Population-based studies of occupational obstructive diseases

Use of databanks, advantages and pitfalls,
Strategies to adjust for biases and confounding

Most clinical cohorts of occupational obstructive diseases are relatively small, and may not be representative of the range of disease due to referral bias.

*Therefore **population-based studies** and **databanks** can provide additional insights and many publications that address **occupational asthma** and **hypersensitivity pneumonitis** are based on data obtained from databases.*

*However there are **important potential limitations to interpretations** of these data that will be addressed in this session.*

Nicole Le Moual & Paul Henneberger

6th Jack Pepys Workshop, Toronto, May 13 2016
Asthma in the Workplace

Population-based studies of occupational obstructive diseases

Use of databanks, advantages and pitfalls

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Aging and chronic diseases. Epidemiological and public health approaches.

6th Jack Pepys Workshop, Toronto, May 13 2016
Asthma in the Workplace

Outline

- Occupational Hypersensitivity pneumonitis
- Occupational asthma
- Population-based studies: advantage, pitfalls, methodological issues
  - Asthma phenotypes definitions
  - Occupational exposure assessment
- Evaluation of work-related asthma in population-based studies

Occupational Hypersensitivity Pneumonitis

- Rare immunologic lung disease : <30 new cases of OHP per year (France, Germany, Finland)

Eng & DeFelice CRAI 2016 ; Quirce et al. Allergy 2016

- Identification of the causal antigen is challenging
  - 200 antigens identified (molds/fungi …): mostly LMW agents; non-IgE mediated

Millerick-May et al. Respir. Medicine 2016; Quirce et al. Allergy 2016

- Diagnosis is often difficult : no gold standard, multiple diagnosis criteria
  - Acute cough, dyspnea, wheezing, crackles on lung exam, fever, fatigue …
  - Farmer's lung disease : the most frequent, underdiagnosed

Cano-Jiménez et al. Arch Bronc. 2016

  - Diagnosis tools
    - Mostly invasive: Inhalation challenge, lung biopsy, chest radiograph, …
    - antigen-specific IgG antibodies : not available for most agents causing OHP
    - Important to improve and standardize diagnosis tools

Eng & DeFelice CRAI 2016; Millerick-May et al. Respir. Medicine 2016; Quirce et al. Allergy 2016 ; Raulf COACI 2016

➔Population-Based survey in general population ?

More appropriate in agriculture industry or in a case-control survey

Farmer's lung disease - AGRICOH Consortium

Consortium of 22 agriculture cohort studies around the world in 5 continents including:

U.S. Agricultural Health Study (AHS), 1993-1997, 1998-2002, 2005-2010, n = 89,655

19% of farmer's lung disease at enrolment

Primary aim : investigate associations between agricultural exposures and health outcome with a particular interest in rare disease, not easily addressed in a sole cohort

Brouwer M et al, OEM 2016; Hoppin JA et al, OEM 2014; Leon ME et al, IJERPH 2011

Respiratory outcome	AHS Prevalence	95% CI	
	All adult participants (%)		
Diseases			
Asthma ever	7.2	6.9	7.4
Asthma—adult-onset	4.3	4.1	4.5
Chronic bronchitis	3.5	3.3	3.7
Emphysema	1.4	1.3	1.5
COPD	1.3	1.2	1.4
Any obstructive disease*	5.1	4.9	5.3
Farmer's lung	1.2	1.1	1.3

Disease	AHS (N=43 548) Incidence rate N/1000 PY	95% CI	
Asthma	2.1	2.0	2.2
Chronic bronchitis	1.2	1.1	1.3
Emphysema	0.8	0.7	0.9
COPD	0.9	0.8	1.0
Farmer's lung	0.3	0.3	0.4
Any obstructive disease*	2.1	2.0	2.2

Hoppin JA et al, OEM 2014

These studies may provide opportunities to:

- ➔ Study respiratory disease including Occupational Hypersensitivity Pneumonitis (OHP)
- ➔ Evaluate the validity of diagnosis tools for OHP, especially by a nested case-control study
- ➔ Improve evaluation of risk factors for OHP

Occupational asthma – Brief reminder

- The most common occupational lung disease in industrial countries
- The number of suspected asthmagens has tripled since 2000
- The burden of the disease is underestimated because of both
  - Underreporting: partly due to the lack of knowledge regarding asthmagen exposures
  - Healthy Worker Effect: a source of selection bias potentially important in asthma
- Underlying mechanisms complex and partly unknown for chemicals products, LMW agents (mostly non-IgE-mediated) and irritants

Dumas O et al. COACI 2016 ; Tarlo S and Lemiere C NEJM 2014

Population-based studies - Advantages

- Population-Based Survey:
  - Evaluate the burden of the disease, impact in public health ➔ allow early disease prevention and treatment
  - Allow to take into account potential confounding factors
  - Less affected by a Healthy Worker Effect than industry-based studies

Johannessen BMCPM *et al 2014;* de Matteis *et al* OEM 2016; Le Moual *et al* AJRCCM 2008

- Authors recently underlined that for irritant-induced asthma with latency, causality can only be inferred from epidemiological studies

Vandenplas *et al* A 2014 ; Tarlo & Lemiere NEJM 2014

- Follow-up of epidemiological birth cohorts would be useful
  - to limit Healthy Worker Effect
  - exposures assessed before participants would be affected by the disease

de Matteis *et al* OEM 2016*;* Le Moual *et al* AJRCCM 2008

Population-based studies
Pitfalls

- Difficult to evaluate occupational asthma ➔ work-related asthma
  - Lack of information to link age of asthma onset and onset of exposure

Gautrin *et al* ERJ 2003; Le Moual *et al* AJE 2004

- Response rates and representativeness?

