ORIGINAL ARTICLE

Pesticides and other occupational exposures are associated with airway obstruction: the LifeLines cohort study

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ABSTRACT

Objectives Occupational exposures are important and possibly modifiable contributors to the global burden of chronic obstructive pulmonary disease (COPD). Exposure to vapours, gases, dusts and fumes (VGDF) has been associated with a two- to threefold higher COPD risk. Less is known about effects of occupational exposure to pesticides and solvents. In the current study, we assessed if VGDF, pesticides and solvents are associated with the level of lung function and the prevalence of airway obstruction in the general population.

Methods We included 11 851 subjects aged 18–89 years from the LifeLines cohort study. Regression models assessing associations between occupational exposures (no/low/high), level of lung function (prebronchodilator FEV_1, FEV_1/FVC) and mild and moderate/severe airway obstruction were adjusted for sex, age, height, weight, current/ex-smoking and packyears. Additionally, we stratified by smoking status and gender and tested for interaction. A second general population cohort (n=2364) was used to verify our initial findings.

Results Occupational exposure to VGDF and pesticides was associated with a lower level of FEV_1 and FEV_1/FVC and with a higher prevalence of mild and moderate/severe airway obstruction in the two general populations investigated. There were no associations with exposure to solvents.

Conclusions Occupational exposure to both VGDF and pesticides is associated with airway obstruction in the general population.

BACKGROUND

Worldwide, millions of people suffer from chronic obstructive pulmonary disease (COPD). About 3 million people died due to COPD in 2005.[1] The morbidity and mortality associated with the disease cause an enormous economic burden; healthcare costs of COPD in the USA alone were estimated to be US$50 billion in 2010.[2] The global burden of COPD is still increasing and the disease is expected to become the third leading cause of death by 2030.[3 4] Yet the cellular and molecular pathways driving COPD are still not fully understood.[5] Tobacco smoking is considered to be the main risk factor for COPD, although a substantial proportion of 15–20% of all COPD cases has been attributed to occupational exposures,[6] with proportions up to 30% in never smokers.[7]

What this article adds

► Various studies have shown that occupational exposure to vapours, gases, dusts and fumes (VGDF) is associated with a decreased level of lung function and a higher prevalence of chronic obstructive pulmonary disease (COPD).

► This study adds to the current knowledge by showing that occupational exposure to pesticides, including herbicides and insecticides, is associated with a lower level of lung function and a higher prevalence of airway obstruction in the general population.

► Since the agricultural sector employs a large share of the population worldwide, especially in developing countries, interventions to reduce exposure levels in this occupational sector could contribute to lowering the global burden of COPD.

Occupational exposure to broadly defined categories like vapours, gases, dusts and fumes and their composite measure (VGDF) have been shown in several studies to increase COPD risk two- to threefold.[8–11] Joint exposure to smoking was shown to increase the risk even 14-fold.[9] Epidemiological studies investigating the effects of more specific occupational exposures, like pesticides and solvents, are scarce. Since the agricultural sector employs more than 1.1 billion workers worldwide (about 34% of the global working force),[12] adverse health effects associated with occupational exposure to pesticides can have a large public health impact. This is especially true in highly exposed populations, such as agricultural workers in developing countries who often use pesticides with insufficient protective equipment and training.[13] Like pesticides, solvents are widely used agents in everyday practice, such as degreasing, cleaning and painting. Possible adverse health effects, for instance, due to their volatile and irritable properties might therefore apply to millions of people worldwide.

Because occupational exposures are common, yet also potentially modifiable contributors to the global burden of COPD, it is important to determine which occupational factors drive the

development of COPD. Although COPD clinically manifests predominantly after age 40, it is relevant to study early phenotypes that may be associated with the development of COPD later in life, such as decreased level of lung function and early signs of airway obstruction. In the current study, we assessed the associations of occupational exposure to gases and fumes, mineral dust, biological dust, their composite measure VGDF, pesticides in general, herbicides and insecticides specifically and various types of solvents on level of lung function and the prevalence of mild and moderate/severe airway obstruction in a general population cohort. Additionally, differential associations for never and ever smokers and men and women were investigated. A second general population cohort from the same area, that is, the Vlagtwedde-Vlaardingen cohort, was used to verify our initial findings.

METHODS

Study sample

We included individuals from the LifeLines cohort study, a multidisciplinary prospective population-based cohort study examining health and health-related behaviours of persons living in the Northern region of The Netherlands.[14] Subjects were recruited via general practitioners. In the current study, we included 13 301 subjects from the second data release of the LifeLines cohort. All LifeLines participants received a medical examination and questionnaires at baseline. The medical examination included prebronchodilator spirometry (FEV_1, FEV_1/FVC) using a Welch Allyn V.1.6.0.489, PC-based SpiroPerfect with Ca Workstation software. The questionnaires included questions regarding personal characteristics, smoking habits, job title and description of current or last held job.

