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Risk of hypersensitivity pneumonitis and other interstitial lung diseases following organic dust exposure

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ABSTRACT

Background Organic dust is associated with hypersensitivity pneumonitis, and associations with other types of interstitial lung disease (ILD) have been suggested. We examined the association between occupational organic dust exposure and hypersensitivity pneumonitis and other ILDs in a cohort study.

Methods The study population included all residents of Denmark born in 1956 or later with at least 1 year of gainful employment since 1976. Incident cases of hypersensitivity pneumonitis and other ILDs were identified in the Danish National Patient Register 1994–2015. Job exposure matrices were used to assign individual annual levels of exposure to organic dust, endotoxin and wood dust from 1976 to 2015. We analysed exposure-response relations by different exposure metrics using a discrete-time hazard model.

Results For organic dust, we observed increasing risk with increasing cumulative exposure with incidence rate ratios (IRR) per 10 unit-years of 1.19 (95% CI 1.12 to 1.27) for hypersensitivity pneumonitis and 1.04 (95% CI 1.02 to 1.06) for other ILDs. We found increasing risk with increasing cumulative endotoxin exposure for hypersensitivity pneumonitis and other ILDs with IRRs per 5000 endotoxin units/m^3-years of 1.55 (95% CI 1.38 to 1.73) and 1.09 (95% CI 1.00 to 1.19), respectively. For both exposures, risk also increased with increasing duration of exposure and recent exposure. No increased risks were observed for wood dust exposure.

Conclusion Exposure-response relations were observed between organic dust and endotoxin exposure and hypersensitivity pneumonitis and other ILDs, with lower risk estimates for the latter. The findings indicate that organic dust should be considered a possible cause of any ILD.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Organic dust exposure has traditionally been associated with hypersensitivity pneumonitis, but associations with other interstitial lung diseases have also been observed.

WHAT THIS STUDY ADDS

⇒ Occupational exposure to organic dust and endotoxins is associated with not only hypersensitivity pneumonitis but also other interstitial lung diseases as well as all interstitial lung diseases combined in an exposure-dependent manner.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings underline the need for further preventive measures against organic dust exposure to decrease the future burden of interstitial lung disease.

INTRODUCTION

Organic dust consists of particles originating from microbes, plants and animals, including bacteria, fungi and pollen.[1] Organic dust exposure can be encountered in many industries and occupations, including agriculture, woodworking and textile processing.[2 3] Considerable exposure to organic dust originating from birds and other sources may also occur outside work.[4] Endotoxin, which is part of the outer membrane of Gram-negative bacteria, is a well-studied organic dust component with strong inflammatory effects[5] and is typically present at high levels in agriculture.[2 6] Different components of organic dust may coexist, such as in wood dust, where both moulds and endotoxins may be found, primarily in fresh wood.[3]

Organic dust exposure has been linked with different types of interstitial lung disease (ILD). ILDs are a group of inflammatory and/or fibrotic lung diseases, often classified according to the presence or absence of a known cause,[7] even though these groups share sometimes indistinguishable clinical and radiological features.[8 9] In Denmark, the incidence of ILDs is approximately 20 per 100 000 per year.[10 11] Hypersensitivity pneumonitis (HP) is a specific type of ILD with an annual incidence in Denmark of 1.16 per 100 000. It is associated with a higher mortality among younger people.[12] Traditionally, the presence of a cause has been integrated into the diagnostic criteria of HP, and even though the new definition of HP introduced in 2020 no longer requires an identified cause,[9] the previous criteria still challenge the examination of causal associations prior to this change. The onset of HP may be acute

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or insidious, with an associated exposure more often identified in cases with acute onset.[9] Besides HP, associations between different organic dust constituents and ILDs without a known cause, such as idiopathic interstitial pneumonias and sarcoidosis, have also been suggested,[13–18] though findings have been mixed.

For HP, the association with organic dust exposure is primarily based on case reports and series, as only a few epidemiological studies are available.[4 19] This leaves a need for more epidemiological studies to verify the association. Epidemiological studies on idiopathic interstitial pneumonias and sarcoidosis do not include quantitative exposure information,[13–18] leading to a lack of knowledge about exposure-response relations, which are central to the evaluation of causal associations.

The aim of this study was to examine the exposure-response relations between exposure to organic dust, endotoxin and wood dust and HP and other ILDs in a cohort study of the Danish general working population 1994–2015.

METHODS

Study population

The study population included past or present residents of Denmark with at least 1 year of gainful employment registered in the Danish Occupational Cohort (DOC*X) since 1976.[20] Only residents born in 1956 or later were included. DOC*X contains annual information on occupation, which is harmonised and coded according to the 1988 International Standard Classification of Occupations (ISCO-88).[21]

From the study population, we also derived a subpopulation restricted to blue-collar workers (ISCO-88 major categories 6–9) at baseline for supplementary analyses.

Hypersensitivity pneumonitis and other ILDs

Within the study population, we identified incident cases as the first diagnosis of HP or other ILDs registered in the Danish National Patient Register,[22] which covers all hospital contacts in Denmark. As HP could only be defined with certainty using the 10th version of the International Classification of Diseases (ICD-10) introduced in Denmark in 1994, we only identified cases from 1994 onwards.

The diagnosis of HP rests on typical radiological findings, bronchoalveolar lavage lymphocytosis, identification of relevant antigenic exposures, including measurement of precipitating antibodies, and, in some cases, a lung biopsy. HP was defined by ICD-10 code J67, which is used in Denmark for all cases of HP, independently of the underlying exposure.

We defined other ILDs by ICD-10 codes D86.0, D86.2, J60-65, J68.4A, J70.1, J70.3, J70.4, J82, J84, J99.0, J99.1, M05.1, M34.8C and M35.0B. In a supplementary analysis, we studied five specific types of ILD within the other ILDs group: pneumoconiosis, drug-related ILDs, connective tissue disease-related ILDs, idiopathic interstitial pneumonias and pulmonary sarcoidosis. Descriptions of the ICD-10 codes included are available in online supplemental table S1.

All prevalent cases of ILD registered in the National Patient Register 1977–1993 were excluded. They were defined by ICD-8 codes 515.0, 515.1, 515.2, 515.9, 516.0, 516.1, 516.2, 519 and 519.20.

For a sensitivity analysis of other ILDs, we excluded all cases with a subsequent diagnosis of HP in the same or following year as the diagnosis of other ILDs.

Exposure assessment

The exposure assessment was based on the work histories (coded according to ISCO-88) provided by DOC*X. If the ISCO-88 code was missing for a worker for a given year, we assigned the latest valid ISCO-88 code up to 5 years back, reducing work history years with missing ISCO-88 codes from 13% to 5%. Years missing an ISCO-88 code after this procedure were assigned an exposure intensity of 0.

Organic dust exposure, covering all exposure to particulate matter of organic origin, was assigned using the expert-based ALOHA+ job exposure matrix (JEM),[23] which assigns three levels of exposure (0=none, 1=low, 2=high). The ALOHA+ JEM exposure intensity estimates were squared to estimate cumulative exposure.

Endotoxin exposure was estimated using a quantitative JEM[24] based on 3384 personal endotoxin measurements from Western Europe and Canada. The JEM provides estimates of endotoxin exposure expressed as endotoxin units (EU) 1990–2009 with an annual trend of −2.9%. For years before and after this period, which are not covered by measurements, we assumed no trend in the JEM estimates.

Wood dust exposure was estimated using a quantitative JEM[25] providing exposure estimates in mg/m^3 based on 12 653 personal wood dust measurements from Europe. From 1978–2007, there is an annual trend of −7.8%, whereas for the years before and after this period, which were not covered by measurements, we assumed no trend in the JEM estimates.

Information on exposed ISCO-88 codes for all three JEMs can be found in online supplemental tables S2–S4.

For all three exposures, we assigned annual individual exposure intensity which was used to estimate individual (1) cumulative exposure as the sum of the annual exposure intensities, (2) duration of exposure in years and (3) recent exposure accrued during the previous year.

For a supplementary analysis, we grouped workers according to ISCO-88 major groups based on the first registered valid ISCO-88 code for each worker.

Statistical analyses

Exposure was assessed from the first registered employment year after 1976, which is the year of first registrations in DOC*X, and until the end of follow-up. We started follow-up in 1994 for those with a first year of employment before 1994. If the first year of employment was 1994 or later, follow-up started the year following the first year of employment, as we had no information on the month or day of employment. For the same reason, we also lagged all independent variables by 1 year. We followed workers until the year of first diagnosis (HP or other ILDs), death, emigration, disappearance or end of follow-up on 31 December 2015, whichever came first. No person could contribute more than one diagnosis, as the first ILD diagnosis led to the end of the follow-up. All cases of ILD diagnosed from 1977 to 1993 were excluded to avoid the inclusion of prevalent cases. After 1994, ILD diagnosed before a participant's beginning of follow-up also led to exclusion.

