**Supplementary Appendix**

**A cohort study on long-term exposure to air pollution and incidence of liver cirrhosis**

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**Table S1. Study population exposure to main air pollutants and PM components.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Statistics** | | | |
|  | **25%** | **Mean** | **75%** | **SD** |
| **Main pollutants** |  |  |  |  |
| **PM10 (µg/m3)** | 33.3 | 36.6 | 38.0 | 5.1 |
| **PM coarse (µg/m3)** | 14.8 | 17.0 | 18.3 | 3.3 |
| **PM2.5 (µg/m3)** | 18.4 | 19.6 | 20.1 | 1.9 |
| **PM2.5abs (1x10-5/m)** | 2.4 | 2.7 | 2.8 | 0.5 |
| **NO2 (µg/m3)** | 35.7 | 42.8 | 48.6 | 10.2 |
| **NOx (µg/m3)** | 67.9 | 85.0 | 100.3 | 24.2 |
| **Metal components** |  |  |  |  |
| **PM10Cu (ng/m3)** | 39.4 | 56.8 | 60.4 | 26.7 |
| **PM10Fe (ng/m3)** | 851.2 | 1166.0 | 1309.3 | 524.1 |
| **PM10K (ng/m3)** | 445.9 | 506.7 | 507.2 | 115.2 |
| **PM10Ni (ng/m3)** | 2.2 | 2.9 | 3.6 | 1.1 |
| **PM10Si (ng/m3)** | 889.9 | 1080.8 | 1249.6 | 281.8 |
| **PM10V (ng/m3)** | 3.9 | 4.3 | 4.5 | 0.7 |
| **PM10Zn (ng/m3)** | 33.3 | 41.7 | 45.4 | 12.3 |
| **PM2.5Cu (ng/m3)** | 12.1 | 15.1 | 16.3 | 4.2 |
| **PM2.5Fe (ng/m3)** | 199.0 | 259.6 | 298.7 | 80.4 |
| **PM2.5Zn (ng/m3)** | 21.1 | 24.1 | 25.7 | 4.5 |

Average 2010 pollutant levels from Land Use Regression Models.

**Table S2. Pearson’s correlation coefficients of standard pollutants and PM components.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **PM10** | **PM coarse** | **PM2.5** | **PM2.5 abs** | **NO2** | **NOx** | **PM10 Cu** | **PM10 Fe** | **PM10 K** | **PM10 Ni** | **PM10 Si** | **PM10 V** | **PM10 Zn** | **PM2.5 Cu** | **PM2.5 Fe** | **PM2.5 Zn** |
| **PM10** | 1.00 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PM coarse** | 0.93 | 1.00 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PM2.5** | 0.93 | 0.91 | 1.00 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PM2.5 abs** | 0.60 | 0.65 | 0.65 | 1.00 |  |  |  |  |  |  |  |  |  |  |  |  |
| **NO2** | 0.59 | 0.71 | 0.65 | 0.61 | 1.00 |  |  |  |  |  |  |  |  |  |  |  |
| **NOx** | 0.55 | 0.62 | 0.61 | 0.52 | 0.71 | 1.00 |  |  |  |  |  |  |  |  |  |  |
| **PM10 Cu** | 0.82 | 0.86 | 0.85 | 0.71 | 0.70 | 0.58 | 1.00 |  |  |  |  |  |  |  |  |  |
| **PM10 Fe** | 0.83 | 0.91 | 0.87 | 0.70 | 0.74 | 0.58 | 0.93 | 1.00 |  |  |  |  |  |  |  |  |
| **PM10 K** | 0.52 | 0.51 | 0.54 | 0.80 | 0.47 | 0.34 | 0.58 | 0.61 | 1.00 |  |  |  |  |  |  |  |
| **PM10 Ni** | 0.15 | 0.32 | 0.22 | 0.24 | 0.46 | 0.64 | 0.24 | 0.26 | 0.08 | 1.00 |  |  |  |  |  |  |
| **PM10 Si** | 0.46 | 0.52 | 0.52 | 0.37 | 0.48 | 0.49 | 0.46 | 0.48 | 0.29 | 0.51 | 1.00 |  |  |  |  |  |
| **PM10 V** | 0.48 | 0.51 | 0.50 | 0.73 | 0.50 | 0.46 | 0.55 | 0.49 | 0.78 | 0.23 | 0.35 | 1.00 |  |  |  |  |
| **PM10 Zn** | 0.83 | 0.88 | 0.86 | 0.74 | 0.62 | 0.56 | 0.91 | 0.92 | 0.56 | 0.26 | 0.47 | 0.51 | 1.00 |  |  |  |
| **PM2.5 Cu** | 0.72 | 0.81 | 0.77 | 0.69 | 0.68 | 0.59 | 0.96 | 0.86 | 0.53 | 0.32 | 0.45 | 0.52 | 0.87 | 1.00 |  |  |
| **PM2.5 Fe** | 0.74 | 0.85 | 0.79 | 0.72 | 0.61 | 0.56 | 0.86 | 0.88 | 0.52 | 0.33 | 0.44 | 0.48 | 0.98 | 0.85 | 1.00 |  |
| **PM2.5 Zn** | 0.50 | 0.61 | 0.55 | 0.81 | 0.62 | 0.50 | 0.74 | 0.69 | 0.86 | 0.29 | 0.34 | 0.72 | 0.65 | 0.79 | 0.66 | 1.00 |

