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Traffic-related air pollution associations with cytokeratin-18, a marker of hepatocellular apoptosis, in an overweight and obese pediatric population

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Abstract

Introduction—Traffic-related air pollution causes fatty liver, inflammation, and fibrosis in animal models, but there have been few studies in humans.

Objectives—To test the hypothesis that traffic-related air pollution causes non-alcoholic fatty liver disease (NAFLD) and increased markers for non-alcoholic steatohepatitis (NASH); and that NAFLD increases liver susceptibility to increased NASH risk.

Methods—Data collected prospectively from 74 overweight or obese children were obtained from the Yale Pediatric Obesity Clinic. Traffic-related air pollution was characterized as vehicle traffic volume on major roads within a one kilometer residential buffer, and as residential nitrogen dioxide (NO₂) exposure. Outcomes were hepatic fat fraction (HFF) measured by magnetic resonance imaging, liver enzymes using standard assays, and plasma cytokeratin-18 (CK-18) by immunosorbent assays.

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Author Contributions:

The idea for this study was developed by Drs. McConnell and Hsieh in consultation with Drs. Caprio and Feldstein, who also contributed the patient outcome data. Dr. Leaderer and Ms. McKay provided air pollution exposure estimation. All co-authors contributed substantive guidance on the content of the manuscript.

Conflicts of Interest Statement: The authors have no conflicts of interest.

Results—Significant non-linear relationships with air pollution and CK-18 were found. Plasma CK-18 at follow-up increased from approximately 150U/L to almost 200U/L as residential traffic volume increased from 220,000vehicle-km to 330,000vehicle-km, after adjustment for baseline CK-18, age and gender. Among patients with NAFLD at baseline, CK-18 increased from 140U/L to 200U/L (a 1.5 standard deviation increase in CK-18) as NO₂ increased from 8ppb to 10ppb.

Conclusions—Traffic-related air pollution was associated with CK-18. Effects were larger in children with pre-existing NAFLD at study entry.

Key terms

NAFLD; liver; air pollution; CK-18

Prevalence of pediatric non-alcoholic fatty liver disease (NAFLD) is typically defined as hepatic fat fraction (HFF) greater than 5%.^{1,2} NAFLD prevalence is currently estimated to be 9.6% in children; however, prevalence in obese children has been reported to be as high as 38%, and it is considered to be the hepatic manifestation of metabolic syndrome.^{1,3} NAFLD encompasses a spectrum of liver abnormalities ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), a condition which can ultimately lead to cirrhosis, hepatocellular carcinoma and liver failure.¹ The development of NAFLD in adolescence can mean life-long risk to liver health, as NAFLD-related cirrhosis is the second-most common reason for liver transplantation in adults in the United States.⁴ NAFLD increases the risk for hepatocellular carcinoma, which has been reported to occur in adolescents with non-fibrotic NAFLD.⁵

Efforts to prevent and mitigate NAFLD have largely focused on weight loss and metabolic intervention to change diet and increase physical activity. However, there has been little investigation of other modifiable risk factors that might moderate the development of NAFLD or progression to NASH. Recent studies of children have found that air pollution, especially near-roadway air pollution, was associated with weight gain and obesity,^{6–9} as well as other metabolic abnormalities indicative of metabolic syndrome.¹⁰ In adults, particulate air pollution has been associated with type 2 diabetes.¹¹ In a mouse model, ambient particulate matter (PM) caused insulin resistance, increased visceral and hepatic fat deposition, and produced a NASH-like phenotype, including hepatic inflammation and ballooning.¹² Although there has been little study of the effects of air pollution on NAFLD or on progression to NASH in humans, one recent study found that hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), markers for injury to the liver, were increased in association with estimates of residential ambient particulate matter less than 2.5µm in aerodynamic diameter (PM_{2.5}) and nitrogen dioxide (NO₂), markers for traffic-related air pollution.¹³

This study investigated the relationship between air pollution and liver health in a sample of overweight and obese youth with prospectively characterized markers for NAFLD and NASH risk. We hypothesized that traffic volume on major roads near children's homes and NO₂ would result in increased hepatic fat, increased ALT and AST, and increased cytokeratin-18 (CK-18), a protein byproduct of hepatocyte apoptosis that has been found to

be an indicator of NASH risk in a pediatric population.¹⁴ Furthermore, we hypothesized that youth with NAFLD would be more susceptible to the effects of air pollution.