For cumulative exposure and duration of exposure, person-years were first categorised as either exposed or non-exposed, and the exposed group was then divided into tertiles based on the distribution of person-years. For recent exposure, we classified exposure accrued outside the 1-year time window as zero and dichotomised exposure within the window by the median, except for organic dust exposure where the semi-quantitative JEM provided only two possible exposure values above zero within 1 year, and these were used to form the two exposed groups.

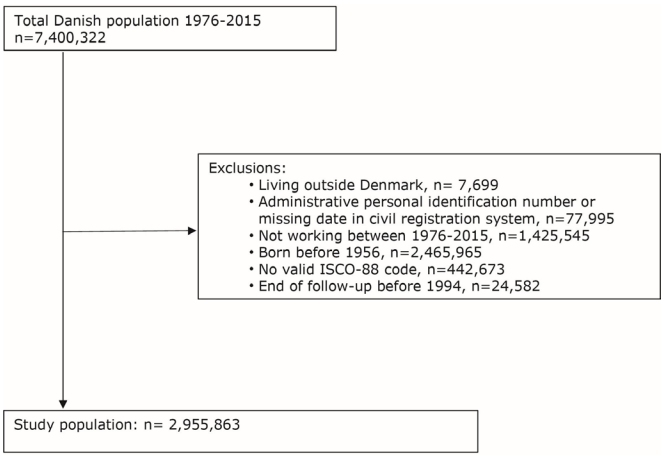

Figure 1 Establishment of the study population. ISCO-88, 1988 International Standard Classification of Occupations.

We used a discrete-time hazard model with person-years as a unit of analysis, yielding incidence rate ratios (IRR) with 95% CIs.[26] Analyses were performed separately for each of the three exposures. The reference was the non-exposed group for the exposure in question. For the analysis based on occupations, ISCO-88 major groups 0 and 1 were used as reference, as these groups are not exposed to organic dust according to the ALOHA+ JEM. Analyses were adjusted for age, sex, calendar year of follow-up, education, JEM estimates of smoking, previously diagnosed connective tissue disease, fibrogenic medications and JEM estimates of cumulative asbestos and crystalline silica exposure. More information on the classification of and rationale for the covariates is available in the supplementary material (online supplemental appendix 1). All variables were treated as time-varying accounting for changes in status and increases in cumulative exposure over time.

We fitted restricted cubic splines with 95% CIs for the cumulative exposure metrics as continuous variables, placing the knots at the 5, 50 and 95 percentiles.[27] The x-axis was cut-off at the 99 percentile to focus on the most relevant results.

Pearson pairwise correlation coefficients were calculated for all exposures.

We used Stata V.17 (StataCorp, College Station, Texas, USA) for all analyses.

The study was registered at the repository of the Central Denmark Region.

RESULTS

The study population comprised 2 955 863 workers accumulating 49 228 874 person-years during follow-up. A flowchart of the establishment of the study population is shown in figure 1. We identified 411 incident cases of HP, 6724 cases of other ILDs, adding up to 7135 cases of all ILDs. The corresponding crude incidence rates per 100 000 person-years were 0.8, 13.7 and 14.5, respectively.

The distribution of person-years by cumulative exposure and worker characteristics showed that higher organic dust exposure was associated with previous exposure to fibrogenic medication; higher cumulative endotoxin exposure with male sex, being a skilled blue-collar worker and vocational or higher secondary education; and higher cumulative wood dust exposure with male sex and being unskilled blue-collar worker (online supplemental table S5).

Correlations between the three main exposures were 0.45 between cumulative organic dust and endotoxin exposure, 0.50 between cumulative organic dust and wood dust exposure and 0.02 between cumulative endotoxin and wood dust exposure. For cumulative silica and asbestos exposure all correlations with the three main exposures were below 0.40.

For organic dust exposure, we observed increasing IRRs of HP with increasing cumulative exposure with a fully adjusted IRR of 1.19 (95% CI 1.12 to 1.27) per 10 unit-years (table 1). Similarly, we observed increasing IRRs with increasing cumulative exposure for other ILDs and all ILDs but with lower risk estimates. The fully adjusted IRRs for other ILDs and all ILDs were 1.04 (95% CI 1.02 to 1.06) and 1.05 (95% CI 1.03 to 1.07) per 10 unit-years, respectively. IRR for the highest exposed tertile compared with the non-exposed group was 1.82 (95% CI 1.39 to 2.38) for HP and 1.18 (95% CI 1.10 to 1.26) for other ILDs. The IRRs also increased with increasing exposure duration for all three outcomes.

Increasing risk of HP was also found with increasing cumulative endotoxin exposure, with a fully adjusted IRR of 1.55 (95% CI 1.38 to 1.73) per 5000 EU/m^3-years (table 1). We observed similar results for other ILDs and all ILDs with IRRs of 1.09 (95% CI 1.00 to 1.19) and 1.16 (95% CI 1.08 to 1.25) per 5000 EU/m^3-years, respectively. For HP, IRR in the highest exposure tertile compared with the non-exposed group was 6.53 (95% CI 4.10 to 10.42), while it was 1.26 (95% CI 1.07 to 1.48) for other ILDs. We also observed increasing IRRs with increasing exposure duration for all three outcomes.

No increasing risks were observed for cumulative wood dust exposure (table 1). The fully adjusted IRR was 0.91 (95% CI 0.76 to 1.08) per 5 mg/m^3-years for HP, 1.00 (95% CI 0.95 to 1.04) for other ILDs and 0.99 (95% CI 0.95 to 1.03) for all ILDs. Duration of exposure was also not associated with increased risk.

An expanded version of table 1 is shown in online supplemental table S6.

In spline analyses, risk of HP increased with increasing cumulative organic dust exposure, with the strongest increase up to around 20 unit-years (figure 2). Risk of other ILDs and all ILDs increased up to around 20 unit-years, after which it levelled off. For cumulative endotoxin exposure, increases for all three outcomes were seen up to around 5000 EU/m^3-years, after which it reached a plateau. The increase was strongest for HP. For cumulative wood dust exposure, no clear pattern of increasing risk with increasing exposure was seen for any of the outcomes.

When excluding cases with subsequent HP diagnosis in the same or following year, the sensitivity analysis for other ILDs showed risk estimates similar to the main analysis (online supplemental table S7).

In the population restricted to blue-collar workers, we found similar risk estimates for cumulative organic dust exposure per 10 unit-years, but the IRR for the highest exposure tertile was only increased for HP (online supplemental table S8). The findings for cumulative endotoxin and wood dust exposure were similar to those of the total study population.

Increasing risk of HP with increasing recent exposure was observed for both organic dust (IRR per 10 units 15.58 (95% CI 6.44 to 37.68)) and endotoxin (IRR per 5000 EU/m^3 24.30 (95% CI 8.64 to 68.35)) (table 2). Risk of other ILDs and all ILDs also increased with increasing recent exposure to organic dust and endotoxin. The number of cases with recent wood dust exposure was too low for meaningful analyses (results not shown). More details are available in online supplemental table S9.

Table 1 Incidence rate ratios (IRR) of hypersensitivity pneumonitis (HP), other interstitial lung diseases (ILDs) and all ILDs following exposure to organic dust, endotoxin and wood dust among 2 955 863 workers born in 1956 or later, in Denmark

