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HISTOLOGICAL AND ULTRASTRUCTURAL ADAPTATION OF THE LIVER TO EXERCISE, DIETARY PATTERN AND ENVIRONMENTAL STRESSORS: A NARRATIVE REVIEW

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ABSTRACT

Background: The liver is a highly plastic organ, remodeling at the histological and ultrastructural level in response to physiological and environmental demands. Exercise, dietary pattern and environmental stressors are all known to modify liver structure but are usually studied separately and from a metabolic rather than a histomorphological perspective.

Aims: This narrative review brings together and critically compares recent evidence (2022-2026) on liver histological and ultrastructural adaptation across these three-exposure area, contradiction, identifying shared mechanism and knowledge gaps.

Findings: The same factors were repeated in all three areas: lipid handling, oxidative balance, mitochondrial function and zonal susceptibility. Together they made a common, mostly non-specific pattern of liver damage including inflammation, steatosis and hepatocyte degeneration. The difference was mainly in the direction of the effect. Exercise protected the liver while dietary excess and environmental toxicants damaged it. The effects reported were also highly dose- and species-dependent, as illustrated by the contrasting responses of the liver to fructose in rodent's vs larger animals. A limitation that pervades much of this research is that whereas animal studies can directly examine the liver using histology, human studies must depend on non-invasive surrogate measures.

Conclusion: Recognizing the mechanistic convergence across exposure, addressing biological sex and combined exposure and adopting emerging digital pathology and spatial omics approaches are priorities for advancing a currently fragmented field.

Keywords: Hepatic histology, Liver zonation, Digital pathology, Dietary steatosis, Hepatotoxicity, Exercise adaptation and metabolic dysfunction- associated liver disease (MASLD)

1 INTRODUCTION

The liver holds a special place among the internal organs. It has a dual blood supply and a great potential to regenerate and plays a crucial function in coordinating the metabolism of the whole body. Alongside its conventional role in detoxification, protein synthesis and bile generation, liver tissue is continuously rebuilt at the microscopic level to meet physiological and environmental needs. It is this structural plasticity that distinguishes the liver from many other organs and makes it a particularly good model for investigating how external stimuli are translated into observable histologic change.

The clinical significance of this adaptability is exemplified by the increasing global burden of disease of metabolic liver disease. Metabolic dysfunction-associated steatotic liver disease (MASLD) is predicted to affect 16.1% of the world population, or 1.3 billion people in 2023, with a significant prevalence in the Middle East and North Africa region [1]. Since lifestyle related exposures (diet, physical exercise and environmental stressors) are recognized modifiable contributors to this burden, recognizing their direct histological impact on liver tissue is of both mechanistic and translational interest. While there is a considerable amount of work on each of these exposures individually, most of the available reviews consider exercise, food and environmental stressors as independent areas of inquiry. They also tend to look at them from a metabolic or molecular signaling standpoint as opposed to a histomorphological one. To our knowledge, few narrative syntheses have compared these three domains at the level of tissue and cellular architecture, or critically assessed where their reported effects coincide, diverge or remain unresolved. This fragmentation hinders researchers and physicians in identifying common molecular pathways that may be responsible for histology response in seemingly unrelated situations.

This narrative review intends to: 1: synthesize recent histological and ultrastructural findings on liver adaptation to exercise, dietary patterns and four environmental stressors (heat stress, pesticides, air specific matter and heavy metals). 2: examine findings critically across various categories, noting areas of agreement and contradiction. 3: suggest possible explanations for discordant findings and 4: point out areas of ignorance to guide future studies. The review is not a systematic comprehensive synthesis. It is not a systematic review, however, but a critically assessed integrated narrative account, the aim of which is to pull together a body of information that is currently dispersed.

2 METHODS: SEARCH STRATEGY AND SELECTION CRITERIA

This narrative review is based on a structured non-systematic literature search of peer reviewed literature. We performed a search of PubMed/MEDLINE, Scopus, Web of science and ScienceDirect for articles published between January 2022 and 2026 using the combination of the term's hepatic, liver, histology, steatosis, ultrastructure, exercise, ''physical activity, MASLD/NAFLD, diet, fructose, high fat, caloric restriction, cadmium, heat stress, heavy metals, pesticides, air pollution and particulate matters. We chose the 2022-2026 window to highlight the most current findings primarily due to the recent clarification of steatotic liver disease nomenclature and the rapid increase of tissue level and spatial analytic tools throughout this time.

