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### **Supplemental Material**

#### **Lung Cancer Risks Associated with Occupational Exposure to Pairs of Five Lung Carcinogens: Results from a Pooled Analysis of Case-Control Studies (SYNERGY)**

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**Figure S1.** Heatmaps of Cramer's V statistics (Corr) between the never/ever occupational exposures by lag time in years.



Asbestos & silica									
Never exposed to both	7971	5050	1 [Reference]	1383	1 [Reference]	1972	1 [Reference]	789	1 [Reference]
Never exposed to asbestos and ever exposed to silica	1678	1597	1.35 (1.23, 1.47)	365	1.20 (1.03, 1.37)	711	1.48 (1.31, 1.65)	282	1.44 (1.21, 1.67)
Ever exposed to asbestos and never exposed to silica	4340	3906	1.27 (1.19, 1.35)	982	1.20 (1.08, 1.31)	1665	1.33 (1.21, 1.44)	602	1.23 (1.08, 1.38)
Ever exposed to both	2462	3052	1.57 (1.45, 1.69)	595	1.26 (1.11, 1.41)	1480	1.80 (1.63, 1.97)	527	1.61 (1.39, 1.83)
<i>p-value multiplicative interaction</i>			0.14		0.16		0.24		0.40
RERI			-0.05 (-0.21, 0.11)		-0.14 (-0.36, 0.08)		-0.01 (-0.23, 0.21)		-0.06 (-0.35, 0.24)
Chromium-VI & PAH									
Never exposed to both	10794	7785	1 [Reference]	2028	1 [Reference]	3207	1 [Reference]	1231	1 [Reference]
Never exposed to chromium-VI and ever exposed to PAH	1837	1689	1.09 (1.00, 1.18)	401	1.01 (0.88, 1.14)	738	1.16 (1.03, 1.28)	268	1.12 (0.94, 1.29)
Ever exposed to chromium-VI and never exposed to PAH	1580	1799	1.35 (1.23, 1.46)	401	1.20 (1.04, 1.35)	797	1.44 (1.29, 1.59)	328	1.45 (1.24, 1.67)
Ever exposed to both	2240	2332	1.23 (1.13, 1.32)	495	1.08 (0.95, 1.21)	1086	1.33 (1.21, 1.46)	373	1.32 (1.14, 1.5)
<i>p-value multiplicative interaction</i>			0.01		0.30		0.01		0.09
RERI			-0.21 (-0.37, -0.05)		-0.12 (-0.35, 0.1)		-0.27 (-0.48, -0.05)		-0.25 (-0.55, 0.06)
Chromium-VI & silica									
Never exposed to both	10081	6932	1 [Reference]	1908	1 [Reference]	2732	1 [Reference]	1083	1 [Reference]
Never exposed to chromium-VI and ever exposed to silica	2550	2542	1.28 (1.19, 1.38)	521	1.05 (0.93, 1.17)	1213	1.44 (1.3, 1.57)	416	1.28 (1.1, 1.45)
Ever exposed to chromium-VI and never exposed to silica	2230	2024	1.17 (1.08, 1.27)	457	1.02 (0.90, 1.14)	905	1.27 (1.14, 1.39)	308	1.19 (1.01, 1.36)
Ever exposed to both	1590	2107	1.55 (1.42, 1.68)	439	1.31 (1.14, 1.48)	978	1.75 (1.57, 1.93)	393	1.74 (1.49, 2.00)
<i>p-value multiplicative interaction</i>			0.67		0.05		0.64		0.23
RERI			0.09 (-0.07, 0.26)		0.24 (0.02, 0.46)		0.05 (-0.18, 0.28)		0.28 (-0.03, 0.59)
Nickel & PAH									
Never exposed to both	11383	8551	1 [Reference]	2188	1 [Reference]	3546	1 [Reference]	1397	1 [Reference]
Never exposed to nickel and ever exposed to PAH	1928	1838	1.10 (1.01, 1.19)	434	1.02 (0.89, 1.14)	801	1.15 (1.04, 1.27)	293	1.10 (0.94, 1.26)
Ever exposed to nickel and never exposed to PAH	991	1033	1.26 (1.13, 1.39)	241	1.17 (0.98, 1.36)	458	1.31 (1.14, 1.49)	162	1.17 (0.94, 1.39)

