Review

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Andrea Borghini *, Mariangela Palazzo, Alessandro Tonacci, Fabrizio Minichilli, Haotian Wu, Francesca Gorini *

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Environmental Exposure to Micro- and Nanoplastics: Linking Cardiovascular Disease and Cancer Through Shared Biological Pathways

Andrea Borghini [1,*], Mariangela Palazzo [1], Alessandro Tonacci [1], Fabrizio Minichilli [1], Haotian Wu [2] and Francesca Gorini [1,*]

[1] Institute of Clinical Physiology, National Research Council, 56126, Pisa, Italy

[2] Columbia University Mailman School of Public Health, New York, NY 10032, United States

* Correspondence: andrea.borghini@cnr.it (A.B.); francesca-gorini@cnr.it (F.G.)

Abstract

Micro- and nanoplastics (MPs/NPs) are ubiquitous environmental contaminants increasingly detected in air, food, drinking water, and human tissues, raising concerns about their potential long-term health effects. Accumulating evidence indicates that these particles can enter the human body, cross biological barriers, and elicit cellular and molecular responses relevant to disease development. This review synthesizes current mechanistic evidence linking MP/NP exposure to cardiovascular disease (CVD) and cancer, two leading global causes of morbidity and mortality that share interconnected pathogenic pathways. Key mechanisms include chronic inflammation, oxidative stress, gut microbiota dysbiosis, genotoxicity, and epigenetic alterations, all widely implicated in both conditions. However, the available evidence is still largely derived from in vitro and animal studies, with limited human epidemiological data. Important uncertainties remain regarding real-world exposure characterization, dose–response relationships, and long-term clinical outcomes, underscoring the need for standardized analytical approaches, validated exposure and effect biomarkers, and large-scale longitudinal studies to clarify causal associations for both cancer and CVD. Taken together, current evidence suggests that MPs/NPs may represent emerging environmental contributors to shared pathogenic pathways linking CVD and cancer; however, establishing causality in humans will require well-designed longitudinal studies integrating exposure assessment and clinical outcomes.

Keywords: microplastics; nanoplastics; cardiovascular disease; cancer; oxidative stress; inflammation; immune dysregulation; genetics; gut microbiota

1. Introduction

Global plastic production has increased exponentially over recent decades, rising from 234 million tons (Mt) in 2000 to 460 Mt in 2019, with no indication of a future decline [1,2]. Owing to their favorable physicochemical properties - including versatility, durability, hydrophobicity, low density, and low production costs - plastics are used across nearly all industrial and consumer sectors, with demand further amplified during the COVID-19 pandemic [3,4]. As a consequence, plastics have become ubiquitous in all environmental compartments, and their waste now represents a persistent and pervasive pollutant [4,5]. Global plastic use is projected to reach 884 Mt by 2050, with waste generation expected to double over the same period, even if packaging recycling rates exceed 75% [1].

Microplastics (MPs) and nanoplastics (NPs), generated through the degradation of plastic waste, have emerged as major environmental and public health concerns due to their widespread distribution across ecosystems and their potential to infiltrate human tissues and barriers [5,6]. Although MPs and NPs are often considered relatively inert materials, they can absorb substances

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such as additives, heavy metals, proteins, and microorganisms on their surface, potentially increasing their toxicity [7]. While the environmental impact of MPs and NPs is well documented, their effects on human health remain incompletely understood due to uncertainties related to exposure routes, detection methods, and toxicity evaluation [6,8]. However, recent evidence suggests that plastic particles are increasingly detected in various human organs and may trigger adverse biological responses, including inflammation, oxidative stress, and cytotoxicity, with possible serious health consequences [9,10].

Among these, cancer and cardiovascular disease (CVD), two of the leading causes of global morbidity and mortality, are increasingly recognized to exhibit overlapping biological processes despite being distinct diseases [11]. Shared mechanisms include chronic inflammation, oxidative stress, immune dysregulation, clonal hematopoiesis, gut dysbiosis, and genetic and epigenetic alterations [11,12].

Given the growing body of evidence—largely derived from preclinical studies—showing that plastic particles may adversely affect the cardiovascular system and contribute to tumor initiation and progression, this review aims to provide an integrated overview of the current mechanistic evidence. In particular, it explores how MPs and NPs may trigger or exacerbate biological pathways that are commonly implicated in both CVD and cancer.

To this end, a comprehensive literature search was conducted in the PubMed database to identify studies published in English between January 2000 and April 2026 investigating the potential role of MPs and NPs in CVD and cancer. The search strategy combined terms related to plastic particles ("microplastics", "nanoplastics") with terms associated with cardiovascular and oncological outcomes ("cardiovascular disease", "atherosclerosis", "thrombosis", "cancer", "carcinogenesis") and shared pathogenic mechanisms ("inflammation", "oxidative stress", "gut dysbiosis", "genotoxicity", "epigenetic modifications", and "cellular senescence"). In addition, the reference lists of relevant articles were screened to identify further eligible studies.

Beyond summarizing the mechanisms underlying MP/NP-associated cardiovascular and cancer risk, with particular attention to the role of antioxidant defenses in modulating plastic-induced adverse effects, this review also seeks to highlight current research gaps and propose future directions for risk assessment and translational investigations.

2. Microplastics and Nanoplastics: Sources, Characteristics, and Routes of Human Exposure

MPs are commonly defined as plastic particles with a diameter smaller than 5 mm and originate from the progressive degradation of larger plastic materials [13]. This process can occur over hundreds or even thousands of years, depending on the physicochemical properties of the plastics and the surrounding environmental conditions, and involves a complex interplay of mechanisms including ultraviolet radiation, mechanical abrasion, temperature fluctuations, and, to a lesser extent, biodegradation [8,14]. Besides resulting from the degradation of larger plastic waste (secondary MPs), primary MPs can also be deliberately produced for consumer and commercial uses, such as cleaning products, cosmetics, drug delivery systems, and sandblasting applications [8]. Polyethylene (PE), polypropylene (PP), and polystyrene (PS) are among the most prevalent polymers detected in environmental microplastic contamination [8]. The small size of MPs, which confers a high surface-to-volume ratio and enhanced mobility, enables them to act as "Trojan horses," facilitating the transport of heavy metals, persistent organic pollutants, plastic additives (e.g., phthalates and bisphenol A - BPA), harmful pathogens, and engineered nanoparticles [8,15,16]. Furthermore, plastic particles exhibit a wide range of morphologies, and differences in shape (e.g., fibers, foams, cylindrical or spherical beads, and granules) critically modulate their interactions with biological surfaces, leading to heterogeneous cellular and tissue responses [17].

Notably, despite being widely distributed in the environment, microplastics (MPs) are subject to bioaccumulation and potentially biomagnification along aquatic food webs [18]. Accordingly, human exposure to MPs occurs primarily through the consumption of seafood, marine salt,

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vegetables, honey, and mineral water, as well as through ingestion from plastic food packaging. In addition, exposure occurs through the inhalation of outdoor air, particularly in urban environments, and indoor dust containing MPs, while dermal contact via cosmetics and personal care products appears to represent a comparatively minor exposure route [2,5,7]. Annual human intake of MPs from food is estimated to reach approximately 1.42×10^5–1.54×10^5 particles per capita, an amount considered equivalent to the ingestion of about 50 plastic bags [19]. Plastic microparticles can further fragment into nanoparticles, typically defined as particles smaller than 1 μm [8]. However, unlike their microplastic counterparts, current research on NPs has mainly focused on aquatic systems, and knowledge of their potential impacts on human health - although exposure may occur through the food chain - remains limited [8,15].

