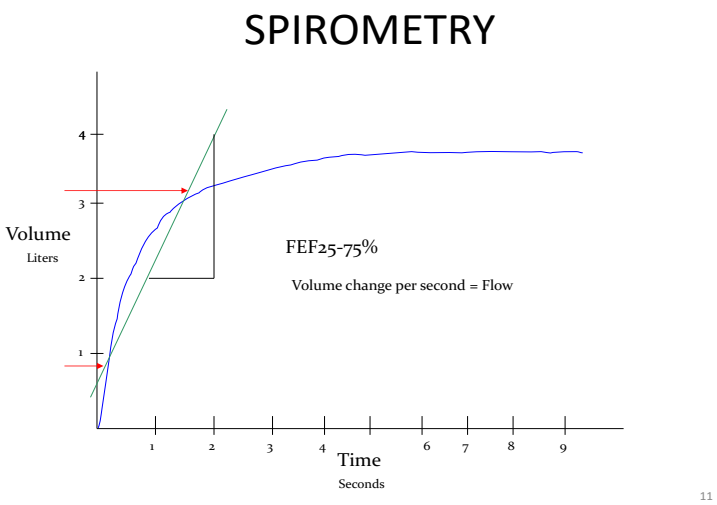
SPIROMETRY



10

An FEV1/FVC ratio less than 70% defines a person as having COPD, and FEV1/FVC ratio >80 is considered normal. ***Note that there is no "% of normal" for FEV1/FVC ratio – it is a simple ratio of FEV1 and FVC.***

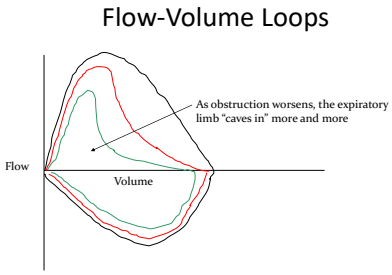
Based on this measurement, however, spirometry would lead to over-diagnosis of COPD in the elderly, and the National Institute for Health and Care Excellence criteria *additionally* requires an FEV1 less than 80% of predicted.



The **FEF_{25-75}%**, also called in some spirometry reports as the **MMEF** (maximal mid-expiratory flow), is useful for two reasons:

- The greatest weakness of spirometry as a diagnostic test is that it is effort-dependent (on the part of the person being tested *and* the person doing the test). Effort is most pronounced at the initiation of spirometry (the initial 25% -- "blow, blow, blow") and the final continuation of spirometry (the final 25% -- "keeping pushing, keep pushing"). The FEF_{25-75}% removes these two most-effort-portions of the study.
- Second, this measurement is the very first measurement to become abnormal in spirometry, giving a "hint of things to come" in smokers undergoing pre-symptomatic spirometry.
- Underwriters evaluating possible lung disease by spirometry should be aware of the difficulty in correctly performing spirometry. Spirometry done in hospital laboratories, pulmonary physician offices, and sometimes allergy offices are usually reliable. Any spirometry with normal results can always be accepted as valid, but abnormal results should be judged by the source of the study.

Flow-Volume Loops



Although the VT (Volume-Time) curves continue to be required for disability determination by many states, for practical purposes the FV (Flow-Volume) curves are the visual representation of spirometry in clinical medicine. The reasons for this are two-fold. First, sub-optimal or frankly poor effort are much more easily seen on FV, rather then VT, curves. Secondly, the degree of "cave-in" of the exahational curve is an easy visualization ofthe degree of spirometric abnormality, as seen in the figure above.

It should be noted that I have left out "maximal ventilation" measurements. In my experience, they are rarely "normal" and add little value to interpretation of a spirometry report.

SPIROMETRY

OBSTRUCTION	RESTRICTION
FEV1 is reduced	FEV1 is reduced
FVC is also reduced, but reduced to a lesser degree than FEV1	FVC is also reduced, but reduced in proportion to reduction in FEV1
FEV1/FVC therefore is reduced	***FEV1/FVC therefore is normal (or increased)***
Diagnosis is valid, but addition of lung volume measurements and lung diffusion may help define emphysema or other concomitant interstitial lung diseases	Diagnosis of restriction cannot be made by spirometry alone because poor effort may be the cause. Further testing with measurements of lung volume and lung diffusion is needed

GOLD Criteria for COPD

- FEV1/FVC ratio < 70%
    - *Defines person as having COPD*
- FEV1 % of predicted (FEV1%p)
    - *Defines severity of COPD*
        - Mild Stage I FEV1%p ≥ 80%
        - Moderate Stage II FEV1%p 50% – 79%
        - Severe Stage III Fev1%p 30% - 49%
        - Very Severe Stage IV FEV1% < 30%

It is important to remember that there are only three diagnoses in spirometry:

- Normal
- Obstruction
- Restriction

When "Restriction" is the spirometric diagnosis, then suboptimal or poor effort may be the cause and further testing is *always* indicated. Normally, measurements of **lung volume** and **lung diffusion** is recommended as follow-up measurements to a spirometry read as "restriction".

