

Occupational and Environmental Cough: The Missing History

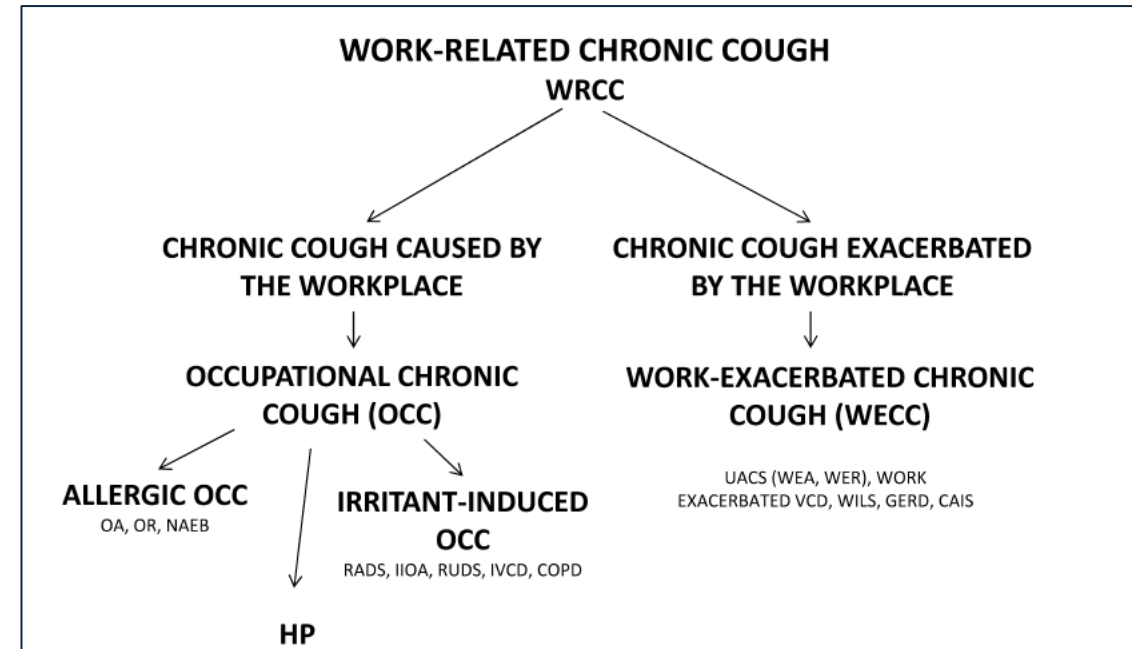
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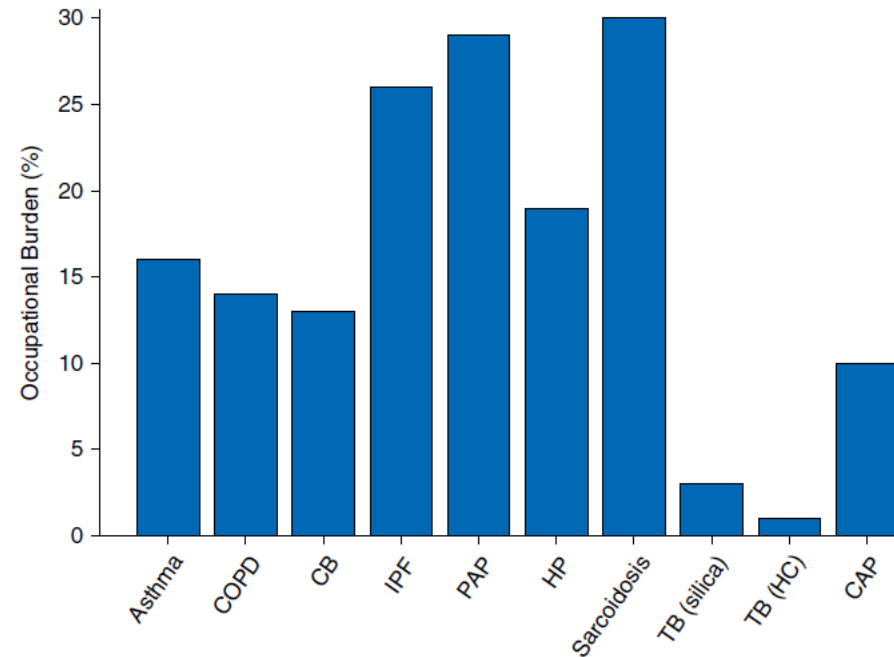
Classification of Work-Related Chronic Cough

- Work-related rhinitis and upper airway cough
- Occupational eosinophilic bronchitis
- Work-related asthma
 - Work-aggravated asthma
 - Occupational asthma
 - Allergic occupational asthma
 - Irritant-induced occupational asthma
- Hypersensitivity pneumonitis
- Occupational ILD
- Laryngeal disorders



Epidemiology

- Workplace exposures contribute to of adult respiratory diseases
 - 16% of adult asthma, 14% of COPD, and 13% of chronic bronchitis
- The population attributable risk of WRCC is estimated at 4% to 18%
 - High-exposure cohorts show increased prevalence rates – e.g. stone cutters (66.5%), sewage workers (34%)
 - Rescue workers exposed to highly alkaline dust at World Trade Center collapse (10–29.1%)



Pathophysiology of Occupational & Environmental Cough

- Direct vs. Indirect
 - Direct effects → Particle or gas itself stimulate cough receptors
 - Indirect effect → Associated with secondary infectious or noninfectious sinusitis, bronchitis, and cough-variant asthma.
- Sensitizers vs. Irritants
- Anatomic/disease specific pathophysiology

Table 1 Causal agents of work-related chronic cough

Occupation

Miners
Cement and glass bottle production
Construction workers
Farming workers
Food industry
Mushroom factory
Wood industry
Dental technicians
Fire-fighters
Bakery
Mechanic and repair jobs
Spice factory
Greenhouse
Cleaners