Occupational exposure

Job title and description were coded according to the International Standard Classification of Occupations V.1988 (ISCO-88).[15] These four-digit classification codes were used to estimate job-specific exposures to VGDF (subcategories gases and fumes, mineral dust and biological dust), pesticides (subcategories herbicides and insecticides) and various types of solvents (aromatic, chlorinated, other) using the ALOHA+ job exposure matrix (JEM).[8] The ALOHA+ JEM classifies subjects based on the ISCO-88 job codes into no, low and high exposure categories (0/1/2). In case a participant had two different jobs simultaneously, exposures of both jobs were averaged and rounded to the nearest integer (0.5=1 and 1.5=2).

Statistical analysis

Associations of the specific occupational agents with prebronchodilator level of lung function (FEV_1 and FEV_1/FVC) and mild and moderate/severe airway obstruction were assessed using linear and logistic regression adjusted for sex, age, height, weight, current/ex-smoking and packyears (log packyears+1), all at enrolment. Mild obstruction was defined as prebronchodilator FEV_1/FVC<70%. To assess associations with more severe obstruction, we defined moderate/severe obstruction as having prebronchodilator FEV_1/FVC<70% and FEV_1<80% predicted and no obstruction as having prebronchodilator FEV_1/FVC≥70% and FEV_1≥80% predicted.[16] Subjects with mild obstruction (prebronchodilator FEV_1/FVC<70% and FEV_1≥80% predicted) or with possible other pathology, like restrictive lung disease (prebronchodilator FEV_1/FVC≥70% and FEV_1<80% predicted) were excluded from this analysis (LifeLines n=1517 (13%) and Vlagtwedde-Vlaardingen n=436 (18%)).

Because of substantial co-exposure between the specific occupational agents (see online supplementary table S1), we additionally adjusted the models with exposure to VGDF, gases, fumes, mineral dust and biological dust for exposure to pesticides, whereas the models with exposure to pesticides, herbicides and insecticides were additionally adjusted for exposure to VGDF. Since subjects with high exposure to pesticides always were highly exposed to VGDF, it was not possible to formally test for interaction between the two exposures.

In additional analyses, we stratified by smoking status (never/ever) and by gender. A subject was defined as ever smoker when being either a current or an ex-smoker. Interactions between the exposures and smoking or gender were tested by including their interaction terms in the unstratified models (ie, low exposure × ever smoker; high exposure × ever smoker; low exposure × gender and high exposure × gender, respectively). p Values <0.05 were considered statistically significant. All analyses were performed in SPSS V.20.0 (IBM Corporation, USA).

Verification cohort

Subjects who participated in the last survey (1989/1990) of the Vlagtwedde-Vlaardingen cohort were used to verify our initial findings (table 1). The Vlagtwedde-Vlaardingen cohort is a general population-based cohort that has started in 1965 and has been followed for 25 years. During each survey, information was collected by questionnaires and spirometry, using a slow inspiratory manoeuvre, was performed with a water-sealed spirometer (Lode Instruments, Groningen, the Netherlands). We used current job, or the last held job in case of current

Table 1 Characteristics of the included study populations from the LifeLines and Vlagtwedde-Vlaardingen cohorts

	LifeLines	Vlagtwedde-Vlaardingen
N with non-missing data	11 851	2364
Men, n (%)	4878 (41)	1265 (54)
Age (years), median (minimum–maximum)	47 (18–89)	52 (35–79)
Smoking status		
Never, n (%)	5091 (43)	760 (32)
Ever, n (%)	6760 (57)	1604 (68)
Ex, n (%)	4267 (36)	753 (32)
Current, n (%)	2493 (21)	851 (36)
Packyears in ever smokers, median (25–75th centiles)	10 (5–19)	19 (9–31)
Lung function, mean (SD)		
FEV_1% predicted*	103 (14)	93 (16)
FEV_1/FVC (%)†	76 (7)	74 (9)
Airway obstruction		
No (FEV_1/FVC≥70%), n (%)	10 097 (85)	1725 (73)
FEV_1% predicted, mean (SD)	105 (13)	98 (13)
Mild (FEV_1/FVC<70%), n (%)	1754 (15)	639 (27)
FEV_1% predicted, mean (SD)	89 (15)	79 (16)
Moderate/severe‡, n (%)	458 (4)	314 (13)
FEV_1% predicted, mean (SD)	70 (9)	67 (11)

*FEV_1% predicted is FEV_1 as percentage predicted based on reference equations by Quanjer et al.[16]
†Vlagtwedde-Vlaardingen: FEV_1/IVC.
‡Moderate/severe obstruction: subjects with moderate/severe obstruction=prebronchodilator FEV_1/FVC<70% and FEV_1<80%, subjects without obstruction=prebronchodilator FEV_1/FVC≥70% and FEV_1≥80%. Subjects with mild obstruction (prebronchodilator FEV_1/FVC<70% and FEV_1≥80% predicted) or prebronchodilator FEV_1/FVC≥70% and FEV_1<80% predicted were excluded from this analysis (LifeLines n=1517 (13%) and Vlagtwedde-Vlaardingen n=436 (18%)).

unemployment (eg, retirement) that was reported at the last survey (1989/1990). Job coding, exposure assessment and statistical analyses were performed according to the same protocol as in the LifeLines cohort.

