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Combined Lifestyle and Air Pollution Drivers of Liver Injury: A Literature Review

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MASLD; PM2.5; Unhealthy Lifestyle; Liver Injury; Oxidative Stress.

ABSTRACT

This literature review aimed to summarize recent studies regarding the combined effects of unhealthy lifestyle behaviors and air pollution exposure on the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). A literature search was conducted using the ScienceDirect and PubMed databases from December 2025 onward. Relevant studies examining the relationship between air pollution, lifestyle factors, and MASLD or hepatic injury were identified using Medical Subject Headings (MeSH) terms and free-text keywords related to MASLD, particulate matter ($PM_{2.5}$), unhealthy lifestyle behaviors, inflammation, oxidative stress, and metabolic dysfunction. Eligible articles included original research and review articles published in English that investigated hepatic outcomes associated with lifestyle factors and/or particulate matter exposure. Evidence indicates that both particulate matter exposure and lifestyle-related factors, including unhealthy dietary patterns, sedentary behavior, smoking, alcohol consumption, and circadian rhythm disruption, independently contribute to liver injury through shared biological mechanisms. These mechanisms include inflammation, oxidative stress, insulin resistance, mitochondrial dysfunction, and gut dysbiosis. Exposure to $PM_{2.5}$ promotes reactive oxygen species (ROS) generation, activation of Kupffer cells (KCs), stimulation of hepatic stellate cells (HSCs), and the release of pro-inflammatory cytokines. Meanwhile, unhealthy lifestyle behaviors contribute to metabolic imbalance and impaired antioxidant defense mechanisms. Emerging evidence suggests that the coexistence of high air pollution exposure and unhealthy lifestyle patterns produces synergistic effects that accelerate hepatic steatosis, inflammation, fibrosis, and progression toward MASLD. The combined effects of prolonged particulate matter exposure and unhealthy lifestyle behaviors represent important and underrecognized contributors to MASLD progression. Understanding the underlying pathophysiological mechanisms of these combined exposures may support the development of more comprehensive prevention and intervention strategies.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), progresses through several stages. It initially develops as metabolic dysfunction-associated steatosis (MASL), progresses to metabolic dysfunction-associated steatohepatitis (MASH), and may subsequently lead to hepatic fibrosis and, ultimately, liver cirrhosis (EASL-EASD-EASO, 2024; Sindato et al., 2025). MASLD is recognized as the most common risk factor for chronic liver disease (CLD), with recent global meta-analysis data indicating that it affects more than 38% of adults and 7%–14% of children, with prevalence continuing to increase (Younossi et al., 2023; Paik et al., 2022). MASLD has therefore become a rapidly emerging global health concern with substantial impacts on healthcare systems, economies, and societies worldwide (Guo et al., 2022).

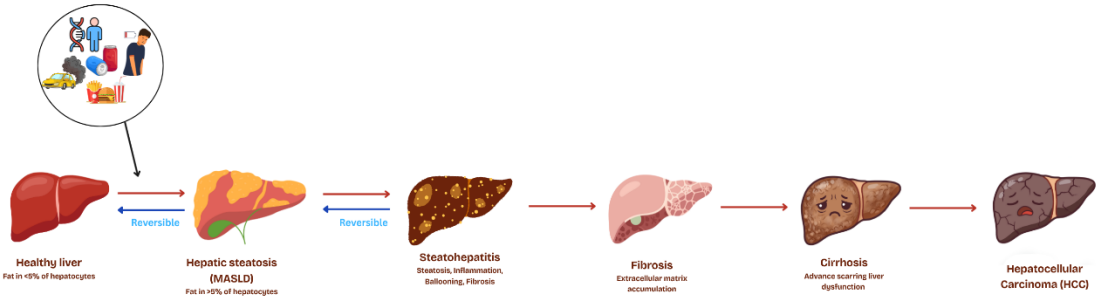

Figure 1. Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) from Steatosis to Hepatocellular Carcinoma

The development of MASLD is strongly associated with obesity, which represents one of the major risk factors for this condition (Mitra et al., 2020). Overweight and obesity increase the risk of type 2 diabetes mellitus, arterial hypertension, atherosclerosis, cardiovascular disease (Wasniewska et al., 2023; Di Bonito et al., 2023), and metabolic dysfunction-associated steatotic liver disease (MASLD), along with various other comorbidities and complications (Portincasa et al., 2024). Furthermore, the increasing prevalence of sedentary behavior and reduced physical activity contributes to the rising incidence of obesity and metabolic syndrome-related disorders, including MASLD (Mitra et al., 2020).

Lifestyle factors, including smoking, alcohol consumption, dietary patterns, physical activity, and sleep behavior, play important roles in regulating hepatic lipid metabolism (Li et al., 2026). The mechanisms through which unhealthy lifestyles contribute to hepatic injury involve altered inflammation-related gene expression, dysregulation of lipid metabolism pathways, increased oxidative stress, and changes in gut microbiome-derived metabolites (Iannone et al., 2023). Recent studies have demonstrated a global increase in the consumption of ultra-processed foods and sedentary lifestyles, which are closely correlated with rising obesity rates and metabolic disorders, thereby accelerating the progression of hepatic injury (Shu et al., 2023; Monda et al., 2024; Amrynia & Prameswari, 2022).