Agents

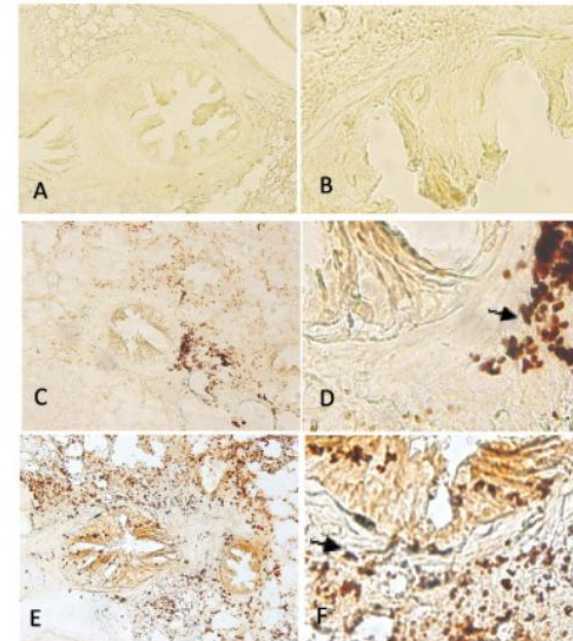
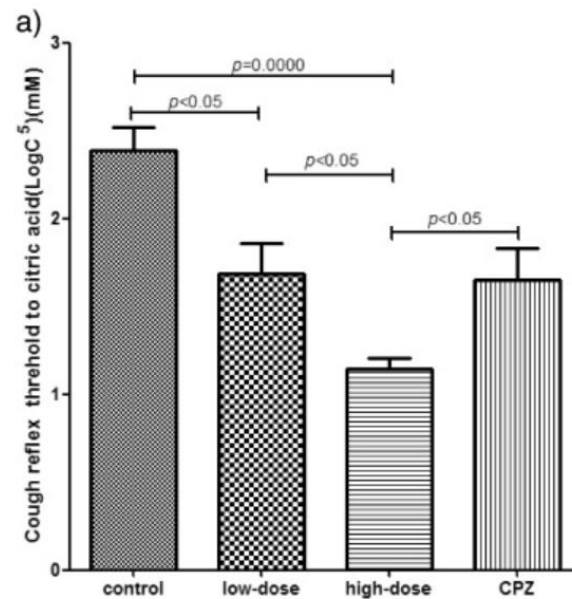
Methyl methacrylate
Aliphatic polyamines
Grain and flour mills
Spices
Dust due to World Trade Center collapse
Vapour, gases, dusts, fumes
Cattle and swine confinement farms
Cleaning products
Second-hand smoking

- **Airway inflammation**

- Inflammatory cells (eosinophils, mast cells, neutrophils) by chronic irritant exposure
- Inflammatory mediators (histamines, prostanoids, substance P, etc.)
 - Enhance cough reflex at sensory level
 - Direct cause of TRPV-1 stimulation
- Airway remodeling
 - Inflammatory cytokines and eosinophil mediators damage epithelial linings and expose sensory nerves.
 - Goblet cell hyperplasia
 - Stimulate cough through the resultant mucous hypersecretion
 - Impair mucociliary clearance

- **TRPV1 & TRPA1 receptor modulation**

- Direct activation by environmental pollutants (isothiocyanate, acrolein, other aldehydes)
- Activation by secondary produced irritants and inflammation
- Upregulation of transient receptor potential channels



Work-Related Rhinitis and Upper Airway Cough

- Common symptoms
 - Sneezing, nasal pruritus, rhinorrhea, cough – work relation
 - May accompanied with conjunctivitis and/or asthma
- No consensus on the definition of work-related rhinitis
 - Mostly based on temporal relationship
- Higher prevalence than occupational asthma, often preceding
- Allergic vs. non-allergic (irritant-induced rhinitis)
- Low-molecular weight chemical sensitizers
 - Difficult to diagnose due to less commonly IgE-mediated
- Diagnosis
 - Immunologic tests (low sensitivity~ 42%)
 - Skin prick test
 - Specific IgE
 - Nasal provocation test (gold standard)

Table 1: Prevalence and aetiological agents in occupational rhinitis (adapted from reference [9]).

Agents	Occupation	Prevalence (%)
High molecular weight agents		
Laboratory animals	Laboratory workers	6–33
Other animal-derived allergens	Swine confinement workers	8–23
Insects & mites	Laboratory workers, farm workers	2–60
Grain dust	Grain elevators	28–64
Flour	Bakers	18–29
Latex	Hospital workers, textile factory	9–20
Other plant allergens	Tobacco, carpet, hot pepper, tea, coffee, cocoa, dried fruit and saffron workers	5–36
Biological enzymes	Pharmaceutical & detergent industries	3–87
Fish and seafood protein	Trout, prawn, shrimp, crab & clam workers; aquarists & fish-food factory workers	5–24
Low molecular weight agents		
Diisocyanates	Painters, urethane mould workers	36–42
Anhydrides	Epoxy resin production, chemical workers, electric condenser workers	10–48
Wood dust	Carpentry & furniture making	10–36
Metals (<i>platinum</i>)	Platinum refinery	43
Drugs (<i>psyllium, spiramycin, piperacillin</i>)	Health care & pharmaceutical workers	9–41
Chemicals	Reactive dye, synthetic fibre, cotton, persulphate, hairdressing, pulp & paper, shoe manufacturing	3–30

Work-Related Asthma

- Work-aggravated asthma
 - Pre-existing asthma, aggravated by non-specific factors in workplace
 - Extreme temperature, humidity, exertion, workplace stress/anxiety, exposure to dust/fumes
- Occupational asthma
 - Caused by airborne exposures in working environment
 - About 16% of adult-onset asthma

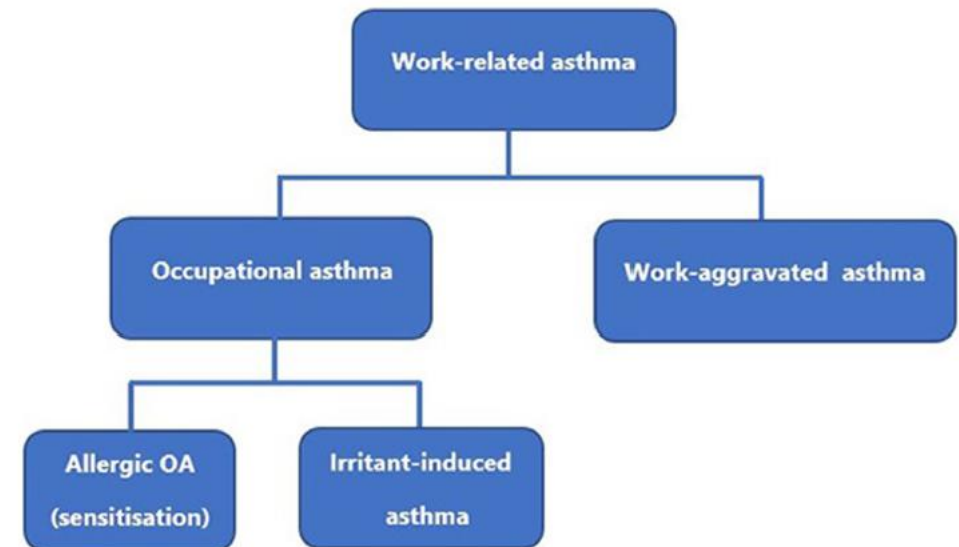


Figure 1 Classification of work-related asthma.