Rothman et al IJE 2013 ; Richiardi et al IJE 2013; Johannessen BMCPM *et al 2014;* de Matteis *et al* OEM 2016 ; Abrahamsen *et al BMJ Open 2016*

  - Response rates need to be high (>70%) to reduce potential biases
  - Representativeness and response rate at baseline less important than high response rate at follow-up

Richiardi et al IJE 2013

  - Representativeness and scientific inference recently discussed

Rothman et al IJE 2013

- Prospective survey *versus* cross-sectional survey
  - More expensive but more powerful

Gautrin *et al* ERJ 2003; Toledano *et al* Plos One 2015

  - Less likely to be affected by selection or survivor biases

de Matteis *et al* OEM 2016

➔ However, each epidemiological study, whatever its design, may play a role

Pearce IJE 2011

Population-based studies
Methodological issues

- Record complete histories, precise definitions and favor specificity over sensitivity, for both exposure and asthma

  Le Moual AJE 2004; Tarlo & Lemiere NEJM 2014

  ➔Improvement of asthma phenotypes by non-invasive methods, for a better understanding of underlying mechanisms

  ➔Improvement of lifetime occupational exposure assessment is crucial

  Heederick D et al CEA 2014

- Perform sensitivity analyses to test robustness of the results by checking consistency of the results among sub-groups

  de Matteis OEM 2016

Asthma phenotypes evaluation

Questionnaire

Current asthma: Ever asthma & in past 12 months: ≥1 asthma attack, respiratory symptom or asthma medication

Adult asthma-onset (≥ 16)

Treatment : ICS

Asthma symptom score : a proxy of asthma incidence

Asthma control: ACT, GINA guidelines

Non-invasive Biological markers

SpT

IgE

Blood eosinophil, neutrophil counts

Fraction of exhaled nitric oxide (FeNO)

Exhaled breath Condensate (EBC)

Lung function

FEV1

PD20

Small airway disease

Other tools

Drug prescription databank

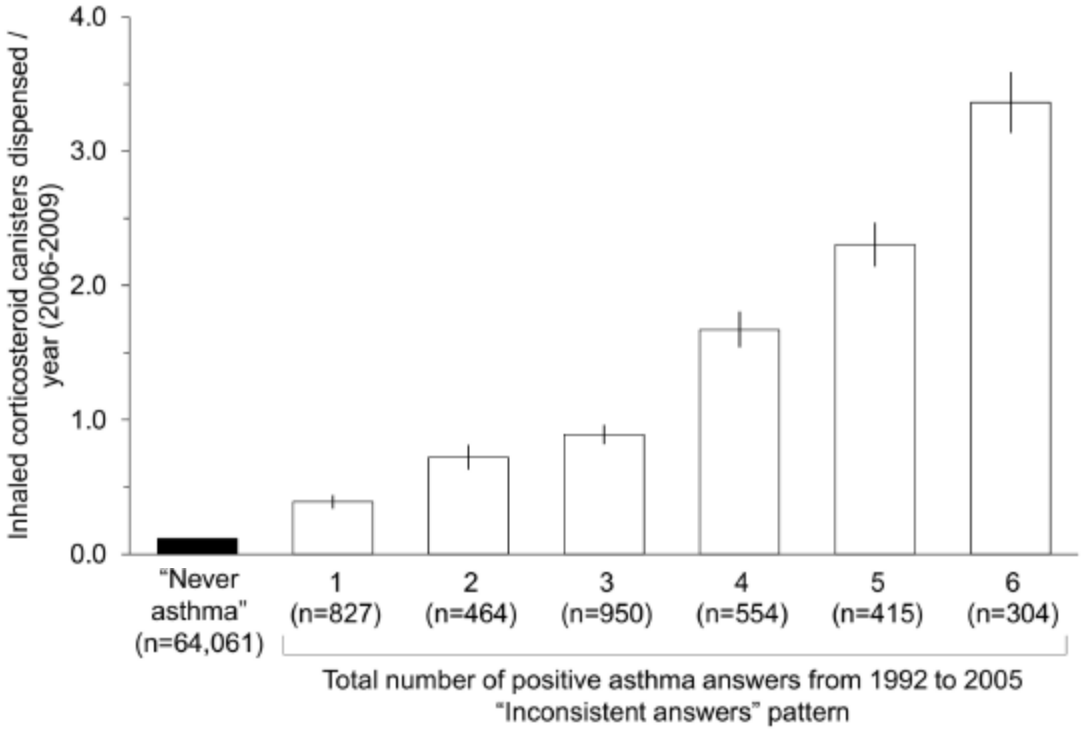
➔Ethic issues?

Gautrin *et al* ERJ 2003; Lemière et al, JACI 2014; Nadif et al ERJ 2014; Dumas O et al COACI 2016

Asthma defined by questionnaire and dispensed drugs databank

E3N French women Cohort, 1992-2005, n = 70,428
French national health insurance plant (MGEN)
Asthma ever : ' Have you ever had asthma', recorded in 7 questionnaires
Drug reimbursement database (2004-2009)
Age : 40-65 years old at baseline
Primary aim : major chronic diseases

Sanchez et al, Plos One 2014



Asthma : a time-varying expression during life

➔ **The number of ICS canisters dispensed increased with the number of positive answers to asthma question**

