# Population-attributable fraction for occupation and asthma

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## Abstract

Here we review the use of the concept of population-attributable risk (PAR) of asthma associated with occupation and give the context for its interpretation. For asthma there is major interest in delineating the "burden of disease", because such assessments can inform health care priorities, intervention policies, and assessment of impact once such steps are implemented. For asthma, the burden of disease from occupational factors is of particular relevance because asthma is a common disease that affects persons of working age and because asthma can be associated with major morbidity and economic cost. In 1999, we carried out a systematic review of the published literature relevant to the occupational PAR in asthma. Of 23 published PAR estimates identified, the median value was 9%, but among those, the 10 estimates based on population-based studies yielded a median PAR estimate of 15%. A few years later a task force of the American Thoracic Society (ATS) summarized the general population-based studies in this field, ending up with a median value of 15%. We have summarized data from publications that have appeared since 2000 and the median value from these publications is 14.4% (range 6–31%).

We show in this analysis that 3 in 20 cases of asthma among adults are likely to be linked to occupational factors. Longitudinal incidence-based estimates, which should be the most reliable, suggest that, if anything, the actual PAR may even be higher. Other measures such as impaired quality of life and economic disadvantage are also important, but are not addressed in this review as there is lack of studies. This points to future research needs to address this knowledge gap in the field of work-related asthma. In the meantime, the consistency of the PAR data that we do have certainly underscores the importance of workplace factors in the overall burden of asthma.

## Introduction

The aim of this chapter on the population-attributable risk (PAR) of asthma associated with occupation is to provide both the data germane to this topic and a context for its interpretation. For chronic conditions generally, there is major interest in delineating the "burden of disease", because such assessments can inform health care priorities, intervention policies, and assessment of impact once such steps are implemented. For asthma, estimating the burden of disease from occupational

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factors is of particular relevance because asthma is a common disease that affects persons of working age and because asthma can be associated with major morbidity and economic cost. Moreover, certain agents have long been recognized to cause new-onset asthma among persons exposed at work, making occupational asthma a widely recognized medical entity. Because of these factors, there is considerable accumulated evidence pertinent to the population burden of asthma attributable to occupation. In this chapter, we first address general epidemiological aspects of attributable risk estimation. We then review the body of evidence that yields such attributable risk estimates, summarizing previous systematic reviews of the literature and presenting data from key analyses that have appeared in the last 10 years. Finally, we place these data in their public health context.

## Estimating PAR

The relative risk (RR) and the odds ratio (OR), the two risk measures most widely familiar to non-epidemiologists, compare the likelihoods of disease among exposed as opposed to non-exposed groups. The measure "population-attributable risk", PAR, is a less familiar construct and, to a certain extent, a less intuitive one. The PAR takes into account both comparative risk (RR or OR) and the frequency of exposure in the population studied. Based on these two components, or risk and exposure, the PAR estimates the proportion of the disease burden among exposed people that is likely to have been caused by the exposure of interest. The PAR is commonly interpreted as the amount of disease that would be prevented (the reduced burden) were the risk factor in question to be removed altogether.

A synonymous term, "population-attributable fraction" (PAF) is preferred by some authors; the expanded term PAR percent also is frequently used. In addition to a lack of familiarity with the construct and inconsistencies in terminology (PAR, PAR%, PAF) that can lead to unnecessary confusion, PAR estimates have other attributes that further complicate their interpretation. As noted above, the PAR estimation can utilize either an RR or OR value in its calculation, but the exposure prevalence (which is a major driver in the ultimate value derived) also has two variants: either the proportion of cases exposed or the overall population exposure rate. Provided that either the RR or OR and that either the case exposure rate or overall exposure proportion has been provided, then the PAR can be estimated *post hoc* from a published study, even if it failed to include an explicit PAR calculation. If the RR or OR used is derived from a multivariate predictive model, then the point estimate of the PAR does reflect the role of any confounding variables included in the model. *Post hoc* calculations without access to the original data set, however, cannot take into account the variance of such covariates, and thus cannot estimate confidence intervals (CI) around PAR estimates derived from published risk and exposure values.

