

**Occupational exposure to respirable crystalline silica and incident idiopathic interstitial pneumonias and pulmonary sarcoidosis: a national prospective follow-up study**

Supplementary material

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## Appendix 1

We adjusted analyses for age divided into 5-year groups (<50, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, ≥80 years for all analyses except in the inception population where age groups were redefined (<35, 35-39, 40-44, 45-49, ≥50 years), sex (male, female) and calendar year of follow-up (1977-84, 1985-94, 1995-2004, 2005-15 for the population with begin of follow-up in 1977 and 1994-2004, 2005-2015 for the population with begin of follow-up in 1994).

We adjusted for educational level divided into the following groups: lower secondary, vocational or higher secondary, short-, medium-, and long-cycle higher education and unknown. Information on educational level for each individual was obtained from Statistics Denmark.

Smoking is a risk factor for several ILDs, including IPF (1, 2). As individual information on smoking was not available, we adjusted for estimated probability of smoking for each worker (5-30%, 31-50%, 51-74%) using a smoking job exposure matrix that was developed for the DOC\*X cohort (3). It is based on extensive Danish survey information on probability of tobacco smoking and provides sex- and calendar year-specific estimates of smoking prevalence for all ISCO-88 occupations and has been shown to prospectively predict 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 military or non-valid 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.

As CTDs are known risk factors for ILD, we adjusted for previously diagnosed CTD. We identified participants with previously diagnosed CTD in the National Patient Register by ICD-8 codes 446, 712, 716 and 734 and ICD-10 codes M05, M06, M08, M09 and M30-M36.

We adjusted for redeemed prescriptions obtained from the National Prescription Registry which contains information on all prescription drugs sold in Danish pharmacies since 1994 (6). We identified the date of first redemption of one of the following drugs (classified according to the Anatomical Therapeutic Chemical (ATC) classification) which have been associated with increased risk of ILD: Antineoplastic and immunomodulating agents (ATC code L), nitrofurans derivatives (ATC code J01XE), and amiodarone (C01BD01).

The National Prescription Registry does not contain information on drugs dispensed by hospital departments, which is often the case for antineoplastic drugs. As a proxy for exposure to antineoplastic drugs and radiation therapy, which is also a risk factor for ILD, we identified participants with diagnoses of cancer, except non-melanoma skin cancer, in the National Patient Register by ICD-8 codes 140-172 and 174-209; and ICD-10 codes C00-C43 and C45-C96.

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**Supplementary table S1.** Incidence rate ratios (IRRs) of idiopathic interstitial pneumonias (IIPs), pulmonary sarcoidosis and silicosis following exposure to respirable crystalline silica as assessed by a job exposure matrix, Denmark

