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Commentary

NAFLD's possible link to exposure to environmental contaminants and overnutrition

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Over the past two decades, global rise in insulin resistance, obesity, and metabolic syndrome has led to a corresponding increase in nonalcoholic fatty liver disease (NAFLD) [1]. Particularly, NAFLD represents the hepatic manifestation of metabolic syndrome and is characterized by hepatic fat accumulation exceeding 5% in the absence of excessive alcohol consumption, hepatotoxic medication use, or other established liver diseases such as viral hepatitis [2]. Functionally, NAFLD encompasses two primary subtypes - (i) nonalcoholic fatty liver (NAFL), also known as metabolic dysfunction-associated steatotic liver (MASL), and (ii) nonalcoholic steatohepatitis (NASH), now known as metabolic dysfunction-associated steatohepatitis (MASH) [3]. NASH/MASH is increasingly referred to as metabolic dysfunction-associated steatotic liver disease (MASLD) in the current literature. Global prevalence of NAFLD ranges from 20% to 30%, with higher incidence rates documented in the Middle East, South Asia, and Southeast Asia [4–7]. Prevalence of NAFLD increases with age, particularly in post-menopausal women [8]. Current estimates indicate that NAFLD has reached epidemic proportions, affecting approximately 30.2% of all adults, 57.5% of adults with obesity, 14.3% of children, and 38.0% of children with obesity as of 2023 [9]. These figures translate to over 2.4 billion adults and 315 million children worldwide as of 2023, a number that has been steadily increasing and is projected to rise further. **Figure 1** schematically illustrates various aspects of nonalcoholic fatty liver disease (NAFLD).

Excessive energy intake from saturated fats, fructose, sugar-sweetened beverages, and refined carbohydrates is linked to weight gain and obesity—key contributors to NAFLD development [10]. Nut consumption has been contraindicated in NAFLD management, while prolonged soft drink intake shows prospective association with markers of liver injury, particularly elevated alanine aminotransferase (ALT) levels—an indicator of liver inflammation that may develop following NAFLD onset [11,12]. Healthy diet, in comparison to weight reduction, is recommended for the management of NAFLD [13]. Emerging therapeutic approaches include pegozafermin, a PEGylated form of fibroblast growth factor 21 (FGF21), currently in Phase 3 clinical trials. As a master metabolic regulator, FGF21 ameliorates hypertriglyceridemia, insulin resistance, obesity, and NAFLD through receptor-mediated mechanisms [14].

Various animal models have been developed to investigate NAFLD pathogenesis and the progression to steatohepatitis (NASH). These models incorporate either genetic modifications or dietary manipulations. Genetic models include sterol regulatory element binding protein (SREBP) transgenic mice, as well as Ob/ob, Db/db, KK-Ay, PTEN-null, PPARα-knockout, AOX-deficient, and