A key attribute of the PAR metric is that, for any given outcome with multiple risk factors, the sum of the estimated risk factors derived form a multivariate model can add up to more the 100% of the risk [1]. This phenomenon is consistent with the effects of risk factors that are inter-related in a more than additive fashion. Although there are no established examples of this in the case of occupational asthma, such a relationship could be possible in the example of estimates for the PAR for chronic obstructive pulmonary disease (COPD) associated with occupation and smoking [2]. There are also other conceptual as well as computational nuances to the estimation and interpretation of attributable risk that are beyond the scope of this chapter; these issues are addressed in a seminal paper by Greenland and Robbins, as well as in a recent review by Benichou [3, 4].

It should also be kept in view that estimates of proportional attribution can be arrived at by other means, although the limitations of such approaches have to be taken into consideration. This is particularly relevant to the occupational asthma literature where incident occupational asthma may be estimated based on a clinically cased attribution, and the "numerator" so generated is divided by the general incidence of asthma from all causes. This proportion can be approached as one form of attributable risk estimate, bearing in mind the limitations of under-diagnosis or over-attribution. Using occupational asthma surveillance data for the numerator in such an exercise (taking the denominator from age-equivalent population incidence) is especially fraught with limitations of under-diagnosis (under-reporting).

## Previous systematic reviews of occupationally associated PAR for asthma

In 1999, we carried out a systematic review of the published biomedical literature dating back to 1966 relevant to the occupational PAR in asthma [5]. This review applied very generous inclusion criteria that captured full publications including PAR estimates and those that only provide data that allowed *post hoc* calculation, as well as published letters and abstracts and even consensus-based estimates in reviews. Of 23 published PAR estimates identified the median values was 9%, but among those, the 10 estimates based on population-based studies yielded a median PAR estimate of 15%. A series of estimates derived *post hoc* from 8 other population-based studies yielded a somewhat higher median PAR value of 20%. Because of the heterogeneity of the data set, we also applied a quality rating schema to the publications. This yield a weighted mean PAR of 15% ($n = 28$ values, excluding 3 non-data-based estimates); the median PAR value among the 12 studies that scored highest in quality was also 15%. Finally, we also extrapolated PAR estimates based on surveillance data for occupational data from 12 systems and presuming an adult general incidence of 1 per 1000 per year. The median PAR extrapolation using that approach was 5%. Of note, in that subset, Finish surveillance-based data yield an extrapolation close to overall central tendency of the data, in the 14–17% range.

Shortly after that systematic review appeared, a task force of the ATS embarked on a similar data synthesis intended to summarize the general population-based studies in this field. This eventually led to the formal adoption (2002) of a statement, *Occupational Contribution to the Burden of Airway Disease* [6]. The ATS systematic review used stricter selection criteria, excluding consensus estimates, letters, and abstracts. Many, but not all of the publications in the ATS review also had been included in the previous review. Even with this different approach, however, the PAR estimates for asthma summarized in the ATS statement also yielded a median value of 15%.

The ATS estimate of 15% was based on 21 different publications. Of these, 7 were asthma cohorts or case series in which the estimated occupational contribution was not based on an epidemiological estimate, but rather the proportion of occupationally attributed cases to all asthma cases. The remaining 14 studies were all population-based and either reported a PAR estimate or provided data from which a PAR estimate could be calculated for the purposes of the ATS review. Table 1 lists the findings from those 14 studies, many of which were quite large in size [7–20]. One study was based on an analyses of the European Community Respiratory Health Survey (ECRHS I), including 22 countries from three continents [7]. The range of the PAR was wide from 5% to 51%, with a mean value of 19.5%.

*Table 1. The occupational contribution to the burden of asthma. General population studies reviewed in the ATS document*

| Endpoints | Number of studies | PAR median | PAR range | Reference |
|---|---|---|---|---|
| Bronchial hyperreactivity and symptoms | 1 | 10% | NA | [7] |
| Clinical diagnosis | 6 | 34.5% | 5–51% | [8–13] |
| Self-reported asthma, including physician-diagnosed | 7 | 19% | 15–29% | [14–20] |
| Total | 14 | 19.5% | 5–51% | [7–20] |

## Recent longitudinal studies of PAR

The variability in previous PAR estimates, even with a central tendency in the 15–20% range (depending on the study range included) underscores the value in evaluating additional relevant studies that have appeared in the interim. Because we have the benefit of such a rich data set of previously analyzed material, the field has sufficiently evolved so that more restricted analysis is appropriate. To that end, we

emphasize here estimates derived from general population sampling. Moreover, we highlight in particular data obtained through longitudinal follow-up, as opposed to cross-sectional analyses.