In addition to lifestyle-related determinants, MASLD is increasingly recognized as a multifactorial disease in which environmental pollutants, including particulate matter, may contribute to hepatic injury pathogenesis. Particulate matter ($PM_{2.5}$) is a fine airborne pollutant characterized by an aerodynamic diameter of less than 2.5 μm (Lim & Thurston, 2019). $PM_{2.5}$ can cross the air–blood barrier and enter systemic circulation, allowing it to reach various organs, including the nervous system, cardiovascular system, and liver, where it may contribute to metabolic disturbances and organ dysfunction (Bulot et al., 2019). Several studies have demonstrated that $PM_{2.5}$ exposure is associated with an increased risk of metabolic disorders and related conditions, including hypertension and diabetes (Li et al., 2021; Mannucci & Ancona, 2021; Sofianopoulou et al., 2019; Zhang et al., 2021).

The biological mechanisms through which $PM_{2.5}$ contributes to liver injury include increased oxidative stress, inflammatory activation, and promotion of fibrosis. $PM_{2.5}$ exposure can also disrupt plasma lipid profiles and hepatic lipid metabolism, thereby exacerbating systemic and liver-specific inflammation (Yang et al., 2021; Wang et al., 2021). Furthermore,

$PM_{2.5}$ may disturb oxidative balance and induce oxidative damage, leading to hepatic stellate cell activation (Lin et al., 2022). With prolonged exposure, $PM_{2.5}$ particles may accumulate in Kupffer cells, triggering inflammatory responses and stimulating collagen production by hepatic stellate cells (Guo et al., 2023). These mechanisms contribute to hepatocellular injury and subsequent release of liver enzymes into the bloodstream, which may explain the elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) observed among individuals exposed to higher $PM_{2.5}$ concentrations (Dales et al., 2023).

Long-term exposure to air pollutants combined with unhealthy lifestyle behaviors is associated with an increased risk of developing MASLD. Individuals exposed to higher levels of ambient air pollution while simultaneously engaging in unhealthy lifestyle practices demonstrate a higher incidence of MASLD compared with those exposed to either risk factor alone (Kong et al., 2024). Previous studies have largely examined air pollutants and lifestyle factors independently in relation to MASLD risk, overlooking their combined effects and potential interactions, which may provide important insights into disease development and support the development of more effective MASLD prevention strategies (Younossi et al. 2025).

Conducting a literature review on this topic is important for understanding how lifestyle factors and $PM_{2.5}$ exposure jointly influence the development and progression of liver injury. Although numerous studies have examined these determinants individually, evidence regarding their combined or synergistic effects remains limited. Therefore, this review aimed to summarize the interactions between air pollution exposure and unhealthy lifestyle behaviors in contributing to the development and progression of MASLD.

The novelty of this review lies in its integrated examination of converging molecular pathways, including oxidative stress, insulin resistance, mitochondrial dysfunction, and inflammasome activation, through which lifestyle factors and air pollution jointly contribute to hepatic injury. By bridging traditionally separate areas of research on behavioral and environmental determinants of liver disease, this review provides a comprehensive framework for understanding synergistic mechanisms. The objectives of this review were to: (1) synthesize epidemiological and experimental evidence regarding the individual and combined effects of lifestyle factors and air pollution on liver health; (2) elucidate overlapping molecular mechanisms underlying hepatic injury; and (3) identify implications for integrated prevention strategies. This review contributes to future research on gene–environment interactions, informs public health strategies addressing both behavioral and environmental determinants, and highlights opportunities for multilevel interventions. These findings may benefit researchers, clinicians, and policymakers seeking to address the complex and multifactorial nature of MASLD prevention amid rapid urbanization and environmental change.

METHOD

An electronic literature search was conducted using PubMed and ScienceDirect in December 2025 to identify relevant studies examining the effects of air pollution and lifestyle factors on the development of MASLD. The search strategy combined Medical Subject Headings (MeSH) terms in PubMed with free-text keywords related to MASLD, air pollution, and unhealthy lifestyle factors in ScienceDirect.

The PubMed search strategy was as follows, with similar terms adapted for other databases: (("Metabolic Dysfunction-Associated Steatotic Liver Disease"[Mesh] OR "Non-alcoholic Fatty Liver Disease"[Mesh] OR MASLD OR NAFLD OR "fatty liver") AND ("Air Pollution"[Mesh] OR "Particulate Matter"[Mesh] OR "$PM_{2.5}$" OR "Environmental Exposure"[Mesh]) AND ("Life Style"[Mesh] OR lifestyle OR "Sedentary Behavior"[Mesh] OR "Diet"[Mesh] OR "Physical Activity"[Mesh] OR "Exercise"[Mesh] OR "Smoking"[Mesh] OR "sleep" OR "sleep duration" OR "unhealthy lifestyle")).