RESULTS
Characteristics of the LifeLines study population and prevalence of exposure
From the initial LifeLines sample of 13 301 subjects, a total of 1450 subjects were excluded because of insufficient quality of spirometry (n=725) or lacking information on covariates (n=725). Characteristics of the included and excluded subjects can be found in the online supplementary table S2. Table 1 shows the characteristics of 11 851 LifeLines participants who were included in the final sample. High level of occupational exposure (category 2) to the broadly defined category VGDF was quite common (11%) (for an overview of the type of workers with high exposure to VGDF, see online supplementary table S3). Only a small number of people had high exposure to pesticides (1%) (for numbers and prevalence of each exposure, see table 2). Men were more often exposed and had more often high exposure (category 2) than women.

VGDF exposure
Occupational exposure to VGDF in general (figure 1A), and the subcategory gases and fumes, was associated with a lower level of FEV_1 (table 2) and FEV_1/FVC (table 3) and a higher prevalence of mild and moderate/severe airway obstruction (table 4), with the strongest associations for the groups with high exposure. The negative association of high exposure to VGDF and gases and fumes with level of FEV_1 was significantly stronger in ever smokers than never smokers (ie, p values for interaction <0.05), whereas the associations with FEV_1/FVC were not significantly different between never and ever smokers. Exposure to mineral dust was associated with a lower level of FEV_1 and with a higher prevalence of mild and moderate/severe airway obstruction, whereas the association with level of FEV_1/FVC was less consistent. The association between low exposure to mineral dust and level of FEV_1 was significantly stronger in ever smokers compared with never smokers. Exposure to biological dust was not significantly associated with level of FEV_1 (table 2) and FEV_1/FVC (table 3) or airway obstruction (table 4). There were no significant differences in the associations between occupational exposures and level of FEV_1 or FEV_1/FVC between men and women.

Pesticide exposure
Exposures to pesticides (figure 1B) and the subcategories herbicides and insecticides were associated with significantly lower levels of FEV_1 in an exposure-dependent way (table 2). Exposure to pesticides was also associated with a lower level of FEV_1/FVC (table 3) and a higher prevalence of mild and moderate/severe airway obstruction (table 4), yet these associations only reached significance for exposure to herbicides. The association between low exposure to pesticides and level of FEV_1 was significantly stronger in the ever smokers compared with the never smokers (p value for interaction <0.05). There was no difference between ever smokers and never smokers for high exposure to pesticides. Associations of exposure to pesticides with FEV_1/FVC were not significantly different between ever smokers and never smokers or men and women.

Solvent exposure
Low exposure to aromatic solvents was associated with a marginally lower level of FEV_1/FVC (see online supplementary table S4) and a higher prevalence of mild airway obstruction (see online supplementary table S5). There were no associations between low exposure to aromatic solvents and level of FEV_1 or moderate/severe airway obstruction and no associations between high exposure and level of FEV_1, FEV_1/FVC or prevalence of airway obstruction. There were no associations between exposure to chlorinated and other types of solvents and level of FEV_1, FEV_1/FVC (see online supplementary table S4) or prevalence of airway obstruction (see online supplementary table S5).

Verification of associations in the Vlagtwedde-Vlaardingen cohort
Full data on all covariates were available for 2364 subjects participating in the last survey of the Vlagtwedde-Vlaardingen cohort. These subjects were slightly older, more often men, more often ever smokers, had a lower level of lung function and more often had airway obstruction than subjects from the LifeLines cohort (table 1). Exposure to high levels of VGDF (33%) and pesticides (12%) was more common than in the LifeLines cohort (for the prevalence of all exposures in the Vlagtwedde-Vlaardingen cohort, see online supplementary table S6).

The associations of VGDF and the subcategory gases and fumes with level of FEV_1 (see online supplementary table S6), FEV_1/FVC (see online supplementary table S7) and the prevalence of mild and moderate/severe airway obstruction (table 4) in the Vlagtwedde-Vlaardingen cohort were comparable with the LifeLines cohort. Contrary to findings in the LifeLines cohort, the associations with level of lung function were not stronger in the ever smokers. Moreover, the associations of exposure to mineral dust with level of FEV_1 and prevalence of airway obstruction could not be replicated.

Associations between occupational exposure to pesticides and a lower level of FEV_1/FVC (see online supplementary table S7) and a higher prevalence of mild and moderate/severe airway obstruction (table 4) in the Vlagtwedde-Vlaardingen cohort were comparable with associations in the LifeLines cohort. The negative associations between exposure to pesticides and level of FEV_1 were replicated in the ever smokers only (see online supplementary table S6).