Once ingested, the absorption and translocation of MPs/NPs across the gastrointestinal tract largely depend on particle size [16]. Particles smaller than 150 μm have the potential to penetrate the intestinal epithelium and entering the systemic circulation, whereas most particles larger than 150 μm are eliminated via feces [16]. A small fraction of these larger particles may be retained in the gut, where they can potentially alter the composition of the colonic microbial community [16,20]. Similarly, inhalation represents an additional exposure route, with the entry of MPs/NPs into the respiratory system being largely restricted to the lower airways for particles with aerodynamic diameters smaller than 5 μm [21]. Notably, nanosized plastic particles can penetrate the alveolar region, traverse the pulmonary epithelial barrier, and subsequently enter the systemic circulation [20]. In parallel, although the ability of plastic particles to cross the skin barrier remains a matter of debate, the direct application of cosmetics containing MPs/NPs may allow nanosized particles to be absorbed via percutaneous uptake and, upon dermal entry, to reach the dermis and gain access to the bloodstream or lymphatic system, thereby potentially enabling systemic distribution [22,23].

Of note, beyond being detected in a variety of human tissues and body fluids, including breast milk and semen, MPs may also cross the placental barrier, enter the fetal bloodstream, and ultimately reach the fetal gut, where they can be excreted in meconium [17,24]. In addition, their detection in the olfactory bulb suggests the existence of a potential translocation pathway to the brain [17,25]. MPs and NPs exhibit size-dependent clearance and biodistribution, with overall in vivo elimination occurring on the order of hours, as evidenced by experimental tracking studies in animal models [26] . Recent estimates indicate that total MP accumulation may range from 14,230 to 17,091 particles, corresponding to a mass of 37.26–46.53 mg, with predominant localization in the lungs and higher accumulation observed in females compared with males [27]. Organ-specific distribution appears to be size-dependent, with particles smaller than 20 μm detected in greater abundance, likely reflecting differences in the permeability of biological membranes [28,29]. Furthermore, in addition to fecal elimination, MPs/NPs or their associated additives may also be excreted via urine, a process that is hypothesized to primarily reflect the renal clearance of plastic-associated contaminants, such as BPA and phthalates, commonly used in food packaging, personal care products, rather than intact particles [9].

Overall, the ubiquitous environmental presence of MPs/NPs, combined with multiple exposure routes and evidence of systemic distribution and organ accumulation, highlights their potential to interfere with biological processes relevant to human health. However, despite increasing evidence of widespread exposure and systemic distribution, current estimates of human MP/NP exposure remain highly uncertain due to methodological heterogeneity and lack of standardized analytical approaches.

To provide the reader with a schematic overview, Figure 1 summarizes the generation and characteristics of MPs and NPs, routes of human exposure, and biological uptake and distribution.

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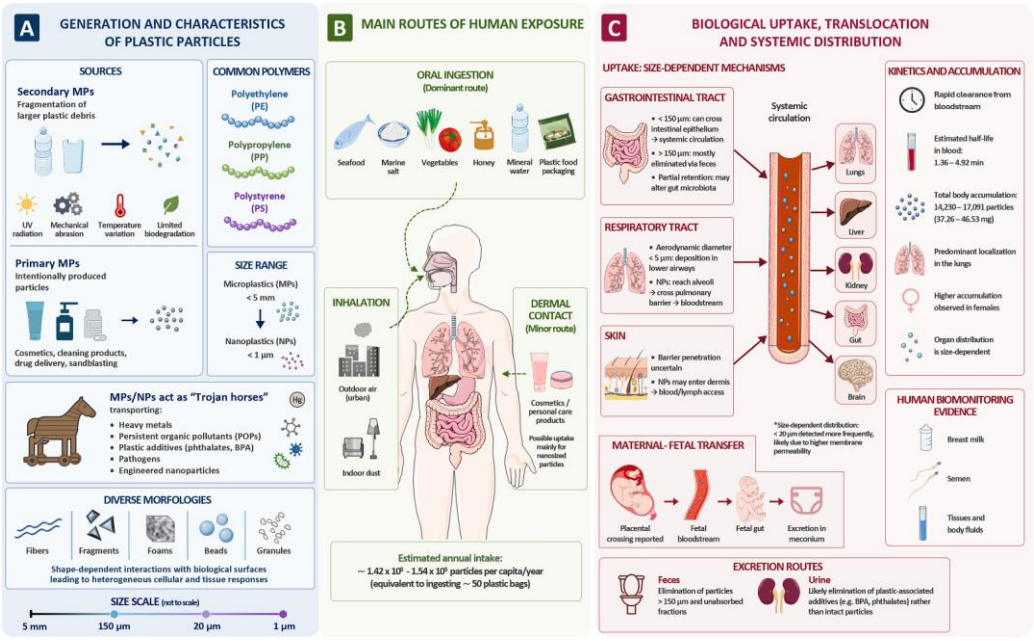

Figure 1. Micro- and nanoplastics (MPs/NPs): generation and characteristics, routes of human exposure, and biological uptake and distribution. Overview of MPs/NPs, including their origin and physicochemical characteristics, major routes of human exposure, and subsequent biological uptake and systemic distribution. The figure illustrates the generation of MPs/NPs from primary and secondary sources, their entry into the human body through inhalation, ingestion, and dermal contact, and their potential translocation across biological barriers with accumulation in multiple tissues and organs.

3. Shared Mechanisms Linking Microplastic/Nanoplastic Exposure, Cancer and Cardiovascular Disease

CVD and cancer remain the leading causes of morbidity and mortality worldwide [30]. According to the World Health Organization, CVD accounted for approximately 19.8 million deaths in 2022, representing about 32% of all deaths [31]. In the same year, the International Agency for Research on Cancer estimated around 20 million new cancer cases and 9.7 million cancer-related deaths [32]. Although long viewed as separate contributors to mortality, growing evidence indicates that CVD and cancer are closely interconnected and frequently coexist within a complex and bidirectional relationship in which cancer and CVD distinctly can influence the development, progression, and outcomes of the other, thereby significantly affecting long-term survival [30]. Thus, despite being distinct clinical entities, CVD and cancer tend to overlap, an interplay driven by shared risk factors and multiple convergent pathophysiological processes [10]. Chronic systemic inflammation, oxidative stress, metabolic dysregulation, intestinal dysbiosis, epigenetic modifications and genetic instability, cellular senescence, and clonal hematopoiesis have been identified as shared mechanisms underlying both CVD and cancer [10,11,33].

As discussed in the previous section, once MPs/NPs enter the human body, they can disseminate systemically via the circulatory system to multiple organs and, at relatively low concentrations in experimental setting, may induce oxidative stress, leading to the production of pro-inflammatory cytokines, apoptosis, cytotoxicity, and alterations in gene expression [34]. Moreover, an increasing body of evidence indicates that plastic particles are present and accumulate in human cardiovascular tissues as well as in tumor tissues.

