

Review article

Have the prevalence and incidence of occupational asthma and rhinitis because of laboratory animals declined in the last 25 years?

Background: Data for time trends in the prevalence of occupational asthma (OA) and rhinitis (OR) are not known.

Objective: To investigate the prevalence and incidence of OA and OR over time.

Methods: We chose to review studies on the prevalence and incidence of OA and OR due to laboratory animals (LA) as a marker of changing OA and OR patterns over time and analysed 15 cross-sectional and 4 longitudinal studies published from 1980 to 2006.

Results: The estimated prevalence of OA, defined as work-related chest symptoms (WRCS), declined from 8.2% in 1976 to 4.2% in 2001 ($P < 0.005$). When defined by WRCS and positive skin prick test (SPT) to LA, the estimated prevalence of OA was 6.7% in 1977 and 2.9% in 1999 ($P < 0.02$). The prevalence of OR, defined by WRNS or WRNS and SPT to LA, was not related to study date but was inversely associated with mean exposure duration. In four longitudinal studies no clear trend emerged over time.

Conclusions: This review suggests a trend toward a progressive decline in the prevalence of occupational asthma due to laboratory animals, which may be due to the reduction of exposure since the early 1980s. A further reduction of exposure is needed to prevent the onset of occupational rhinitis.

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Over much of the last 40 years the prevalence of asthma and related atopic diseases has been increasing and since 1989 the hygiene hypothesis has repeatedly been advocated to explain this trend (1, 2). Several recent reports, however, have provided evidence of a plateau in the previous upward trend (1–4). Data for time trends in the prevalence of occupationally related asthma (OA) and occupational rhinitis (OR) could be particularly relevant to such temporal trends, but are scarce. McDonald showed an increase in OA cases in the UK (1989–1997), because of latex and glutaraldehyde and a drop in cases because of isocyanates over the same time period; based on small numbers, annual mean incidence rates for 1992–1997, compared with 1989–1991, suggested no change in laboratory technicians (5). In Finland, time trends from 1986 to 1993 for persistent asthma and OA increased (6); the incidence of OA rose from 1986 to 1995, decreased between 1995 and 1998, and remained stable between 1999 and 2002 (6, 7). Cases of OA because of animal epithelia (< 90% cow epithelia) increased in Finland from

1986 to 1990, remained stable between 1990 and 1995, and decreased from 1995 to 2002 (7). In both instances, multiple factors may have impacted incidence estimates, including changing exposures, heightened recognition of specific causes, and new reporting criteria. As far as we know no temporal trend data for OR have been published.

The frequency of OA and OR because of laboratory animals (LA) may be a particularly useful marker of changing disease patterns because this form of sensitization is well recognized, specific allergy can be tested fairly easily, and we do not know if exposure has changed substantially recent decades because of new work practices or changing technologies. To investigate trends in the prevalence and incidence of OA and OR over time, we reviewed the available published literature for both (8–27).

Methods

Citation inclusion and exclusion

Published reports were identified from PubMed covering the years 1980–2006, inclusive. We used the following key words search strategy: 'animals, laboratory and occupational exposure and

Abbreviations: LA, laboratory animals; LAA, laboratory animal allergy; OA, occupational asthma; OR, occupational rhinitis; SPT, skin prick test; WRCS, work-related chest symptoms; WRNS, work-related nasal symptoms.

asthma', 'animals, laboratory and occupational exposure and rhinitis', and 'animals, laboratory and occupational exposure and allergy'. There was no restriction used with respect to the language of publication. Using this schema we identified 65 potentially eligible citations. Twenty-one papers were discarded because they were not in the field of LA allergy (LAA) and 37 because they did not report the prevalence or incidence of OA and OR or were a re-analysis of a group of animal workers included in an already selected study. We also reviewed all papers for reference citations within the 1980–2006 time frame that had not been otherwise identified in the initial search and for these, further reviewed their reference citations. In total, we identified an additional 12 studies for inclusion. Then, this paper analyses the results of 15 cross-sectional and four longitudinal studies.

Data extraction

The prevalence of work-related symptoms of OA and OR was available in all 15 cross-sectional studies, while the prevalence based on symptoms and positive skin prick test (SPT) to LA was not done or not given in four instances for OA and in seven for OR. In four longitudinal studies the incidence of OA and OR was standardized as incidence/100 person years.

