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MINIREVIEWS

Exposure to ambient air particulate matter and non-alcoholic fatty liver disease

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Abstract

The present study was designed to alert the public opinion and policy makers on the supposed enhancing effects of exposure to ambient air particulate matter with aerodynamic diameters < 2.5 mm ($PM_{2.5}$) on non-alcoholic fatty liver disease (NAFLD), the most common chronic liver disease in Western countries. For far too long literature data have been fixated on pulmonary diseases and/or cardiovascular disease, as consequence of particulate exposure, ignoring the link between the explosion of obesity with related syndromes such as NAFLD and air pollution, the worst characteristics of nowadays civilization. In order to delineate a clear picture of this major health problem, further studies should investigate whether and at what extent cigarette smoking and exposure to ambient air $PM_{2.5}$ impact the natural history of patients with obesity-related NAFLD, *i.e.*, development of non alcoholic steatohepatitis, disease characterized by a worse prognosis due its progression towards fibrosis and hepatocarcinoma.

Key words: Non-alcoholic fatty liver disease; Particulate matter with aerodynamic diameters < 2.5 μm; Cytochrome P-450; Reactive oxygen species

Core tip: Important arguments Diesel exhaust particles are known to be major constituents of atmospheric particulate matter (PM) in metropolitan areas. Exposure to PM is positively associated with increases in the morbidity and daily mortality. Obesity-related health complications include cardiovascular disease, type 2 diabetes, hyperlipidemia, hypertension and non-alcoholic fatty liver disease (NAFLD). Exposure to ambient air PM may induce/worsen NAFLD.

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INTRODUCTION

The rising incidence of obesity in today's environment is associated with many obesity-related health complications, including cardiovascular disease, type 2 diabetes, hyperlipidemia, hypertension, and non-alcoholic fatty liver disease (NAFLD)[1-4]. This constellation is also recognized as the metabolic syndrome and is characterized by underlying insulin resistance. NAFLD or generally speaking hepatic steatosis is defined as the accumulation of lipid, primarily in the form of triacylglycerols in individuals who do not consume significant amounts of alcohol

(< 20 g ethanol/d) and in whom other known causes of steatosis, such as certain drugs and toxins, have been excluded[5]. The spectrum of NAFLD includes simple fatty liver, non alcoholic steatohepatitis (NASH) characterized by inflammation, apoptosis, ballooning degeneration, Mallory hyaline, fibrosis, cirrhosis post NASH, hepatocellular carcinoma and advanced liver disease, which leads to liver-related death[5-10].

Some epidemiological studies, deeply informed and full of insights, have demonstrated that exposure to ambient particulate matter (PM) is positively associated with increases in the morbidity and daily mortality caused by diseases, including ischemic heart disease[11,12] and chronic obstructive pulmonary disease[13,14], which are closely related to life habits. Diabetes mellitus and its complications are the other typical diseases related to life habits. Over the past several decades, prevalence of type 2 diabetes mellitus has reached epidemic levels in Western countries[15], which is a significant public health interest. The prognosis of patients with diabetes mellitus is worsened generally by a variety of complications including macro- or micro-angiopathy[16], fatty liver[17-20], nephropathy and infection in the presence or absence of overweight/obesity. Some epidemiological studies have reported a positive association between mortality in patients with diabetes mellitus and ambient levels of PM[21,22].

Air pollutants expelled from diesel engine-powered automobiles include diesel exhaust particles (DEP), which are known to be major constituents of atmospheric PM in metropolitan areas. DEP generate reactive oxygen species (ROS)[23], through a non enzymatic process[24], or enzymatic reactions catalyzed by cytochrome P-450 (Cyp)[25]. Furthermore, DEP enhance the gene expression for Cyp enzymes[25]. DEP induce a variety of biological damage at least partly through oxidative stress[25].

The present study was designed to alert the public opinion, international media and policy makers on the negative effects of exposure to ambient air particulate matter with aerodynamic diameters < 2.5 mm on NAFLD, a most common chronic liver disease in Western countries, which represents the first indication of liver transplantation.

SMOKING AND NAFLD

A growing body of evidence supports the potential effects of exposure to some environmental factors on liver diseases. Environmental exposure related to toxic waste sites was associated with an increased prevalence of autoimmune liver disease[26,27]. Therefore, increasing attention is being given to the effects of environmental factors on liver diseases, including NAFLD. Several recent studies have too reported the association of smoking with the incidence of and acceleration of disease progression in NAFLD, as well as with advanced fibrosis in this process[28-32].

Cigarette smoke exposure, whether passive or active, carries a high disease burden worldwide[33] and is considered a worldwide major cause of preventable morbidity and mortality[34].