The marginal association between low exposure to aromatic solvents and a lower level of FEV_1/FVC in the LifeLines cohort was replicated in the Vlagtwedde-Vlaardingen cohort (see online supplementary table S8).

DISCUSSION
Main findings
Occupational exposure to VGDF and pesticides was associated with a lower level of FEV_1 and FEV_1/FVC and a higher prevalence of airway obstruction. There were no consistent associations with exposure to solvents.

Results in relation to other studies
In line with previous findings in the literature, we showed that occupational exposure to VGDF was clearly associated with lower levels of FEV_1 and FEV_1/FVC as well as with a higher prevalence of airway obstruction in both our general populations investigated.[8–11] [17] [18] Associations in our study were exposure dependent. In the European Community Respiratory Health Survey (ECRHS) study, high exposure to VGDF was associated with a 61 mL lower FEV_1 in current smokers,

Table 2 Associations between occupational exposures and level of FEV$_1$ (mL) in the LifeLines cohort

LifeLines				FEV$_1$ (mL)						
	All		Never smokers		Ever smokers		Men		Women	
Exposure†	b (95% CI)	N (%)	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N
VGDF										
Non-exposed	Ref	6534 (55)	Ref	2910	Ref	3624	Ref	2580	Ref	3954
Low	−9 (−28 to 9)	3985 (34)	−4 (−31 to 23)	1633	−14 (−38 to 11)	2352	−23 (−61 to 15)	1167	−5 (−23 to 13)	2818
High	**−83 (−115 to −51)*****	1332 (11)	**−65 (−114 to −16)****	548 ‡	**−96 (−138 to −55)*****	784	**−83 (−125 to −40)*****	1131	−65 (−138 to 8)	201
Gases/fumes										
Non-exposed	Ref	7007 (59)	Ref	3154	Ref	3853	Ref	2702	Ref	4305
Low	−13 (−31 to 5)	4159 (35)	−4 (−31 to 23)	1692	−21 (−45 to 4)	2467	−34 (−71 to 2)	1566 ‡	−3 (−22 to 16)	2593
High	**−73 (−110 to −35)*****	685 (6)	−35 (−95 to 24)	245 ‡	**−96 (−144 to −47)*****	440	**−76 (−125 to −27)****	610	−36 (−122 to 51)	75
Mineral dust										
Non-exposed	Ref	9389 (79)	Ref	4121	Ref	5268	Ref	3366	Ref	6023
Low	**−28 (−52 to −5)***	1924 (16)	−9 (−45 to 26)	754 ‡	**−45 (−75 to −14)****	1170	**−56 (−96 to −17)****	1037 ‡	−4 (−31 to 24)	887
High	**−65 (−111 to −18)****	538 (5)	**−79 (−151 to −7)***	216	−57 (−118 to 4)	322	**−65 (−125 to −5)***	475	−69 (−186 to 48)	63
Biological dust										
Non-exposed	Ref	8127 (69)	Ref	3514	Ref	4613	Ref	3729	Ref	4398
Low	−7 (−26 to 13)	3256 (28)	−10 (−39 to 18)	1355	−4 (−30 to 22)	1901	−3 (−47 to 41)	783	−11 (−30 to 8)	2473
High	−35 (−85 to 16)	468 (4)	−7 (−80 to 65)	222 ‡	−58 (−128 to 12)	246	−46 (−113 to 22)	366	29 (−75 to 133)	102
All pesticides										
Non-exposed	Ref	11 369 (96)	Ref	4844	Ref	6525	Ref	4523	Ref	6846
Low	**−51 (−102 to 0)***	370 (3)	−19 (−88 to 50)	192 ‡	**−91 (−165 to −17)***	178	−54 (−127 to 18)	264	−26 (−103 to 50)	106
High	**−113 (−201 to −25)***	112 (1)	−102 (−223 to 20)	55	**−127 (−253 to −1)***	57	−94 (−213 to 24)	91	−110 (−274 to 54)	21
Herbicides										
Non-exposed	Ref	11 680 (99)	Ref	5008	Ref	6672	Ref	4746	Ref	6934
Low	−59 (−140 to 22)	132 (1)	−34 (−146 to 77)	64	−82 (−197 to 33)	68	−38 (−148 to 72)	104	−81 (−223 to 61)	28
High	**−204 (−350 to −58)****	39 (0.3)	−175 (−376 to 26)	19	**−241 (−450 to −32)***	20	−172 (−379 to 35)	28	−191 (−416 to 34)	11
Insecticides										
Non-exposed	Ref	11 425 (96)	Ref	4870	Ref	6555	Ref	4576	Ref	6849
Low	−50 (−105 to 5)	315 (3)	−1 (−75 to 73)	166	**−109 (−190 to −28)****	149	−56 (−137 to 25)	212	−21 (−99 to 56)	103
High	**−109 (−197 to −21)***	111 (1)	−98 (−219 to 24)	55	−124 (−251 to 4)	56	−91 (−210 to 28)	90	−109 (−273 to 55)	21