	HP		Other ILDs		All ILDs	
Exposure	**Cases**	**IRR (95% CI)***	**Cases**	**IRR (95% CI)***	**Cases**	**IRR (95% CI)***
Organic dust						
Cumulative exposure (unit-years)						
0	115	1	2080	1	2195	1
1–2	54	1.17 (0.84 to 1.63)	953	1.09 (1.01 to 1.18)	1007	1.09 (1.01 to 1.18)
3–8	91	1.32 (1.00 to 1.75)	1631	1.18 (1.10 to 1.26)	1722	1.18 (1.11 to 1.26)
9–156	151	1.82 (1.39 to 2.38)	2060	1.18 (1.10 to 1.26)	2211	1.21 (1.14 to 1.29)
Per 10 unit-years		1.19 (1.12 to 1.27)		1.04 (1.02 to 1.06)		1.05 (1.03 to 1.07)
Duration (years)						
0	115	1	2080	1	2195	1
1–2	60	1.18 (0.86 to 1.63)	1036	1.09 (1.01 to 1.17)	1096	1.09 (1.01 to 1.18)
3–6	79	1.32 (0.98 to 1.77)	1354	1.16 (1.08 to 1.25)	1433	1.17 (1.09 to 1.25)
7–39	157	1.78 (1.37 to 2.32)	2254	1.20 (1.12 to 1.28)	2411	1.22 (1.15 to 1.30)
Per 5 years		1.12 (1.04 to 1.21)		1.02 (1.00 to 1.04)		1.03 (1.01 to 1.05)
Endotoxin						
Cumulative exposure (EU/m^3-years)						
0	340	1	6245	1	6585	1
15–810	13	2.73 (1.45 to 5.13)	139	1.10 (0.92 to 1.32)	152	1.16 (0.98 to 1.38)
811–2520	19	3.43 (2.02 to 5.83)	151	1.19 (1.00 to 1.41)	170	1.28 (1.09 to 1.51)
2521–79 400	39	6.53 (4.10 to 10.42)	189	1.26 (1.07 to 1.48)	228	1.46 (1.26 to 1.70)
Per 5000 EU/m^3-years		1.55 (1.38 to 1.73)		1.09 (1.00 to 1.19)		1.16 (1.08 to 1.25)
Duration (years)						
0	340	1	6245	1	6585	1
1	11	3.66 (1.89 to 7.11)	76	0.99 (0.79 to 1.26)	87	1.10 (0.88 to 1.37)
2–5	15	2.38 (1.33 to 4.26)	189	1.21 (1.04 to 1.42)	204	1.26 (1.08 to 1.46)
6–39	45	6.84 (4.30 to 10.88)	214	1.26 (1.08 to 1.48)	259	1.47 (1.27 to 1.71)
Per 5 years		1.68 (1.45 to 1.95)		1.10 (1.04 to 1.16)		1.15 (1.09 to 1.20)
Wood dust						
Cumulative exposure (mg/m^3-years)						
0	362	1	5896	1	6258	1
0.2–2.3	12	0.78 (0.43 to 1.43)	270	1.17 (1.02 to 1.33)	282	1.14 (1.00 to 1.30)
2.4–6.9	16	0.95 (0.56 to 1.63)	277	1.24 (1.09 to 1.42)	293	1.22 (1.08 to 1.39)
7.0–53.0	21	0.90 (0.54 to 1.49)	281	1.00 (0.87 to 1.15)	302	0.99 (0.87 to 1.13)
Per 5 mg/m^3-years		0.91 (0.76 to 1.08)		1.00 (0.95 to 1.04)		0.99 (0.95 to 1.03)
Duration (years)						
0	362	1	5896	1	6258	1
1	5	0.57 (0.23 to 1.41)	148	1.14 (0.96 to 1.35)	153	1.10 (0.93 to 1.30)
2–5	25	1.15 (0.73 to 1.79)	341	1.19 (1.05 to 1.34)	366	1.18 (1.06 to 1.33)
6–39	19	0.75 (0.45 to 1.26)	339	1.08 (0.95 to 1.22)	358	1.05 (0.93 to 1.19)
Per 5 years		0.90 (0.73 to 1.11)		1.02 (0.98 to 1.07)		1.02 (0.97 to 1.06)

IRRs were derived using a discrete-time hazard model with person-years as a unit of analysis.
*Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, fibrogenic medications and cumulative exposure to asbestos and respirable crystalline silica.
EU, endotoxin units.

Risk of HP was increased in ISCO-88 major group 6 'Skilled agricultural and fishery workers' (online supplemental table S10). Less pronounced increases were found in ISCO-88 major groups 7–9 comprising other blue-collar workers. For other ILDs, risks were increased for ISCO-88 major groups 6–8, whereas no increase in risk was observed for white-collar workers in ISCO-88 major groups 2–4.

In analyses of specific types of ILD within the other ILDs group, we observed an increasing risk of pulmonary sarcoidosis with increasing cumulative organic dust exposure and risk

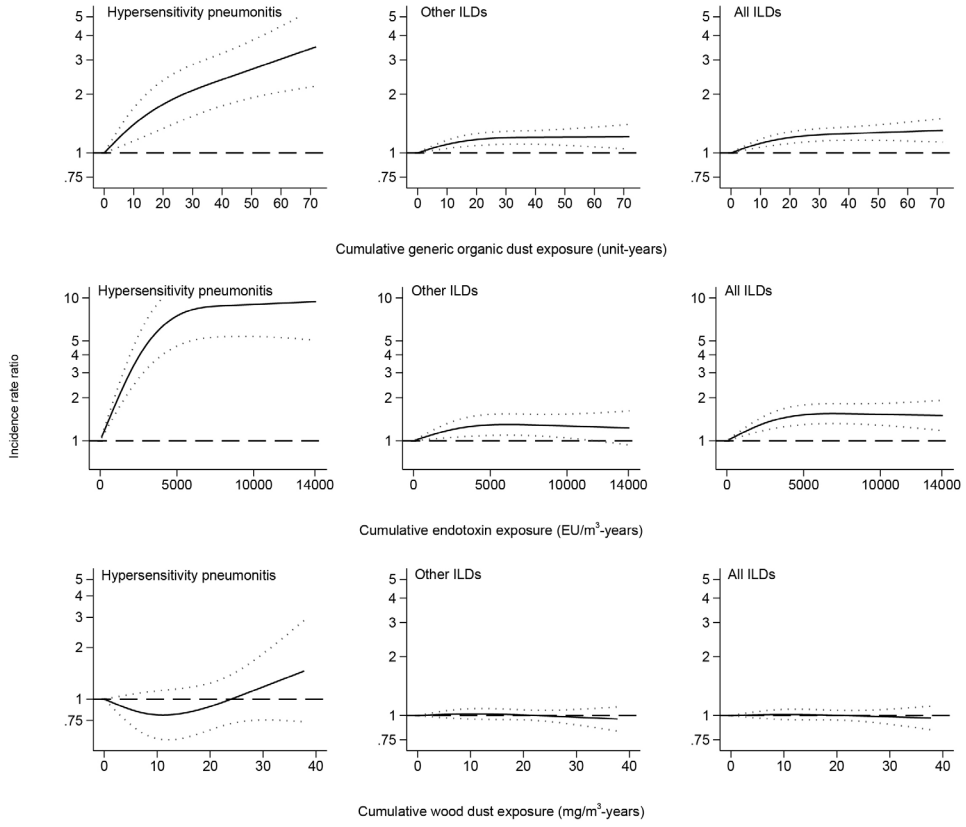

Figure 2 Restricted cubic spline fits of incidence rate ratios of hypersensitivity pneumonitis, other ILDs and all ILDs by cumulative organic dust exposure, cumulative endotoxin exposure and cumulative wood dust exposure. Dotted lines mark 95% CIs. EU, endotoxin units; ILDs, interstitial lung disease.

Table 2 Incidence rate ratios (IRR) of hypersensitivity pneumonitis, other interstitial lung diseases (ILDs) and all ILDs following recent exposure to organic dust and endotoxins among 2 955 863 workers, in Denmark

	HP		Other ILDs		All ILDs	
Exposure	Cases	IRR (95% CI)*	Cases	IRR (95% CI)*	Cases	IRR (95% CI)*
Organic dust						
Cumulative exposure 1 year prior						
0	275	1	5106	1	5381	1
1	95	1.18 (0.93 to 1.50)	1359	0.94 (0.88 to 1.00)	1454	0.95 (0.90 to 1.01)
4	41	3.12 (2.19 to 4.46)	259	1.12 (0.98 to 1.28)	300	1.23 (1.09 to 1.39)
AIC		10 387.13		130 594.25		137 908.45
Per 10 units		15.58 (6.44 to 37.68)		1.10 (0.81 to 1.49)		1.37 (1.03 to 1.83)
AIC		10 386.06		130 599.45		137 916.09
Endotoxin						
Cumulative exposure 1 year prior						
0	376	1	6602	1	6978	1
<405	15	3.74 (2.21 to 6.34)	85	1.19 (0.96 to 1.47)	100	1.32 (1.08 to 1.61)
≥405	20	11.00 (6.73 to 17.96)	37	1.08 (0.78 to 1.50)	57	1.59 (1.22 to 2.07)
AIC		10 349.51		130 599.33		137 905.95
Per 5000 EU/m^3		24.30 (8.64 to 68.35)		0.90 (0.42 to 1.96)		1.59 (0.86 to 2.95)
AIC		10 397.45		130 599.76		137 918.76

IRRs were derived using a discrete-time hazard model with person-years as a unit of analysis.
*Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, fibrogenic medications, cumulative exposure to asbestos and respirable crystalline silica.
AIC, Akaike's Information Criterion; EU, endotoxin units.

also tended to increase with increasing cumulative endotoxin exposure (online supplemental table S11). We observed no clear exposure-response relations for the other types of ILD studied.