Methods

A secondary analysis was conducted of data from subjects in a prospective study on the pathophysiology of type 2 diabetes at the Yale Pediatric Obesity Clinic.¹⁵ Patients who were taking medications or had medical conditions that could affect lipid metabolism were excluded from study. Only patients with baseline and follow-up measurements two years later on at least one liver outcome were included in the sample. One participant with a post office box address was also excluded, as residential air pollution exposure could not be assigned. Prospectively collected measurements of hepatic fat fraction, transaminases, and CK-18 were available for 75, 70 and 53 subjects, respectively. One patient was excluded from analyses because of an outlying CK-18 measurement (larger than three SD from the mean) leading to an analytic sample of 74 for HFF, 69 for the transaminases, and 52 for CK-18. Comparison of the subjects missing CK-18 on follow-up showed no significant differences by age and sex at enrollment. In the group missing CK-18, body mass index (weight in kg/[height in m]²) z-score (BMIZ), 2.4 (SD=0.4) and ALT, 29 U/L (SD=23) were slightly higher than in the analytic sample, BMIZ 2.2 (SD=0.4) and 22 U/L (SD=11), respectively.

Hepatic fat was measured using MRI with the 2-point Dixon Technique as modified by Fishbein.¹⁶ ALT and AST were measured using standard automated kinetic enzymatic assays. Cytokeratin-18 was measured using enzyme-based immunosorbent assay.¹⁵

Residential address at enrollment was geocoded, and traffic volume assignments were made within 1km of each residential location using automated procedures in ArcGIS (ArcGIS Desktop: Release 10. Environmental Systems Research Institute, 2015. Redlands, CA.) Average daily traffic (ADT) counts were assigned for every 50 meter segment of road on a numbered highway and interstate. Residential traffic volume was estimated by summing the product of all 50 meter segments within each 1km buffer by their corresponding ADT.¹⁷

Residential two-year annual average NO₂ exposure was calculated by averaging daily NO₂ estimates over two years, starting the day of baseline measurement. These estimates were modeled using previously described prediction models.¹⁷ Briefly, between 2006 and 2009 up to four one-month NO₂ measurements (one for each season) were made using Palmes tubes¹⁸ placed outside the back door of 985 homes across Connecticut to estimate an annual average.¹⁹ NO₂ was estimated based on the 1-km residential buffer traffic volumes and 12 categories of land-use (developed, deciduous forest, coniferous forest, turf and grass, other grasses, agricultural field, water, non-forested wetland, forested wetland, tidal wetland, barn, utility rights-of-way), population density from United States Census data, elevation based on United States Geological Survey national maps, and prevailing wind direction.

Statistical Analysis

Linear regression was used to model the effect of air pollution exposure on liver outcomes at follow-up. All models were adjusted for age, sex and baseline measurement of each

outcome. Models were further assessed for non-linear relationships and effect modification by NAFLD diagnosis at baseline. Models were checked for normality of the distribution of residuals, and outcomes were transformed as appropriate to satisfy model assumption of normality of the residuals. Predicted follow-up CK-18 was calculated by exponentiation of the predicted log-CK-18 estimated by the final non-linear models.

Results

Of 74 patients in the original sample, 47 (63%) were females and 27 (36%) were males. Mean age was 14 years (standard deviation, (SD) =2.7) at enrollment (Table 1), BMIZ was 2.3 (SD=0.4), plasma CK-18 was 134 U/L (SD=40), mean hepatic fat fraction 8% (SD=11), and ALT and AST were 23 U/L (SD=16) and 25U/L (SD=20), respectively. The distribution of some outcomes were right skewed, as reflected by lower median concentrations (CK-18 123 U/L (interquartile range (IQR) 33), hepatic fat fraction 2.9% (IQR 9.9) and ALT 18 U/L (IQR 12), not tabulated). At follow-up all outcomes except CK-18 (mean 150 U/L [SD=48]) had concentrations similar to enrollment (Table 1). Twenty-nine participants (39%) had NAFLD at baseline.