Statistically significant associations are depicted in bold.
Associations between occupational exposures and level of FEV$_1$ (mL) using linear regression with adjustment for sex, age, height, weight, current, ex-smoking and (log) packyears smoked in the LifeLines cohort study. The analyses with VGDF, gases, fumes, mineral dust and biological dust were additionally adjusted for pesticide exposure, whereas the analyses with pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure. Stratification according to smoking status (never/ever) and gender is shown.
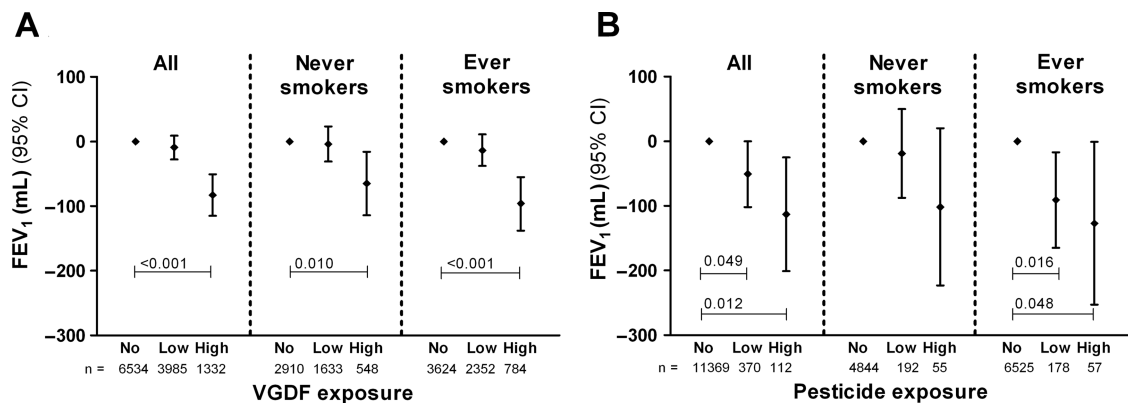*p<0.05.
**p<0.01.
***p<0.001.
†Occupational exposures (no/low/high) were estimated based on job title and function using the ALOHA+job exposure matrix. Non-exposed subjects were assigned as reference category (Ref).
‡Significantly different for never and ever smokers or men and women (ie, p value for interaction <0.05).
VGDF, vapours, gases, dust and fumes.

Workplace

Figure 1 The association between occupational exposure (no/low/high) to vapours, gases, dust and fumes (VGDF) (A) and to pesticides (B) and the level of FEV$_1$ in the whole group and stratified by smoking status (never/ever).

whereas in our study we found a 96 mL lower FEV$_1$ associated with high exposure to VGDF in ever smokers. Contrary to our findings, there was no association in never smokers from the ECRHS study.[18] These differences might relate to the lower average age of the ECRHS population, which consisted mainly of young adults (range 20–44 years) compared with LifeLines (18–89 years). We found consistent associations with the subcategory gases and fumes in both cohorts. The association between exposure to mineral dust, lower level of FEV$_1$ and higher prevalence of airway obstruction was present in the LifeLines cohort but not in the Vlagtwedde-Vlaardingen cohort. This might be due to differences between both cohorts, for example, regarding exposure intensity within the exposed. In general, findings in both cohorts confirm that occupational exposure to VGDF is associated with lower levels of lung function and a higher prevalence of airway obstruction.

To our knowledge, this is the first study showing associations of exposure to pesticides, including herbicides and insecticides, with a lower level of lung function and a higher prevalence of airway obstruction in two general populations from a westernised country. Exposure to specific types of pesticides has been associated with chronic bronchitis in US farmers[19] and their spouses[20] enrolled in the Agricultural Health Study. To date, few studies showed that pesticide exposed farming or manufacturing workers had lower lung function levels than non-exposed workers,[21] whereas others found no associations.[22–24] These studies were all performed in specific subgroups, like plantation or pesticide factory workers, in developing countries. In contrast, we investigated a general population and occupational exposure to pesticides appeared to be associated with a significant loss of FEV$_1$ and FEV$_1$/FVC, especially in smokers. For example, if mean lifetime exposure to pesticides would be about 20 years, a total loss of 200 mL FEV$_1$ for exposure to herbicides implies a loss of 10 mL per year. This corresponds to smoking of one package of cigarettes per day for 1 year, which was associated with an 11 mL loss of FEV$_1$ per packyear smoked in our study.