MPs have been identified in cardiac and pericardiac tissues of patients undergoing cardiac surgery, predominantly composed of polyethylene terephthalate (PET) and polyurethane (PU), which together account for approximately 90% of the total MPs detected, with particle sizes ranging from 20 to 469 µm [35]. However, differences in MP size and composition observed between pre- and post-surgical blood samples suggest that the use of medical devices containing plastic components

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during surgery may have influenced the detected MP distribution [36] In line with these findings, MPs - including polyamide 66 (PA66), polyvinyl chloride (PVC), and PE - have been detected in 80% of thrombus samples from patients undergoing arterial or venous thrombectomy for ischemic stroke, myocardial infarction (MI), or deep vein thrombosis [36]. Median MP concentrations were 61.75 μg/g, 141.80 μg/g, and 69.62 μg/g, respectively, and a positive association was observed between disease severity and MP concentration within thrombi [36]. Furthermore, MPs (mean concentration 118.66 μg/g), with PET, PA-66, PVC, and PE being the predominant components, are significantly enriched in atherosclerotic coronary and carotid plaques compared with plaque-free aortic tissue, suggesting an association with atherosclerosis [37]. Consistently, the presence of plastic particles within carotid plaques—mainly PE and PVC, with mean concentrations of 21.7 and 5.2 μg/g per plaque—has been associated with a 4.5-fold increased incidence of non-fatal MI, stroke, or all-cause mortality [38]. Furthermore, PVC, detectable in 95.4% of blood samples from patients undergoing coronary angiography for MI, was significantly associated with a 9% increase in the risk of major adverse cardiac events, following a dose–response relationship [39]. This finding further corroborates the emerging links between MP/NP exposure or accumulation, cardiovascular risk markers, and adverse clinical outcomes. Yang and colleagues reported a correlation between MP exposure and vascular pathology complexity in patients with acute coronary syndrome (ACS) [40]. Blood MP concentrations, with PE present at the highest levels, were significantly higher in ACS patients compared to controls (161.65 μg/g vs. 100.13 μg/g) and were further elevated in patients with MI compared to those with unstable angina [40]. Notably, while low-risk ACS patients showed no significant association with MP exposure, this relationship became significant in medium- to high-risk groups, suggesting a potential prognostic value of MP levels in ACS [40].

Although human studies investigating the relationship between MP/NP exposure and cancer development are still in their infancy, MPs have been detected in several human tumors. Zhao et al. [41] recently identified MPs in 42.6% of tumor samples from patients who had not received prior treatment. PS was the predominant polymer, with a mean concentration of 59.56 ng/g, followed by PVC (51.98 ng/g) and PE (86.94 ng/g). Lung cancer exhibited the highest detection rate (80%), whereas pancreatic, colorectal, gastric, and cervical tumors showed rates of 70%, 50%, 40%, and 17%, respectively [41]. Notably, MPs were not detected in esophageal tumor specimens, suggesting heterogeneous adhesive affinities of MPs across tumor types, potentially reflecting site-specific binding properties or, alternatively, differences in clearance efficiency among tumors [41]. Nine types of MPs - predominantly PE, PP, and PVC - have also been detected in over 85% of penile cancer samples, with an average abundance of 6.42 particles per gram and most particles falling within the 20–50 μm size range [42]. Additionally, MPs not only showed a higher detection rate and greater abundance in cancerous tissue compared with adjacent normal tissue but were also characterized by a richer and more diverse polymeric profile [42]. Consistently, the mean abundance of MPs in human prostate samples was 290.3 μg/g in tumor tissue and 181.0 μg/g in para-tumor tissue, with particle diameters ranging from 20 to 50 μm [43]. Comparable findings have also been reported for colorectal cancer (CRC) (with PE, PET, PP, PS, and PVC as the most prevalent particle types) and cervical cancer (with PE, polyethylene-co-polypropylene, and PP as the predominant types), with significant differences between tumor and adjacent non-tumor tissues [10,44]. Together, these observations suggest a relationship between MP accumulation and the tumor microenvironment, supporting the hypothesis that MPs could be involved in carcinogenic pathways. Moreover, a recent case–control study offered the first epidemiological indication of a possible association between MP exposure and CRC, reporting significantly higher fecal MP concentrations in CRC patients compared with controls and an approximately 11-fold increase in CRC risk among individuals with higher fecal MP levels [45].

In the following subsections, we examine how MPs/NPs may be associated with the risk of both CVD and cancer by acting through the shared etiopathogenic mechanisms that underpin these two distinct disease groups (Figure 2).

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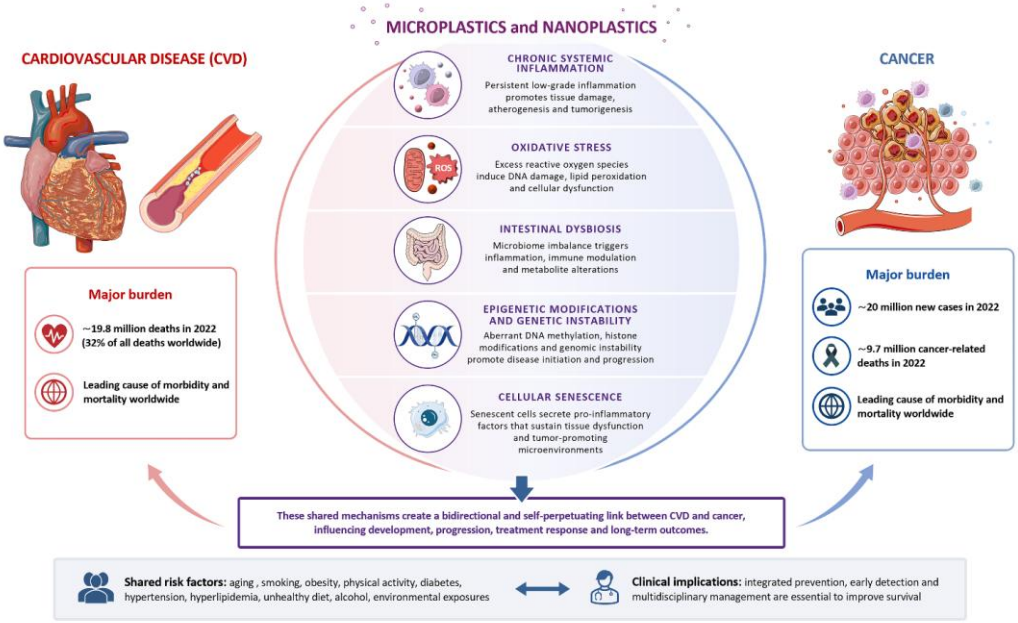

Figure 2. Micro- and nanoplastics (MPs/NPs) as potential environmental drivers of cardiovascular disease and cancer through shared pathogenic pathways. This schematic illustration summarizes the main shared biological pathways potentially triggered or amplified by MP/NP exposure, including oxidative stress, chronic inflammation, endothelial dysfunction, immune dysregulation, metabolic alterations, genotoxicity, and epigenetic modifications. These interconnected processes may promote both cardiovascular damage and tumor initiation and progression, supporting the hypothesis that MPs/NPs act as common environmental drivers of chronic non-communicable diseases.

3.1. Inflammation

Chronic inflammation plays a central role in the pathogenesis of CVD, as persistent low-grade systemic immune activation drives atherogenesis and increases the risk of hypertension, hyperlipidemia, and type 2 diabetes, well-established CVD risk factors [11,33]. In parallel, sustained activation of pro-inflammatory signaling pathways also promotes cancer initiation and progression by enhancing tumor cell proliferation, survival, and metastatic potential, processes that are further facilitated by inflammation-induced immune suppression [11,33].

Exposure to MPs/NPs has been increasingly associated with persistent inflammatory responses characterized by elevated pro-inflammatory cytokines, oxidative stress, and activation of key inflammatory signaling pathways [46,47]. Recent evidence indicates that MPs/NPs promote the expression of senescence markers such as p16, p21, and senescence-associated β-galactosidase (SA-β-gal) activity, together with the development of a senescence-associated secretory phenotype (SASP) that further amplifies inflammatory signaling [47]. This inflammation–senescence axis is increasingly linked to the pathogenesis of age-related diseases, including cardiovascular, neurodegenerative, metabolic, and chronic inflammatory disorders, suggesting that MPs/NPs exposure may contribute to disease onset and progression [47].