Occupational Asthma

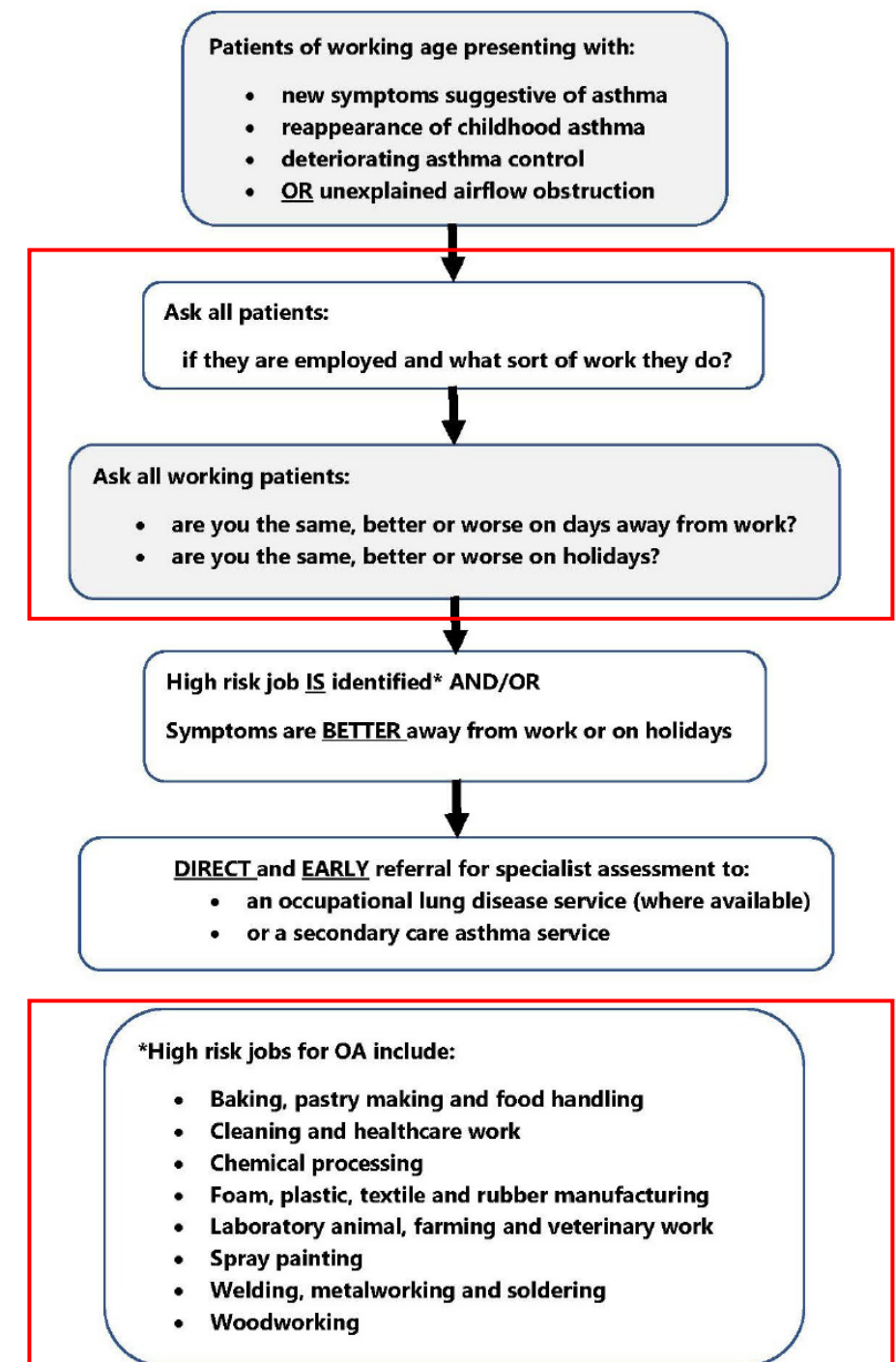
- Causes
 - Sensitization
 - Over 400 causes of OA has been described
 - High molecular weight agents vs. low molecular weight agents
 - Requires a period of repeated allergen exposure
 - "latent period" may exist but highly variable, ranging from a few weeks to many years
 - Irritant-induced asthma
 - Accidental high exposure to respiratory irritant agent
 - "World Trade Center cough"
- Risk factors of OA
 - Level of exposure
 - Underlying allergic tendency
 - Cigarette smoking
 - Genetic polymorphisms

Table 1 Frequently reported causes of occupational asthma, by molecular weight

	Agents and source	Workers at risk
High molecular weight agents	Animal urine and proteins (eg, mice, rats, cows, horses, insects).	Laboratory work, veterinarians, farmers, animal handlers, greenhouse workers.
	Cereal grains and flour (eg, wheat, rye, barley).	Bakers, pizza and pastry makers, grain storage handlers, millers.
	Enzymes (eg, amylase, protease, lipase).	Bakers, pastry makers, food process workers (amylase), cleaners, healthcare workers, detergent manufacturers.
	Natural rubber latex.	Healthcare workers, rubber glove makers.
	Other animal or plant-derived products: milk and egg protein, beans (eg, green coffee, castor, soy), spices, gums (eg, acacia, guar).	Food producers and processors, bakers, cooks. Pharmaceutical industry, printing, carpet making (gums).
	Seafood proteins (eg, fish, crustaceans, molluscs).	Fish and seafood processing.
Low molecular weight agents	Acid anhydrides (eg, tri-mellitic anhydride, phthalic anhydride).	Makers and processors of epoxy resins (adhesives, surface coatings).
	Acrylic monomers (eg, cyanoacrylate, methyl methacrylate).	Adhesive work, dental professionals, aestheticians, printing.
	Biocides (eg, aldehydes, chlorine releasing agents, quaternary ammonium compound).	Healthcare workers, cleaners, swimming pool attendants.
	Colophony (rosin) in solder flux (abietic acid).	Electronic soldering, work with adhesives and surface coatings.
	Di-isocyanates (eg, toluene di-isocyanate, methylene diphenyl di-isocyanate, hexa-methylene di-isocyanate).	Spray painters, foundry workers, makers and processors of polyurethane substances (eg, adhesives, foams, hard surface coatings).
	Drugs (eg, opiates, penicillins, other antibiotics).	Pharmaceutical manufacture, healthcare workers with repeated exposures.
	Metals (eg, chromium, cobalt, nickel, zinc) and metalworking fluids.	Welders, metal platers, hard metal manufacturing. CNC grinders and lathe operators.
	Persulphates and henna.	Hairdressers.
	Platinum and other precious metal salts.	Refinery workers.
	Some wood dust (eg, iroko, obeche, sapele, western red cedar) and MDF (medium-density fibreboard)	Carpenters, joiners, millers, forestry workers.

