



What is the role of acute and chronic exposure to irritants in the development of asthma?

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Outline

- Asthma and work
- Asthma after an acute exposure to irritants
- Asthma and chronic exposure to irritants

Asthma and work

Definitions

Asthma and work Definitions

- **Occupational asthma**
Asthma that is **caused** (specifically) by exposure to an agent present at work
- **Work-aggravated / work-exacerbated asthma**
Pre-existing asthma that is **aggravated** (non-specifically) by work (cold, exercise, irritants)

Work-aggravated asthma

- Exposures at work are frequently evoked as causes of exacerbations
 - Henneberger *et al.* *OEM* 2006, 63, 551-7
 - 598 adult asthmatics (HMO), telephone questionnaire
 - workplace exacerbation in **23%**
 - Berger *et al.* *JOEM* 2006, 48, 833-9
 - 301 working asthmatics (low-income minority, NY)
 - workplace exacerbation of respiratory symptoms reported by **51%** (current job) - 71% (ever)

Work-aggravated asthma

- Henneberger *et al.* The occupational contribution to severe exacerbation of asthma. *ERJ* 2010, 36, 743-50
- ECRHS-I & II
 - 966 working adults with current asthma
 - 74 (7.7%) at least 1 self-reported **severe** exacerbation in past year
 - If high exposure to dust, gas or fumes: RR **3.1**
→ PAR **14.7%** among workers with asthma

American Thoracic Society Documents

An Official American Thoracic Society Statement: Work-Exacerbated Asthma

Fred K. Henesberger, Carrie A. Redlich, David B. Calhoun, Philip Harber, Catherine Lewin, James Martin, Susan M. Taha, Olivier Vandenberg, and Ajell Touss, on behalf of the ATS Ad Hoc Committee on Work-Exacerbated Asthma

This official American Thoracic Society (ATS) Statement was approved by the ATS Board of Directors, March 2011

Am J Respir Crit Care Med. Vol 184, pp 368-378, 2011

- Work-exacerbated asthma (WEA)
- Median prevalence: **21.5%** among adults with asthma
- "WEA should be considered in any patient with asthma that is getting worse or who has work-related symptoms"
- "Management of WEA should focus on reducing work exposures and optimizing standard medical management, with a change in job only if these measures are not successful"

Occupational asthma Types

1. Occupational asthma caused by **immunological** sensitisation to a workplace agent (i.e. **allergy**)
2. Occupational asthma not caused by immunological sensitisation

Occupational asthma Types

1. Occupational asthma caused by **allergic** sensitisation
(occupational asthma "*stricto sensu*")
 - symptom-free latency period
 - "**occupational asthma with latency**"*
 - reaction to (extremely) low amounts
 - "minority" of exposed workers

* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI. (Eds) *Asthma in the workplace* (2nd Ed.) Marcel Dekker, 1999

Occupational asthma Types

2. Occupational asthma without immunological sensitisation
 - caused by irritants ("irritant-induced asthma")
 - single exposure (**RADS**)
 - multiple peaks
 - caused by organic dust and microbial contaminants (**asthma-like syndrome**)

Asthma and work

Epidemiology

How much asthma is work-related?

[Balmes J. (chair) *et al.*] American Thoracic Society Statement. Occupational contribution to the burden of airway disease.

Am J Respir Crit Care Med 2003, 167, 787-97

Literature-based estimation of **population attributable risk (PAR)** for asthma «due» to occupational exposures: median **15%**
(21 studies: 4% to 58%)

How much asthma is work-related?

- Karjalainen *et al.* AJRCCM 2001, 164, 565-8
 - 3 cohorts of all employed Finns (25 - 59 y) without pre-existing asthma in 1985, 1990, 1995
 - followed for **incident** asthma for 4 years
 - **49,575** incident cases of adult asthma in Finland
 - 1.65 (M) - 2.47 (F) / 1,000 / year
 - 2,464 cases of recognized occupational asthma

How much asthma is work-related?

