Reducing Attenuation in Exposure-Response Relationships by Exposure Modeling and Grouping: The Relationship Between Wood Dust Exposure and Lung Function

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Background *In a study of wood dust exposure and lung function, we tested the effect on the exposure–response relationship of six different exposure metrics using the mean measured exposure of each subject versus the mean exposure based on various methods of grouping subjects, including job-based groups and groups based on an empirical model of the determinants of exposure.*
Methods *Multiple linear regression was used to examine the association between wood dust concentration and forced expiratory volume in 1s (FEV_1), adjusting for age, sex, height, race, pediatric asthma, and smoking.*
Results *Stronger point estimates of the exposure–response relationships were observed when exposures were based on increasing levels of aggregation, allowing the relationships to be found statistically significant in four of the six metrics. The strongest point estimates were found when exposures were based on the determinants of exposure model.*
Conclusions *Determinants of exposure modeling offers the potential for improvement in risk estimation equivalent to or beyond that from job-based exposure grouping.* Am. J. Ind. Med. 46:663–667, 2004. *© 2004 Wiley-Liss, Inc.*

KEY WORDS: determinants of exposure; occupational exposure; epidemiology

INTRODUCTION

A major focus of recent methodological work in the field of occupational epidemiology has been the development of exposure assessment and analysis strategies for reducing attenuation in exposure–response relationships [Armstrong, 1990; Kromhout and Heederik, 1995; Kromhout et al., 1995; Seixas and Sheppard, 1996; Tielemans et al., 1998; Werner and Attfield, 2000]. Initial work built on statistical theory to estimate the number of measurements per subject required to minimize attenuation, based on the distribution of the components of variance between- and within-subjects [Snedecor and Cochran, 1967; Lui et al., 1978]:

$$\beta^* = \left(\frac{\sigma^2_{BS}}{\sigma^2_{BS} + (\sigma^2_{WS})/n}\right)\beta \qquad (1)$$

where β is the true coefficient of the relationship between exposure and response, β* is the estimated coefficient, σ^2_{BS} is between-subject exposure variance, σ^2_{WS} is within-subject exposure variance, and n is the number of exposure measurements per subject.

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In the last decade, the benefit of grouping similarly-exposed workers has been recognized: the group mean exposure is more precisely estimated than individual subject means and exposure–response analyses are less biased to the null [Armstrong, 1990; Seixas and Sheppard, 1996]. The following expression [Tielemans et al., 1998] illustrates that increasing the number of subjects per group can be as effective in reducing the attenuation of exposure–response relationships as increasing the number of measurements per subject, usually a considerably more costly proposition:

$$\beta^* = \left(\frac{\sigma^2_{BG} + (\sigma^2_{WG}\ /k}{\sigma^2_{BG} + (\sigma^2_{WG})/k + (\sigma^2_{WS})/kn}\right)\beta \qquad (2)$$

where σ^2_{BG} is between-group exposure variance, σ^2_{WG} is within-group exposure variance, and k is the number of subjects per group. Recent attention has focussed on methods to group study subjects to optimize this effect [Tielemans et al., 1998].

In a cross-sectional study of the effects of wood-related exposures on lung function [Demers et al., 2000], we explored the impact on exposure–response relationships of a number of methods for assigning exposures to subjects: using the measured exposure of each individual versus using the mean exposure resulting from various grouping methods. Groups were based on subjects' measured exposures, on jobs, and on an empirical model of the determinants of exposure [Teschke et al., 1999; Demers et al., 2000]. In screening analyses, with wood dust exposures of subjects' jobs categorized as less than 1, 1–1.9, and 2 mg/m^3 or more, both forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) decreased monotonically with increasing exposure (3.58, 3.45, 3.36 L, respectively for FEV_1 and 4.67, 4.51, and 4.43 L for FVC). In this article, we focus on FEV_1 as an example and report the effect of the different exposure metrics on the strength of the linear exposure–response relationship with wood dust concentration.