DISCUSSION

In the present study, we observed an increasing risk of HP, other ILDs and all ILDs with increasing cumulative exposure to organic dust and endotoxin, but not to wood dust. Risk of all three outcomes also increased with increasing recent organic dust and endotoxin exposure. No increased risk was observed for wood dust exposure.

Our results are in accordance with organic dust being a known cause of HP.[15] Furthermore, we found that increasing exposure entailed increasing risk of HP, and while an association between increasing antigen exposure and disease progression has previously been suggested, results have been inconsistent.[28 29]

HP is associated with farming, and endotoxin is abundant in livestock farming, pigeon coops and poultry houses.[2 30 31] Our findings support a causal role of endotoxins in the development of HP. We cannot, however, rule out that endotoxin is a marker of other organic dust constituents that may contribute to the association observed.

An association between woodworking and HP has been suggested and may be caused by fungal and bacterial antigen contamination.[32 33] Our findings did not confirm an association between wood dust exposure and HP. The JEM does, however, not distinguish between fresh and dry wood exposure or include information on the level of microorganisms present.

Results of previous studies on idiopathic interstitial pneumonias, which are mainly case–control studies, have been inconsistent with regard to organic dust exposure.[13 14 16 34–37] However, studies of organic dust exposure and sarcoidosis have, though few, consistently reported an association.[17 18 38] We observed an association between cumulative organic dust and endotoxin exposure and the entire group of other ILDs, attributable primarily to pulmonary sarcoidosis. Our findings for other ILDs are confirmed by the sensitivity analysis of other ILDs excluding cases with a subsequent HP diagnosis, which rules out that the findings for other ILDs can be attributed to cases of HP not diagnosed initially but only after further examination.

The observed association between cumulative organic dust and endotoxin exposure and other ILDs and all ILDs signal that organic dust exposure may not only be a risk factor for HP, but also for other types of ILD. This indicates that the importance of organic dust and other work-related exposures for the development of ILD will be underestimated, if only ILDs traditionally attributed to work, such as HP, are taken into account. The observed associations between all ILDs and the blue-collar trades suggest that these occupations in particular need to be targeted to decrease the future burden of ILD.

Integration of a cause in the diagnostic criteria of a disease, as has traditionally been the case with HP, challenges the investigation of the association with this cause, which was what this study aimed for. In time, the new definition of HP introduced in 2020 focusing on objective findings rather than identification of specific exposures will provide better opportunities for studying causal associations for HP. For now, however, the issue remains, and we chose to circumvent it by analysing other ILDs and all ILDs, as done previously in a study of ILD risk in pigeon breeders.[4] Our confidence in the associations observed for other ILDs is increased by the similar findings in the main and sensitivity analyses. However, we consider the findings for all ILDs the main findings of our study, as these risk estimates should not be affected by the inclusion or exclusion of exposure in the disease definitions. Another potential way to circumvent disease definitions is studies of associations for disease phenotype, defined for instance by radiological findings, which to our knowledge has not been done for organic dust exposures yet.

Strengths and limitations

This study included the total Danish working population, and we retrieved diagnoses from a national health register with information on all hospital contacts, which means that selection bias is unlikely to have affected our results. We did not have access to individual clinical information, but in Denmark all suspected cases of ILD are referred to the four Danish national ILD centres. The extensive diagnostic programme carried out consists of a detailed medical history including occupational and avocational exposures, symptoms and findings related to autoimmune rheumatic diseases and other underlying diseases, as well as a clinical examination, including pulmonary function tests, a 6-minute walk test and blood tests. All patients undergo a high-resolution CT scan and are discussed at a multidisciplinary team conference. If necessary, lung biopsies are performed.

Because of clinical and radiological similarities between especially HP dominated by fibrosis and other ILDs such as idiopathic pulmonary fibrosis, diagnostic misclassification of HP as other ILDs may have contributed to the increased risk of other ILDs. However, this will not have affected the results for all ILDs combined, and we consider this way of addressing both diagnostic misclassification and the problem of integration of causes in disease definitions a major strength of this study.

Another strength is that the exposure assessment did not rely on self-reported exposure information that may be subject to recall bias, and the two quantitative JEMs used were based on large numbers of personal measurements. While the use of JEMs enables the study of an entire working population, it may lead to non-differential misclassification of exposure because the JEMs do not capture within-occupation exposure variation. However, this will mainly lead to Berkson-type error, resulting in increased uncertainty of risk estimates but an unbiased exposure-response association.[39]

We adjusted the risk estimates for a number of known causes of pulmonary fibrosis,[7] but adding more confounders than age, sex and calendar year of follow-up only slightly attenuated the exposure-response relations. For HP, smoking is generally considered a protective factor,[40] whereas it may be a risk factor for some types of other ILDs.[41] We adjusted for smoking using a lifestyle JEM, which has previously predicted acute myocardial infarction in this population as expected.[42] Individual smoking information would be preferable, but we do not expect the use of a JEM to be problematic when studying diseases where smoking is not a strong risk factor. We were not able to adjust for non-occupational sources of organic dust exposures associated with HP such as domestic birds or mould-contamination at home, and this may have resulted in residual confounding. Cumulative endotoxin and wood dust exposure were both moderately correlated with cumulative organic dust exposure, but we chose not to conduct mutual adjustment to avoid over-adjustment.

Conclusion

In this study, we observed strong exposure-response relations between organic dust and endotoxin exposure and HP. Exposure-response relations were also observed for other ILDs and all ILDs, but with lower risk estimates. No associations were observed for wood dust. We consider the estimates for all ILDs

most representative of the true associations, as organic dust and other antigenic exposures have traditionally been integrated into the definition of HP, thereby predefining an association. Our findings indicate that organic dust exposure may contribute to the development of any ILD, underscoring the importance of preventive measures against organic dust exposure to decrease the future burden of ILD.

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Contributors IBI and HAK conceived and designed the study. HK contributed to the development of the ALOHA+ job exposure matrix (JEM). IB, VS and HK developed the endotoxin and wood dust JEMs. IBI and JMV established the data set for analysis. IBI analysed the data and drafted the manuscript. IBI, JMV, IB, JO, SP, EB, JPEB, VS, FR, ZAS, MBA, HK and HAK have contributed to interpreting the results, reviewed the paper for important intellectual content, approved the final version of the manuscript and take responsibility for the integrity of the work as a whole. IBI and HAK are guarantors for the paper.

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Supplementary material

Contents supplementary material

Appendix 1

Definition of covariates		
Covariate	**Categories**	**Data source**
Age	<40, 40-44, 45-49, 50-54, ≥55 years	Population register
Sex	Male, female	Population register
Calendar year of follow-up	1994-2004, 2005-15	
Educational level	Lower secondary, vocational or higher secondary, short, medium, and long cycle higher education and unknown	Highest attained education according to Statistics Denmark's education registry
Connective tissue disease	Yes, no	National Patient Register by ICD-8 codes 446, 712, 716 and 734 and ICD-10 codes M05, M06, M08, M09 and M30-M36
Fibrogenic medications	Yes, no	National Prescription Registry by ATC codes Antineoplastic and immunomodulating agents (all ATC codes with first letter L), nitrofuran derivatives (ATC code J01XE), and amiodarone (C01BD01).
Cumulative silica exposure	Tertiles	Estimated using SYN-JEM ISCO-88 estimates for respirable crystalline silica.
Cumulative asbestos exposure	Tertiles	Estimated using SYN-JEM ISCO-88 estimates for asbestos.
Probability of smoking	Tertiles: 5-30, 31-50, 51-74%	Estimated using a smoking job exposure matrix developed for the DOC*X cohort

Silica and asbestos: SYN-JEM provides quantitative estimates of annual silica and asbestos exposure (1) which are linked with occupational history for each worker. Annual exposure was summed to yield cumulative silica and organic dust exposure, respectively, which was then divided into tertiles for the analyses.

Smoking probability: The smoking job exposure matrix is based on Danish survey information on smoking (3). The JEM contains sex- and calendar year-specific estimates of smoking prevalence for all ISCO-88 occupations and predicts mortality and acute myocardial infarction independent of other determinants as expected (4, 5). We assigned years without employment the same smoking probability as in the latest previous year with employment. If there was no previous information on smoking probability available due to ISCO-88 codes that

could not be linked with the smoking JEM, we assigned the same smoking habit as in the next later period where smoking habit could be assigned.

All covariates were decided upon a priori based on a review of the literature and the availability of relevant information in the registers (6-10).

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Table S1. Description of ICD-10 (International Classification of Diseases, 10th version) codes used to define the outcomes.