Older landmark studies were included if they were critical to the definition of core concepts, mechanisms or terminology such as the foundational description of hepatic metabolic zonation. High-quality recent reviews and human trials where available were only given priority over original research with direct histology or ultrastructural endpoints, where applicable. Studies were selected on the basis of relevance to hepatic structural adaptation rather than on the basis of a formal quantitative screen and thus this review represents a critically appraised narrative synthesis rather than a systematic review or meta-analysis and no formal risk of bias assessment or quantitative pooling was performed. This approach has been deliberately chosen to facilitate an integrative, cross domain comparison although this does entail the limitations of narrative synthesis which are described below.

3 LIVER HISTOARCHITECTURE: STRUCTURAL BACKGROUND

The primary anatomical and functional unit of the liver is the hepatic lobule. It is arranged peripherally around a portal triad (hepatic artery, portal vein and bile duct) and centrally around a central vein. Hepatocytes constitute around 70-80% of the liver's cell mass and are organized according to a well-recognized phenomenon known as metabolic zonation. This organization leads to functional zonation of cells into periportal (zone 1), midzonal (zone 2) and pericentral (zone 3) populations along gradients of oxygen, nutrients and signaling chemicals [2,3]. Such spatial division of labor allows different processes such as gluconeogenesis and glycolysis to occur in the same organ without interfering with each other [4].

The hepatic sinusoids are lined by fenestrated endothelial cells and contain Kupffer cells, the resident macrophages of the liver, responsible for immunological monitoring and clearing gut generated antigens. In normal settings the principal storage

location for vitamin A is the hepatic stellate cells which are in the space of Disse. However, upon activation they switch to a myofibroblast similar collagen generating phenotype. This process is important to fibrosis [5]. Such cellular and zonal heterogeneity gives rise to varying susceptibilities of various parts of the liver to distinct types of injury. For instance, pericentral hepatocytes are particularly hypoxic and more susceptible to oxidative and toxic assaults. Periportal zones are the first to come into contact with entering nutrients and xenobiotics [3]. This zonal susceptibility concept is used throughout the next sections as a means of interpreting how exercise, food and environmental stressors produce unique zone-specific histology fingerprints.

3.1 Hepatic adaptation to exercise

Physical activity is now a first line intervention of MASLD management. But the histology foundation of its actions on the liver demands more consideration than the typical statement of "liver fat reduction" suggests. Evidence is derived from two different forms of investigation. In human trials practically all the measurements are non-intrusive, however in animal research liver tissue and ultrastructure can be directly examined. At the heart of understanding the field is the integration of these two kinds of evidence.

Regular aerobic and resistance training significantly lower liver fat in persons with MASLD. Cuthbertson et colleagues employed a previously verified threshold of at least 30% relative reduction in liver fat as assessed by MRI. They argued that exercise may influence histological features other than steatosis including fibrosis even when weight reduction is moderate (<3%) [6]. This ''weight neutral'' benefit is essential mechanistically. It shows that exercise has effects on liver tissue not only through fat loss dependent mechanisms [7].

A major restriction, however, is that there are essentially no human trials that explicitly look at liver histology. Repeated biopsy is limited by ethical and practical issues, hence imaging measures (MRI-PDFF, elastography) and serum biomarkers are used rather than tissue level assessment. This leads to an inferential gap. Histological improvement is inferred from reduction in liver fat but the underlying cellular changes (lipid droplet dynamics in hepatocytes, Kupffer cell activation and stellate cell quiescence) are mostly unseen in people.