Lung volume measurement is most commonly done via body plethysmography, done in a large plexiglass booth, with measurement of the **FRC (Functional Reserve Capacity** – **see lung volumes below**) **and then addition of the IC (Inspiratory Capacity) to arrive at the TLC (Total Lung Capacity).** When reading lung volume studies, keep in mind that FRC%p is measured; TLC%p depends on adding the maximal inspiratory capacity (IC%p) to the FRC%p, which may introduce suboptimal effort on the maximal inspiration phase.

Lung diffusion (**DLCO**) is done by the inhalation of a tiny amount of carbon monoxide with a 10-second breath-hold, and then measuring exhalation of the carbon monoxide over the subsequent several minutes. Decreased DLCO correlates with decreases in alveolar-capillary volume, such as emphysema or interstitial lung disease. Falsely low DLCO may be seen in anemic persons, or if the person has recently smoked -- the carboxyhemoglobin (COHb) level of 1% results in a proportionate 1% decrease in the measured DLCO.

PFT reports commonly include the term DLCO/VA. This has been misinterpreted as a correction factor for low lung volume, which leads to a misinterpretation of DLCO results. DLCO/VA (also known as KCO) reflects alveolar CO uptake efficiency at a given lung volume. I have recommended to medical directors and underwriters to ignore this measurement, as it generally reflects certain clinical situations (incomplete lung expansion, pneumonectomy) that can be readily detected in the medical record, and can otherwise lead to erroneous assessment.

The combination of these findings may lead to the following diagnoses:

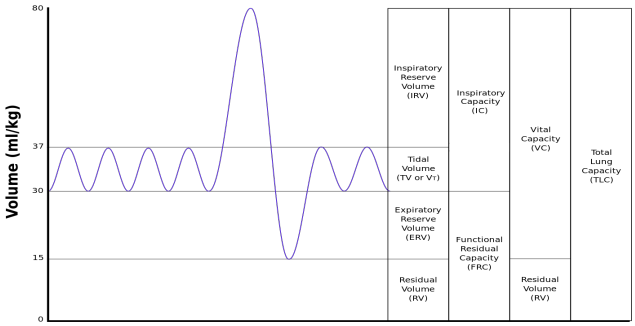
- Decreased TLC but normal DLCO → extra-thoracic (obesity, pleural effusion or thickening, or kyphoscoliosis) or neuromuscular diseases
- Decreased TLC with decreased DLCO → Interstitial Lung Disease or Fibrosis
- Normal TLC with decreased DLCO → Pulmonary Vascular Disease (Pulmonary Hypertension or pulmonary embolism)

Definitions

- **PFTs = Pulmonary Function Tests**
- **FVC = Forced Vital Capacity** (total volume of air exhaled in a forced exhalation from total inspiration to total exhalation -- ideally with the best of three efforts recorded)
- **FEV1 = Forced Expiratory Volume in one second** (total volume of air exhaled in the first second of a FVC maneuver -- ideally should be 6 seconds or more of exhalation effort with the best of three efforts recorded)
- **FEV1/FVC** = **Percentage expired in one second**
- **FEF25-75 = Forced Expiratory Flow in the 25th to 75th portion of flow-volume curve** (also sometimes listed as MMEF 25-75: Maximal Mid-expiratory Flow Rate)
- **TLC = Total Lung Capacity**
- **FRC = Functional Residual Capacity** (amount of air in the lung at end-of-normal tidal volume exhalation)
- **DLCO = Diffusing Capacity for Carbon Monoxide**

5

LUNG VOLUMES



SOLITARY PULMONARY NODULES (SPNs)

Rodney C Richie MD, DBIM, FACP, FCCP

A not uncommon problem for underwriters reviewing medical records is the finding of an isolated pulmonary nodule, often found incidentally – say, for instance, on an abdominal CT done for some intra-abdominal condition, with the radiology mentioning a nodule on imaging. What to do?