Environmental MPs (25–300 μm; 100 ng/mL–1 mg/mL) have been shown to trigger the secretion of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and IL-6, in human monocytic THP-1 cells, a widely used model to investigate monocyte and macrophage function in the cardiovascular system [48,49]. The inflammatory response increased with prolonged exposure and followed a clear dose–response relationship, reaching maximal levels at 1 mg/mL [48].

In THP-1 cells, amine-modified PS particles (50 nm; 50 μg/cm²) have also been shown to directly activate the NOD-like receptor protein 3 (NLRP3) inflammasome, a key driver of atherosclerotic inflammation, thereby promoting the release of IL-1β and IL-18 [50,51]. However, other particle types, including polyethylene terephthalate (PET), polyacrylonitrile, and polyamide 6 (nylon), were able to

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stimulate IL-8 secretion even in NLRP3 knockout cells, suggesting that MPs may also activate alternative pro-inflammatory pathways depending on their physicochemical properties [50].

Consistent with these findings, stimulation of myocardial microvascular endothelial (MyEnd) cells with PS particles (1 μm; 10^7 particles/mL) resulted in upregulation of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), indicative of endothelial activation, a hallmark of early atherogenesis [52]. In vivo, C57BL/6N mice injected with PS particles (1 μm; 2.5 mg) exhibited significantly increased IL-1β levels and marked endothelial activation, as reflected by elevated VCAM-1 and ICAM-1 expression in aortic tissue [52].

Long-term exposure studies further support these observations. In male Sprague–Dawley rats, PS-MP exposure (5 μm; 0.5 mg/L for 120 days) induced mild vascular alterations, including increased calcification in small cardiac vessels and the ascending aorta, accompanied by elevated plasma levels of IL-1β, IL-6, and tumor necrosis factor alpha (TNF-α) [53]. Similarly, Wistar rats exposed for 90 days to PS-MPs (0.5–50 mg/kg/day) showed increased myocardial enzyme levels and elevated expression of inflammatory markers (IL-1, IL-1β, ICAM-1) in cardiac and aortic tissues, although no overt histopathological changes were observed [54]. Mechanistically, PS-MP exposure activates the caspase-1–dependent NF-κB/NLRP3/gasdermin D (GSDMD) signaling axis, promoting pyroptosis, an inflammatory form of programmed cell death implicated in vascular inflammation and cardiovascular disease progression [55–57]. This was confirmed by increased levels of cleaved GSDMD, IL-1β, and IL-18 in cardiac tissue, alongside evidence of cardiomyocyte pyroptosis [55].

Importantly, human data further support the relevance of these findings. In patients with detectable MPs in carotid artery plaques (PE and PVC) and in coronary blood (PS and PVC), MP presence was associated with elevated inflammatory markers, including IL-1β, IL-18, IL-8, and TNF-α, as well as increased plaque collagen content and higher levels of CD3 and CD68, markers of lymphocyte and macrophage infiltration, respectively [38,39]. Furthermore, in patients with acute coronary syndrome (ACS), circulating MP levels were positively associated with IL-6 and IL-12p70, as well as with increased B cell and natural killer (NK) cell abundance [40]. Notably, different MP types exerted distinct immunological effects, likely reflecting their specific physicochemical characteristics [40].

MPs may contribute to tumor development by modulating inflammatory responses. In skin squamous cell carcinoma models (SCL-1 and A431), exposure to PE-MPs (≤1 mg/mL) promoted cell proliferation in a dose- and time-dependent manner through activation of the NLRP3 inflammasome via a mitochondrial DNA (mtDNA)-mediated mechanism [58]. In contrast, treatment of normal human keratinocytes (HaCaT cells) with PE-MPs inhibited proliferation and induced pyroptosis through the same mtDNA–NLRP3 signaling axis, suggesting that MPs may exert divergent effects by promoting tumor growth while damaging healthy cells [58].

In lung cancer models, exposure to PS-NPs (800 nm; 10–500 μg/mL, 48 h) induced cellular senescence in A549 human lung adenocarcinoma cells, as evidenced by enlarged morphology, irreversible cell cycle arrest, increased SA-β-gal activity, and metabolic dysregulation [59]. This phenotype was accompanied by increased expression of IL-1α, IL-1β, IL-6, and IL-8/CXCL8, key components of the senescence-associated secretory phenotype (SASP) [59]. While SASP can reinforce growth arrest via autocrine and paracrine signaling, it may also promote tumorigenic processes, including angiogenesis, stemness, genotoxicity, chronic inflammation, invasion, migration, and immunosuppression, representing a well-recognized “double-edged sword” in cancer biology [60]. Accordingly, NP-induced senescence and associated inflammatory signaling may impair tissue repair and contribute to persistent pathological alterations in lung tissue [59].

In vivo evidence, although still limited, supports the role of MP/NP-induced inflammation in shaping tumor-promoting microenvironments. Oral administration of PS-NPs (10 mg/kg/day for 7 days) in BALB/c mice impaired intestinal barrier function and increased infiltration of IL-1β–producing macrophages in the colon [61]. This was associated with polarization of $CD4^+$ T cells toward Th17 and Treg subsets, along with T-cell exhaustion, collectively contributing to the establishment of a pro-tumorigenic microenvironment that may favor tumor initiation [61].

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Inflammation appears as a central mechanism linking MP/NP exposure to disease. Across both cardiovascular and cancer contexts, evidence consistently implicates NLRP3 activation and cytokine-driven inflammatory signaling as key shared pathways. However, most of the available evidence derives from experimental models, often involving exposure levels exceeding those encountered under real-world conditions, thereby limiting direct extrapolation to human disease.

Overall, the level of evidence can be considered high for cardiovascular outcomes, supported by mechanistic, in vivo, and prospective human data, whereas it remains low for cancer, due to the lack of longitudinal human studies, with current evidence derived from limited in vitro and emerging in vivo data.

3.2. Oxidative Stress

Defined as an imbalance between reactive oxygen species (ROS) and antioxidant defenses generated endogenously through metabolic reactions and exogenously via exposure to toxic determinants, oxidative stress is a major driver of CVD development [12,33,62]. Given the abundance of mitochondria in cardiomyocytes and their essential role in ROS production, mitochondrial dysregulation predisposes to CVD onset [11]. Excessive ROS generation damages cellular lipids, proteins, and DNA, alters signaling pathways, compromises genomic integrity, and promotes tumor initiation and progression [33].

Oxidative stress is one of the most frequently reported adverse effects of MP/NP exposure [62]. Elevated ROS levels induce lipid peroxidation, protein oxidation, mitochondrial dysfunction, and DNA damage, ultimately disrupting cellular redox homeostasis and linking MP/NP exposure to systemic toxicity through inflammation, cell death, and organ dysfunction [62,63].

Exposure to NPs (25 nm; 0.1–10 μg/mL for 24 h) induces premature cellular senescence in porcine coronary artery endothelial cells, as shown by upregulation of p53, p16, and p21, increased SA-β-gal activity, and reduced endothelial nitric oxide synthase expression, consistent with enhanced oxidative stress [64]. NP treatment downregulates Sirt1, a key stress and energy sensor activated by an increased NAD^+/NADH ratio, thereby promoting endothelial dysfunction and NADPH oxidase–dependent ROS production, ultimately contributing to vascular senescence and atherosclerosis development [64–67].

In human embryonic stem cell–derived cardiomyocytes, PS-NP exposure (20–40 μg/mL for 7 days) increased CAT expression and superoxide anion levels, indicating oxidative stress independent of the SOD pathway [68,69]. ROS accumulation triggered endoplasmic reticulum stress and apoptosis, as evidenced by increased cleaved caspase-3 levels, leading to irregular contractile rhythms [68,70].