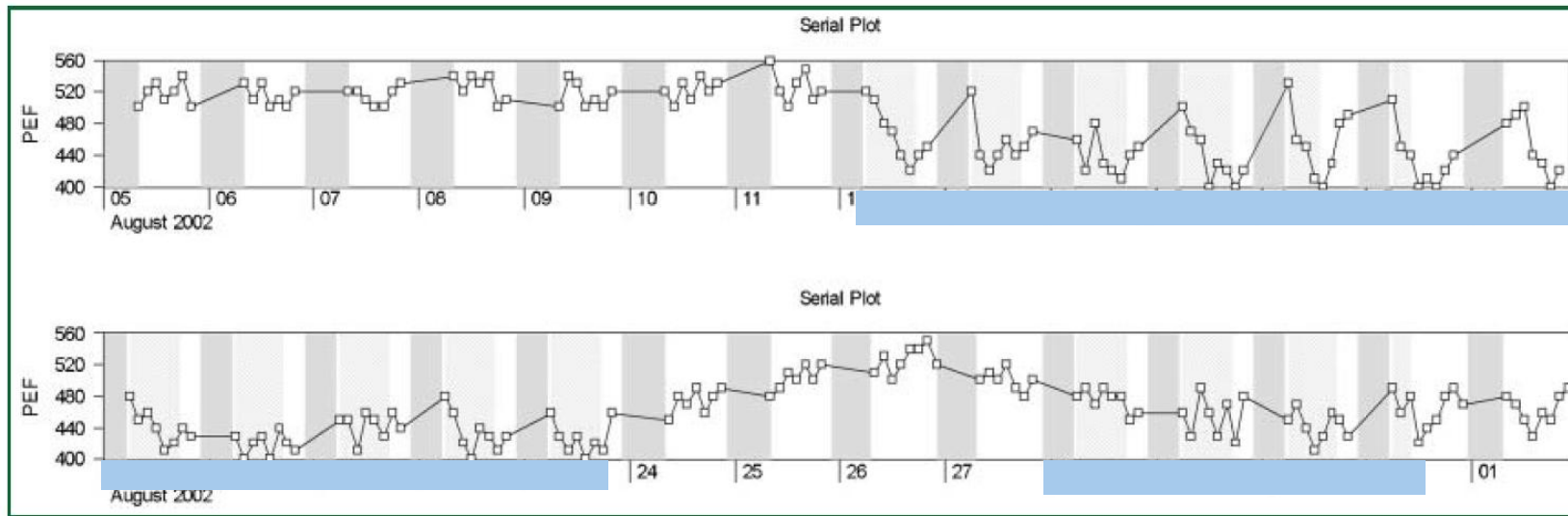
Diagnosis of occupational asthma

- **History taking plays a key role**
 - Suspicion of work relation → neutral questions
 - Full occupational history if OA is suspected
 - However, history alone is not sufficient
- **Spirometry**
 - FEV1, FVC, PEF with bronchodilator testing
 - Lose sensitivity over time after exposure
- **FeNO, sputum eosinophil**
 - Limited study in OA diagnosis
 - May be useful in HMW agents than LMW agents



- **Serial Peak Expiratory Flow recordings**

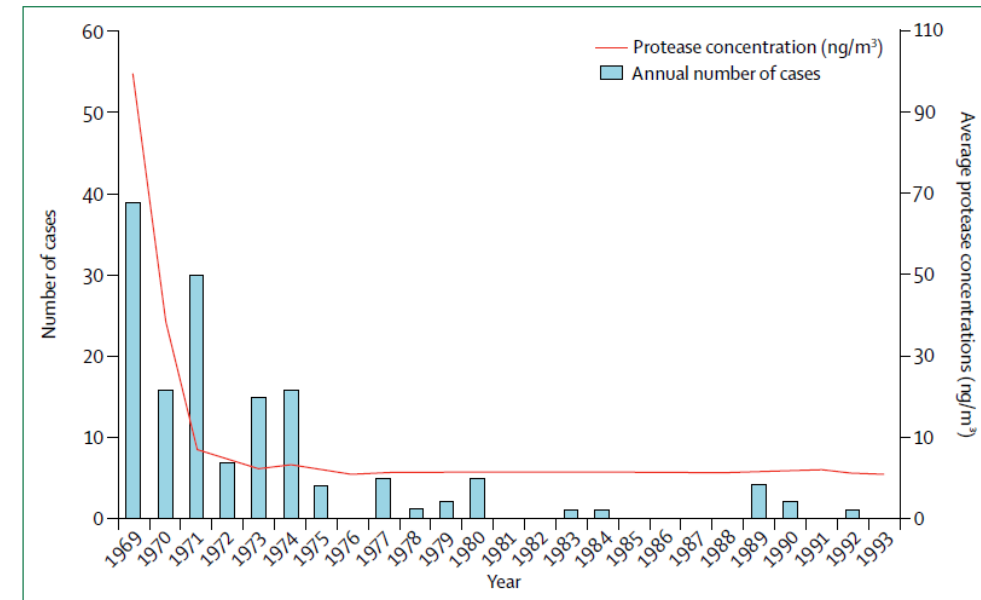
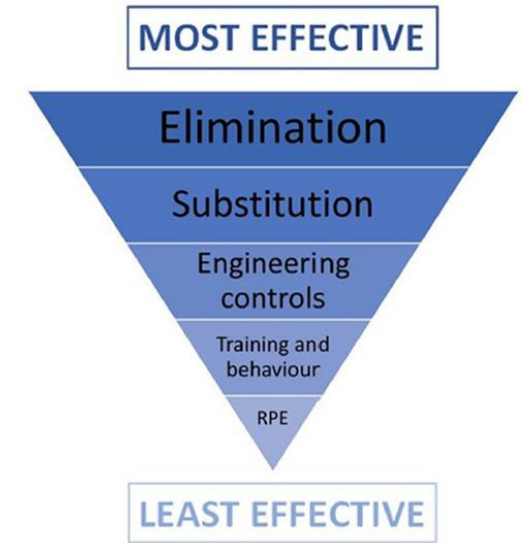
- Cheap and simple first-line approach
- May be positive in work-aggravated asthma and occupational HP
- High sensitivity (75%) and specificity (79%)
- OASYS-2: Analyze via computer-generated system. Score >2.5 indicates highly significant work-related variability



- **Minimum requirements for serial PEF**
 - Frequency: Record at least 4 times daily
 - Duration: At least 3 weeks
 - At least 3 consecutive days at work
 - 3 series of working/away periods
 - Maintenance of medication should be constant
- **Other diagnostic tests**
 - Immunologic tests
 - Skin prick or specific IgE
 - Useful in HMW (enzymes, laboratory animals, latex, wheat)
 - Nonspecific bronchial challenge test
 - Relatively low sensitivity for OA (36-64%)
 - Airway reactivity resolves within a few days off work
 - Specific inhalation/workplace challenge
 - Not widely available

Management of occupational asthma

- Pharmacologic management is same as asthma unrelated to work
- Workplace intervention
 - In most cases, non-exposed work role is not available
 - Receiving standard asthma medication with same or reduced level of exposure is acceptable
 - Respiratory protective equipment: simple and cheap, but least effective measure
- Prognosis
 - Cessation of exposure
 - 25-30% full recovery
 - 30-35% reduction of symptoms
 - 14 times higher risk of unemployment
 - Continued exposure
 - 80% without improvement or worsening despite pharmacologic therapy
 - Increased risk of FEV1 decline (~100ml/yr)



Thorax. 2022;77(5):433-442.
Lancet Respir Med. 2017;5(5):445-455.