- Karjalainen *et al.* AJRCCM 2001, 164, 565-8
 - **attributable fraction** of occupation for adult-onset asthma (controls = administrative workers):
 - **29 %** (men) - **17 %** (women)
 - not confounded by smoking
 - known sectors (agriculture, manufacture, services) and occupations (bakers, ...), but also less known jobs (cleaners, ...)
 - share of recognised cases of OA << 50 %

How much asthma is work-related?

Kogevinas M. *et al.* Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007, 370, 336-341

- ECRHS-I (1990-95), 28 centres, 13 countries, 20-44 y
 - ECRHS-II (1998-2003): follow-up of 6,837 subjects without asthma or respiratory symptoms
 - New-onset asthma (symptoms or medication): n=134
 - Occupational exposures (high-risk job; job-exposure matrix; inhalation accidents)
- PAR due to occupation: **10-25%** (250-300 cases/10⁶/y)

Astma severity and occupation

- Le Moual N. *et al.* Asthma severity and exposure to occupational asthrogens. *Am J Respir Crit Care Med* 2005, 172, 440-5
 - Retrospective study of tertiary referral centres (France): 148 asthmatics
 - 8 grade score of severity (frequency of attacks, persistence of symptoms, hospitalizations)
 - **Asthma more likely to be "severe" if exposure to known occupational asthrogens (HMW & LMW sensitizers; irritants)**

Irritant-induced asthma after acute exposure

RADS

("Reactive Airways Dysfunction Syndrome")

Case A

- previously healthy woman (50 y) exposed accidentally to "chlorine" fumes when opening a flask containing a few "bleach tablets" (**dichloroisocyanic acid**) + moisture



Case A

- previously healthy woman (50 y) exposed accidentally to "chlorine" fumes when opening a flask containing a few "bleach tablets" (**dichloroisocyanic acid**) + moisture
 - immediate cough, dyspnea, retrosternal pain
 - hospitalization: hypoxemia, normal chest x-ray
 - budgerigar later found dead
 - mild obstruction when discharged after 2 days
 - severe asthmatic symptoms, airway obstruction & hypoxemia after two weeks
 - persistent labile asthma and airway hyperresponsiveness (= **RADS**)

Case B

- Man, 32 y, never smoker
- No atopy, no previous respiratory disease
- Security agent: transport of bank notes



Case B

- 28.05.2004: accidental collision
 - automatic lock of all doors of van
 - + security cases triggered to release fumes



Case B

- 28.05.2004: accidental collision
 - automatic lock of all doors of van
 - + security cases triggered to release fumes
- Sustains mild traumatic injuries
 - + helps his two more severely injured colleagues to escape through a manhole in roof of cabin

Case B

In hospital:

- intubated + ventilated (24h)
- no x-ray changes
- discharged after 3 days

After discharge:

- cough persisting for 6 months
- "normal" pulmonary function, but decreased exercise capacity
- bronchial hyperreactivity = **RADS**

RADS

Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposure. *Chest*, 1985, 8, 376-84

= **de novo asthma caused by an acute inhalation injury**

RADS – criteria

1. Documented **absence of preceding** respiratory complaints
2. Onset of symptoms after a **single** specific exposure incident
3. Exposure to gas, smoke, fume or vapour present in very **high** concentration and with **irritant** properties
4. **Onset** of symptoms **within 24 h** after exposure
5. **Persistence** of symptoms for at least **3 months**
6. Symptoms simulate **asthma** (cough, wheezing, dyspnoea)
7. Pulmonary function tests may show airflow **obstruction**
8. Positive **methacholine/histamine** test
9. Other disease ruled out

RADS

- Many **case reports** or **case series** of RADS following a wide variety of inhaled agents
 - chlorine
 - inorganic gases & vapours (HCl, SO₂, NO₂, NH₃, H₂S, ...)
 - organic chemicals (isocyanates, acids, aldehydes, tear gas, pesticides, solvents, ...)
 - poorly defined mixtures (fire smoke, welding fumes, diesel exhaust, irritant aerosols, ...)