**Table S3. Adjusted Hazard Ratios (HRs), 95% confidence intervals (95% CI) and p-trend values for the association between ambient air pollution and liver cirrhosis, according to quartiles of the distribution.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Main pollutants** | | | | **PM10 metal components** | | | | **PM2.5 metal components** | | | |
| **Pollutant** | **Quartile** | **HR** | **(95% CI)** | **Pollutant** | **Quartile** | **HR** | **(95% CI)** | **Pollutant** | **Quartile** | **HR** | **(95% CI)** |
| **PM10** | 1 | 1.00 |  | **PM10Cu** | 1 | 1.00 |  | **PM2.5Cu** | 1 | 1.00 |  |
|  | 2 | 1.07 | (1.01-1.13) |  | 2 | 1.08 | (1.02-1.13) |  | 2 | 1.08 | (1.02-1.13) |
|  | 3 | 1.07 | (1.02-1.13) |  | 3 | 1.10 | (1.04-1.15) |  | 3 | 1.10 | (1.04-1.15) |
|  | 4 | 1.09 | (1.03-1.14) |  | 4 | 1.10 | (1.04-1.15) |  | 4 | 1.15 | (1.09-1.21) |
|  | p-trend | 0.005 | |  | p-trend | 0.001 | |  | p-trend | <0.001 | |
| **PM coarse** | 1 | 1.00 |  | **PM10Fe** | 1 | 1.00 |  | **PM2.5Fe** | 1 | 1.00 |  |
|  | 2 | 1.06 | (1.00-1.12) |  | 2 | 1.04 | (0.99-1.10) |  | 2 | 1.07 | (1.01-1.12) |
|  | 3 | 1.10 | (1.05-1.16) |  | 3 | 1.11 | (1.05-1.16) |  | 3 | 1.11 | (1.06-1.17) |
|  | 4 | 1.11 | (1.05-1.16) |  | 4 | 1.07 | (1.01-1.12) |  | 4 | 1.15 | (1.09-1.21) |
|  | p-trend | <0.001 | |  | p-trend | 0.006 | |  | p-trend | <0.001 | |
| **PM2.5** | 1 | 1.00 |  | **PM10K** | 1 | 1.00 |  | **PM2.5Zn** | 1 | 1.00 |  |
|  | 2 | 1.06 | (1.01-1.12) |  | 2 | 0.99 | (0.94-1.05) |  | 2 | 1.07 | (1.02-1.13) |
|  | 3 | 1.06 | (1.01-1.12) |  | 3 | 0.98 | (0.93-1.04) |  | 3 | 1.08 | (1.03-1.14) |
|  | 4 | 1.11 | (1.05-1.16) |  | 4 | 1.03 | (0.97-1.08) |  | 4 | 1.10 | (1.04-1.15) |
|  | p-trend | 0.001 | |  | p-trend | 0.424 | |  | p-trend | 0.002 | |
| **PM2.5 abs** | 1 | 1.00 |  | **PM10Ni** | 1 | 1.00 |  |  |  |  |  |
|  | 2 | 1.04 | (0.99-1.10) |  | 2 | 1.03 | (0.97-1.09) |  |  |  |  |
|  | 3 | 1.08 | (1.02-1.14) |  | 3 | 1.08 | (1.02-1.14) |  |  |  |  |
|  | 4 | 1.15 | (1.10-1.21) |  | 4 | 1.14 | (1.09-1.20) |  |  |  |  |
|  | p-trend | <0.001 | |  | p-trend | <0.001 | |  |  |  |  |
| **NO2** | 1 | 1.00 |  | **PM10Si** | 1 | 1.00 |  |  |  |  |  |
|  | 2 | 1.06 | (1.00-1.12) |  | 2 | 1.08 | (1.02-1.14) |  |  |  |  |
|  | 3 | 1.10 | (1.05-1.16) |  | 3 | 1.06 | (1.00-1.11) |  |  |  |  |
|  | 4 | 1.11 | (1.06-1.17) |  | 4 | 1.11 | (1.05-1.16) |  |  |  |  |
|  | p-trend | <0.001 | |  | p-trend | 0.002 | |  |  |  |  |
| **NOx** | 1 | 1.00 |  | **PM10V** | 1 | 1.00 |  |  |  |  |  |
|  | 2 | 1.06 | (1.00-1.12) |  | 2 | 1.06 | (1.00-1.12) |  |  |  |  |
|  | 3 | 1.12 | (1.07-1.18) |  | 3 | 1.09 | (1.04-1.15) |  |  |  |  |
|  | 4 | 1.20 | (1.14-1.25) |  | 4 | 1.10 | (1.05-1.16) |  |  |  |  |
|  | p-trend | <0.001 | |  | p-trend | <0.001 | |  |  |  |  |
|  |  |  |  | **PM10Zn** | 1 | 1.00 |  |  |  |  |  |
|  |  |  |  |  | 2 | 1.06 | (1.00-1.11) |  |  |  |  |
|  |  |  |  |  | 3 | 1.11 | (1.06-1.17) |  |  |  |  |
|  |  |  |  |  | 4 | 1.15 | (1.09-1.20) |  |  |  |  |
|  |  |  |  |  | p-trend | <0.001 | |  |  |  |  |

