2016년도 대한결핵및호흡기학회 제43차 Workshop

직업성 천식
occupational asthma (OA)

한양대학교병원 호흡기알레르기내과

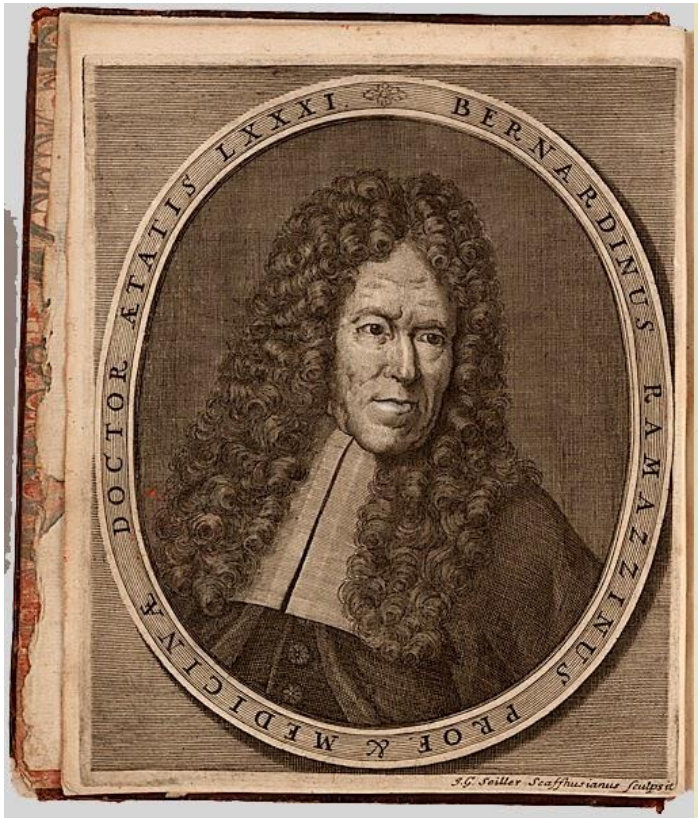
김 상 헌

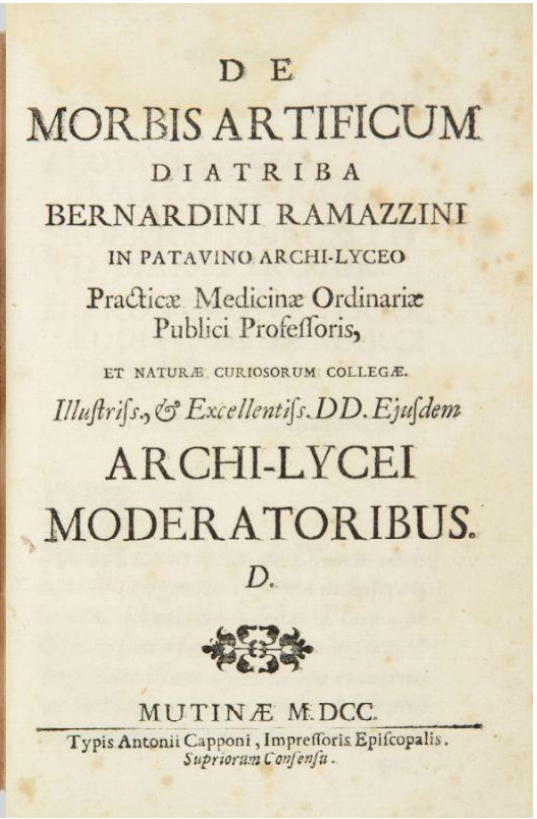
Overview: Occupational Asthma

1. Classification and Etiology
2. Epidemiology and Diagnosis
3. Management and Prevention

1700: Ramazzini discovers occupational asthma

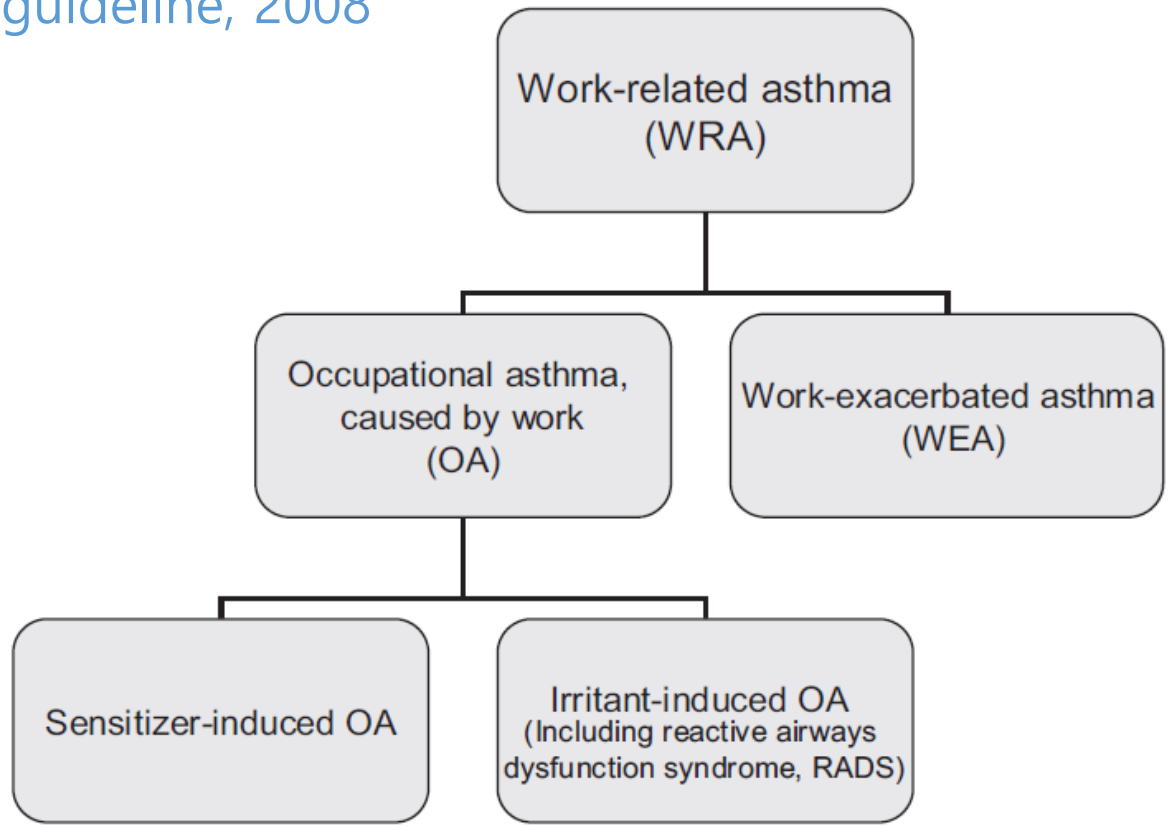
- De morbis artificum diatriba (diseases of workers)




DE
MORBIS ARTIFICUM
DIATRIBA
BERNARDINI RAMAZZINI
IN PATAVINO ARCHI-LYCEO
Practicæ Medicinæ Ordinariæ
Publici Professoris,
ET NATURÆ CURIOSORUM COLLEGÆ.
Illustriss., & Excellentiss. DD. Ejusdem
ARCHI-LYCEI
MODERATORIBUS.
D.
MUTINÆ M.DCC.
Typis Antonii Capponi, Impressoris Episcopalis.
Superiorum Consensu.