In vivo, zebrafish embryos exposed to NPs (25–1000 μg/mL) developed pericardial edema, impaired angiogenesis, and dose-dependent cardiovascular dysfunction, including reduced cardiac output and blood flow velocity, with increased thrombosis risk [71]. These alterations were associated with ROS overproduction, endothelial barrier disruption, and a pro-inflammatory, procoagulant state [71]. Temperature further modulated NP toxicity (PS-NH_2 NPs toxicity: 50 nm; 0.1 mg/L), partially improving cardiac performance while exacerbating oxidative stress and mortality, highlighting the interaction between environmental factors and NP-induced cardiotoxicity [72].

Consistent findings were observed in Wistar rats, where 90-day exposure to PE-MPs (5 and 50 mg/L) increased malondialdehyde (MDA) levels and reduced SOD, CAT, and GPx activities, indicating oxidative imbalance [73]. Such dysregulation may activate the Wnt/β-catenin pathway, promoting profibrotic and hypertrophic remodeling [73,74]. Similarly, long-term exposure to high concentrations of PS-MPs resulted in myocardial damage associated with reduced antioxidant defenses and increased lipid peroxidation [54]. In male adult C57BL/6 mice, chronic exposure to MPs via drinking water (5 μm; 1000 μg/L for 180 days) worsened vascular lesions and cardiac abnormalities, partially attributable to oxidative stress [75].

Additional evidence from aquatic models supports this mechanism. In carp, PS-NP exposure (50–400 nm; 1000 μg/L) increased ROS and MDA levels while impairing antioxidant defenses [76]. These alterations were associated with activation of the TLR4/NOX2 pathway, Th1-skewed immune

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responses, and apoptosis via the IGFBP3/p53/ACHE axis, leading to size-dependent myocardial injury, with greater toxicity observed for smaller particles [76].

Experimental studies also indicate a role for oxidative stress in MP/NP-associated carcinogenic processes. Exposure to PS-NPs (0.5 μm; 5 μg/mL, 48 h) or chronic treatment with NPs or PS-MPs (2 μm; 20 μg/mL, 4 weeks) increased ROS generation in normal human intestinal CCD-18Co cells, driving metabolic reprogramming toward enhanced glycolysis, lactate production, and glutamine utilization [77]. Notably, this metabolic shift parallels the changes induced by the carcinogen azoxymethane (AOM) and observed in HCT15 colon cancer cells, highlighting a canonical cancer-associated adaptation involving the decoupling of glucose and glutamine metabolism under stress conditions [77]. Treatment of lipopolysaccharide (LPS)-stimulated human colorectal adenocarcinoma Caco-2 cells with PS-NPs (20 nm; 125, 250, and 500 μg/mL) for 24 h induced lipid peroxidation and increased intracellular ROS levels [78]. In Caco-2 cells, exposure to PS-MPs (0.1 and 5 μm; 200 mg/mL for 12 h) also significantly increased intracellular ROS generation without detectable cytotoxicity, whereas lower concentrations (≥20 mg/mL for 0.1 μm and ≥1 mg/mL for 5 μm) induced mitochondrial depolarization, with larger particles exerting greater toxicity [79]. In contrast, PE-MP exposure (5–60 μm; 0.25–1.0 mg/mL for 48 h) in Caco-2 and HT-29 cells increased cytotoxicity and oxidative stress primarily through a dose-dependent rise in mitochondrial superoxide production, without affecting total ROS or cytosolic superoxide levels [80]. Ethanol extracts of PE particles further demonstrated that leached chemicals contribute to toxicity by inducing both total ROS and mitochondrial superoxide generation in a cell line-dependent manner [80]. Although these differential responses warrant further investigation, they support the ability of MPs to induce oxidative stress–related toxicity under high exposure conditions.

In skin squamous cell carcinoma models (SCL-1 and A431), PE-MP exposure (1 μm; 0.25–1 mg/mL) promoted proliferation in a dose- and time-dependent manner via activation of the ROS–mtDNA–NLRP3 signaling pathway [58]. Increased mitochondrial ROS disrupted membrane potential and promoted the release of oxidized mtDNA, as indicated by 8-oxo-2′-deoxyguanosine, which subsequently triggered inflammasome activation and sustained tumor-promoting inflammatory signaling [58].

In human lung adenocarcinoma A549 cells, exposure to PS-NPs (10–25–50–100–250–500 μg/mL) for 24, 48, or 96 h induced a significant, dose- and time-dependent increase in hydrogen peroxide production at all tested concentrations [59]. Concomitantly, increased expression of antioxidant enzymes, including superoxide dismutase (SOD)1/2, catalase (CAT), glutathione peroxidase (GPx)1, and heme oxygenase-2, was observed, consistent with activation of oxidative stress–responsive defense pathways [59]. Similarly, exposure of human bronchial epithelial and mesothelial cells (BEAS-2B and CRL-9609) to PS-NPs (80 nm; 100 μg/L for 24 h) increased ROS and MDA levels, accompanied by upregulation of antioxidant genes (*SOD*, *CAT*, *GPX*, and *Nrf*2) and depletion of reduced glutathione, indicating concurrent oxidative damage and activation of the Keap1–Nrf2 adaptive response [81]. PS-NPs also impaired mitochondrial function, as evidenced by membrane depolarization and calcium dysregulation, further amplifying ROS production [81]. Elevated ROS levels promoted inflammation, DNA damage, and necrosis, thereby potentially contributing to lung disease, including cancer [81]. Moreover, integrin $\alpha 5\beta 1$ overexpression enhanced NP internalization and exacerbated oxidative damage, amplifying downstream inflammatory and genotoxic responses and suggesting a potential role for this receptor in mediating NP-induced toxicity [81].

In vivo, administration of PS-NPs (20 nm; 0.1–10 mg/kg) in an a AOM/dextran sodium sulfate (DSS)–induced colorectal cancer model in BALB/c mice resulted in a significantly higher number of tumor nodules, accompanied by increased ROS production compared with control and AOM/DSS groups [78]. In healthy male Sprague–Dawley rats exposed to PS-NPs (varying particle sizes; 5 mg/L/day), gastric tissues exhibited oxidative stress accompanied by DNA damage, a marker of potential carcinogenic effects [81]. Notably, SOD, CAT, and GPx activities were reduced, whereas MDA levels were increased, with significant alterations observed exclusively in association with the smallest PS-NPs (80 nm) [82], consistent with previous observations [76].

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In summary, oxidative stress emerges as a central mechanism underlying MP/NP-induced toxicity across both cardiovascular and cancer contexts. In both disease domains, evidence is supported by mechanistic and functional data from in vitro and in vivo studies. Nonetheless, despite the consistency of these findings, most of the available evidence derives from experimental models, often involving exposure levels exceeding those encountered under real-world conditions, thereby limiting direct extrapolation to human health. Overall, oxidative stress represents a converging biological pathway linking environmental exposure to downstream pathological processes, highlighting the importance of redox imbalance in plastic-induced toxicity and suggesting that antioxidant defenses may represent potential targets for mitigation strategies. Future studies should further investigate whether modulation of antioxidant pathways may represent a viable strategy to counteract MP/NP-induced biological effects

3.3. Gut Dysbiosis

The human gastrointestinal tract harbors a diverse microbial community (microbiota) comprising approximately 100 trillion microorganisms, representing the largest microbial consortium in the body [83,84]. Disruption of gut microbiota homeostasis (dysbiosis), characterized by alterations in microbial composition and metabolite profiles, leads to immune dysregulation and chronic inflammation, thereby promoting the development of various diseases, including CVD and cancer [83,85].