Models adjusted for educational level, occupational status, marital status, place of birth, area-level SEP and stratified by sex, age as the time scale.

**Table S4. Adjusted Hazard Ratios (HRs) and 95% confidence intervals (95% CI) for the association between ambient air pollution and liver cirrhosis by interquartile range (IQR) increments.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Exposure** | | **Incidence of cirrhosis**  **(n = 10,111)** | |
| **HRa** | **(95% CI)** |
| **Main pollutants** | **PM10** | 1.02 | (1.01-1.04) |
|  | **PM coarse** | 1.04 | (1.02-1.06) |
|  | **PM2.5** | 1.03 | (1.01-1.04) |
|  | **PM2.5abs** | 1.03 | (1.02-1.05) |
|  | **NO2** | 1.04 | (1.02-1.07) |
|  | **NOx** | 1.07 | (1.05-1.10) |
|  |  |  |  |
| **Metal components** | **PM10 Cu** | 1.03 | (1.01-1.04) |
|  | **PM10 Fe** | 1.02 | (1.01-1.04) |
|  | **PM10 K** | 1.01 | (1.00-1.02) |
|  | **PM10 Ni** | 1.07 | (1.05-1.10) |
|  | **PM10 Si** | 1.04 | (1.02-1.07) |
|  | **PM10 V** | 1.04 | (1.02-1.05) |
|  | **PM10 Zn** | 1.04 | (1.03-1.06) |
|  | **PM2.5 Cu** | 1.05 | (1.03-1.07) |
|  | **PM2.5 Fe** | 1.06 | (1.04-1.09) |
|  | **PM2.5 Zn** | 1.04 | (1.02-1.06) |

Models adjusted for educational level, occupational status, marital status, place of birth, area-level SEP and stratified by sex, age as the time scale.

Hazard Ratios per interquartile range increments of pollutants: PM10 4.7 µg/m3; PM coarse 3.5 µg/m3; PM2.5 1.7 µg/m3; PM2.5abs 0.4x10-5/m; NO2 12.9 µg/m3; NOx 32.5 µg/m3; PM10Cu 20.9 ng/m3; PM10Fe 458.1 ng/m3; PM10K 61.3 ng/m3; PM10Ni 1.5 ng/m3; PM10Si 359.7 ng/m3; PM10V 0.7 ng/m3; PM10Zn 12.1 ng/m3; PM2.5Cu 4.2 ng/m3; PM2.5Fe 99.8 ng/m3; PM2.5Zn 4.6 ng/m3.