Table 2 summarizes the data from 12 publications relevant to occupational risk for asthma based on general population studies or other systematic recruitment that have appeared since 2000 [21–32]. Overall, the studies summarized in Table 2 support and amplify the findings of the earlier ATS statement. In total, these studies represent 51 294 subjects, excluding the large longitudinal cohort study from Finland, which included 829 351 additional subjects [25]. For the data shown in Table 2, we derived all of the PAR estimates, based either on the published PAR value or by calculating the PAR using the published risk estimates and exposure proportions according to the same methods that were also used in the ATS statement [6].

Three of the studies (Tab. 2) are prospective longitudinal investigations, based on follow-up of previous general population samples [21, 24, 25]. The Norwegian study represents a follow-up of a general population sample of 3886 subjects investigated in 1985 [21]. The age at study baseline in 1985 ranged from 15 to 70 years. The study participants were investigated 10 years later, 1996, with a new questionnaire that was completed by 2819 subjects (89% of the baseline group). Asthma at follow-up was defined as an affirmative answer to "having been hospitalized or treated by a physician for asthma". The occupational exposure was defined by the self-report questionnaire item "Have you ever had a workplace with much dust or fumes in the air?" The exposure prevalence was 28%, with a considerable difference between males (44%) and females (13%). The risk for incident asthma during follow-up in relation to ever exposed to dust or fumes was analyzed using logistic regression models, yielding a 60% increased odds of disease associated with exposure (OR 1.6, 95% CI 1.01–2.5). The PAR associated with dust or fumes and incident asthma, presented in the published paper, was 14.4% (95% CI 1.2–27.6). Risk estimates stratified by sex were not included. Strengths of this study, over and above its relatively large, population-based cohort, include the longitudinal design, thus assessing incident asthma, the high subject retention rate, mitigating selection effects, and the provision of a PAR estimates that includes 95% CI values. Because the exposure and incident asthma occurred over the follow-up period is not analyzed in terms of specific time points, a potential study weakness lies in lack of a temporal anchor (i.e., in some cases exposure might have followed disease onset). Because of job stability and the low likelihood that persons with asthma will migrate from low exposure to high exposure jobs this concern is more theoretical than practical. In addition, risk estimates stratified by sex were not provided. Other weaknesses include the lack of sex-stratified risk estimates and the reliance on a single exposure metric.

The second study with high quality is the follow-up analysis of the European Respiratory Health Survey (ECRHS II) [24]. The ECRHS is an international cross-

*Table 2. The occupational contribution to the burden of asthma: Population-based studies published since 2000*

| Ref. | N | Design | Country | Asthma definition | Occupational exposure | PAR |
|---|---|---|---|---|---|---|
| 21 | 2819 | Longi-tudinal cohort | Norway | Self report of physician-diagnosed asthma | Self-reported exposure to much dust or fumes | 14.4% |
| 22 | 13 826 | Cross-sectional cohort | South Africa | Self report of physician or nurse diagnosed asthma | Ever regularly exposed to smoke, dust, fumes or strong smells or worked underground in a mine | 13.6% |
| 23 | 1922 | Cross-sectional cohort | Brazil | BHR and work-related asthma symptoms | Self-reported exposure to vapor, gas, fumes, chemical products, paints and humidity | 22.9% |
| 24 | 6837 (3994, BHR tested subset) | Longi-tudinal cohort | Inter-national | Asthma symptoms or asthma medication; above definition + BHR | Job Exposure Matrix defined occupational risk | 11% 23% Med = 17% |
| 25 | 892351 | Longi-tudinal cohort of all employed Finns | Finland | Physician diagnosis based on asthma symptoms and at least one criteria of airway reversibility | Occupations a priori classified as exposed | 29% (Males) 17% (Females) Weighted = 22% |
| 26 | 5331 | Cross-sectional cohort | New Zealand | Self-report of physician-diagnosed, adult-onset asthma | Occupations a priori classified as exposed | 9.5% |
| 27 | 14151 | Cross-sectional cohort | France | Dyspnea with wheezing or asthma attacks; asthma onset after start of current job | Self reported exposure; occupations a priori classified as exposed using a JEM | 9%, 14%; 1%; 3% Med = 6% |
| 28 | 376 | Cross-sectional case control | France | Specialist physician diagnosis | Occupations a priori classified as exposed using a JEM | 10% |
| 29, 30 | 6827 | Cross-sectional cohort | USA | Self-report of physician-diagnosed asthma and work-related symptoms | Industries a priori classified as exposed; Occupations a priori classified as exposed | 36.5%; 26% Med = 31% |