METHODS

Sawmill Subjects

In the summer of 1996, 229 personal inhalable particulate samples were collected on 112 sawmill workers in 37 jobs in 6 departments using 0.45-μm pore size, 25-mm Teflon filters (Corning, Costar, Acton, MA) mounted in 7-hole samplers (JS Holdings, Stevenage, UK) with air drawn at 2 L/min. The wood-specific concentrations were estimated based on gravimetric analysis (triplicate weighings with a microbalance) and the resin acid content of the particulate (extraction with dichloromethane and quantification by gas chromatography/mass spectrometry) [Demers et al., 2000]. The number of exposure measurements per subject ranged from 1 to 5 with a mean of 2.0; the number per job ranged from 2 to 17 with a mean of 6.2.

Data on mill, department, and job characteristics were recorded concurrently with exposure measurements used to derive an empirical model predicting wood dust exposure [Teschke et al., 1999]. The final model included factors such as tree species, wood condition, location in the mill, job, task, booth enclosure, and weather conditions. It explained 73% of the exposure variance.

Pulmonary function tests were conducted on 235 sawmill subjects using a 10 L dry-rolling-seal spirometer (S&M Instruments, Louisville, CO), according to techniques recommended by the American Thoracic Society. Three acceptable forced expiratory maneuvers were obtained from seated participants wearing nose clips with expiration continued until a visible 1-s volume plateau was achieved. The best FEV_1 values were used for analysis. Concurrent data on known and potential correlates of lung function (age, sex, race, height, smoking, asthma) were collected.

For inclusion in the analyses reported here, subjects needed usable data on wood dust exposure (from either personal samples or estimates based on job or empirical modeling) and lung function. Maintenance, supervisory, office, and logging staff were excluded. This left 105 sawmill subjects with 211 exposure measurements for inclusion in this study. All could be assigned exposures based on their job or the empirical exposure model; two were missing personal exposure measurements.

Unexposed Subjects

Subjects (483) from two previous studies of marine transportation workers and bus mechanics, similar in work activity levels to the sawmill workers and without prior asbestos exposure, were included to stabilize the analyses. Lung function data were collected in a manner identical to the sawmill study, using the same lung function technician and instrumentation. These subjects were assumed to be unexposed to wood dust, since none of their jobs involved direct or indirect contact with wood.

Exposure–Response Relationships

Multiple linear regression was used to examine the associations between wood dust concentration and FEV_1, i.e., a linear exposure–response model, as suggested by our screening analyses and as used elsewhere in lung function analyses [van Tongeren et al., 1999; Heederik and Attfield, 2000]. The model was adjusted for age (continuous variable, units = years), sex, height (continuous variable, units = cm), race (Caucasian or not), pediatric asthma (yes or no), and pack-years of smoking (as separate variables for current and ex-smokers). All analyses were done using SPSS 11.0 (SPSS, Inc., Chicago, IL).

Wood dust exposure levels were assigned to sawmill subjects using six metrics. Three involved either no or very little grouping, with each subject assigned:

- the mean of their own exposure measurements (103 subjects had personal exposure measurements);
- the mean exposure of their job(s) (39 jobs or job combinations, since some employees held more than one job); and
- the exposure predicted by applying the determinants of exposure model to the subject's work conditions (94 predicted exposure levels).

Three additional metrics were created by assigning the sawmill subjects to larger exposure groups using each of the exposure assignment methods described above. The same cutpoints were used for each of the "grouping" metrics: $\geq$0.03–0.6, $\geq$0.6–1.0, $\geq$1.0 mg/m^3, producing three groups of sawmill employees for each of the following metrics.

- Groups based on the individual subject mean exposure levels.
- Groups based on the job mean exposure levels.
- Groups based on the model-predicted exposures.

For each of the grouping metrics, sawmill subjects were assigned the mean exposure of their group, i.e., a continuous exposure measure.