**Table S5. Modification of the association between main pollutants and cirrhosis by participants’ characteristics.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **PM10** | **PM coarse** | **PM2.5** | **PM2.5**  **absorbance** | **NO2** | **NOx** |
|  | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **Age class** |  |  |  |  |  |  |
| 30-49 | 1.03 (0.94-1.13) | 1.08 (0.94-1.24) | 1.02 (0.90-1.17) | 1.07 (0.98-1.18) | 1.04 (0.99-1.08) | 1.06 (1.02-1.10) |
| 50-64 | 1.01 (0.94-1.08) | 1.03 (0.92-1.14) | 1.03 (0.93-1.17) | 1.01 (0.94-1.09) | 1.00 (0.96-1.03) | 1.01 (0.98-1.04) |
| 65-74 | 1.07 (1.01-1.15) | 1.12 (1.01-1.24) | 1.11 (1.02-1.35) | 1.11 (1.04-1.19) | 1.05 (1.02-1.09) | 1.06 (1.03-1.09) |
| >=75 | 1.08 (0.99-1.17) | 1.19 (1.05-1.35) | 1.11 (1.00-1.38) | 1.14 (1.05-1.24) | 1.04 (0.99-1.08) | 1.05 (1.01-1.09) |
| p for interaction | 0.482 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| **Gender** |  |  |  |  |  |  |
| Males | 1.03 (0.99-1.09) | 1.07 (0.99-1.16) | 1.05 (0.98-1.18) | 1.08 (1.02-1.14) | 1.02 (1.00-1.05) | 1.04 (1.02-1.06) |
| Females | 1.08 (1.02-1.14) | 1.17 (1.07-1.28) | 1.12 (1.04-1.36) | 1.10 (1.04-1.17) | 1.05 (1.02-1.08) | 1.06 (1.03-1.08) |
| p for interaction | 0.310 | 0.119 | 0.196 | 0.573 | 0.177 | 0.279 |
| **Educational level** |  |  |  |  |  |  |
| Very High | 1.08 (0.96-1.21) | 1.13 (0.94-1.35) | 1.10 (0.95-1.42) | 1.11 (0.98-1.26) | 1.02 (0.96-1.09) | 1.07 (1.01-1.13) |
| High | 1.00 (0.92-1.09) | 1.06 (0.93-1.20) | 1.04 (0.93-1.20) | 1.09 (1.00-1.18) | 1.02 (0.98-1.07) | 1.05 (1.01-1.09) |
| Intermediate | 1.05 (0.98-1.13) | 1.13 (1.01-1.26) | 1.06 (0.96-1.23) | 1.08 (1.00-1.16) | 1.04 (1.00-1.08) | 1.04 (1.01-1.07) |
| Low | 1.07 (1.01-1.14) | 1.13 (1.03-1.23) | 1.12 (1.03-1.35) | 1.09 (1.02-1.16) | 1.04 (1.01-1.07) | 1.04 (1.02-1.07) |
| p for interaction | 0.550 | 0.850 | 0.667 | 0.985 | 0.932 | 0.817 |
| **Area-level SEP** |  |  |  |  |  |  |
| Very High | 1.11 (1.01-1.22) | 1.15 (0.99-1.33) | 1.14 (1.01-1.48) | 1.12 (1.01-1.24) | 1.03 (0.98-1.08) | 1.07 (1.02-1.12) |
| High | 0.99 (0.91-1.08) | 0.98 (0.85-1.12) | 0.98 (0.87-1.07) | 1.06 (0.96-1.16) | 1.00 (0.95-1.04) | 1.02 (0.98-1.06) |
| Intermediate | 1.01 (0.94-1.09) | 1.06 (0.94-1.20) | 1.02 (0.92-1.16) | 1.04 (0.96-1.14) | 1.03 (0.99-1.07) | 1.02 (0.98-1.05) |
| Low | 1.07 (0.98-1.16) | 1.17 (1.04-1.32) | 1.09 (0.98-1.33) | 1.06 (0.98-1.16) | 1.06 (1.02-1.10) | 1.05 (1.01-1.08) |
| Very Low | 1.11 (1.02-1.21) | 1.22 (1.07-1.40) | 1.24 (1.10-1.73) | 1.16 (1.07-1.26) | 1.05 (1.01-1.09) | 1.08 (1.05-1.12) |
| p for interaction | 0.202 | 0.140 | 0.045 | 0.357 | 0.347 | 0.054 |
| **Occupational status** |  |  |  |  |  |  |
| Employed | 1.00 (0.92-1.08) | 1.06 (0.94-1.19) | 1.02 (0.92-1.15) | 1.04 (0.96-1.13) | 1.03 (0.99-1.07) | 1.04 (1.01-1.08) |
| Housewife | 1.13 (1.05-1.22) | 1.25 (1.11-1.42) | 1.18 (1.06-1.56) | 1.11 (1.02-1.21) | 1.07 (1.02-1.11) | 1.08 (1.04-1.12) |
| Unemployed | 1.01 (0.86-1.18) | 0.97 (0.76-1.23) | 1.03 (0.84-1.32) | 1.06 (0.90-1.24) | 1.00 (0.93-1.08) | 1.03 (0.97-1.10) |
| Retired | 1.06 (1.00-1.12) | 1.13 (1.03-1.23) | 1.10 (1.01-1.30) | 1.12 (1.05-1.19) | 1.04 (1.01-1.07) | 1.04 (1.01-1.06) |
| Other | 1.00 (0.88-1.14) | 0.97 (0.79-1.18) | 0.96 (0.80-1.10) | 1.04 (0.91-1.19) | 0.96 (0.90-1.03) | 1.02 (0.96-1.07) |
| p for interaction | 0.222 | 0.114 | 0.189 | 0.618 | 0.114 | 0.309 |

SEP: Socio-economic Position; p for interaction according to Likelihood Ratio test. Models adjusted for educational level, occupational status, marital status, place of birth, area-level SEP and stratified by sex, age as the time scale.

