Long-term exposure to fine particulate matter and non-alcoholic fatty liver disease: a prospective cohort study

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease and is associated with a higher risk of all-cause and cause-specific morbidity and mortality.[1–3] Animal studies suggest that air pollution may play a role in the development of NAFLD.[4 5] However, evidence from human studies is limited.[6]

Here, we prospectively estimated the association between long-term exposure to fine particulate matter ($PM_{2.5}$) and risk of NAFLD in 58 026 Taiwan residents who received a standard medical screening programme between 2001 and 2016. We excluded participants with (a) missing values of covariates; (b) excess alcohol intake; (c) liver disease at baseline; (d) NAFLD at baseline and (e) only one medical examination (online supplemental figure S1). The final analytic sample included 35 614 participants for fatty liver index (FLI)-based cohort and 34 741 participants for hepatic steatosis index (HSI)-based cohort. We defined the incident NAFLD as the first occurrence of values of FLI>30 or HSI>36, which have been validated in the Asian population.[7 8] We estimated annual $PM_{2.5}$ levels at participants' residential addresses using multiple satellite-based aerosol optical depth data combined with a chemical transport model.[9] Physical examinations were conducted by trained technicians using a standardised protocol. Demographic characteristics and lifestyle data were collected using a standard self-administered questionnaire. We used time-varying Cox proportional hazards models to estimate HRs of the association between continuous and categorical $PM_{2.5}$ estimates and risk of NAFLD. We conducted stratified analyses to identify vulnerable populations.

Table 1 Association between long-term exposure to fine particulate matter ($PM_{2.5}$) and risk of non-alcoholic fatty liver disease in Taiwanese population

Exposure	Number of events	Minimally adjusted model* HR (95% CI)	Partially adjusted model† HR (95% CI)	Fully adjusted model‡ HR (95% CI)
Outcome for fatty liver index (FLI)				
First quartile (median 14.5 μg/m^3)	1738	Reference	Reference	Reference
Second quartile (median 22.0 μg/m^3)	1262	1.02 (0.95 to 1.10)	1.00 (0.93 to 1.08)	1.00 (0.93 to 1.08)
Third quartile (median 25.0 μg/m^3)	1809	1.03 (0.96 to 1.10)	1.03 (0.96 to 1.10)	1.03 (0.96 to 1.10)
Fourth quartile (median 27.5 μg/m^3)	2064	1.30 (1.21 to 1.40)	1.34 (1.25 to 1.44)	1.34 (1.25 to 1.44)
P for trend		<0.001	<0.001	<0.001
Continuous per 1 μg/m^3 increase in $PM_{2.5}$ (>breakpoint§)	6873	1.06 (1.03 to 1.08)	1.07 (1.04 to 1.09)	1.06 (1.04 to 1.08)
Outcome for hepatic steatosis index (HSI)				
First quartile (median 14.5 μg/m^3)	1905	Reference	Reference	Reference
Second quartile (median 22.0 μg/m^3)	1332	0.98 (0.91 to 1.05)	0.99 (0.92 to 1.06)	0.99 (0.92 to 1.06)
Third quartile (median 25.0 μg/m^3)	2031	1.02 (0.96 to 1.09)	1.04 (0.97 to 1.10)	1.03 (0.97 to 1.10)
Fourth quartile (median 27.5 μg/m^3)	2391	1.20 (1.12 to 1.28)	1.20 (1.12 to 1.29)	1.20 (1.12 to 1.28)
P for trend		<0.001	<0.001	<0.001
Continuous per 1 μg/m^3 increase in $PM_{2.5}$ (>breakpoint¶)	7659	1.07 (1.05 to 1.09)	1.06 (1.04 to 1.08)	1.06 (1.04 to 1.07)