Animal models address this deficiency and provide a more comprehensive understanding. Studies on rodents have shown that endurance training lowers the buildup of lipids in hepatocytes and increases mitochondrial biogenesis, which is accompanied by increased PGC-1 α and SIRT3 signaling [8]. Long-term aerobic training in Wistar rats decreased mitochondrial dysfunction and oxidative stress that come with getting older in liver tissue. This was done by increasing the activity of antioxidant enzymes and decreasing lipid peroxidation [9]. In line with this, a study of several tissues showed how mitochondria adapt over time in rat tissue and found molecular responses specific to endurance training in the liver, this shows that hepatic mitochondria respond actively to exercise [10].

The animal literature is not homogeneous however, and its contradictions are instructive. High intensity interval training (HIIT) and moderate intensity continuous training (CT) have been compared in rodent models and resulted in different outcomes. Some data indicate that CT enhances hepatic mitochondrial biogenesis and fatty liver markers better than HIIT [8] in human, but the situation is more settled: a systematic review and meta-analysis of 19 trials (745 participants) showed that HIIT and moderate intensity continuous training resulted in similar reductions in MRI-measured liver fat (-2.85% and -3.14%, respectively) with no significant difference between them (-34%, 95% CI -2.20 to 1.52) [11]. This apparent discordance between rodent and human data is itself instructive and there are several factors which may account for it.

First, species specific metabolic scaling means that rodent exercise protocols do not translate linearly to human training intensities. Second, "HIIT and CT are inconsistently defined across studies in terms of duration, frequency, and relative intensity, which makes it difficult to compare them directly. Third, the outcome measures differ fundamentally: rodent studies report molecular and histological endpoints, whereas human studies report imaging measures, so apparent contradiction may reflect a mismatch in measurement rather a true biological disagreement. Another theme not yet resolved is the role of biological sex in hepatic exercise adaptation, which has been understudied despite evidence of sex differences in liver mitochondrial responses. This gap is especially relevant in view of the known sex differences in MASLD prevalence and progression [12].

Summary, Exercise reliably improves hepatic lipid and mitochondrial parameters in models. However, there is a translational gap in the research, with the richest histologic evidence in animals and the most therapeutically important groups only studied indirectly. Closing this gap (using verified noninvasive histology assessments or developing imaging-based approaches) is a focus for future development.

3.2 Hepatic adaptation to dietary patterns

food composition is arguably the factor which has the most direct and reproducible histological influence on the liver of the three areas studied here. As opposed to exercise, where there is limited human histology data, food effects have been well documented at the tissue level, mostly in animal models. This has resulted in a detailed, but not fully consistent. Imagine High-fat, high-fructose diets reproducibly yield the histologic features of human steatotic liver disease in rodents. High fat and sugar diets induce a gradual cascade beginning with macrovesicular steatosis, progressing to hepatocyte ballooning, lobular inflammation and ultimately fibrosis [13,14]. In the well documented DIAMOND mouse model a Western diet plus a fructose-glucose solution resulted in macrovesicular steatosis and a higher steatosis activity score within 8 weeks. Steatohepatitis (the inflammatory, progressive type of the disease, termed as metabolic dysfunction-associated steatohepatitis or MASH) and Mallory-Denk bodies developed over 16-24 weeks and hepatocellular carcinoma developed with continuous feeding [13]. These models are appreciated precisely because their histologic progression mimics that of human illness.

The relative impacts of specific dietary components are still debated nevertheless and the research here is informatively contradictory. While fructose is frequently implicated as a main cause of de novo lipogenesis and histological damage, its effects are remarkable in their dose and species dependency. Very high fructose consumption (>60% of calories) resulted in significant buildup of hepatic lipids in rodents. In pigs, a similar high fructose diet did not elicit steatosis or hepatocellular ballooning, but rather moderate inflammatory and connective tissue alterations [15]. This divergence is mechanistically telling. Thus, the fructose-steatosis link observed in rats may not be applicable to species with distinct metabolic structures, indicating a need for caution when directly applying findings to human contexts.

Another element that could alter the interpretation of these results is sex. In a 6-month model of high-fat, high-fructose diet, hepatocellular ballooning was statistically significant only in females, whereas males displayed numerical increases in several histological markers that were not statistically significant [16]. These results indicate that the hepatic response to dietary challenges may be gender-dependent and underline the need to include both genders in experimental research. Therefore, studies including only one sex may miss crucial biological distinctions and limit the broader applicability of their findings.