Alberts WM, de Pico GA. *Chest*, 1996, 109, 1618-28

RADS

- Inhalation accidents and RADS may occur
 - at **work**: industry, agriculture, services
 - specific risk (petrochemical industry, firefighters, maintenance workers, industrial cleaning, ...)
 - nonspecific risk
 - at **home**:
 - cleaning (e.g. bleach + acids or NH₃), DIY, ...
 - in the **community**:
 - transportation accidents
 - fires & explosions

RADS – epidemiology

- Jajosky *et al.* MMWR CDC SS, 1999, 48, 1-20
 - USA, SENSOR (CA, MA, MI, NJ), 1993-95
 - 1101 cases of work-related asthma
 - work-aggravated asthma: 210 (19.1%)
 - new-onset asthma: 891 (80.9%)
 - occupational asthma 768 (69.8%)
 - RADS: 123 (11.2%)

RADS – epidemiology

- Kopferschmitt-Kubler *et al.* ERJ, 2002, 19, 84-9
 - France, ONAP, 1997
 - 559 cases of occupational asthma
 - typical occupational asthma: 460 (82%)
 - "atypical asthma syndrome": 71 (13%)
 - RADS: 26 (5%)

RADS – epidemiology

- Ross & McDonald. AOH 1996, 40, 645-50
 - England, SWORD, 1990-93
 - follow-up of 734 reported inhalation accidents
 - 50/683 (9%) had asthma symptoms > 1 month
 - 34/47 of these were compatible with RADS
 - chest physicians: 27/214 accidents (13%)
 - occupational physicians: 7/406 accidents (2%)
 - various causes (including known sensitizers, such as isocyanates, glutaraldehyde)

RADS – criteria (3')

- Exposure to gas, smoke, fume or vapour present in **very high** concentration and with irritant properties
 - yes, in typical cases
 - inhalation injury requiring medical treatment (emergency room admission, infirmary, ...)
 - some cases do **not** appear to involve “very high” concentrations, nor clinically severe injury needing (immediate) medical attention

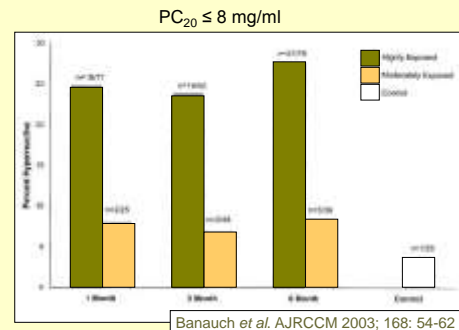
RADS and severity of initial injury

- Cohort studies do **not** indicate that RADS only occurs after a clinically severe inhalation injury *
 - Kern. ARRD 1991, 144, 1058-64
 - spill of **glacial acetic acid** in hospital
 - Cone *et al.* Chest 1994, 106, 500-8
 - derailment → metam sodium in river → MITC (CH₃NCS)
 - Banauch *et al.* AJRCCM 2003, 168, 54-62
 - NYFD after 9/11 WTC collapse
- * Nemery B. (Editorial). AJRCCM 2003, 168, 2-3

“WTC 9/11”

- Prezant *et al.* NEJM, 2002, 347, 806-15
 - 11,336 FDNY firefighters
 - 343 died - 10,116/10,993 evaluated
 - 1636 (16%) high exposure (present at WTC collapse)
 - 6958 (69%) moderate exposure (within first 2 days)
 - 1320 (13%) low exposure (3-7 days after collapse)

Bronchial hyperreactivity



RADS at WTC

- RADS = « bronchial hyperreactivity with respiratory symptoms at 6 months »
 - 17/83 (20%) of highly exposed
 - 3/40 (8%) of moderately exposed
 - all nonsmokers, except one
 - no evidence of clinically severe initial injury