Asthma in the Workplace: Classification

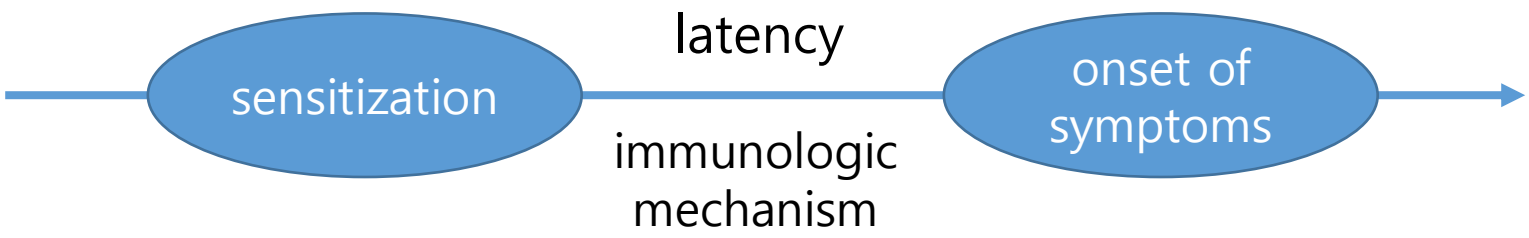
ACCP guideline, 2008



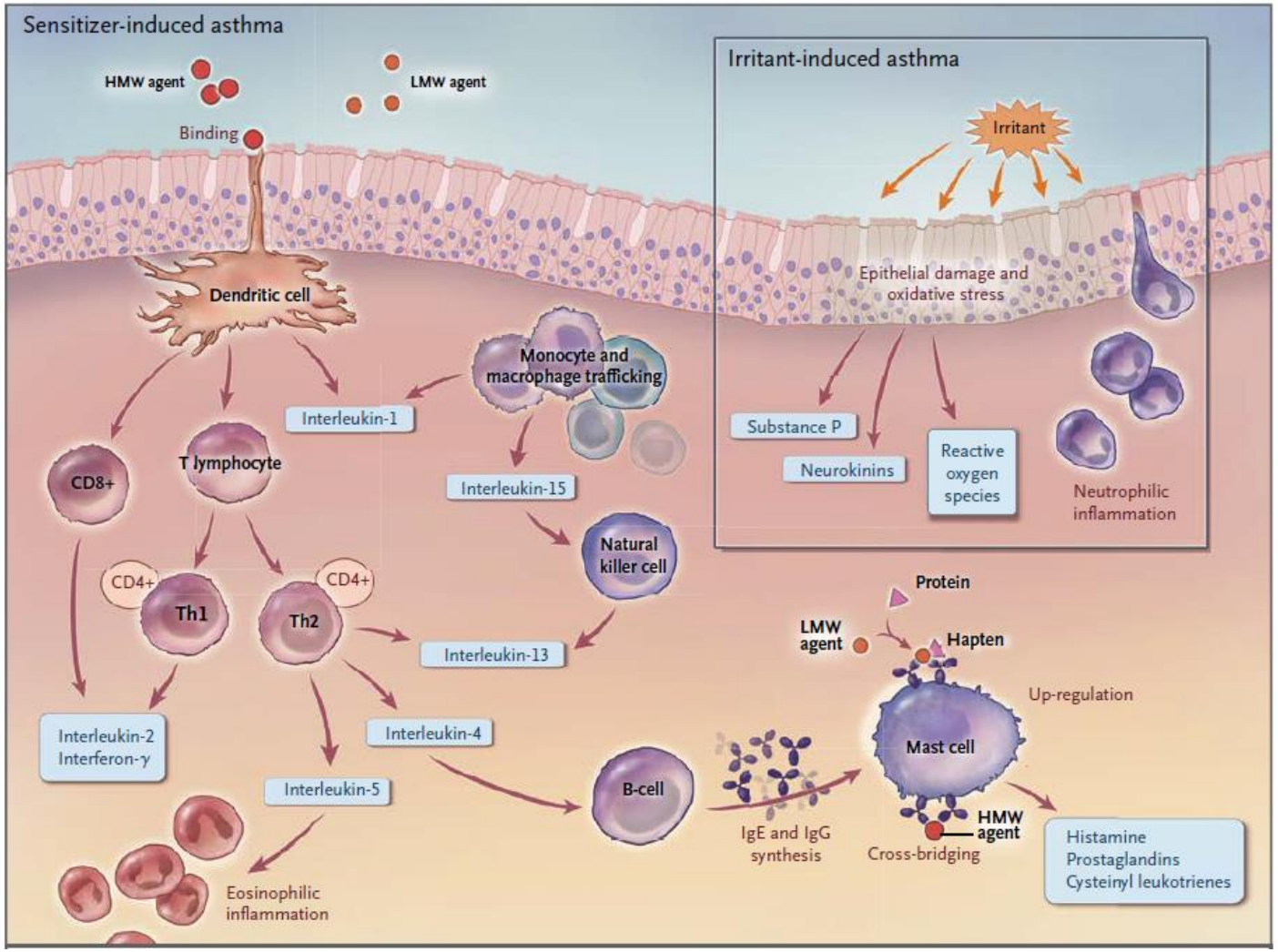
These groupings are not mutually exclusive; e.g. OA can be followed by WEA

Tarlo SM et al., Chest 2008; 134:1s-41s

Sensitizer-induced OA



Pathogenesis



Tarlo SM, Lemiere C. N Engl J Med 2014; 370:640-9

Sensitizer-Induced OA: High MW

Table 1. Common Causative Agents in Sensitizer-Induced Occupational Asthma.

Agent	Workers at Risk of Exposure
High-molecular-weight agents	
Animal allergens	Farmers, persons who work with laboratory animals, veterinarians
Plants	Greenhouse workers, farmers
Plant products (e.g., natural rubber latex)	Latex-glove makers and users, makers of other latex products
Cereals and grains	Farmers, grain workers, bakery workers
Other foods (e.g., milk powder and egg powder)	Food-production workers, cooks
Fungi	Office workers, laboratory workers
Enzymes	Laboratory workers, pharmaceutical workers, bakery workers
Insects	Farmers, greenhouse workers
Fish and crustaceans	Workers handling herring or snow crabs
Vegetable gums (e.g., guar and acacia)	Printers, including carpet makers

Tarlo SM, Lemiere C. N Engl J Med 2014; 370:640-9

Sensitizer-Induced OA: Low MW

Table 1. Common Causative Agents in Sensitizer-Induced Occupational Asthma.

Low-molecular-weight agents	
Diisocyanates (e.g., toluene diisocyanate, hexamethylene diisocyanate, and methylene diphenyl diisocyanate)	Makers of rigid or flexible polyurethane foam, installers of polyurethane foam insulation, urethane spray painters, those who work with urethane adhesives or urethane molds in foundries
Acid anhydrides (e.g., phthalic anhydride, maleic anhydride, and trimellitic anhydride)	Makers of epoxy resins for plastics
Acrylic monomers	Chemical-industry workers, dental workers, aestheticians applying artificial nails
Wood dusts (e.g., from red cedar and exotic woods)*	Carpenters, sawmill workers, forestry workers
Complex platinum salts	Refinery workers, jewelry workers
Other metal salts (e.g., nickel chromium)	Metal-plating workers, welders of stainless steel
Biocides (e.g., glutaraldehyde and chlorhexidine)	Health care workers
Phenol-formaldehyde resin	Makers of wood products, foundry workers
Persulfates and henna	Hairdressers
Drugs (e.g., antibiotics)	Pharmaceutical workers, pharmacists
Aliphatic amines (e.g., ethylenediamines and ethanolamines)	Lacquer handlers, soldering workers, spray painters, professional cleaners

Tarlo SM, Lemiere C. N Engl J Med 2014; 370:640-9

High MW vs. Low MW

TABLE 59-3 Main Differences between High- and Low-Molecular-Weight Agents Causing Occupational Asthma

Feature	High-Molecular-Weight Agents	Low-Molecular-Weight Agents
Nature	(Glyco)proteins derived from plants and animals	Highly reactive chemicals, metals, and wood dusts
Immunologic mechanisms	IgE-mediated	Uncertain; specific IgE for some agents (e.g., platinum salts, reactive dyes, acid anhydrides)
Type of airway inflammation	Eosinophils	Eosinophils and sometimes neutrophils
Type of asthmatic reactions	Immediate and dual	Often isolated late and atypical
Associated disorders		
Rhinoconjunctivitis	Common (~90%)	Less common (~50%)
Contact dermatitis	Rare, but protein contact dermatitis may occur (e.g., flour, seafood)	May occur (e.g., epoxy resins, acrylates, metals)
Urticaria and, anaphylaxis	Frequent with some agents (e.g., latex)	Rare

IgE, Immunoglobulin E.

Occupational Allergy and Asthma, Middleton's Allergy Principles and Practice 8th Ed

Reactive Airway Dysfunction Syndrome (RADS)

8 factors	description
History	absence of preceding respiratory complaints
occurrence	after a single specific exposure incident or accident.
exposure	high concentrations of gas, smoke, fume or vapor
onset & duration	symptoms occurred within 24 hrs after exposure and persisted for >3 mos
symptoms	asthma symptoms with cough, wheezing and dyspnea predominating
lung function	airflow obstruction
AHR	positive methacholine challenge testing was positive
Exclusion	other types of pulmonary diseases were ruled out

Brooks SM et al., Chest 1985; 88:376-84.

RADS vs. Irritant Induced Asthma

Table 2. Features of Irritant-Induced Occupational Asthma.