Ever exposed to both	2149	2183	1.17 (1.08, 1.26)	462	1.05 (0.92, 1.17)	1023	1.26 (1.14, 1.38)	348	1.22 (1.05, 1.39)
<i>p-value multiplicative interaction</i>			0.02		0.27		0.05		0.72
RERI			-0.19 (-0.36, -0.01)		-0.14 (-0.39, 0.11)		-0.20 (-0.43, 0.03)		-0.04 (-0.35, 0.26)
Nickel & silica									
Never exposed to both	10107	6972	1 [Reference]	1917	1 [Reference]	2749	1 [Reference]	1086	1 [Reference]
Never exposed to nickel and ever exposed to silica	3204	3417	1.34 (1.25, 1.43)	705	1.10 (0.98, 1.21)	1598	1.5 (1.37, 1.63)	604	1.43 (1.26, 1.6)
Ever exposed to nickel and never exposed to silica	2204	1984	1.17 (1.07, 1.26)	448	1.01 (0.89, 1.14)	888	1.26 (1.13, 1.38)	305	1.20 (1.02, 1.37)
Ever exposed to both	936	1232	1.55 (1.39, 1.71)	255	1.34 (1.12, 1.56)	593	1.75 (1.53, 1.97)	205	1.61 (1.32, 1.91)
<i>p-value multiplicative interaction</i>			0.97		0.09		0.37		0.65
RERI			0.05 (-0.14, 0.24)		0.23 (-0.02, 0.48)		-0.01 (-0.27, 0.25)		-0.01 (-0.36, 0.34)
PAH & silica									
Never exposed to both	9468	6455	1 [Reference]	1772	1 [Reference]	2546	1 [Reference]	1012	1 [Reference]
Never exposed to PAH and ever exposed to silica	2906	3129	1.36 (1.26, 1.45)	657	1.13 (1.00, 1.25)	1458	1.53 (1.39, 1.67)	547	1.44 (1.26, 1.62)
Ever exposed to PAH and never exposed to silica	2843	2501	1.11 (1.03, 1.19)	593	0.99 (0.88, 1.10)	1091	1.21 (1.09, 1.32)	379	1.16 (1.00, 1.31)
Ever exposed to both	1234	1520	1.44 (1.30, 1.57)	303	1.19 (1.02, 1.37)	733	1.64 (1.45, 1.83)	262	1.54 (1.28, 1.8)
<i>p-value multiplicative interaction</i>			0.46		0.49		0.14		0.50
RERI			-0.03 (-0.19, 0.14)		0.08 (-0.14, 0.3)		-0.1 (-0.33, 0.13)		-0.05 (-0.37, 0.26)

ORs were adjusted for study centre, age group (category), smoking pack-years (current and former smokers: <10, 10-19, and ≥ 20 pack-years, never-smokers) and time since quitting smoking (current smokers; former smokers: <7, 8–15, 16–25, and ≥ 26 years; never-smokers).

Table S2. Pairwise interactions between five occupational lung carcinogens (asbestos, chromium VI, nickel, PAH, and silica) in relation to lung cancer risk overall and for major lung cancer subtypes in female workers in SYNERGY pooled analyses