ICD-10 code	**Description**
D86.0	Sarcoidosis of lung
D86.2	Sarcoidosis of lung with sarcoidosis of lymph nodes
J60	Coalworker pneumoconiosis
J61	Pneumoconiosis due to asbestos and other mineral fibres
J62	Pneumoconiosis due to dust containing silica
J63	Pneumoconiosis due to other inorganic dusts
J64	Unspecified pneumoconiosis
J65	Pneumoconiosis associated with tuberculosis
J67	Hypersensitivity pneumonitis due to organic dust
J68.4A	Pulmonary fibrosis due to chemicals, gases, fumes and vapours
J70.1	Chronic and other pulmonary manifestations due to radiation
J70.3	Chronic drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
J82	Pulmonary eosinophilia, not elsewhere classified
J84	Other interstitial pulmonary diseases
J99.0	Rheumatoid lung disease
J99.1	Respiratory disorders in other diffuse connective tissue disorders
M05.1	Rheumatoid lung disease
M34.8C	Systemic sclerosis with lung involvement
M35.0B	Sicca syndrome (Sjögren) with lung involvement
Pneumoconiosis: J60-65 Drug-related ILDs: J70.3 and J70.4 Connective tissue disease-related ILDs: J99.0, J99.1, M05.1, M34.8C and M35.0B Idiopathic interstitial pneumonias: J84 Pulmonary sarcoidosis: D86.0 and D86.2	

Supplementary Table S2. Most frequent codes in the study population according to ALOHA+ JEM exposure levels	
5 most frequent ISCO-88 codes with exposure level 2	
7124	Carpenters and joiners
6130	Market-oriented crop and animal producers
9211	Farm-hands and labourers
7412	Bakers, pastry-cooks and confectionery makers
8240	Wood-products machine operators
5 most frequent ISCO-88 codes with exposure level 1	
9132	Helpers and cleaners in offices, hotels and other establishments
5132	Institution-based personal care workers
5133	Home-based personal care workers
9330	Transport labourers and freight handlers
3231	Nursing associate professionals
5 most frequent ISCO-88 codes with exposure level 0	
5220	Shop salespersons and demonstrators
5131	Child-care workers
4115	Secretaries
2331	Primary education teaching professionals
4000	Clerks

Supplementary Table S3. Exposed ISCO-88 codes in the endotoxin job exposure matrix	
5 highest exposed ISCO-88 codes	
9321	Assembling labourers
9322	Hand packers and other manufacturing labourers
9330	Transport labourers and freight handlers
9332	Drivers of animal-drawn vehicles and machinery
9333	Freight handlers
5 lowest exposed ISCO-88 codes	
9133	Hand-launderers and pressers
9140	Building caretakers, window and related cleaners
9141	Building caretakers
9142	Vehicle, window and related cleaners
9150	Messengers, porters, doorkeepers and related workers
All other exposed ISCO-88 codes: 9151, 9152, 9153, 9160, 9161, 9162, 9200, 9210, 9211, 9212, 9213, 9300, 9310, 9311, 9312, 9313, 9320	

Supplementary Table S4. Exposed ISCO-88 codes in the wood dust job exposure matrix	
5 highest exposed ISCO-88 codes	
7132	Floor layers and tile setters
9313	Building construction labourers
7131	Roofers
7420	Wood treaters, cabinetmakers and related trades workers
7124	Carpenters and joiners
6 lowest exposed ISCO-88 codes	
8140	Wood-processing- and papermaking-plant operators
7330	Handicraft workers in wood textile, leather and related materials
8141	Wood-processing-plant operators
7423	Woodworking machine setters and setter-operators
9212	Forestry labourers
6141	Forestry workers and loggers
All other exposed ISCO-88 codes: 7129,7312,7331,7421,7422,8240,8285	

Supplementary Table S5. Distribution of person-years at risk (%) by time-varying worker characteristics and cumulative organic dust, endotoxin and wood dust exposure level among 2,955,863 workers, Denmark, 1994-2015

		Cumulative organic dust exposure (unit-years)				Cumulative endotoxin exposure (EU/m^3-years)				Cumulative wood dust exposure (mg/m^3-years)			
		0	1-2	3-8	9-156	0	15-810	811-2520	2521-79400	0	0.2-2.3	2.4-6.9	7.0-53.0
		19,096,012 person-years	7,880,364 person-years	11,293,223 person-years	10,900,455 person-years	46,997,887 person-years	694,633 person-years	718,610 person-years	758,924 person-years	45,313,261 person-years	1,395,004 person-years	1,221,639 person-years	1,240,150 person-years
Sex	Male	53.3	47.8	48.1	52.0	49.8	71.4	70.9	82.8	47.8	85.7	86.7	93.2
	Female	46.7	52.2	51.9	48.0	50.2	28.6	29.1	17.2	52.2	14.3	13.3	6.8
Occupations during follow-up[a]	Armed forces	1.4	1.2	0.7	0.2	1.0	0.6	0.7	0.1	1.0	1.2	0.7	0.1
	White-collar workers	57.0	55.0	54.8	43.3	54.6	20.8	23.8	16.2	56.1	20.6	20.4	14.4
	Skilled blue-collar workers	8.0	7.3	9.5	17.9	9.7	18.1	20.8	39.5	8.6	31.2	30.7	33.8
	Unskilled blue-collar workers	5.4	19.0	19.3	26.2	14.4	44.4	37.9	29.8	13.8	31.4	32.9	37.4
	Unemployed or retired	17.7	16.3	13.6	9.8	15.0	14.3	11.5	6.2	15.0	14.2	12.7	11.1
	Missing	10.4	1.2	2.1	2.6	5.3	1.8	5.3	8.3	5.6	1.4	2.6	3.1
Age	<40	76.7	82.0	73.7	47.9	71.2	63.3	61.5	45.5	71.4	74.6	63.2	40.8
	40-44	11.1	8.9	13.1	21.4	13.2	15.8	16.9	21.7	13.2	12.1	16.8	23.1
	45-49	7.3	5.6	8.3	17.2	9.2	12.1	12.8	18.3	9.1	8.2	12.3	19.7
	50-54	3.8	2.8	4.0	10.5	5.0	6.9	7.0	11.4	5.0	4.1	6.2	12.7
	≥55	1.1	0.7	0.9	3.0	1.4	1.8	1.8	3.2	1.4	1.0	1.4	3.7
Decade of follow-up	1994-2004	48.9	40.5	42.0	37.0	43.5	35.6	43.4	39.8	43.6	32.5	44.6	45.2
	2005-2015	51.1	59.5	58.0	63.0	56.5	64.4	56.6	60.2	56.4	67.5	55.4	54.8
Probability of smoking	5-30%	70.5	60.8	58.3	57.9	63.7	54.5	54.0	57.4	64.7	54.5	47.0	41.7
	31-50%	28.2	37.5	39.2	39.3	34.4	41.9	41.1	39.7	33.6	43.5	48.1	50.6
	51-74%	1.2	1.8	2.4	2.7	1.8	3.6	4.9	2.9	1.7	2.0	5.0	7.7
Education	Unknown	6.2	2.5	1.9	1.5	3.6	3.3	2.3	1.6	3.7	2.5	2.0	2.6
	Lower secondary	24.7	29.4	23.8	29.2	25.7	47.4	38.0	27.1	24.9	42.0	37.4	44.9
	Vocational or high secondary	45.6	43.0	43.3	48.7	45.2	39.3	46.9	61.7	45.2	45.3	49.8	46.4
	Short cycle higher	5.2	4.3	4.5	3.5	4.5	2.7	4.5	4.2	4.6	2.9	3.3	2.4
	Medium cycle higher	11.2	14.4	18.1	12.7	14.1	4.5	4.5	2.3	14.3	5.5	6.1	3.2
	Long cycle higher	7.2	6.4	8.5	4.5	6.9	2.8	3.9	3.0	7.2	1.9	1.3	0.6
Connective tissue disease[b]	No	99.4	99.2	99.2	99.1	99.2	99.3	99.3	99.4	99.2	99.4	99.5	99.5
	Yes	0.6	0.8	0.8	0.9	0.8	0.7	0.7	0.6	0.8	0.6	0.5	0.5
Fibrinogenic medication[b]	No	97.4	96.9	96.4	96.1	96.7	97.4	97.6	98.1	96.6	98.3	98.3	98.5
	Yes	2.6	3.1	3.6	3.9	3.3	2.6	2.4	1.9	3.4	1.7	1.7	1.5
Cumulative asbestos exposure	0	79.9	70.5	63.1	59.4	70.5	50.3	56.1	71.7	72.8	33.8	36.4	40.7
(f/ml-years)	1st tertile	11.3	19.6	21.1	18.5	16.2	26.0	23.0	16.4	15.2	43.9	30.2	18.5
	2nd tertile	5.7	7.5	11.7	16.0	9.4	17.4	16.9	9.9	8.4	18.5	27.9	28.1
	3rd tertile	3.1	2.4	4.0	6.0	3.9	6.4	4.0	2.0	3.6	3.9	5.5	12.7
Cumulative respirable crystalline silica exposure	0	95.2	94.1	90.2	75.8	93.0	11.9	21.7	12.4	93.7	48.7	41.9	31.7
(mg/m^3-years)	1st tertile	2.6	4.2	6.7	9.6	3.9	67.6	35.1	9.8	3.5	37.2	29.5	11.1
	2nd tertile	1.2	1.2	2.2	8.5	1.7	16.0	38.5	42.3	1.8	10.2	16.4	29.9
	3rd tertile	1.0	0.5	0.9	6.2	1.4	4.5	4.8	35.5	1.0	3.9	12.2	27.3
Duration of exposure (years)[c]	0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0
	1st tertile	0.0	100.0	5.3	0.0	0.0	56.2	6.5	0.7	0.0	50.3	4.2	0.0
	2nd tertile	0.0	0.0	75.2	9.7	0.0	41.6	71.4	8.7	0.0	47.9	62.5	13.4
	3rd tertile	0.0	0.0	19.6	90.3	0.0	2.2	22.1	90.6	0.0	1.8	33.3	86.6