Asthma defined by questionnaire and allergic phenotype

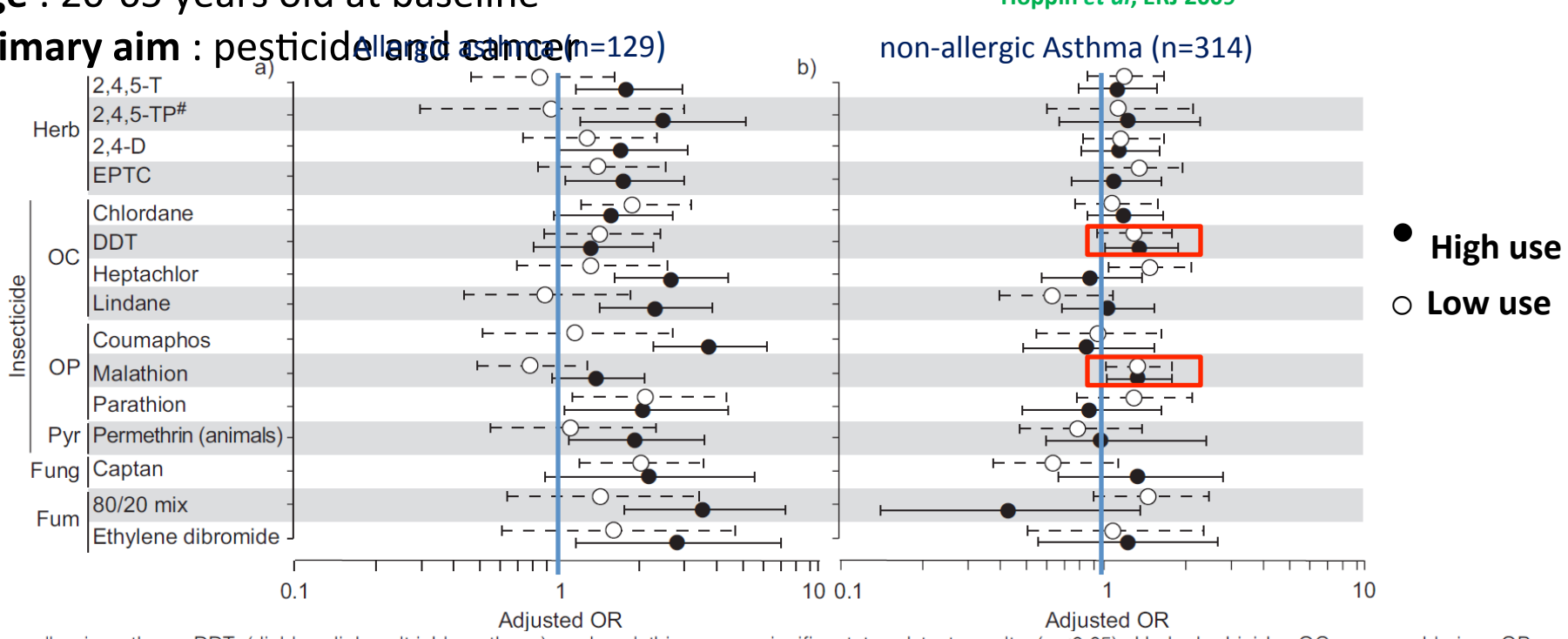
AHS COHORT : U.S. Agricultural Health Study, 2005-2007, pesticide applicators, 19,700 men

Asthma: adult-onset doctor diagnosed asthma (≥ 19 years); **allergic status** based on doctor-diagnosed eczema or hay fever