Date of study

To identify time points from which to analyze temporal trends in the prevalence or incidence of OA and OR, we extracted from each publication the time period in which the actual study was performed. The precise calendar period of study was clearly ascertainable for seven of 15 cross-sectional studies. In the remaining eight, we attempted to contact the study authors to verify the years of data collection reported. In four of eight we did obtain such data, leaving four studies in which this data remained unconfirmed. To assign a study performance data, we calculated the mean lag between data collection and publication for the 11 studies in which we had such data. The mean delay of 3.96 years was then used as to extrapolate a date of data collection for the four outstanding studies missing such data.

Prevalence rates

Prevalence rates were reported by the authors in six studies (15, 18–22). We calculated prevalence rates in the others (8–14, 16, 17) as the percentage of cases of OA or OR divided by the number of subjects in each study (Table 1).

Statistical analysis

We assumed that, conditionally on the number of subjects at risk in each study, the number of cases of OA and OR were distributed as binomial variables. A logistic regression model was used to describe how the probability of being a case depended on the year of the study and participation rate. However, to take into account that the average exposure was different across studies, we allowed the intercept of the regression model to differ according to whether the average exposure was up to 4 years (five studies, Table 1), more than 4 years (six studies), or not available (six studies). When the study date extended over two or more years, the median time point was used. As noted previously, we were unable to determine the study date (calendar years of study performance) for four studies. However, in the 11 studies with a known collection period, study dates and publication year were linearly related with a slope of 1.03

(SE 0.04) and the estimated delay between study dates and publication was 3.96 years (SE 0.35). Thus, for the four studies with unknown date of data collection we extrapolated back from the publication date. A MatLab function was used to fit the logistic regression model.

Results

Cross-sectional studies

Between 1980 and 2004, 15 prevalence reports studied OA and OR in workers exposed to LA (Table 1) (8–22). The participation rate ranged from 61% to 100%, median 77–78%. Two studies were utilized twice in the analysis (see Table 1) (18, 20); one because the authors provided separate analyses for exposure to rat and mouse (18) and the other because it included two separately analysed groups of workers exposed to LA (20). Subjects were exposed to rats in 14 (82.4%) of studies, to mice in 12 (70.6%), to rabbits and guinea pigs in nine (52.9%), to cats and hamsters in two studies, and to sheep, dogs, and monkeys in one study each. In one study exposure to which LA was not specified, but they were small mammals used in a pharmaceutical company (9). Exposure to one animal only was found in six studies: to a rat in four (17–19, 21) and a mouse in two (Table 1) (11, 18). Positive SPT to common aeroallergens, performed in 12 studies, ranged from 15.6% to 60.0%, median 40%.

In workers exposed to LA the prevalence of OA, when defined as work-related chest symptoms (WRCS), ranged from 2.2% to 11.7%; when defined as WRCS and positive SPT to at least one LA, it was 1.4–9.5% (Table 1). The prevalence of OR, defined as work-related nasal symptoms (WRNS), ranged from 6.7% to 41.7%; when defined as WRNS and positive SPT to LA, it was from 2.9% to 18.8%. Almost all cases of OA were associated with OR (mean 93%; range: 70–100%, Table 1).

The ratio between prevalences of OR and OA, defined as WRNS and WRCS, respectively, was between 1.5 and 7.6, median 3.0; when defined by symptoms and positive SPT to LA, it ranged from 0.6 and 7.9, median 1.8.

Logistic model analysis of the prevalence of OA by study date showed a significant decreasing trend over time. The estimated prevalence of OA, defined as WRCS, declined from 8.2% in 1976 to 4.2% in 2001 ($P < 0.005$, Fig. 1). The average length of exposure and the participation rate had no effect. When OA was defined by WRCS and positive SPT to LA, the estimated prevalence was 6.7% in 1977 and 2.9% in 1999 ($P < 0.02$). Again, duration of exposure and participation rate had no effect. When we selected the 13 studies with exposure to at least one of the following LA: rat, mouse, rabbit, or guinea pig, the estimated prevalence of OA was 6.5% in 1976 and 4.7% in 2001 but this declining trend was not significant ($P = 0.16$).