Figure 6: Annual incidence of occupational asthma and average concentrations of protease exposure in factory air in 1969-93 in five UK detergent powder factories
Data adapted from Cathcart and colleagues.⁹⁶

Occupational Eosinophilic Bronchitis

- Diagnosis relies on demonstration of eosinophilic airway inflammation
- Test at the end of a working week, with reduction of sputum eosinophilia during periods off work
- More than 3% increase of sputum eosinophil after specific inhalation challenge
- FeNO change after challenge: low sensitivity (43%), high specificity (90%)

Threshold value of post-SIC change in FENO	Sensitivity	Specificity	Positive predictive value	Negative predictive value
>8 ppb (“optimal” cutoff)*	43 (24-67)	90 (83-95)	50 (30-70)	87 (83-92)
>14 ppb (cutoff value providing a specificity >95%)*	33 (14-52)	96 (92-100)	70 (43-100)	86 (82-90)
>17.5 ppb†	24 (9-43)	97 (92-100)	82 (29-100)	84 (81-88)

Table III

Sensitivity and specificity of the postchallenge increase in FENO in identifying an isolated increase in sputum eosinophils

TABLE II. Causal agents of OEB

Causal agent	No. of subjects	Job/industry	Skin prick testing*	Specific IgE*
LMW agents (n = 24)				
Isocyanates				
Methylene diphenyl diisocyanate (MDI)	10	Development of thermoplastic elastomers; mixing of PU components; manufacture of coatings; plastic industry maintenance; PU resin molding; automotive parts manufacture; use of PU glues for windows manufacture or plastic sheets lamination; PU coating in printing process	Negative 8/8	Negative 8/8
Hexamethylene diisocyanate (HDI)	1	Glass painter	Negative 1/1	Negative 1/1
Mixture of isocyanates	2	Luggage manufacture (PU glue); foam rubber production	ND	Positive 1/2
Persulfate salts	2	Hairdressers	Negative 2/2	ND
Disinfectant containing QAC	1	Nurse	ND	ND
Disinfectant containing QAC and glutaraldehyde	1	Nurse	ND	ND
Chloramine-T (<i>N</i> -chloro 4-methylbenzenesulfonamide)	1	Chloramine-T powder conditioner	ND	Negative 1/1
Methylchloroisothiazolinone	1	Offset printing	ND	ND
Paraphenylenediamine	1	Hairdresser	Negative 1/1	ND
Styrene	1	Resin lamination worker	ND	ND
Metals (chromium and cobalt)	1	Electronic industry assembler	Negative 1/1	ND
Metal working fluid	1	Blade grinder	ND	ND
Stainless steel welding	1	Welder	ND	ND
HMW agents (n = 9)				
Flour (wheat, rye)	7	Bakers	Positive 7/7	Positive 7/7
Latex	1	Hospital maintenance technician	Negative 1/1	Positive 1/1
Mold (<i>Penicillium notatum</i>)	1	Nurse (damp building)	Positive 1/1	Positive 1/1

Occupational HP/ILD

Table 1 Proposed classification of occupational hypersensitivity pneumonitis

Characteristics	Acute/subacute OHP	Chronic OHP
Exposure to causal antigen at work	Intermittent high-level exposure (e.g. farmers)	Continuous low-level exposure (e.g. bird breeders)
Onset of symptoms	2–9 h after exposure; may evolve to gradually increasing symptoms over days to weeks	Insidious, over weeks to months
Nature of symptoms	Cough and dyspnea, but predominantly influenza-like symptoms	Progressive symptoms (dyspnea, cough, and weight loss), sometimes punctuated by intermittent attacks of symptoms or slowly increasing
Physical signs	Fever	Inspiratory crackles; cyanosis; digital clubbing; cor pulmonale
Outcome	Symptoms peak within 6–24 h after exposure; last hours to days; and recur on re-exposure; may progress to severe dyspnea	End-stage fibrotic disease and/or emphysema; exacerbations may occur despite avoidance of exposure

Classification derived and adapted from the cluster analysis of the HP Study Group (13).

Occupational HP/ILD

Table 4. *Interstitial lung diseases due to emerging agents or new settings for established agents.*

Exposure	Interstitial lung disease
Denim sandblasting	Silicosis
Inhaled nanoparticles (<i>polyacrylate</i>)	Interstitial pneumonia
Organic chemicals	
<i>Isocyanates</i>	Hypersensitivity pneumonitis
<i>Polyhexamethylene guanidine phosphate (PHMG) and oligo (2-(2-ethoxy) ethoxyethyl guanidinium chloride (PGH) compounds</i>	Interstitial pneumonia; pulmonary fibrosis
<i>5-chloro-2-methyl-4-isothiazolin-3-one (CMIT) and 2-methyl-4-isothiazolone-3-one (MIT)</i>	Interstitial pneumonia
<i>Cross-linked acrylic acid-based polymer (L-PAA)</i>	Interstitial pneumonia; pulmonary fibrosis
Military deployment (<i>desert dust particulate matter, burn pit emission products, vehicular diesel exhaust, jet fuel exhaust, oil well fires, debris from detonation, industrial fires, exposures to chemicals, fumes, gases and dusts</i>)	Bronchiolitis obliterans; acute eosinophilic pneumonia; granulomatous pneumonitis; rapidly progressive pulmonary fibrosis
Flavouring materials (<i>diacetyl (2,3-butanedione) and acetylpropionyl (2,3-pentanedione)</i>)	Bronchiolitis obliterans
Nylon flock	Nonspecific interstitial pneumonia/fibrosis with bronchiolocentric lymphoid nodules and lymphocytic bronchiolitis; diffuse alveolar damage; organizing pneumonia
Indium tin oxide	Interstitial pneumonia, pulmonary alveolar proteinosis
Man-made disasters (<i>World Trade Center-related lung disease</i>)	Sarcoidosis; interstitial pneumonia; pulmonary fibrosis
Welder's lung (<i>welding fumes from electrode, filler wire and fluxes; base metal, shielding gases; paint or surface coating; metal oxides</i>)	Respiratory bronchiolitis (with risk of progression to desquamative interstitial pneumonia with ongoing exposure)

Vocal Demand and Laryngeal Trauma

- Phonation is a major cough trigger in ~33% of chronic cough patients
- Cough induces mucosal edema and vocal fold trauma
- Occupational consideration: high vocal cord demand
 - Teachers
 - Singers
 - Call-center operators
- Management requires speech therapy and voice retraining