Age : 20-65 years old at baseline

Primary aim : pesticide and cancer

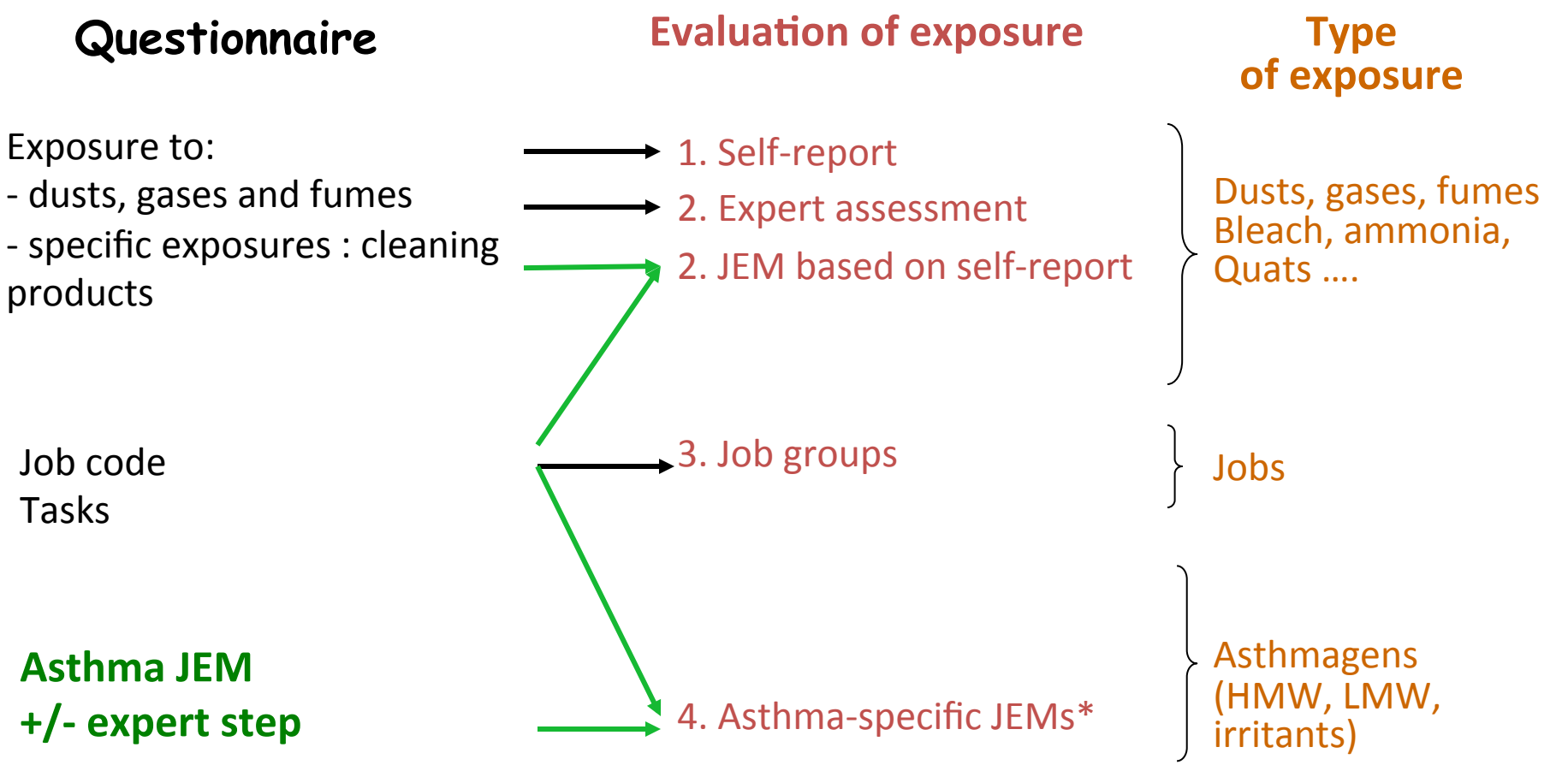
Hoppin *et al*, ERJ 2009



For nonallergic asthma, DDT (dichlorodiphenyltrichloroethane) and malathion gave significant trend test results ($p<0.05$). Herb: herbicide; OC: organochlorine; OP: organophosphate; Pyr: pyrethroid; Fung: fungicide; Fum: fumigant; OR: odds ratio. #: fenoprop.

➔**Significant exposure-response associations between these pesticides and allergic and non-allergic asthma**

Occupational exposure assessment



Adapted from **Le Moual *et al*, AJE 2004**

*** 3 AsJEMs: *Kennedy et al, OEM 2000 ; Tagiyeva et al, Eur Respir J 2010 ; Lillienberg et al, Ann Occup Hyg 2014***

JEM : job exposure-matrix; HMW : high ; LMW : low molecular weight

Asthma-specific JEM

Kennedy et al., OEM, 2000

freely available on

- Asthma-specific JEM most frequently used
  - Asthma JEM applied in publications, n=39
- Various populations:
  - Europe (France, Spain, Germany, UK, Northern, Estonia) and Outside Europe (Taiwan, Australia, Canada)

Exposure estimate in yes (1) / no (0) for each ISCO88 code						
ISCO88 job codes, n=505	Asthmagens - high probability, n18			Other allergens, irritants, n=4		Expert review step
	(1)*	(2) ° …	(18)	(1) …	(4)	
5132, personal care workers	1	0 …	0	0 …	0	0
7412, bakers	0	1 …	0	0 …	0	1

*cleaning /disinfecting products, ° flour

YES
Job badly defined or with heterogeneous exposure

NO
Estimate by job and ascribed to each subject with this job

Expert step
Exposure attributed by the JEM to a given subject **is checked by an expert**

- JEM designed in 2000, based on a list of 150 asthmagens, but new asthmagens are reported each year

Cartier et al., COACI 2015

- Need to improve estimations (e.g., cleaning products, irritants, endotoxins)
- Need to adapt to country-specific work situations (England; Northern Europe)

Tagiyeva et al., Eur Respir J 2010 ; Lillienberg et al., Ann Occup Hyg, 2014

➔ **Updates of the Asthma JEM (in progress in Europe & U.S.)**

Le Moual et al. & Henneberger et al. *Submitted EPICOH/X Congress , September 2016, Barcelona*

Evaluation of exposure by new tools

- Brand names, safety data sheets ➔ main active compounds

Saito et al. *AJRCCM* 2015

- The use of bar code might be useful to identify the compounds of the agent, especially for cleaning products/disinfectants

Bennett et al. *J Expo Sci Environ Epidemiol* 2012

- Development of a barcode-based exposure assessment method to evaluate occupational exposure to disinfectants (in progress)

Quinot et al. *Submitted X Congress , September 2016, Barcelona*

  - Confidentiality of data regarding active substances
  - Smartphone application, ethic aspects ?

- Biological markers of exposure to chlorine-based cleaning agents (such as trihalomethanes (THM))

Charisiadis et al, EST 2014

Work-related asthma in population-based studies

Asthma and Occupation in the 1958 Birth Cohort

1958 Birth Cohort : UK, 1992-2005, n = 7,406

Population-Based study

Age : 33 and 42 years old when occupational history were recorded

Evaluation of exposure : Asthma-specific JEM, Large job groups

Ghosh et al, Thorax 2013

Table 3 Association of adult onset asthma with ever having worked in a high-risk exposure group by age 42

		Adult onset asthma					Adult onset asthma with airflow limitation†			
Exposure group	Case/total	OR	OR*	95% CI	p Value	q Value	Case/total	OR*	95% CI	p Value
Main categories of high-risk exposures										
Reference group (always worked in non-exposed)	147/1864	1.00	1.00	–	–	–	24/1567	1.00	–	–
Any exposure to HMW	183/1897	1.26	1.33	1.05 to 1.68	0.018	N/A	37/1593	1.45	0.86 to 2.47	N/A
Any exposure to LMW	189/1966	1.25	1.49	1.18 to 1.89	0.001	N/A	37/1637	1.51	0.88 to 2.59	N/A
LMW reactive cleaning/disinfecting products	92/755	1.63	1.67	1.26 to 2.22	0.000	0.000	20/627	1.91	1.03 to 3.56	0.041

*Adjusted for sex, smoking, father's social class at birth, region and hay fever.
†Those with asthma but no airflow limitation were coded 'no' for this analysis.
HMW, high molecular weight; LMW, low molecular weight; N/A, correction for multiple testing not applied.