First, the underwriter must know how a "solitary pulmonary nodule" is defined. In short, it is:

- ≤ 30 mm in diameter (anything larger is a "mass" and is malignant until proven otherwise)
- Surrounded by aerated lung (i.e., not associated with atelectasis or fibrosis)
- Generally, SPNs denote no clinical history of prior malignancy that may significantly raise the likelihood of lung metastatic disease. If the person has a history of prior malignancy, then the nodule should be assumed to be metastatic
- And, by definition of this review, multiple nodules are for another discussion

A solitary pulmonary nodule evaluation always requires CT imaging. For nodules > 7mm, FDG-PET imaging may be even more essential for correct evaluation.

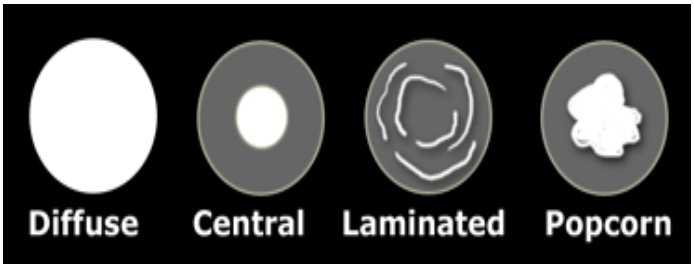
The size, morphology, person's age, and presence of calcium are the four primary determinants of cancer risk. Other major concerns include the applicant's smoking history, COPD, and the nodule being in an upper lung zone.

CT imaging of SPNs always include a description of the nodule's margins.

- Spiculated = high concern for malignancy
- Scalloped = intermediate concern for malignancy
- Smooth = lower concern for malignancy

For spherical lesions, a 30% increase in diameter on sequential imaging represents a doubling of volume.

Presence of calcification is reassuring of the nodule's being benign. The benign patterns of calcification are:



The one exception to the benignity of calcification is "ectopic calcification", when the calcification is on the edge of the lesion.

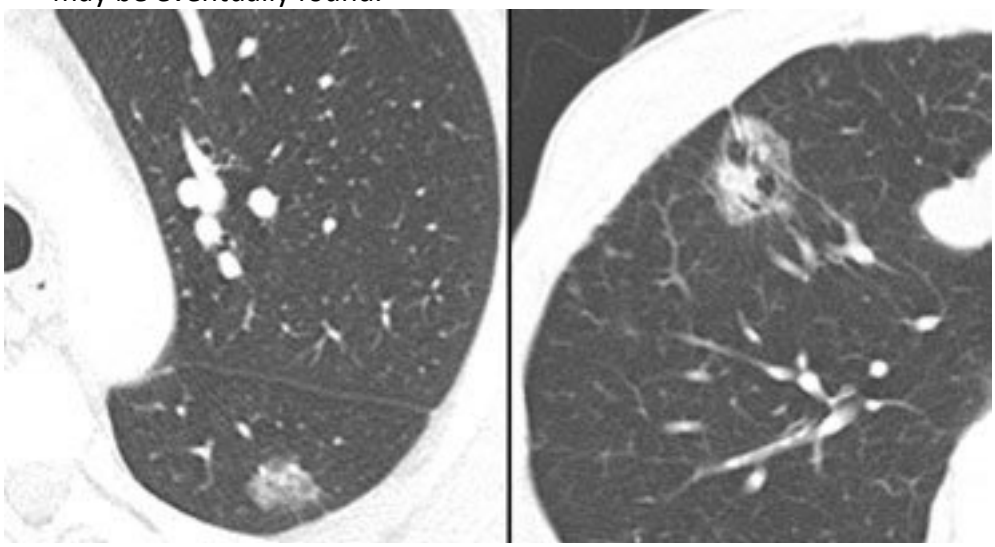
The likelihood of malignancy also corresponds to its **size**.

Size	Likelihood of malignancy
< 5 mm	< 0.1%
5-9 mm	0.2-6%
8-20 mm	18%
>20 mm	>50%

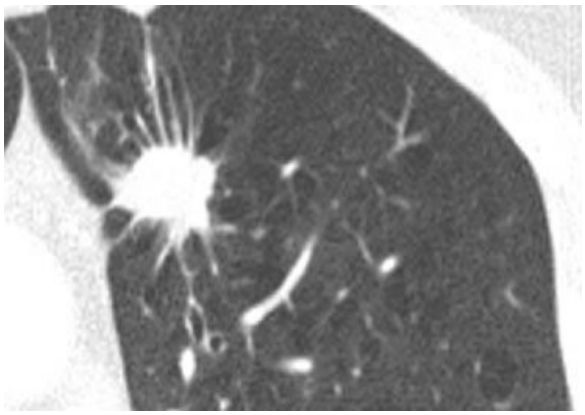
With introduction of multi-detector row CT, the identification of focal rounded pulmonary opacities (nodules) as small as 1-2 mm in diameter has become routine and most will be benign.