Criteria for RADS*	Modifications to Criteria for RADS†
History of new-onset asthma	History of new-onset asthma or recurrence of childhood asthma
Symptom onset related to a single high-level exposure (usually accidental)	Symptom onset related to one or more high-level exposures
Onset of symptoms ≤24 hr after exposure	Symptoms can begin >24 hr (in some reports, up to several days) after exposure
Exposure to a very high concentration of gas, fume, or spray with known irritant properties	List of exposures includes highly irritating dust (e.g., after the World Trade Center collapse)
Airway hyperresponsiveness or reversible airflow obstruction	
Symptoms persistent for ≥3 mo	
No previous lower respiratory tract symptoms	Previous airway disease associated with smoking or atopy may be difficult to rule out

Tarlo SM, Lemiere C. N Engl J Med 2014; 370:640-9

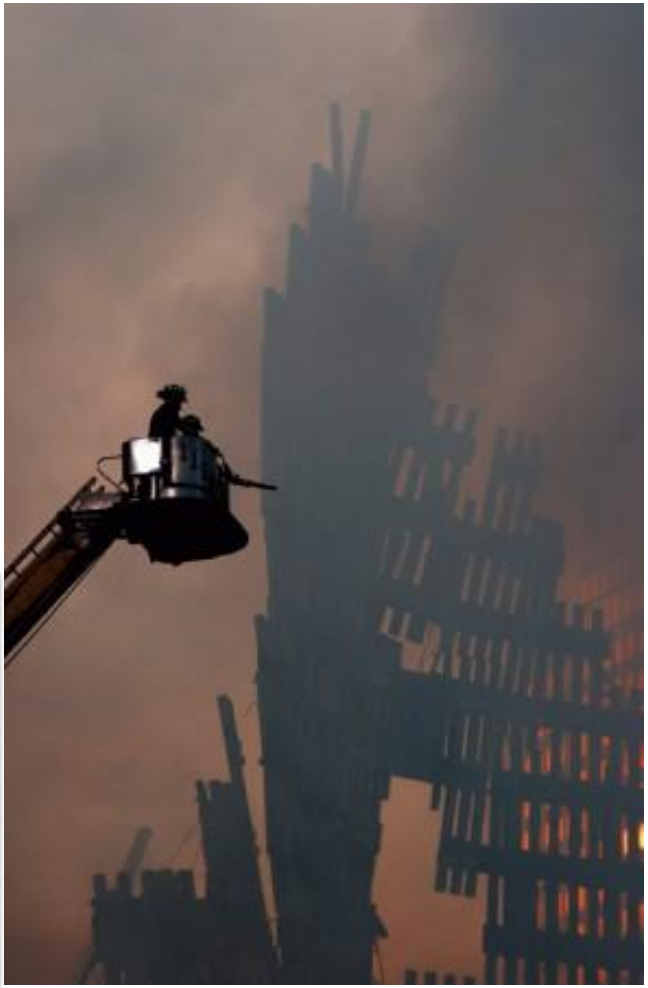
Exposure & Causes of RADS (acute-onset IIA)

Table 2 Examples of exposures causing acute-onset irritant-induced asthma

Exposure	Examples
Gases	Chlorine (e.g. released by mixing sodium hypochlorite with acids), chloramines (released by mixing sodium hypochlorite with ammonia) sulfur dioxide, nitrogen oxides, dimethyl sulfate
Acids	Acetic, hydrochloric, hydrofluoric, and hydrobromic acids
Alkali	Ammonia, calcium oxide (lime), hydrazine
Biocides	Formalin, ethylene oxide, fumigating agents, insecticides (sodium methyldithiocarbamate, dichlorvos)
Halogenated derivatives	Bromochlorodifluoromethane (fire extinguisher), trifluoromethane, chlorofluorocarbons (CFC) (thermal degradation products of freons), orthochlorobenzylidene malonitrile (tear gas), uranium hexafluoride, hydrogen and carbonyl fluoride
Solvents	Perchloroethylene
Fumes	Diesel exhaust, paint fumes, urea fumes, fire smoke, fumes of iodine and aluminum iodide, diethylaminoethanol (corrosion inhibitor)
Sprays	Various paints (not specified), floor sealant (aromatic hydrocarbons)
Dusts	World Trade Centre alkaline dust, calcium oxide (lime)
Potential sensitizers	Isocyanates, phthalic anhydride

EAACI position paper: irritant-induced asthma. Allergy 2014; 69:1141-53

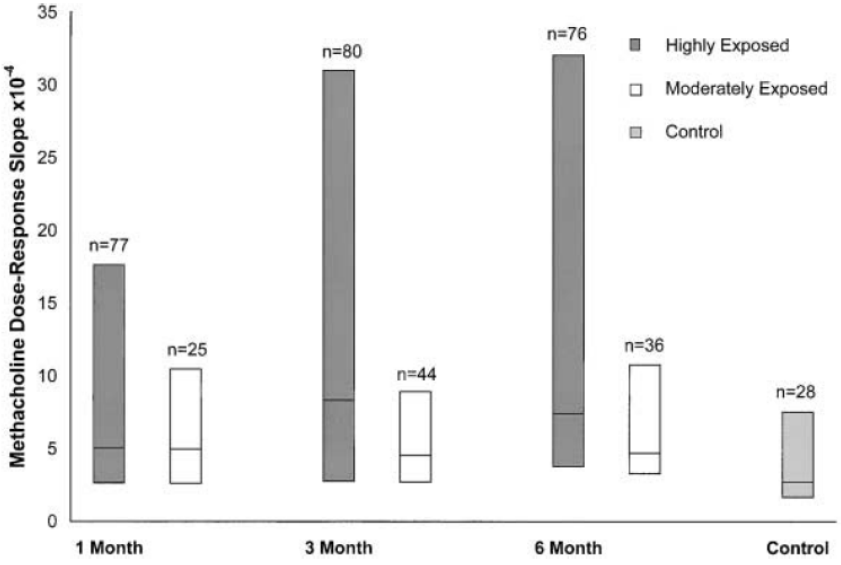
World Trade Center Attack on Sep 11, 2001

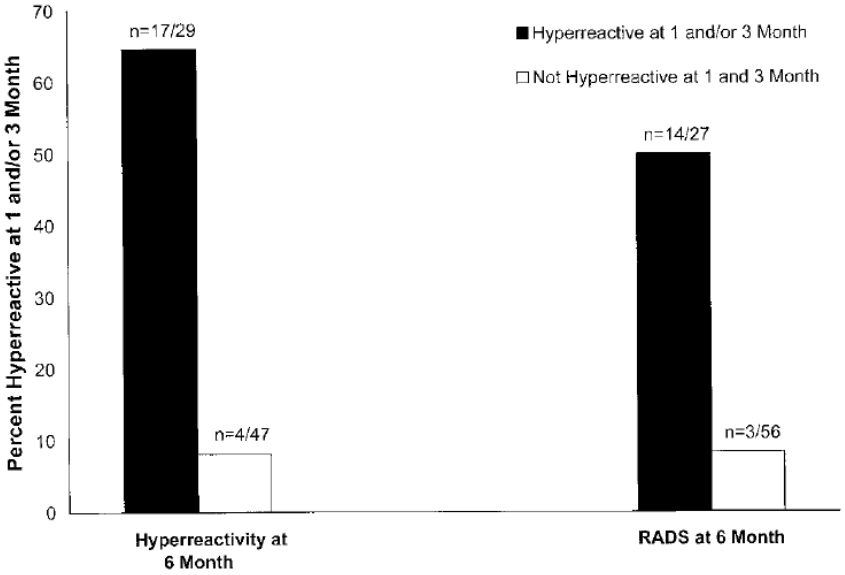


Persistent Hyperreactivity and Reactive Airway Dysfunction in Firefighters at the World Trade Center

Gisela I. Banauch, Dawn Alleyne, Raoul Sanchez, Kattia Olender, Hillel W. Cohen, Michael Weiden, Kerry J. Kelly, and David J. Prezant

- A representative sample of 179 rescue workers without current smoking or prior respiratory disease
- AHR shortly post-collapse predicted RADS

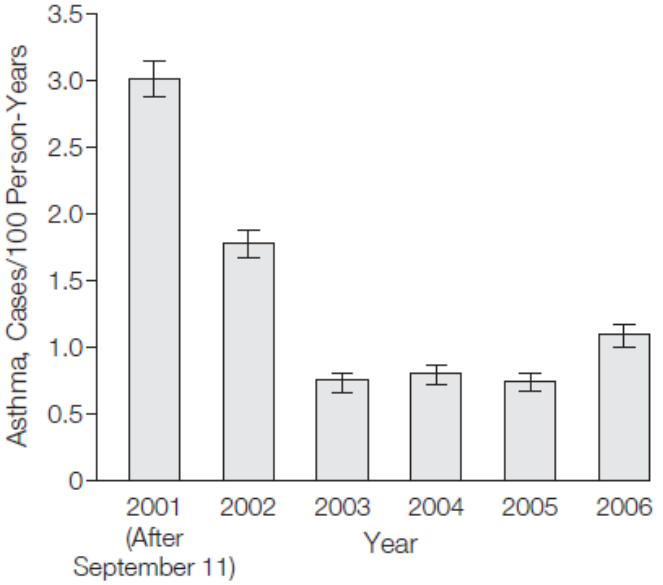




Banauch GI et al. Am J Respir Crit Care Med 2003; 168:54-62

Asthma 5-6 years after WTC dust exposure

Figure 2. Asthma Newly Diagnosed Since the September 11, 2001, World Trade Center Terrorist Attack, by Year of Diagnosis (n=2483)