*Table 2 (continued)*

| Ref. | N | Design | Country | Asthma definition | Occupational exposure | PAR |
|---|---|---|---|---|---|---|
| 31 | 566 | Cross-sectional case control | Sweden | General MD diagnosis | Occupations a priori classified as exposed | 18% |
| 32 | 1482 | Cross-sectional cohort | USA | Self-report of MD diagnosis | Self-report of exposure; Occupations a priori classified as exposed using a JEM | 17%; 5% Med = 11% |

BHR, Bronchial hyperreactivity measured by methacholine challenge; JEM, job exposure matrix; Med, midpoint or median value

sectional investigation drawing on data from 28 centers in 13 countries. At baseline data collection (1990–1995), each center mailed a questionnaire to 3000 randomly selected subjects aged 20–44 years of age. From the responders there was further selection of a random smaller sample and a sample enriched with subjects with asthma and asthma symptoms. At baseline, a cross-sectional analysis was performed observing increased risks for asthma among farmers, painters and cleaners, and this was included in the ATS review [6]. Ten years later, follow-up was performed in which the participants completed extensive questionnaires including detailed occupational histories covering interval job duties and potential exposures. Subjects with asthma, wheezing and dyspnea at baseline were excluded from the analysis in order to study incident disease. Asthma during follow-up was defined in several ways, but the most restrictive definition used reporting an asthma attack or having used asthma medication in the 12 months preceding the follow-up interview, in combination with a positive methacholine-challenge test at the follow-up visit. Work-related exposure was assessed by linking the occupations held during follow-up to an asthma-specific job-exposure matrix (JEM) used in the previous cross-sectional analyses. A second measure of risk was based on broadly classified "high-risk" occupations. The reported PAR of the JEM-classified occupational exposure for new-onset asthma was 23% (95% CI 1–40%). The broader occupational risk definition yielded a slightly higher PAR estimate of 26%. Using a less strict definition of asthma that did not include methacholine responsiveness, the estimated PAR (JEM-based exposures) was 11% (95% CI 1–20%). This analysis allowed utilization of a larger study number (6788 vs 3994). The strengths of this study, in addition to its large, international scope and its longitudinal design, include the multiple measures of exposure and the conservative (as well as more liberal) definitions of disease. One limitation in the ECRHS is its low overall follow-up successful response rate of 58%, and the further loss of subjects in the methacholine-based analyses. In

addition, CIs for the PAR estimates were not provided nor was PAR estimated for sex-specific strata.

The Finnish study included in Table 2 was based on follow-up of three cohorts of employed Finns aged 25–59 years at baseline [25]. The cohorts were defined 1985, 1990 and 1995 and followed for 5 years each. Hence, by design these cohorts do not overlap in time. Onset of asthma during follow-up was obtained from a National Register for Reimbursement, based on asthma medication cost coverage. To be qualified for reimbursement, a physician must certify a valid diagnosis of asthma including objective documentation of variable airway obstruction or hyperresponsiveness (reversible $FEV_1$, serial peak flow measurements, or a positive methacholine-challenge test) and the presence of symptoms consistent with disease. Subjects with asthma at baseline were excluded from the analysis. Work-related exposure was defined on the basis of certain occupations held at baseline and considered *a priori* to carry increased risk of causing asthma. Incidence rates of asthma in each occupation were estimated, and incidence ratios using log-linear models adjusting for age were calculated. The PAR for occupational exposure and new-onset asthma, provided in the published study results, was 29% (95% CI 25–33%) for men and 17% (95% CI 15–19%) for women. This study has high internal and external validity, utilizing national registry data. One weakness is that the study is biased towards more severe asthma, given that only cases reimbursed for medication are included. This is counter-balanced by a reduction in classification error for disease in the direction of non-asthmatics being classified as ill. In addition, the broad, occupation-based exposure is a fairly crude metric. Finally, although the study provides sex-stratified PAR estimates with accompanying CIs, no calculation of attributable risk is provided for males and females combined. A weighted PAR value of 22% can be derived from the data.