The likelihood of malignancy also corresponds to its **morphology**. Concerns for potential malignancy rise with the following:

- Ground-glass appearance around the nodule
    - Requires > 2-years of CT follow-up.
    - Bronchoalveolar carcinoma (new terminology is AIS – Adenocarcinoma in situ) may be eventually found.



Ground-glass infiltrate on the left has a 1 in 5 chance of malignancy. The ground-glass + solid component lesion on the right as a 2 in 3 likelihood of malignancy.



- **Spiculated border of the nodule** (noted above) **is highly indicative of malignancy.**
- Cavitation, air bronchograms through the nodule, and location in the upper lung zones also carry a significant risk of malignancy.

Finally, radiologists on CT imaging may comment on the nodule's "doubling time" if serial imaging is done:

- Less than 1 month or greater than 1 year → usually benign
- One month to one year → usually malignant

On CT imaging done specifically in evaluation for these nodules, radiologists may mention:

- CT densitometry, which involves measurement of attenuation values expressed in Hounsfield units. In one large multicenter trial only one 1 nodule among 66 with Hounsfield unit > 264 ultimately proved to be malignant.
- Use of contrast enhancement – an increase in attenuation of > 20 Hounsfield units may suggest a nodule to be malignant.

For SPNs > 8 mm and larger: ****PET (Positive Emission Tomography)**** is more sensitive than CT at identifying cancerous nodules, and PET reports should be sought out in the medical records. Postponement of an underwriting decision until PET imaging is available in one option for underwriters concerned with an **8+ mm nodules** that have not been evaluated – **PET imaging for SPNs is that important!**

- (+) PET – likelihood of lung cancer is > 85%.
- (-) PET – likelihood of lung cancer is low with negative predictive value > 90%. Even with this negative likelihood, it is generally recommended that serial *CT imaging* be done at 6-month intervals for the following 2 years.
- ****Note that PET imaging becomes unreliable with nodules < 7 mm****
- And also note that PET imaging always requires a glucose test prior to starting the procedure. 18-flourodeoxyglucose positron emission tomography (FDG-PET) requires the uptake of the radioactive isotope of glucose by metabolically active tissue, which is much less likely to occur in the setting of systemic hyperglycemia.
- Also, the underwriter needs to be aware that a (+) PET imaging study may equally suggest non-malignant inflammatory diseases and granulomas as well as malignancy – which cause (+) uptake of glucose in metabolically-active tissue.

The likelihood of malignancy probability in SPNs per Brock calculator:

Spiculated Margins	5.54
Age > 70 years old	4.16
Size 2.1-3.0 cm	3.67
Doubling time < 465 days	3.40
Smoker	2.27
Age 50-69	1.90
Size 1.1-2.0 cm	0.74
<1 cm	0.52
Smooth margins	0.30
Never Smoker	0.19

Other Solitary Pulmonary Nodule (SPN) Malignancy Risk calculators are available from the Mayo Clinic and the Society of Thoracic Surgeons -- **found by Googling SPN risk calculators**.

Fleischner Society Guidelines for Management of Incidentally Detected Pulmonary Nodules are divided into **Solid Nodules** and **Subsolid Nodules** (groundglass) and generally advice CT imaging or follow-up only for "high-risk" persons for nodules measuring < 6 mm.

Recommendation for CT imaging begins at nodules 6-8 mm and larger, with a frequency of roughly 6-12 months, up to 2 years for solid lesions without size change, and up to 5 years for subsolid (i.e., lesions. CT and/or CT/PET imaging is recommended at nodules > 8 mm.

Underwriters may Google Fleischner Society Guidelines for further drill-down on recommendations.

In high-risk populations, low-dose computed tomography (LDCT) reduces lung cancer-related mortality by 21% compared with controls.

- Bonney et al. Impact of low-dose computed tomography (LDCT) screening on lung cancer-related mortality. *Cochrane Database Syst Rev* 2022 Aug 3; 8: CD013829. DOI: 10.1002/14651858.CD013829.pub2

Underwriters will likely be encountering more SPNs with the Centers for Medicare & Medicaid Services (CMS) determination to expand low-dose CT imaging screening to more at-risk people that was **announced February 10, 2022**. The starting age has been dropped from 55 to 50 years, and the tobacco smoking history has been reduced from 30 packs per year to 20 packs per year. Although the vast majority of nodules discovered by such screening will ultimately be determined to be benign, the fact that lung cancer in both sexes remains the #1 cause of cancer mortality in the U.S. (exceeding deaths due to breast, colon, and prostate *combined*) is the rational for more aggressive screening. Early lung cancer, defined as an SPN < 30 mm with no evidence of metastases, may have 5-year survival rates as high as 75-80%.

