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REVIEW

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Nanoplastics as emerging cardiovascular hazards: a narrative review of current evidence

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Abstract

Background Nanoplastics (NPs) have emerged as significant environmental pollutants, raising concerns due to their ubiquitous presence and potential adverse effects on human health. The migration and fate of NPs in the environment are subjects of intense study, with human exposure pathways expanding through ingestion, inhalation, and dermal contact.

Body Studies indicate that NPs can infiltrate the cardiovascular system, potentially causing adverse effects. Mechanistic insights from in vitro and animal studies suggest that oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction contribute to nanoplastic-induced cardiovascular toxicity. Animal models demonstrate altered heart rate, myocardial fibrosis, and dysfunction following NPs exposure, with specific adverse effects observed in cardiac valves and mitochondrial structure. Clinical studies provide further evidence of NPs accumulation in cardiovascular tissues, with implications for cardiovascular pathologies such as atherosclerosis and myocardial infarction. Notably, patients with higher levels of nanoplastics in carotid plaque exhibit an increased risk of adverse cardiovascular outcomes.

Conclusion However, challenges in studying nanoplastics persist, including methodological limitations, ethical considerations, and the need for standardized detection methods. Addressing these challenges requires interdisciplinary collaboration, innovative research approaches, and robust regulatory measures to mitigate NPs pollution and protect cardiovascular health.

Keywords Nanoplastics, Cardiovascular health, Toxicity, Oxidative stress

Introduction

Microplastics (MPs) are among the newly recognized persistent organic pollutants (POPs), emerging as critical environmental concerns in recent years [1]. Described by Thompson et al. in 2004 as plastic debris less than 5 mm in diameter [2], MPs have dual origins: degradation of larger plastic debris and pre-production pellets used for the already limited size [3]. Environmental factors such as physical processes, chemical weathering, and biological activity can further degrade MPs into even smaller nanoparticles (NPs) ranging from 1 to 1000 nm. Due to their diminutive size, extensive surface area, and high

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tissue affinity, these NPs are readily ingested by organisms, potentially disrupting various biological processes [4–6].

Currently, microplastic (nano)plastics (MNPs) represent a novel form of environmental pollution, garnering considerable research attention. Their migration and ultimate fate in nature are subjects of intense study. Of greater concern is their impact on human health; some studies suggest possible adverse outcomes [7–9]. As environmental concentrations of MNPs rise, human exposure pathways expand, with inhalation, ingestion, and dermal penetration identified as primary routes of entry into the body [7]. While a significant portion of current research focuses on the health hazards associated with ingesting NPs from aquatic sources, such as drinking water and seafood [8, 9], the complexity of human exposure is increasing [10]. For example, NPs have been found in lakes, rivers, and even treated drinking water [10, 11], potentially leading to human ingestion post-consumption [12]. Moreover, marine organisms like fish, shellfish, and crustaceans have been shown to accumulate MNPs, thus entering the human diet upon consumption [13, 14]. Notably, MNPs have been detected in seemingly unrelated food items such as table salt and beer [15], indicating their potential presence in a variety of foods.

Inhalation serves as another exposure route for NPs, originating from various sources like clothing fibers, building materials, 3D printing, tire wear, waste incineration, and urban dust [16]. Their small size allows easy airborne transport, with oceanic microplastics also contributing to atmospheric dispersion [17, 18]. COVID-19 mask usage has intensified respiratory exposure [19]. While ingestion is primary, dermal absorption is notable [20, 21]. Research confirms MNPs' translocation from the digestive tract and lungs to various organs, including the heart [7]. These multiple pathways underscore the significant health risks, demanding further investigation.