Taking the three studies above as yielding the highest quality PAR estimates, the summary values to be considered are: 14%, 11–23% (depending on the asthma definition, the mid-point is 17%) and 22%.

## Cross-sectional studies

All of the remaining nine studies whose results are summarized in Table 2 are cross-sectional rather than longitudinal [22, 23, 26–31]. Some yielded multiple PAR estimates using differing measures of exposure or asthma outcome or both, including two published analyses of the same national survey data, one based on industry and one based on occupation [27, 29, 30, 32]. Where multiple PAR values were presented, Table 2 also provides a mid-point (median) value. All but two studies explicitly presented a PAR estimate; the values were calculated for these [23, 28].

The eight summary PAR values yielded by these nine cross-sectional studies range from 6% to 31%, with a median of 12.4%. The heterogeneity in results is

not surprising. The definitions of asthma differed considerably. Of particular note, the highest PAR estimate was derived from a study that defined asthma as both the report of a physician's diagnosis and self-report of work-related symptoms; this is treated by the authors as a measure of "work-related asthma" [29, 30]. In general, JEM-based PAR estimates were lower than those based on self-report: 1–3% compared to 9–14% in one study and 5% compared to 17% in another [27, 32].

One the studies shown did not provide risk and exposure data to yield a classic PAR estimate, but rather attributable risk based on the number cases of adult onset asthma with work-related symptoms asthma symptoms and onset of new asthma on that job [23]. The 22.9% PAR in that series is the second highest estimate among the cross-sectional studies. This study is special interest, however, because it represents one of only two estimates from studies in developing economies, the other being a PAR of 13.6% from South Africa [22].

Cross-sectional studies of asthma broadly defined to include onset at any age may be at risk of under-estimating occupational risk. To the extent that persons with life-long asthma either manifest no association with workplace factors or self-select into lower exposure jobs, this will bias to the null or even a negative occupational association. Even limited to adult-onset asthma, cross-sectional analyses ascertaining current occupations rather than the job held at the onset of disease run the risk of survivor bias towards the null. Cross-sectional studies may also face reporting biases if they depend on self-report of exposure, although this phenomenon may be less important that sometimes presumed [33].

If all 11 summary PAR estimates from Table 2 are considered together, the median value is 14.4% (range 6–31%). Once again, this wholly in line with previous ATS estimate.

## Other data sources

There are also a few additional reports not included in Table 2 that, nonetheless, should be mentioned. An analysis of the Singapore Chinese Health Study included 52 325 subjects [34]. Although this study does not provide PAR estimates, it does include risk estimates for adult-onset asthma for three categories or workplace exposures; dusts, smokes, and vapors. Although these three exposure categories yield PAR estimates of 2.7,%,1.7% and 4.2%, respectively, it is not clear to what extent the exposure categories overlap and only for vapors does the 95% CI for the OR exclude 1.0.

There have also been two recent U.S. studies of asthma incidence in which an attribution of work-relatedness was made. In one study of incident adult asthma in a large health maintenance organization (HMO) data set (203 701 person years of observation) concluded that 33% of incident asthma (which could include "recurrent" asthma previously in remission) was work-related [35]. Another large HMO

study (109 125 person years of observation) found that 24% of the cases had at least moderate evidence of an occupational trigger [36]. These studies have limitations due to subject participation in the structured interviews forming the basis of attribution, a selection effect that may in part account for the relatively high proportional attributions.

Finally, it should be noted that occupational disease registries continue to provide estimates of occupational asthma incidence, which can be used to extrapolate an attributable fraction as a proportion of incidence among all persons of working age. Our 1999 extrapolations used registry and other surveillance data from Canada (British Columbia and Quebec), the U.S. (California and Michigan), the United Kingdom (including Shield and Sword), Finland, Sweden, and Germany [5]. Since that time, surveillance-based data (annual rates per 100 000 workers) have been reported from Norway (10.1), France (2.4), Belgium (2.4), Italy (Piedmont region, 2.4), Spain (Catalonia, 7.7), Australia (3.1), New Zealand (3.1), and South Africa (1.3 overall; 3.8 from the Western Cape) [37–44]. Even assuming a relatively low general asthma incidence of 100 per 100 000 in adults of working age, these rates would equate to an attributable proportion of only 1–10%. It is well recognized, however, that such registry data fail to capture the majority of true cases. For example, data from Finland indicate that, even after excluding officially recognized occupational asthma cases, excess risk of disease was still evident on epidemiological grounds; the remaining risk was consistent with under-detection of one half to two-thirds of cases proportionally, even for well-recognized risk groups such as bakers, fur workers, and painters [45]. Consistent with this, survey data from three U.S. states found that, although 5.8% to 6.1% of adults with asthma had been told that by a physician that their condition was work related, the total increased to 7.4–9.7% if the respondents own assessment was included, an incremental increase proportionally of up to two-thirds greater prevalence [46]. Thus, it should be presumed that any PAR value extrapolated from registry sources would be a woeful underestimate.