*Models were adjusted for age and year of enrolment.
†Models were additionally adjusted for season of measurement, gender, smoking status, alcohol consumption, occupational exposure, educational attainment, vegetable intake, fruit intake, sugar drink intake, fried food intake, habitual physical activity, and physical activity at work. HSI takes gender into account, so we did not adjust for it in the models.
‡Models were additionally adjusted for cancer, long-term use of hyperlipidemia drugs, cardiovascular disease, and hypertension.
§Breakpoints of $PM_{2.5}$ exposure were identified by using piecewise Cox proportional hazards regression with 'Segmented' R package. The breakpoints of FLI for minimally, partially and fully adjusted models were 23.4 μg/m^3, 23.5 μg/m^3 and 23.5 μg/m^3, respectively.
¶Breakpoints of $PM_{2.5}$ exposure were identified by using piecewise Cox proportional hazards regression with 'Segmented' R package. Breakpoints of HSI for minimally, partially and fully adjusted models were 23.8 μg/m^3, 23.6 μg/m^3 and 23.5μg/m^3, respectively.

We documented 6873 incidence of FLI-defined NAFLD and 7659 incidence of HSI-defined NAFLD during the study period. Risks of NAFLD were associated with $PM_{2.5}$ at concentrations above 23.5 $\mu g/m^3$; each 1 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an HR of 1.06 (95% CI: 1.04 to 1.08) for FLI-defined NAFLD and an HR of 1.06 (95% CI: 1.04 to 1.07) for HSI-defined NAFLD. Those living in the highest quartile of $PM_{2.5}$ had a 34% higher rate of FLI-defined NAFLD (95% CI: 1.25 to 1.44) and a 20% higher rate of HSI-defined NAFLD (95% CI: 1.12 to 1.28) than those in the lowest quartile (table 1). Our results were not materially different in sensitivity analyses adjusting for metabolic syndrome, restricting analyses among never drinkers, or using concentrations of $PM_{2.5}$ at the previous year of the medical measurement as a proxy for air pollution exposure (online supplemental tables S1–S3). The association was more pronounced among physically inactive participants, but we found no evidence of effect modification by other personal characteristics (figure 1).

To our knowledge, this is the first prospective cohort study to examine the association between long-term $PM_{2.5}$ exposure and risk of NAFLD. Our findings are consistent with an analysis among 2513 participants from the Framingham (Massachusetts) Offspring Study and Third Generation Cohort,[6] the only study so far that directly examined the association between long-term exposure

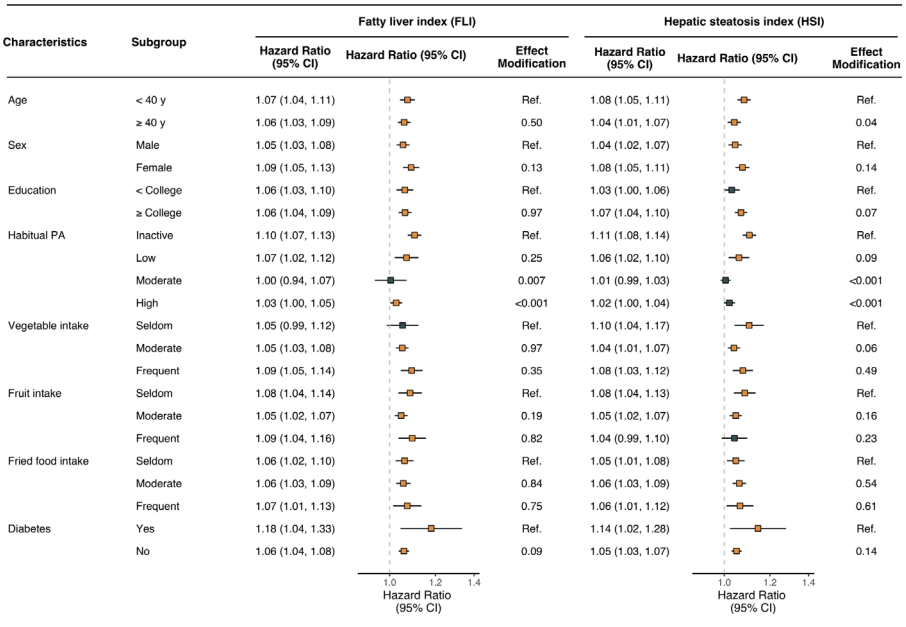

Figure 1 The HRs of non-alcoholic fatty liver disease associated with fine particulate matter above 23.5 μ/g/m^3 with each 1 μ/g/m^3 increase in fine particulate matter by personal characteristics. P value for effect modification was tested using two-sample Z test. Squares in orange represent the risk estimates are statistically significant. CI, confidence interval; PA, physical activity.