Much of the deleterious food effects above have been derived from animal histology. In contrast, the protective end of the dietary spectrum has been researched predominantly in humans and so is more consistent but dominated by surrogate rather than histological endpoints. Continuous or intermittent caloric restriction improves hepatic steatosis in patients with MASLD. A randomized controlled experiment demonstrated the effectiveness of both intermittent (5:2) and continuous restriction in reducing liver fat with no significant benefit of the intermittent scheme when the caloric deficit was matched .

This underlines that the operative variable is total calorie restriction, not meal timing [17]. Another study showed that intermittent restriction is safe and superior to standard therapy in reducing steatosis, especially in obese patients [18].

In addition to the general restriction of energy, the quality of the diet per se modifies the hepatic histology, and the most documented protective pattern has been the Mediterranean diet. It is the proposed pattern of diet according to current clinical guidelines for MASLD. In the randomized controlled MEDINA study, adherence to a Mediterranean diet reduced intrahepatic lipid content by approximately 39% and improved insulin resistance during a short time of intervention 19 . A larger randomized trial of 250 adults with MASLD found that the Mediterranean and low fat diets were equally effective at reducing steatosis and fibrosis and that the PNPLA3 risk genotype did not modify the response suggesting that the histological benefit is driven by improved diet quality and accompanying weight reduction rather than a specific macronutrient profile [20]. This is a repetition of a topic that runs through the nutrition literature, that the direction of change (beneficial or detrimental) is less dependent on any individual nutrient than on the total energy balance and dietary pattern.

A common constraint throughout the food literature is the use of imaging and biochemical surrogates in humans against direct histology in animals, the same translational asymmetry found in the exercise field. Therefore, it remains weakly documented whether the clinically observed positive fat fraction changes reflect a true reversal of ballooning inflammation or early fibrosis at the tissue level. This is a serious information gap especially for the preventive dietary measures currently extensively advised.

3.3 Hepatic adaptation to environmental stressors

Of the three sectors, environmental exposures are the least standardized, but provide some of the clearest direct histology data, as tissue evaluation is a routine main endpoint in toxicological research. The hepatic environmental stressor spectrum

is broad and we consider here four of the best characterized categories (heavy metals, thermal or heat stress, air particulate matter and pesticides) that together highlight both the reproducibility and interpretive challenges of the literature.

Heavy metals are among the most investigated liver toxicants at the histological level. Cadmium and lead induce a distinctive pattern of tissue injury, including lobular disorganization, vacuolar and hydropic degeneration of hepatocytes, sinusoidal congestion, inflammatory infiltration and, with chronic exposure, necrosis and early fibrosis [21]. The combined exposure of lead and cadmium in mice promotes oxidative stress markers (upregulated malondialdehyde with altered superoxide dismutase activity) and affects hepatic lipid metabolism. Thus, structural damage is coupled with considerable metabolic disturbance [22]. The common mechanism is oxidative stress because these no redox metals reduce antioxidant defenses and trigger lipid peroxidation. Pericentral hepatocytes are more vulnerable, in keeping with the model of zonal susceptibility described above.

Thermal stress results in a partially overlapping but distinct histological signature. Chronic heat exposure in broiler models induces microvesicular steatosis, hepatocyte degeneration and apoptosis mediated by endoplasmic reticulum stress and unfolded protein response [23]. Broadly, the heat-induced hepatic changes observed in the different cattle species are classified into degenerative changes (fatty and hydropic degeneration), necrosis, circulatory abnormalities (congestion, bleeding) and inflammatory foci [24]. More recent mechanistic study points to chaperone-mediated autophagy-mediated ferroptosis (an iron-dependent form of cell death triggered by lipid peroxidation) in heat-induced hepatocyte injury [25]. This broadens the known spectrum of cell-death processes beyond classical apoptosis and necrosis.

More recently, air particulate matter has been identified as a stressor to the liver. Epidemiological data associate fine particulate matter (PM2.5) exposure with MASLD and in animal models, PM2.5 exposure causes substantial histological alteration.