General Environmental Exposures and Chronic Cough

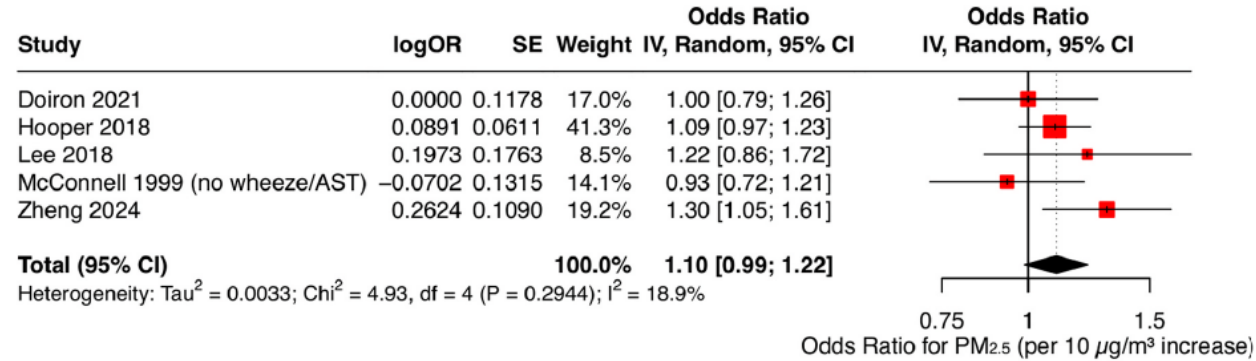
- Non-occupational indoor exposure
- Air pollutants
- Cigarette smoking

Non-occupational Indoor Exposure

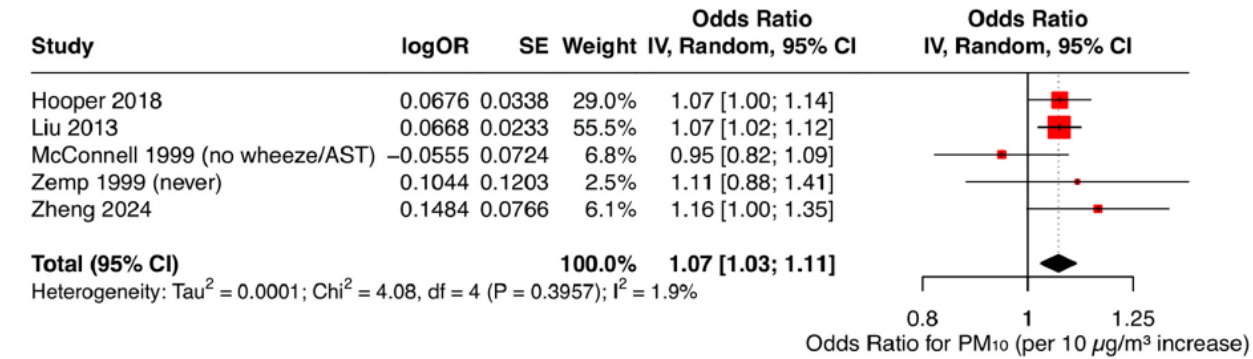
- Common allergens
 - Dust mite, animal, cockroach, fungi, and pollen
- Water damaged building
 - Increased respiratory symptoms, associated with dust mite, endotoxin, or fungi
- Indoor biomass
 - Cooking or heating
 - Usually in developing countries and rural area
- Low-level respiratory irritants
 - Cough and asthma-like symptoms are relatively common component of sick building syndrome