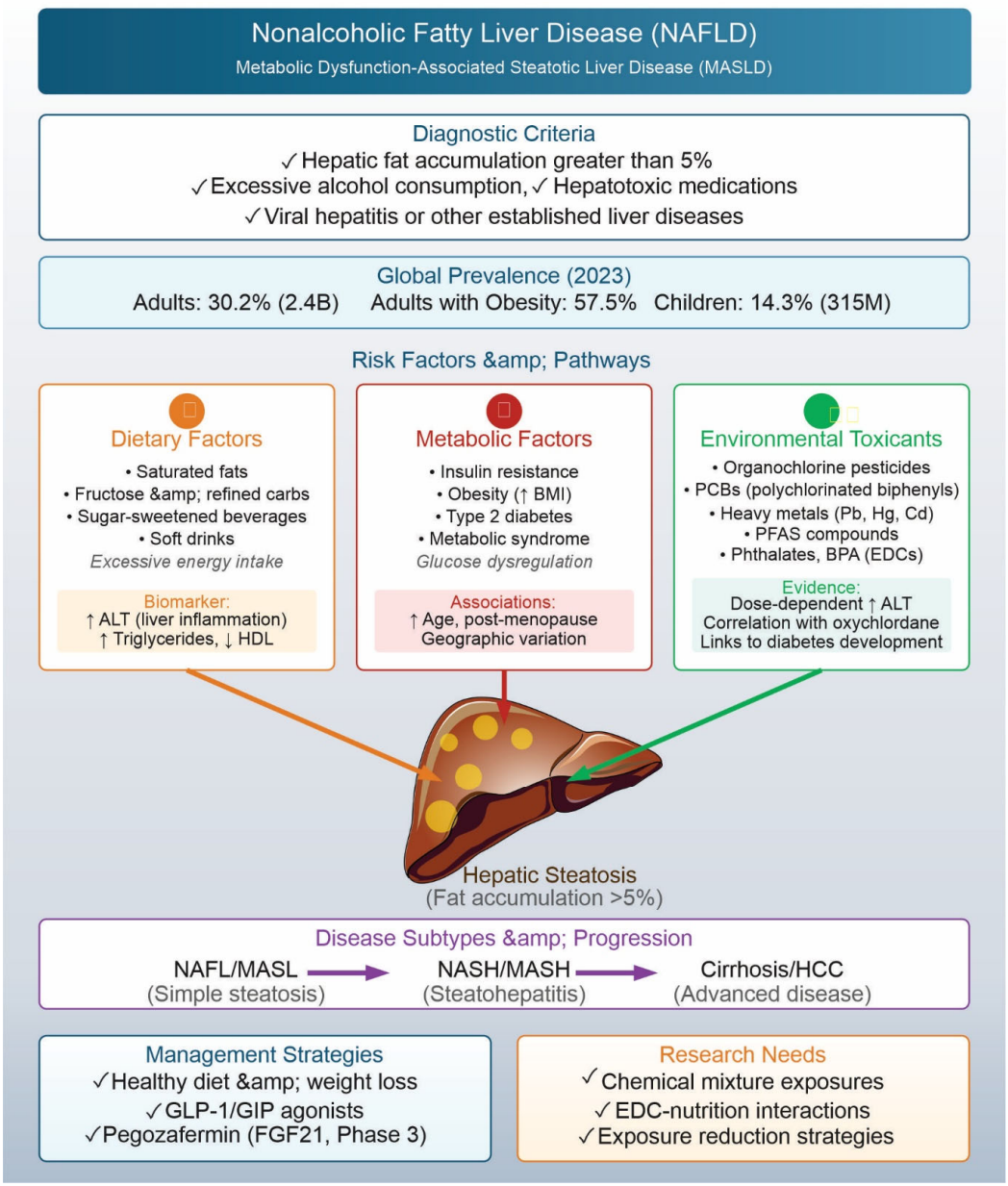

Figure 1. Schematic illustration of various aspects of nonalcoholic fatty liver disease (NAFLD).

MTA1A-deficient mice. Dietary models utilize excessive cholesterol or fructose supplementation, or methionine- and choline-deficient diets [15]. These animal studies underscore nutrition's critical role in NAFLD development, particularly among diabetic and obese older adults. Beyond caloric content, dietary contamination with persistent organic pollutants (POPs), including organochlorine (OC) insecticides, many of which function as endocrine-disrupting chemicals (EDCs), has emerged as a significant concern in NAFLD pathogenesis. Animal studies show that exposure to these environmental contaminants may contribute to fat accumulation in liver. Oxychlordane level is correlated with NAFLD in humans while other OC insecticides were not directly associated with NAFLD. However, pesticides, like *p, p-DDT, p'p'-DDE* are linked to increase in BMI, triglycerides, insulin resistance, and reductions in HDL cholesterol, ailments very common to NAFLD—NAFLD is common to individuals with obesity, metabolic syndrome, and insulin resistance [16]. Serum ALT levels serve as one biomarker for monitoring NAFLD, though with limitations. Population studies reveal that low-level exposures to environmental toxicants demonstrate dose-dependent associations with elevated ALT levels and increased odds ratios for suspected NAFLD in the general U.S. adult population [17]. These environmental toxicants include polychlorinated biphenyls (PCB), phthalates, bisphenol A, mercury, lead, and cadmium are known risk factors of NAFLD while limited