A fun note: generally, a pulmonary nodule much reach 10 mm in diameter before it can be identified on a routine chest x-ray. For a malignant nodule to reach this size, approximately 30 doublings would have occurred. The average doubling time for a malignant tumor is 120 days

(much shorter for small cell lung cancers and much longer for bronchoalveolar cell (now called AIS – Adenocarcinoma In Situ) carcinomas). This means that the lesion may in fact have been present for as long as 10 years before being discovered on chest radiograph.

INTERSTITIAL PULMONARY DISEASES

Rodney C Richie, MD, DBIM, FACP, FCCP

The diffuse parenchymal lung diseases, often collectively referred to as the interstitial lung diseases (ILDs), are a heterogeneous group of disorders that are classified together because of similar clinical, radiographic, physiologic, or pathologic manifestations. The descriptive term "interstitial" reflects the pathologic appearance that the abnormality begins in the interstitium of the lung, but the term is misleading as most of these disorders are also associated with extensive alteration of alveolar and airway architecture.

The diffuse parenchymal lung diseases are divided into those that are associated with known causes and those that are idiopathic. The most common identifiable causes of ILD are exposure to occupational and environmental agents, especially to inorganic (asbestosis, silicosis) or organic dusts, drug-induced pulmonary toxicity, and radiation-induced lung injury.

ILD can also complicate the course of most of the connective tissue diseases:

- polymyositis/dermatomyositis
- rheumatoid arthritis
- systemic lupus erythematosus
- scleroderma
- mixed connective tissue disease

and in most cases leads to increased mortality.

Idiopathic causes of ILD include

- Sarcoidosis
- cryptogenic organizing pneumonia
- and the idiopathic interstitial pneumonias:
  - Idiopathic pulmonary fibrosis (usual interstitial pneumonia – UIP)
  - Desquamative interstitial pneumonia (DIP)
  - Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
  - Acute interstitial pneumonia (AIP)
  - Nonspecific interstitial pneumonia (NSIP)

Clinical presentation of ILD is typically because of unusual dyspnea-on-exertion and/or a nonspecific cough, an abnormal chest x-ray or CT Lung, and occasionally because of "restriction" found on spirometry:

- Reduced FVC% predicted and FEV1% predicted but with normal FEV1/FVC ratio

A history of current or past smoking is more commonly seen in desquamative interstitial pneumonitis, respiratory bronchiolitis-interstitial lung disease, and idiopathic pulmonary fibrosis. No history of smoking is more common in sarcoidosis and hypersensitive pneumonitis.

Relevant studies that may help identify and quantify the significance of ILDs are:

- Spirometry revealing reduced FVC% predicted and reduced FEV1% predicted but with a normal FEV1FVC ratio (>80% predicted)
- Lung volume determination revealing a <90% reduction in FRC% predicted and/or TLC% predicted
- Lung diffusion (DLCO) < 70% predicted
- Significant reduction of 6-minute walk test (< 60% predicted)
- High-resolution CT (HRCT) imaging of the lung
    - HRCT for ILD involves volumetric, rather than sequential, imaging with <1.5 mm slice thickness. Images of the entire chest are obtained with the patient in the supine (and in some institutions prone) position at sustained end-inspiration and then at sustained end-expiration.
    - HRCT findings help to narrow the differential diagnosis of ILD.
        - Bilateral symmetric hilar adenopathy and upper lung zone reticular opacities suggest sarcoidosis or other granulomatous disease
        - Pleural plaques with linear calcification in association with a basilar predominance of reticular opacities suggest asbestosis
        - Centrilobular nodules that spare the subpleural region are seen in hypersensitivity pneumonitis, sarcoidosis, Langerhans cell histiocytosis, and also respiratory, follicular, and cellular bronchiolitis
        - Irregular cysts associated with nodules in the upper and middle lung zones suggest pulmonary Langerhans cell histiocytosis
        - **Reticular opacities, traction bronchiectasis, and honeycombing (clustered airspaces 3 to 10 mm in diameter) in a predominantly subpleural and basal distribution are the imaging features associated with a histopathologic pattern of usual interstitial pneumonitis (UIP)** While ground glass opacities may be present, they should be superimposed on reticular opacities to be considered indicative of UIP
        - A UIP pattern is seen in idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonitis, and ILD-associated with rheumatic diseases, such as rheumatoid arthritis and systemic sclerosis

As an underwriter, the finding of an interstitial lung disease admitted by an applicant, or finding this diagnosis in the medical records, will require some homework -- as the number of diseases and their prognosis is long and varied. The most helpful criteria at arriving at an impairment rating will be:

- The severity of disease at its worse and currently
- The on-going requirement for any steroids or other suppressive medication
- And the time-course of the disease, as the longer the course, generally the less the impact the disease will have on morbidity and mortality.