Cardiovascular disease (CVD) remains a leading global health concern, with air pollution being a significant contributing factor. Investigations indicate that air particulate matter (PM) negatively impacts cardiovascular activity, leading to vascular dysfunction, hypertension, and myocardial infarction [22, 23]. Oxidative stress induced by PM exposure is believed to play a key role in this process [22–24]. Emerging evidence suggests that NPs, as a novel environmental pollutant, also pose a threat to cardiovascular health [23]. A growing body of research indicates the heart as a potential target site for NP accumulation, potentially establishing it as a new cardiovascular risk factor [25]. Studies using mammalian models have demonstrated that nanoparticle exposure can adversely affect cardiac function [7]. The proposed mechanism involves interactions between NPs and ion channels within cardiac muscle cells (cardiomyocytes), ultimately disrupting their function [7]. While the potential for NPs to impact the cardiovascular system is gaining recognition, current research primarily focuses on elucidating the underlying mechanisms. The broader impacts of NP exposure on various aspects of cardiovascular health remain largely unexplored. This study aims to contribute to this critical area by providing new insights into the cardiotoxic potential of NPs.

Methodology

Literature search strategy

A literature search was conducted to identify relevant studies examining the cardiovascular hazards of nanoplastics (Table 1). Electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched using relevant keywords and Medical Subject Headings (MeSH) terms. Key search terms included "nanoplastics," "microplastics," "cardiovascular effects," "heart disease," and related variations. Boolean operators (AND, OR) were utilized to refine search queries and broaden the scope of relevant articles. The search was limited to articles published in English up to February 2024 to ensure the currency of the review.

Study selection criteria

Studies were included in the review if they met the following inclusion criteria:

- Published in peer-reviewed journals.
- Investigated the cardiovascular effects of nanoplastics.
- Provided relevant data or insights into the mechanisms underlying nanoplastic-induced cardiovascular toxicity.
- Included experimental studies and observational studies.

The exclusion criteria were as follows:

- Non-English language articles.
- Studies focusing solely on other environmental pollutants without specific mention of nanoplastics.
- Studies lacking relevance to cardiovascular health or lacking mechanistic insights into nanoplastic toxicity.
- Reviews, metanalyses, and conference papers.

Data extraction and synthesis

Two reviewers independently performed data extraction to ensure accuracy and reliability. Any discrepancies between reviewers were resolved through discussion and consensus. Following data extraction, a narrative

Table 1 Methodology

2.1. Literature search strategy	
Search criteria	**PubMed/MEDLINE, Scopus, Web of Science, Google Scholar**
Keywords	"nanoplastics,""microplastics,""cardiovascular effects,""heart disease"
Search filters	Boolean operators (AND, OR)
Language restriction	English
Time frame	Up to February 2024
2.2. Study selection criteria	
Inclusion criteria	Published in peer-reviewed journals
	Investigated cardiovascular effects of nanoplastics
	Provided relevant data or insights into mechanisms of nanoplastic toxicity
	Included experimental and observational studies
Exclusion criteria	Non-English articles
	Studies focusing solely on other pollutants without mention of nanoplastics
	Lack of relevance to cardiovascular health or mechanistic insights
	Reviews, meta-analyses, conference papers
2.3. Data extraction and synthesis	
Data extraction	Independently performed by two reviewers
	Discrepancies resolved through discussion and consensus
Synthesis approach	Narrative synthesis
	Organized thematically based on cardiovascular outcome and experimental model
	Mechanistic insights synthesized for comprehensive overview

synthesis approach was employed to summarize the findings of the included studies. Results were organized thematically based on the cardiovascular outcome assessed (e.g., cardiac function, vascular health) and the experimental model utilized (in vitro, in vivo). Mechanistic insights into nanoplastic-induced cardiovascular toxicity were synthesized to provide a comprehensive overview of the current understanding in the field.

Nanoplastics and cardiovascular system

Despite a substantial body of animal-based studies validating the adverse health effects of NPs, there remains to be more data on their impacts on various human organ systems [26] (Fig. 1). While many of the published studies have explored the forms of MPs, their routes of entry into human systems, and their toxicity, significant gaps persist in understanding the mechanisms underlying these NPs' toxicity [27, 28]. NPs can gain entry into the human body through several means, including ingestion, inhalation, and skin contact [29]. Evidence of NPs in human stool validates their entry through diet, drinking water, and food packaging [30]. Moreover, NPs have been detected in both indoor and outdoor particulates, such as synthetic textiles, construction materials, and abrasions of plastic materials, supporting their entry through inhalation [31]. While the skin membrane typically presents a barrier to MP and NP penetration, studies suggest that NPs can penetrate through wounds, sweat glands, or hair follicles [32].

