Occupational inhalant exposures and longitudinal lung function decline

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Shareable abstract (ERSpublications)
Accelerated lung function decline in recent years is not associated with selected occupational exposures https://bit.ly/3aqie8K


Abstract

Background Airborne exposures at the workplace are believed to be associated with lung function decline. However, longitudinal studies are few, and results are conflicting.

Methods Participants from two general population-based cohorts, the Copenhagen City Heart Study and the Copenhagen General Population Study, with at least two lung function measurements were followed for a mean of 9 years (range 3–27 years). Occupational exposure was assigned to each year of follow-up between the two lung function measurements by a job exposure matrix. Associations between mean occupational exposure per year and mean annual decline in forced expiratory volume in 1 s (FEV1) were investigated using linear mixed-effects models according to cohort and time period (1976–1983 and 2001–2015). We adjusted for sex, height, weight, education, baseline FEV1 and pack-years of smoking per year during follow-up.

Results A total of 16144 individuals were included (mean age 48 years and 43% male). Occupational exposure to mineral dusts, biological dusts, gases and fumes and a composite category was not associated with FEV1 decline in analyses with dichotomised exposure. In analyses with an indexed measure of exposure, gases and fumes were associated with an FEV1 change of −5.8 mL per unit per year (95% CI −10.8– −0.7 mL per unit per year) during 1976–1983, but not during 2001–2015. We adjusted for sex, height, weight, education, baseline FEV1 and pack-years of smoking per year during follow-up.

Conclusion In two cohorts from the Danish general population, occupational exposure to dusts, gases and fumes was not associated with excess lung function decline in recent years but might have been of importance decades ago.

Introduction

Lung function peaks in the twenties, and naturally declines with increasing age thereafter [1]. Tobacco smoking is the most important risk factor for accelerated lung function decline, and may lead to chronic obstructive pulmonary disease (COPD) [2]. Along with smoking, occupational airborne exposures are also associated with lung function decline and COPD [3, 4]. The population attributable fraction of COPD due to occupational exposure has been estimated to be 15–20% [5]. Prior studies have mostly focused on high-risk occupations such as coal mining [6, 7], welding [8, 9] and wood processing [10, 11]. Studies

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examining the association between ongoing exposure and change in lung function in the general
population are few and inconclusive [12–20]. A recent study based on data from the Framingham Heart
Study found an excess decline in forced expiratory volume in 1 s (FEV₁) of 4.5 mL per year in “more
likely dust exposed” individuals [14]. Another study based on two general population studies reported an
excess decline of 0.6–0.8 mL per year for low and 2–3 mL per year for high exposure to biological and
mineral dusts and metals [20]. A third study showed no excess decline in workers exposed to vapours,
gases, dusts and fumes, unless concomitant exposure to pesticides was present [12]. Discrepancies between
the estimated impact of occupational airborne exposures and actual findings call for further exploration.

Accounting for occupational exposure in the period between two lung function measurements as an
indication of ongoing rather than delayed health effects like tobacco smoking may be crucial [21, 22].
However, prior general population studies on occupational exposure and lung function decline have relied
on a single or a few selected jobs held during follow-up [12–15], occupation at study entry [16, 17] or
self-reported exposure either at baseline [18] or at the final examination [19].

In the present study, we investigated the association between occupational airborne exposure and
longitudinal change in lung function, expressed as annual decline in FEV₁, in two population-based cohort
studies from Denmark.

Methods

Study design

Individuals were recruited from two large Danish prospective population-based cohorts [23–25]: the
Copenhagen City Heart Study and the Copenhagen General Population Study. The Copenhagen City Heart
Study was initiated in 1976 and enrolled 19825 individuals with subsequent follow-up examinations in
that was initiated in 2003; 109538 participants were available for this study. A follow-up examination was
initiated from 2014, which at the time of the present analyses included 29884 participants [26]. Individuals
in both cohorts were aged 20 years or older. All participants completed a questionnaire and a physical
health examination including spirometry at each visit.