The pre-read on Sarcoidosis is available as an example of interstitial lung disease.

Although quite dated, my JIM article of 2007 still is reasonably accurate regarding the diagnosis and *mortality* of the various forms of idiopathic interstitial lung diseases:

- Richie, RC. Underwriting Idiopathic Interstitial Lung Diseases. *J Insur Med* 2007; 39: 270-279

Diffusing Capacity (DLCO)

- DLCO decreased in obstruction
  Increased FRC } Emphysema

- DLCO decreased in restriction
  Decreased FRC } Interstitial Lung Disease

- DLCO decreased without obstruction
  or restriction } Pulmonary Vascular Disease

- Pulmonary Vascular Diseases: Occult Pulmonary Embolus
  Pulmonary Hypertension
  Pulmonary Veno-occlusive disease
  Sickle Cell Disease (SS Hemoglobin)

- DLCO Increased } Left to Right Shunt
  } Pulmonary Hemorrhage

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Sarcoidosis

Rodney C Richie MD DBIM FACP FCCP

(information largely sourced from UpToDate – Sarcoidosis)

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized pathologically by the presence of noncaseating granulomas in involved organs. It typically affects young adults and initially presents with one or more of the following abnormalities:

- Bilateral hilar adenopathy
- Pulmonary reticular opacities
- Skin, joint, and/or eye lesions (and more rarely heart and CNS lesions)

In the Unites States, the incidence is 7 to 11 per 100,000, with it being 2-3x more common in Black Americans than White Americans. The lifetime risk of sarcoidosis among Black Americans is estimated to be 2.4 percent, compared with a lifetime risk of 0.85 percent in White Americans. In a large United States database study of adults over age 18, females were twice as likely to have sarcoidosis compared with males, with the highest prevalence of sarcoidosis being in Black American females.

Approximately 5 percent to 10 percent of persons with sarcoidosis eventually die — 78% because of their lung involvement. Persons who die of CNS or cardiac sarcoidosis die younger and with a shorter clinical course. Most people with sarcoidosis live normal lives, with 60% undergoing spontaneous remission, 30% having progressive disease, and 10% developing steadily worsening lung fibrosis or more sudden CNS or cardiac disease leading to their death.

Although sarcoidosis is a disease commonly seen in young adults, the age at diagnosis has steadily increased over the past 75 years such that now more than half of cases are diagnosed over age 40 years.

Sarcoidosis most frequently involved the lung, but up to 30 percent of patients present with extrathoracic manifestations. Common presenting respiratory symptoms include cough, dyspnea, and chest pain; these are frequently accompanied by fatigue, malaise, fever, and weight loss. Affected persons may also present with new skin lesions (particularly around tattoos or scars), visual changes, dry eyes or mouth, parotid swelling, palpitations, syncope, joint pain or swelling, or muscle weakness.

Even in the presence of lung parenchyma sarcoidosis, crackles are not commonly heard on chest examination. Wheezing may be present when there is endobronchial involvement.

There are no definitive laboratory tests for sarcoidosis — the diagnosis is made when all other causes of granulomatous disease have been evaluated and ruled out.

- Hypercalciuria is more commonly observed than hypercalcemia.
- A moderate elevation in the serum alkaline phosphatase concentration suggests diffuse granulomatous hepatic involvement.
- Hypergammaglobulinemia (30 to 80 percent) and a positive rheumatoid factor may be present (but these are rarely ordered).
- Serum angiotensin converting enzyme is elevated in 75 percent of untreated patients with sarcoidosis but is not used diagnostically because of unacceptable false negative results (poor sensitivity) and false positive results (insufficient specificity).
- Serum soluble interleukin-2 receptor (sIL2R) has been suggested as a useful marker for determination of extra-pulmonary involvement in sarcoidosis patients.