## Conclusion

Prior systematic reviews of the literature identified a wide range of estimates for the PAR for occupational exposures in asthma, but with a central tendency close to 15% [5, 6]. As we have shown, emerging data continue to support the estimation that 3 in 20 cases of asthma among adults are likely to be linked to occupational factors. Moreover, longitudinal incidence-based estimates that should be the most reliable suggest that, if anything, the actual PAR may even be higher.

Certain limitations of this analysis should also be borne in mind. First of all, we have not addressed the burden of work-aggravated asthma, i.e., pre-existing asthma made worse by work. Epidemiological analysis of this complex problem

is challenging and far beyond the scope of this review. It has been suggested that PAR estimates of exacerbation of chronic disease (e.g., work-aggravated asthma) may also need to take causation into account so that the burden of disease is not underestimated [47].

Beyond this, use of the PAR as a measure of risk itself has been questioned. It is important to remember that a basic assumption is that the relative risk upon which the PAR is based must accurately reflect exposure effects in the target population [3, 48]. Another assumption is that the dichotomous classification of exposure into two levels, exposed and unexposed, yields an unbiased estimate of the PAF when there is non-differential misclassification of exposure, an assumption that has been challenged [49].

Finally, the burden of disease, which the PAR attempts to capture, may transcend simplistic notions of the presence or absence of a diagnosis. One alternative measure of burden is 'disability adjusted life years' (DALYS). To apply this to a specific health condition, such as occupationally related asthma, requires an assumption of the proportional risk. In other words, the PAR as conceptualized above is intrinsically linked to such an exercise. For example, Driscoll et al. [50] presumed an occupational PAF of 21% to estimate a global burden of occupationally associated asthma DALYS of 1 621 000.

Beyond DALYS, which address disability, other manifestations of the burden of disease, such as impaired quality of life and economic disadvantage, are by no means trivial. This points the way to future research, which needs to address this knowledge gap in the field of work-related asthma. In the meantime, the consistency of the PAR data that we do have certainly underscores the importance of workplace factors in the overall burden of asthma.

## References


1 Rowe AK, Powell KE, Flanders D. Why population attributable fractions can sum to more than one. *Am J Prev Med* 2004; 26: 243–9

2 Blanc PD, Toren K. Occupation in COPD and chronic bronchitis: An update. *Int J Tuberc Lung Dis* 2007; 11: 251–7

3 Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fractions. *Am J Epidemiol* 1988; 128: 1185–97

4 Benichou J. Biostatistics and epidemiology: Measuring the risk attributable to an environmental or genetic factor. *C R Biologies* 2007; 220: 281–98

5 Blanc PD, Torén K. How much adult asthma can be attributed to occupational factors? *Am J Med* 1999; 107: 580–587

6 Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Torén K, Viegi G. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003; 167: 787–797