Table 5 Population attributable fraction (PAF) of lifetime occupational exposures for adult onset asthma by age 42

Exposure categories	Prevalence*	PAF (%)	95% CI (%)
Considering all exposures combined			
Exposure to any occupation exposure (low, high or both)	5224 (73.7%)	16.3	3.8 to 27.1

*309 individuals who had provided insufficient information to be certain regarding exposure status for their entire working life were excluded.
ASJEM, Asthma Specific Job Exposure Matrix.

➔**Significant associations observed between**
- **HMW/LMW agents and new adult-onset asthma**
- **Disinfectants and asthma & airflow limitation**

➔**Population attributable fraction estimate to 16%**

Occupational exposures and ever, current physician-diagnosed and treated asthma

Estonian cohort, 2001, n = 34,015

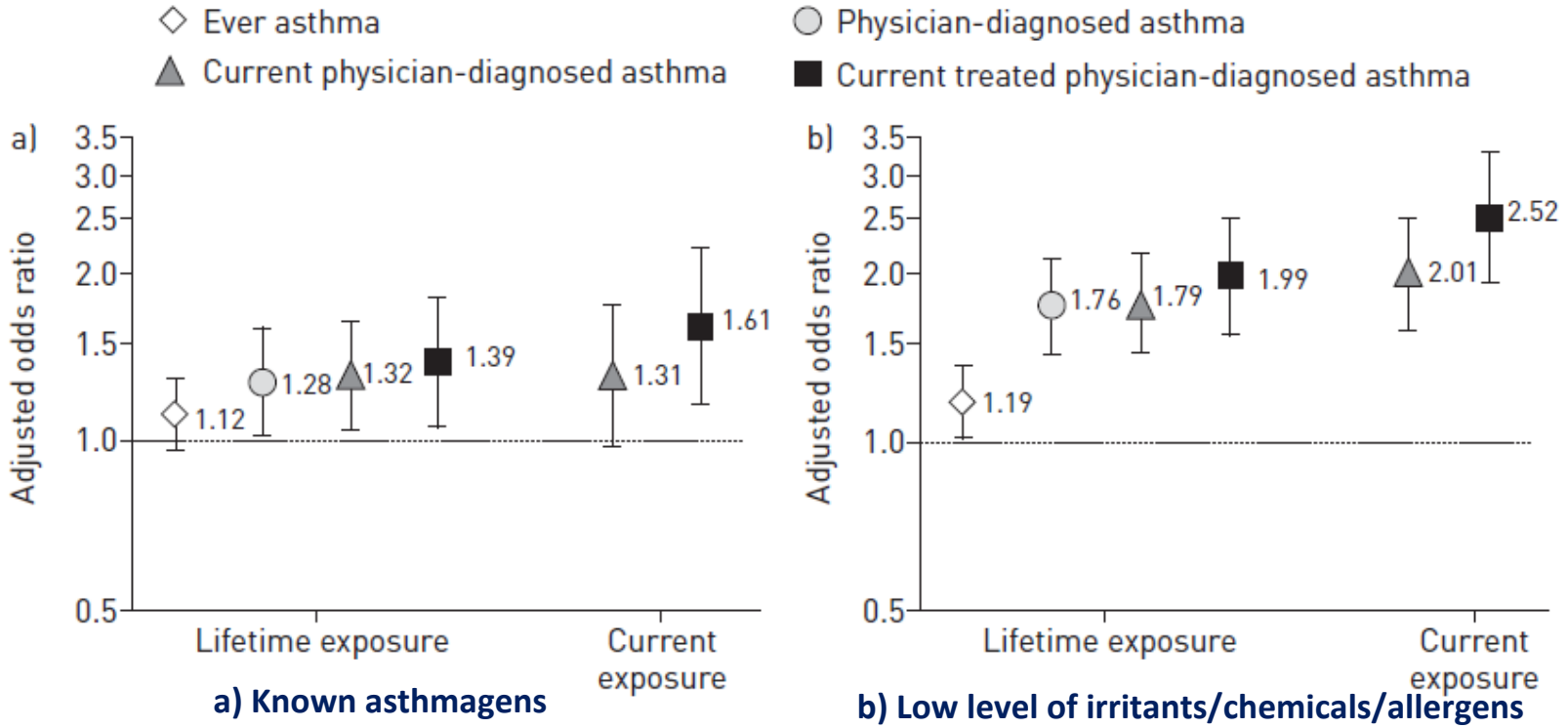
Population-based study from Estonian Genome Center of University of Tartu (EGCUT)

Age : 18-65 years old, 67% women

Asthma phenotypes: self-reported, ever, physician diagnosed, treatment

Evaluation of exposures : Asthma-specific JEM (Kennedy et al) Dumas et al, ERJ 2014

Primary aim : genetic research for human health



a) Known asthmagens

b) Low level of irritants/chemicals/allergens

➔ **The strength of associations increased with more specific asthma definitions**

Healthy worker effect

- Cohort of teenagers (16-18 years), ISAAC-II, Germany, n=478
  - Without expert step evaluation
  - Teenagers with recent rhinitis symptoms seem to would like to perform less exposed jobs (0.6[0.3-1.1])

  Radon K et al, ERJ 2006
- British birth cohort 1958, job history at 33 years, n=5020
  - History of hay fever/allergic rhinitis in childhood was associated with a lower probability to be exposed to asthmagenic products (0.8[0.6-1.0])

  Butland BK et al, OEM 2011
- Follow-up of adults, ECRHS survey, n=19,784
  - A healthy worker hire effect (less likely to hold exposure jobs) was observed in subjects with low and high exposures to dusts, gases and fumes (0.9[0.8-1.0] and 0.8[0.7-0.9])

  Olivieri O et al, ERJ 2010
- Follow-up of children, French EGEA survey, n=298
  - A healthy worker hire effect was observed in subjects with more severe or more symptomatic asthma in childhood (0.3[0.1-0.8] and 0.5[0.2-0.9]).