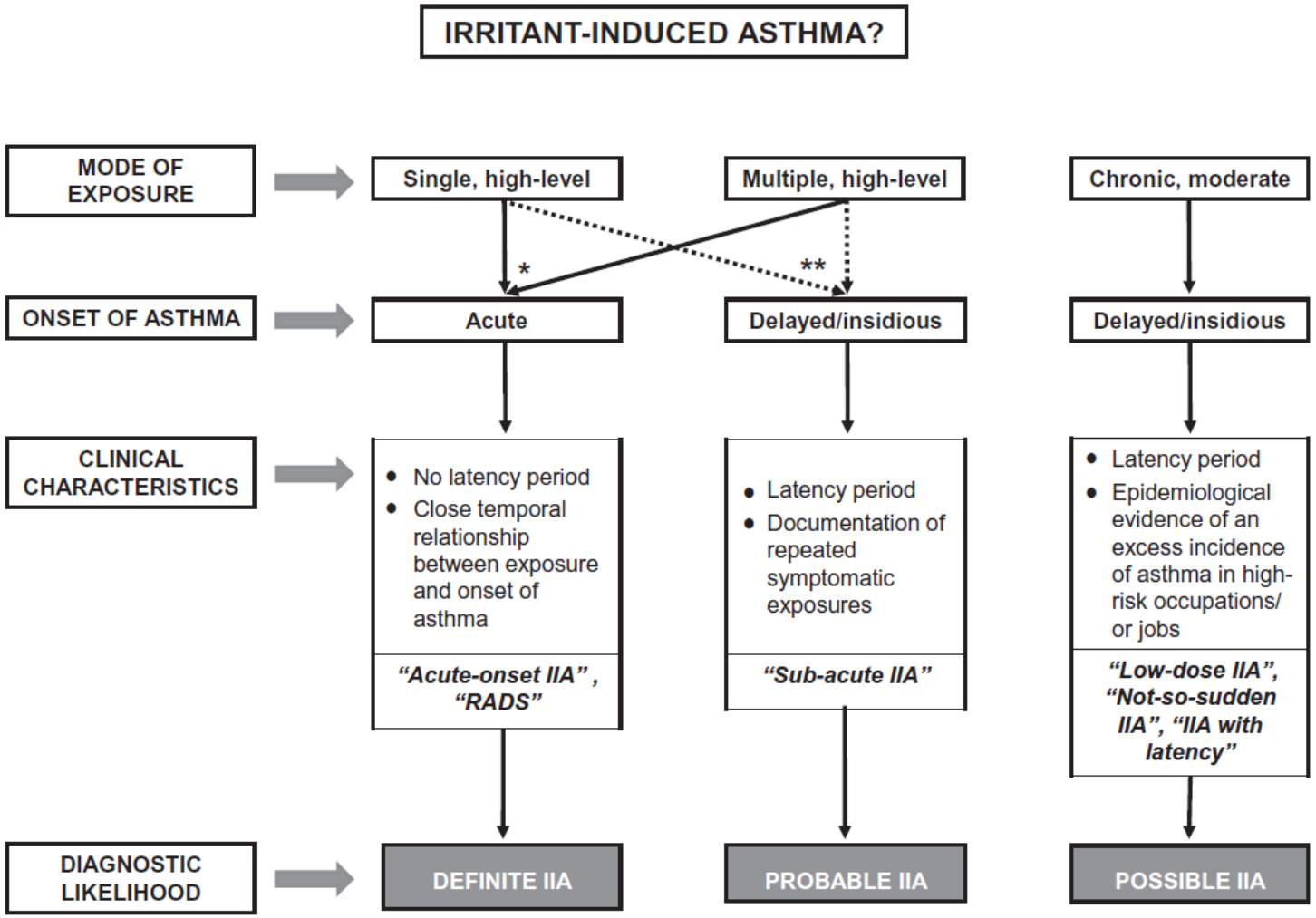


Error bars indicate 95% confidence intervals.

Risk Factor	Asthma, No. (%)[a]	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
	Rescue/Recovery Workers and Volunteers (n = 19 161)		
Total adults	2347 (12.2)		
Dust cloud exposure			
None	1208 (9.6)	1 [Ref]	1 [Ref]
Some	200 (12.3)	1.3 (1.1-1.5)	1.0 (0.8-1.2)
Intense	807 (19.1)	2.1 (1.9-2.3)	1.5 (1.4-1.7)

Brackbill RM et al. JAMA 2009; 302:502-16

IIA Phenotypes: EAACI Position Paper 2014



EAACI position paper: irritant-induced asthma. Allergy 2014; 69:1141-53

Causes of Possible IIA (chronic exposure)

Table 6 Examples of work exposures involved in possible irritant-induced asthma

High-risk occupation	Irritants	Irritants with a sensitizing potential
Cleaners	Bleach, ammonia, cleaning/degreasing sprays	Disinfectants (glutaraldehyde, QACs, chloramine-T, isothiazolinone), ethanolamines, enzymes, surfactants
Aluminum smelting	Fluorides, SO_2	Aluminum
Swine and dairy production	Aerosols from endotoxins and organic dusts, manure gases	QACs, animal allergens
Dark-room environment	SO_2, acetic acid	Glutaraldehyde, formaldehyde
Sulfurization	SO_2	None identified
Welding	Nitrogen oxides, fluorides, ozone	Chromium, nickel
Pesticides	Organophosphates, methylcarbamates, ...	Pyrethroids, phytophagous and predatory mites
Wood industry	Wood dust	Wood dust (e.g. plicatic acid)

EAACI position paper: irritant-induced asthma. Allergy 2014; 69:1141-53

Exposure to substances in the workplace and new-onset asthma

- Longitudinal cohort study
- 6,837 participants from 13 EU countries, the European Community Respiratory Health Survey (ECRHS), 1990–95

	Group total	Cases of asthma (%)	Relative risk*	95% CI	Population attributable risk	95% CI
Participant has had asthma attack or used asthma medication in past 12 months						
Occupation						
Reference group	4143	74 (1·8%)	1	n/a	n/a	n/a
High-risk occupations	1181	37 (3·1%)	1·69	(1·14–2·52)	14%	(2–24)
Job-exposure matrix						
Not exposed	5433	93 (1·7%)	1	n/a	n/a	n/a
Exposed	1355	40 (3·0%)	1·58	(1·09–2·29)	11%	(1–20)
Participant has had asthma attack or used asthma medication in the past 12 months and has had bronchial hyper-reactivity†						
Occupation						
Reference group	2433	19 (0·8%)	1	n/a	n/a	n/a
High-risk occupations	703	14 (2·0%)	2·55	(1·27–5·10)	26%	(2–44)
Job-exposure matrix						
Not exposed	3173	22 (0·7%)	1	n/a	n/a	n/a
Exposed	821	16 (2·0%)	2·40	(1·25–4·60)	23%	(1–40)

High-risk occupations=baking, plastics or rubber industries, printing, chemical processing, spray printing and other painting, nursing, hairdressing, electrical processing, welding, metal works, agriculture and forestry, cleaning and caretaking. Reference group=professional, clerical, and administrative jobs. Participants included in neither the reference or high-risk group were excluded. *Adjusted for age, sex, smoking status, and centre. †Data for bronchial hyper-reactivity and asthma available for 4438 participants, of whom 4001 are included in the analysis. Also excluded were 437 participants who had positive bronchial hyper-reactivity but no symptoms or vice versa.

Table 2: **Incidence of asthma and occupation**

Kogevinas M et al. Lancet 2007; 370:336-41

OA: population-attributable fraction (PAR)

- Meta-analysis (1999-2007)

Table 5: Synthesis of previously and currently reviewed studies regarding population attributable fraction (PAR) for occupational exposures and asthma.

Type of study	Studies Included	Ref	Range	Mean	Median
Current review					
Longitudinal	6	19–24	8.6%–44%	19.3%	16.3%
Case-control	3	26–29	9.5%–21.4%	14.8%	13.5%
Cross-sectional	7	31–37	7.0%–31.3%	16.1%	13.6%
Current and earlier review					
Longitudinal	6	19–24	8.6%–44.0%	19.3%	16.3%
Case-control	6	26–29, 41–43	9.5%–36.0%	20.7%	12.2%
Cross-sectional	14	31–37, 44–51	7%–51%	21.2%	17.6%
All	26	See above	7%–51%	20.7%	17.6%
All, adult-onset asthma only	17	19–24, 26, 28–31, 34–36, 42, 43, 45	8.6%–44.0%	18.8.5%	16.9%

Toren K et al. BMC Pulm Med 2009; 9:7

Inhalation event and new-onset asthma

- Longitudinal cohort study
- 6,837 participants from 13 EU countries, the European Community Respiratory Health Survey (1990–95)

	Cases of asthma (%)	Relative risk* (95% CI)
Participant has had asthma attack or used asthma medication in past 12 months		
No inhalation event	114/5977 (1·9%)	1 (n/a)
Inhalation event	10/323 (3·1%)	1·60 (0·82–3·14)
No inhalation event or asymptomatic inhalation event	118/6121 (1·9%)	1 (n/a)
Symptomatic inhalation event	4/136 (2·9%)	1·56 (0·58–4·19)
Participant has had asthma attack or used asthma medication in past 12 months and has bronchial hyper-reactivity		
No inhalation event	33/3600 (0·9%)	1 (n/a)
Inhalation event	3/201 (1·5%)	1·31 (0·38–4·53)
No inhalation event or asymptomatic inhalation event	33/3692 (0·9%)	1 (n/a)
Symptomatic inhalation event	3/78 (3·8%)	3·33 (1·00–11·13)

*Adjusted for age, sex, smoking status, occupational exposure (job-exposure matrix), and centre.