RADS – Prognosis

- Malo *et al.* Long-term outcomes of acute irritant-induced asthma. AJRCCM 2009, 179, 923-8
- 35 subjects with RADS, 13.6 y [4 – 24 y] after accident
- All had respiratory symptoms (34% inhaled steroids)
 - No improvement in spirometry
 - Methacholine test (n=23): normal or improved in 6+3 (better starting values)
 - Induced sputum (n=27):
 - eosinophils >2% (n=6), pmn >60% (n=8);
 - ↑ mediators of inflammation & remodelling (~ occupational asthma)
 - Abnormal depression score: n=12

RADS – research questions

- What proportion of victims of inhalation accidents evolve to RADS?
 - Registration and good follow-up of all victims
- Why do some victims evolve to RADS?
 - Severity of damage (agent, dose, ...)
 - Individual predisposition? (pre-existing NSBHR, atopy, abnormal epithelial repair, ...)
 - Treatment modalities? (oxygen, steroids, antioxidants, ...)
- Role of irritants in (occupational) asthma?

Irritant-induced asthma and repeated/chronic exposure to irritants

RADS – criteria (2')

2. Onset of symptoms after a **single** specific exposure incident

- yes, in typical cases
- also after **repeated high-level respiratory irritant exposures**

Tarlo SM, Broder I. *Chest*, 1989, 96, 297-300

Case C

- male, 47 y
referred 04/1995 for advice on possible occupational origin of asthma (compensation refused)
- life-long nonsmoker, no atopy
- safety engineer in several companies from 1975
- perfect health until 1989

Clinical history (1)

- 1989: started work in oil refinery:
 - progressive symptoms of
 - rhinitis (→ nasal septum correction + conchotomy)
 - excessive sputum production
 - dyspnea on exercise
 - wheezing at night
 - intolerance to nonspecific irritants

Clinical history (2)

- 10/1994: claimed compensation, left job
 - improvement of symptoms, but persistent asthma needing medication
 - 05/04/1995: VC 99%
FEV₁ 97%
histamine PC₂₀ 1.1 mg/ml
 - no identified causes of allergic asthma

Exposure history (safety interventions)

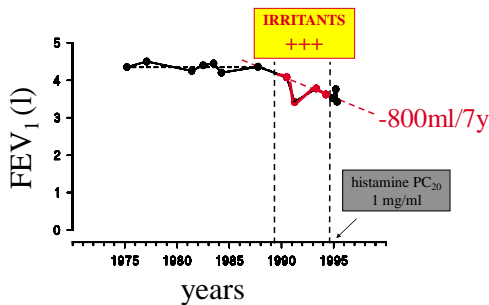
incidents	1989	1990	1991	1992	1993	1994
leaks to process equipm.	18	28	52	32	65	72
requiring compr. air eq.	66	55	140	55	124	72
interv. for gas leaks	4	6	16	13	17	9
interv. for fires	19	19	32	26	19	7
interv. for liquid leaks	15	44	87	135	158	31

mainly H₂S and S-compounds, some very serious incidents with deaths (n=3)
& severe inhalation injuries (n=5)

Previous pulmonary function data?

- being a safety engineer, he had undergone yearly medical examinations and fitness tests for wearing breathing apparatus

male, 48y, safety engineer, nonsmoker, no atopy



Case C – conclusion

- good documentation of repeated exposure to peaks of respiratory irritants (H₂S, SO₂, ...)
- availability of good longitudinal lung function data
- confident diagnosis of “irritant-induced asthma”
- compensation awarded

Non-RADS irritant-induced asthma – own experience

- 2000-02 (Kempeneers, unpublished)
 - 15 subjects with adult-onset work-related asthma, regularly exposed to excessive levels of irritants, without evidence of acute inhalation injury, nor sensitization (including specific provocation tests in some cases)
 - vegetable industry (metabisulphite + acid → SO₂)
 - rubber industry (HCl)
 - cleaning of silos (HCl)
 - cleaning of metals (H₃PO₄)
 - emptying cess-pits (H₂S)
 - hospital (HClO; formaldehyde)
 - laboratory (photographic emulsion)

Asthma and irritants?