- Serum chitotriosidase (of the chitinase family) are produced by activated macrophages, and substantially higher levels are present in serum from persons with sarcoidosis compared with health controls. Serum chitotriosidase is increased in persons with greater disease activity and has promise as a bio marker of disease activity and response to therapy.
- It should be noted that there is diminished skin test reactivity in sarcoidosis, so a positive tuberculin skin test or an interferon gamma release assay is strong evidence in favor of mycobacterial disease.

Lung involvement occurs in over 90 percent of persons with sarcoidosis. Sarcoidosis staging is based on a **2-view chest radiograph** (*and not CT imaging*).

- **Stage I** — defined by the presence of bilateral hilar adenopathy, with 50 percent of affected persons presenting with Stage I disease. Regression of hilar nodes within 1 to 3 years occurs in 75 percent of persons, while another 10% may develop chronic enlargement that may persist for 10 years or more.
- **Stage II** — consists of bilateral hilar adenopathy and lung parenchyma involvement, most commonly reticulonodular opacities. These findings are present at initial diagnosis in 25 percent of persons. Two-thirds of such persons undergo spontaneous resolution, while the remainder either have progressive disease or display little change over time. Persons with stage II disease usually have mild to moderate symptoms, most commonly cough, dyspnea, fever, and/or easy fatigue.
    - If symptoms will allow, it is preferable not to treat this stage with corticosteroids -- which will lead to prompt remission of symptoms and lung infiltrates – because *spontaneous remission* is usually permanent, whereas *steroid-induced remission* is commonly followed by relapse once steroids are discontinued
- **Stage III** — consists of parenchyma involvement without lymphadenopathy
- **Stage IV** — characterized by fibrosis, manifested as reticular opacities with or without cystic changes, predominantly distributed in the upper lung zones. Conglomerated masses with marked traction bronchiectasis, and extensive calcification and cavitation or cyst formation may also be seen.

Less commonly, the chest radiograph may show multiple, bilateral lung nodules or consolidation mass-like opacities and minimal hilar adenopathy, findings that may simulate metastatic disease.

High-resolution CT (HRCT) imaging is usually done and most commonly reveals small nodules (2 to 5 mm) *with mid-to-upper zone predominance*. Later disease may reveal large nodules and masses and ground-glass opacities, and even later disease will exhibit fibrosis, again predominantly in the upper lung zones.

Pulmonary Function Testing (PFTs), including spirometry, lung volume measurement, diffusing capacity for carbon monoxide (DLCO), and 6-minute walk test (6MWT), should be obtained in persons with pulmonary sarcoidosis to assess the severity of respiratory impairment and to monitor the course of disease with sequential measurements. PFTs, however, are not a reliable means for detecting lung parenchyma sarcoidosis (HRCT is better), nor do they provide an accurate estimate of the extent of parenchyma disease. Clinicians cannot predict the natural course of lung involvement or response to therapy solely on the basis of these tests.

PFTs characteristically reveal a restrictive pattern (reduced functional residual capacity and total lung capacity) associated with a reduction in DLCO, although is it not unusual for lung function to be normal.

Endobronchial sarcoidosis may lead to impairment of airflow and obstructive respiratory physiology on PFTs.

Approximately 20 percent of patients with stage I sarcoidosis have abnormal PFTs. In contrast, PFTs are abnormal in 40 to 70 percent of persons with stage II to IV disease.

Fiberoptic Bronchoscopy with bronchoalveolar levage (BAL), endobronchial biopsy, and transbronchial biopsy are traditional methods for the minimally invasive diagnosis of sarcoidosis.

- **BAL** is done mainly to exclude alternative diagnoses, such as chronic beryllium disease, eosinophilia lung disease, infections (eg, actinomycosis, mycobacteria, fungi), and malignancy. A number of studies have examined the patterns of lymphocyte subsets in sarcoidosis and reported a reduced number of CD8 cells, an elevated CD4 to CD8 ratio (eg, >4:1), and increased proportions of activated T cells, CD4 cells, immunoglobulins, and IgG-secreting cells. The triad of a CD4 to CD8 ratio >4:1, a lymphocyte percentage > 16 percent, and a transbronchial biopsy demonstrating noncaseating granulomas is the most specific test for sarcoidosis. BAL fluid with >2 percent neutrophils or >1 percent eosinophils suggest that sarcoidosis is not the correct diagnosis.
- **Endobronchial biopsy** is done for endobronchial lesions such as erythema or a modular, granular, or cobblestone appearance. Endobronchial disease exists in approximately 40 percent of persons with stage I disease and approximately 70 percent of persons with stages II or III disease.
- **Transbronchial lung biopsy** has a relatively high yield (50 to 75 percent).
- **Transbronchial Needle aspiration with ultrasound** may be used for both lung masses and mediastinal lymph nodes.