Table 1. Prevalence of occupational asthma and rhinitis in cross-sectional studies of workers exposed to laboratory animals

References	Study year	Subjects (n)	Participation rate (%)	Mean age (years)	Exposure to LA (animal types)	Duration of exposure to LA (years)	Prevalence of OA WRCS* (%)	Prevalence of OA WRCS + SPT† (%)	Prevalence of OR WRNS‡ (%)	Prevalence of OR WRNS + SPT§ (%)	Prevalence of OA and OR¶ (%)
Gross (8)	1976	399	100	30.9	R, M, Rb, G	4.3	7.5	ND	14.8	ND	7.5
Slovak and Hill (9)	1978	146	100	NG	LA	NG	10.3	8.9	22.6	5.5	NG
Cockcroft et al. (10)	NG	179	61	NG	R, M, Rb, G, S	NG	11.7	9.5	24.6	13.4	11.7
Schumacher et al. (11)	NG	121	82	NG	M	3.0**	4.1	3.3	24.0	10.7	NG
Beeson et al. (12)	NG	62	87	NG	R, M, Rb, G	NG	4.8	3.2	21.0	4.8	4.8
Agurp et al. (13)	NG	101	100	36.0	R, M, Rb, G, C, H	NG	9.9	8.9	29.7	18.8	9.9
Lutsky et al. (14)	1980–1981	90	NG	42.7	R, M, Rb, G	8.9	4.4	4.4	6.7	6.7	4.4
Venables et al. (15)	1984	138	87	32.3	R, M, Rb, G	8.8	10.9	5.1	37.0	NG	10.1
Aoyama et al. (16)	1986–1987	5641	64	33.2	R, M, Rb, G, H, D, C, Mn	NG	6.4	ND	18.9	ND	5.2
Cullinan et al. (17)	1990	238	88	24**	R	1.7**	7.1	4.2	13.4	2.9	5.0
Hollander et al. (18)	1992–1993	458	77	NG	R	10.8	6.1	5.0	16.8	NG	5.6
Hollander et al. (18)	1992–1993	377	77	NG	M	10.3	3.2	1.9	9.0	NG	2.4
Heederik et al. (Sweden) (19)	1990–1991 and 1995–1996	74	82	32.0	R	<4.0	2.7	NG	12.2	NG	NG
Filon et al. (North Italy) (20)	1999–2000	45	96	31.5	R, M, Rb, G	3.9	2.2	2.2	11.1	8.9	2.2
Filon et al. (central Italy) (20)	1999–2000	80	96	38.5	R, M, Rb, G	11.8	3.7	3.7	10.0	8.7	3.7
Lieutier-Colas et al. (21)	1997–1998	113	100	37.9	R	NG	4.4	1.4††	33.6	11.0††	NG
Ruoppi et al. (22)	2001	156	65	34.0	R (71%), M (59%)	2.3	5.8	ND	41.7	ND	NG

LA, laboratory animals; R, rat; M, mouse; Rb, rabbit; G, guinea pig; S, sheep; C, cat; H, hamster; D, dog; Mn, monkey; OA, occupational asthma; OR, occupational rhinitis; WRCS, work-related chest symptoms; WRNS, work-related nasal symptoms; SPT, positive skin prick test to at least one LA; ND, skin prick tests were not done; NG, results not given.

Definition of OA: *based on WRCS; †based on WRCS and SPT, unless otherwise stated. Definition of OR: ‡based on WRNS; §based on WRNS and SPT, unless otherwise stated. ¶Based on WRCS and WRNS. **Median. ††Definition based on WRCS or WRNS and positive serum IgE to at least one LA.

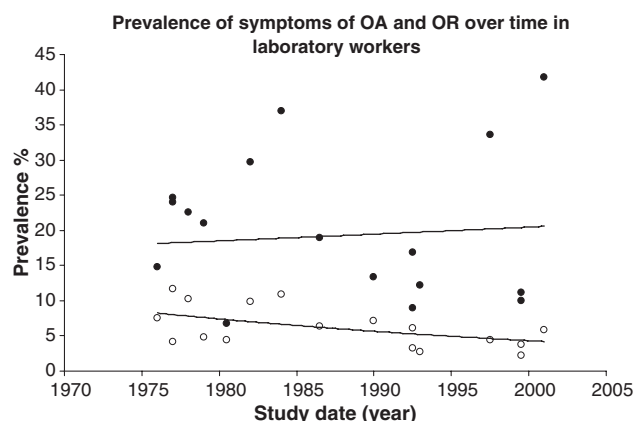


Figure 1. Changes in prevalence of symptoms of occupational asthma (OA, ○) and rhinitis (OR, ●) from 1976 to 2001. The two continuous lines show the prevalence of OR [upper line, not significant (NS)] and OA (lower line, $P < 0.005$) as estimated by the logistic model.