<b>WOMEN</b>	Lung cancer			Adenocarcinoma		Squamous cell cancers		Small cell lung cancer	
	Controls N=4514	Cases N=3296	OR (95% CI)	Cases N=1427	OR (95% CI)	Cases N=675	OR (95% CI)	Cases N=530	OR (95% CI)
<b>Asbestos &amp; chromium-VI</b>									
Never exposed to both	3915	2726	1 [Reference]	1216	1 [Reference]	539	1 [Reference]	416	1 [Reference]
Never exposed to asbestos and ever exposed to chromium-VI	89	88	1.15 (0.75, 1.54)	33	1.08 (0.60, 1.55)	19	1.11 (0.45, 1.77)	20	1.96 (0.73, 3.2)
Ever exposed to asbestos and never exposed to chromium-VI	453	411	1.11 (0.93, 1.3)	156	0.99 (0.78, 1.2)	100	1.26 (0.90, 1.61)	77	1.37 (0.92, 1.82)
Ever exposed to both	57	71	1.32 (0.79, 1.85)	22	0.93 (0.43, 1.43)	17	1.10 (0.39, 1.82)	17	2.99 (0.94, 5.03)
<i>p-value multiplicative interaction</i>			0.89		0.71		0.61		0.84
RERI			0.06 (-0.61, 0.74)		-0.14 (-0.85, 0.57)		-0.26 (-1.27, 0.75)		0.65 (-1.72, 3.01)
<b>Asbestos &amp; nickel</b>									
Never exposed to both	3923	2730	1 [Reference]	1218	1 [Reference]	539	1 [Reference]	418	1 [Reference]
Never exposed to asbestos and ever exposed to nickel	81	84	1.26 (0.81, 1.71)	31	1.18 (0.64, 1.72)	19	1.25 (0.5, 2.01)	18	2.10 (0.71, 3.48)
Ever exposed to asbestos and never exposed to nickel	460	415	1.11 (0.93, 1.3)	159	1.00 (0.79, 1.21)	99	1.24 (0.89, 1.59)	79	1.42 (0.96, 1.89)
Ever exposed to both	50	67	1.38 (0.8, 1.96)	19	0.91 (0.39, 1.43)	18	1.26 (0.43, 2.08)	15	2.56 (0.71, 4.41)
<i>p-value multiplicative interaction</i>			0.95		0.50		0.65		0.76
RERI			0.01 (-0.74, 0.75)		-0.27 (-1.03, 0.5)		-0.24 (-1.38, 0.91)		0.04 (-2.26, 2.34)
<b>Asbestos &amp; PAH</b>									
Never exposed to both	8343	5537	1 [Reference]	1477	1 [Reference]	2201	1 [Reference]	893	1 [Reference]
Never exposed to asbestos and ever exposed to PAH	478	446	1.19 (1.0, 1.38)	176	1.09 (0.86, 1.31)	105	1.61 (1.17, 2.05)	92	1.75 (1.21, 2.30)
Ever exposed to asbestos and never exposed to PAH	352	310	1.10 (0.90, 1.31)	126	1.03 (0.78, 1.27)	66	1.15 (0.77, 1.54)	60	1.51 (0.96, 2.07)
Ever exposed to both	158	172	1.31 (0.97, 1.65)	52	0.92 (0.6, 1.25)	51	1.71 (1.02, 2.39)	34	2.00 (1.03, 2.98)
<i>p-value multiplicative interaction</i>			0.98		0.41		0.76		0.40
RERI			0.02 (-0.41, 0.44)		-0.19 (-0.63, 0.26)		-0.06 (-0.9, 0.78)		-0.26 (-1.44, 0.92)
<b>Asbestos &amp; silica</b>									
Never exposed to both	3719	2617	1 [Reference]	1167	1 [Reference]	517	1 [Reference]	397	1 [Reference]
Never exposed to asbestos and ever exposed to silica	285	197	1.03 (0.81, 1.26)	82	1.06 (0.77, 1.35)	41	1.05 (0.62, 1.47)	39	1.27 (0.69, 1.85)
Ever exposed to asbestos and never exposed to silica	447	405	1.07 (0.89, 1.25)	151	0.92 (0.72, 1.13)	98	1.15 (0.82, 1.48)	73	1.26 (0.84, 1.68)
Ever exposed to both	63	77	1.57 (0.97, 2.16)	27	1.46 (0.75, 2.17)	19	1.91 (0.70, 3.12)	21	4.32 (1.35, 7.29)
<i>p-value multiplicative interaction</i>			0.13		0.19		0.24		0.02
RERI			0.46 (-0.18, 1.1)		0.47 (-0.30, 1.24)		0.72 (-0.55, 1.99)		2.79 (-0.19, 5.76)