For all analyses, unexposed non-sawmill subjects were assigned a wood dust exposure concentration of 1/10 of the detection limit (0.03 mg/m^3): 0.003 mg/m^3.

Ethics

All study methods were approved by the University of British Columbia Ethical Review Committee and informed consent was obtained from study subjects for all exposure and lung function measurements.

RESULTS

The measured inhalable wood dust exposures of the sawmill employees ranged from 0.03 to 15 mg/m^3 (mean = 1.01 mg/m^3, geometric mean = 0.54 mg/m^3, geometric standard deviation = 2.9, n = 103). Table I summarizes personal characteristics of the sawmill workers and unexposed subjects.

Table II lists the coefficients of the exposure–response relationships estimated for each of the six exposure metrics. Figure 1 shows the relationships graphically. Stronger point estimates of the exposure–response relationships were observed when exposures were assigned based on increasing aggregation, e.g., when sawmill subjects were assigned exposures based on their jobs (metric 2) versus their own exposure measurements (metric 1), and when sawmill subjects were categorized into large exposure groups (metrics 4, 5, and 6). The strongest relationships were observed when exposures were estimated using an empirical model of the determinants of exposure (metrics 3 and 6).

The analyses were also performed without the unexposed subjects. The relative pattern of regression coefficients across the various exposure metrics was the same but confidence intervals were wider as expected given the smaller sample size (results not shown).

DISCUSSION

These results support the theoretical benefit postulated for assigning subjects the mean exposure of their group, because of the resulting increase in precision of the exposure estimates and the partial Berkson error structure [Armstrong, 1990; Seixas and Sheppard, 1996; Tielemans et al., 1998]. They also agree with the results of a number of other studies that have shown benefits of grouping on exposure–response relationships [Kromhout et al., 1997; van Tongeren et al., 1999; Heederik and Attfield, 2000; Werner and Attfield, 2000].

Greater aggregation produced stronger point estimates of the exposure–response relationship, as predicted by the

TABLE I. Personal Characteristics of Sawmill Workers and Subjects Unexposed to Wood Dust

Characteristic	Sawmill subjects (n = 105)	Unexposed subjects (n = 483)
Age, mean (range)	39.4 years (18–61)	44.4 years (22–64)
Height, mean (range)	172 cm (151–190)	175 cm (152–196)
Male	83.8%	88.6%
Caucasian	59.0%	87.8
Pediatric asthma	4.8%	5.2%
Non-smokers	46.7%	35.4%
Current smokers (mean pack-years)	33.3% (18.8 pack-years)	24.6% (22.7 pack-years)
Ex-smokers (mean pack-years)	20.0% (12.5 pack-years)	40.0% (16.9 pack-years)

TABLE II. Comparison of Exposure–Response Relationships Using Six Different Exposure Metrics; Coefficients Indicate the Decline in Forced Expiratory Volume in 1 s (FEV_1, in Liters) per Unit Increase in Wood Dust Concentration (mg/m^3)

Exposure metric: method of assigning wood dust exposure to each study subject	Number of exposure levels (including unexposed controls)	Coefficient[a] (95% CI)
No/little grouping		
1. Mean exposure of subject	104	−0.034 (0.010 to −0.078)
2. Mean exposure of subject's job	40	−0.073 (−0.018 to −0.128)
3. Exposure predicted by determinants model	95	−0.106 (−0.012 to −0.200)
Grouping		
4. Groups based on mean exposure of subject[b]	4	−0.065 (0.008 to −0.138)
5. Groups based on mean exposure of subject's job[b]	4	−0.086 (−0.013 to −0.158)
6. Groups based on exposure predicted by determinants model[b]	4	−0.123 (−0.021 to −0.225)

[a]Relationships adjusted for age, height, sex, non-Caucasian race, pediatric asthma, pack-years of smoking (current smokers), and pack-years of smoking (ex-smokers).
[b]Each subject was assigned the mean wood dust concentration of his or her group.

attenuation Equation 2 of Tielemans et al. [1998]. As the number of subjects per group increased, attenuation in the exposure–response relationship decreased. For example, metric 2, based on all 39 job categories included only 2.7 sawmill subjects per group on average; whereas metric 5, also based on job, included 35 sawmill subjects per group on average resulting in a stronger point estimate of the relationship. The greatest increase in grouping also produced the greatest relative increase in the exposure–response relationship (i.e., from metric 1 to metric 4). The stronger point estimates based on grouping allowed the relationship between wood dust and FEV_1 to be found statistically significant in metrics 2, 3, 5, and 6.