Baseline sample characteristics stratified by baseline NAFLD diagnosis are shown in Table S1. Serum concentrations of CK-18 and of markers of liver injury, AST and ALT (in addition to HFF), were greater among children with NAFLD.

Traffic volume on major roads within 1km of each child's home ranged from 0 to 460,000 vehicle-kilometers, and mean traffic volume was 80,000 vehicle-kilometers (SD =99,000; Table 2). Two-year average nitrogen dioxide ranged between 3.5ppb and 11ppb. Mean NO₂ was 7.0ppb (SD=1.7).

An increase of one interquartile range (IQR) in average NO₂ (1.91ppb) was associated with 11.4 U/L greater plasma CK-18 (SE=5.4; p=0.04; Table 3). An increase of one IQR (110,000 vehicle-kilometers) of traffic volume, was associated with 15 U/L greater plasma CK-18 (Standard Error (SE) = 5.2; p<0.01). Models with quadratic terms for NO₂ and traffic volume required log-transformation of CK-18 to achieve normality in the residuals. Significant quadratic terms for each exposure indicated non-linear effects (Supplemental Tables S2 and S3). There was also a significant interaction between NAFLD at baseline with NO₂ (Table S3) but not of NAFLD with traffic volume (Table S2). There were no statistically significant associations of AST, ALT or NAFLD with traffic volume or with NO₂.

Predicted CK-18 by traffic and NO₂ exposures are shown in Figures 1 and 2, respectively. No effect was observed at lower levels of traffic volume. CK-18 increased from less than 150 U/L to almost 200 U/L over the IQR of 110,000vehicle-km (from 220,000vehicle-km to 330,000vehicle-km of traffic on interstates and major roads within a 1km residential buffer). For NO₂, little effect was observed among patients without NAFLD at baseline. However, among patients with NAFLD, there was a marked increase in CK-18 from 140 U/L to over 200 U/L (nearly 1.5 standard deviations of CK-18) as NO₂ increased from 8ppb to 10ppb at the upper end of the distribution.

Discussion

Increased CK-18 was associated with NO₂ and with traffic volume on major roads and interstates within one kilometer of participants homes in this overweight and obese population of adolescents. In addition, stronger effects were found among participants with NAFLD at study enrollment, and these differences were statistically significant for NO₂. Cytokeratin-18 is a protein fragment produced by hepatocellular apoptosis.¹⁴ Plasma CK-18 has been reported to be strongly correlated with hepatic fibrosis and has been recommended as a non-invasive marker for NASH risk in pediatric populations such as ours in which liver biopsy is not feasible.¹⁴ Stronger CK-18 association with increasing NO₂ among those with NAFLD suggests that air pollution may have promoted the progression of NAFLD in this population.

NO₂ and traffic volume are both commonly used measures of traffic-related air pollution, and in this study relatively large effects were observed at low levels of ambient exposure. For example, average annual NO₂ levels in communities in the Los Angeles Basin commonly exceed 20ppb,²⁰ compared with a maximum of 11ppb in this study, and the annual average ambient air quality standard for NO₂, set in the United States by the Environmental Protection Agency, is 53ppb.²¹ It is possible that the traffic and NO₂ exposures were proxies for other pollutants that might have had a larger range, for example PM_{2.5}, which we did not estimate. Previous studies of air pollution effects on NAFLD in animal models have been conducted with PM_{2.5}.¹² These studies found that PM_{2.5} exposure caused increased fat deposition in the liver and a NASH-like phenotype including ballooning and fibrosis. These studies also found that PM_{2.5} caused other metabolic effects, including insulin resistance and increased visceral fat, suggesting that air pollution causes NAFLD as one manifestation of the metabolic syndrome.¹¹

CK-18 is also increased in association with idiopathic pulmonary fibrosis (IPF).²² Air pollution has been implicated in acute exacerbations of IPF, but there is little evidence that air pollution causes IPF, which generally does not develop until late-adulthood.^{23,24} In addition, because associations of NO₂ with CK-18 were stronger among children with NAFLD, it is more likely that air pollution exposure reflected a hepatic source than IPF, despite not finding an association of air pollution with liver transaminases or hepatic fat.