The inclusion criteria consisted of full-text articles that investigated the effects of lifestyle factors (smoking, diet, physical activity, or circadian rhythm) and air pollution exposure on MASLD/NAFLD or hepatic steatosis; reported outcomes related to liver injury markers, metabolic dysfunction, or hepatic inflammation; and were original research articles or reviews published in English. Studies involving animal or in vitro models, focusing on liver disorders unrelated to MASLD, or lacking full-text availability were excluded. All identified articles were initially screened based on titles and abstracts, followed by full-text assessment according to the predefined inclusion and exclusion criteria.

RESULTS AND DISCUSSION

Air Pollution as an Environmental Trigger

Recent epidemiological studies have explored the role of air pollution as a main driver of liver injury. Chronic exposure to air pollutions such as Particulate matter (PM2.5), Nitrogen Dioxide (NO2), and Carbon Monoxide (CO) contributes as a risk factor for liver damage. Several cohort studies explained that prolonged exposure to PM2.5 was associated with an elevated risk of Non-Alcoholic Fatty Liver Disease (NAFLD) in China (Deng et al., 2023), the United Kingdom (Li et al., 2023), and Taiwan Region (Sun et al., 2022). In addition, there is a consistent positive correlation between air pollution and the increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) which are the main biomarkers of hepatocellular injury (Dales et al., 2023).

The inhalation of PM2.5 into pulmonary alveoli can directly enter the bloodstream and finally reach the liver because of its tiny size. These particles may accumulate in the liver, then interact with Kupffer cells and hepatocytes (Xing et al., 2023), and subsequently induce oxidative stress by activating hepatic stellate cell (Lin et al., 2022). Mechanistically, the translocation of particles induces excessive production of reactive oxygen species (ROS), activates pro-inflammatory signalling pathways, and interrupt lipid metabolism, therefore promoting hepatic steatosis, fibrosis, and progression to cirrhosis or hepatocellular carcinoma (HCC) (Li et al., 2023).

Furthermore, recent findings suggest that the impact of air pollution goes beyond direct translocation, involving the lung-gut-liver axis. Inhaled PM2.5 not only causes lung injury but also compromises gut and liver barrier integrity by amplifying oxidative stress, promoting chronic inflammation, and accelerating the lung and liver injury progression (Iaccarino et al., 2025). The long exposure of PM2.5 may reduce the beneficial bacteria such as Lactobacillus and Bifidobacterium, of pro-inflammatory bacteria including Desulfovibrio and Oscillibacter. This microbial imbalance (dysbiosis) leads to elevated intestinal permeability and facilitating the translocation of lipopolysaccharide into the portal circulation (Zhao et al., 2022).

Ultimately, it will accumulate in the liver and leads to inflammation and fibrosis (Fu et al., 2025) which triggers the activation of stellate cells and lipid dysregulation (Xiao et al., 2024).

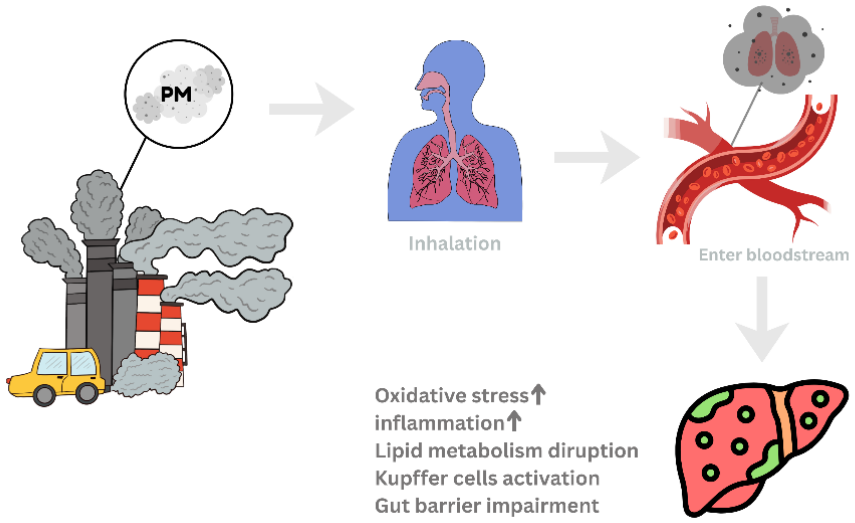

Figure 2. Pathophysiological Pathway of Air Pollution-Induced Liver Injury Through PM2.5 Exposure

Modern Lifestyle Drivers

Beside the important of air pollution exposure, the pathogenesis of liver injury is basically driven by modern lifestyle habits, which often act in tandem with air pollution exposure. Several studies have revealed that the exposure of air pollution together with poor behaviour such as smoking, alcohol consumption, bad diet habits, low physical activity, and sedentary lifestyle may increase the risk of liver disease (Guo et al., 2022; Deng et al., 2023; Li et al., 2023; Sun et al., 2022; VoPham et al., 2022). A large scale study conducted by Wang et al. has proved that Body Mass Index (BMI) is a significant moderator and mediator of the relationship between air pollution and the risk of liver injury (Wang et al., 2025).

Beyond dietary habits, sedentary lifestyle and low physical activity play as a major risk factor for metabolic syndrome. The harmful effect of physical inactivity may cause metabolic syndrome that leads to hepatic injury (Bovolini et al., 2020), through pathways implicate metabolic imbalance, insulin resistance (IR), and enhanced accumulation of hepatic lipid (Kim et al., 2020; Han et al., 2023; Heredia et al., 2022; Zhang et al., 2023).