  Dumas O et al, ERJ 2011
- Follow-up, French EGEA survey, n=1284
  - A healthy worker effect was observed using **marginal structural models** : no association with standard models: OR increased from 0.99[0.7-1.4] to 1.26[0.9-1.8]for asthmagens and from 0.82[0.6-1.2] to 1.6[1.02-2.4]for irritants/low level of allergens

  Dumas O et al, OEM 2013

➔ **Consistent results showing a healthy worker effect**

Population-based studies of occupational obstructive diseases

Strategies to adjust for biases and confounding: Non-participation and exposure assessment as sources of bias

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6th Jack Pepys Workshop, Toronto, May 13 2016
Asthma in the Workplace

Disclaimers

- The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health (NIOSH).

- Mention of a specific product or company does not constitute endorsement by NIOSH.

Non-participation as source of bias

- Epidemiologists have addressed this topic
  - Good reference: Galea 2007
- Social scientists (survey research scientists) have been very attentive to this topic for decades

Participation Rates Have Declined

- Participation rates for population-based studies have been declining (Curtin 2008)
- Telephone surveys
  - Solicitation calls have become frequent events
  - Many people screen calls and do not answer if caller unfamiliar
- Online surveys not a panacea – variable response rates

Desirable and undesirable response rates in epi studies

- Popular wisdom: need close to 100% response, but anything over some high level such as 60% (or 70% or 80%) is acceptable
- Concern – low response rates lead to bias in estimates of:
  - Frequency (e.g., prevalence)
  - Variance
  - Association of outcome with exposure – selection bias

Social scientists have studied relationship of non-response bias to non-response rates

- Groves published meta-analysis in 2008
- Summarized data from 59 surveys that measured both non-response rate and non-response bias in frequency estimates
- Non-response rates: 14 to 72%, mean 36%

Bottom Line: Bias not associated with non-response (Groves 2008)

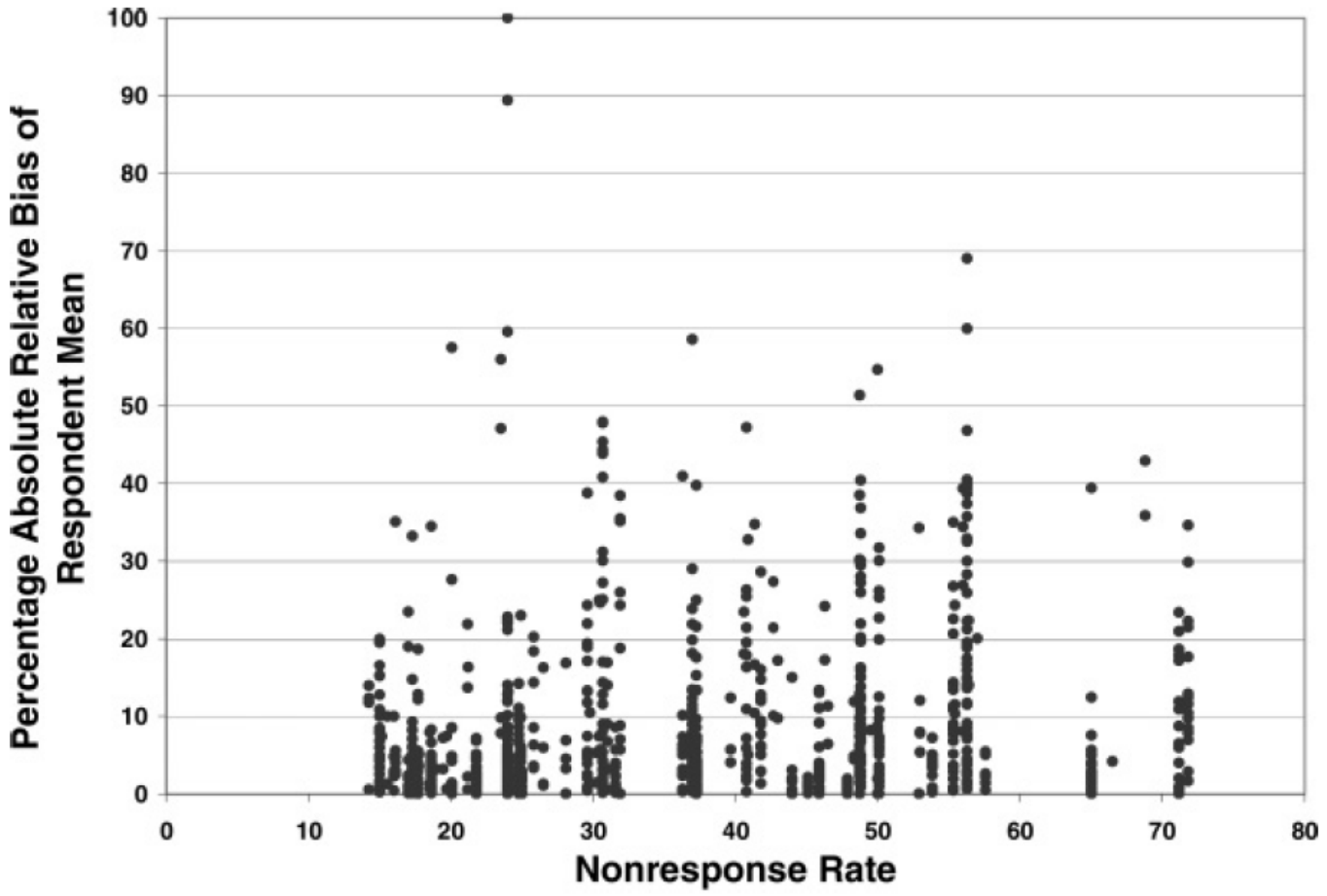


Figure 2. Percentage Absolute Relative Nonresponse Bias of 959 Respondent Means by Nonresponse Rate of the 59 Surveys in Which They Were Estimated.