Hazard Ratios per fixed increments: PM10 10 µg/m3; PM coarse 10 µg/m3; PM2.5 5 µg/m3; PM2.5abs 1x10-5/m; NO2 10 µg/m3; NOx 20 µg/m3; PM10Cu 20 ng/m3; PM10Fe 500 ng/m3; PM10K 100 ng/m3; PM10Ni 2 ng/m3; PM10Si 500 ng/m3; PM10V 3 ng/m3; PM10Zn 20 ng/m3; PM2.5Cu 5 ng/m3; PM2.5Fe 100 ng/m3; PM2.5Zn 10 ng/m3.

**Table S6. Modification of the association between PM components and cirrhosis by participants’ characteristics.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **PM10 Cu** | **PM10 Fe** | **PM10 K** | **PM10 Ni** | **PM10 Si** | **PM10 V** | **PM10 Zn** | **PM2.5 Cu** | **PM2.5 Fe** | **PM2.5 Zn** |
|  | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **Age class** |  |  |  |  |  |  |  |  |  |  |
| 30-49 | 1.01 (0.97-1.04) | 1.01 (0.96-1.05) | 1.03 (0.99-1.07) | 1.17 (1.09-1.25) | 1.11 (1.03-1.19) | 1.31 (1.13-1.49) | 1.03 (0.95-1.10) | 1.02 (0.97-1.08) | 1.02 (0.97-1.08) | 1.07 (0.97-1.17) |
| 50-64 | 1.01 (0.99-1.04) | 1.00 (0.97-1.04) | 1.00 (0.96-1.03) | 1.01 (0.95-1.07) | 1.02 (0.96-1.08) | 1.05 (0.91-1.20) | 1.03 (0.97-1.09) | 1.02 (0.98-1.07) | 1.03 (0.98-1.07) | 1.02 (0.94-1.09) |
| 65-74 | 1.03 (1.01-1.06) | 1.04 (1.00-1.07) | 1.02 (0.99-1.05) | 1.12 (1.06-1.18) | 1.04 (0.98-1.10) | 1.11 (0.97-1.25) | 1.09 (1.04-1.14) | 1.06 (1.02-1.10) | 1.07 (1.03-1.11) | 1.08 (1.01-1.16) |
| >=75 | 1.04 (1.01-1.07) | 1.04 (1.00-1.08) | 1.03 (0.99-1.06) | 1.13 (1.05-1.21) | 1.09 (1.02-1.17) | 1.29 (1.11-1.47) | 1.12 (1.05-1.19) | 1.09 (1.04-1.14) | 1.02 (0.97-1.07) | 1.15 (1.05-1.25) |
| p for interaction | 0.348 | 0.384 | 0.500 | 0.012 | 0.294 | 0.156 | 0.167 | 0.171 | 0.097 | 0.265 |
| **Gender** |  |  |  |  |  |  |  |  |  |  |
| Males | 1.02 (1.00-1.04) | 1.02 (1.00-1.04) | 1.02 (1.00-1.04) | 1.08 (1.03-1.12) | 1.06 (1.01-1.10) | 1.13 (1.03-1.23) | 1.07 (1.03-1.11) | 1.05 (1.02-1.08) | 1.06 (1.02-1.09) | 1.08 (1.02-1.13) |
| Females | 1.03 (1.01-1.06) | 1.04 (1.01-1.06) | 1.02 (0.99-1.04) | 1.14 (1.09-1.20) | 1.06 (1.01-1.12) | 1.23 (1.11-1.36) | 1.09 (1.04-1.14) | 1.07 (1.03-1.10) | 1.08 (1.04-1.11) | 1.09 (1.02-1.16) |
| p for interaction | 0.446 | 0.403 | 0.795 | 0.072 | 0.880 | 0.299 | 0.553 | 0.434 | 0.443 | 0.789 |
| **Educational level** |  |  |  |  |  |  |  |  |  |  |
| Very High | 1.05 (1.01-1.09) | 1.03 (0.97-1.09) | 1.02 (0.97-1.07) | 1.17 (1.04-1.29) | 1.08 (0.97-1.19) | 1.22 (0.97-1.47) | 1.12 (1.02-1.21) | 1.10 (1.02-1.17) | 1.09 (1.01-1.17) | 1.10 (0.96-1.24) |
| High | 1.02 (0.99-1.05) | 1.02 (0.98-1.06) | 1.00 (0.97-1.04) | 1.15 (1.07-1.23) | 1.09 (1.01-1.16) | 1.13 (0.96-1.30) | 1.08 (1.01-1.14) | 1.05 (1.00-1.09) | 1.08 (1.03-1.13) | 1.07 (0.97-1.16) |
| Intermediate | 1.03 (1.00-1.05) | 1.03 (0.99-1.06) | 1.02 (0.99-1.05) | 1.09 (1.03-1.15) | 1.03 (0.97-1.10) | 1.22 (1.07-1.37) | 1.06 (1.00-1.12) | 1.06 (1.02-1.11) | 1.06 (1.01-1.10) | 1.11 (1.03-1.19) |