In addition to diets and low physical activity, smoking and alcohol intake can worsen the onset of liver injury. Smoking may enhance the progression of liver injury through insulin resistance and hepatic fat accumulation which are the main cause to metabolic liver injury (El-Azab et al., 2025). The substances in cigarette smoke such as nicotine, nitrosamine, hydrocarbons, and many carcinogens have a deleterious effect by inducing oxidative stress, mitochondrial dysfunction, and pro-fibrotic signalling that leads to liver injury and fibrosis (Rutledge & Asgharpour, 2020; Marti-Aguado et al., 2022; Premkumar & Anand, 2021; Hashizume et al., 2023; Mihara & Hori, 2024; Kanamori et al., 2024; Li et al., 2025). It also elevated the production of Reactive Oxygen Species (ROS) alongside simultaneous weakening of antioxidant defences such as glutathione (Distefano et al., 2024; Koregol et al., 2020), that results in lipid peroxidation, DNA damage, and hepatocyte apoptosis (Mears et al., 2025; Magna et al., 2024). Many research suggests that even a "moderate" alcohol

consumption can exacerbate mitochondrial oxidative stress, aggravate inflammatory activity, and cause fibrogenesis in MASLD patients (Marti-Aguado et al., 2024). Alcohol metabolism, especially through CYP2E1 induction, results in an accumulation of reducing equivalents (NADH) and a direct increase in reactive oxygen species (ROS) generation, leading to disturbance of the NAD^+/NADH balance and depravation of mitochondrial electron transport chain (ETC) function (Zhang et al., 2025). Mitochondrial ROS accumulation compromises oxidative phosphorylation (OXPHOS), decreases ATP production, and induces transient hyperpolarization of the mitochondrial membrane potential ($\Delta\Psi m$), followed by its collapse, ultimately promoting cytochrome c release and activation of the intrinsic apoptotic pathway (Rice et al., 2024).

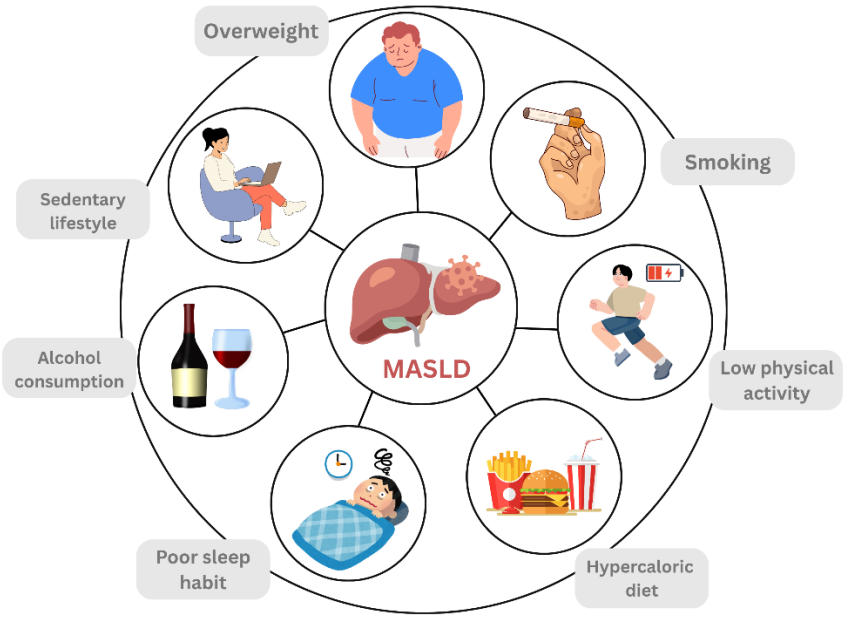

Figure 3. Contribution of Modern Lifestyle Factors to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

The Synergy: Interaction Between Air Pollution and Lifestyle

The collaboration of air pollution and unhealthy lifestyle factors result to synergistic effect that significantly increases the progression of hepatic injury. Lifestyle factors such as high-fat diet, low physical activity, alcohol intake, and cigarette smoking worsen the negative effect of air pollution in the liver (Guo et al., 2022). Study by Kong et al. explain that long exposure to air pollutants combined with unhealthy lifestyle, were significantly associated with a higher risk of liver disorder occurrence. Lifestyle factors emerged as a primary contributor to liver injury, explaining approximately 37% of the population level. Notably, the most significant risk of hepatic injury was identified in participants who experiencing both high level of air pollutant exposure and the worst lifestyle profiles (Kong et al., 2024).

Study by Wang et al. define that Body Mass Index plays a vital role in both mediating and modifying the relationship between air pollutant exposure and the developing of liver injury (Wang et al., 2025). Long exposure to air pollution is connected to oxidative stress and systemic inflammation, while chronic inflammation created by obesity may exacerbate disruptions in lipid metabolism induced by air pollutant exposure (Wang et al., 2022).