Implications of Groves 2008

- Response rates are poor indicators of non-response bias: explain about 11% of non-response bias (Groves 2006)
- Bias can occur with low or high response rates
- Strategies to evaluate and adjust for impact of non-response are useful to confirm validity of results

Non-responders' survey

- Short survey presented to those who did not complete full survey
- Can yield data (demographic, risk factor, and health outcome) to compare to full participants
- And, can ask about reasons for not participating, which could indicate bias

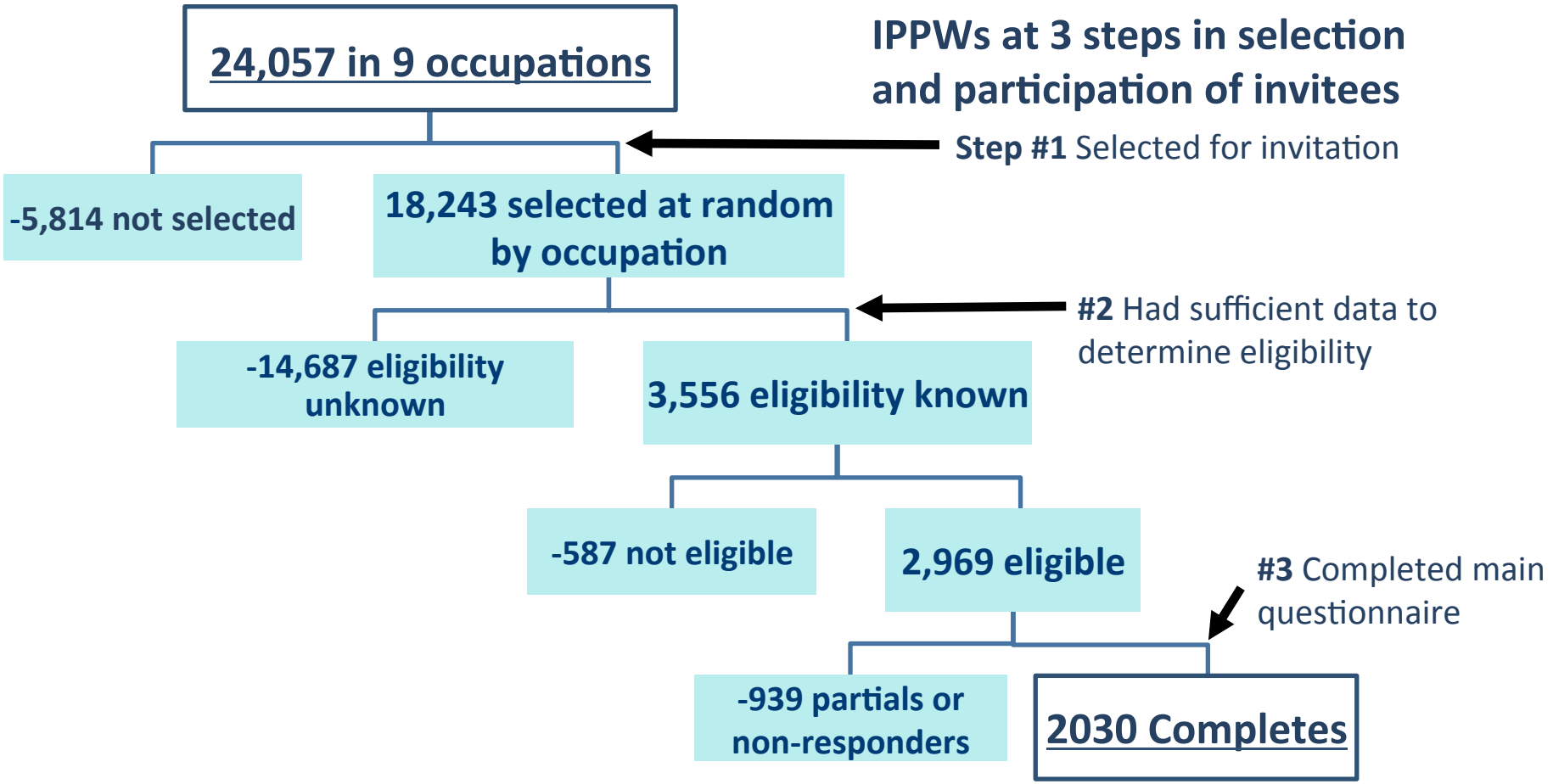
Inverse probability of participation weights (IPPW)

- If have information on non-participants, can develop weights based on inverse probability of participation
  - Up weight responses from those less likely to participate (e.g., young versus old invitees)
  - Down weight responses from those more likely to participate (e.g., female versus male invitees)
- Intermediate IPPWs can be calculated at several steps in selection and participation of invitees
- Final IPPWs = product of intermediate IPPWs

Example from study of healthcare workers

- From 24,057 healthcare workers in 9 occupations
  - Randomly selected 18,243 to be invited
  - Contacted with 4 mailings and ≥7 phone calls attempts
- Low response rate
  - Effective sample size of 15,213 – known or presumed eligible
    - 2,030 (13.3%) completed main questionnaire
    - 434 (2.9%) finished part of main questionnaire
    - 505 (3.3%) completed short non-responder survey

Example from study of healthcare workers



Final IPPW = product of intermediate IPPWs

Example from study of healthcare workers

- Used final IPPWs to weight estimates of prevalence and association
- Weighted values somewhat less than unweighted
  - Prevalence of wheeze in last 12 months:
    14.4% unweighted versus 13.1% weighted
  - Association of wheeze in last 12 months with occupation