| Low | 1.03 (1.00-1.05) | 1.03 (1.00-1.06) | 1.02 (1.00-1.05) | 1.08 (1.03-1.13) | 1.06 (1.01-1.11) | 1.15 (1.02-1.27) | 1.07 (1.02-1.12) | 1.04 (1.01-1.08) | 1.05 (1.02-1.09) | 1.07 (1.00-1.13) |
| p for interaction | 0.754 | 0.958 | 0.861 | 0.401 | 0.770 | 0.873 | 0.858 | 0.624 | 0.792 | 0.869 |
| **Area-level SEP** |  |  |  |  |  |  |  |  |  |  |
| Very High | 1.03 (0.99-1.06) | 1.03 (0.99-1.08) | 1.02 (0.98-1.07) | 1.03 (0.91-1.14) | 1.03 (0.92-1.13) | 1.13 (0.92-1.34) | 1.10 (1.02-1.18) | 1.04 (0.98-1.10) | 1.08 (1.02-1.14) | 1.03 (0.92-1.15) |
| High | 1.01 (0.98-1.04) | 0.99 (0.95-1.03) | 1.00 (0.97-1.04) | 1.07 (0.99-1.16) | 1.03 (0.95-1.12) | 1.11 (0.91-1.30) | 1.02 (0.95-1.09) | 1.04 (0.98-1.09) | 1.02 (0.96-1.07) | 1.05 (0.95-1.16) |
| Intermediate | 1.01 (0.98-1.04) | 1.01 (0.97-1.04) | 0.99 (0.96-1.03) | 1.08 (1.00-1.15) | 1.04 (0.97-1.12) | 1.04 (0.86-1.23) | 1.03 (0.97-1.10) | 1.04 (0.99-1.09) | 1.04 (0.99-1.09) | 1.05 (0.96-1.15) |
| Low | 1.04 (1.00-1.07) | 1.04 (1.00-1.08) | 1.02 (0.98-1.06) | 1.12 (1.06-1.18) | 1.10 (1.03-1.17) | 1.18 (1.01-1.34) | 1.08 (1.01-1.15) | 1.07 (1.02-1.12) | 1.07 (1.02-1.12) | 1.12 (1.03-1.21) |
| Very Low | 1.05 (1.02-1.08) | 1.06 (1.02-1.11) | 1.05 (1.01-1.08) | 1.14 (1.08-1.21) | 1.07 (1.00-1.13) | 1.34 (1.19-1.49) | 1.16 (1.09-1.23) | 1.08 (1.03-1.13) | 1.12 (1.07-1.18) | 1.12 (1.03-1.21) |
| p for interaction | 0.369 | 0.145 | 0.292 | 0.479 | 0.750 | 0.297 | 0.083 | 0.719 | 0.150 | 0.678 |
| **Occupational status** |  |  |  |  |  |  |  |  |  |  |
| Employed | 1.02 (0.99-1.05) | 1.02 (0.98-1.05) | 1.01 (0.98-1.04) | 1.13 (1.06-1.20) | 1.08 (1.01-1.15) | 1.10 (0.94-1.26) | 1.04 (0.98-1.10) | 1.04 (0.99-1.09) | 1.04 (0.99-1.09) | 1.08 (1.00-1.17) |
| Housewife | 1.04 (1.01-1.08) | 1.05 (1.01-1.09) | 1.02 (0.99-1.06) | 1.15 (1.07-1.22) | 1.10 (1.02-1.17) | 1.30 (1.13-1.47) | 1.11 (1.04-1.17) | 1.08 (1.03-1.13) | 1.09 (1.04-1.14) | 1.12 (1.02-1.22) |
| Unemployed | 1.00 (0.94-1.06) | 0.98 (0.90-1.06) | 1.02 (0.96-1.09) | 1.08 (0.96-1.21) | 1.02 (0.88-1.15) | 1.26 (0.96-1.56) | 1.01 (0.88-1.14) | 0.99 (0.90-1.09) | 1.00 (0.90-1.10) | 0.99 (0.83-1.16) |
| Retired | 1.04 (1.01-1.06) | 1.04 (1.01-1.07) | 1.02 (0.99-1.05) | 1.07 (1.02-1.13) | 1.03 (0.98-1.09) | 1.14 (1.01-1.26) | 1.10 (1.05-1.15) | 1.07 (1.03-1.11) | 1.09 (1.05-1.13) | 1.10 (1.03-1.16) |
| Other | 0.98 (0.93-1.04) | 0.97 (0.90-1.03) | 1.02 (0.96-1.07) | 1.06 (0.95-1.17) | 1.07 (0.96-1.18) | 1.16 (0.90-1.43) | 1.00 (0.90-1.11) | 0.99 (0.92-1.07) | 1.00 (0.92-1.08) | 1.00 (0.85-1.15) |
| p for interaction | 0.237 | 0.121 | 0.985 | 0.529 | 0.672 | 0.654 | 0.262 | 0.219 | 0.165 | 0.593 |