In a seven months mouse model with an environmentally realistic exposure (~50 g/m3), PM2.5 cp exposure was an independent modifier of hepatic pathology on a western diet, significantly increasing serum alanine aminotransferase (~55%) and collagen deposition area (4.7-fold) compared to diet alone [26]. Mechanistically, PM2.5 has been associated with lipid accumulation in hepatocytes, mitochondrial dysfunction, and inflammatory and epigenetic changes favoring steatosis [27]. This exposure leads to a steatotic and fibrotic signature that mimics histopathology of nutritional damage, supporting the hypothesis of molecular convergence discussed below.

A fourth class is pesticides. This is directly relevant to the liver due to the important role of the liver in the metabolism of xenobiotics. Repeated correlations of organophosphate pesticides (e.g. chlorpyrifos) with hepatic steatosis, oxidative stress, and disturbance of lipid metabolism have been described [27]. In a systematic review [28], the available studies reported a consistent connection between the exposure to organophosphate residues and NAFLD. The sinusoidal dilation, the centrilobular changes, the degradation of the hepatocytes, and the inflammatory infiltration with oxidative stress and mitochondrial dysfunction are described at tissue level as a repeating mechanism after exposure to organophosphates [29]. For the other environmental categories much of this information is from high dosage animal or in vitro exposure with extrapolation to typical human residual levels problematic.

A major interpretive limitation in this area is that most studies of environmental hepatotoxicity are conducted in nonmammalian, or agricultural species (broilers, fish, goat) chosen for economic or ecological relevance rather than for translational fidelity to human liver biology. In particular, the research on heat stress is predominantly from poultry and animals who have very different hepatic thermoregulatory physiology to humans. This raises the question whether the reported histological markers are representative of preserved liver responses or of species-specific susceptibility. The contrast is made plain in few main texts.

A further problem is that practically all investigations use supraphysiological or sudden high dose exposures. They maximize the detectable histological harm but are poor indicators of the chronic, low level, mixed exposures typical in real human circumstances. In studies at environmentally relevant doses, more subtle and more regular (adaptive) responses are usually observed, not frank tissue damage. These results imply that the significant histologic changes commonly described may overestimate the damage occurring at realistic levels of exposure. This difference in relevance of dosage parallels the fructose dose dependence found in the nutritional arena and is a common methodological difficulty in the environmental research.

Importantly, many of the histological characteristics observed in these four categories (steatosis, degeneration, hepatocyte, oxidative stress driven injury and with chronic exposure, fibrosis) are significantly overlapping with those induced by

hypercaloric diets. This suggests a common downstream mechanism beyond the usual divide of these research areas. The next section looks at that confluence.

3.4 Integrative analysis: convergent mechanism and comparative perspective

Examining the three domains of exposure in combination rather than in isolation, reveals a shared set of mechanical threads. This combination is rarely made explicit in the current research, which tends to treat these disciplines in isolation.

The most visible convergence is mechanical. In all three regions, oxidative stress and altered lipid handling are common end-routes that repeat themselves, albeit in different directions. Exercise improves liver antioxidant defenses and mitochondrial efficiency, whereas hypercaloric diets and environmental toxicants overload these mechanisms, leading to lipid peroxidation and mitochondrial dysfunction.

The result is histologically an identifiable, generally nonspecific damage profile (steatosis, hepatocyte degeneration or ballooning and inflammatory infiltration) that develops independently of the initiating insult, which is dietary, toxicological or thermal as represented in Table 2. The absolute importance of this definition lessness. This implies that exposure history and molecular markers should be incorporated in the interpretation of tissue level data and that histology alone is not adequate to correctly identify the causative exposure.

A second convergent motif is zonal patterning. Due to metabolic zonation pericentral (zone3) hepatocytes are relatively hypoxic and rich in oxidative metabolism and are therefore selectively sensitive to oxidative and toxic damage upon recurrent exposures. Periportal zones are the major location of nutrition and xenobiotic inflow [2,3]. This gives a single common anatomical explanation for the fact that diverse insults that seem unrelated can produce lesions that are overlapping and zone-specific.