Table 4: **New-onset asthma and inhalation events**

Kogevinas M et al. Lancet 2007; 370:336-41

RADS or IIA among OA

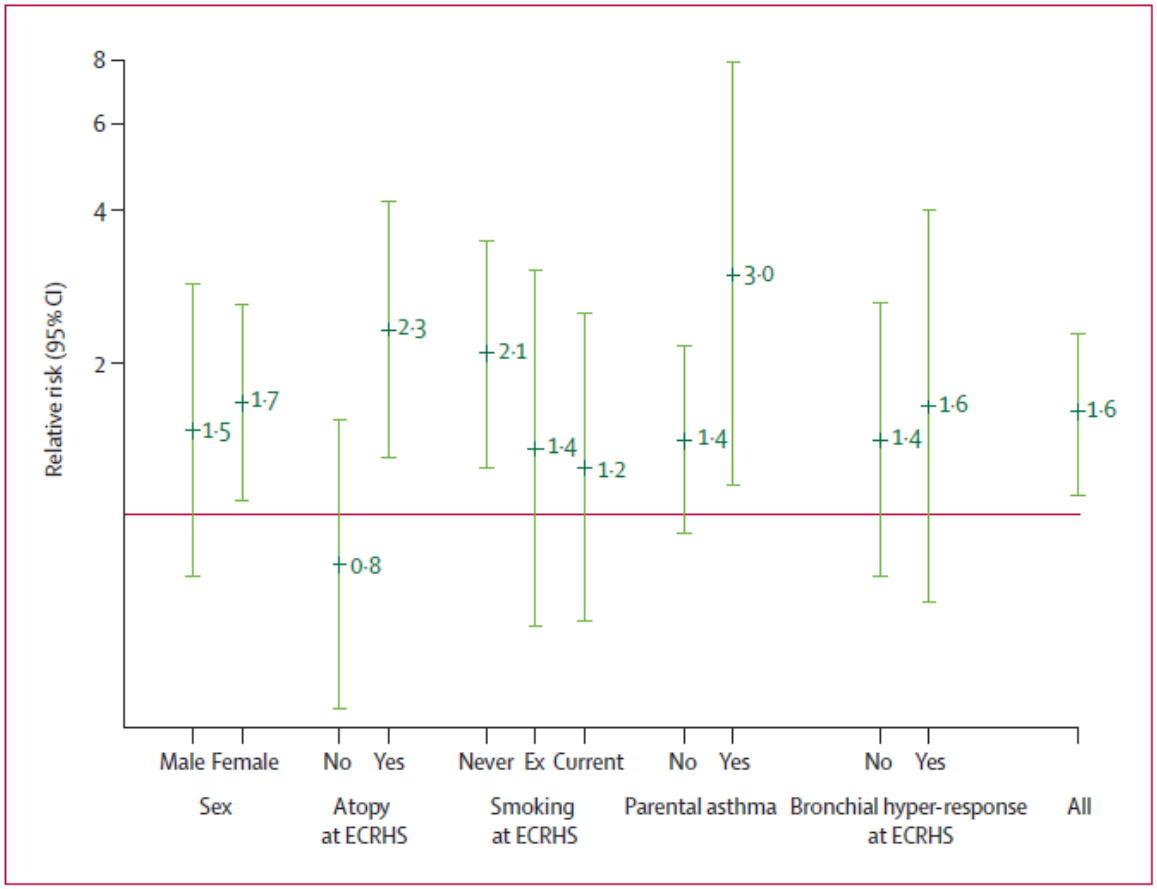
TABLE 6
Percentage of Work-related Asthma Attributed to RADS or Irritant Asthma, from Surveillance in Four Countries

Reference	Country (State, Province, or Region)	Years	Surveillance Program (How Cases Identified)[a]	% RADS or Irritant Asthma
Current analysis	United States (California, Massachusetts, Michigan, New Jersey)	1993–1995	SENSOR (MD, HDD, WCC)	14% RADS (123/891)
Reilly et al, 1994	United States (Michigan and New Jersey)	1988–1992	SENSOR (MD, HDD, WCC)	8% RADS[b] (42/498)
Rosenman et al, 1997	United States (Michigan)	1988–1994	SENSOR (MD, HDD, WCC)	10% RADS[b] (69/672)
Reinisch et al, 2001	United States (California)	1993–1996	Doctor's First Reports (MD)	9% RADS (27/290)[c]
Provencher et al, 1997	Canada (Quebec)	1992–1993	PROPULSE (MD)	5% RADS (14/301)[d]
Chatkin et al, 1999; Tarlo et al, 1995	Canada (Ontario)	1984–1988	Ontario Worker Compensation Board (WCC)	5% RADS (12/235)
Ross et al, 1995	United Kingdom	1994	SWORD (MD)	9% RADS/irritant asthma (93/1034)[e]
Gannon et al, 1993	United Kingdom (West Midlands Region)	1989–1991	SHIELD (MD)	18% irritant asthma
Hnizdo et al, 2001	South Africa	1996–1998	SORDSA (MD, PR, OHN)	13% irritant asthma (30/225)[f]

J Occup Environ Med, 2003

Risk Factors of OA

- Longitudinal cohort study
- 6,837 participants from 13 EU countries, the European Community Respiratory Health Survey (1990–95)



Kogevinas M et al. Lancet 2007; 370:336-41

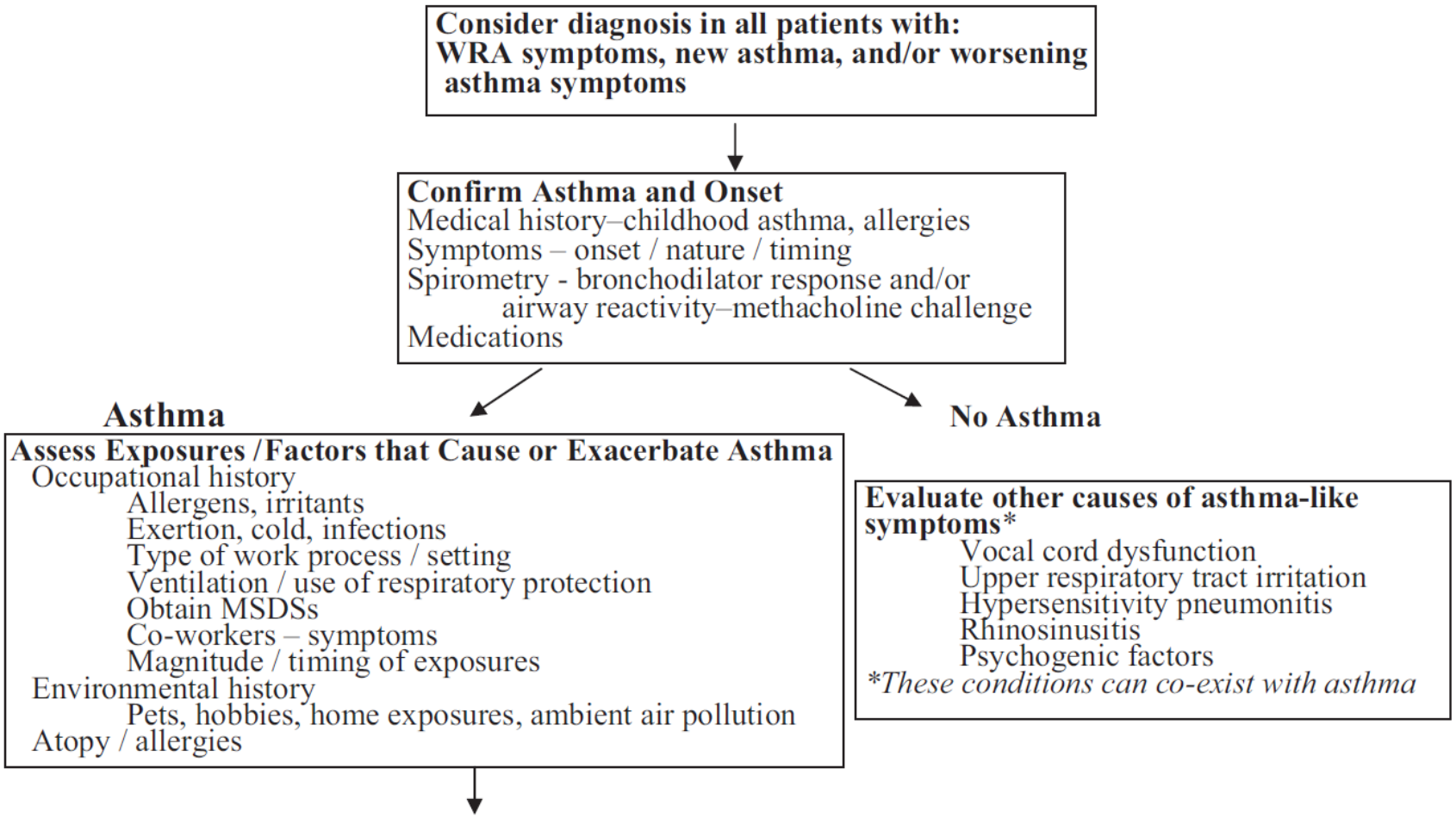
Genetic Associations of OA

- Genetic association with diisocyanate-induced asthma

Gene	Variation	RR; *P* value; OR (95% CI)
HLA-DQB1	*0503	RR = 9.8, $P < .04$
HLA-DQB1	*0501	RR = 0.14, $P < .03$
HLA-DQA1	*0104	$P = .008$
HLA-DRB1-DPB1	*15*05	$P = .001$
GSTM1	Null	1.89 (1.01–3.52)
NAT1	Slow acetylator	7.77 (1.18–51.6)
IL4RA, IL-13 R, CD14	I50V-R110Q-C159T	6.4 (1.57–26.12)
CTNNA3	rs1786929	$P = .015$