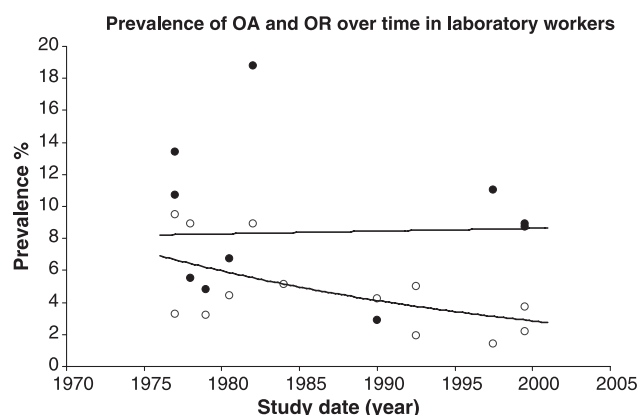


Figure 2. Changes in prevalence of occupational asthma (OA, ○) and rhinitis (OR, ●), defined as symptoms and positive skin prick test to laboratory animals, from 1978 to 2000. The two continuous lines show the prevalence of OR [upper line, not significant (NS)] and OA (lower line, $P < 0.02$) as estimated by the logistic model.

The estimated prevalence of OR, defined as WRNS, was not associated with the study date ($P = 0.17$, Fig. 2) but was strongly associated with mean exposure duration; in fact, in five studies with exposure lasting for up to 4 years the prevalence of OR was higher than in six studies with exposure for over 4 years ($P = 0.0001$) adjusted for study year and participation rate.

Occupational rhinitis was defined as both WRNS and positive SPT to LA in 10 studies. The estimated prevalence was higher in 5/10 studies which did not report duration of exposure than in three studies with exposure lasting for up to 4 years ($P < 0.005$) adjusted for study date and participation rate.

When analysis was restricted to small lab animals (rat, mouse, rabbit, and guinea pig), the prevalence of OR was strongly associated with duration of exposure. Prevalence was higher in studies with up to 4 years exposure than in those with > 4 years exposure ($P < 0.001$) adjusted for study date and participation rate.

Although estimated regression lines were not linear, within a short period of time the trend was nearly linear (Figs 1 and 2). The estimated OR/OA prevalence ratio, based on symptoms, doubled from 1976, when it was 2.2, to 2001, when it was 4.9 (Fig. 1).

Longitudinal studies

Between 1983 and 2005 four longitudinal studies evaluated OR and/or OA in workers exposed to LA, allowing incidence estimates (Table 2) (23–27). Two publications were treated as a single study because the reported analysis came from the same cohort of animal health apprentices (26, 27).

Two studies were published in UK. In 1983 Davies et al. (23) published a 1-year follow-up in 148 LA workers exposed to small animals, 54% of whom had previous limited exposure to LA. The incidence of symptoms of OA and OR/100 person years was 2.0 and 10.1, respectively; it was 1.4 and 4.7/100 person years, respectively, based on symptoms and positive serum IgE to LA (Table 2). Cullinan et al. (24) studied a cohort of 342 employed workers with a participation rate $> 80\%$. Prior exposure to laboratory rats ranged from 1 month to 4 years. In a 3-year follow-up, 1990–1993, they found an incidence of WRCS of 3.5/100 person years, and 1.6/100 person years, when based on symptoms and SPT. The highest annual incidence of symptoms was in the first year of employment and 80% of symptoms occurred within 2 years.

In 495 workers exposed to LA over a 12-year follow-up (1991–2003). Elliott et al. (25) found an estimated incidence rate of LAA of 2.3/100 person year; 87.8% with LAA developed rhinitis (2.0/100 person years) and 18.3% developed asthma (0.4/100 person years), defined as symptoms and positive SPT to LA. In the first 3 years of exposure incidences of OA and OR were 1.3 and 7.4, respectively. The incidence of LAA increased with hours of exposure to tasks associated with working with different species of animals or cages. The authors also described a strong negative cohort effect for age and years of follow-up. This was manifest by increased (> 3 times) incidence rates for workers aged 18–28 years relative to others and for workers with 1–3 year of follow-up compared with others. Moreover, workers without prior baseline exposure to LA had an incidence rate of 4.3/100 person years for LAA symptoms, which was 2.3 times greater than in workers with prior exposure to LA.