to $PM_{2.5}$ and risk of hepatic steatosis. This study found that living closer to a major roadway was associated with more liver fat and higher prevalence of hepatic steatosis.[6] Our findings were also consistent with the evidence from animal studies,[4 5] which showed that exposure to $PM_{2.5}$ was associated with higher levels of hepatic steatosis and fibrosis compared with exposure to filtered air in mice. Underlying mechanisms linking $PM_{2.5}$ exposure with NAFLD are that particulate matter may promote hepatic steatosis through inflammation, oxidative stress, insulin resistance and specific molecular and metabolic derangements.[10]

In conclusion, long-term exposure to ambient $PM_{2.5}$ was associated with a higher risk of NAFLD at relatively higher concentrations. Given that the majority of evidence of association between $PM_{2.5}$ and NAFLD was from animal studies, our findings substantially extended the existing evidence that air pollution is potentially a novel risk factor for the development of human NAFLD.

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Correction notice This article has been corrected since it published Online First. A typographical error has been corrected in table 1.

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Supplementary Material

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Figure S1. Flow chart of the study population.

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Table S1. Association between long-term exposure to fine particulate matter and risk of non-alcoholic fatty liver disease with additionally adjusted for metabolic syndrome among Taiwan residents[*].

Exposure	Number of events	Main model[†] HR (95% CI)	Additionally adjusted for metabolic syndrome HR (95% CI)
Fatty liver index (FLI)			
1st Quartile (median 14.5 μg/m^3)	1,738	Reference	Reference
2nd Quartile (median 22.0 μg/m^3)	1,262	1.00 (0.93, 1.08)	0.99 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	1,809	1.03 (0.96, 1.10)	1.02 (0.95, 1.10)
4th Quartile (median 27.5 μg/m^3)	2,064	1.34 (1.25, 1.44)	1.35 (1.25, 1.45)
p for trend		<0.001	<0.001
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint[‡])	6,873	1.06 (1.04, 1.08)	1.06 (1.04, 1.08)
Hepatic steatosis index (HSI)			
1st Quartile (median 14.5 μg/m^3)	1,905	Reference	Reference
2nd Quartile (median 22.0 μg/m^3)	1,332	0.99 (0.92, 1.06)	1.00 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	2,031	1.03 (0.97, 1.10)	1.05 (0.99, 1.13)
4th Quartile (median 27.5 μg/m^3)	2,391	1.20 (1.12, 1.28)	1.20 (1.12, 1.28)
p for trend		<0.001	<0.001
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint[§])	7,659	1.06 (1.04, 1.07)	1.06 (1.04, 1.07)

Abbreviations: HR=hazard ratio; CI=confidence interval.

[*]Metabolic syndrome was defined by the NCEP ATPIII modified for Asian's criteria.

[†]Models were adjusted for age, year of enrollment, season of measurement, gender, smoking status, alcohol consumption, occupational exposure, educational attainment, vegetable intake, fruit intake, sugar drink, fried food intake, habitual physical activity, physical activity at work, cancer, long-term use of hyperlipidemia drugs, cardiovascular disease, and hypertension. HSI takes gender into account, we did not adjust for it in the models.

[‡]Breakpoints of FLI for minimally, partially, and fully adjusted models were 23.4μg/m^3, and 23.5μg/m^3 respectively.

[§]Breakpoints of HSI for minimally, partially, and fully adjusted models were 23.8μg/m^3, and 23.6μg/m^3 respectively.

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Table S2. Association between long-term exposure to fine particulate matter and risk of non-alcoholic fatty liver disease among never drinkers.