Following absorption into the body, NPs and NPs may bind to cells and biological molecules, leading to the formation of coronated nanoplastic particles for absorption [33]. Endocytic pathways, including phagocytosis, micropinocytosis, as well as clathrin- and caveolae-mediated endocytosis, have been identified as crucial for cellular uptake of nanoparticles [34]. NPs are hypothesized to enter the gastrointestinal system through lymphatic tissue and infiltrate the microfold (M) cells in the Peyer's patches [35]. In the pulmonary route, NPs can permeate the thin alveolar tissue barrier and disperse throughout the body. In the dermal route, NPs leverage the weakening effects of radiation on the skin and the ingredients in body lotions to penetrate the skin barrier [36].

Upon entry into the body, MNPs and NPs can invade the heart and blood vessels, potentially causing adverse effects [37]. While the pathophysiology of nanoplastic-induced cardiovascular toxicity is not fully understood, in vitro studies suggest oxidative stress, inflammation, and apoptosis in vascular cells, while animal models indicate altered heart rate, myocardial fibrosis, and dysfunction [38, 39]. Exposure to PS-MPs has been linked to atrioventricular valve defects, cellular inflammation, mitochondrial lesions, and myocardial fiber destruction [1]. Nanoplastics can pass through the rodent placenta

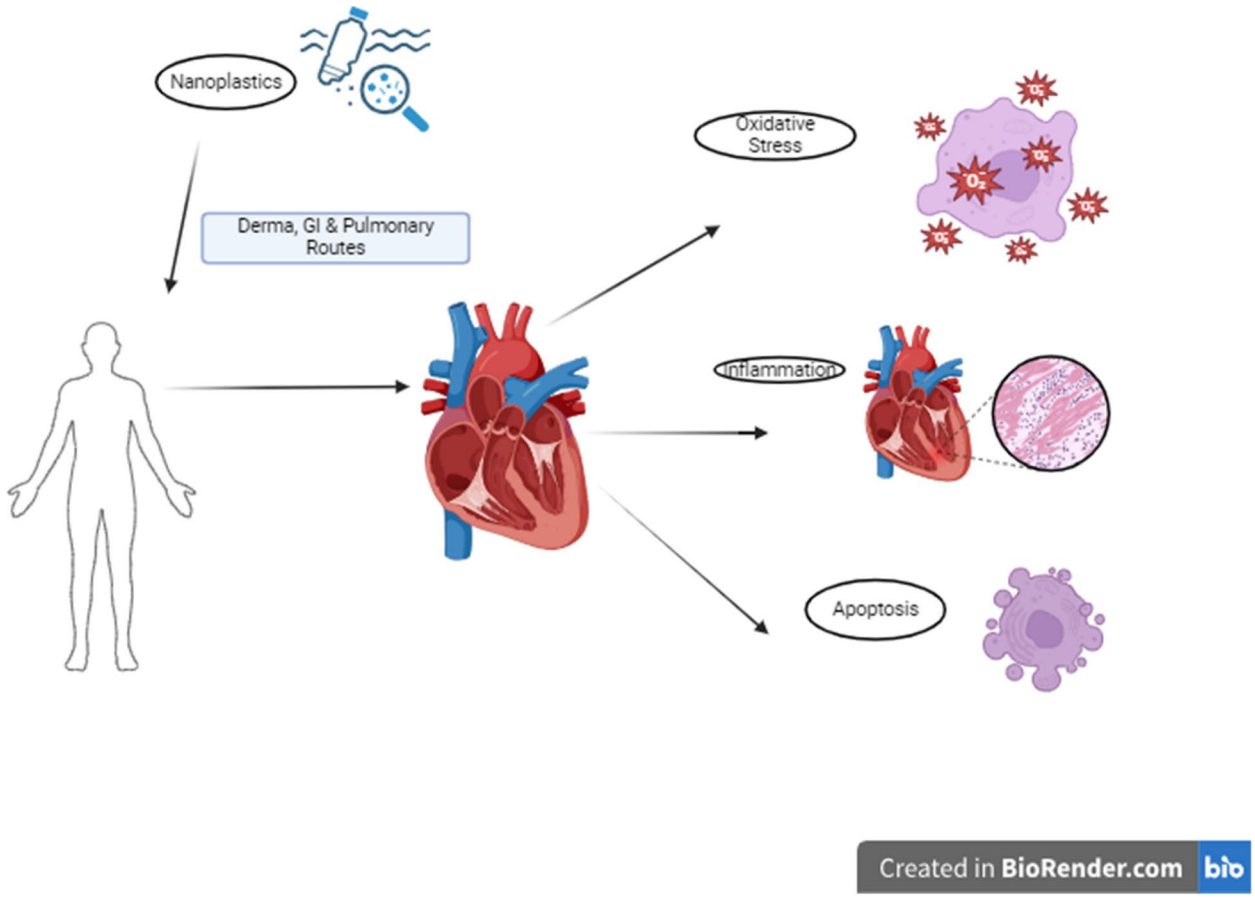

Fig. 1 Nanoplastics and cardiovascular system

and directly harm the fetal heart, bypassing the protective barrier. Additionally, exposure of human blastocysts to polystyrene nanoplastics during early development can hinder the formation of atrioventricular heart valves in newborns [7].

In vitro studies have shed light on the cellular responses to nanoplastic exposure within the cardiovascular system [40, 41]. One of the primary mechanisms implicated in nanoplastic-induced cardiovascular toxicity is oxidative stress, wherein excessive production of reactive oxygen species (ROS) overwhelms the antioxidant defense mechanisms of vascular cells [40]. This imbalance leads to oxidative damage to cellular components, including lipids, proteins, and DNA, ultimately contributing to cellular dysfunction and death [38]. Additionally, NPs exposure has been associated with inflammation within the vascular endothelium [41]. Inflammatory mediators, such as cytokines and chemokines, are upregulated in response to nanoplastic