Though grouping resulted in point estimates of exposure–response relationships that were stronger and more frequently statistically significant, the confidence intervals were wider on an absolute scale (though not relative to the point estimate). Seixas and Sheppard [1996] demonstrated

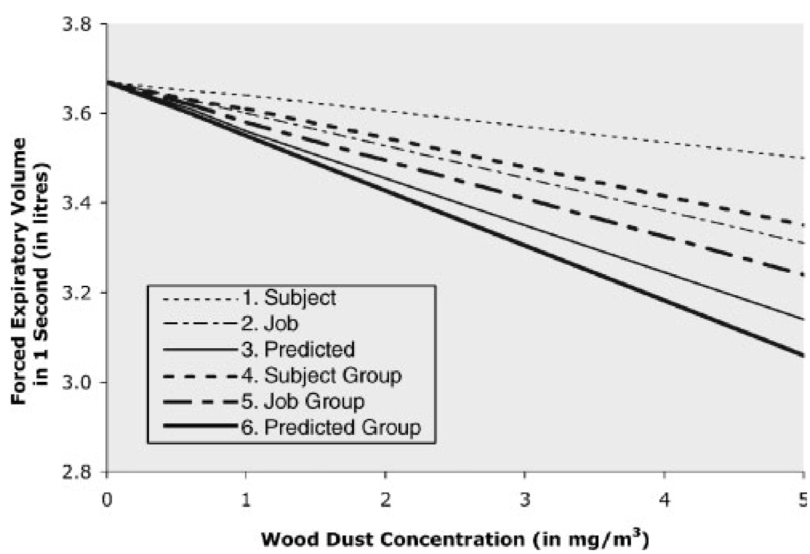

FIGURE 1. Relationship between forced expiratory volume in 1 s (FEV_1) and wood dust concentration, using six different exposure metrics. Baseline FEV_1 (at wood dust concentration = 0 mg/m^3) predicted using adjusted model coefficients with the following data from all study subjects: mean age (43.5 years), mean height (174.1 cm), mean cigarette smoking (5.8 pack-years as "current smokers" and 5.9 pack-years as "ex-smokers;" note that both variables include 0 pack-years for non-smokers), proportion female (12%), proportion not Caucasian (17%), and proportion with pediatric asthma (5%). Exposure metrics labeled using same numbers as in Table II.

this effect and suggested using an estimator that combines the subject-specific and group-based exposure estimates, weighted according to the relative sizes of the within- and between-subject variances.

Most studies that have examined grouping, have based their groupings on the jobs of study subjects. In this study, the strongest point estimates of the exposure–response relationships were found when exposures were estimated using the empirical exposure model, both with and without grouping (metrics 3 and 6). This is likely because the model was able to take into account not just an individual's exposure on a limited number of days in one sampling campaign, nor simply the influence of his or her job, but also many other factors that influenced exposures in the lumber mill (tree species, wood condition, indoor versus outdoor work station, use of sawing and planning equipment, booth enclosure, vehicle cabin, clean-up tasks). The predicted values, by taking into account a wide range of factors that affect exposures, may provide both more accurate and more precise estimates of the long-term average exposure of the sawmill employees.