[a]Grouped according to International Standard Classification of Occupations (ISCO), 1988 revision: Armed forces (ISCO-88 codes 0110), white-collar workers (ISCO-88 codes 1000-5999), skilled blue-collar workers (ISCO-88 codes 6000-7999), unskilled blue-collar workers (ISCO-88 codes 8000-9999), others (unemployed or retired).
[b]As defined in the covariates section in the online supplementary material
[c]Tertiles of duration of generic organic dust exposure (years): 1-2, 3-6, 7-39. Tertiles of duration of endotoxin and wood dust exposure (years): 1, 2-5, 6-39.

Supplementary Table S6. Incidence rate ratios (IRR) of hypersensitivity pneumonitis (HP), other interstitial lung diseases (ILDs) and all ILDs following exposure to generic organic dust among 2,955,863 workers born 1956 or later, Denmark, 1994-2015

	HP				Other ILDs				All ILDs			
Exposure	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[b]	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[b]	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[b]
Cumulative exposure												
0	19,110,938	115	1	1	19,096,894	2080	1	1	19,096,012	2195	1	1
1-2	7,886,845	54	1.20 (0.86-1.65)	1.17 (0.84-1.63)	7,880,844	953	1.15 (1.06-1.24)	1.09 (1.01-1.18)	7,880,364	1007	1.15 (1.07-1.24)	1.09 (1.01-1.18)
3-8	11,304,675	91	1.36 (1.03-1.79)	1.32 (1.00-1.75)	11,293,969	1631	1.27 (1.19-1.36)	1.18 (1.10-1.26)	1,1293,223	1722	1.27 (1.20-1.36)	1.18 (1.11-1.26)
9-156	10,917,580	151	2.14 (1.66-2.75)	1.82 (1.39-2.38)	10,902,298	2060	1.33 (1.25-1.42)	1.18 (1.10-1.26)	10,900,455	2211	1.37 (1.29-1.45)	1.21 (1.14-1.29)
Per 10 unit-years			1.22 (1.16-1.29)	1.19 (1.12-1.27)			1.05 (1.04-1.07)	1.04 (1.02-1.06)			1.07 (1.05-1.08)	1.05 (1.03-1.07)
Duration (years)												
0	19,110,938	115	1	1	19,096,894	2080	1	1	19,096,012	2195	1	1
1-2	8,481,147	60	1.23 (0.90-1.68)	1.18 (0.86-1.63)	8,474,686	1036	1.16 (1.07-1.25)	1.09 (1.01-1.17)	8,474,140	1096	1.16 (1.08-1.25)	1.09 (1.01-1.18)
3-6	9,560,481	79	1.40 (1.05-1.86)	1.32 (0.98-1.77)	9,551,742	1354	1.26 (1.17-1.35)	1.16 (1.08-1.25)	9,551,014	1433	1.27 (1.18-1.35)	1.17 (1.09-1.25)
7-39	12,067,472	157	2.03 (1.58-2.61)	1.78 (1.37-2.32)	12,050,683	2254	1.34 (1.25-1.42)	1.20 (1.12-1.28)	12,048,888	2411	1.37 (1.29-1.45)	1.22 (1.15-1.30)
Per 5 years			1.17 (1.09-1.25)	1.12 (1.04-1.21)			1.05 (1.03-1.06)	1.02 (1.00-1.04)			1.05 (1.03-1.07)	1.03 (1.01-1.05)
Cumulative exposure (EU/m^3-years)												
0	47,044,279	340	1	1	47,000,972	6245	1	1	46,997,887	6585	1	1
15-810	695,570	13	2.47 (1.42-4.31)	2.73 (1.45-5.13)	694,769	139	1.30 (1.10-1.54)	1.10 (0.92-1.32)	694,633	152	1.36 (1.15-1.59)	1.16 (0.98-1.38)
811-2520	719,711	19	3.41 (2.15-5.43)	3.43 (2.02-5.83)	718,773	151	1.38 (1.17-1.62)	1.19 (1.00-1.41)	718,610	170	1.47 (1.27-1.72)	1.28 (1.09-1.51)
2521-79400	760,478	39	6.14 (4.35-8.65)	6.53 (4.10-10.42)	759,491	189	1.38 (1.19-1.60)	1.26 (1.07-1.48)	758,924	228	1.60 (1.40-1.83)	1.46 (1.26-1.70)
Per 5000 EU/m^3-years			1.62 (1.48-1.78)	1.55 (1.38-1.73)			1.14 (1.06-1.23)	1.09 (1.00-1.19)			1.21 (1.14-1.29)	1.16 (1.08-1.25)
Duration (years)												
0	4,7044,279	340	1	1	47,000,972	6245	1	1	4,6997,887	6585	1	1
1	443,318	11	3.29 (1.80-6.00)	3.66 (1.89-7.11)	442,896	76	1.15 (0.92-1.44)	0.99 (0.79-1.26)	442,813	87	1.25 (1.01-1.55)	1.10 (0.88-1.37)
2-5	869,270	15	2.24 (1.33-3.76)	2.38 (1.33-4.26)	868,093	189	1.41 (1.22-1.63)	1.21 (1.04-1.42)	867,906	204	1.45 (1.26-1.66)	1.26 (1.08-1.46)
6-39	863,171	45	6.30 (4.57-8.70)	6.84 (4.30-10.88)	86,204	214	1.40 (1.22-1.61)	1.26 (1.08-1.48)	861,448	259	1.62 (1.43-1.84)	1.47 (1.27-1.71)
Per 5 years			1.65 (1.50-1.81)	1.68 (1.45-1.95)			1.13 (1.08-1.18)	1.10 (1.04-1.16)			1.17 (1.13-1.22)	1.15 (1.09-1.20)
Cumulative exposure (mg/m^3-years)												
0	45,357,135	362	1	1	45,316,643	5896	1	1	45,313,261	6258	1	1
0.2-2.3	1,396,789	12	1.04 (0.58-1.85)	0.78 (0.43-1.43)	1,395,175	270	1.36 (1.20-1.54)	1.17 (1.02-1.33)	1,395,004	282	1.34 (1.19-1.51)	1.14 (1.00-1.30)
2.4-6.9	1,223,726	16	1.45 (0.87-2.40)	0.95 (0.56-1.63)	1,221,790	277	1.50 (1.32-1.69)	1.24 (1.09-1.42)	1,221,639	293	1.49 (1.33-1.68)	1.22 (1.08-1.39)
7.0-53.0	1,242,388	21	1.63 (1.04-2.57)	0.90 (0.54-1.49)	1,240,397	281	1.24 (1.10-1.40)	1.00 (0.87-1.15)	1,240,150	302	1.26 (1.12-1.42)	0.99 (0.87-1.13)
Per 5 mg/m^3-years			1.09 (0.95-1.27)	0.91 (0.76-1.08)			1.07 (1.03-1.11)	1.00 (0.95-1.04)			1.07 (1.04-1.11)	0.99 (0.95-1.03)
Duration (years)												
0	45,357,135	362	1	1	45,316,643	5896	1	1	45,313,261	6258	1	1
1	753,877	5	0.77 (0.32-1.86)	0.57 (0.23-1.41)	752,951	148	1.37 (1.16-1.61)	1.14 (0.96-1.35)	752,894	153	1.33 (1.13-1.56)	1.10 (0.93-1.30)
2-5	1,601,066	25	1.75 (1.16-2.65)	1.15 (0.73-1.79)	1,598,844	341	1.43 (1.28-1.60)	1.19 (1.05-1.34)	1,598,582	366	1.45 (1.31-1.62)	1.18 (1.06-1.33)
6-39	1,507,960	19	1.28 (0.80-2.05)	0.75 (0.45-1.26)	1,505,567	339	1.29 (1.15-1.44)	1.08 (0.95-1.22)	1,505,317	358	1.29 (1.15-1.43)	1.05 (0.93-1.19)
Per 5 years			1.11 (0.93-1.32)	0.90 (0.73-1.11)			1.10 (1.05-1.14)	1.02 (0.98-1.07)			1.10 (1.05-1.14)	1.02 (0.97-1.06)