Moreover, the impairment of lung-gut-axis play an important role to this synergetic effect, as an unhealthy diet compromises intestinal barrier integrity, that may allow the entry of inhaled pollutants and gut microbiota to more readily reach the liver via portal circulation (Iaccarino et al., 2025). Dysbiosis and bothered gut barrier function results to the translocation of microbial product into blood circulation causing hepatic inflammation and immune activation (Pasta et al., 2025).

Alcohol consumption was identified as an alteration effect between the relationship of air pollution and the risk of liver injury. Epidemiological study by Li et al., based on UK Biobank identified that individuals who consume alcohol may experience a greater susceptibility to the toxic effects of air pollution on the progression of liver injury (Li et al., 2023). The metabolism of alcohol plays a crucial role in shaping hepatic redox environment and encouraging lipotoxicity in fatty liver disease (Acierno et al., 2025). The disruption in redox homeostasis ruin hepatic fatty acid oxidation and inhibits gluconeogenesis, ultimately promoting triglyceride accumulation and develop hepatic steatosis (Arumugam et al., 2023).

Low physical activity and sedentary behaviour may synergistically interact with air pollution to aggravates the development of liver injury. Sedentary lifestyle is a recognized risk factor for the progression and development of fatty liver disease, meanwhile high physical activity may reduce hepatic fat accumulation, hepatic inflammation, and fibrosis (Baker et al., 2021). Extended sedentary duration was connected to a greater prevalence of increased ALT and GGT levels (Li et al., 2020). In addition, sedentary lifestyle has been affiliated with gut microbiota dysbiosis and impaired intestinal barrier integrity, which may cause the translocation of inhaled pollutants and microbial products to the liver via the portal circulation (Tilg et al., 2022). Findings from UK biobank study suggest that insufficient physical activity elevates hepatic vulnerability to environmental factors, including PM2.5 (Wang et al., 2025). Collectively, this suggest that low physical activity strengthen the bad effects of air pollution, thereby accelerating liver injury and the onset of metabolic dysfunction–associated steatotic liver disease (MASLD).

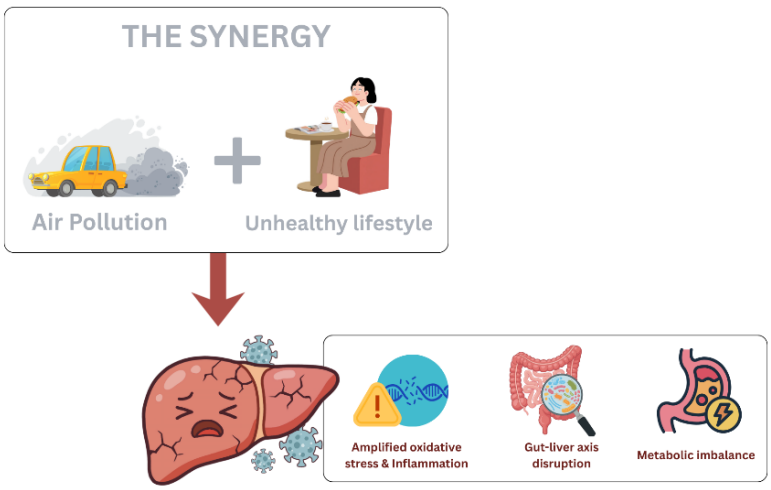

Figure 4. Synergistic Effects of Air Pollution and Unhealthy Lifestyle on Liver Injury Progression

Common Pathophysiological Mechanism

The pathophysiology of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is multifactorial, including insulin resistance (IR), mitochondrial dysfunction, inflammation, and oxidative stress. The pathological progression of MASLD is marked by "three-strike" progress, that is steatosis, lipotoxicity, and hepatic inflammation (Pafili & Roden, 2021). These mechanisms lead to violent cycle that encourage the progression of MASLD, to fibrosis, and eventually, cirrhosis (Bril et al., 2024; Bo et al., 2024).

Insulin resistance (IR) is the main driver of the progression of MASLD (Kuchay et al., 2025), arising from long term exposure to particulate matter (Huang et al., 2026) and the imbalance of diet consumption (Lee et al., 2025) both of which promote fat accumulation in the liver (Lee et al., 2023). Under physiological conditions, insulin regulates hepatic glucose metabolism by encouraging de novo lipogenesis (DNL) and suppressing gluconeogenesis (Lee et al., 2023). However, under IR condition, when the arm of insulin signalling that supresses gluconeogenesis is blunted, the arm that enhance DNL is not distinctly prohibited. The phenomenon called selective insulin resistance (Bo et al., 2024), not only disrupt intrahepatic metabolic regulation, but also participates to systemic metabolic dysregulation comprising other organs.

Mechanistically, increased intracellular free fatty acid (FFA) can elevate diacylglycerol (DAG) via re-esterification and escalate ceramide levels via serine-palmitoyl transferase-mediated synthesis. Increased level of DAG and ceramides inhibit the recruitment of AKT to the plasma membrane and disrupts hepatic insulin signaling (Bo et al., 2024). Within this framework, the liver and adipose tissue engage in reciprocal cross talk during both fasting and postprandial condition...These procedures are integrated within the "multiple-hit" hypothesis, which inter-organ metabolic imbalance, especially between adipose tissue and the liver, contributes to progressive fat accumulation and worsening insulin resistance in MASLD (Lee et al., 2025).