7 Kogevinas M, Antó JM, Sunyer J, Tobias A, Kromhout H, Burney P. A population-based study on occupational asthma in Europe and other industrialised countries. *Lancet* 1999; 353: 1750–1754
8 Ng TP, Hong CY, Koh KTC, Ling SL. Risk of asthma associated with occupation in a community-based case-control study. *Am J Ind Med* 1994; 25: 709–718
9 Isoaho R, Puolijoki H, Huhti E, Kivelä SL, Tala E. Prevalence of asthma in elderly Finns. *J Clin Epidemiol* 1994; 47: 1109–1118
10 Flodin U, Ziegler J, Jönsson P, Axelson O. Bronchial asthma and air pollution at workplaces. *Scand J Work Environ Health* 1996; 22: 451–456
11 Reijula K, Haahtela T, Klaukka T, Rantanen J. Incidence of occupational asthma and persistent asthma in young adults has increased in Finland. *Chest* 1996; 110: 50–61
12 Torén K, Balder B, Brisman J, Lindholm N, Löwhagen O, Palmqvist M, Tunsäter A. The risk of asthma in relation to occupational exposures: A case-control study. *Eur Respir J* 1999; 13: 496–501
13 Katz I, Moshe I, Sosna J. The occurrence, recrudescence and worsening of asthma in a population of young adults. *Chest* 1999; 116: 614–618
14 Blanc PD. Occupational asthma in a national disability survey. *Chest* 1987; 92: 613–617
15 Viegi G, Prediletto R, Paoletti P, Carozzi L, di Pede F, Vellutini M, di Pede C, Giuntini C, Lebowitz M. Respiratory effects of occupational exposure in a general population sample in North Italy. *Am Rev Respir Dis* 1991; 143: 510–515
16 Bakke P, Eide GE, Hanoa G, Gulsvik A. Occupational dust or gas exposure and the prevalences of respiratory symptoms and asthma in the general population. *Eur Respir J* 1991; 4: 273–278
17 Xu X, Christiani D. Occupational exposures and physician-diagnosed asthma. *Chest* 1993; 104: 1364–1370
18 Neijari C, Tessier JF, Letenneur L, Datigues JF, Salamon R. Prevalence of self-reported asthma symptoms in a French elderly sample. *Respir Med* 1996; 90: 401–408
19 Monso E, Munoz-Rino F, Izquierdo J, Roca J, Masia N, Rosell A, Morera J. Occupational asthma in the community: Risk factors in a western Mediterranean population. *Arch Environ Health* 1998; 53: 93–98
20 Forastiere F, Balmes J, Scarinci M, Tager IB. Occupations, asthma and chronic respiratory symptoms in a community sample of older women. *Am J Respir Crit Care Med* 1998; 157: 1864–1870
21 Eagan T, Gulsvik A, Eide GE, Bakke PS. Occupational airborne exposure and the incidence of respiratory symptoms and asthma. *Am J Respir Crit Care Med* 2002; 166: 933–938
22 Ehrlich RI, White N, Norman R, Laubscher R, Steyn K, Lombard C, Bradshaw D. Wheeze, asthma diagnosis and medication use: A national adult survey in a developing country. *Thorax* 2005; 60: 895–901
23 Caldeira RD, Bettiol H, Barboeri MA, Terra-Filho J, Garcia CA, Vianna EO. Prevalence

and risk factors for work related asthma in young adults. *Occup Environ Med* 2006; 63: 694–699

24 Kogevinas M, Zock J-P, Jarvis D, Kromhout H, Lillienberg L, Plana E, Radon K, Torén K, Allikso A, Benke G, 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

25 Karjalainen A, Kurppa K, Martikainen R, Klaukka T, Karjalainen K. Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. *Am J Respir Crit Care Med* 2001; 164: 565–568

26 Johnson A, Toelle BG, Yates D, Belousova E, Ng K, Corbett S, Marks G. Occupational asthma in New South Wales (NSW): A population-based study. *Occup Med* 2006; 56: 258–262

27 Le Moual N, Kennedy SM, Kauffmann F. Occupational exposures and asthma in 14,000 adults from the general population. *Am J Epidemiol* 2004; 160: 1108–1116

28 Kennedy SM, Le Moual N, Choudat D, Kauffmann F. Development of an asthma specific job exposure matrix and its application in the epidemiological study of genetic and environment in asthma (EGEA). *Occup Environ Med* 2000; 57: 635–41

29 Arif AA, Whitehead LW, Delclos GL, Tortolero SR, Lee ES. Prevalence and risk factors of work-related asthma by industry among united Sates workers: Data from the third national health and nutrition examination survey (1988–94). *Occup Environ Med* 2002; 59: 505–511

30 Arif AA, Delclos GL, Whitehead LW, Tortolero SR, Lee ES. Occupational exposures associated with work-related asthma and wheezing among U.S. workers. *Am J Ind Med* 2003; 44: 368–76

31 Flodin U, Jönsson P. Non-sensitizing air pollution at workplaces and adult-onset asthma. *Int Arch Occup Environ Health* 2004; 77: 17–22