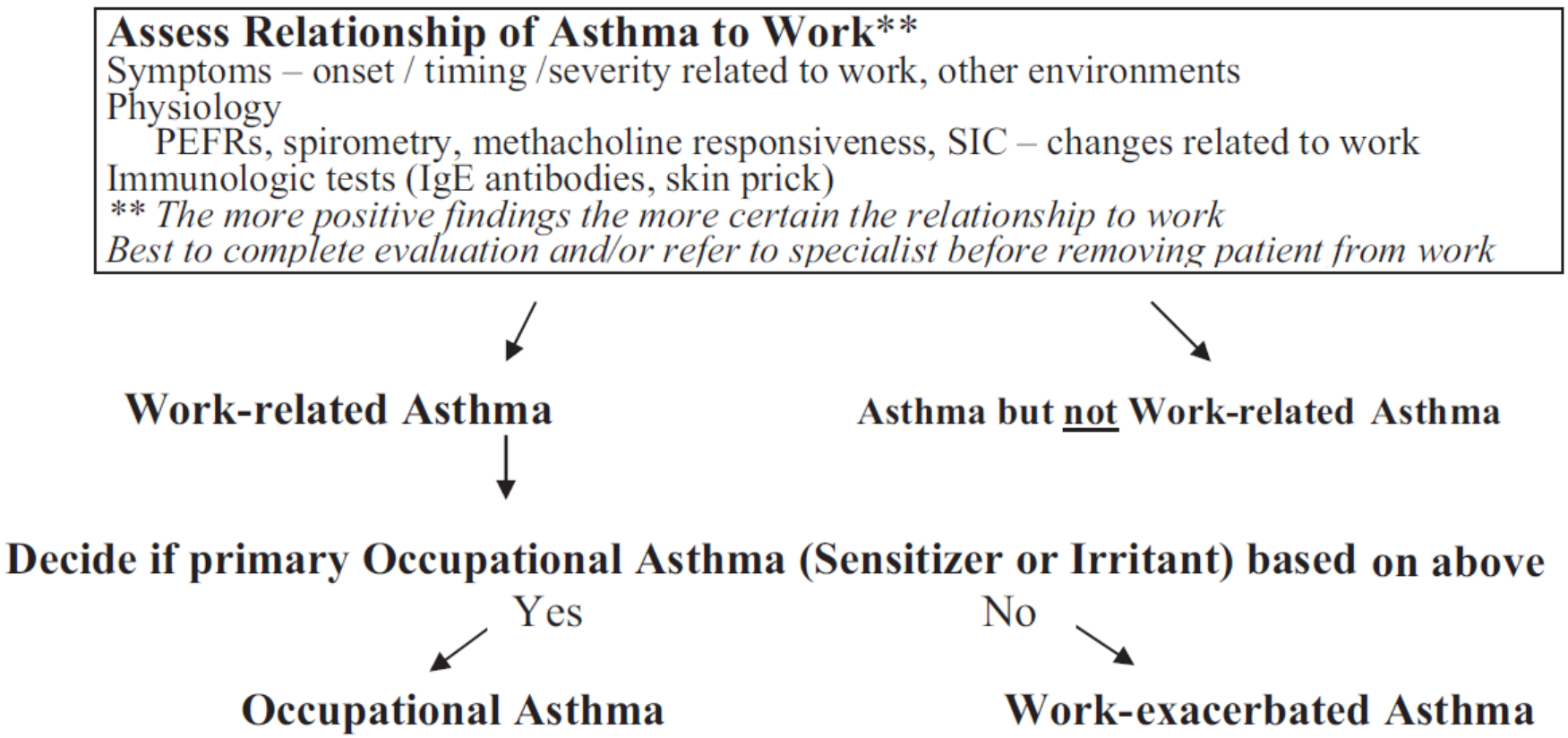
Yucesoy B et al. J Allergy (Cairo) 2011; 2011:346719

Diagnostic Flow of OA



Diagnosis and management of work-related asthma: ACCP Consensus Statement. Chest 2008; 134:1s-41s

Diagnostic Flow of OA



Diagnosis and management of work-related asthma: ACCP Consensus Statement. Chest 2008; 134:1s-41s

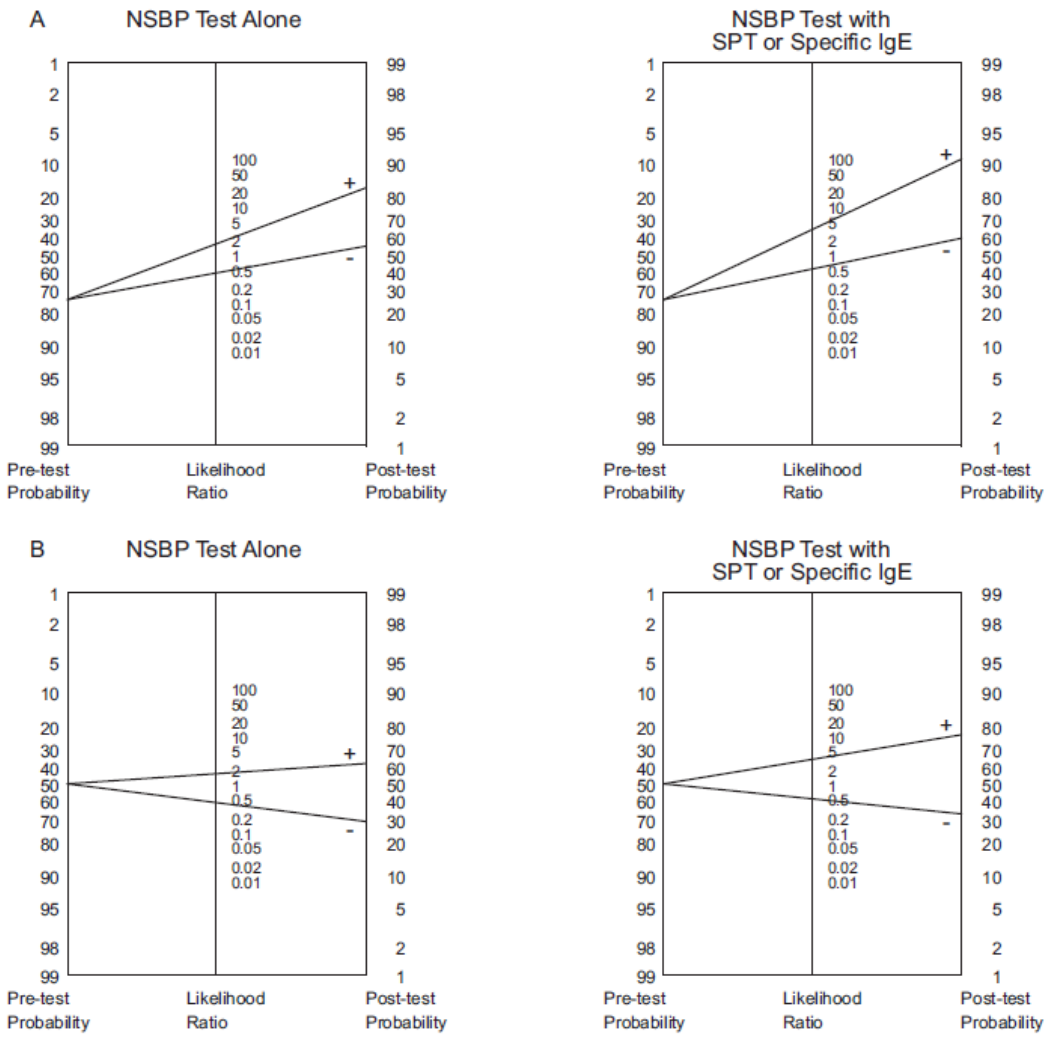
Diagnostic Tests and Validity

TABLE 59-5 Validity of Objective Diagnostic Tests

Test	Sensitivity (%)	Specificity (%)
Single assessment of nonspecific bronchial responsiveness*	84 (69-93)	48 (26-72)
Immunologic tests:		
High-molecular-weight agents (skin-prick tests)*	81 (70-88)	60 (42-75)
Low-molecular-weight agents (specific IgE antibodies)*	31 (23-41)	89 (85-92)
Serial measurements of PEF*	64 (43-80)	77 (66-85)
Serial measurements of PEF and nonspecific bronchial responsiveness†	84-92	61-67
Single assessment of sputum eosinophils‡		
≥1%	50	67
≥3%	22	91
Serial assessments of sputum eosinophils at and away from work§:		
Increase >1%	65 (45-81)	76 (57-88)
Increase >2%	52 (33-71)	80 (61-91)
Increase >6.4%	26 (13-46)	92 (75-98)
Serial assessment§	50 (24-76)	75 (51-90)