A third prevalent pattern is that effects depend on dose and context. The fructose-steatosis relationship is greatly attenuated across species [15]. Effects of environmental toxicants at realistic exposure levels are diminished. Benefits of exercise vary by modality and intensity. Extrapolation from experimental settings at high doses to physiologically relevant human exposures introduce significant uncertainty in each area. All these comparisons are impeded by a methodological asymmetry that constrains the whole area. In humans, most evidence comes from non-invasive surrogates, while direct histologic and ultrastructural data are obtained almost exclusively from animal models, often with questionable translational accuracy. The greatest constant limitation in the explored area is divergence. Table 1 includes representative research from each exposure location and shows the diversity of experimental techniques used and the consistent use of surrogate versus tissue level endpoints.

There are encouraging signs that emerging methods may narrow this gap. Combing digital pathology with artificial-intelligence based image analysis and spatial omics is beginning to transform how liver tissue is examined. These approaches enable quantitative, reproducible and spatially resolved characterization of steatohepatitis that goes beyond conventional semi quantitative scoring [30]. They hold particular promise for detecting the subtle, zone-specific adaptations that traditional histological grading may miss and for eventually connecting animal histology with non-invasive human assessment.

Table 1: Summary of representative studies on hepatic structural responses across exposure domains.

Author (Year)	Study design	Population / Model	Exposure	Main histological / structural finding	Key limitation
Cuthbertson et al. (2024)	Intervention analysis	Adults with MASLD	Aerobic + resistance exercise	≥30% relative reduction in MRI-measured liver fat; possible fibrosis benefit independent of weight loss	Imaging surrogate, not tissue histology
Montero-Vallejo et al. (2024)	Preclinical review	Rodent (DIAMOND and others)	Western / high-fat–high-fructose diet	Sequential macrovesicular steatosis → ballooning → steatohepatitis → fibrosis / HCC	Species-to-human translation

Makri et al. (2024)	Experimental	Mice (both sexes)	6-month HFD + fructose-glucose	Elevated NAFLD activity score; hepatocellular ballooning significant only in females	Single model; sex-limited significance
Schmidt et al. (2021)	Experimental	Pigs	High-fructose (60%) diet	No steatosis or ballooning; only mild inflammatory / connective-tissue change	Contradicts rodent data
Chen et al. (2023)	Experimental	Mice	Combined lead–cadmium	Increased oxidative stress (↑MDA, altered SOD); disrupted hepatic lipid metabolism	High-dose; combined exposure
Ma et al. (2022)	Experimental	Broilers	Chronic heat stress	Microvesicular steatosis; ER-stress-mediated hepatocyte apoptosis	Non-mammalian species
PM2.5 rodent model (2026)	Experimental	Mice (7-month)	Chronic PM2.5 + Western diet	↑ALT (~55%); 4.7-fold increase in collagen deposition vs diet alone	Co-exposure design; single model
Mohamadi et al. (2026)	Systematic review	Human + animal studies	Organophosphate pesticide residues	Consistent correlation with NAFLD; steatosis and oxidative injury	Heterogeneous exposure sources
George et al. (2022)	RCT (MEDINA)	Adults with NAFLD	Mediterranean diet	~39% reduction in intrahepatic lipid; improved insulin resistance	Imaging surrogate; adherence challenges

HFD, high-fat diet; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI, magnetic resonance imaging; MDA, malondialdehyde; SOD, superoxide dismutase; ER, endoplasmic reticulum; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease.

Table 2: Convergent and divergent histological features across the three exposure domains.

Feature	Exercise	Dietary excess	Environmental stressors	Shared mechanism
Steatosis	Reduced	Induced (macrovesicular)	Induced (metals, heat, PM2.5, pesticides)	Lipid-handling balance
Mitochondrial state	Enhanced biogenesis / efficiency	Dysfunction	Dysfunction	Oxidative capacity
Oxidative stress	Decreased (improved defenses)	Increased	Increased	ROS / antioxidant balance
Hepatocyte injury (ballooning / degeneration)	Reduced	Increased	Increased	Cellular stress response
Predominant assessment method	Imaging surrogate (human)	Histology (animal) / imaging (human)	Histology (animal)	-

4 KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

This comparative synthesis points to a number of consistent gaps, each of which indicates to a specific research aim.