Among 373 Canadian apprentices in animal health technology without significant previous exposure to LA,

Table 2. Incidence of occupational asthma and rhinitis in longitudinal studies of workers exposed to laboratory animals

References	Subjects (n)	Study years	Duration of follow-up (years)	Exposure to LA	Incidence of OA ($\times 100$ person years) WRCS*	Incidence of OA ($\times 100$ person years) WRCS + SPT†	Incidence of OR ($\times 100$ person years) WRNS‡	Incidence of OR ($\times 100$ person years) WRNS + SPT§	OR : OA ratio (WRNS : WRCS)
Davies et al. (23)	148	NG	1	R, M, Rb, G	2.0	1.4¶	10.1	4.7¶	5.0
Cullinan et al. (24)	342	1990–1993	3	R	3.5	1.6	7.3	2.3	2.1
Elliott et al. (25)	495	1991–2003	12	R, M, Rb, G, D, H	NG	0.4	NG	2.0	NG
Gautrin et al. (26)	373/387	1993–1999	3.7	R, M, Rb	2.7	1.1**	11.3	4.5	4.2
Rodier et al. (27)									

LA, laboratory animals; r, rat; M, mouse; Rb, rabbit; G, guinea pig; OA, occupational asthma; OR, occupational rhinitis; NG, results not given. WRCS, work-related chest symptoms; WRNS, work-related nasal symptoms; SPT, positive skin prick test to at least one LA; ND, skin prick tests were not done. Definition of OA: *based on WRCS; †based on WRCS and SPT, unless otherwise stated. Definition of OR: ‡based on WRNS; §based on WRNS and SPT, unless otherwise stated. ¶Based on WRCS or WRNS and positive serum IgE to at least one LA; **based on SPT and bronchial hyperresponsiveness.

who were recruited upon starting their training between 1993 and 1995, the incidence of probable OA and OR was 2.7/100 person years and 11.3/100 person years, respectively (26, 27). The follow-up was up to 44 months and the participation rate was 89%. There was a nonsignificant inverse correlation between duration of follow-up and incidence of OA ($r = -0.78$, $P = 0.22$) or OR ($r = -0.89$, $P = 0.11$).

In summary, in longitudinal studies published from 1983 to 2005 the incidence of OA, defined as WRCS, ranged from 2.0/100 person years to 3.5/100 person years; when based on WRCS and positive SPT to LA, it was between 0.4/100 person years and 1.6/100 person years. The incidence of OR, defined as WRNS, ranged from 7.3 to 12.1/100 person years; when based on WRNS and positive SPT to LA, it was between 2.0/100 person years and 4.7/100 person years. The OR : OA ratio, based on symptoms, was between 2.1 and 5.0.

Discussion

Laboratory animal allergy was recognized as an occupational disease in the early 1970s (28) when the prevalence ranged between 15% and 23% (29–31). In the last 20 years several papers showed exposure could be reduced (32) but, despite this, estimates of prevalence and incidence indicate a mixed pattern. A recent paper stated there is no definite evidence that the incidence of LAA is falling (28) while several others observed that reduced exposure helped lower prevalence (13, 16) and incidence (33).

Our review suggests a decline in the prevalence of OA, which this analysis estimated as -1.6% every 10 years, after adjusting for duration of exposure and participation rates. Of interest, the same pattern has not been manifest in studies of the prevalence of OR in LA workers.

In cross-sectional and longitudinal studies on workers exposed to LA, OA, and OR tended to occur within the first 2–3 years of exposure (8, 10, 16, 17, 25). As work-related respiratory symptoms may have induced affected workers to leave their jobs (healthy worker survivor effect) (34), studies with a longer duration of exposure may show a lower prevalence of symptoms. Therefore, as duration of LA exposure may have biased results, in the logistic regression model we analysed prevalence rates in three groups of exposure: up to 4 years, more than 4 years, or not stated duration of exposure. The declining time trend was confirmed for the prevalence of OA but not for OR which seemed biased by the healthy worker survivor effect.