exposure, triggering an inflammatory cascade that can disrupt normal vascular homeostasis [29]. Persistent inflammation within the blood vessels can contribute to endothelial dysfunction, impaired vasodilation, and the development of atherosclerosis [30]. Moreover, studies have demonstrated that NPs exposure can induce apoptosis, or programmed cell death, in vascular cells [32]. This cellular response is mediated by various signaling pathways activated in response to nanoplastic-induced oxidative stress and inflammation [35]. Apoptosis of vascular cells can compromise the structural integrity of blood vessels, impairing their function and predisposing to cardiovascular disorders [33]. A study found that patients with carotid artery plaque containing MNPs had a higher risk of experiencing a combined outcome of myocardial infarction, stroke, or death within 34 months of follow-up, compared to those without MNPs in their plaque [33].

Animal studies have provided valuable insights into the systemic effects of NPs exposure on cardiovascular function [21]. These studies have demonstrated altered heart rate, impaired cardiac contractility, and myocardial fibrosis following chronic nanoplastic exposure [28, 42]. Myocardial fibrosis, characterized by excessive deposition of collagen fibers in the heart muscle, can impair cardiac function and contribute to the development of

heart failure [36]. Furthermore, exposure to polystyrene microplastics (PS-MPs) has been linked to structural abnormalities in cardiac valves, specifically atrioventricular valve defects [43, 44]. These defects can disrupt normal blood flow within the heart chambers, leading to functional impairments and potentially predisposing to cardiovascular complications [45]. Additionally, animal models have revealed mitochondrial lesions in cardiac cells following nanoplastic exposure. Mitochondrial dysfunction can compromise cellular energy production and contribute to oxidative stress-mediated damage, exacerbating cardiovascular pathology [46]. Reviewing available epidemiological studies linking particulate matter exposure to specific cardiovascular outcomes (morbidity, mortality, or hospitalizations), the evidence strongly supports a causal relationship with ischemic heart disease. For heart failure and ischemic stroke, the evidence is moderate and growing. The link to peripheral vascular disease and cardiac arrhythmia/arrest is currently modest or inconsistent [22].