The lipid accumulation and cellular stress in the liver subsequently agitate the activation of Kupffer cells (KCs), the resident macrophage on the liver (Cai et al., 2026; Zhao et al., 2025). Due to the exposure of particulate matter or gut-derived endotoxins, KCs become activated and release pro-inflammatory cytokines including interleukin-6 (IL-6) which binds with IL-6R/gp130 complex on hepatocytes to activating JAK signalling pathway, then stimulate the activation of STAT3. As a transcription factor, the activation of STAT3 elevates the transcription of CCNG1 gene which promote TP53 degradation. When TP53 is degenerate, hepatocyte apoptosis increases significantly (Song et al., 2026). Furthermore, KCs also secrete another proinflammatory cytokine e.g. tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 18 (IL-18), and interleukin 10 (IL-10) to facilitate the recruitment of immune cells to the location of injury (Taru et al., 2024). These cytokines magnify the hepatic inflammatory response, encourage hepatocyte damage, and worsen IR by disturbing the intracellular insulin signalling pathways (Zhao et al., 2025; Chen et al., 2025).

Moreover, mitochondrial dysfunction emerges as a key mechanism that links insulin resistance and oxidative stress to the progression of hepatic damage. In patient with MASLD, hepatic mitochondria are changed structurally and molecularly (Einer et al., 2018). Initially, mitochondria aim to compensate for fat accumulation by elevating fatty acid oxidation. However, due to the increasing burden of free fatty acid (FFA), this mechanism is insufficient.

The excess FFA are subsequently turn into triglyceride synthesis, contributing to the development of hepatic steatosis (Li et al., 2019).

The elevated influx of FFA into mitochondria also increases uncoupling protein 2 (UCP2), which escalates mitochondrial respiration while degrading ATP production, thereby contributing to the production of reactive oxygen species (ROS). These ROS further aggravate cellular injury by impairing respiratory chain activity and inducing mutations in mitochondrial DNA (mtDNA) (Shin et al., 2023). When the efficiency of respiratory chain deteriorates, mitochondria cannot fully oxidize excess FFAs. Furthermore, extra-mitochondrial oxidation pathways are increasingly recruited, resulting in the generation of lipid peroxidation products and additional ROS (Su et al., 2019). These reactive compounds harm mtDNA and mitochondrial proteins e.g. cytochrome c oxidase and the adenine nucleotide translocator, resulting mitochondrial dysfunction (Surugihalli et al., 2019).

When mitochondrial dysfunction occurs, oxidative stress and inflammatory signals activate pathways including nuclear factor kappa B (NF-κB) (Morio et al., 2021), and c-Jun N-terminal kinase (JNK) and indirectly by increasing the appearance of inflammatory cytokines, such as TNF-α and TGF-β, which participate to the development of MASLD (Shin et al., 2023).

Furthermore, oxidative stress plays an important role, characterized by an imbalance between hepatic antioxidant defense mechanism and the over production of pro-oxidant such as ROS. This inconvenience, along with elevated free radical generation in the gut and adipose tissue, resulting hepatocyte apoptosis and tissue damage (Masarone et al., 2018; Chen et al., 2020).

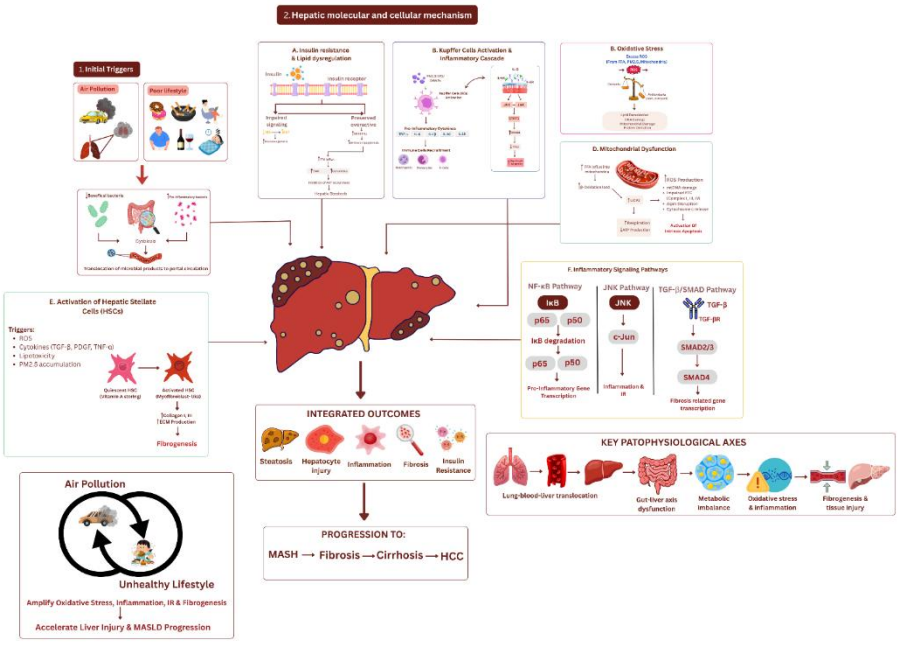

Figure 5. Integrated Pathophysiological Mechanisms Linking Environmental Exposure and Lifestyle Factors in MASLD Development

CONCLUSION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a major global health burden arising from complex interactions among environmental stressors, metabolic disturbances, and lifestyle behaviors. This literature review highlights that air pollution, particularly particulate matter exposure, combined with unhealthy lifestyle behaviors may contribute to liver injury through several mechanisms, including inflammation, insulin resistance (IR), oxidative stress, and mitochondrial dysfunction.