Chromium-VI & PAH									
Never exposed to both	3830	2630	1 [Reference]	1176	1 [Reference]	512	1 [Reference]	393	1 [Reference]
Never exposed to chromium-VI and ever exposed to PAH	538	507	1.20 (1.02, 1.39)	196	1.08 (0.87, 1.29)	127	1.65 (1.23, 2.07)	100	1.57 (1.11, 2.04)
Ever exposed to chromium-VI and never exposed to PAH	48	48	1.19 (0.65, 1.73)	23	1.37 (0.63, 2.12)	7	0.71 (0.07, 1.35)	11	1.85 (0.35, 3.35)
Ever exposed to both	98	111	1.25 (0.85, 1.65)	32	0.86 (0.48, 1.24)	29	1.36 (0.67, 2.06)	26	2.77 (1.19, 4.36)
<i>p-value multiplicative interaction</i>			0.64		0.13		0.78		0.93
RERI			-0.14 (-0.83, 0.54)		-0.60 (-1.45, 0.25)		0.00 (-1.00, 1.00)		0.35 (-1.82, 2.53)
Chromium-VI & silica									
Never exposed to both	4053	2894	1 [Reference]	1273	1 [Reference]	582	1 [Reference]	449	1 [Reference]
Never exposed to chromium-VI and ever exposed to silica	315	243	1.13 (0.90, 1.36)	99	1.18 (0.88, 1.49)	57	1.32 (0.84, 1.79)	44	1.29 (0.72, 1.86)
Ever exposed to chromium-VI and never exposed to silica	113	128	1.22 (0.86, 1.58)	45	1.08 (0.66, 1.49)	33	1.24 (0.65, 1.84)	21	1.53 (0.65, 2.42)
Ever exposed to both	33	31	1.17 (0.52, 1.83)	10	0.86 (0.2, 1.53)	3	0.48 (-0.13, 1.09)	16	5.80 (1.10, 10.51)
<i>p-value multiplicative interaction</i>			0.62		0.38		0.06		0.05
RERI			-0.18 (-0.95, 0.59)		-0.40 (-1.22, 0.43)		-1.09 (-2.06, -0.11)		3.98 (-0.76, 8.72)
Nickel & PAH									
Never exposed to both	3845	2638	1 [Reference]	1181	1 [Reference]	512	1 [Reference]	396	1 [Reference]
Never exposed to nickel and ever exposed to PAH	538	507	1.21 (1.03, 1.39)	196	1.09 (0.88, 1.3)	126	1.66 (1.24, 2.07)	101	1.59 (1.12, 2.07)
Ever exposed to nickel and never exposed to PAH	33	40	1.57 (0.75, 2.38)	18	1.76 (0.67, 2.85)	7	1.05 (0.04, 2.06)	8	1.84 (0.10, 3.57)
Ever exposed to both	98	111	1.24 (0.85, 1.64)	32	0.86 (0.48, 1.24)	30	1.40 (0.69, 2.1)	25	2.56 (1.09, 4.02)
<i>p-value multiplicative interaction</i>			0.18		0.05		0.70		0.81
RERI			-0.53 (-1.45, 0.39)		-0.98 (-2.15, 0.18)		-0.31 (-1.58, 0.96)		0.12 (-2.16, 2.40)
Nickel & silica									
Never exposed to both	4055	2896	1 [Reference]	1275	1 [Reference]	582	1 [Reference]	449	1 [Reference]
Never exposed to nickel and ever exposed to silica	328	249	1.11 (0.89, 1.33)	102	1.16 (0.86, 1.45)	56	1.24 (0.79, 1.69)	48	1.41 (0.8, 2.01)
Ever exposed to nickel and never exposed to silica	111	126	1.25 (0.87, 1.62)	43	1.08 (0.66, 1.50)	33	1.29 (0.67, 1.91)	21	1.61 (0.67, 2.55)
Ever exposed to both	20	25	1.59 (0.52, 2.66)	7	1.05 (0.06, 2.04)	4	0.88 (-0.23, 1.99)	12	5.86 (0.26, 11.45)
<i>p-value multiplicative interaction</i>			0.72		0.74		0.39		0.11
RERI			0.23 (-0.91, 1.37)		-0.19 (-1.29, 0.92)		-0.65 (-1.98, 0.68)		3.84 (-1.81, 9.48)
PAH & silica									
Never exposed to both	3587	2480	1 [Reference]	1113	1 [Reference]	480	1 [Reference]	368	1 [Reference]
Never exposed to PAH and ever exposed to silica	291	198	1.03 (0.80, 1.25)	86	1.10 (0.80, 1.4)	39	1.04 (0.62, 1.47)	36	1.19 (0.63, 1.76)
Ever exposed to PAH and never exposed to silica	579	542	1.15 (0.98, 1.33)	205	1.02 (0.82, 1.21)	135	1.53 (1.15, 1.91)	102	1.48 (1.05, 1.91)
Ever exposed to both	57	76	1.76 (1.07, 2.45)	23	1.39 (0.66, 2.12)	21	2.40 (0.88, 3.91)	24	5.12 (1.77, 8.48)

<i>p-value multiplicative interaction</i>			0.09		0.48		0.30		0.01
RERI			0.58 (-0.14, 1.30)		0.27 (-0.52, 1.06)		0.82 (-0.75, 2.39)		3.45 (0.10, 6.8)

ORs were adjusted for study centre, age group (category), smoking pack-years (current and former smokers: <10, 10-19, and ≥ 20 pack-years, never-smokers) and time since quitting smoking (current smokers; former smokers: <7, 8–15, 16–25, and ≥ 26 years; never-smokers).