SEP: Socio-economic Position; p for interaction according to Likelihood Ratio test. Models adjusted for educational level, occupational status, marital status, place of birth, area-level SEP and stratified by sex, age as the time scale. Hazard Ratios per fixed increments of pollutants: PM10 10 µg/m3; PM coarse 10 µg/m3; PM2.5 5 µg/m3; PM2.5abs 1x10-5/m; NO2 10 µg/m3; NOx 20 µg/m3; PM10Cu 20 ng/m3; PM10Fe 500 ng/m3; PM10K 100 ng/m3; PM10Ni 2 ng/m3; PM10Si 500 ng/m3; PM10V 3 ng/m3; PM10Zn 20 ng/m3; PM2.5Cu 5 ng/m3; PM2.5Fe 100 ng/m3; PM2.5Zn 10 ng/m3.

**Table S7. Adjusted Hazard Ratios (HRs) and 95% confidence intervals (95% CI) for the association between ambient air pollution and liver cirrhosis in the Rome Longitudinal Study (main analysis), and corresponding e-values. Rome 2001-2015.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | | **HR** | **(95% CI)** |  | **e-value (HR)** | **e-value (95% CI)** |
| **Main pollutants** | **PM10** | 1.05 | (1.01-1.09) |  | 1.29 | 1.14 |
|  | **PM coarse** | 1.11 | (1.05-1.17) |  | 1.46 | 1.29 |
|  | **PM2.5** | 1.08 | (1.03-1.13) |  | 1.38 | 1.21 |
|  | **PM2.5abs** | 1.09 | (1.05-1.13) |  | 1.40 | 1.28 |
|  | **NO2** | 1.03 | (1.02-1.05) |  | 1.22 | 1.14 |
|  | **NOx** | 1.04 | (1.03-1.06) |  | 1.26 | 1.20 |
|  |  |  |  |  |  |  |
| **Metal components** | **PM10Cu** | 1.03 | (1.01-1.04) |  | 1.19 | 1.12 |
|  | **PM10Fe** | 1.03 | (1.01-1.04) |  | 1.19 | 1.09 |
|  | **PM10K** | 1.02 | (1.00-1.04) |  | 1.16 | 1.05 |
|  | **PM10Ni** | 1.10 | (1.07-1.14) |  | 1.44 | 1.34 |
|  | **PM10Si** | 1.06 | (1.03-1.09) |  | 1.31 | 1.19 |
|  | **PM10V** | 1.17 | (1.09-1.25) |  | 1.62 | 1.41 |
|  | **PM10Zn** | 1.07 | (1.04-1.11) |  | 1.36 | 1.25 |
|  | **PM2.5Cu** | 1.05 | (1.03-1.08) |  | 1.29 | 1.21 |
|  | **PM2.5Fe** | 1.06 | (1.04-1.09) |  | 1.33 | 1.24 |
|  | **PM2.5Zn** | 1.08 | (1.04-1.13) |  | 1.38 | 1.24 |

Models adjusted for educational level, occupational status, marital status, place of birth, area-level SEP and stratified by sex, age as the time scale. Hazard Ratios per fixed increments of pollutants: PM10 10 µg/m3; PM coarse 10 µg/m3; PM2.5 5 µg/m3; PM2.5abs 1x10-5/m; NO2 10 µg/m3; NOx 20 µg/m3; PM10Cu 20 ng/m3; PM10Fe 500 ng/m3; PM10K 100 ng/m3; PM10Ni 2 ng/m3; PM10Si 500 ng/m3; PM10V 3 ng/m3; PM10Zn 20 ng/m3; PM2.5Cu 5 ng/m3; PM2.5Fe 100 ng/m3; PM2.5Zn 10 ng/m3.