Asthma risk by occupation

- Reinisch *et al.* AJIM 2001, 39, 72-83
 - California: 945 reported cases of work-related asthma (1993-96) + structured telephone interview (n = 444)
 - 25/1,000,000 workers/y, but actually estimated at 78
 - janitors & cleaners, firefighters, ...
 - mostly no exposure to known sensitizer, probably irritant exposures

Asthma risk by occupation

- Wang *et al.* AJRCCM 2010, 182, 1369-76
 - Taiwan, case-control study
 - 504 adult cases of asthma, 504 community controls, 504 hospital-based controls
 - Exposure assessed by asthma-specific JEM
 - Atopic asthma associated with occupational exposure to HMW asthrogens (aOR 4.0)
 - Nonatopic asthma associated with occupational exposure to LMW asthrogens (aOR 2.6), including irritants

Risks of Exposure to Occupational Asthrogens in Atopic and Nonatopic Asthma A Case-Control Study in Taiwan

Ann J Respir Crit Care Med. Vol 182, pp 1669-1676, 2010

Tzu-Hsiung Wang^{1,2*}, Meng-Chih Liu^{3*}, Chia-Chen Wu⁴, Tsun-Yee Tsang⁵, Ming-Myan Huang⁶, Hsueh-Yi Chang^{1,2}, Chien-Hung Lee⁷, Deng-Chyang Wu⁸, Hsi-Shuan Hsu⁹, Albert Min-Shan Kuo¹⁰, Yu-Na Chang¹¹, and King-Chia Ko¹²

TABLE 3. SPECIFIC EXPOSURE GROUP FREQUENCY AND ODDS ESTIMATES FOR ALL SUBJECTS WITH CURRENT ASTHMA (n = 504) AND COMMUNITY CONTROL SUBJECTS (n = 504)

Specific Occupational Exposure	Community Control (n = 504)		Total Control (n = 504)		Asthma with Atopy ¹		Asthma without Atopy ²	
	n	%	n	%	n	aOR	n	aOR
Use of bleach exposure	420	83.3	4	0.8	4	1.00	1	1.00
any asthrogens ³	75	14.9	22 (7.5-31.1)	4.3	2 (1.3-3.4)	39	2.3 (1.4-3.9)	2 (1.0-4.1)
High-MW asthrogens, any	10	2.0	22 (7.5-31.1)	24	4.0 (1.6-8.9)	4	1.0 (0.3-3.3)	1
Low-MW asthrogens, any	3	0.6	2 (0.8-8.8)	9	3.8 (1.2-12.7)	1	0.9 (0.1-7.9)	1
Highly reactive chemicals	22	4.4	1 (0.1-2.0)	44	1.0 (0.1-2.7)	49	2.6 (1.0-6.5)	1
Organic solvents	18	3.6	1 (0.0-2.2)	18	1.2 (0.1-2.8)	30	1.8 (0.9-3.6)	1
Organic dusts	5	1.0	1 (0.0-4.8)	3	2.0 (0.4-11.8)	2	1.3 (0.3-7.0)	1
Industrial cleaning agents	7	1.4	2 (0.1-4.1)	4	1.3 (0.6-4.8)	12	1.2 (0.5-2.7)	1
Wood dust	4	0.8	2 (0.0-78.1)	3	0.8 (0.1-10.8)	3	0.8 (0.1-21.8)	1
Wood varnishes, formal	11	2.2	2 (1.0-3.2)	11	1.2 (0.2-2.9)	11	0.7 (0.4-10.2)	1
Wood varnishes, nonformal	22	4.4	3 (0.1-5.1)	48	2.0 (1.0-3.2)	46	3.1 (1.6-6.2)	1
Wood sawdust, combined	1	0.2	1 (0.0-4.1)	4	1.0 (0.1-2.0)	1	1.0 (0.1-78.2)	1
Automotive	7	1.4	4 (1.2-10.9)	29	1.8 (0.9-3.6)	11	6.1 (1.7-22.0)	1
Textile production	4	0.8	2 (1.0-7.8)	1	1.1 (0.0-10.7)	4	0.8 (0.1-7.1)	1
Textile prints	4	0.8	2 (1.0-7.8)	4	1.9 (0.1-3.2)	10	0.8 (0.1-11.8)	1