When can a biopsy be deferred? The main exceptions to the need for a biopsy are the presence of bilateral hilar adenopathy in an asymptomatic person (Stage I) who can be monitored to ensure stability; classical Lofgren syndrome with fever, erythema nodosum, arthralgias, and bilateral hilar lymphadenopathy; Hereford syndrome of uveoparotid fever; and lupus pernicious.

For underwriters/medical directors doing international business

Air pollution cuts life expectancy by more than two years
University of Chicago's Energy Policy Institute (EPIC)

Summary:

- South Asians lose 5 years of life due to smog
- On worst days, breathing India's Delhi air is equivalent to smoking two packages of cigarettes that day
- No country met WHO's air-quality standard in 2021

Shanghai, June 14 (Reuters) – Chronic air pollution cuts average global life expectancy by more than two years per person, a study published showed, an impact comparable to that of smoking and far worse than HIV/AIDS or terrorism.

More than 87% of the global population lives in areas where air pollution exceeds recommended levels, per the University of Chicago's Energy Policy Institute (EPIC) aid in its latest Air Quality Life Index, which used satellite data to measure levels of PM2.5, hazardous floating particles that damage the lungs.

They said that if global PM2.5 levels were reduced to the 5 micrograms per cubic meter recommended by the World Health Organization (WHO), average life expectancy would rise by an average of 2.2 years.

Air pollution has been neglected as a public health issue, with funding to address the problem still inadequate, the study warned.

"Now that our understanding of pollution's impact has improved, there's a stronger case for governments to priorities it as an urgent policy issue," said Christa Hasenkopf, director of EPIC's Air Quality Life Index.

Residents of South Asia lose an estimated five years of life as a result of smog, the study said, with India accounting for around 44% of the world's increase in air pollution since 2013, when the country began a "war on pollution" that cut PM2.5 by around 40%.

EPIC's calculations were based on a previous study showing that sustained exposure to an additional 10 micrograms per cubic meter of PM2.5 would reduce life expectancy by nearly a year.

Not a single country managed to meet the WHO's 5-microgram standard in 2021, according to a survey of pollution data published earlier this year. Only 3.4% of surveyed cities met the standard in 2021, according to data compiled by IQAir, a Swiss pollution technology company that monitors air quality. As many as 93 cities saw PM2.5 levels at 10 times the recommended level.

"There are a lot of countries that are making big strides in reduction," said Christi Schroeder, air quality science manager with IQAir. "China started with some very big numbers and they are continuing to decrease over time. But there are also places in the world where it is getting significantly worse." India's overall pollution levels worsened in 2021 and New Delhi remained the world's most polluted capital, the data showed. Bangladesh was the most polluted country, also unchanged from the previous year, while Chad ranked second after the African country's data was included for the first time.

China, which has been waging war on pollution since 2014, fell to 22nd in the PM2.5 rankings in 2021, down from 14th place a year earlier, with average readings improving slightly over the year to 32.6 micrograms, IQAir said.

Hotan in the northwestern region of Xinjiang was China's worst performing city, with average PM2.5 readings of more than 100 micrograms, largely caused by sandstorms.

It fell to third on the list of the world's most polluted cities after being overtaken by Bhiwadi and Ghaziabad, both in India.

Reported by David Stanway in Reuters March 22,2022 – section on Environment

Lawrence, KG, Niehoff, NM, Keil, AP et al. Associations between airborn crude oil chemicals and symptom-based asthma. *Environment International* 9/2022;167:107433. doi.org/10.1016/j.envint.2022.107433

The 2010 Deepwater Horizon (DWH) oil spill response and cleanup (OSRC) workers were exposed to airborne total hydrocarbons (THC), benzene, toluene, ethylbenzene, o-, m-, and p-xylenes, and n-hexane (BTEX-H). The study focused on the 19,018 workers without asthma before the spill, compared to workers trained but not utilized, who developed symptomatic asthma within 3 years following the spill.

Findings: OSRC workers had greater asthma risk then nonworkers (RR: 1.60, 95%CI, 1.38-1.85). Higher THC exposure levels were associated with increased risk in an exposure-dependent manner (linear trend test $p<0.0001$). Asthma risk also increased with increasing exposure to individual BTEX-H chemicals and the chemical mixture: A simultaneous quartile increase in the BTEX-H mixture was associated with an increased asthma risk of 1.45 (95% CI, 1.35-1.55).

Conclusions: THC and BTEX-H were associated with increased asthma risk defined using wheeze symptoms with a physician diagnosis.