Exposure	Number of events	Minimally adjusted model* HR (95% CI)	Fully adjusted model† HR (95% CI)
Fatty liver index (FLI)			
1st Quartile (median 15.0 μg/m^3)	1,550	Reference	Reference
2nd Quartile (median 22.0 μg/m^3)	1,110	1.01 (0.93, 1.09)	0.99 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	1,597	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)
4th Quartile (median 27.5 μg/m^3)	1,849	1.32 (1.22, 1.42)	1.35 (1.25, 1.45)
p for trend		<0.001	<0.001
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint‡)	6,106	1.06 (1.04, 1.08)	1.06 (1.04, 1.09)
Hepatic steatosis index (HSI)			
1st Quartile (median 14.5 μg/m^3)	1,723	Reference	Reference
2nd Quartile (median 22.0 μg/m^3)	1,216	0.99 (0.92, 1.06)	1.00 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	1,867	1.04 (0.98, 1.11)	1.05 (0.99, 1.13)
4th Quartile (median 27.5 μg/m^3)	2,183	1.19 (1.12, 1.28)	1.20 (1.12, 1.28)
p for trend		<0.001	<0.001
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint§)	6,989	1.08 (1.06, 1.10)	1.06 (1.04, 1.08)

Abbreviations: HR=hazard ratio; CI=confidence interval.

*Models were adjusted for age, and year of enrollment.

†Models were additionally adjusted for season of measurement, gender, smoking status, alcohol consumption, occupational exposure, educational attainment, vegetable intake, fruit intake, sugar drink, fried food intake, habitual physical activity, physical activity at work, cancer, long-term use of hyperlipidemia drugs, cardiovascular disease, and hypertension. HSI takes gender into account, we did not adjust for it in the models.

‡Breakpoints of FLI for minimally and fully adjusted models were 23.5μg/m^3 and 23.6μg/m^3 respectively.

§Breakpoints of HSI for minimally and fully adjusted models were 23.7μg/m^3 and 23.6μg/m^3 respectively.

Table S3. Association between long-term exposure to fine particulate matter at the previous year of the medical measurement **and risk of non-alcoholic fatty liver disease among Taiwan residents.**

Exposure	Number of events	Minimally adjusted model* HR (95% CI)	Fully adjusted model† HR (95% CI)
Fatty liver index (FLI)			
1st Quartile (median 13.0 μg/m^3)	1,434	Reference	Reference
2nd Quartile (median 21.0 μg/m^3)	1,499	0.98 (0.92, 1.06)	0.99 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	1,375	1.13 (1.05, 1.21)	1.14 (1.06, 1.23)
4th Quartile (median 28.0 μg/m^3)	2,565	1.13 (1.06, 1.21)	1.16 (1.08, 1.24)
p for trend		<0.001	<0.001
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint‡)	6,873	1.06 (1.03, 1.08)	1.06 (1.04, 1.08)
Hepatic steatosis index (HSI)			
1st Quartile (median 13.0 μg/m^3)	1,599	Reference	Reference
2nd Quartile (median 21.0 μg/m^3)	1,607	0.93 (0.87, 1.00)	0.94 (0.87, 1.00)
3rd Quartile (median 25.0 μg/m^3)	1,477	1.03 (0.96, 1.10)	1.04 (0.97, 1.11)
4th Quartile (median 28.0 μg/m^3)	2,976	1.08 (1.00, 1.15)	1.08 (1.02, 1.15)
p for trend		0.010	0.005
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint§)	7,659	1.07 (1.05, 1.09)	1.06 (1.04, 1.07)

Abbreviations: HR=hazard ratio; CI=confidence interval.