Moreover, we showed that workers exposed to pesticides had an almost 2 times higher prevalence of moderate/severe airway obstruction than non-exposed workers. These associations were similar in both populations investigated. Subjects who were highly exposed to pesticides included gardeners, field-grown crop and vegetable growers and mixed crop and animal farmers. Associations in the LifeLines sample remained present when each of these three main occupational groups with high exposure to pesticides was excluded one by one, yet associations were

clearly strongest in the field crop and vegetable growers. Between 1985 and today, about 90% of agriculture in the Northern Dutch Provinces consisted of arable crops, on average ~30% potatoes, ~30% cereals, ~15% beets and ~15% maize (personal communication, M Brouwer, University of Utrecht). In terms of pesticide use, this means that mainly herbicides have been applied (cereals, beets, maize) and substantial fungicide use on potatoes (mainly dithiocarbamate fungicides) (for more specific information, see online supplementary file: additional information 1). In a global perspective, the agricultural sector employs a large share of the population worldwide, especially in developing countries where workers often use pesticides with insufficient protective equipment and training.[13] Therefore, interventions to reduce exposure levels in this occupational sector could contribute to lowering the global burden of COPD.

Strengths and limitations

A limitation of this study was the incomplete occupational history within the LifeLines cohort study. However, since we believe that people are more likely to move from so-called blue-collar to white-collar occupations, for example, due to symptoms or objective disease, than the other way around, we hypothesise that with using current or last held job we rather have underestimated than overestimated the association between occupational exposures and lung function level. Second, we have used prebronchodilator spirometry to define airway obstruction and assessed associations in a sample, including subjects below 40 years of age. However, the associations did not change when we restricted our analysis to subjects aged 40 years and older. When the analyses on level of lung function were stratified by age (<40 and ≥40 years), we found that the association between exposure to pesticides and level of lung function remained only in the group with older age, which may be due to a longer time of exposure or the use of better protective equipment nowadays. The associations between exposure to VGDF and level of lung function remained in both age groups. Finally, we have assessed associations with actual mL-values FEV$_1$, with extensive adjustment for individual predictors of lung function level rather than percentage predicted values using an external reference population. However, associations did not change when we used FEV$_1$ as percentage predicted instead of the actual level of FEV$_1$ in mL.

Because of the considerable sample size and inclusion of subjects from rural parts of the Netherlands, we were able to assess associations of exposures with low prevalence, like pesticides, and additionally the interaction between occupational exposures

Table 3 Associations between occupational exposures and level of FEV$_1$/FVC (%) in the LifeLines cohort

LifeLines					FEV$_1$/FVC (%)					
	All		Never smokers		Ever smokers		Men		Women	
Exposure†	b (95% CI)	N (%)	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N
VGDF										
Non-exposed	Ref	6534 (55)	Ref	2910	Ref	3624	Ref	2580	Ref	3954
Low	**−0.3 (−0.6 to −0.1)**	3985 (34)	−0.1 (−0.5 to 0.3)	1633	**−0.5 (−0.9 to −0.2)**	2352	−0.5 (−0.9 to 0)	1167	−0.3 (−0.6 to 0)	2818
High	**−0.7 (−1.2 to −0.3)**	1332 (11)	−0.6 (−1.3 to 0.1)	548	**−0.8 (−1.4 to −0.2)**	784	**−0.8 (−1.3 to −0.2)**	1131	−0.7 (−1.9 to 0.5)	201
Gases/fumes										
Non-exposed	Ref	7007 (59)	Ref	3154	Ref	3853	Ref	2702	Ref	4305
Low	**−0.4 (−0.6 to −0.1)**	4159 (35)	−0.1 (−0.5 to 0.2)	1692	**−0.5 (−0.9 to −0.2)**	2467	−0.4 (−0.9 to 0)	1566	**−0.3 (−0.6 to 0)***	2593
High	**−0.7 (−1.3 to −0.2)**	685 (6)	−0.6 (−1.4 to 0.3)	245	**−0.8 (−1.6 to −0.1)***	440	**−0.8 (−1.4 to −0.1)***	610	−0.6 (−2.1 to 0.8)	75
Mineral dust										
Non-exposed	Ref	9389 (79)	Ref	4121	Ref	5268	Ref	3366	Ref	6023
Low	**−0.4 (−0.8 to −0.1)***	1924 (16)	−0.4 (−0.9 to 0.1)	754	**−0.5 (−1.0 to −0.1)***	1170	**−0.6 (−1.1 to −0.1)***	1037	−0.2 (−0.7 to 0.2)	887
High	−0.1 (−0.8 to 0.5)	538 (5)	−0.3 (−1.3 to 0.7)	216	−0.1 (−0.9 to 0.8)	322	−0.4 (−1.1 to 0.4)	475	1.2 (−0.7 to 3.2)	63
Biological dust										
Non-exposed	Ref	8127 (69)	Ref	3514	Ref	4613	Ref	3729	Ref	4398
Low	−0.1 (−0.4 to 0.2)	3256 (28)	0.1 (−0.3 to 0.5)	1355	−0.2 (−0.6 to 0.1)	1901	0.4 (−0.2 to 1.0)	783 ‡	−0.3 (−0.6 to 0)	2473
High	−0.2 (−0.9 to 0.5)	468 (4)	−0.3 (−1.3 to 0.7)	222	−0.1 (−1.1 to 0.9)	246	−0.2 (−1.0 to 0.7)	366	0.6 (−1.1 to 2.4)	102
All pesticides										
Non-exposed	Ref	11 369 (96)	Ref	4844	Ref	6525	Ref	4523	Ref	6846
Low	−0.4 (−1.1 to 0.3)	370 (3)	−0.5 (−1.5 to 0.5)	192	−0.3 (−1.4 to 0.7)	178	−0.3 (−1.3 to 0.6)	264	−0.5 (−1.7 to 0.8)	106
High	−1.1 (−2.3 to 0.2)	112 (1)	−0.7 (−2.4 to 1.0)	55	−1.4 (−3.3 to 0.4)	57	−0.7 (−2.2 to 0.8)	91	−2.5 (−5.2 to 0.2)	21
Herbicides										
Non-exposed	Ref	11 680 (99)	Ref	5008	Ref	6672	Ref	4746	Ref	6934
Low	−0.3 (−1.5 to 0.8)	132 (1)	0.3 (−1.3 to 1.8)	64	−0.9 (−2.6 to 0.8)	68	0 (−1.4 to 1.4)	104	−1.5 (−3.8 to 0.9)	28
High	**−2.8 (−4.8 to −0.7)**	39 (0.3)	−2.7 (−5.5 to 0.1)	19	−2.7 (−5.7 to 0.3)	20	**−2.9 (−5.5 to −0.3)***	28	−2.4 (−6.1 to 1.4)	11
Insecticides										
Non-exposed	Ref	11 425 (96)	Ref	4870	Ref	6555	Ref	4576	Ref	6849
Low	−0.4 (−1.2 to 0.3)	315 (3)	−0.5 (−1.6 to 0.5)	166	−0.4 (−1.6 to 0.8)	149	−0.4 (−1.4 to 0.6)	212	−0.5 (−1.8 to 0.8)	103
High	−1.1 (−2.3 to 0.2)	111 (1)	−0.7 (−2.4 to 1.0)	55	−1.5 (−3.3 to 0.4)	56	−0.7 (−2.2 to 0.8)	90	−2.5 (−5.2 to 0.2)	21