[a]Adjusted for age, sex and calendar year

[b]Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, medications and cumulative exposure to asbestos and respirable crystalline silica

Table S7. Incidence rate ratios (IRR) of other ILDs with exclusion of all cases with a subsequent diagnosis of hypersensitivity pneumonitis in the same or next year following exposure to generic organic dust, endotoxins and wood dust

	Other ILDs		
Exposure metrics	Cases	IRR (95% CI)[a]	IRR (95% CI)[b]
Generic organic dust			
Cumulative exposure (units)			
0	2046	1	1
1-2	948	1.16 (1.08-1.26)	1.10 (1.02-1.19)
3-8	1611	1.27 (1.19-1.36)	1.18 (1.10-1.26)
9-156	2036	1.34 (1.26-1.43)	1.18 (1.11-1.27)
Per 10 unit-years		1.05 (1.04-1.07)	1.04 (1.02-1.06)
Duration (years)			
0	2046	1	1
1-2	1029	1.17 (1.08-1.26)	1.09 (1.01-1.18)
3-6	1335	1.26 (1.18-1.35)	1.16 (1.08-1.25)
7-39	2231	1.35 (1.26-1.43)	1.20 (1.13-1.28)
Per 5 years		1.05 (1.03-1.06)	1.02 (1.00-1.04)
Endotoxins			
Cumulative exposure (EU/m^3-years)			
0	6166		1
15-810	137	1.30 (1.09-1.54)	1.10 (0.92-1.32)
811-2520	151	1.39 (1.19-1.64)	1.20 (1.01-1.43)
2521-79400	187	1.39 (1.20-1.61)	1.26 (1.07-1.49)
Per 5000 EU/m^3-years		1.14 (1.06-1.23)	1.09 (1.00-1.19)
Duration (years)			
0	6166		1
1	76	1.17 (0.93-1.46)	1.01 (0.79-1.27)
2-5	187	1.41 (1.22-1.63)	1.21 (1.03-1.42)
6-39	212	1.41 (1.22-1.61)	1.27 (1.08-1.49)
Per 5 years		1.13 (1.08-1.18)	1.10 (1.04-1.16)
Wood dust			
Cumulative exposure (mg/m^3-years)			
0	5823		1
0.2-2.3	266	1.36 (1.20-1.53)	1.16 (1.02-1.32)
2.4-6.9	276	1.51 (1.34-1.71)	1.25 (1.10-1.42)
7.0-53.0	276	1.24 (1.09-1.40)	0.99 (0.87-1.14)
Per 5 mg/m^3-years		1.07 (1.03-1.11)	0.99 (0.95-1.03)
Duration (years)			
0	5823		1
1	146	1.36 (1.16-1.61)	1.13 (0.95-1.35)
2-5	338	1.44 (1.29-1.61)	1.19 (1.05-1.34)
6-39	334	1.28 (1.15-1.44)	1.07 (0.95-1.22)
Per 5 years		1.09 (1.05-1.14)	1.02 (0.98-1.07)

[a]Adjusted for age, sex and calendar year
[b]Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, medications and cumulative exposure to asbestos and respirable crystalline silica

Table S8. Incidence rate ratios (IRR) of hypersensitivity pneumonitis (HP), other interstitial lung diseases (ILDs) and all ILDs following exposure to generic organic dust, endotoxins and wood dust among 840,464 blue-collar workers, Denmark

	HP		Other ILDs		All ILDs	
Exposure	Cases	IRR (95% CI)[a]	Cases	IRR (95% CI)[a]	Cases	IRR (95% CI)[a]
Generic organic dust						
Cumulative exposure (units)						
0	14	1	416	1	430	1
1-2	18	1.53 (0.75-3.12)	270	0.78 (0.67-0.92)	288	0.81 (0.69-0.94)
3-8	26	1.31 (0.68-2.53)	535	0.91 (0.80-1.04)	561	0.92 (0.81-1.05)
9-156	85	2.30 (1.27-4.17)	1098	0.94 (0.83-1.06)	1183	0.98 (0.87-1.11)
Per 10 units		1.21 (1.12-1.31)		1.02 (0.99-1.04)		1.03 (1.01-1.05)
Duration (years)						
0	14				430	1
1-2	19	1	416	1	324	0.80 (0.69-0.93)
3-6	25	1.41 (0.70-2.85)	305	0.78 (0.67-0.91)	477	0.90 (0.79-1.03)
7-39	85	1.35 (0.70-2.61)	452	0.88 (0.77-1.01)	1231	1.00 (0.89-1.13)
Per 5 years		2.34 (1.29-4.23)		0.96 (0.85-1.08)		1.00 (0.97-1.03)
Endotoxins						
Cumulative exposure (EU/m^3-years)						
0	99	1	2005	1	2104	1
15-810	7	2.64 (1.12-6.22)	85	1.11 (0.88-1.40)	92	1.16 (0.93-1.46)
811-2520	9	2.59 (1.21-5.56)	87	1.17 (0.93-1.47)	96	1.23 (0.99-1.53)
2521-79400	28	5.39 (2.97-9.79)	142	1.23 (1.01-1.50)	170	1.41 (1.18-1.70)
Per 5000 EU/m^3-years		1.54 (1.33-1.79)		1.11 (1.01-1.22)		1.17 (1.07-1.27)
Duration (years)						
0	99	1	2005	1	2104	1
1	5	3.21 (1.23-8.40)	42	0.95 (0.70-1.31)	47	1.03 (0.77-1.39)
2-5	8	2.03 (0.91-4.52)	110	1.15 (0.94-1.42)	118	1.19 (0.97-1.45)
6-39	31	5.53 (3.04-10.08)	162	1.30 (1.08-1.57)	193	1.48 (1.24-1.77)
Per 5 years		1.60 (1.34-1.90)		1.10 (1.03-1.16)		1.13 (1.07-1.20)
Wood dust						
Cumulative exposure (mg/m^3-years)						
0	109	1	1775	1	1884	1
0.2-2.3	5	0.63 (0.25-1.59)	140	1.09 (0.91-1.31)	145	1.06 (0.89-1.27)
2.4-6.9	12	1.05 (0.56-1.97)	170	1.13 (0.96-1.34)	182	1.13 (0.96-1.32)
7.0-53.0	17	0.88 (0.50-1.56)	234	0.95 (0.81-1.10)	251	0.94 (0.81-1.09)
Per 5 mg/m^3-years		0.88 (0.72-1.08)		0.98 (0.93-1.02)		0.97 (0.93-1.01)
Duration (years)						
0	109	1	1775	1	1884	1
1	n.r.	0.45 (0.11-1.84)	76	1.04 (0.82-1.32)	78	1.00 (0.79-1.27)
2-5	n.r.	1.18 (0.67-2.07)	206	1.14 (0.98-1.33)	222	1.14 (0.98-1.33)
6-39	n.r.	0.77 (0.43-1.37)	262	0.97 (0.84-1.12)	278	0.95 (0.83-1.09)
Per 5 years		0.90 (0.72-1.13)		0.99 (0.94-1.05)		0.99 (0.94-1.04)

n.r.: not reported, cells with less than five cases

[a]Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, medications and cumulative exposure to asbestos and respirable crystalline silica

Table S9. Incidence rate ratios (IRR) of hypersensitivity pneumonitis, other interstitial lung diseases (ILDs) and all ILDs following recent exposure to generic organic dust and endotoxins among 2,955,863 workers, Denmark