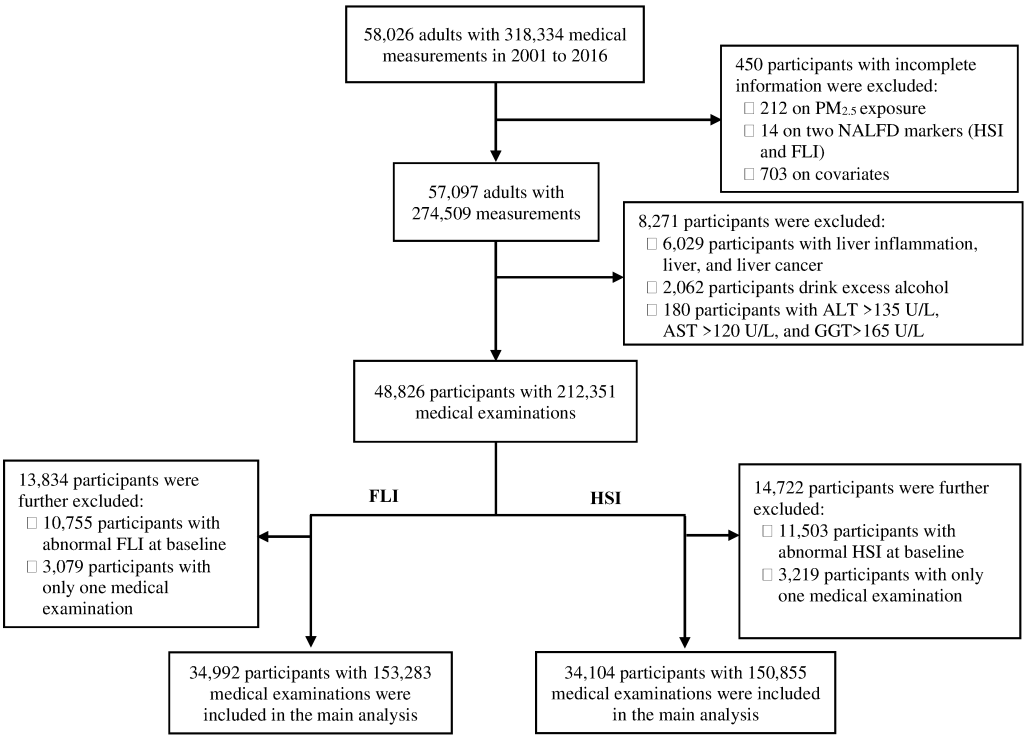
*Models were adjusted for age, and year of enrollment.

†Models were additionally adjusted for season of measurement, gender, smoking status, alcohol consumption, occupational exposure, educational attainment, vegetable intake, fruit intake, sugar drink, fried food intake, habitual physical activity, physical activity at work, cancer, long-term use of hyperlipidemia drugs, cardiovascular disease, and hypertension. HSI takes gender into account, we did not adjust for it in the models.

‡Breakpoints of FLI for minimally and fully adjusted models were 23.5μg/m^3 and 23.5μg/m^3 respectively.

§Breakpoints of HSI for minimally and fully adjusted models were 23.8μg/m^3 and 23.5μg/m^3 respectively.

Figure S1. Flow chart of the study population. NALFD=nonalcoholic fatty liver disease, $PM_{2.5}$=fine particulate matter, FLI=fatty liver index, HSI= hepatic steatosis index, ALT= Alanine aminotransferase test; AST= Aspartate aminotransferase test; GGT= Gamma-glutamyl transferase**.**



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2nd Quartile (median 22.0 μg/m^3)	1,262	1.00 (0.93, 1.08)	0.99 (0.92, 1.07)
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2nd Quartile (median 22.0 μg/m^3)	1,332	0.99 (0.92, 1.06)	1.00 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	2,031	1.03 (0.97, 1.10)	1.05 (0.99, 1.13)
4th Quartile (median 27.5 μg/m^3)	2,391	1.20 (1.12, 1.28)	1.20 (1.12, 1.28)
p for trend		<0.001	<0.001
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Abbreviations: HR=hazard ratio; CI=confidence interval.

[*]Metabolic syndrome was defined by the NCEP ATPIII modified for Asian's criteria.

[†]Models were adjusted for age, year of enrollment, season of measurement, gender, smoking status, alcohol consumption, occupational exposure, educational attainment, vegetable intake, fruit intake, sugar drink, fried food intake, habitual physical activity, physical activity at work, cancer, long-term use of hyperlipidemia drugs, cardiovascular disease, and hypertension. HSI takes gender into account, we did not adjust for it in the models.

[‡]Breakpoints of FLI for minimally, partially, and fully adjusted models were 23.4μg/m^3, and 23.5μg/m^3 respectively.

[§]Breakpoints of HSI for minimally, partially, and fully adjusted models were 23.8μg/m^3, and 23.6μg/m^3 respectively.