Table S3. Risk of lung cancer (OR), relative excess risk due to interaction (RERI), and test for multiplicative interaction (P-value) associated with single and pairwise combinations of occupational exposure to asbestos, chromium VI, nickel, PAH, and silica in male workers in SYNERGY by smoking status (never, former, and current cigarette smokers)

Combinations of occupational exposures in men	Never Smokers			Former Smokers			Current Smokers*		
	Control s N=4437	Cases N=490	OR (95% CI)	Control s N=7328	Cases N=4787	OR (95% CI)	Control s N=4686	Cases N=8328	OR (95% CI)
<b>Asbestos &amp; chromium-VI</b>									
Never exposed to both	2517	240		3502	1857		2103	3024	
Ever exposed to asbestos and never exposed to chromium-VI	1075	134	1.38 (1.06, 1.7)	2038	1533	1.38 (1.25, 1.51)	1396	2686	1.25 (1.14, 1.37)
Never exposed to asbestos and ever exposed to chromium-VI	374	45	1.34 (0.88, 1.8)	691	508	1.29 (1.11, 1.46)	462	973	1.39 (1.20, 1.57)
Ever exposed to both	471	71	1.81 (1.28, 2.34)	1097	889	1.46 (1.29, 1.63)	725	1645	1.42 (1.26, 1.58)
<i>p-value multiplicative interaction</i>			0.92			0.04			0.02
<i>RERI</i>			0.09 (-0.60, 0.77)			-0.20 (-0.45, 0.04)			-0.22 (-0.45, 0.02)
<b>Asbestos &amp; nickel</b>									
Never exposed to both	2611	258		3686	2007		2210	3311	
Ever exposed to asbestos and never exposed to nickel	1124	144	1.37 (1.06, 1.67)	2181	1684	1.39 (1.26, 1.51)	1499	2985	1.24 (1.13, 1.35)
Never exposed to asbestos and ever exposed to nickel	280	27	1.08 (0.62, 1.53)	507	358	1.27 (1.07, 1.47)	355	686	1.24 (1.06, 1.43)
Ever exposed to both	422	61	1.68 (1.16, 2.20)	954	738	1.39 (1.22, 1.55)	622	1346	1.32 (1.17, 1.48)
<i>p-value multiplicative interaction</i>			0.63			0.02			0.11
<i>RERI</i>			0.23 (-0.45, 0.91)			-0.27 (-0.53, 0.00)			-0.16 (-0.40, 0.08)
<b>Asbestos &amp; PAH</b>									
Never exposed to both	2598	250		3596	1996		2149	3291	
Ever exposed to asbestos and never exposed to PAH	949	129	1.48 (1.13, 1.82)	1828	1423	1.36 (1.22, 1.49)	1254	2495	1.21 (1.09, 1.32)
Never exposed to asbestos and ever exposed to PAH	293	35	1.25 (0.77, 1.72)	597	369	1.02 (0.86, 1.17)	416	706	1.05 (0.90, 1.19)
Ever exposed to both	597	76	1.47 (1.06, 1.89)	1307	999	1.33 (1.18, 1.47)	867	1836	1.26 (1.13, 1.40)
<i>p-value multiplicative interaction</i>			0.37			0.68			1.00
<i>RERI</i>			-0.25 (-0.91, 0.40)			-0.05 (-0.27, 0.17)			0.01 (-0.19, 0.21)
<b>Asbestos &amp; silica</b>									
Never exposed to both	2412	229		3414	1750		2145	3071	
Ever exposed to asbestos and never exposed to silica	1053	129	1.41 (1.08, 1.74)	1938	1327	1.31 (1.18, 1.44)	1349	2450	1.21 (1.10, 1.32)
Never exposed to asbestos and ever exposed to silica	479	56	1.34 (0.91, 1.76)	779	615	1.34 (1.16, 1.51)	420	926	1.38 (1.19, 1.56)
Ever exposed to both	493	76	1.77 (1.25, 2.29)	1197	1095	1.64 (1.45, 1.82)	772	1881	1.46 (1.30, 1.62)





Never exposed to both	2815	278		4056	2253		2597	3924	
Ever exposed to PAH and never exposed to silica	650	80	1.34 (0.98,1.7)	1296	824	1.05 (0.94,1.17)	897	1597	1.12 (1.01, 1.23)
Never exposed to PAH and ever exposed to silica	732	101	1.48 (1.10, 1.86)	1368	1166	1.33 (1.19, 1.47)	806	1862	1.35 (1.21, 1.49)
Ever exposed to both	240	31	1.41 (0.84,1.98)	608	544	1.47 (1.27, 1.68)	386	945	1.38 (1.19, 1.57)
<i>p-value multiplicative interaction</i>			0.19			0.58			0.33
RERI			-0.41 (-1.13, 0.31)			0.09 (-0.15, 0.34)			-0.09 (-0.32, 0.15)

All models were adjusted for study centre and age group (category). For current smokers, models were also adjusted for smoking pack-years (log[ cPY+1]). For former smokers, models were also adjusted for smoking pack-years and time since quitting smoking ( <7, 8–15, 16–25, and ≥ 26 years).