Microbiota-derived metabolites, such as trimethylamine N-oxide and bile acids, contribute to CVD pathogenesis by promoting endothelial dysfunction and atherosclerosis [86,87]. Alterations in microbiota composition and reduced diversity have also been linked to the development and progression of heart failure [83]. In addition, dysbiosis contributes to oncogenesis and tumor progression by promoting aberrant signal transduction, DNA damage, epigenetic alterations, and immune suppression, while also acting as a key regulator of the tumor microenvironment, with the potential to exert both pro- and anticancer effects. [88,89].

Although research on the interaction between MPs/NPs and the gut microbiota is still in its early stages, both in vitro and in vivo studies have demonstrated that plastic particles can alter microbial composition and exert variable effects on microbial diversity and richness [90]. MP exposure also appears to interfere with the production of short-chain fatty acids, key metabolites derived from microbial fermentation that support intestinal barrier integrity and modulate immune responses [90].

To date, a limited number of studies have addressed cardiovascular endpoints potentially associated with MP-induced gut microbiota alterations, whereas a single study has examined their relevance in the oncological context. Collectively, recent evidence highlights a key role of gut microbiota alterations and related metabolic changes in mediating the cardiovascular toxicity of microplastics. Yan et al. demonstrated that PS-MPs (5 μm; 0.5 mg/L) promoted vascular calcification in male Sprague–Dawley rats through perturbation of the gut microbiota, impairment of the intestinal barrier, and induction of inflammatory responses [53]. Exposure resulted in a marked increase in Proteobacteria, a major source of LPS endotoxin, and in the dominance of *Escherichia_Shigella* at the genus level, while non-exposed animals were enriched in short-chain fatty acid–producing taxa, which contribute to gut microbiota homeostasis and intestinal barrier integrity. These findings support a mechanistic link between MP-induced gut dysbiosis and vascular calcification [53]. The same study reported higher concentrations of microplastics in fecal samples from patients with vascular calcification compared with those without, supporting the clinical relevance of these findings [53]. Consistently, Wang et al. showed that oral exposure to PS-MPs (5 μm; 1–2 mg/L) for 8 weeks in BALB/c mice induced hypertension and cardiac injury, characterized by increased systolic, diastolic, and mean blood pressure, as well as cardiac hypertrophy and fibrosis [91]. These effects were mediated by microbiota alterations, as evidenced by the enrichment of specific bacterial genera, including *Candidatus Arthromitus*, *Akkermansia*, *Anaeroplasma*, and *Prevotella*, which positively correlated with cardiovascular injury markers [91]. Importantly, modulation of gut microbiota through a high-fiber diet or antibiotic treatment significantly attenuated these alterations,

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while fecal microbiota transplantation from MP-exposed donors transferred the hypertensive phenotype and exacerbated cardiovascular damage in recipient mice, supporting a potential causal role of gut dysbiosis in experimental models [91]. The authors also reported higher concentrations of PS-MPs (0–30 μm) in hypertensive patients compared with normotensive individuals, further supporting the relevance of gut microbiota alterations and associated metabolic changes as mechanistic mediators linking MP exposure to CVD [91]. In line with these findings, Song et al. reported that prolonged exposure to PS-MPs (0.5, 5, and 50 mg/kg/day) in SPF male Wistar rats induced dose-dependent alterations in systemic metabolic profiles, with significant upregulation of metabolites with antioxidant and anti-inflammatory properties, including equol and 4-hydroxybenzoic acid, suggesting adaptive microbiota-related metabolic responses [54].

In the oncological framework, Tian et al. further confirmed that exposure to PS-NPs induces significant alterations in gut microbial composition, contributing to cancer progression [57]. In an AOM/DSS mouse model, PS-NPs (20 nm; 10 mg/kg) caused significant changes in gut microbiota diversity, with enrichment of Allobaculum, a colitogenic bacterium, and a decreased abundance of Lactobacillus, thereby weakening its cancer-protective effects [57]. Both Allobaculum and Lactobacillus species are involved in lipid metabolism, suggesting that PS-NPs may partly affect metabolic processes through microbiota modulation in this model [57].

Overall, current evidence suggests that MP-induced gut microbiota dysbiosis and related metabolic alterations may represent a relevant mechanistic pathway linking MP exposure to both cardiovascular and oncological outcomes. oHwever, consistent with other mechanisms discussed, most of the available evidence derives from experimental studies, with only limited human data, and is often affected by substantial heterogeneity in exposure assessment and microbiota characterization.

Taken together, microbiota-mediated effects may represent an indirect but potentially important pathway through which MPs/NPs contribute to systemic disease processes, although further studies are required to clarify their causal and translational relevance.

3.4. Genotoxicity

DNA damage and defective repair mechanisms are widely recognized as central processes in disease development, including cancer and cardiovascular disease. Damage to DNA, whether caused by endogenous processes or by external agents, can lead to mutations and genomic instability [92]. In cancer, the accumulation of such genetic alterations in key regulatory genes drives uncontrolled cell proliferation and malignant transformation [93]. Similarly, in CVD, DNA damage in vascular endothelial cells and smooth muscle cells contributes to cellular dysfunction, inflammation, and impaired tissue repair. Over time, these processes promote atherosclerosis, vascular stiffening, and plaque instability [94]. Therefore, genotoxic stress and defective DNA repair mechanisms represent a shared biological foundation underlying both cancer and cardiovascular disease, linking genomic integrity to long-term disease risk.

The genotoxicity of MPs/NPs stems from their interactions with cellular structures, particularly DNA, leading to genetic damage and impaired cellular function. This is primarily driven by ROS overproduction and direct intracellular interactions, which compromise chromosomal integrity and disrupt mitotic processes, ultimately causing genomic instability [62,95].

Consistent experimental evidence shows that MP/NP exposure induces DNA strand breaks, chromosomal alterations, and oxidative lesions. Persistent oxidative stress can overwhelm antioxidant defenses and DNA repair mechanisms, further exacerbating genomic instability and activating stress-related signaling pathways [95]. Although direct evidence in human cardiovascular systems is absent, these mechanisms are closely linked to vascular aging and atherogenesis.

Increasing evidence links MP exposure to carcinogenic processes, largely through DNA damage–related mechanisms. Recent findings highlight a mechanistic connection between MPs/NPs, particularly PS-NPs, and the progression of colitis-associated cancer. Tian et al. demonstrated that PS-NPs exacerbate tumor development by inducing oxidative stress, disrupting cellular metabolism, and promoting DNA damage [57]. In an AOMe/DSS-induced murine model, chronic 20 nm PS-NP

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exposure, administered by oral gavage at low (0.1 mg/kg), medium (1.0 mg/kg), or high (10 mg/kg) doses, increased tumor burden, induced DNA damage, and promoted histopathological features consistent with more aggressive tumor phenotypes. Mechanistically, PS-NPs activated the PI3K/AKT/mTOR signaling pathway, a central regulator of cellular metabolism, proliferation, and survival [57].

Moreover, in an in vitro study, MEF Ogg1−/− mouse embryonic fibroblasts (deficient in oxidative DNA base repair) were exposed to chronic low-dose exposure to PS-NPs (0.05 μm; 25 μg/mL) [96]. After 12 weeks of exposure, and particularly under co-exposure with arsenic, a known human carcinogen, the cells exhibited increased DNA damage, enhanced anchorage-independent growth, increased migration and invasion, as well as acquisition of malignant transformation features [96].