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Exposure	Number of events	Minimally adjusted model* HR (95% CI)	Fully adjusted model† HR (95% CI)
Fatty liver index (FLI)			
1st Quartile (median 15.0 μg/m^3)	1,550	Reference	Reference
2nd Quartile (median 22.0 μg/m^3)	1,110	1.01 (0.93, 1.09)	0.99 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	1,597	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)
4th Quartile (median 27.5 μg/m^3)	1,849	1.32 (1.22, 1.42)	1.35 (1.25, 1.45)
p for trend		<0.001	<0.001
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint‡)	6,106	1.06 (1.04, 1.08)	1.06 (1.04, 1.09)
Hepatic steatosis index (HSI)			
1st Quartile (median 14.5 μg/m^3)	1,723	Reference	Reference
2nd Quartile (median 22.0 μg/m^3)	1,216	0.99 (0.92, 1.06)	1.00 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	1,867	1.04 (0.98, 1.11)	1.05 (0.99, 1.13)
4th Quartile (median 27.5 μg/m^3)	2,183	1.19 (1.12, 1.28)	1.20 (1.12, 1.28)
p for trend		<0.001	<0.001
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint§)	6,989	1.08 (1.06, 1.10)	1.06 (1.04, 1.08)

Abbreviations: HR=hazard ratio; CI=confidence interval.

*Models were adjusted for age, and year of enrollment.

†Models were additionally adjusted for season of measurement, gender, smoking status, alcohol consumption, occupational exposure, educational attainment, vegetable intake, fruit intake, sugar drink, fried food intake, habitual physical activity, physical activity at work, cancer, long-term use of hyperlipidemia drugs, cardiovascular disease, and hypertension. HSI takes gender into account, we did not adjust for it in the models.

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Exposure	Number of events	Minimally adjusted model* HR (95% CI)	Fully adjusted model† HR (95% CI)
Fatty liver index (FLI)			
1st Quartile (median 13.0 μg/m^3)	1,434	Reference	Reference
2nd Quartile (median 21.0 μg/m^3)	1,499	0.98 (0.92, 1.06)	0.99 (0.92, 1.07)
3rd Quartile (median 25.0 μg/m^3)	1,375	1.13 (1.05, 1.21)	1.14 (1.06, 1.23)
4th Quartile (median 28.0 μg/m^3)	2,565	1.13 (1.06, 1.21)	1.16 (1.08, 1.24)
p for trend		<0.001	<0.001
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint‡)	6,873	1.06 (1.03, 1.08)	1.06 (1.04, 1.08)
Hepatic steatosis index (HSI)			
1st Quartile (median 13.0 μg/m^3)	1,599	Reference	Reference
2nd Quartile (median 21.0 μg/m^3)	1,607	0.93 (0.87, 1.00)	0.94 (0.87, 1.00)
3rd Quartile (median 25.0 μg/m^3)	1,477	1.03 (0.96, 1.10)	1.04 (0.97, 1.11)
4th Quartile (median 28.0 μg/m^3)	2,976	1.08 (1.00, 1.15)	1.08 (1.02, 1.15)
p for trend		0.010	0.005
Continuous per 1μg/m^3 increase in $PM_{2.5}$ (>breakpoint§)	7,659	1.07 (1.05, 1.09)	1.06 (1.04, 1.07)

Abbreviations: HR=hazard ratio; CI=confidence interval.

*Models were adjusted for age, and year of enrollment.

†Models were additionally adjusted for season of measurement, gender, smoking status, alcohol consumption, occupational exposure, educational attainment, vegetable intake, fruit intake, sugar drink, fried food intake, habitual physical activity, physical activity at work, cancer, long-term use of hyperlipidemia drugs, cardiovascular disease, and hypertension. HSI takes gender into account, we did not adjust for it in the models.

‡Breakpoints of FLI for minimally and fully adjusted models were 23.5μg/m^3 and 23.5μg/m^3 respectively.

§Breakpoints of HSI for minimally and fully adjusted models were 23.8μg/m^3 and 23.5μg/m^3 respectively.

Figure S1. Flow chart of the study population. NALFD=nonalcoholic fatty liver disease, $PM_{2.5}$=fine particulate matter, FLI=fatty liver index, HSI= hepatic steatosis index, ALT= Alanine aminotransferase test; AST= Aspartate aminotransferase test; GGT= Gamma-glutamyl transferase**.**