Yuan *et al*[35] provide novel evidence demonstrating that tobacco smoke exposure may accelerate the development of experimental NAFLD. The study extends an earlier report from the group showing that in apo B transgenic mice, chronic environmental (second-hand) smoke exposure is associated to features of atherosclerotic plaque initiation[36]. Using the same model, the former authors now show that exposure to second-hand smoke potentiates steatogenesis elicited by a high-fat diet, as assessed by red oil staining and hepatic triglyceride quantification[35]. Since increased hepatic lipogenesis has been shown to account for about 30% of triglyceride accumulation in steatotic livers[37], the investigators subsequently review the impact of second-hand smoke on liver lipogenic pathways. Interestingly, cultured hepatocyte cell lines exposed to second-hand smoke display enhanced accumulation of triglycerides and increased expression of acetyl CoA carboxylase (ACC) and fatty acid synthase (FAS), two key enzymes governing hepatic synthesis of fatty acids. These data therefore indicate that the steatogenic properties of tobacco smoke are at least partly explained by a direct effect on hepatocytes.

In deciphering molecular determinants underlying tobacco-dependent activation of lipogenesis, the research focus on two key regulators of lipid metabolism, Sterol regulatory element binding protein-1c (SREBP-1c) and AMP-activated protein kinase (AMP kinase). SREBPs are a family of basic-helix-loop-helix-leucine zipper transcription factors synthesized as inactive precursors embedded in the endoplasmic reticulum[38]. Activation of SREBPs requires proteolytic cleavage, thereby allowing nuclear translocation and transcriptional activation of target lipogenic genes[39]. Whereas SREBP-2 governs synthesis of cholesterol, SREBP-1c promotes biosynthesis of fatty acids by upregulating enzymes such as ACC and FAS. The serine/threonine protein kinase AMP kinase is an energy sensor that acts as a metabolic master switch[40]. The phosphorylated active form of the enzyme simultaneously inhibits energy-consuming biosynthetic pathways such as lipogenesis and activates ATP-producing catabolic pathways such as fatty acid oxidation[40]. It has been shown that AMP kinase inhibits fatty acid synthesis both by phosphorylating target lipogenic enzymes and downregulating expression of transcription factors such as SREBP-1c[41-43]. In accordance with these data, Yuan *et al*[35] demonstrated that second-hand smoke exposure inhibits phosphorylation and activation of AMP kinase, thereby resulting in increased SREBP-1 activity and enhancement of fatty acid synthesis. Zein *et al*[44] showed that cigarette smoking were associated with increased fibrosis severity in human NALFD, suggesting it may accelerate disease progression.

Moreover, Yuan *et al*[35] extends this assumption to NAFLD and provides compelling evidence indicating that tobacco smoke might alter the regulatory effect of AMP kinase on lipid metabolism. Future studies should

closely investigate the clinical relevance of these findings. Nevertheless, in the meantime, tobacco cessation might be considered in the management of patients with NAFLD.

NAFLD AND AIR POLLUTION

The harmful effects of air pollutants on atherosclerotic cardiovascular diseases are well-documented[31]. These effects might be mediated through oxidative stress and insulin resistance[45], which are also known to have pivotal roles in the pathogenesis of fatty liver[46]. Therefore, it can be assumed that such environmental factors might be too associated with NAFLD. It is well-documented that DEP, which are major constituents of atmospheric PM in urban areas, generate ROS[47]. The ROS are generated *via* enzymatic reactions catalyzed by Cyp[48], or by a non-enzymatic route[49].

Folkmann *et al*[50] assessed the effects of oxidative stress elicited by DEP in the aorta, liver, and lungs of dyslipidemic ApoE(-/-) mice, at the age when visual plaques appeared in the aorta. Vascular effects secondary to pulmonary inflammation were omitted by injecting DEP into the peritoneum. Six hours later, the expression of inducible nitric oxide synthase mRNA increased in the liver. Injection of DEP did not induce inflammation or oxidative damage to DNA in the lungs and aorta. Therefore, the study proposed a direct effect of DEP on inflammation and oxidative damage to DNA in the liver of dyslipidemic mice[50].

Another study[51] evaluated the effects of following exposure of male C57BL/6 mice fed high fat chow to concentrated air particulate matter or filtered air for 6 wk, progression of NAFLD was evaluated by standardized histological assessment of hepatic inflammation and fibrosis. Progression of NAFLD was evaluated by histology cal examination of hepatic inflammation and fibrosis. Tan *et al*[51] indicated that ambient PM that reaches the liver has the potential to induce Kupffer cell cytokine secretion. Circulating fine PM may then accumulate in both atherosclerotic plaques and hepatic Kupffer cells[51]. The activation of cytokine release by Kupffer cells may then trigger inflammation and hepatic stellate cell collagen synthesis[51]. It is extraordinary that interleukin-6, the concentration of which increased up to 7-fold in the above-mentioned study, is too significantly abundant in cases of human NAFLD[52]. Some human studies confirmed the harmful effects of environmental toxins on liver diseases.