Other possible biases are a prevalent recruitment of workers with work-related or nonwork-related respiratory symptoms, who are more interested in participating in the study, or, on the contrary, a prevalent recruitment of healthy workers, because symptomatic workers do not

report symptoms or do not participate to the study because of fear of job loss. Only one cross-sectional study mentioned that 20 subjects, some with work-related symptoms, did not participate because of fear that the survey information might be passed to their management (15). In all other cross-sectional studies all workers who were exposed to LA were recruited.

In the four longitudinal studies it was not possible to show a reduction of incidence over time also because in three, study years were overlapping (Table 2) (24–27). Only a strong negative cohort effect seemed to emerge in one study, as incidences of OA and OR was inversely correlated with follow-up duration and age (25). The OA incidence rate was 1.3 for workers with 1–3 years follow-up (25). Incidence rates in workers with up to 4 years follow-up did not change much, being between 1.1 (26) and 1.6 (24). On the contrary, incidence rates of OR for workers with follow up <4 years were more variable, ranging from 2.3 (24) to 7.4 (25), but without a clear time trend.

The prevalence of OR defined by WRNS tend to be disproportionately higher (more than double) than when defined as WRNS and positive SPT. Other nonallergenic pollutants, such as endotoxins, may be responsible for WRNS in subjects with negative SPT to LA, even though the relation between endotoxin levels and WRNS was not confirmed in workers exposed to rats (21). Moreover, some SPT-negative symptomatic worker may have local immunoglobulin E production to LA allergens in the nasal mucosa, may have been tested with a low quality LA extract or may have been sensitized to another allergen in the workplace that was not tested in SPT (21).

The factors that might account these differing temporal trends remain to be elucidated. Exposure, atopy, and smoking have been studied as possible determinants of OA and OR because of LAA (35, 36) and in several studies exposure – OA (37) and exposure – OR relationships have emerged (9–11, 17, 24). Moreover, reports have often shown an association between atopy and OA (9, 10, 14, 15, 17, 33) and, less frequently, between atopy and OR (11) in laboratory workers. In most of these articles (9–11, 15, 17, 33) atopy was defined as at least one positive SPT to common allergens. Lutsky et al. (14) used a more conservative definition: at least two positive SPT to common allergens and a personal or family history of rhinitis, asthma or eczema. There is little evidence that a putative changing prevalence of cigarette smoking has modified the risk of OA or OR in any way, let alone in the opposite directions (35, 36).

As the prevalence of atopy has not decreased over the last 25 years (38–41), the decline in OA because of LA may be linked to the decrease in exposure. As far back as 1980, Gordon et al. (32) showed simple practical measures in the work environment substantially reduced the exposure of LA personnel to rat urinary aeroallergens. In 1986 Bland et al. (42) showed a dose–response relationship between number of species of LA handled or hours per week of exposure to LA, and LAA. They also showed that the use of protective measures, such as gloves, mask, laboratory coat, shoe covers, and of a respirator, helped to reduce symptoms in 58% of workers with LAA. Moreover, in a longitudinal study published in 1987, Botham et al. (33) demonstrated that introducing measures, such as mandatory use of personal protective equipment and extensive use of educational programs that were designed to reduce exposure, reduced the incidence of LAA from 37% to 12% over a 5-year period. Finally, in 1998 Fisher et al. (43) showed prevention could be achieved. They developed a comprehensive program included education and training, modification of work practices, engineering controls, and the use of personal protective equipment. During a prospective survey of 5 years, the incidence of LAA was reduced to zero during the last 2 years of observation.

It remain to be explained why the possible reduction of exposure impacted upon the decline of OA, but not of OR, over the last 25 years. The nose is more exposed to airborne contaminants than the bronchi, it is the first to encounter inhaled particles, and it filters large particles. Moreover, protective masks may protect lower airways more than the nose. Consequently, OR is three times more frequent than OA (35). It seems that exposure to LA needs to be further reduced or eliminated to prevent the onset of OR.

In conclusion, this review of 15 cross-sectional and four cohort studies (Tables 1 and 2) suggests a trend toward a progressive decline in the prevalence of OA because of LA (Figs 1 and 2). This decline may be due to the reduction of exposure since the early 1980s, while atopy and smoking are probably not involved. A further reduction of exposure is needed to prevent the onset of OR. Changes over time of OA and OR deserve more attention and studies.

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