Ding and colleagues reported that long-term exposure to PS-MPs (5 mg/L for 90 days) in rats resulted in their wide distribution in tissues, together with a significant increase in ROS levels, reduced activity of antioxidant enzymes (SOD, CAT, GPx and increased oxidative DNA damage (8-oxo-dG; phosphorylated histone H2AX) [82].

Collectively, MPs/NPs appear to induce chromosomal instability, DNA damage and impaired DNA repair through ROS-mediated mechanisms and intracellular interactions.

While these mechanisms are well supported in cancer models, their role in CVD remains largely indirect and has not yet been specifically addressed in dedicated experimental or human studies. The level of evidence can be considered moderate for cancer outcomes, supported by in vitro and in vivo studies, whereas it remains limited for CVD, highlighting the need for further research to clarify the relevance of genotoxic pathways in vascular pathology.

3.5. Epiregulation

Epigenetics refers to reversible changes in gene expression mediated by mechanisms such as DNA methylation, histone modifications, and non-coding RNAs, which occur without alterations to the underlying DNA sequence and allow environmental and cellular cues to regulate biological function. These changes can also be mitotically heritable, raising important considerations within the framework of the developmental origins of health and disease. Accordingly, early-life or chronic exposure to MPs/NPs may predispose individuals—and potentially future generations—to an increased risk of cancer and other chronic conditions, including cardiovascular disorders [18].

DNA methylation, mediated by DNA methyltransferases (DNMTs), is essential for normal cellular processes and enables the transmission of regulatory information across cell divisions. Aberrant DNA methylation is recognized as bona fide hallmarks of cancer [97] and can dysregulate pathways involved in coronary heart disease, heart failure, and hypertension, thereby contributing to disease onset and progression [98]. Histone modifications modulate chromatin structure by regulating histone–DNA interactions, thereby influencing gene accessibility and transcriptional activity. Dysregulated histone modification patterns can lead to aberrant gene expression programs, including activation of oncogenes or repression of tumor suppressor genes, contributing to uncontrolled cell proliferation and malignant transformation [99]. In CVD, abnormal histone post-translational modifications, such as methylation, acetylation, crotonylation, and lactylation, play a key role in disease pathogenesis by reshaping transcriptional programs without altering the DNA sequence [100]. In addition to these mechanisms, dysregulation of noncoding RNAs, including miRNAs, is strongly associated with cancer development and CVD. Pro-inflammatory miRNAs promote atherosclerosis, whereas others exert protective effects in MI [101]. Dysregulation of specific miRNAs further contributes to disease progression, including plaque formation, cardiac fibrosis, and disturbances in cardiac conduction [102–104].

Within this context, MPs/NPs have emerged as potential environmental stressors capable of inducing toxicity, at least in part, through complex epigenetic reprogramming. By engaging multiple interconnected regulatory layers, these particles can reshape cellular identity and function, thereby contributing to disease-related pathways. PS-NPs have been shown to disrupt both global and gene-specific methylation patterns. This includes dysregulation of key enzymes such as DNMT3A in

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human fibroblasts and induced pluripotent stem cells exposed to 50 nm PS-NPs at a concentration of 50 μg/mL, leading to broad downstream effects on gene regulatory programs [105]. These changes perturb fundamental biological pathways governing pluripotency, oncogenic transformation, and inflammatory signaling, while extending beyond nuclear DNA to mitochondrial DNA methylation, thereby impairing mitochondrial energy metabolism and redox balance [105].

Zhang et al. reported that N6-methyladenosine (m6A) modification of non-coding RNAs contributes to MP-induced cardiac injury [106]. The authors observed that MPs accumulated across multiple organs and triggered increased apoptosis in cardiac cells [106]. In the myocardium, exposure to 10 μm MPs (10 mg/kg/day) was associated with elevated global m6A levels and upregulation of METTL3 expression. RNA-sequencing further revealed extensive transcriptomic changes in the hearts of MP-exposed mice, with more than 300 lncRNAs and circRNAs differentially expressed [106]. These changes were primarily associated with pathways related to endocytosis, cellular senescence, and cell cycle regulation, highlighting potential mechanisms underlying MP-induced cardiotoxicity [106].

RNA sequencing analysis of vascular tissues also revealed the differential expression of 674 mRNAs, 39 lncRNAs, 196 miRNAs, and 565 circRNAs in chronically exposed MP-treated mice (size: ~5 μm; dose and time of exposure: 1000 μg/L MPs through their drinking water for 180 days) compared with controls [75]. Consistent with these transcriptomic changes, pathway enrichment analyses highlighted mechanisms associated with MPs toxicity, including oxidative stress, apoptosis, and fibrosis [75]. In parallel, exposure to plastics such as PET has been shown to alter the microRNA cargo of serum-derived extracellular vesicles (EVs), with predicted target genes enriched in cardiovascular and metabolic disease pathways, suggesting that MPs/NPs may exert effects beyond directly exposed tissues by propagating through EV-mediated intercellular communication and potentially amplifying systemic toxicity [107]. Specifically, PET microplastics were administered to immature pigs for 4 weeks at two exposure levels: a low dose of 0.1 g/day and a high dose of 1 g/day. The particles were ingested orally and induced dose-dependent alterations in serum-derived extracellular vesicle cargo, affecting 24 metabolites in the low-dose group and 31 metabolites in the high-dose group. These metabolic changes were enriched for pathways involved in lipid signaling, mitochondrial dysfunction, glucose metabolism, and steroidogenesis. Although the evidence remains preliminary, the convergence of epigenetic [107]. reprogramming with established cardiovascular pathogenic pathways supports further investigation into MP/NP-induced epigenetic alterations as potential novel mechanisms of cardiovascular toxicity [108].

Regarding the impact of MPs/NPs on cancer risk driven by epigenetic alterations, growing experimental evidence indicates that environmental contaminants, including MPs/NPs, can induce significant epigenetic modifications. These changes may increase cancer susceptibility by altering gene expression, disrupting DNA methylation patterns, and impairing cellular homeostasis, thereby promoting oncogenic processes [109].

MP exposure has been associated with DNA hypomethylation in a zebrafish model, a well-established molecular marker linked to carcinogenesis [110]. In addition, exposure to PS-NPs can dysregulate miRNA profiling, interfering with the fine-tuned regulation of oncogenes and tumor suppressor genes that is critical for maintaining normal cellular function [110]. A disruption in a cluster of miRNAs closely associated with oncogenic processes was also observed by Barguilla and colleagues following long-term (180 days) in vitro exposure of mouse embryonic fibroblasts to 50–100 nm polystyrene nanoplastics (PS-NPs) [111]. Most of these miRNAs were upregulated (miR-21, miR-23a, miR-25, miR-30c, miR-30d, miR-96, miR-135b, miR-148b, miR-155, miR-199b, miR-200a, miR-210, miR-218, and miR-502) while only miR-34a and miR-203a appeared significantly downregulated in mouse embryonic fibroblasts [111].

Taken together, these findings support a model in which MP/NP exposure triggers a coordinated cascade of molecular events, including alterations in DNA methylation, histone remodeling, dysregulation of non-coding RNAs, and extracellular vesicle mediated signaling. Such processes, ultimately leading to persistent reprogramming of gene expression and cellular function. However,

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despite promising mechanistic insights, most of the available evidence derives from in vitro and animal studies, and the relevance of MP/NP-induced epigenetic alterations in human disease remains largely uncharacterized. The level of evidence remains low for both cardiovascular and cancer outcomes, reflecting the limited number of studies, the predominance of early mechanistic evidence, and the lack of validation in human populations.