We included participants with lung function measurements at two or more time points (supplementary
figure S1). To examine a working population in an age group in which lung function is thought to decline
in a linear fashion [27], we excluded participants younger than 35 years at first lung function measurement
and older than 65 years at follow-up. Individuals with no employment in the follow-up period or with
missing information on smoking habits or education were also excluded. None of the participants appeared
in more than one of the cohorts. The cohort studies were approved by the Danish Ethical Committees and
were carried out according to the Declaration of Helsinki. Written informed consent was obtained from all
participants.

Lung function

Pre-bronchodilator FEV₁ and forced vital capacity (FVC) were measured in a standing position and
repeated at least three times at each study visit under strict instructions from a trained healthcare
professional. The test was accepted when the visual appearance of the spirometry tracing was within the
acceptable range, and at least two tests from a single visit did not differ by >5%. The highest values of
FEV₁ and FVC were recorded. Three spirometers were used in the Copenhagen City Heart Study: a
Monaghan M-403 Spirometer (Littleton, CO, USA) from 1976 to 1983, a Vitalograph Spirometer (Maids
Moreton, UK) from 1991 to 2003 and an EasyOne Spirometer (NDD Medical Technologies, Zurich,
Switzerland) from 2011 to 2015. In the Copenhagen General Population Study, the Vitalograph Spirometer
was used in the first 14625 participants from 2003 to 2005 and the EasyOne Spirometer in the remaining
participants from 2005 to 2015. Spirometers were replaced when they stopped functioning, and therefore a
direct comparison was not possible; however, measurements from the Vitalograph and EasyOne
spirometers have previously been compared with no major systematic differences of importance to the
present study [28, 29]. As recommended by the manufacturers, the Monaghan and the Vitalograph were
calibrated daily with a 1-L syringe, and the EasyOne Spirometer was verified regularly with a 3-L syringe.

Occupational exposure

Data on occupational airborne exposure were obtained through several steps. Every Danish citizen is given
a unique identification number at birth or on immigration (the Civil Registration number) that is recorded
in the national Danish Civil Registration System. The national Danish Civil Registration System was
combined with the Danish Occupational Cohort (DOC*X) [30] to obtain complete job histories during
follow-up. Data included annual employment status (employed/not employed) and job codes according to
We studied the association between occupational airborne exposure and change in FEV$_1$ using linear mixed-effects models with unstructured covariance. In the main analyses, exposure during follow-up was calculated by dividing the number of exposed years during a follow-up period by the total number of years. In subsequent analyses, mean units of indexed exposure per year were estimated by summing the units of exposure values for each year of follow-up divided by the total number of years. The outcome was expressed as mean annual change in FEV$_1$ and calculated for each follow-up period as the difference between the latter and the first of two sequential lung function measurements divided by the number of years separating them. A fixed set of a priori explanatory variables were selected: sex, baseline height (cm), weight (kg), smoking (mean annual pack-years in the follow-up period), educational level (elementary, high school and academic) and baseline FEV$_1$ (L). We assumed that FEV$_1$ decline in the included age group was linear and therefore did not adjust for age in the main analyses but carried out sensitivity analyses including age in one model, and age and age$^2$ in another model. Interaction of occupational exposure with smoking (mean pack-years) and sex was investigated. Each cohort was analysed separately.

Supplementary analyses included men only, never-smokers only, excluding baseline FEV$_1$ and annual percentage change in FEV$_1$/FVC as an alternative outcome. An analysis of co-exposure was conducted to indicate whether the association between occupational exposure and lung function change varied over time, a secondary analysis was performed with data from the first two rounds of the Copenhagen City Heart Study (1976–1978 and 1981–1983) as opposed to later years (2001–2015). Excluded participants from the Copenhagen City Heart Study and the Copenhagen General Population Study aged 35–65 years were characterised. All analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

**Results**

In total, 16,144 individuals were included (supplementary figure S1). Mean age at study inclusion was 48 years, and 61% in the Copenhagen City Heart Study were smokers at baseline as opposed to 20% in the Copenhagen General Population Study. Other characteristics are summarised in table 1 and supplementary table S3. Follow-up time ranged from 3 to 27 years with a mean of 9 years. All participants from the Copenhagen General Population Study and the majority from the Copenhagen City Heart Study contributed with a baseline and a single follow-up visit, while 563 contributed with three lung function measurements. DISCO-88 codes were complete with all four digits in 66% of all employed years, whereas 4%, 1% and 29% were only available at the first, second and third level, respectively.