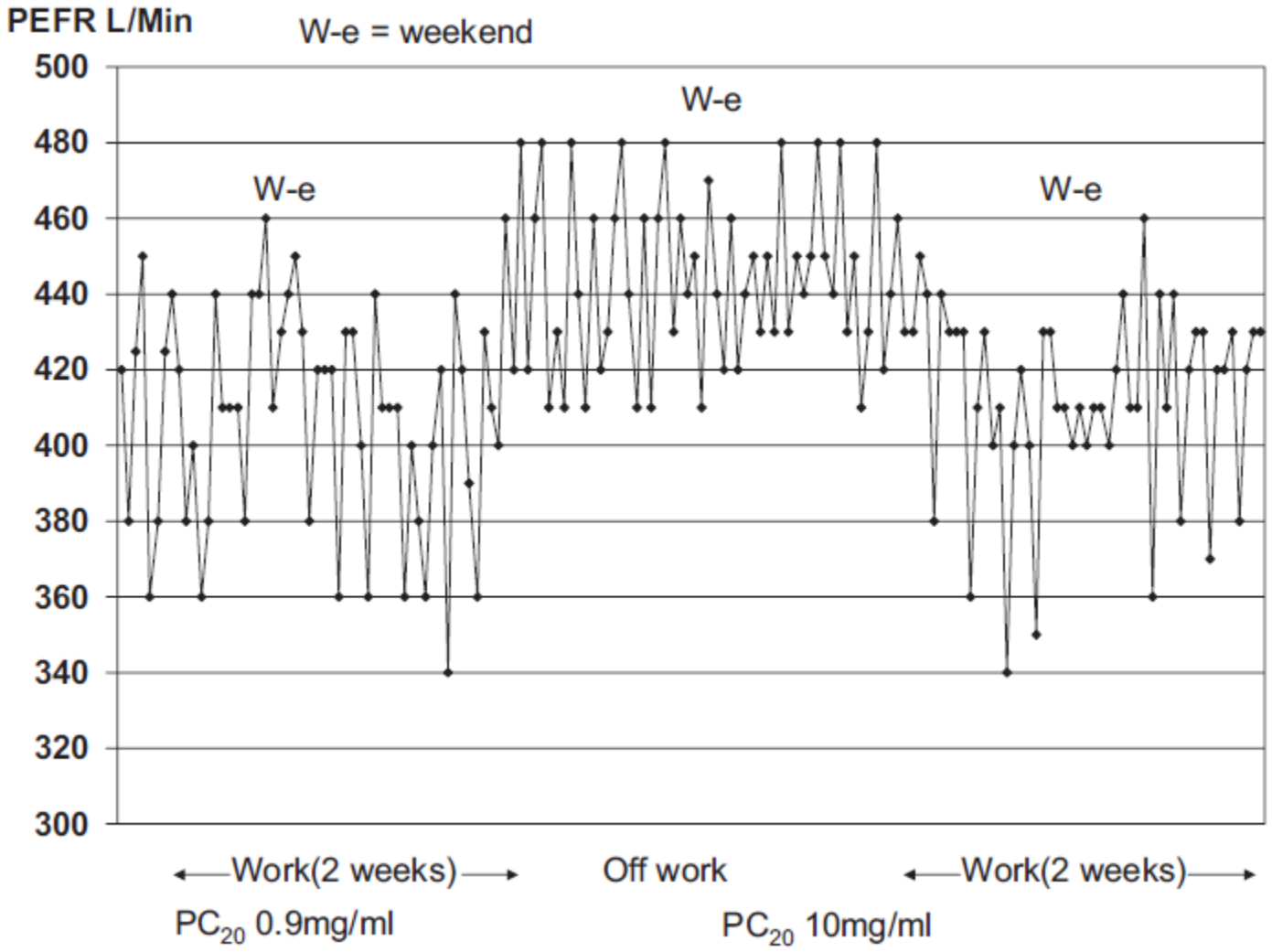
Occupational Allergy and Asthma, Middleton's Allergy Principles and Practice 8th Ed

NSBP + SPT (or specific IgE)

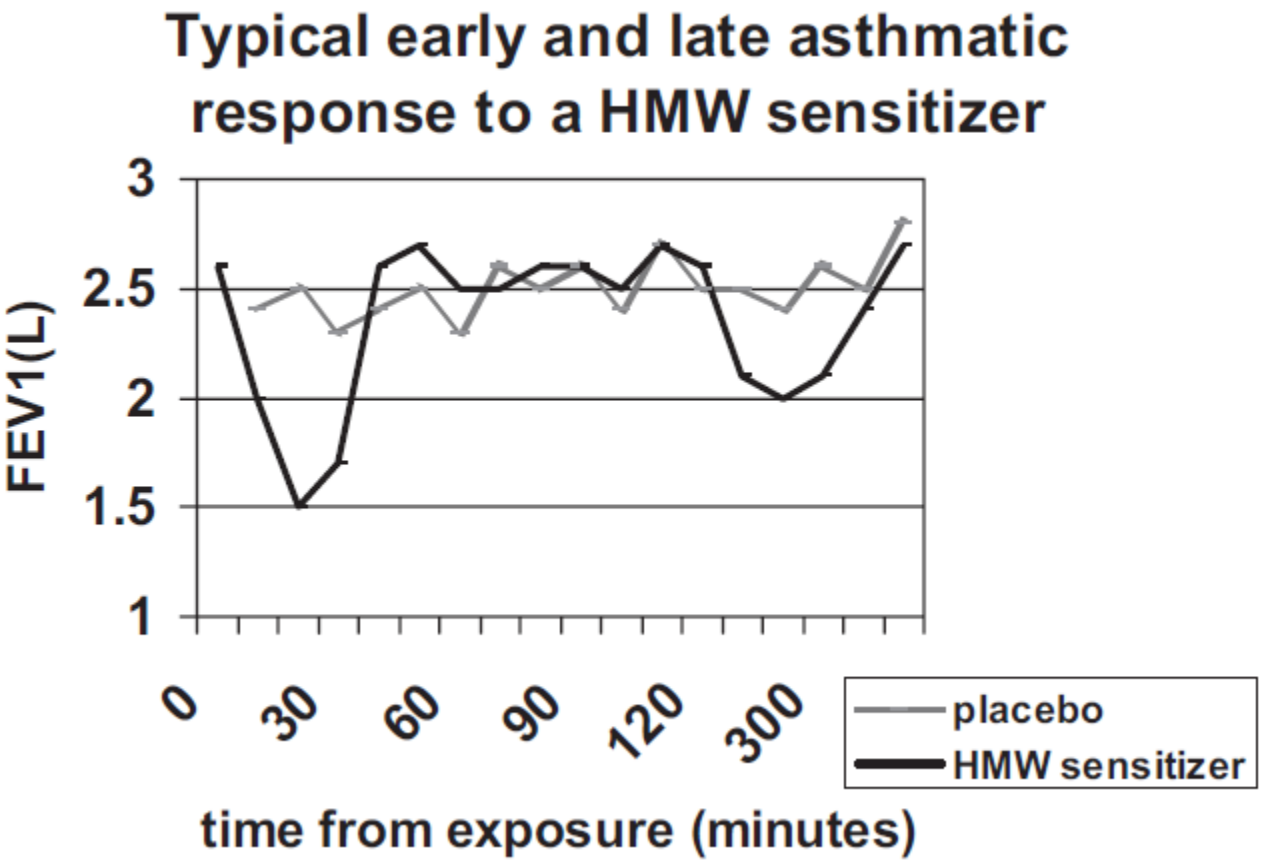


Beach J et al. Chest 2007; 131:569-78

Peak Flow and AHR from OA patient



Specific Inhalation Challenge (SIC)

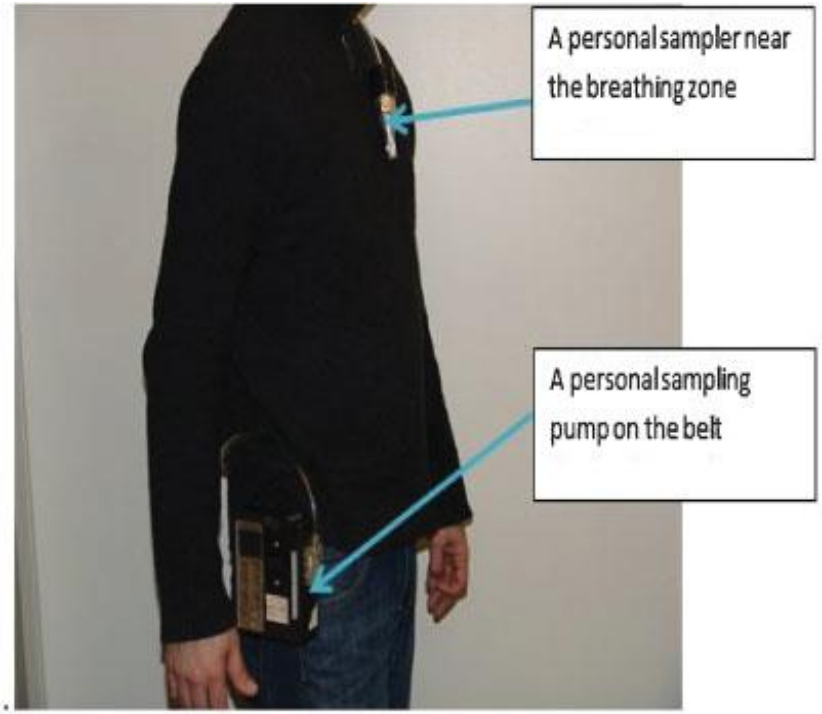


Diagnosis and management of work-related asthma: ACCP Consensus Statement. Chest 2008; 134:1s-41s