While the precise molecular mechanisms underlying nanoplastic-induced cardiovascular toxicity require further elucidation, likely, a complex interplay of oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction contributes to the observed adverse effects [31]. NPs directly interact with vascular cells, triggering intracellular signaling cascades that culminate in cellular dysfunction and tissue damage [33]. Moreover, nanoplastic-induced alterations in systemic inflammation and oxidative stress exacerbate pre-existing cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes, further predisposing individuals to cardiovascular disease development [46].

Current evidence

Preclinical studies

Studies have explored the risks of various NPs and the potential association with cardiovascular events (Table 2). Laboratory-based experimental studies detailing the results of different cardiac manifestations from cardiac fibrosis in rats exposed to polystyrene, thrombosis, and impairment of myocardial contractility (Table 3). In 2020, an experimental study was carried out by Li Zekang et al. [1] to ascertain the effect of polystyrene NPs causing fibrosis of the cardiac tissue by activating the Wnt/β-catenin signaling pathway and promoting cardiomyocyte apoptosis in 32 male Wister rats. They found out that among the exposure group, oxidative stress was significantly increased compared to the control. There was also evidence of collagen fiber expression; this was assessed by integrated optical density of collagen under Masson's trichrome staining and Sirius red staining. Among the exposure group, this was statistically significant compared to the control group. Additionally, fibronectin was elevated, and Troponin I and CK-MB were increased in rats exposed to microplastics.

In the following year, Sun et al. [47] attempted to examine the level of cardiovascular toxicity among developing zebrafish embryos exposed to polyethylene nanoplastics. 30 zebrafish embryos in each experimental group were used and pericardial toxicity, hemodynamic changes, thrombosis, ROS generation, and inflammation were examined. The results showed that with treatment with 48 hpf (high-performance films) the group treated with polyethylene, exhibited elevated heart rates averaging 173 beats per minute, although there was no statistically significant difference compared to the control group. Atrial rates and ventricular rates were unchanged in the concentration group, demonstrating that nanoplastics have no effect on the heart rates of zebrafish embryos. Additionally, it did not induce atrioventricular block. Conversely, with increased dose to 96 hpf led to pericardial edema.

NPs have been hypothesized to impair the cardiac contractility of cardiac myocytes. In 2021, Amir et al. [7], performed a laboratory-based experiment in neonatal rats. The study focused on tracing surface charge-dependent nanoplastics in the cytosol of neonatal rats ventricular myocytes (NRVMs) and also to measure the contractile force. The outcome showed that the higher internalization of positively charged nanoplastics during the acute exposure resulted in reduced contractility of the myocardium due to alterations in the intracellular calcium levels. NPs are also known to promote senescence of the endothelial cells of coronary arteries. To assess the possibility of this, Saugat et al. (2022) used a pig's heart in a laboratory-based experimental study [40]. Nanoplastics were internalized and accumulated in endothelial cells in a time-dependent manner, increasing the Senescence-associated beta-galactosidase activity in a concentration-dependent manner highlighting its capability to cause senescence in coronary arteries. Noteworthily, nanoplastics preferentially affect the endothelium rather than the smooth muscles. The exposure also increased the formation of reactive active species (ROS) leading to oxidative-induced aging of endothelial cells.

In another experimental study, Zhang, Tianyi et al. (2023) sorted to evaluate cardiotoxicity in mice after respiratory exposure to polystyrene nana-plastics [41]. 72 mice were grouped with exposure to low, medium, and high doses. At 4 and 12 weeks of exposure, In-Vivo Imaging System (IVIS) showed an accumulation of nanoplastics in the abdomen and chest of mice. It was noted that after 12 weeks of exposure, the weight of the heart in mice as well as body weight was significantly reduced. Swollen mitochondria, disrupted myocardial fibers, and