Notably, recent evidence suggests that these risk factors do not act independently but instead exert synergistic effects that accelerate disease progression. Air pollution exposure can disrupt hepatic lipid metabolism, promote inflammatory responses, and impair gut–liver axis integrity. Furthermore, unhealthy lifestyle factors, including poor dietary habits, sedentary behavior, smoking, and alcohol consumption, may aggravate disease development. Together, these factors amplify metabolic dysregulation, exacerbate hepatic steatosis, and increase susceptibility to fibrosis and progressive liver injury.

The combination of these risk factors creates a pathological cycle involving insulin resistance, Kupffer cell activation, oxidative stress, and mitochondrial dysregulation, ultimately leading to progressive hepatic injury. The integration of these pathways within the "multiple-hit" hypothesis provides a comprehensive framework for understanding MASLD progression in the context of modern lifestyle and environmental exposures.

Despite growing evidence, current research remains limited regarding the combined and interactive effects of air pollution and lifestyle behaviors, as most studies have examined these factors separately. Therefore, future studies should focus on elucidating synergistic mechanisms through longitudinal and mechanistic investigations.

REFERENCES

Acierno, C., Barletta, F., Caturano, A., Nevola, R., Sasso, F. C., Adinolfi, L. E., & Rinaldi, L. (2025). Alcohol consumption and liver metabolism in the era of MASLD: Integrating nutritional and pathophysiological insights. *Nutrients, 17*(13), 2229.

Amrynia, S., & Prameswari, G. (2022). Hubungan pola makan, sedentary lifestyle, dan durasi tidur dengan kejadian gizi lebih pada remaja: Studi kasus di SMA Negeri 1 Demak. *Indonesian Journal of Public Health Nutrition, 2*, 112–121.

Arumugam, M. K., Gopal, T., Kalari Kandy, R. R., Boopathy, L. K., Perumal, S. K., Ganesan, M., Rasineni, K., Donohue, T. M., Jr., Osna, N. A., & Kharbanda, K. K. (2023). Mitochondrial dysfunction-associated mechanisms in the development of chronic liver diseases. *Biology, 12*(10), 1311.

Baker, C. J., Martinez-Huenchullan, S. F., D'Souza, M., et al. (2021). Effect of exercise on hepatic steatosis: Are benefits seen without dietary intervention? A systematic review and meta-analysis. *Journal of Diabetes, 13*, 63–77.

Bovolini, A., Garcia, J., Andrade, M. A., & Duarte, J. A. (2020). Relative contribution of fat diet and physical inactivity to the development of metabolic syndrome and non-alcoholic fatty liver disease in Wistar rats. *Physiology & Behavior, 225*, 113040.

Bril, F., Kalavalapalli, S., Lomonaco, R., Frye, R., Godinez Leiva, E., & Cusi, K. (2024). Insulin resistance is an integral feature of MASLD even in the presence of PNPLA3 variants. *JHEP Reports, 6*(7), 101092.

Bulot, F. M. J., Johnston, S. J., Basford, P. J., Easton, N. H. C., Apetroaie-Cristea, M., Foster, G. L., Morris, A. K. R., Cox, S. J., & Loxham, M. (2019). Long-term field comparison

of multiple low-cost particulate matter sensors in an outdoor urban environment. *Scientific Reports, 9*, 1–13.

Cai, Q., Chen, Y., & Tang, L. (2026). Kupffer cells: Orchestrators of liver physiology. *Liver Research*.

Chen, L., Guillot, A., & Tacke, F. (2025). Reviewing the function of macrophages in liver disease. *Expert Review of Gastroenterology & Hepatology, 19*(6), 621–637. https://doi.org/10.1080/17474124.2025.2508963

Chen, Z., Tian, R., She, Z., Cai, J., & Li, H. (2020). Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. *Free Radical Biology and Medicine, 152*, 116–141.

Dales, R., Mitchell, K., Lukina, A., Brook, J., Karthikeyan, S., & Cakmak, S. (2023). Does ambient air pollution influence biochemical markers of liver injury? Findings of a cross-sectional population-based survey. *Chemosphere, 340*, 139859.

Deng, P., Tang, H., Zhu, L., Duan, J., Li, F., Li, Y., Wang, J., Wu, J., Meng, C., Wang, W., Yang, Y., Chen, Z., Wang, J., Yuan, H., Huang, Z., Cai, J., & Lu, Y. (2023). Association of long-term ambient fine particulate matter (PM2.5) and incident non-alcoholic fatty liver disease in Chinese adults. *Environmental Pollution, 329*, 121666.