Table 2 shows the distribution of follow-up years according to type of exposure during different time periods. The proportion of exposed years was relatively constant in all exposure categories. The Copenhagen General Population Study contributed with 86% of follow-up years from the year 2000. Overall results are presented in table 3, and the fully adjusted model in supplementary table S4. Mineral dust, biological dust, gases and fumes, and VGDF were not associated with change in FEV$_1$. In contrast, smoking one pack-year per year (corresponding to 20 cigarettes per day) was associated with a change in
FEV\textsubscript{1} of \(-17\) mL per year (95% CI \(-19--15\) mL per year) (supplementary table S3). In addition, baseline FEV\textsubscript{1} and female sex were significantly associated with change in FEV\textsubscript{1}.

In analyses exploring differences between the two included cohorts and time periods using the indexed exposure measure, gases and fumes were associated with a change in FEV\textsubscript{1} of \(-5.8\) mL per year (95% CI \(-10.8--0.7\) mL per year) per exposed unit in the Copenhagen City Heart Study, but not in the Copenhagen General Population Study (table 4). In stratified analyses, the association was only seen in early years of the study period (1976–1983) and not in later years. No associations were observed between mean dichotomised or indexed exposure and % change in FEV\textsubscript{1}/FVC per year (supplementary tables S5 and S6). Analyses restricted to men or never-smokers or including age as well as age\(^2\) or excluding baseline FEV\textsubscript{1} or education as covariates did not change our results. We found no interactions between occupational exposure and smoking or sex. A correlation table between indexed exposure measures according to cohort is presented in supplementary table S7. Entering exposure to mineral dusts, biological dusts, and gases and fumes in the same model did not change the results, and indexed exposure to gases and fumes in the Copenhagen City Heart Study remained significantly associated with FEV\textsubscript{1} decline (supplementary tables S8 and S9).

### TABLE 1 Baseline characteristics according to cohort

<table>
<thead>
<tr>
<th></th>
<th>CCHS</th>
<th>CGPS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>8202</td>
<td>7942</td>
<td>16144</td>
</tr>
<tr>
<td>Age in years, mean±sd</td>
<td>48±7</td>
<td>47±5</td>
<td>48±6</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>3763 (46)</td>
<td>3231 (41)</td>
<td>6994 (43)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1711 (21)</td>
<td>3554 (45)</td>
<td>5265 (33)</td>
</tr>
<tr>
<td>Former</td>
<td>1509 (18)</td>
<td>2765 (35)</td>
<td>4274 (26)</td>
</tr>
<tr>
<td>Current</td>
<td>4982 (61)</td>
<td>1623 (20)</td>
<td>6605 (41)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>543 (7)</td>
<td>1939 (24)</td>
<td>2485 (15)</td>
</tr>
<tr>
<td>High school</td>
<td>2629 (32)</td>
<td>5268 (66)</td>
<td>7897 (49)</td>
</tr>
<tr>
<td>Elementary</td>
<td>5027 (61)</td>
<td>735 (9)</td>
<td>5762 (36)</td>
</tr>
<tr>
<td>Height in cm, mean±sd</td>
<td>169±9</td>
<td>173±9</td>
<td>171±9</td>
</tr>
<tr>
<td>Weight in kg, mean±sd</td>
<td>72±14</td>
<td>76±15</td>
<td>74 ±15</td>
</tr>
<tr>
<td>FEV\textsubscript{1} L, mean±sd</td>
<td>2.9±0.8</td>
<td>3.3±0.8</td>
<td>3.1±0.8</td>
</tr>
<tr>
<td>FEV\textsubscript{1} % pred, mean±sd</td>
<td>87±16</td>
<td>96±13</td>
<td>91±16</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC, mean±sd</td>
<td>0.80±0.10</td>
<td>0.80±0.10</td>
<td>0.80±0.10</td>
</tr>
</tbody>
</table>

CCHS: Copenhagen City Heart Study; CGPS: Copenhagen General Population Study; FEV\textsubscript{1}: forced expiratory volume in 1 s; FVC: forced vital capacity. FEV\textsubscript{1} predicted values are based on Danish reference values [33].