Exposure	IIPs <sup>a</sup>		Pulmonary sarcoidosis <sup>a</sup>		Silicosis <sup>b</sup>	
	IRR (95% CI) <sup>c</sup>	IRR (95% CI) <sup>d</sup>	IRR (95% CI) <sup>c</sup>	IRR (95% CI) <sup>d</sup>	IRR (95% CI) <sup>c</sup>	IRR (95% CI) <sup>d</sup>
Cumulative exposure ( $\mu\text{g}/\text{m}^3\text{-years}$ )						
0	1	1	1	1	1	1
<43.6	1.12 (1.03-1.21)	1.04 (0.96-1.13)	1.39 (1.25-1.54)	1.30 (1.17-1.44)	1.53 (1.05-2.24)	1.45 (0.99-2.13)
43.6-153.1	1.22 (1.13-1.31)	1.15 (1.07-1.23)	1.59 (1.42-1.78)	1.58 (1.41-1.76)	2.54 (1.99-3.24)	1.86 (1.45-2.39)
153.2-1300	1.15 (1.09-1.22)	1.14 (1.08-1.21)	1.56 (1.40-1.73)	1.61 (1.45-1.78)	2.30 (1.83-2.89)	2.95 (2.31-3.76)
Per 50 $\mu\text{g}/\text{m}^3\text{-years}$ , incl. non-exposed	1.03 (1.02-1.04)	1.03 (1.02-1.03)	1.06 (1.04-1.07)	1.06 (1.04-1.07)	1.14 (1.11-1.16)	1.19 (1.16-1.22)
Per 50 $\mu\text{g}/\text{m}^3\text{-years}$ , excl. non-exposed <sup>f</sup>	1.02 (1.01-1.04)	1.03 (1.01-1.04)	1.01 (1.00-1.03)	1.03 (1.01-1.05)	1.10 (1.06-1.13)	1.16 (1.12-1.20)
Highest attained exposure ( $\mu\text{g}/\text{m}^3$ ) <sup>e</sup>						
0	1	1	1	1	1	1
<13.8	1.20 (1.11-1.29)	1.11 (1.03-1.20)	1.46 (1.33-1.60)	1.34 (1.22-1.47)	1.52 (1.03-2.25)	2.31 (1.55-3.45)
13.8-22.4	1.22 (1.11-1.34)	1.13 (1.03-1.23)	1.62 (1.40-1.87)	1.65 (1.43-1.90)	2.62 (1.89-3.63)	2.45 (1.76-3.40)
22.5-105.4	1.13 (1.07-1.19)	1.12 (1.06-1.18)	1.51 (1.36-1.66)	1.57 (1.42-1.74)	2.33 (1.91-2.85)	2.34 (1.91-2.86)
Per 5 $\mu\text{g}/\text{m}^3$ , incl. non-exposed	1.03 (1.03-1.04)	1.03 (1.02-1.03)	1.05 (1.04-1.06)	1.05 (1.04-1.07)	1.17 (1.15-1.20)	1.18 (1.16-1.20)
Per 5 $\mu\text{g}/\text{m}^3$ , excl. non-exposed <sup>f</sup>	1.04 (1.03-1.05)	1.04 (1.02-1.05)	1.00 (0.98-1.02)	1.02 (1.00-1.04)	1.23 (1.19-1.27)	1.23 (1.19-1.27)
Duration (years) <sup>e</sup>						
0	1	1	1	1	1	1
1 – 2	1.13 (1.02-1.24)	1.06 (0.96-1.17)	1.29 (1.13-1.47)	1.23 (1.08-1.41)	2.66 (1.94-3.65)	2.24 (1.63-3.07)
3 – 8	1.22 (1.14-1.30)	1.15 (1.08-1.23)	1.47 (1.32-1.63)	1.43 (1.29-1.59)	2.68 (2.13-3.39)	2.29 (1.81-2.90)
9 – 39	1.14 (1.08-1.20)	1.12 (1.06-1.18)	1.67 (1.52-1.83)	1.67 (1.52-1.83)	1.68 (1.30-2.17)	2.54 (1.94-3.34)
Per 5 years, incl. non-exposed	1.04 (1.02-1.06)	1.03 (1.01-1.05)	1.18 (1.15-1.21)	1.17 (1.14-1.20)	1.19 (1.11-1.28)	1.40 (1.29-1.51)
Per 5 years, excl. non-exposed <sup>f</sup>	0.98 (0.96-1.01)	1.00 (0.97-1.03)	1.10 (1.06-1.15)	1.10 (1.05-1.14)	0.87 (0.77-0.98)	1.09 (0.94-1.25)

<sup>a</sup>Followed from 1994-2015, 5,100,706 workers<sup>b</sup>Followed from 1977-2015, 5,439,728 workers<sup>c</sup>Adjusted for age and sex<sup>d</sup>Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, cancer and medications<sup>e</sup>For silicosis: all analyses for this metric are not adjusted for education<sup>f</sup>For silicosis: not adjusted for education

**Supplementary table S2.** Incidence rate ratios (IRR) of idiopathic interstitial pneumonias (IIPs), pulmonary sarcoidosis and silicosis following exposure to respirable crystalline silica as assessed by a job exposure matrix among workers born 1956 or later, Denmark

Exposure	IIPs <sup>a</sup>		Pulmonary sarcoidosis <sup>a</sup>		Silicosis <sup>b</sup>	
	Cases	IRR (95% CI) <sup>c</sup>	Cases	IRR (95% CI) <sup>c</sup>	Cases <sup>e</sup>	IRR (95% CI) <sup>d</sup>
Cumulative exposure ( $\mu\text{g}/\text{m}^3\text{-years}$ )						
0	2128	1	3353	1	18	1
<24.6	177	1.19 (1.02-1.39)	312	1.34 (1.19-1.51)	n.r.	1.57 (0.36-6.93)
24.6-89.5	121	1.34 (1.11-1.62)	225	1.67 (1.45-1.91)	n.r.	1.91 (0.55-6.68)
>89.5	88	1.45 (1.16-1.80)	154	1.62 (1.37-1.91)	n.r.	4.34 (1.84-10.25)
Per 50 $\mu\text{g}/\text{m}^3\text{-years}$ , incl. non-exposed		1.05 (1.02-1.08)		1.07 (1.05-1.10)		1.26 (1.17-1.36)
Highest attained exposure ( $\mu\text{g}/\text{m}^3$ )						
0	2128	1	3353	1	18	1
<9.7	230	1.30 (1.13-1.49)	391	1.42 (1.27-1.58)	n.r.	1.33 (0.30-5.91)
9.7-20.0	58	1.17 (0.89-1.52)	129	1.89 (1.58-2.25)	n.r.	2.97 (1.06-8.33)
>10.0	98	1.34 (1.09-1.66)	171	1.44 (1.23-1.68)	n.r.	3.91 (1.56-9.78)
Per 5 $\mu\text{g}/\text{m}^3$ , incl. non-exposed		1.04 (1.02-1.07)		1.06 (1.04-1.08)		1.21 (1.11-1.32)
Duration (years)						
0	2128	1	3353	1	18	1
1	103	1.11 (0.91-1.35)	186	1.26 (1.08-1.46)	n.r.	1.50 (0.20-11.34)
2-5	158	1.37 (1.16-1.61)	271	1.48 (1.30-1.67)	n.r.	0.65 (0.09-4.97)
6-39	125	1.38 (1.14-1.66)	234	1.78 (1.55-2.04)	n.r.	4.62 (2.06-10.34)
Per 5 years, incl. non-exposed		1.11 (1.05-1.17)		1.20 (1.16-1.25)		1.52 (1.23-1.87)