Air pollutants

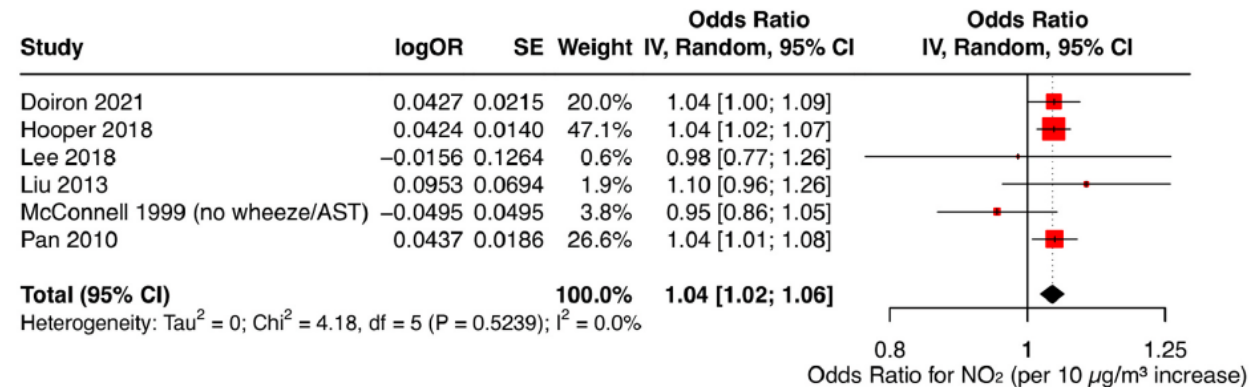
a) PM_{2.5}



b) PM₁₀



c) NO₂



Air pollutants

- Long-term exposure to ozone and respiratory symptoms

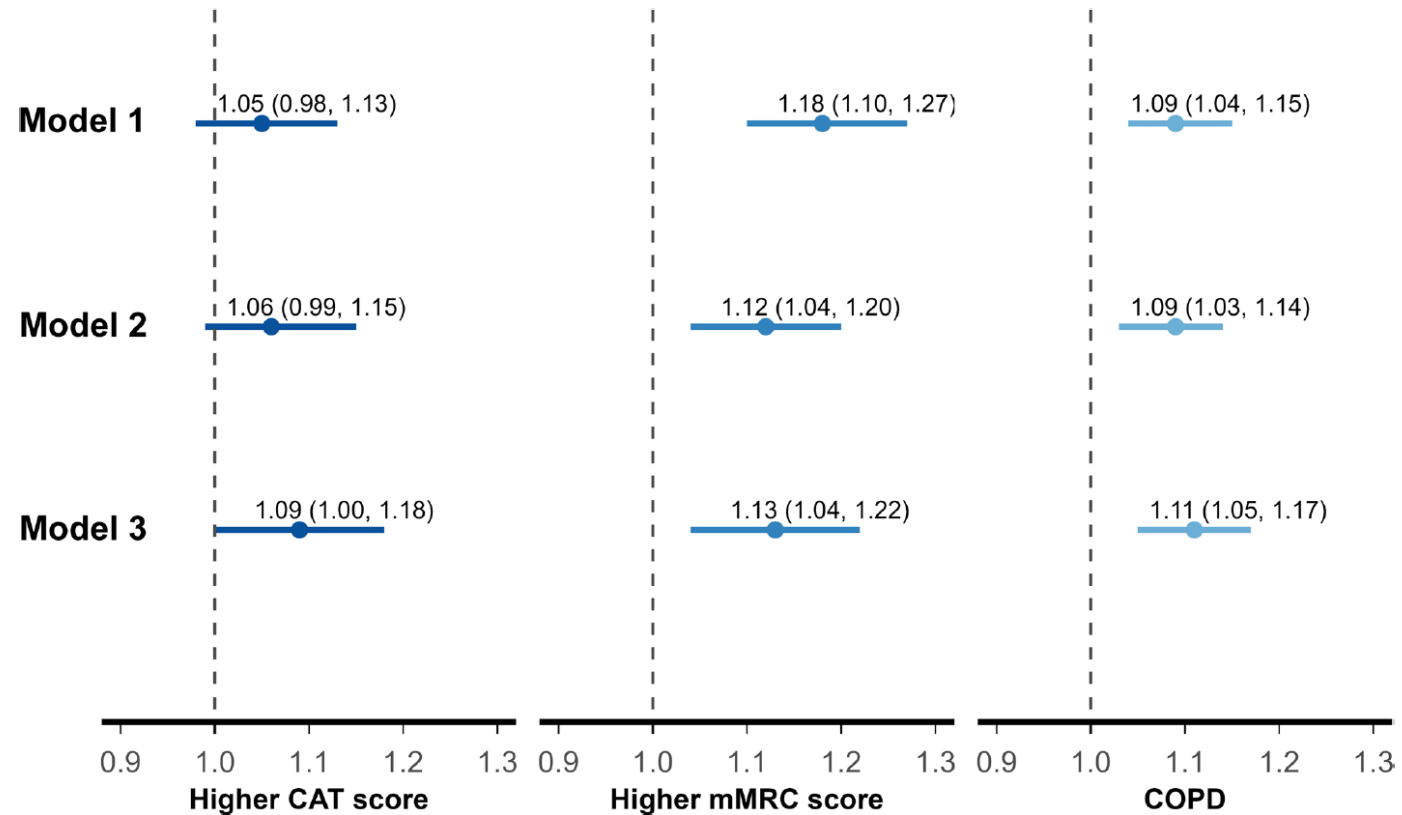
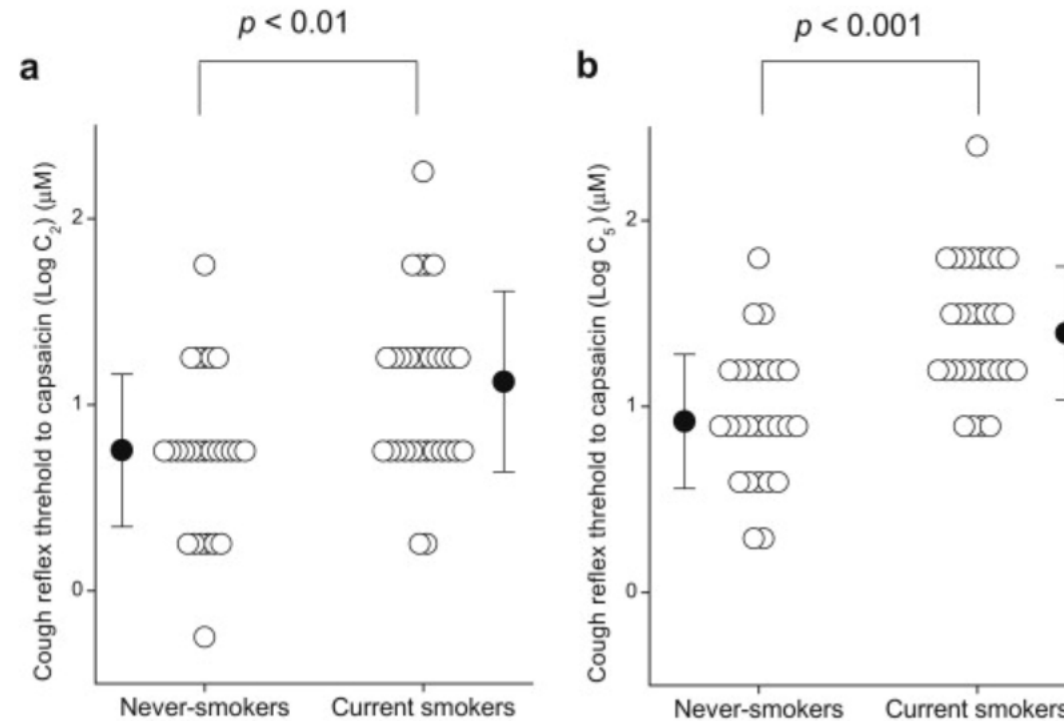


Fig. 1 Associations between 10 $\mu\text{g}/\text{m}^3$ increments in O_3 concentration and high CAT scores, high mMRC scores, and prevalence of spirometry-defined COPD. Model 1 was adjusted for age, sex, BMI, education, occupational status, residential area, and geographic region. Model 2 was additionally adjusted for smoking status and biomass use. Model 3 was additionally adjusted for temperature. CAT, COPD Assessment Test; mMRC, modified Medical Research Council Dyspnea Scale; COPD, chronic obstructive pulmonary disease

Cigarette smoking

- Cigarette smoking itself decreases cough reflex sensitivity
- Capsaicin sensitivity recovers in 2 weeks after smoking cessation
- Cascade of inflammatory cell recruitment, especially of neutrophils, activation, and mediator release
 - Apoptosis and necrosis of epithelial cells
 - Mucus secretion