### TABLE 2 Distribution of follow-up years according to occupational airborne exposure and calendar period

<table>
<thead>
<tr>
<th></th>
<th>Prior to 1980, n (%)</th>
<th>1980–1989, n (%)</th>
<th>After 2000, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vapours, gases, dusts or fumes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>14489 (64)</td>
<td>16864 (71)</td>
<td>73321 (70)</td>
</tr>
<tr>
<td>Exposure</td>
<td>8097 (36)</td>
<td>5578 (29)</td>
<td>31304 (30)</td>
</tr>
<tr>
<td>Mineral dust</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>17850 (79)</td>
<td>21392 (83)</td>
<td>84270 (81)</td>
</tr>
<tr>
<td>Exposure</td>
<td>4736 (21)</td>
<td>4530 (17)</td>
<td>20355 (20)</td>
</tr>
<tr>
<td>Biological dust</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>20855 (92)</td>
<td>24616 (93)</td>
<td>90241 (86)</td>
</tr>
<tr>
<td>Exposure</td>
<td>1731 (8)</td>
<td>1846 (7)</td>
<td>14384 (14)</td>
</tr>
<tr>
<td>Gases and fumes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>20426 (90)</td>
<td>23835 (90)</td>
<td>97308 (93)</td>
</tr>
<tr>
<td>Exposure</td>
<td>2160 (10)</td>
<td>2627 (10)</td>
<td>7317 (7)</td>
</tr>
</tbody>
</table>

Years of unemployment not included in the number of follow-up years.
baseline FEV1 were associated with decline in FEV1, as indicated previously [1, 36].

In two longitudinal population-based cohort studies including 16144 participants, we found that occupational exposure in the follow-up period to mineral dust, biological dust, gases and fumes, and Vapours, gases, dusts or fumes four decades ago was associated with an excess annual FEV1 decline.

Previous longitudinal general population studies of lung function decline are highly heterogenic and show small associations with airborne occupational agents [12, 14, 18, 20], a greater decline with exposure to an increasing number of agents [19] or no associations at all [13]. The studies rely mostly on self-reported job history or exposures obtained once, they assess exposure differently or they differ in study populations, which may explain the discrepancies. The most recent longitudinal general population study with similar exposure assessment, participant age and a long follow-up concluded that 1 year of low exposure to mineral dust, biological dust or metals was associated with 0.6–0.7 mL lower FEV1, and 1 year of high exposure with 2–3 mL lower FEV1 [20]. Nine other categories of exposure, including gases and fumes and VGDF, were not associated with lower FEV1. The participants were selected from 38 out of 55 sites located in 23 countries, possibly with different working conditions than in Denmark. Importantly, the study reported that 25 pack-years of smoking was associated with a statistically insignificant decrease in FEV1 of 11 mL, corresponding to 0.4 mL per pack-year. This is inconsistent with both our findings and previous studies showing a mean difference of height-adjusted FEV1 of 300 mL following 25 pack-years [33] or a decrease in FEV1 of 6–11 mL per pack-year [34, 35]. In addition to pack-years, in our study female sex and baseline FEV1 were associated with decline in FEV1, as indicated previously [1, 36].

A meta-analysis based on five longitudinal studies from 1987 to 2003 on occupational exposure to mineral dust found an excess decline in FEV1 of 1.6 mL per 1 unit (mg·m⁻³·years) of respirable mineral dust [37]. The most prevalent high mineral dust exposed job in our population was construction workers. The geometric mean of respirable dust among indoor demolition workers in Denmark from 2012 to 2014 has increased from 0.71 mg·m⁻³ per year in 2012 to 1.7 mg·m⁻³ per year in 2014.