Statistically significant associations are depicted in bold.
Associations between occupational exposures and level of FEV$_1$/FVC (%) using linear regression with adjustment for sex, age, height, weight, current, ex-smoking and (log) packyears smoked in the LifeLines cohort study. The analyses with VGDF, gases, fumes, mineral dust and biological dust were additionally adjusted for pesticide exposure, whereas the analyses with pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure. Stratification according to smoking status (never/ever) and gender is shown.
*p<0.05.
**p<0.01.
***p<0.001.
†Occupational exposures (no/low/high) were estimated based on job title and function using the ALOHA+job exposure matrix. Non-exposed subjects were assigned as reference category (Ref).
‡Significantly different for men and women (ie, p value for interaction <0.05).
VGDF, vapours, gases, dust and fumes.

Table 4 Associations between occupational exposures and airway obstruction in the LifeLines and Vlagtwedde-Vlaardingen cohorts

| | LifeLines | | | | | | Vlagtwedde-Vlaardingen | | | | | |
| | Mild obstruction (FEV$_1$/FVC<70%) | | | Moderate/severe obstruction† | | | Mild obstruction (FEV$_1$/IVC<70%) | | | Moderate/severe obstruction† | | |
Exposure*	OR (95% CI)	N‡	p Value	OR (95% CI)	N‡	p Value	OR (95% CI)	N‡	p Value	OR (95% CI)	N‡	p Value
VGDF												
Non-exposed	Ref	917		Ref	233		Ref	196		Ref	76	
Low	1.08 (0.96 to 1.22)	578	0.199	1.05 (0.84 to 1.31)	145	0.662	1.22 (0.95 to 1.59)	167	0.124	**1.82 (1.27 to 2.60)**	89	**0.001**
High	**1.41 (1.16 to 1.70)**	259	**<0.001**	**1.39 (1.00 to 1.92)**	80	**0.047**	1.29 (0.95 to 1.74)	276	0.101	**1.85 (1.23 to 2.79)**	149	**0.003**
Gases/fumes												
Non-exposed	Ref	985		Ref	251		Ref	227		Ref	97	
Low	1.10 (0.98 to 1.24)	631	0.116	1.03 (0.83 to 1.28)	164	0.787	1.11 (0.87 to 1.42)	334	0.401	**1.45 (1.04 to 2.01)**	182	**0.028**
High	**1.44 (1.16 to 1.80)**	138	**0.001**	**1.47 (1.02 to 2.11)**	43	**0.039**	1.32 (0.92 to 1.89)	78	0.130	1.55 (0.95 to 2.53)	35	0.081
Mineral dust												
Non-exposed	Ref	1317		Ref	328		Ref	348		Ref	165	
Low	**1.19 (1.03 to 1.37)**	331	**0.018**	1.22 (0.95 to 1.56)	91	0.128	1.16 (0.87 to 1.54)	104	0.318	1.29 (0.88 to 1.90)	50	0.199
High	**1.46 (1.11 to 1.92)**	106	**0.007**	**1.76 (1.15 to 2.72)**	39	**0.010**	1.10 (0.76 to 1.58)	187	0.619	0.99 (0.61 to 1.61)	99	0.972
Biological dust												
Non-exposed	Ref	1196		Ref	314		Ref	324		Ref	141	
Low	1.04 (0.92 to 1.18)	481	0.502	0.99 (0.79 to 1.24)	121	0.916	**1.34 (1.04 to 1.73)**	243	**0.022**	**1.74 (1.24 to 2.43)**	137	**0.001**
High	0.91 (0.66 to 1.25)	77	0.550	0.77 (0.45 to 1.33)	23	0.345	1.25 (0.84 to 1.84)	72	0.271	1.54 (0.92 to 2.55)	36	0.098
All pesticides												
Non-exposed	Ref	1667		Ref	428		Ref	478		Ref	227	
Low	0.83 (0.60 to 1.14)	59	0.241	1.15 (0.69 to 1.93)	20	0.595	1.33 (0.87 to 2.01)	52	0.185	1.08 (0.61 to 1.90)	23	0.791
High	1.28 (0.79 to 2.09)	28	0.322	1.95 (0.92 to 4.13)	10	0.083	**1.48 (1.04 to 2.10)**	109	**0.029**	**1.78 (1.14 to 2.79)**	64	**0.011**
Herbicides												
Non-exposed	Ref	1711		Ref	444		Ref	511		Ref	241	