	Unweighted		Weighted	
Occupations	**OR**	**95% CI**	**OR**	**95% CI**
Respiratory therapists	2.0	1.02, 3.7	1.9	1.02, 3.6
Licensed practical nurses	1.5	1.0, 2.1	1.3	0.9, 1.8

OR = odds ratio; 95% CI = 95% confidence interval
Regression models controlled for age, gender, and smoking
Reference for occupations was nursing assistants

Adjusting for non-responses using IPPWs: weaknesses and strengths

- Weaknesses
  - Only as good as the data you have
  - Need some data on all invitees, ideally with data on exposure and outcome
- Strengths
  - Can adjust estimates of frequency and association
  - Relevant software in SAS and other stat packages

Exposure assessment as source of bias: Examples for work-related asthma

- Self-reported exposures and asthma: Issues of accuracy
- Self-reports can:
  - Bias effect estimates
  - Be similar to job-exposure matrix (JEM) assessment
  - Underestimate exposure

DeVocht 2005: Self-reported exposure depended on health status of participant

- Compared self-reports to JEM in ECRHS

	Specificity	Sensitivity
Asthmatics	0.83	0.48
Non-asthmatics	0.87	0.42

- Self-reports of exposure more prevalent in areas with higher community prevalence of asthma
- Bottom Line: Associations between self-reported occupational exposure and asthma are likely to be positively biased

Delclos 2009 study of asthma in healthcare: sometimes self-reports are OK

- Compared self-reports to workplace JEM
- Little difference in accuracy between asthmatics and non-asthmatics for many exposures
- Some differences in specificity of self-reports
  - Asthmatics – better agreement with patient-care-related cleaning
  - Non-asthmatics – specificity better for instrument cleaning and exposure to adhesives/solvents
- Bottom Line
  - Use externally-developed exposure assessment
  - But, info from non-diseased persons can be useful

Donnay 2011 study of hospital workers: under-reporting of occupational exposures

- Sample of workers in the Epi Study of the Genetics and Environment of Asthma (EGEA)
- Compared self-reports to expert assessment for 8 agents
- Underestimation of exposure for 4 agents
  - Formaldehyde: 27% vs 33%
  - Ammonia: 7% vs 19%
  - Alcohol: 65% vs 93%
  - Quaternary ammonium components: 17% vs 71%
- Bottom Line: workers were unaware of contents of products and underestimated exposures

Population-based JEMs for asthma

- Many function with the ISCO-88 job codes
  - JEM maintained by Nicole LeMoual and colleagues at INSERM (cesp.vjf/inserm.fr/asthmajem) (Kennedy 2005, LeMoual 2014)
  - Northern European JEM, or N-JEM (Lillienberg 2012)
  - ALOHA JEM used in study of work-exacerbated asthma in ECRHS (Sunyer 2005, Henneberger 2010)
- New asthma-specific JEM functions with U.S. SOC-2010 codes – abstract to be presented at 2016 EpiCOH (Henneberger 2016)
- Others . . .

Population-based JEMs for asthma

- Weaknesses
  - Only as good as the 'intelligence' built into them – expert opinion can be of variable quality
  - Since based on existing knowledge, not useful to identify new harmful exposures
- Strengths
  - Objective – not biased by self-reports
  - Better if based on objective indicators of exposure and reflect work conditions of the country of study

References

- Curtin, Richard, Stanley Presser, and Eleanor Singer. 2005. Changes in telephone survey nonresponse over the past quarter century. Public Opinion Quarterly 69 (1): 87–98.
- Delclos GL, Gimeno D, Arif AA, et al. Occupational exposures and asthma in health-care workers: comparison of self-reports with a workplace-specific job exposure matrix. Am J Epidemiol 2009;169:581-587.
- de Vocht F, Zock JP, Kromhout H, et al. Comparison of self-reported occupational exposure with a job exposure matrix in an international community-based study on asthma. Am J Ind Med 2005; 47: 434–442.
- Doney B, Hnizdo E, Graziani M, et al. Occupational risk factors for COPD phenotypes in the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. COPD 2014 Aug;11(4):368-80.
- Donnay C, Denis M-A, Magis R, et al. Under-estimation of self-reported occupational exposure by questionnaire in hospital workers. Occup Environ Med 2011;68:611-617.
- Galea S, Tracy M. Participation rates in epidemiologic studies. Annals Epidem 2007;17(9): 643-653.
- Groves, Robert M. Nonresponse rates and nonresponse bias in household surveys. Public Opinion Quarterly 2006; 70 (5): 646–75.
- Groves RM, Peytcheva E. The impact of nonresponse rates on nonresponse bias: A meta-analysis. Public Opinion Quarterly 2008;72:167-189.
- Henneberger PK, Mirabelli MC, Kogevinas M, et al. The occupational contribution to severe exacerbation of asthma. Eur Respir J 2010; 36: 743–750.
- Kennedy SM, Le Moual N, Choudat D, et al. Development of an asthma specific job exposure matrix and its application in the epidemiological study of genetics and environment in asthma (EGEA). Occup Environ Med 2000;57: 635–641.
- Le Moual N, Carsin A-E, Siroux V, et al. Occupational exposures and uncontrolled adult-onset asthma in the ECRHS II. Eur Respir J 2014; 43: 374–386.
- Lillienberg L, Andersson E, Janson C, et al. Occupational exposure and new-onset asthma in a population-based study in northern Europe (RHINE). Ann Occup Hyg. 2012.
- Sunyer J, Zock JP, Kromhout H, et al. Lung function decline, chronic bronchitis, and occupational exposures in young adults. Am J Respir Crit Care Med 2005; 172: 1139–1145.