Few others have examined the potential value of exposure modeling on risk estimation. Preller et al. [1995], in their study of endotoxin exposure in pig farmers and FEV_1, found a stronger exposure–response relationship when exposures were based on a determinants model, rather than the measured exposures of each subject. Wameling et al. [2000] showed that under certain assumptions, including large enough sample size, empirically modeled exposures are a better estimate of the long-term mean than a single exposure measurement. As a corollary, a better estimate of the true within-person mean can be provided by modeled exposures than by the mean of a series of personal exposure measurements. To meet the sample-size requirement, the number of subjects must be roughly twice (or more) the number of determinants in the model. Both our predictive model (112 subjects, 220 exposure measurements, 26 independent variables, $R^2 = 0.73$) and that of Preller et al. [1995] (198 subjects, 350 exposure measurements, 21 independent variables, $R^2 = 0.37$) easily met this criterion.

In summary, our results support the value in exposure-effect analyses of aggregating study subjects into large groups. In addition, they provide empirical evidence that using determinants of exposure models, which take into account multiple factors that influence exposure, may provide further improvements in risk estimation.

REFERENCES

Armstrong BG. 1990. The effects of measurement errors on relative risk regressions. Am J Epidemiol 132(6):1176–1184.

Demers PA, Teschke K, Davies HW, Kennedy SM, Leung V. 2000. Exposures to dust, resin acids, and monoterpenes in softwood lumber mills. Am Ind Hyg Assoc J 61:521–528.

Heederik D, Attfield M. 2000. Characterization of dust exposure for the study of chronic occupational lung disease: A comparison of different exposure assessment strategies. Am J Epidemiol 151(10):982–990.

Kromhout H, Heederik D. 1995. Occupational epidemiology in the rubber industry: Implications of exposure variability. Am J Ind Med 27:171–185.

Kromhout H, Loomis DP, Mihlan GJ, Peipins LA, Kleckner RC, Iriye R, Savitz DA. 1995. Assessment and grouping of occupational magnetic field exposure in five electric utility companies. Scand J Work Environ Health 21:43–50.

Kromhout H, Loomis DP, Kleckner RC, Savitz DA. 1997. Sensitivity of the relation between cumulative magnetic field exposure and brain cancer mortality to choice of monitoring data grouping scheme. Epidemiol 8(4):442–445.

Lui K, Stamler J, Dyer A, McKeever J, McKeever P. 1978. Statistical methods to assess and minimize the role of intra-individual variability in obscuring the relationship between dietary lipids and serum cholesterol. J Chronic Dis 31:399–418.

Preller L, Kromhout H, Heederik D, Tielen MJM. 1995. Modeling long-term average exposure in occupational exposure–response analysis. Scand J Work Environ Health 21:504–512.

Seixas NP, Sheppard L. 1996. Maximizing accuracy and precision using individual and group exposure assessments. Scand J Work Environ Health 22:94–101.

Snedecor GW, Cochran WG. 1967. Statistical methods, 6th edn. Ames, IA: Iowa State University Press.

Teschke K, Demers PA, Davies HW, Kennedy SM, Marian SA, Leung V. 1999. Determinants of exposure to inhalable particulate, wood dust, resin acids, and monoterpened in a lumber mill environment. Ann Occup Hyg 43(4):247–255.

Tielemans E, Kupper L, Kromhout H, Heederik D, Houba R. 1998. Individual-based and group-based exposure assessment: Some equations to evaluate different strategies. Ann Occup Hyg 42:115–119.

van Tongeren MJA, Kromhout H, Gardiner K, Calvert IA, Harrington JM. 1999. Assessment of the sensitivity of the relation between current exposure to carbon black and lung function parameters when using different grouping schemes. Am J Ind Med 36:548–556.

Wameling A, Schäper M, Kunert J, Blaszkewicz M, van Thriel C, Seeber A. 2000. Individual toluene exposure in rotary printing: Increasing accuracy of estimation by linear models based on protocols of daily activity and other measures. Biometrics 56:1218–1221.

Werner MA, Attfield MD. 2000. Effect of different grouping strategies in developing estimates of personal exposures: Specificity versus precision. Appl Occup Environ Hyg 15:21–25.