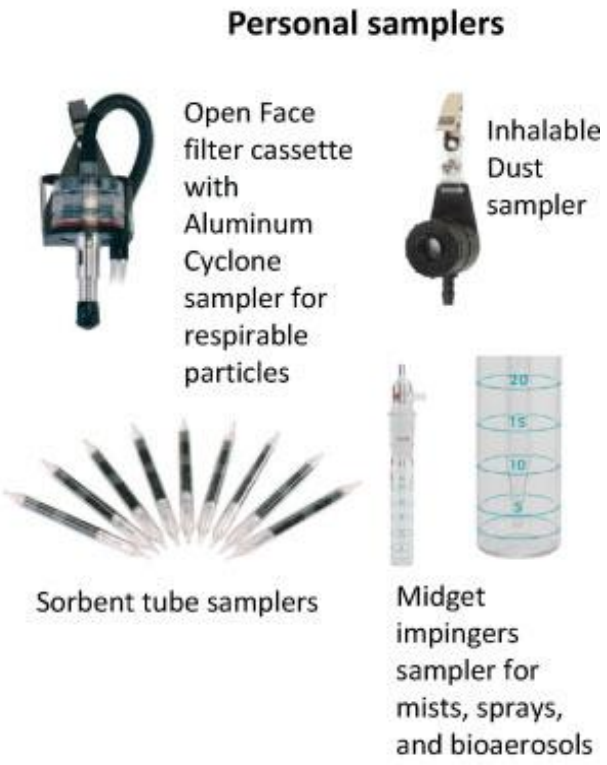
Primary Prevention of OA

- Avoid introducing new sensitizing agents
- Replace sensitizers, if safer alternatives are available
- Reduce exposure to work sensitizers
  - use of robotics or containment
  - ventilation and respirators
- Educate workers
- Monitor and control levels of exposure

Personal Sampling Device



NIOSH researcher demonstrating sampling devices
http://blogs.cdc.gov/niosh-science-blog/files/2013/03/sampling3.jpg
http://blogs.cdc.gov/niosh-science-blog/2013/03/26/silica-fibercementdust/



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Friedman-Jimenez G et al. Semin Respir Crit Care Med 2015; 36:388-407

Respiratory Protective Equipment (RPE)

"RPE does not provide complete protection"

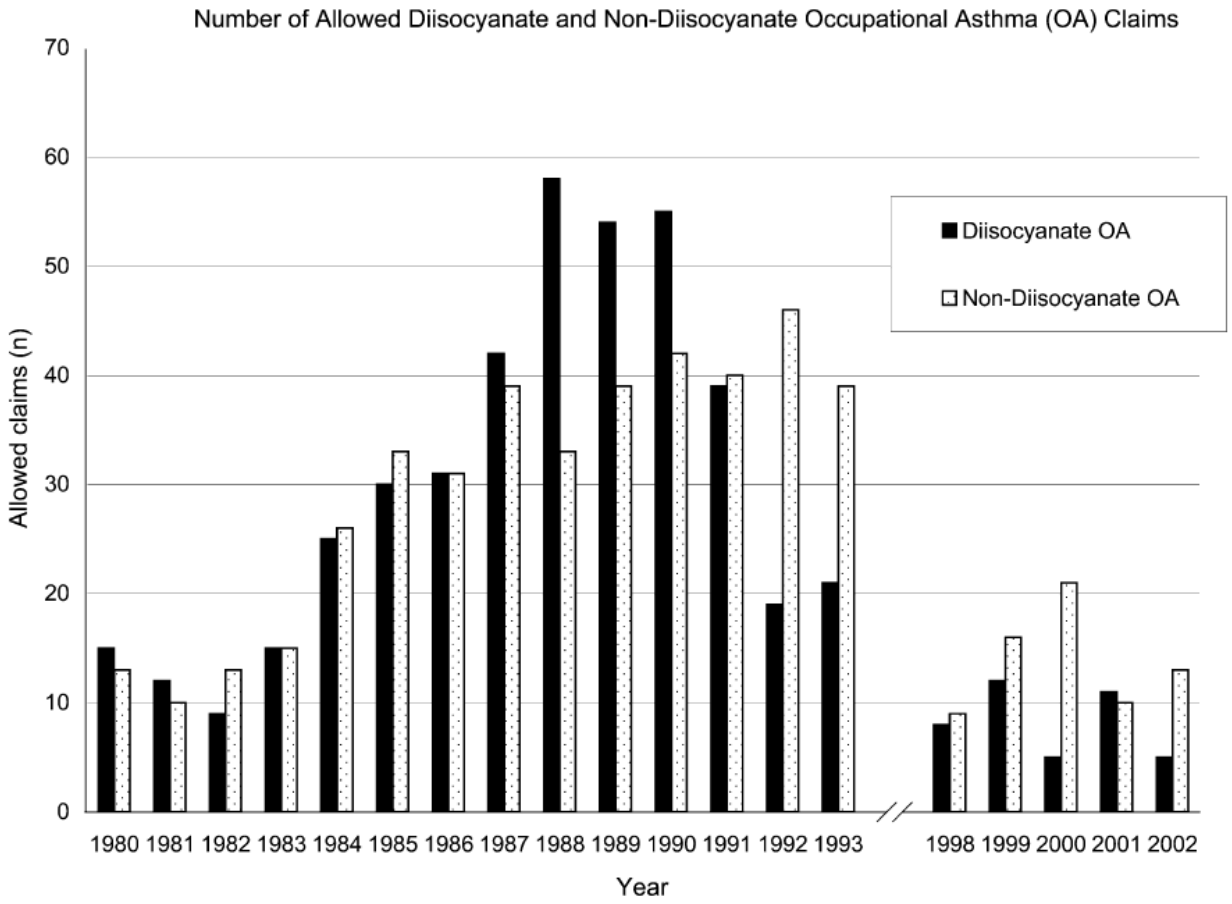
TABLE 4 Assessment of respiratory protective equipment (RPE)

First author [ref.]	Design	Agent	Type of RPE	Effects of RPE
Muller-Wening [54]	Laboratory challenge Non-RCT study n=26 Exposure: 1 h, not quantified	Organic farm allergens	RPE with P2 filter: "Dustmaster" (n=21), "Airstream helmet" (n=4), "Airlite" (n=1)	Suppression of symptoms in 11 out of 26, reduction in 15 out of 26, but 4 required inhaled bronchodilator Reduction of the increase in airway resistance
Laoprasert [55]	Laboratory challenge RCT study with placebo n=9 Exposure: 1 h, quantified	Latex	Laminar flow HEPA–filtered helmet	Reduction of symptom score Reduction of the decline in FEV_1
Slovak [56]	Workplace exposure Non-controlled study n=8 Exposure: 6 weeks, not-quantified	Laboratory animals	Powered helmet respirator with AS-23-3 filter	Worsening of symptoms in 2 out of 8 (score not available) Peak flow variation at work in 2 out of 8
Kongerud [57]	Workplace exposure RCT study n=19 workers with nonsevere disease Exposure: 2 weeks, not quantified	Aluminium pot room	AH60 Airsteam helmet	Reduction of symptom score in 10 out of 17 subjects (nonsignificant) Improvement in the mean peak flow values
Taivainen [58]	Workplace exposure Non-RCT study n=24 Exposure: 10 months, not quantified	Farming	Powered dust respirator helmet with P2 filter	No effect on respiratory symptoms with the exception of sputum, rhinitis symptoms, corticosteroid treatment, and number of sick leaves Increase in morning peak flow and reduced daily peak flow variability

ERS Task Force on the Management of Work-related Asthma. Eur Respir Rev 2012; 21:97-104.

Reduction of diisocyanate-induced asthma

- Annual number of allowed diisocyanate and non-diisocyanate occupational asthma claims, Ontario, Canada



Buyantseva LV et al. J Occup Environ Med 2011; 53:420-6.

Secondary Prevention (Early Detection)

- surveillance of workers at risk
  - preplacement and periodic respiratory questionnaires
  - spirometry and immunologic tests
- Educate workers about the risks of OA

Tertiary Prevention (Treatment)

- Remove workers from further exposure
- Control other triggers
- Use pharmacologic measures if necessary
- Consider immunotherapy
- Assist the patient with a workers' compensation claim
- Monitor the patient's asthma in future work locations to ensure safe placement

Summary: Occupational Asthma

- OA is a form of work-related asthma and divided into sensitizer-induced asthma and irritant-induced asthma (RADS).
- Since OA is relatively common, OA should be suspected and diagnosed with various methods.
- Primary, secondary and tertiary prevention should be instituted for the management of OA.