Low	1.04 (0.65 to 1.67)	27	0.872	1.11 (0.51 to 2.45)	8	0.791	1.29 (0.85 to 1.98)	50	0.235	1.60 (0.93 to 2.76)	28	0.090
High	**2.11 (1.03 to 4.30)**	16	**0.040**	**3.56 (1.28 to 9.88)**	6	**0.015**	1.36 (0.93 to 2.00)	78	0.112	**1.66 (1.02 to 2.69)**	45	**0.040**
Insecticides												
Non-exposed	Ref	1675		Ref	430		Ref	494		Ref	237	
Low	0.81 (0.58 to 1.15)	51	0.241	1.21 (0.70 to 2.09)	18	0.497	1.04 (0.64; 1.70)	36	0.867	0.66 (0.33 to 1.33)	13	0.249
High	1.32 (0.81 to 2.16)	28	0.268	2.05 (0.96 to 4.35)	10	0.062	1.39 (0.98 to 1.98)	109	0.067	**1.62 (1.04 to 2.52)**	64	**0.033**

Statistically significant associations are depicted in bold.
Associations between occupational exposures (no/low/high) and mild (prebronchodilator FEV$_1$/FVC<70%) and moderate/severe airway obstruction using logistic regression adjusted for sex, age, height, weight, ever smoking (no/yes) and (log) packyears smoked in the LifeLines and Vlagtwedde-Vlaardingen cohorts. The analyses with VGDF, gases, fumes, mineral dust and biological dust were additionally adjusted for pesticide exposure, whereas the analyses with pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure.
*Occupational exposures (no/low/high) were estimated based on job title and function using the ALOHA+ job exposure matrix. Non-exposed subjects were assigned as reference category (Ref).
†Moderate/severe airway obstruction=prebronchodilator FEV$_1$/FVC<70% and FEV$_1$<80%, without obstruction=prebronchodilator FEV$_1$/FVC≥70% and FEV$_1$≥80%. Subjects with mild obstruction (prebronchodilator FEV$_1$/FVC<70% and FEV$_1$≥80%predicted) or prebronchodilator FEV$_1$/FVC≥70% and FEV$_1$<80% predicted were excluded from this analysis (LifeLines n=1517 (13%) and Vlagtwedde-Vlaardingen n=436 (18%)). For Vlagtwedde-Vlaardingen: FEV$_1$/IVC instead of FEV$_1$/FVC.
‡Number of subjects with obstruction.
VGDF, vapours, gases, dust and fumes.

and smoking. Second, findings were verified in a second independent cohort. Another strength of the study was the use of the ALOHA+ JEM, which was built specifically for use in general population studies. In general, JEM-based exposure estimates are less likely to be affected by recall bias and differential misclassification of exposure compared with self-reported exposures.[25][26] Finally, we have adjusted our models to overcome possible confounding resulting from co-exposure to pesticides/VGDF. Unadjusted models (not shown) yielded considerably stronger associations, suggesting that workers in occupations exposed to both VGDF and pesticides might be at higher risk than suggested by the adjusted associations that were shown in the current article.

CONCLUSIONS

To conclude, we showed large and clinically relevant losses of lung function level signified by airway obstruction in individuals occupationally exposed to VGDF and pesticides within two general populations. Interventions to reduce exposure levels at the workplace could therefore significantly contribute to lowering the global burden associated with COPD.

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