High levels of ALT and AST can indicate disease or injury, but ALT and AST levels have large variation between individuals, and modest increased levels can have a wide variety of causes.^{25,26} Therefore, subtle effects of air pollution might not have been detected in the small sample size in this study. Additionally, we may not have detected an effect on ALT and AST due to the low exposure levels observed in the study area. One previous study found associations of NO₂ and PM_{2.5} with ALT and AST, but mean NO₂ concentration in that study was 36.2ppb compared to 7.0ppb in the present study.¹³

Although there was no association of NO₂ or traffic volume with NAFLD, the stronger association of NO₂ with CK-18 among children with NAFLD than among those without NAFLD suggests that NAFLD makes the liver vulnerable to the deleterious effects of air pollution. This pattern of association is consistent with the “multiple hit” hypothesis of the

pathophysiology of NASH;²⁷ air pollution may contribute to the development of NASH by acting as a second hit to a liver already compromised by NAFLD. If this were the case, then regulatory or other interventions to reduce air pollution exposure could potentially reduce the number and intensity of hits to the liver and the risk of development NASH. Examination of other pollutants, particularly PM_{2.5}, and of other potential confounders, including dietary intake, social or behavioral characteristics, and other factors that may be correlated with traffic-related air pollution, is needed.

A strength of this study was the prospective design which made it possible to adjust for each individual's plasma CK-18 at study entry. However, the design did not account for effects of earlier life exposures. Our findings merit further investigation to determine whether the results are reproducible and to characterize these effects at higher exposure levels.

Evidence from animal models suggests that air pollution affects multiple aspects of metabolism, including adiposity and insulin resistance. Recent epidemiologic studies have found associations of air pollution with metabolic syndrome,^{10,28} for which NAFLD is the hepatic manifestation.²⁹ This study provides novel results on potential air pollution effects on progression of NAFLD and associated risk of NASH among overweight and obese children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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List of Abbreviations

ADT	Average Daily Traffic
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
BMIZ	Body Mass Index Z-score
CK-18	Cytokeratin-18
IQR	Interquartile Range
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
NO₂	Nitrogen Dioxide
PPB	Parts per Billion

PM_{2.5}	Particulate matter less than 2.5µm in aerodynamic diameter
SD	Standard Deviation
SE	Standard Error