	Hypersensitivity pneumonitis				Other ILDs				All ILDs			
Exposure	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[b]	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[b]	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[b]
Generic organic dust												
Cumulative exposure 1 year prior (units)												
0	36,965,032	275	1	1	36,929,103	5106	1	1	36926347	5381	1	1
1	10,690,825	95	1.21 (0.96-1.53)	1.18 (0.93-1.50)	10,681,971	1359	0.95 (0.89-1.01)	0.94 (0.88-1.00)	10681162	1454	0.96 (0.91-1.02)	0.95 (0.90-1.01)
4	1,564,181	41	3.35 (2.40-4.68)	3.12 (2.19-4.46)	1,562,931	259	1.17 (1.03-1.33)	1.12 (0.98-1.28)	1562545	300	1.28 (1.14-1.44)	1.23 (1.09-1.39)
AIC			10382.86	10387.13			131776.14	130594.25			139072.99	137908.45
Per 10 units			18.99 (8.24-43.77)	15.58 (6.44-37.68)			1.23 (0.91-1.65)	1.10 (0.81-1.49)			1.54 (1.17-2.04)	1.37 (1.03-1.83)
AIC			10381.70	10386.06			131781.66	130599.45			139080.90	137916.09
Endotoxins												
Cumulative exposure 1 year prior (EU/m^3)												
0	48,526,861	376	1	1	48,481,377	6602	1	1	48477736	6978	1	1
<405	491,807	15	3.80 (2.27-6.38)	3.74 (2.21-6.34)	491,407	85	1.21 (0.98-1.50)	1.19 (0.96-1.47)	491299	100	1.35 (1.11-1.64)	1.32 (1.08-1.61)
≥405	201,370	20	11.17 (7.07-17.64)	11.00 (6.73-17.96)	201,221	37	1.12 (0.81-1.55)	1.08 (0.78-1.50)	201019	57	1.64 (1.26-2.13)	1.59 (1.22-2.07)
AIC			10346.76	10349.51			131782.19	130599.33			139072.32	137905.95
Per 5000 EU/m^3			28.81 (10.57-78.51)	24.30 (8.64-68.35)			0.96 (0.45-2.05)	0.90 (0.42-1.96)			1.69 (0.92-3.10)	1.59 (0.86-2.95)
AIC			10397.71	10397.45			131783.48	130599.76			139087.41	137918.76

AIC: Akaike's Information Criterion

[a]Adjusted for age, sex and calendar year

[b]Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, medications, cumulative exposure to asbestos and respirable crystalline silica

Table S10. Incidence rate ratios (IRR) of hypersensitivity pneumonitis (HP), other interstitial lung diseases (ILDs) and all ILDs by ISCO-88 major groups, 2,955,863 workers, Denmark, 1994-2015

	HP				Other ILDs				All ILDs			
Exposure	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[c]	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[c]	Person-years	Cases	IRR (95% CI)[a]	IRR (95% CI)[c]
ISCO-88 major groups												
0/1: Armed forces/legislators, senior officials and managers	1,498,556	11	1	1	1,497,144	214	1	1	1,497,059	225	1	1
2: Professionals	2,200,288	7	0.43 (0.17-1.12)	0.47 (0.18-1.25)	2,198,530	234	0.74 (0.62-0.89)	0.96 (0.79-1.17)	2,198,457	241	0.73 (0.60-0.87)	0.93 (0.77-1.13)
3: Technicians and associate professionals	3,286,907	20	0.84 (0.40-1.78)	0.81 (0.38-1.75)	3,283,813	419	0.92 (0.78-1.09)	1.06 (0.89-1.26)	3,283,586	439	0.91 (0.78-1.08)	1.04 (0.88-1.23)
4: Clerks	6,456,475	47	1.03 (0.53-2.01)	1.00 (0.50-1.99)	6,450,468	810	0.92 (0.79-1.08)	1.03 (0.87-1.20)	6,450,065	857	0.93 (0.80-1.08)	1.02 (0.88-1.20)
5: Service workers and shop and market sales workers	12,186,359	79	1.02 (0.54-1.95)	0.97 (0.50-1.88)	12,177,230	1330	0.90 (0.78-1.05)	0.98 (0.84-1.14)	12,176,511	1409	0.91 (0.79-1.05)	0.98 (0.84-1.14)
6: Skilled agricultural and fishery workers	588,885	30	7.37 (3.69-14.72)	5.58 (2.66-11.68)	588,345	110	1.39 (1.10-1.75)	1.36 (1.07-1.73)	587,994	140	1.68 (1.36-2.08)	1.62 (1.30-2.02)
7: Craft and related trades workers	6,820,812	65	1.28 (0.68-2.43)	1.17 (0.61-2.24)	6,812,409	1203	1.21 (1.05-1.40)	1.17 (1.01-1.36)	6,811,846	1268	1.21 (1.05-1.40)	1.17 (1.01-1.35)
8: Plant and machine operators and assemblers	4,088,528	50	1.66 (0.86-3.20)	1.52 (0.78-2.96)	4,083,869	714	1.22 (1.05-1.42)	1.18 (1.01-1.39)	4,083,394	764	1.24 (1.07-1.44)	1.20 (1.03-1.40)
9: Elementary occupations	12,093,228	102	1.25 (0.67-2.35)	1.13 (0.59-2.14)	12,082,197	1690	1.08 (0.93-1.24)	1.08 (0.94-1.25)	12,081,142	1792	1.08 (0.94-1.25)	1.08 (0.94-1.25)

[a]Adjusted for age, sex and calendar year
[b]Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, medications and cumulative exposure to asbestos and respirable crystalline silica

Supplementary Table S11. Incidence rate ratios (IRR) of subtypes of other interstitial lung diseases (ILDs) following exposure to generic organic dust, endotoxins and wood dust among 2,955,863 workers born 1956 or later, Denmark

	Pneumoconiosis		Drug-related ILDs		CTD-related ILDs		IIPs		Pulmonary sarcoidosis	
Exposure	Cases	IRR (95% CI)[a]	Cases	IRR (95% CI)[a]	Cases	IRR (95% CI)[a]	Cases	IRR (95% CI)[a]	Cases	IRR (95% CI)[a]
Cumulative generic organic dust exposure										
0	42	1	11	1	43	1	661	1	1272	1
1-2	21	1.28 (0.75-2.18)	6	1.40 (0.51-3.84)	22	1.16 (0.69-1.96)	308	1.13 (0.98-1.29)	569	1.05 (0.95-1.16)
3-8	38	1.31 (0.83-2.06)	13	1.66 (0.73-3.78)	28	0.85 (0.52-1.39)	583	1.25 (1.12-1.41)	932	1.14 (1.04-1.24)
9-156	35	0.68 (0.42-1.10)	13	1.07 (0.46-2.52)	40	0.79 (0.49-1.25)	776	1.12 (1.00-1.25)	1146	1.27 (1.16-1.38)
Per 10 unit-years		0.88 (0.77-1.01)		0.93 (0.73-1.19)		0.87 (0.74-1.03)		1.01 (0.98-1.05)		1.06 (1.04-1.09)
Cumulative endotoxin exposure										
0	127	1		*	127	1	2167	1	3625	1
15-810	n.r.	0.49 (0.12-2.08)			n.r.	0.94 (0.21-4.18)	44	0.97 (0.70-1.33)	87	1.23 (0.98-1.55)
811-2520	n.r.	0.25 (0.03-1.85)			n.r.	0.77 (0.17-3.38)	61	1.39 (1.06-1.83)	85	1.16 (0.92-1.46)
2521-79400	n.r.	0.98 (0.39-2.48)			n.r.	0.62 (0.14-2.82)	56	1.10 (0.81-1.48)	122	1.42 (1.15-1.75)
Per 5000 EU/m^3-years		0.86 (0.46-1.62)				0.50 (0.12-2.10)		1.07 (0.92-1.25)		1.14 (1.02-1.26)
Cumulative wood dust exposure										
0	119	1	33	1	122	1	2057	1	3416	1
0.2-2.3	7	1.04 (0.46-2.34)	n.r.	4.32 (1.39-13.41)	n.r.	0.63 (0.15-2.65)	80	1.10 (0.87-1.39)	172	1.19 (1.01-1.40)
2.4-6.9	5	0.63 (0.25-1.61)	n.r.	0.93 (0.12-7.25)	n.r.	1.32 (0.50-3.48)	90	1.18 (0.94-1.48)	172	1.31 (1.11-1.55)
7.0-53.0	5	0.35 (0.13-0.93)	n.r.	2.76 (0.88-8.69)	n.r.	0.66 (0.22-2.01)	101	0.96 (0.76-1.20)	159	1.08 (0.90-1.29)
Per 5 mg/m^3-years		0.66 (0.47-0.94)		1.04 (0.71-1.52)		0.79 (0.53-1.18)		1.00 (0.93-1.07)		1.02 (0.96-1.08)

n.r.: not reported, cells with less than five cases; CTD: Connective tissue disease; IIPs: Idiopathic interstitial pneumonias

*Too few exposed cases for meaningful analyses

[a]Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, medications and cumulative exposure to asbestos and respirable crystalline silica