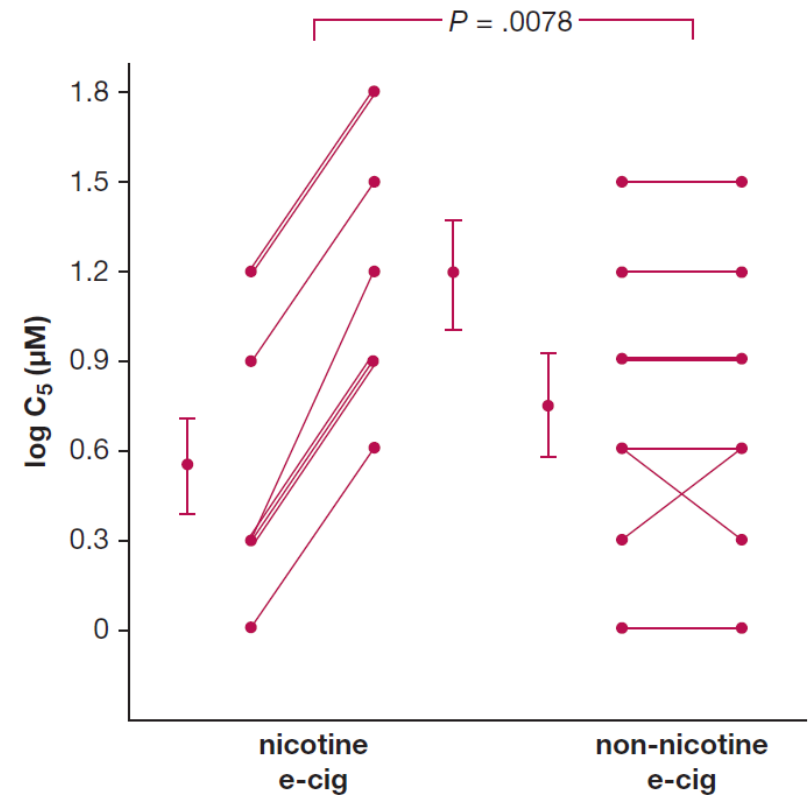
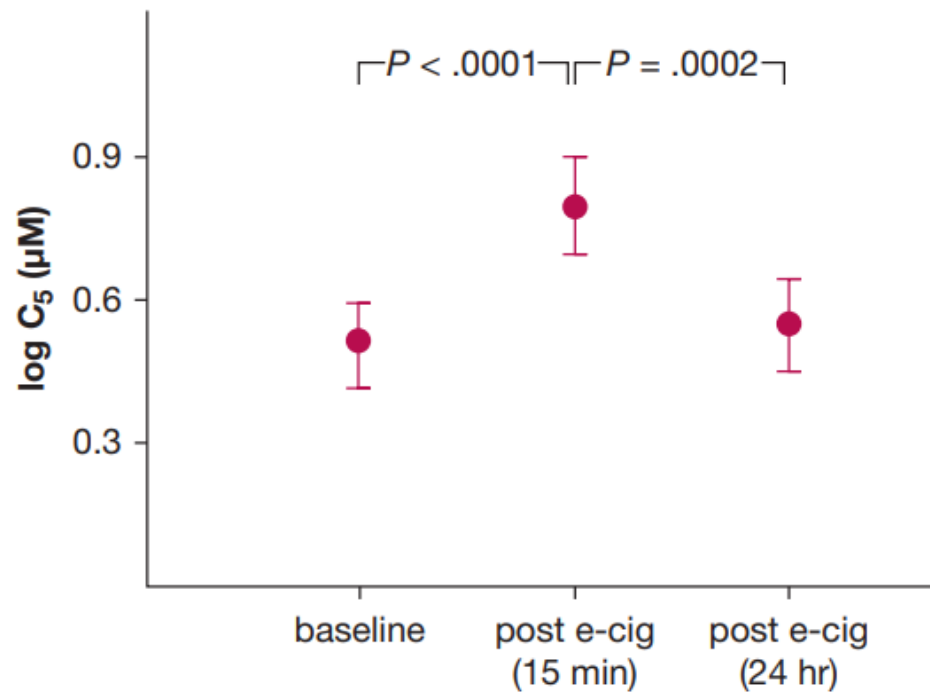


Cigarette smoking

- Secondhand or environmental smoking
 - Air-diluted sidestream smoke + exhaled mainstream smoke
 - Generated at lower temperature (400 °C vs. 900 °C)
 - Median particle size is smaller
 - Associated with various respiratory symptoms and morbidities
 - Nasal irritation
 - Middle ear disease
 - Cough, phlegm, wheezing
 - Persistent effect on lung function in childhood exposure

E-cigarette and Cough

- Single use of E-cigarette decreases cough reflex sensitivity
- Nicotine
 - Rapid-onset cough inducing effect in periphery
 - Delayed cough reducing effect in central



E-cigarette and cough

- E-cigarette additionally contains solvent (propylene glycol) and flavorings (diacetyl, diketone)
 - Cytotoxicity and proinflammatory effect
 - Increased bronchitis symptoms
 - Associated with asthma risk
 - Bronchiolitis obliterans, acute lung injury, and lipoid pneumonia are reported

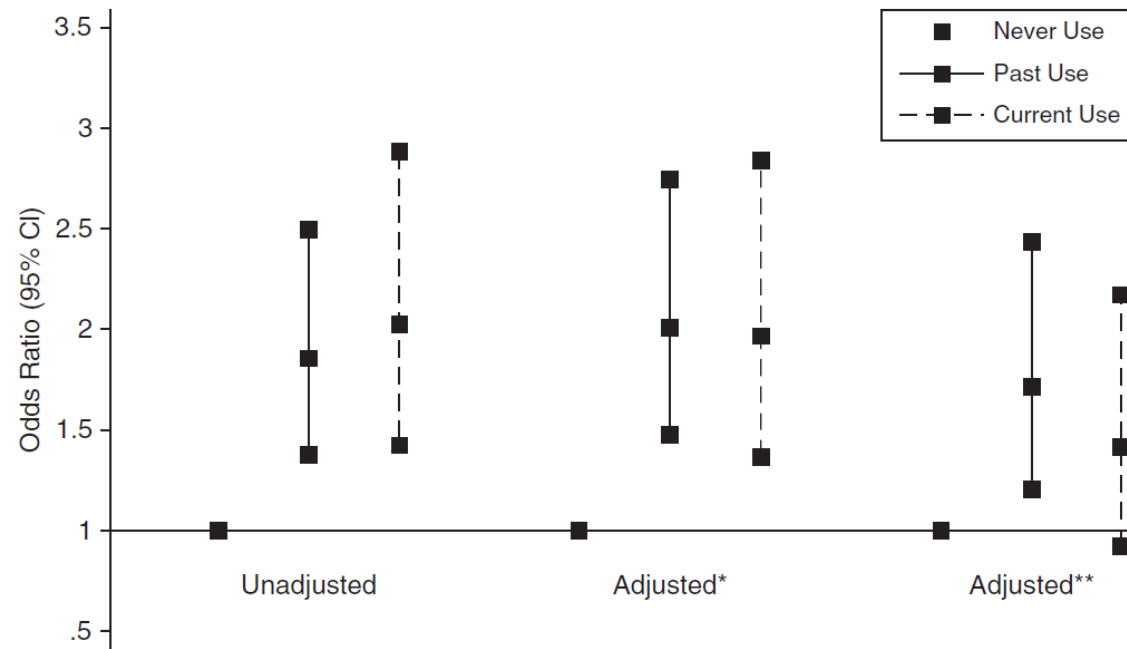


Figure 1. Association of current and past electronic cigarette use with bronchitis, adjusted for sociodemographic characteristics, smoking history, and secondhand tobacco smoke exposure (n = 1,922). *Adjusted for sex, ethnicity, parental education, and community. **Adjusted for sex, ethnicity, parental education, community, secondhand smoke, and lifetime number of cigarettes smoked. CI = confidence interval.

Take Home Message

- Almost every respiratory disease has an occupational equivalent
 - Rhinitis, asthma, eosinophilic bronchitis, COPD, HP, ILD, lung cancer, etc.
- Diagnosis begins with suspicion and history taking
 - However, confirmation of diagnosis often requires more than history
- Exposure intervention may improve prognosis
 - Elimination > Substitution >> Respiratory protective equipment
- Non-occupational environmental causes