Abbreviations: aOR = adjusted odds ratio; MW = molecular weight.
 aORs were calculated after adjusting for age, sex, body mass index, smoking, education, history of occupational asthma, and exposure to pesticides, cockroaches, and indoor mouse farming.
 *Subjects were performed for specific asthrogens when at least two positive and two control subjects were exposed.
¹Subjects with atopy was defined as having positive IgE antibody to common inhalant allergens with an increase in total IgE (>100 IU/L) or a positive skin test result (≥3 mm).
²These categories are not mutually exclusive; the total number for "high-MW + low-MW + mixed" is higher than that for "any asthrogens."

Asthma and cleaning agents

- Higher risk of asthma in female cleaners
 - Zock *et al.* SJWEH 2001; 27: 76-81: P.R. 1.7
 - Karjalainen *et al.* ERJ 2002; 19: 90-5: R.R. 1.50
 - Medina-Ramón *et al.* Thorax 2003; 58: 950-4: O.R. 1.46
- “hidden sensitizers”?
 - Quaternary ammonium cpds (disinfectants / preservatives)
 - Isothiazolinones (preservatives)
 - Ethanol amines (wax-removal agents)
 - d-Limonene, terpenes (perfumes)
- exposure to irritants and sprays ?



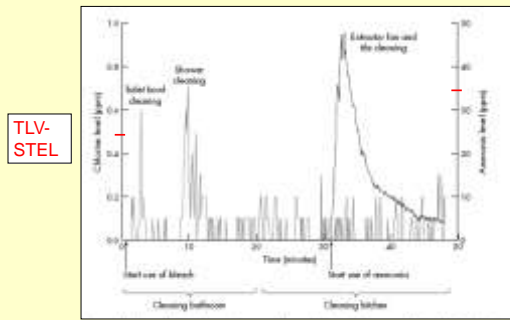
Asthma and cleaning agents

- Medina-Ramón *et al.* OEM 2005, 62, 598-606
 - (Nested) case-control study of female cleaners (30-65 y)
 - 40 cases (asthma or chronic bronchitis) – 155 controls
- Higher risk of asthma if use of bleach (dose-related)
- Higher risk of asthma if reported inhalation incident (frequent!)

Table 4 Multivariate associations (adjusted odds ratios and 95% confidence intervals) between different cleaning products, symptoms, and risk factors