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

<sup>a</sup>Followed from 1994-2015, 2,955,863 workers<sup>b</sup>Followed from 1977-2015, 2,980,445 workers<sup>c</sup>Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, cancer and medications<sup>d</sup>Adjusted for age, sex, calendar year (1977-94, 1995-2004, 2005-15), probability of smoking, connective tissue disease and medications<sup>e</sup>Total number of silicosis cases: 32

**Supplementary table S3.** Incidence rate ratios (IRR) of idiopathic interstitial pneumonias (IIPs), pulmonary sarcoidosis and silicosis following exposure to respirable crystalline silica as assessed by a job exposure matrix among blue collar workers, Denmark

Exposure	IIPs <sup>a</sup>		Pulmonary sarcoidosis <sup>a</sup>		Silicosis <sup>a</sup>	
	Cases	IRR (95% CI) <sup>c</sup>	Cases	IRR (95% CI) <sup>c</sup>	Cases	IRR (95% CI) <sup>d</sup>
Cumulative exposure ( $\mu\text{g}/\text{m}^3\text{-years}$ )						
0	3213	1	1501	1	256	1
<43.6	329	1.06 (0.95-1.19)	210	1.14 (0.99-1.32)	22	1.40 (0.91-2.17)
43.6-153.1	376	1.14 (1.02-1.27)	229	1.46 (1.27-1.68)	66	2.62 (2.00-3.44)
153.2-1300	1019	1.01 (0.94-1.10)	358	1.51 (1.33-1.70)	86	3.42 (2.65-4.41)
Per 50 $\mu\text{g}/\text{m}^3\text{-years}$ , incl. non-exposed		1.01 (1.00-1.02)		1.05 (1.03-1.06)		1.13 (1.09-1.17)
Per 50 $\mu\text{g}/\text{m}^3\text{-years}$ , excl. non-exposed		1.02 (1.00-1.03)		1.03 (1.01-1.05)		1.08 (1.02-1.15)
Highest attained exposure ( $\mu\text{g}/\text{m}^3$ )						
0	3213	1	1501	1	256	1
<13.8	472	1.12 (1.01-1.24)	286	1.18 (1.04-1.35)	18	1.65 (1.02-2.69)
13.8-22.4	242	1.03 (0.90-1.18)	154	1.68 (1.42-1.99)	33	1.73 (1.20-2.48)
22.5-105.4	1010	1.02 (0.95-1.10)	357	1.45 (1.29-1.64)	123	3.34 (2.69-4.15)
Per 5 $\mu\text{g}/\text{m}^3$ , incl. non-exposed		1.02 (1.01-1.02)		1.04 (1.03-1.06)		1.15 (1.13-1.17)
Per 5 $\mu\text{g}/\text{m}^3$ , excl. non-exposed		1.02 (1.00-1.04)		1.01 (0.99-1.04)		1.17 (1.12-1.21)
Duration (years)						
0	3213	1	1501	1	256	1
1 – 2	199	1.09 (0.94-1.26)	129	1.13 (0.95-1.36)	39	2.43 (1.73-3.40)
3 – 8	360	1.08 (0.97-1.21)	228	1.32 (1.14-1.52)	76	2.51 (1.94-3.25)
9 – 39	1165	1.03 (0.96-1.11)	440	1.51 (1.35-1.69)	59	2.99 (2.20-4.07)
Per 5 years, incl. non-exposed		1.00 (0.98-1.03)		1.13 (1.10-1.17)		1.40 (1.28-1.53)
Per 5 years, excl. non-exposed		0.98 (0.95-1.02)		1.08 (1.03-1.14)		1.12 (0.96-1.30)

<sup>a</sup>Followed from 1994-2015, 1,375,815 workers<sup>b</sup>Followed from 1977-2015, 1,454,098 workers<sup>c</sup>adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, cancer and medications<sup>d</sup>Adjusted for age, sex, calendar year, probability of smoking, connective tissue disease, cancer and medications