Cave *et al*[53] has showed that non-obese chemical workers highly exposed to vinyl chloride may develop insulin resistance and toxicant-associated steatohepatitis. Limited data exists on the potential role of environmental pollution on liver disease in the general population. Another study was conducted, by Cave *et al*[54] always, on 4582 adult participants without viral hepatitis, hemochromatosis, or alcoholic liver disease, from the National Health and Nutrition Examination Survey in 2003-2004, to investigate whether environmental pollutants are associated with an elevation in serum alanine aminotransferase (ALT) and suspected NAFLD. The ORs for ALT elevation were estabilished across exposure quartiles for 17 pollutants, after adjustments for age, race/ethnicity, sex, body mass index, poverty income ratio, and insulin resistance[54]. It showed that exposure to polychlorinated biphenyls in addition heavy metals, evident lead and mercury, was correlated with unexplained ALT elevation, and increased adjusted ORs for ALT elevation in a dose-dependent form[54].

Therefore, a growing number of studies suggest that air pollution can aggravate the adverse effects of obesity and insulin resistance[29,55,56]. Similarly, some other studies have documented the association of exposure to air pollutants with metabolic syndrome, as well as predisposition to diabetes mellitus and aggravation of its complications[57-59]. Given the inflammatory and oxidative properties of air pollutants, in addition their association with insulin resistance and metabolic syndrome, and considering the interaction of the latter conditions with fatty changes in liver, more studies about the effects of environmental factors, notably air pollution, on NAFLD are warranted. The high susceptibility of the young age group to the harmful effects of air pollutants, especially pertaining to early stages of chronic diseases[13,60-64], further stresses that more attention should be given to preventing late-onset effects of air pollutants.

FUTURE DIRECTIONS

It has been reported that ambient PM containing elementary carbon, sulfate, heavy metals, and organic compounds can cause and enhance cardiopulmonary diseases[65,66]. DEP form a large constituent of ambient urban PM. Inhalation or intratracheal instillation of DEP or the components of DEP has been shown to enhance lung inflammation and asthma[67,68], and to deteriorate biological cardiovascular functions[69]. On the other hand, cardiovascular disorders are critical participants in life habit diseases. Diabetes mellitus is another typical life habit disease and is characterized by complicated cardiovascular risk factors[70-72]. In epidemiological studies, individuals with diabetes mellitus have higher risk for death from exposure to polluted ambient air[73,74]. However, few experimental studies have elucidated the association between ambient air pollution and NAFLD.

In fact, Zein *et al*[44] showed that smoking may accelerate the progression of human NALFD and these observations may support a recommendation of smoking cessation in patients with NAFLD. This recommendation is added to the general recommendations of dietetic or lifestyle approach right for NAFLD patients[75].

As reported by Tan *et al*[51], exposure to ambient air particulate matter with aerodynamic diameters < 2.5 μm ($PM_{2.5}$) may be a significant risk factor for NAFLD progression. In other words, could air pollution be the so-called "second hit", according to the well-known theory?

A better understanding of the impact of ambient PM

exposure on NAFLD progression may require studies utilizing a variety of ambient PM sources[51].

CONCLUSION

So far it has been known that $PM_{2.5}$ result from fuel combustion (motor vehicles, power generation, industrial facilities), residential fireplaces and wood stoves. $PM_{2.5}$ are usually selected as indicators of air pollution since those particles cause morbidity[76]. In fact, $PM_{2.5}$ alone exposure could cause inflammation *via* tumor necrosis factor alpha[77], endothelial function and autonomic nervous system injuries, ozone potentiating these effects[78].

Further studies should investigate the effects of long-lasting exposures to cigarette smoking and to ambient air $PM_{2.5}$ on specific pathways of the hepatic metabolism, better delineating the cellular and molecular mechanisms involved. Importantly, very informative reports should clarify whether cigarette smoking, habit started at very young age, and early exposure to ambient air $PM_{2.5}$ impact the obesity, also the adolescents' one, and the obesity-related NAFLD, favouring development of NASH, disease characterized by a worse prognosis due its progression towards fibrosis, liver cirrhosis and hepatocarcinoma.

By modifying the natural history of patients with NAFLD, air pollution adds a new argument in the debate of regulating the toxic emissions.

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