References

1. Paschos P, Paletas K. Non alcoholic fatty liver disease and metabolic syndrome. *Hippokratia*. 2009; 13(1):9–19. [PubMed: 19240815]
2. Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. *Clinics in Liver Disease*. 2007; 11(1):1–16. vii. [PubMed: 17544968]
3. Lavine JE, Schwimmer JB. Nonalcoholic fatty liver disease in the pediatric population. *Clinics in Liver Disease*. 2004; 8(3):549–558. viii–ix. [PubMed: 15331063]
4. Zazos P, Renner EL. Liver transplantation and non-alcoholic fatty liver disease. *World J Gastroenterol*. 2014; 20(42):15532–15538. [PubMed: 25400437]
5. Crespo M, Lappe S, Feldstein AE, Alkhouri N. Similarities and differences between pediatric and adult nonalcoholic fatty liver disease. *Metabolism*. 2016; 65(8):1161–1171. [PubMed: 26961580]
6. Jerrett M, McConnell R, Chang CC, et al. Automobile traffic around the home and attained body mass index: a longitudinal cohort study of children aged 10–18 years. *Prev Med*. 2010; 50(Suppl 1):S50–58. [PubMed: 19850068]
7. Jerrett M, McConnell R, Wolch J, et al. Traffic-related air pollution and obesity formation in children: a longitudinal, multilevel analysis. *Environmental Health*. 2014; 13(1):13–49. [PubMed: 24612632]
8. McConnell R, Shen E, Gilliland FD, et al. A Longitudinal Cohort Study of Body Mass Index and Childhood Exposure to Secondhand Tobacco Smoke and Air Pollution: The Southern California Children's Health Study. *Environmental Health Perspectives*. 2014; 123(4):360–366. [PubMed: 25389275]
9. Rundle A, Hoepner L, Hassoun A, et al. Association of Childhood Obesity With Maternal Exposure to Ambient Air Polycyclic Aromatic Hydrocarbons During Pregnancy. *American Journal of Epidemiology*. 2012; 175(11):1163–1172. [PubMed: 22505764]
10. Thiering E, Cyrus J, Kratzsch J, et al. Long-term exposure to traffic-related air pollution and insulin resistance in children: results from the GINIplus and LISAplus birth cohorts. *Diabetologia*. 2013; 56(8):1696–1704. [PubMed: 23666166]
11. Rao X, Patel P, Puett R, Rajagopalan S. Air pollution as a risk factor for type 2 diabetes. *Toxicol Sci*. 2015; 143(2):231–241. [PubMed: 25628401]
12. Zheng Z, Xu X, Zhang X, et al. Exposure to ambient particulate matter induces a NASH-like phenotype and impairs hepatic glucose metabolism in an animal model. *Journal of Hepatology*. 2013; 58(1):148–154. [PubMed: 22902548]
13. Kim KN, Lee H, Kim JH, Jung K, Lim YH, Hong YC. Physical Activity- and Alcohol-dependent Association Between Air Pollution Exposure and Elevated Liver Enzyme Levels: An Elderly Panel Study. *J Prev Med Public Health*. 2015; 48(3):151–169. [PubMed: 26081652]
14. Feldstein AE, Alkhouri N, De Vito R, Alisi A, Lopez R, Nobili V. Serum cytokeratin-18 fragment levels are useful biomarkers for nonalcoholic steatohepatitis in children. *The American Journal of Gastroenterology*. 2013; 108(9):1526–1531. [PubMed: 23752877]
15. Kim G, Giannini C, Pierpont B, et al. Longitudinal Effects of MRI-Measured Hepatic Steatosis on Biomarkers of Glucose Homeostasis and Hepatic Apoptosis in Obese Youth. *Diabetes Care*. 2013; 36(1):130–136. [PubMed: 22933439]
16. Fishbein MH, Gardner KG, Potter CJ, Schmalbrock P, Smith MA. Introduction of fast MR imaging in the assessment of hepatic steatosis. *Magn Reson Imaging*. 1997; 15(3):287–293. [PubMed: 9201675]
17. Skene KJ, Gent JF, McKay LA, Belanger K, Leaderer BP, Holford TR. Modeling effects of traffic and landscape characteristics on ambient nitrogen dioxide levels in Connecticut. *Atmos Environ* (1994). 2010; 44(39):5156–5164. [PubMed: 21076636]