In order to better define the level of evidence derived from the publications analyzed for the different shared mechanisms, we developed a composite scoring system based on both the type and the quantity of available evidence, according to the following formula: LE=T×Q, where T represents the score assigned to the type of evidence and Q represents the score assigned to the quantity of evidence.

The type of evidence (T) was categorized according to the experimental model used in the included studies: cellular studies were assigned a score of 1, animal studies a score of 2, and human studies a score of 3. Combined evidence from multiple experimental models received higher scores, specifically: cellular + animal = 4, cellular + human = 5, animal + human = 6, and cellular + animal + human = 8.

The quantity of evidence (Q) was determined by the number of scientific articles available for each topic. A single study was assigned a score of 1, the presence of 2–4 studies a score of 2, and the availability of five or more studies a score of 3.

The final LE score was interpreted according to the following categories: scores between 1 and 3 indicated very low evidence (LE=1), 4–6 low evidence (LE=2), 7–12 moderate evidence (LE=3), 13–18 high evidence (LE=4), and scores greater than 18 were considered indicative of very high evidence (LE=5).

As no standardized framework currently exists to integrate heterogeneous mechanistic evidence in this field, this composite scoring system was developed as an exploratory, semi-quantitative approach. Although it presents several limitations, including the arbitrary weighting of evidence types, the lack of formal validation, and the absence of methodological quality and risk-of-bias assessment, it was developed as an exploratory, semi-quantitative framework aimed at integrating heterogeneous preclinical and clinical evidence into a unified comparative model. Importantly, this approach should be considered interpretative rather than a validated tool for evidence grading, and its results should be interpreted with caution. Nevertheless, it provides a pragmatic strategy to facilitate an overall comparison of shared biological mechanisms across studies characterized by substantial methodological heterogeneity.

Table 1 summarizes the results obtained for each shared mechanism discussed, where the circles represent the corresponding LE score achieved (from 1 to 5 circles).

Table 1. Qualitative assessment of the evidence linking MP/NP exposure to cardiovascular and oncological outcomes.

Mechanism	Cardiovascular evidence	References	Cancer evidence	References
Inflammation	(in vitro + in vivo + prospective human)	[38–40,48,50,52–54]	(in vitro + limited in vivo)	[58,59,61]
Oxidative stress	(mechanistic and functional evidence in vitro and-model in vivo)	[54,64,68,71–73,75,76]	(mechanistic and functional evidence in vitro and-model in vivo)	[58,59,77–82]
Gut dysbiosis	(in vivo)	[53,54,91]	(limited in vitro)	[57]
Genotoxicity	NA	[95]	(in vitro + in vivo)	[57,82,96]

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	(only indirect experimental evidence)			
Epigenetic modifications	(in vitro + limited in vivo)	[75,106,107]	(in vitro + limited in vivo)	[109–111]

Abbreviations: one circle = very low; two circles = low; three circles = moderate; four circles = high; five circles = very high; NA: not available.

4. Conclusions and Future Challenges

The evidence summarized in this review supports the emerging concept that MPs/NPs may represent previously underestimated contributors to the pathogenesis of both CVD and cancer, which together account for a substantial proportion of global morbidity and mortality. This is of particular importance, since CVD and cancer together account for a substantial proportion of global morbidity and mortality; CVD alone is responsible for approximately 32% of all global deaths, while cancer accounts for about 16%, meaning that together they contribute to nearly half of worldwide mortality [31,32].

These particles appear capable of activating several interconnected mechanisms, including chronic inflammation, oxidative stress, gut microbiota alterations, and genotoxic and epigenetic changes, that are already recognized as central drivers of both carcinogenesis and cardiovascular injury. Among these, oxidative stress emerges as a key and converging mechanism, likely representing one of the earliest and most consistent biological responses to MP/NP exposure and a central hub linking environmental exposure to downstream pathological effects.

Inflammation plays a prominent role in mediating the toxic effects of MPs/NPs, particularly in the cardiovascular system, where human evidence supports an association between MP accumulation and inflammatory biomarkers. In contrast, evidence linking MP/NP-induced inflammation to cancer remains largely based on experimental studies, with limited direct translation to human disease. Similarly, increasing evidence suggests that alterations in gut microbiota composition may contribute to systemic inflammation and cardiometabolic dysfunction, although the role of microbiota-mediated pathways in cancer remains less clearly defined.

Emerging mechanistic insights also indicate that MPs/NPs may promote cancer and CVD through genotoxic and epigenetic mechanisms, including DNA damage, altered DNA methylation patterns, and miRNA dysregulation. However, current data remain largely experimental and require further validation in huma populations. In this context, an additional and still underexplored area of interest is clonal hematopoiesis of indeterminate potential (CHIP), a condition characterized by the accumulation of somatic mutations in hematopoietic stem cells and associated with both hematological malignancies and increased cardiovascular risk, partly through enhanced inflammatory signaling [11]. Given that cancer and CVD are key outcomes potentially linked to MP/NP exposure, it is plausible that chronic exposure may influence the emergence or expansion of CHIP clones. In particular, MP/NP-induced oxidative stress, DNA damage, and systemic inflammation could create a pro-mutagenic environment favoring CHIP development. However, this hypothesis remains unexplored and represents an important gap for future research.

Despite the growing body of mechanistic evidence, major uncertainties remain. Most available data derive from in vitro and animal studies, often involving exposure conditions that may not accurately reflect real-world human scenarios. In addition, the lack of standardized methodologies for MP/NP detection, quantification, and characterization limits comparability across studies and hampers robust exposure assessment. The heterogeneity of particle characteristics, exposure routes, and experimental models further complicates the interpretation and generalizability of current findings. In addition, accurately quantifying microplastic exposure in human biospecimens remains technically challenging due to the high risk of contamination during sample collection, processing, and analysis. Recent studies have highlighted that some reported microplastic measurements may be influenced by analytical artifacts or insufficient contamination control procedures, underscoring

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the need for standardized protocols and rigorous quality assurance measures. Addressing these methodological limitations will be essential for improving exposure characterization and strengthening causal inference in future studies [112].

Further research should prioritize large-scale epidemiological studies integrating accurate exposure assessment, validated biomarkers, and long-term clinical outcomes. In this context, further investigation into antioxidant defense systems and redox-regulating pathways is warranted, particularly to determine whether antioxidant-based strategies may mitigate MP/NP-induced biological damage and reduce disease risk.

Finally, although definitive causal evidence is still lacking, current data strongly suggest that MPs/NPs should no longer be considered biologically inert environmental contaminants. Rather, they may represent emerging exposome-related risk factors contributing to complex disease pathways shared by CVD and cancer, highlighting the need for coordinated public health and regulatory strategies targeting plastic production, waste management, food packaging, and environmental contamination. Addressing these knowledge gaps through interdisciplinary research will be essential to define their real impact on human health and to support evidence-based preventive strategies.

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Abbreviations

The following abbreviations are used in this manuscript:

Acute coronary syndrome	ACS
Bisphenol A	BPA
Catalase	CAT
Cardiovascular disease	CVD
clonal hematopoiesis of indeterminate potential	CHIP
DNA methyltransferase	DNMT
Glutathione peroxidase	GPx
Interleukin	IL
Lipopolysaccharide	LPS
Malondialdehyde	MDA
Myocardial infarction	MI
Microplastic	MP
Nanoplastic	NP
Polyamide 66	PA66
Polyethylene	PE
Polyethylene terephthalate	PET
Polypropylene	PP
Polystyrene	PS
Polyvinyl chlorine	PVC
Reactive oxygen species	ROS

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Senescence-associated β-galactosidase	SA-β-gal
Senescence associated secretory phenotype	SASP
Superoxide dismutase	SOD
Tumor necrosis factor alpha	TNF-α

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