link between PFAS and NAFLD warrants further research [18,19]. Data from NHANES (2003–2004) indicate significantly elevated liver enzyme levels among individuals with the highest PCB and OC insecticide exposures. Accumulating epidemiological and toxicological evidence supports associations between environmental chemical exposures, particularly PCBs, and NAFLD development [20]. The levels of ALT are not confirmed markers of NALFD; however, its levels are increased during liver injury, alcoholic fatty liver disease, and viral liver infection [21,22]. Consequently, using ALT levels to monitor fatty liver disease following industrial chemical exposure has limited reliability [23,24]. The established links between mercury, lead, and liver disease suggest that multiple environmental contaminants may act synergistically, creating conditions that promote hepatic steatosis [25–27].

Exposure to environmental chemicals, such as OC insecticides and other pesticides, are linked to the incidences of diabetes and are components involved in the development of NAFLD. Older women who handled pesticides for agricultural activities in Iowa and North Carolina were found to report higher incidence of diabetes [28]. In addition to OC insecticides, specifically dieldrin, and potentially dioxin-contaminated herbicides, 2,4,5-T and 2,4,5-TP, demonstrated associations with diabetes [29,30]. Besides OC insecticide, exposure to certain organophosphates (OP) also increases the risk of diabetes [28]. Similarly, presence of OC insecticide correlated with the risk of diabetes among North Indian population [31]. Higher levels of β-hexachlorocyclohexane (γ-HCH), dieldrin, and *p,p'-DDE*, a metabolite of *p,p'-DDT,* were found in the prediabetes and newly detected diabetic groups as compared to normal glucose tolerance group [31]. The accidental and occupational exposure are reported to modify glucose metabolism, therefore increased risk of type 2 diabetes, and insulin resistance [32,33]. The prevalence of diabetes among people exposed to OP correlated well with the hemoglobin A1c diabetic levels, while chronic treatment of mice with OP for 180 days produced glucose intolerance [34].

Many of the POPs are endocrine disruptors with possible link to development of fatty liver [35]. Animal exposure studies with perfluoralkyl acids (PFAAs), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorononanoicacid (PFNA) induce hepatic steatosis [36,37]. Industrial exposure with vinyl chloride increases the sensitivity of hepatosteatosis after high fat diet [18]. Non-POPs, industrial chemicals, such as drugs for chronic usage (e.g., amiodarone, valproic acid, tetracycline, methotrexate, and corticosteroids) are implicated in hepatosteatosis in humans [38–41].

Taken all, current epidemiological surveys inadequately elucidate the complex etiology underlying the burgeoning incidence of diabetes and its relationship to NAFLD. The confluence of POP exposure, industrial chemical contamination, antibiotic usage, and medications for cardiovascular disease appear to increase hepatic lipid accumulation risk, particularly in the context of contemporary overnutrition. Weight loss management through glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptor agonist therapy not only improves glycemic control but also reduces hepatic fat content. However, comprehensive animal studies examining defined chemical mixtures are needed to establish definitive links between exposures to environmental chemical mixture and NAFLD development. The worldwide prevalence of NAFLD suggests significant environmental contributions, particularly given the widespread application of OCs, POPs, and OPs. Biological researcher must investigate the combined effects of OC/POP/OP mixture exposure in overnutrition settings to demonstrate whether concurrent nutritional and environmental toxicant/EDC exposures can induce NAFLD. While genetic factors undoubtedly contribute to disease susceptibility, the relatively recent emergence of dietary contaminants that were absent a century ago may represent a critical, modifiable risk factor for NAFLD development. Thorough investigation of these environmental-nutritional interactions could enable risk remediation through exposure reduction strategies and informed development of targeted therapeutic interventions against chemically induced hepatic steatosis.

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