18. Palmes ED, Gunnison AF, DiMaggio J, Tomczyk C. Personal sampler for nitrogen dioxide. *Am Ind Hyg Assoc J*. 1976; 37(10):570–577. [PubMed: 983946]
19. Belanger K, Holford TR, Gent JF, Hill ME, Kezik JM, Leaderer BP. Household levels of nitrogen dioxide and pediatric asthma severity. *Epidemiology*. 2013; 24(2):320–330. [PubMed: 23337243]
20. Gauderman, WJ., Urman, R., Avol, E., et al. Association of Improved Air Quality with Lung Development in Children. 2015. <http://dx.doi.org/10.1056/NEJMoa1414123>
21. US EPA. National Ambient Air Quality Standards Table. Vol. 2016. Washington, DC: US EPA; 2016 Mar 29.
22. Cha SI, Ryerson CJ, Lee JS, et al. Cleaved cytokeratin-18 is a mechanistically informative biomarker in idiopathic pulmonary fibrosis. *Respir Res*. 2012; 13:105. [PubMed: 23167970]
23. Johansson KA, Vittinghoff E, Lee K, et al. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J*. 2014; 43(4):1124–1131. [PubMed: 24176998]
24. Smith ML. Update on Pulmonary Fibrosis: Not All Fibrosis Is Created Equally. *Arch Pathol Lab Med*. 2016; 140(3):221–229. [PubMed: 26927716]
25. Giboney PT. Mildly elevated liver transaminase levels in the asymptomatic patient. *Am Fam Physician*. 2005; 71(6):1105–1110. [PubMed: 15791889]
26. Oh RC, Hustead TR. Causes and evaluation of mildly elevated liver transaminase levels. *Am Fam Physician*. 2011; 84(9):1003–1008. [PubMed: 22046940]
27. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism*. 2016; 65(8):1038–1048. [PubMed: 26823198]
28. Rao, X., Patel, P., Puett, R., Rajagopalan, S. *Toxicol Sci*. Vol. 143. United States: The Author; 2015. Air pollution as a risk factor for type 2 diabetes. Published by Oxford University Press on behalf of the Society of Toxicology For Permissions, please e-mail: journals.permissions@oup.com; 2015:231–241
29. Kim CH, Younossi ZM. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. *Cleve Clin J Med*. 2008; 75(10):721–728. [PubMed: 18939388]

What is already known about the subject

- In mouse models, exposure to air pollution caused insulin resistance, increased visceral and hepatic fat, and hepatic inflammation and ballooning. There has been little human study of hepatic effects of air pollution exposure.

What this study adds

- In this prospective study of obese children, air pollution was associated with increasing cytokeratin-18, a marker for liver injury. These effects were larger in children with pre-existing nonalcoholic fatty liver disease

Figure 1. Predicted Mean Follow-up Cytokeratin-18 (with standard errors) by Residential Traffic Volume*

*Model Adjusted for Baseline CK-18, Age and Sex

Figure 2. Predicted Mean Follow-up Plasma Cytokeratin-18 (with standard errors) by Residential Nitrogen Dioxide Exposure*

*Model Adjusted for Baseline CK-18, Age and Sex

Table 1

Sample Characteristics at Enrollment and Follow-up

Participants	Enrollment		Follow-up	
	n	Mean (SD)	n	Mean (SD)
Age, y	74	14 (2.7)	74	16 (2.8)
BMI z-score	73	2.3 (0.4)	69	2.2 (0.5)
CK-18, U/L	66	134 (40)	52	150 (48)
Hepatic Fat, %	74	7.6 (11)	74	8.8 (11)
ALT, U/L	73	25 (20)	70	23 (16)
AST, U/L	73	23 (16)	70	21 (9)

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Table 2

Distribution of Air Pollution Exposure Estimates

	n	Mean (SD)	Median (IQR)	Min.	Max.
Average daily residential traffic, within 1km (in <i>vehicle-kilometers</i>)	74	79,000 (98,000)	41,000 (11,000)	0	460,000
Two-Year Average NO ₂ (in <i>ppb</i>)	74	7.0 (1.7)	7.0 (1.9)	3.5	11

Table 3

Associations of Air Pollution Exposure with Follow-up Liver Outcomes

Air Pollution Metric	Liver Outcome at Follow-Up							
	CK-18 (N=52)		ALT (N=69)		AST (N=69)		HFF (N=74)	
	Estimate* (SE)	p	Estimate* (SE)	p	Estimate* (SE)	p	Estimate* (SE)	p
Average two-year NO ₂	11.4 (5.4)	0.04	-0.95 (1.8)	0.60	-0.39 (0.8)	0.62	-0.49 (0.9)	0.58
Average daily traffic within 1km*	14.8 (5.2)	<0.01	-1.95 (1.9)	0.31	-1.06 (0.8)	0.20	0.23 (0.9)	0.79

* Scaled to an increase of one interquartile range (1.91 ppb NO₂; 110,000 Vehicle-Km), adjusted for baseline measurement of each outcome, age, and sex.