### Discussion

In two longitudinal population-based cohort studies including 16144 participants, we found that occupational exposure in the follow-up period to mineral dust, biological dust, gases and fumes, and VGDF was not associated with accelerated lung function decline from 2003 to 2015. However, exposure to gases and fumes four decades ago was associated with an excess annual FEV1 decline.

Previous longitudinal general population studies of lung function decline are highly heterogenic and show small associations with airborne occupational agents [12, 14, 18, 20], a greater decline with exposure to an increasing number of agents [19] or no associations at all [13]. The studies rely mostly on self-reported job history or exposures obtained once, they assess exposure differently or they differ in study populations, which may explain the discrepancies. The most recent longitudinal general population study with similar exposure assessment, participant age and a long follow-up concluded that 1 year of low exposure to mineral dust, biological dust or metals was associated with 0.6–0.7 mL lower FEV1, and 1 year of high exposure with 2–3 mL lower FEV1 [20]. Nine other categories of exposure, including gases and fumes and VGDF, were not associated with lower FEV1. The participants were selected from 38 out of 55 sites located in 23 countries, possibly with different working conditions than in Denmark. Importantly, the study reported that 25 pack-years of smoking was associated with a statistically insignificant decrease in FEV1 of 11 mL, corresponding to 0.4 mL per pack-year. This is inconsistent with both our findings and previous studies showing a mean difference of height-adjusted FEV1 of 300 mL following 25 pack-years [33] or a decrease in FEV1 of 6–11 mL per pack-year [34, 35]. In addition to pack-years, in our study female sex and baseline FEV1 were associated with decline in FEV1, as indicated previously [1, 36].

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We studied the association of ongoing occupational exposure with decline in FEV₁ and disregarded prior unexposed participants were affected equally owing to random sampling. The studies spanning several decades and reflects the development in the field. Fortunately, exposed and towards healthier individuals. The use of different spirometers was a limitation, which is a consequence of not exclude participants with lung disorders at baseline because this could worsen the selection bias included subjects did not, however, differ significantly with regards exposure (results not shown). We did the Copenhagen City Heart Study and the Copenhagen General Population Study of the same age group as healthier subjects choose the most exposed jobs, has previously been shown [17]. Excluded subjects from occupation, it may lead to non-differential misclassification. The ACE JEM relied on UK thresholds, which might differ from the Danish occupational exposure limits. The European Union (EU) releases both indicative and mandatory occupational exposure limits [42]. A recent report found strong similarities between systems for setting and achieving compliance with occupational exposure limits in the EU [43]. The major players in setting limits at the EU level are reported to be the larger northern European countries, the Nordic countries and the Netherlands. Although a comparative study of the actual values is to our knowledge not available, the differences between the countries are believed to be minor.

Occupational history was based on data from the DOC*X database, and we carried prior occupation forwards in years of employment where job titles were missing, which created a risk of misclassification. Exposure was estimated based upon JEM. This approach has strengths as well as some limitations. The JEM was based upon expert judgements made by experienced occupational exposure assessors, but rigorous validation studies using workplace measurements as the gold standard are not available. JEM tends to reduce degree of recall bias and hence differential misclassification as compared with self-reported exposure. However, because JEM may not capture how exposure varies between workers within the same occupation, it may lead to non-differential misclassification. The ACE JEM relied on UK thresholds, which which might differ from the Danish occupational exposure limits. The European Union (EU) releases both indicative and mandatory occupational exposure limits [42]. A recent report found strong similarities between systems for setting and achieving compliance with occupational exposure limits in the EU [43]. The major players in setting limits at the EU level are reported to be the larger northern European countries, the Nordic countries and the Netherlands. Although a comparative study of the actual values is to our knowledge not available, the differences between the countries are believed to be minor.