First and foremost, the field suffers from a translational gap between direct histologic data available in animal and indirect surrogate assessments available in human. Too far, no human intervention study has directly documented the biological changes (lipid droplet dynamics, Kupffer cell activation, and stellate cell quiescence) suggested by imaging. Bridging this gap would need confirmed non-invasive histological measures, or systematic inclusion of tissue level outcomes in human studies when biopsy is already clinically required.

Second, biological sex is not sufficiently considered. The diet-induced ballooning may only be significant in females [16], and there are known sex differences in liver mitochondrial adaptation to exercise. Single-sex study designs, which are still common, risk producing conclusions of limited generalizability. In future studies, sex should be considered a planned variable, rather than a confounder.

Third, the almost entire separation of the three exposure areas is a lost opportunity. Real world exposure is combinatorial: people are exposed to particular diets, activity levels and environmental stressors at the same time. However, hardly no study investigates their interaction e.g. if exercise alleviates metal or heat produced histological injury, or hypercaloric diet aggravates environmental hepatotoxicity. Such interactions should be tested in a factorial design that would better resemble the human situation and that may show protective or synergistic effects that cannot be seen in single exposure studies.

Fourth, the use of supraphysiological doses and non-mammalian or agricultural models (especially in the environmental sector) restricts translational confidence. Studies with environmentally realistic exposure levels and mammalian models with liver biology closer to that of human are needed to establish which of the identified histological markers are actually relevant to human health.

Finally, the emerging blend of digital pathology, AI-based quantification and spatial omics offers a methodological way forward [30]. Use of these technologies for uniform zone resolved analysis across exposure types would make the current fragmented, partially quantitative data base comparable and reproducible. Ultimately, it may allow the little adaptive changes observed throughout this investigation to be detected in a non-invasive way in humans.

Limitations of this review. Several limits should be noted. Papers were picked here on the basis of relevance and expert judgment, rather than a pre-registered process, formal screening or quantitative pooling as in a systematic review which can introduce the possibility for selection bias. Here the environmental domain has been extended to four exposure categories but is still not fully covered. Other stressors such as endocrine disrupting chemicals and microplastics are not covered. The synthesis is further constrained by the literature itself. Much of the direct histology evidence is based on heterogeneous animal models, with variability in species, technique and exposure time, making it difficult to compare directly between studies. The limitations should be taken into account while interpreting the integrative conclusions offered here.

5 CONCLUSION

Key to this integrated viewpoint and the first feasible strategy to tackling subtle, zone-specific hepatic abnormalities across exposures and finally in humans will be the advent of new digital and spatial technologies. The next most crucial step for the field is to go away from parallel, exposure-specific literatures and toward this unified perspective. Histological and ultrastructural traces in the liver from exercise, environmental pressures and dietary choices. But these have been studied largely in isolation and with different methodological techniques. the main point of this review is to show that these seemingly unrelated exposures are side by side Consistent on a common set o mechanism (mitochondrial function, oxidative balance, lipid handling and zonal susceptibility) causing a common large nonspecific Pattern of injury differing primarily in direction

This convergence has two practical implications. The study design highlights investigations that involve integrated vs isolated exposure, biological sex as an intended variable, and linking tissue-level objectives with non-invasive procedures in individuals. “It reminds us that when we interpret histology, a given pattern of damage rarely indicates a single cause and must be interpreted in combination with exposure history and molecular data.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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The author declares no conflict of interest.

Author contributions

The sole author conceived, designed and drafted the manuscript, conducted the literature search and critical appraisal, prepared the tables and approved the final version for submission.

Data availability statement

Data sharing is not applicable to this article, as new data were created on analyzed in this review. All studies discussed are available from the cited published sources.

Use of artificial intelligence

The author used AI based large language model as assistive tool to support drafting, language editing and organization of the manuscript. All scientific n=content, interpretations and cited references were reviewed, verified against their original sources and approved by the author who takes full responsibility for the integrity and accuracy of the work.

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