**Table S8. Adjusted Hazard Ratios (HRs) and 95% confidence intervals (95% CI) for the association between main pollutants and liver cirrhosis: two pollutant models.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Standard**  **pollutants** | **Single pollutant**  **model** | **+PM10** | **+PM coarse** | **+PM2.5** | **+PM2.5 abs** | **+NO2** | **+NOx** |
| **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **PM10** | 1.05 (1.01-1.09) |  |  |  | 1.00 (0.96-1.05) | 1.02 (0.97-1.06) | 0.99 (0.95-1.04) |
| **PM coarse** | 1.11 (1.05-1.17) |  |  |  | 1.05 (0.97-1.12) |  | 1.01 (0.93-1.08) |
| **PM2.5** | 1.08 (1.03-1.13) |  |  |  | 1.03 (0.90-1.16) | 1.07 (0.93-1.20) | 0.98 (0.85-1.11) |
| **PM2.5 abs** | 1.09 (1.05-1.13) | 1.09 (1.04-1.14) | 1.07 (1.02-1.12) | 1.08 (1.03-1.13) |  | 1.07 (1.02-1.12) | 1.04 (0.99-1.09) |
| **NO2** | 1.03 (1.02-1.05) |  |  | 1.03 (1.00-1.05) | 1.01 (0.99-1.04) |  |  |
| **NOx** | 1.04 (1.03-1.06) | 1.05 (1.03-1.07) | 1.04 (1.02-1.06) | 1.05 (1.03-1.07) | 1.04 (1.02-1.06) |  |  |

Models adjusted for educational level, occupational status, marital status, place of birth, area-level SEP and stratified by sex, age as the time scale.

Hazard Ratios per fixed increments of pollutants: PM10 10 µg/m3; PM coarse 10 µg/m3; PM2.5 5 µg/m3; PM2.5abs 1x10-5/m; NO2 10 µg/m3; NOx 20 µg/m3.

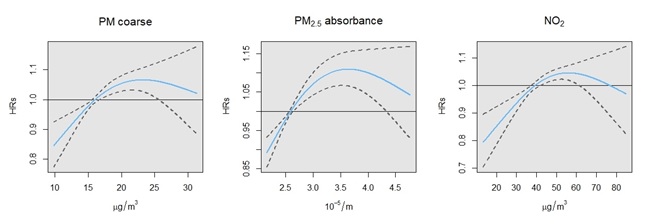
**Table S9. Adjusted Hazard Ratios (HRs) and 95% confidence intervals (95% CI) for the association between PM components and liver cirrhosis: two pollutant models.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Single pollutant**  **model** | **+PM10** | **+PM2.5** |
| **PM constituents** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **PM10 Cu** | 1.03 (1.01-1.04) |  |  |
| **PM10 Fe** | 1.03 (1.01-1.04) |  |  |
| **PM10 K** | 1.02 (1.00-1.04) | 1.01 (0.99-1.03) |  |
| **PM10 Ni** | 1.10 (1.07-1.14) | 1.10 (1.06-1.13) |  |
| **PM10 Si** | 1.06 (1.03-1.09) | 1.05 (1.01-1.09) |  |
| **PM10 V** | 1.17 (1.09-1.25) | 1.15 (1.06-1.24) |  |
| **PM10 Zn** | 1.07 (1.04-1.11) |  |  |
| **PM2.5 Cu** | 1.05 (1.03-1.08) |  |  |
| **PM2.5 Fe** | 1.06 (1.04-1.09) |  |  |
| **PM2.5 Zn** | 1.08 (1.04-1.13) |  | 1.06 (1.01-1.12) |

Models adjusted for educational level, occupational status, marital status, place of birth, area-level SEP and stratified by sex, age as the time scale.

Hazard Ratios per fixed increments of pollutants: PM10Cu 20 ng/m3; PM10Fe 500 ng/m3; PM10K 100 ng/m3; PM10Ni 2 ng/m3; PM10Si 500 ng/m3; PM10V 3 ng/m3; PM10Zn 20 ng/m3; PM2.5Cu 5 ng/m3; PM2.5Fe 100 ng/m3; PM2.5Zn 10 ng/m3.

**Figure S1. Estimated exposure-response curves (solid lines) and 95% CI (dashed lines) for PM coarse, PM2.5 absorbance, and NO2 and incidence of cirrhosis.**



Models adjusted for educational level, occupational status, marital status, place of birth, area-level SEP and stratified by sex, age as the time scale. The curves were obtained by replacing the linear term with natural splines (two degrees of freedom). Associations with statistical evidence of non-linearity are reported only.

**List of ICD-9-CM codes**

**Cirrhosis**

571.2, 571.5, 571.6

**Cirrhosis complications**

456.0, 456.1, 456.2, 456.20, 456.21

572.2, 572.3, 572.4

**Viral hepatitis**

070, 070.0, 070.1, 070.2, 070.20, 070.21, 070.22, 070.23, 070.3, 070.30, 070.31, 070.32, 070.33, 070.4, 070.41, 070.42, 070.43, 070.44, 070.49, 070.5, 070.51, 070.52, 070.53, 070.54, 070.59, 070.6, 070.9

**Other at-risk conditions**

273.4, 275.0, 275.1

303.90, 303.91, 303.92, 303.93,

453.0

571.0, 571.1, 571.2, 571.3, 571.40, 571.41, 517.42, 517.49, 571.8, 571.9, 573.0, 573.2, 573.3, 573.8, 573.9, 576.1

V11.3