	Quaternary (n=127)	All uses (n=49)	OH (PFC) CI	Alcohol (n=26)	OH (PFC) CI	Chlorine bleach without sodium (n=18)	OH (PFC) CI
Wash (both combined and diluted)	25	8	1.0	1.0	1.0	1.0	1.0
-2/dl times/year	32	11	3.5 (2.0 to 7.1)	4	30 (1.7 to 52)	3	0.9 (0.1 to 6.2)
-3/dl times/year	42	21	4.9 (2.8 to 10)	12	32 (2.1 to 47)	9	1.9 (0.9 to 12)
Use of liquid multi-use cleaning products	35	23	1.0	1.0	1.0	1.0	1.0
-2/dl times/year	41	22	0.8 (0.7 to 0.8)	4	0.8 (0.2 to 0.7)	4	0.8 (0.1 to 1.6)
-3/dl times/year	31	8	0.2 (0.1 to 0.3)	5	0.1 (0.0 to 0.3)	3	0.2 (0.0 to 1.2)
Washing dishes	34	19	1.0	1.0	1.0	1.0	1.0
-2/dl times/year	37	22	1.3 (0.8 to 1.9)	4	0.8 (0.2 to 0.9)	4	7.1 (1.0 to 52)
-3/dl times/year	21	18	1.1 (0.7 to 0.9)	6	0.8 (0.0 to 1.4)	6	6.1 (0.0 to 47)
Insulation of car (reported quantity of repairs, gas, or tires related to washing system)	73	4	1.0	1.0	1.0	1.0	1.0
None	77	36	2.3 (0.9 to 5.9)	19	0.8 (0.1 to 7)	16	0.9 (0.2 to 4.2)
Employment in non-domestic cleaning	160	8	1.0	1.0	1.0	1.0	1.0
None	11	31	0.3 (0.0 to 2.0)	19	0.2 (0.0 to 0.6)	12	7.9 (1.4 to 39)
Smoking	127	20	1.0	1.0	1.0	1.0	1.0
Current	15	11	4.7 (1.7 to 13)	2	0.3 (0.1 to 0.9)	4	23 (3.6 to 137)
Former	18	8	1.2 (0.7 to 1.9)	2	1.5 (0.4 to 6)	1	0.7 (0.1 to 3.9)

Multiple logistic regression models, adjusted for all listed variables and age (years).
*This table has had missing values for one or more of the exposure variables and were not included in the multivariate model.



Asthma and cleaning agents

Zock *et al. AJRCCM* 2007, 176, 735-741

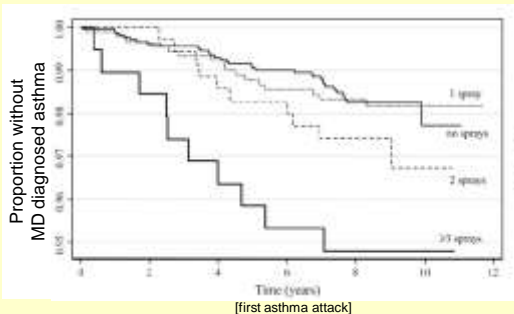
- ECRHS-I → ECRHS-II [+ 9 y]
- N = 3,503 (69% women), 20-48 y [→ 28-57 y]
 - ECRHS-I: free of asthma at baseline
 - ECRHS-II: "doing cleaning at home"
 - face-to-face interview
 - use of 15 products for domestic cleaning and washing?
 - never, <1 d/w, 1-3 d/w, 4-7d/w

Asthma and cleaning agents

Zock *et al. AJRCCM* 2007, 176, 735-741

- use of cleaning sprays ≥1d/w: RR 1.49 for incidence of asthma symptoms/medication
- use of cleaning sprays ≥4d/w: RR 2.11 for incidence of physician-diagnosed asthma
- sprays for glass-cleaning, furniture and air-refreshing
- no association with cleaning products not applied as sprays
- no modification of risk by atopy

Zock *et al. AJRCCM* 2007, 176, 735-741



Asthma and irritants ?

- Experimental research needed using animal models of asthma
 - which "irritants"? ["inflammagens"]
 - gaseous agents
 - particulates
 - endotoxin
 - role of irritants?
 - in nonspecific bronchial hyperresponsiveness
 - in bronchial inflammation
 - in allergic sensitisation to HMW and LMW agents

How much asthma is work-related?

“In adults, asthma is caused (directly or indirectly) by work in approximately 15 % of cases”

- Work-aggravated asthma? **some**
- Occupational allergic asthma? **minority**
- Irritant-induced asthma? **many??**

Thank you for your attention

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