We only included participants with two or more lung function measurements; ideally, a higher number of follow-up examinations and measurements would have been preferable. Positive selection, i.e. that healthier subjects choose the most exposed jobs, has previously been shown [17]. Excluded subjects from the Copenhagen City Heart Study and the Copenhagen General Population Study of the same age group as included subjects did not, however, differ significantly with regards exposure (results not shown). We did not exclude participants with lung disorders at baseline because this could worsen the selection bias towards healthier individuals. The use of different spirometers was a limitation, which is a consequence of the studies spanning several decades and reflects the development in the field. Fortunately, exposed and unexposed participants were affected equally owing to random sampling.

We studied the association of ongoing occupational exposure with decline in FEV₁ and disregarded prior exposure. It is possible that the effect of airborne exposure is time-dependent: either more harmful at the beginning or following many years of exposure. The response could also be delayed. We were not able to address this in our study. Although studies of the time effect of specific exposures on lung function are emerging [10], much is still unknown. However, if the effects of occupational exposure on FEV₁ resemble those of cigarette smoking, we would expect that the primary effect occurs concurrently with exposure. The degree of synergy between tobacco and occupational inhalant exposures and lung function decline is complex and could not be accounted for with the present study design. Yet, no interaction between smoking and occupational inhalant exposures was found in associations with FEV₁ decline. We did not have data on cumulative exposure before baseline, and we lacked the power to take within-subject variation in exposure into consideration. However, jobs were highly robust, with only a few participants changing exposure status during follow-up.

Because our study population was limited to white European adults aged 35–65 years in an urban setting, our results cannot be generalised to other groups without caution. We used educational level as a proxy for
so socioeconomic status. Because background and upbringing (i.e. passive smoking, living conditions, medical treatment of diseases) vary across social classes, there is a risk of residual confounding. Furthermore, jobs with exposure to airborne agents are primarily held by people of a lower socioeconomic background, which may confound the results. Characteristics of participants from the Copenhagen City Heart Study and the Copenhagen General Population Study differed greatly regarding smoking habits and educational levels and reflect the overall development in Denmark, as in most Western societies. Consequently, direct comparison of results from the two cohorts cannot be made without caution. We adjusted for education and smoking habits to mitigate bias due to cohort differences and to enhance comparability. Estimates from crude and adjusted analyses in both cohorts were largely similar, suggesting less influence of residual confounding. Pesticide exposure may be associated with lung function decline but was only classified in a broader category of mists in the ACE JEM. Study participants were inhabitants of Copenhagen (the capital of Denmark) and exposure to pesticides was believed to be rare.

Our results suggest that none of the selected airborne occupational exposures are currently associated with an excess decline in FEV₁ and consequently do not lead to an increased risk of developing COPD. However, exposure to gases and fumes was associated with a decline in FEV₁ in the early study period. This is plausible because most airborne occupational exposures in high-income countries including Denmark have declined substantially since the 1970s [44], and the access to and use of respiratory protective equipment has increased. JEM-assigned exposure to gases and fumes is highly correlated with exposure to mineral dust, and in 81% of all gases and fumes-exposed years, exposure to mineral dust was also present. Our study relied on cumulative exposure during follow-up, thus interaction analyses based on ever-versus never-exposure or groups of exposure did not seem appropriate. Co-exposure analyses did not change the main results. The lack of extensive interaction analyses is, however, a limitation to our study design because results are most likely carried by a joint effect.

In conclusion, we found no association between exposure to mineral dust, biological dust or gases and accelerated lung function decline in recent years.

Conflict of interest: S. Skaaby has nothing to disclose. E.M. Flachs has nothing to disclose. P. Lange has nothing to disclose. V. Schlünsens has nothing to disclose. J.L. Marott has nothing to disclose. C. Brauer has nothing to disclose. Y. Çolak reports personal fees from Boehringer Ingelheim, AstraZeneca and Sanofi Genzyme, outside the submitted work. S. Afzal has nothing to disclose. B.G. Nordestgaard has nothing to disclose. S. Sadhra has nothing to disclose. O. Kurmi has nothing to disclose. J.P.E. Bonde has nothing to disclose.

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