32 Blanc PD, Eisner MD, Balmes JR, Trupin L, Yelin EH, Katz PP. Exposure to vapours, gas, dust or fumes: Assessment by a single survey item compared to a detailed exposure battery and a job exposure matrix. *Am J Ind Med* 2005; 48: 110–117

33 Quinlan PJ., Earnest G, Eisner MD, Yelin EH, Katz PP, Balmes JR, Blanc PD. Performance of self-reported occupational exposure compared to a job exposure matrix approach in asthma and chronic rhinitis. *Occup Environ Med* 2009; 66: 154–160

34 LeVan TD, Koh W-P, Lee H-P, Koh D, Yu MC, London SJ. Vapor, dust, and smoke exposure in relation to adult-onset asthma and chronic respiratory symptoms. *Am J Epidemiol* 2006; 163: 1118–28

35 Vollmer WM, Heumann MA, Breen VR, Henneberger PK, O'Connor EA, Villnave JM, Frazier EA, Buist AS. Incidence of work-related asthma in members of a health maintenance organization. *J Occup Environ Med* 2005; 47: 1292–97

36 Sama SR, Milton DK, Hunt PR, Houseman EA, Henneberger PK, Rosiello RA. Case-by-case assessment of adult-onset asthma attributable to occupational exposures among members of a health maintenance organization. *J Occup Environ Med* 2006; 48: 400–407

37 Leira HL, Bratt U, Slåstad S. Notified cases of occupational asthma in Norway: Exposure and health consequences for health and income. *Am J Ind Med* 2005; 48: 359–64
38 Amielle J, Pauli G, Calastren-Crinquand A, Vervloët D, Iwatsubo Y, Popin E, et al. Reported incidence of occupational asthma in France, 1996–99: The ONAP program. *Occup Environ Med* 2003; 60: 136–41
39 Vandenplas O, Larbanois A, Bugli C, Kempeneers E, Nemery B. Épidémiologie de l'asthme professionel en Belgique. *Rev Mal Respir* 2005; 22: 421–30
40 Bena A, D'Errico A, Mirabelli D. Un sistema di rilevazione atriva dell'asma bronchiale professionale: I resultati di due anni di attività del programma PRiOR. *Med Lav* 1999; 90: 4: 556–571
41 Orriols R, Costa R, Albanell M, Alberti C, Castejon J, Monso E, et al. Reported occupational respiratory diseases in Catalonia. *Occup Environ Med* 2006; 63: 255–260
42 Elder D, Abramson M, Fish D, Johnson A., McKenzie D, Sim M. Surveillance of Australian workplace Based Respiratory Events (SABRE): Notifications for the first 3.5 years and validation of occupational asthma cases. *Occup Med* 2004; 54: 395–00
43 Walls C, Crane J, Gillies J, Wilsher M, Wong C. Occupational asthma cases notified to OSH from 1996 to 1999. *N Z Med J* 2000; 113: 491–2
44 Hnizdo E, Esterhuizen TM, Rees D, Lalloo UG. Occupational asthma as identified by the Surveillance of Work-related and Occupational Respiratory Diseases programme in South Africa. *Clin Expir Allergy* 2001; 31: 32–9
45 Karjalainen A, Kurppa K, Martikainen R, Karjalainen J, Klaukka T. Exploration of asthma risk by occupation – Extended analysis of an incidence study of the Finnish population. *Scand J Work Environ Health* 2002; 28: 49–57
46 Flattery J, Davis L, Roseman KD, Harrison R, Lyon-Callo S, Filios M. The proportion of self-reported asthma associated with work in three states: California, Massachusetts, and Michigan, 2001. *J Asthma* 2006; 43: 213–8
47 Kunzli N, Perez L, Lurmann F, Hricko A, Penfld B, McConnell R. An attributable risk model for exposures assumed to cause both chronic disease and its exacerbations. *Epidemiology* 2008; 19: 179–85
48 Greenland S. Attributable fractions: Bias from broad definition of exposure. *Epidemiology* 2001; 12: 518–520
49 Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN. Attributable risk: Advantages of a broad definition of exposure. *Am J Epidemiol* 1994; 140: 303–309
50 Driscoll T, Nelson DI, Steenland K, Leigh J, Concha-Barrientos M, Fingerhut M, Prüss-Üstün A. The global burden of non-malignant respiratory disease due to occupational airborne exposures. *Am J Ind Med* 2005; 48; 432–45