Di Bonito, P., Di Sessa, A., Licenziati, M. R., Corica, D., Wasniewska, M., Umano, G. R., Morandi, A., Maffeis, C., Faienza, M. F., Mozzillo, E., Calcaterra, V., Franco, F., Maltoni, G., & Valerio, G. (2023). Is metabolic syndrome useful for identifying youths with obesity at risk for NAFLD? *Children, 10*(2), 233.

Distefano, A., Orlando, L., Partsinevelos, K., Longhitano, L., Emma, R., Caruso, M., et al. (2024). Comparative evaluation of cigarette smoke and a heated tobacco product on microglial toxicity, oxidative stress and inflammatory response. *Journal of Translational Medicine, 22*(1), 876.

El-Azab, G., Elkhouly, E., Abouyoussef, R., & Nagdy, H. (2025). Smoking and liver diseases: An updated review of pathogenesis, progression, and therapeutic implications. *Clinical and Experimental Medicine, 26*(1), 51.

Einer, C., Hohenester, S., Wimmer, R., Wottke, L., Artmann, R., Schulz, S., et al. (2018). Mitochondrial adaptation in steatotic mice. *Mitochondrion, 40*, 1–12.

Guo, B., Guo, Y., Nima, Q., Feng, Y., Wang, Z., Lu, R., Baimayangji, Ma, Y., Zhou, J., Xu, H., Chen, L., Chen, G., Li, S., Tong, H., Ding, X., & Zhao, X. (2022). Exposure to air pollution is associated with an increased risk of metabolic dysfunction-associated fatty liver disease. *Journal of Hepatology, 76*(3), 518–525.

Guo, B., Huang, S., Li, S., Han, X., Lin, H., Li, Y., Qin, Z., Jiang, X., Wang, Z., Pan, Y., Zhang, J., Yin, J., & China Multi-Ethnic Cohort (CMEC) Collaborative Group. (2023). Long-term exposure to ambient PM2.5 and its constituents is associated with MAFLD. *JHEP Reports, 5*(12), 100912.

Han, Q., Han, X., Wang, X., Wang, C., Mao, M., Tang, S., et al. (2023). Association of accelerometer-measured sedentary behavior patterns with nonalcoholic fatty liver disease among older adults: The MIND-China study. *American Journal of Gastroenterology, 118*, 569–573.

Hashizume, T., Ishikawa, S., Matsumura, K., Ito, S., & Fukushima, T. (2023). Chemical and in vitro toxicological comparison of emissions from a heated tobacco product and the 1R6F reference cigarette. *Toxicology Reports, 10*, 281–292.

Heredia, N. I., Zhang, X., Balakrishnan, M., Daniel, C. R., Hwang, J. P., McNeill, L. H., et al. (2022). Physical activity and diet quality in relation to non-alcoholic fatty liver disease: A cross-sectional study in a representative sample of U.S. adults using NHANES 2017–2018. *Preventive Medicine, 154*, 106903.

Huang, H. Y., Huang, Y. Y., Wu, C. L., Huang, W. C., & Lai, C. H. (2026). Smog, sugar, and synapses: Unraveling the PM2.5-insulin resistance-Alzheimer's disease axis. *Redox*

Biology, 90, 104031.
Iaccarino, J., Mignini, I., Maresca, R., Giansanti, G., Esposto, G., Borriello, R., et al. (2025). The impact of air pollution on the lung-gut-liver axis: Oxidative stress and its role in liver disease. *Antioxidants, 14*(10), 1148.
Iannone, V., Lok, J., Babu, A. F., Gómez-Gallego, C., Willman, R. M., Koistinen, V. M., Klåvus, A., Kettunen, M. I., & Kårlund, A. (2023). Associations of altered hepatic gene expression in American lifestyle-induced obesity syndrome diet-fed mice with metabolic changes during NAFLD development and progression. *Journal of Nutritional Biochemistry, 115*, 109009.
Kanamori, K., Ahmad, S. M., Hamid, A., & Lutfy, K. (2024). Chronic exposure to e-cigarettes elevates CYP2A5 activity, protein expression, and cotinine-induced production of reactive oxygen species in mice. *Drug Metabolism and Disposition, 52*(3), 171–179.
Kim, D., Vazquez-Montesino, L. M., Li, A. A., Cholankeril, G., & Ahmed, A. (2020). Inadequate physical activity and sedentary behavior are independent predictors of nonalcoholic fatty liver disease. *Hepatology, 72*, 1556–1568.
Kong, X., Huang, R., Geng, R., Wu, J., Li, J., Wu, Y., et al. (2024). Associations of ambient air pollution and lifestyle with the risk of NAFLD: A population-based cohort study. *BMC Public Health, 24*(1), 2354.
Koregol, A. C., Kalburgi, N. B., Pattanashetty, P., Warad, S., Shirigeri, N. S., & Hunasikatti, V. C. (2020). Effect of smokeless tobacco use on salivary glutathione levels among chronic periodontitis patients before and after non-surgical periodontal therapy. *Tobacco Prevention & Cessation, 6*, 15.
Kuchay, M. S., Choudhary, N. S., & Molina, B. R. (2025). Pathophysiological underpinnings of metabolic dysfunction-associated steatotic liver disease. *American Journal of Physiology-Cell Physiology, 328*, C1637–C1666.