**Supplementary table S4.** Incidence rate ratios (IRR) of idiopathic pulmonary fibrosis (IPF) following exposure to respirable crystalline silica as assessed by a job exposure matrix among 5,100,706 workers, Denmark 1994-2015

Exposure	IPF	
	Cases	IRR (95% CI) <sup>a</sup>
Cumulative exposure ( $\mu\text{g}/\text{m}^3\text{-years}$ )		
0	321	1
<43.6	13	0.91 (0.52-1.59)
43.6-153.1	20	1.35 (0.85-2.15)
153.2-1300	37	1.00 (0.70-1.44)
Per 50 $\mu\text{g}/\text{m}^3\text{-years}$ , incl. non-exposed		1.01 (0.97-1.06)
Per 50 $\mu\text{g}/\text{m}^3\text{-years}$ , excl. non-exposed <sup>b</sup>		1.03 (0.96-1.10)
Highest attained exposure ( $\mu\text{g}/\text{m}^3$ )		
0	321	1
<13.8	21	1.19 (0.76-1.88)
13.8-22.4	12	1.23 (0.68-2.22)
22.5-105.4	37	0.95 (0.66-1.36)
Per 5 $\mu\text{g}/\text{m}^3$ , incl. non-exposed		1.00 (0.96-1.05)
Per 5 $\mu\text{g}/\text{m}^3$ , excl. non-exposed <sup>b</sup>		0.99 (0.91-1.07)
Duration (years)		
0	321	1
1 – 2	8	0.92 (0.45-1.86)
3 – 8	19	1.15 (0.72-1.85)
9 – 39	43	1.05 (0.75-1.48)
Per 5 years, incl. non-exposed		1.02 (0.92-1.13)
Per 5 years, excl. non-exposed <sup>b</sup>		1.06 (0.89-1.27)

<sup>a</sup>Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, cancer and medications

<sup>b</sup>Not adjusted for education



**Table S5.** Distribution of exposed person-years at risk by ISCO-88 codes in the total study population.

ISCO-88	Description	Person-years	Percent
2452	Sculptors, painters and related artists	48,895	0.90
6110	Market gardeners and crop growers	324	0.01
6111	Field crop and vegetable growers	82,577	1.53
6112	Tree and shrub crop growers	213,010	3.93
6113	Gardeners, horticultural and nursery growers	34,610	0.64
6130	Market-oriented crop and animal producers	231,362	4.27
7100	Extraction and building trades workers	62,219	1.15
7110	Miners, shotfirers, stone cutters and carvers	215	0.00
7111	Miners and quarry workers	861	0.02
7112	Shotfirers and blasters	313	0.01
7113	Stone splitters, cutters and carvers	9,061	0.17
7120	Building frame and related trades workers	654,767	12.09
7121	Builders, traditional materials	13,933	0.26
7122	Bricklayers and stonemasons	442,314	8.17
7123	Concrete placers, concrete finishers and related workers	6,975	0.13
7129	Building frame and related trades workers not elsewhere classified	61,477	1.14
7131	Roofers	28,441	0.53
7132	Floor layers and tile setters	26,692	0.49
7133	Plasterers	5,510	0.10
7143	Building structure cleaners	31,624	0.58
7211	Metal moulders and coremakers	24,236	0.45
7321	Abrasive wheel formers, potters and related workers	14,530	0.27
8110	Mining- and mineral-processing plant operators	21	0.00
8111	Mining-plant operators	117	0.00
8112	Mineral-ore- and stone-processing-plant operators	9,835	0.18
8113	Well drillers and borers and related workers	13,032	0.24
8130	Glass, ceramics and related plant operators	3,035	0.06
8131	Glass and ceramics kiln and related machine operators	56,651	1.05
8139	Glass, ceramics and related plant operators not elsewhere classified	13,409	0.25
8210	Metal- and mineral-products machine operators	65	0.00
8212	Cement and other mineral products machine operators	47,480	0.88
8223	Metal finishing-, plating- and coating-machine operators	48,335	0.89
8330	Agricultural and other mobile-plant operators	7,264	0.13
8331	Motorised farm and forestry plant operators	42,992	0.79
8332	Earth-moving- and related plant operators	101,738	1.88
9160	Garbage collectors and related labourers	58,473	1.08
9161	Garbage collectors	28,266	0.52
9162	Sweepers and related labourers	27,572	0.51
9211	Farm-hands and labourers	1,457,115	26.91
9300	Labourers in mining, construction, manufacturing and transport	42,620	0.79
9310	Mining and construction labourers	149,577	2.76
9311	Mining and quarrying labourers	2,695	0.05
9312	Construction and maintenance labourers: roads, dams and similar constructions	617,009	11.40
9313	Building construction labourers	693,234	12.80
<b>Total</b>		<b>5,414,481</b>	<b>100.00</b>

**Supplementary figure S1.** Establishment of the study population.