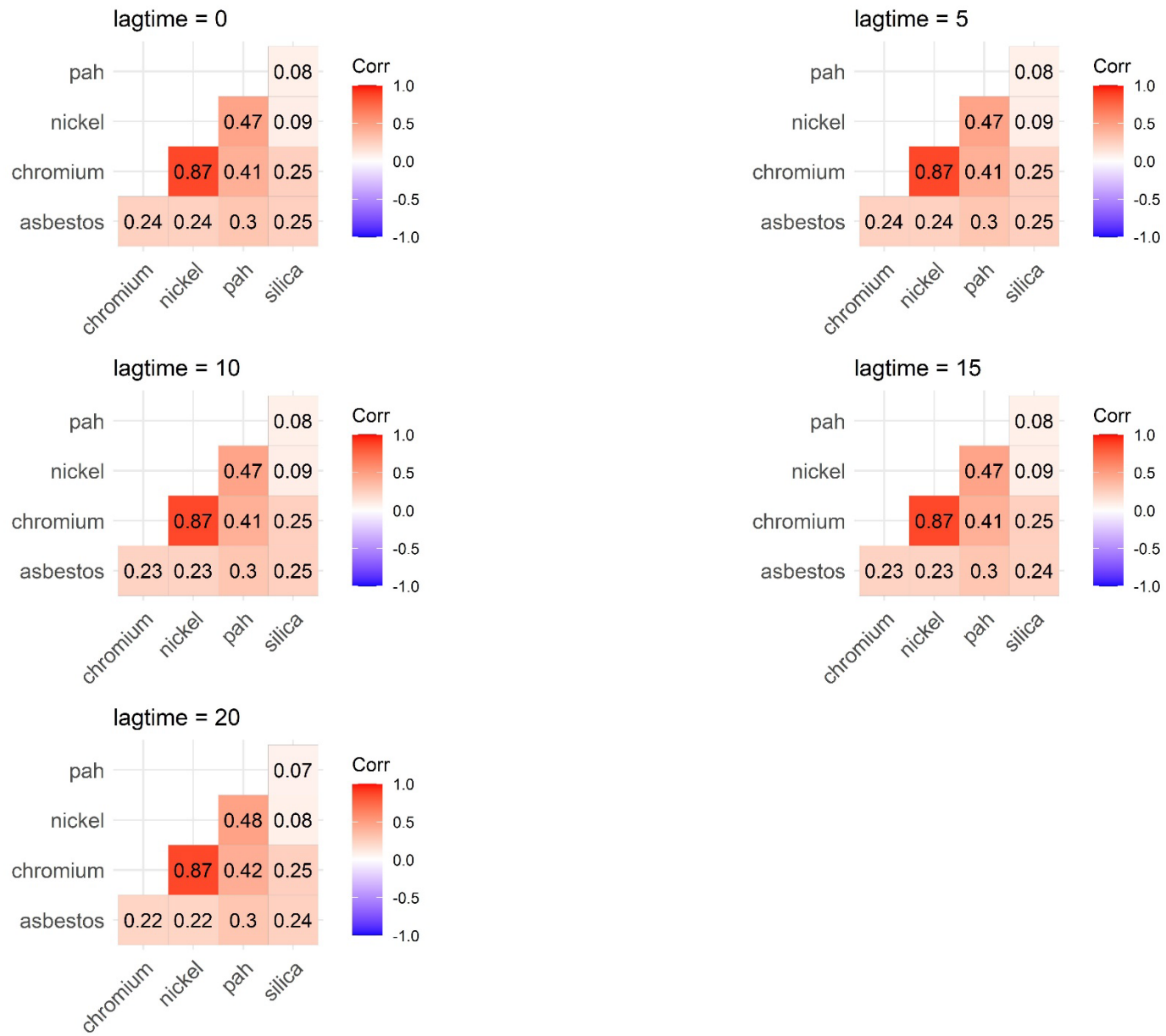


Figure S1. Heatmaps of Cramer's V statistics (Corr) between the never/ever occupational exposures by lag time in years