Table 2 Summary of clinical studies

Author and year	Study design	Sample size	Positive outcome	Negative
Yang, Yunxiao et al. (2023) [45]	Observational study (cross-sectional study design	15 patients	Microplastics were not universally present in all tissue samples, but nine types were found across all five types of samples (five types of normal tissue samples, including pericardia, epicardial adipose tissue (EAT), pericardial adipose tissue (PAT), myocardia, and left atrial appendage (LAA) were collected) with diameter ranging from 20 to 469 µm in diameter. Nine types of microplastics were also detected in pre- and postoperative blood samples with a maximum diameter of 184 µm, and the type and diameter distribution of microplastics in the blood showed alterations following the surgical procedure. Moreover, the presence of poly(methyl methacrylate) in the left atrial appendage, epicardial adipose tissue, and pericardial adipose tissue cannot be attributed to accidental exposure during surgery, providing direct evidence of microplastics in patients undergoing cardiac surgery	Further research is needed to examine the impact of surgery on microplastic introduction and the potential effects of microplastics in internal organs on human health.
Marfella, Raffaele et al. (2024) [33]	Prospective observational study (multicenter)	304	A total of 304 patients were enrolled in the study, and 257 completed a mean (± SD) follow-up of 33.7 ± 6.9 months. Polyethylene was detected in carotid artery plaque of 150 patients (58.4%), with a mean level of 21.7 ± 24.5 µg per mg of plaque; 31 patients (12.1%) also had measurable amounts of polyvinyl chloride, with a mean level of 5.2 ± 2.4 µg per milligram of plaque. Patients with evidence of MNPs were younger; more likely to be men; less likely to have hypertension; more likely to have diabetes, cardiovascular disease, and dyslipidemia; more likely to smoke; and had higher creatinine values than those without evidence of plastics in excised plaque	Patients in whom MNPs were detected within the atheroma were at higher risk for a primary end-point event (nonfatal myocardial infarction, nonfatal stroke, or death from any cause) than those in whom these substances were not detected (hazard ratio, 4.53; 95% confidence interval, 2.00 to 10.27; $P < 0.001$).

Table 2 (continued)

Author and year	Study design	Sample size	Positive outcome	Negative
Liu, Sheng et al. (2024) [46]	Experimental laboratory study	17	Sample donors's daily plastic-related behaviors (smoking, consumption of bottled water, consumption of take-out food, and consumption of prepackaged food), and obtained information on air quality (air quality index, particulate matter 2.5, and particulate matter 10) at the location where the patients resided at the China National Environmental Monitoring Center was investigated. The correlation between these factors and the concentration of microplastics in the arteries was examined using Spearman's correlation analysis hat there was no significant correlation between these factors and the concentration of microplastics in the arteries (all factors, $P > 0.05$). The concentrations of microplastics in both the coronary artery samples (156.50 ± 42.14 vs. 76.26 ± 14.86 μg/g tissue, $P = 0.039$) and the carotid artery samples (133.37 ± 60.52 vs 76.26 ± 14.86 μg/g tissue, $P = 0.015$) were higher than those in the aortic samples. While there was no statistical difference between the concentration of microplastics in the coronary artery samples and the carotid artery samples (156.50 ± 42.14 vs. 133.37 ± 60.52 μg/g tissue, $P = 0.426$).	Both coronary and carotid artery samples had many atherosclerotic plaques, whereas the aortic samples were from patients with aortic dissection and did not contain atherosclerotic plaques. This implies that microplastics may be associated with atherosclerosis.

Table 3 Summary of preclinical studies

Author and year	Study design	Sample size	Findings	Conclusion
Li et al. (2020) [1]	Experimental study	32 male Wister rats	Effects of PS MPs on oxidative stress: The MDA level was significantly increased by 1.4 and 1.7 (in nmol/mgprot) in 5 and 50 mg/L PS MPs groups compared to control ($p < 0.05$). Collagen fiber expression: integrated optical density of collagen under Masson's trichrome (12) staining and Sirius red (41) staining significantly increased in the 50 mg/L PS MPs group ($p < 0.05$), while no difference was found in the 0.5 and 5 mg/L PS MPs groups compared to the control group ($p > 0.05$). Immunohistochemical analysis of fibronectin in the heart appeared tan. The result showed that in 5 and 50 mg/L PS MPs groups, the IOD of fibronectin was significantly increased by (52 and 76) respectively compared to the control group ($p < 0.05$). ELISA showed the levels of CK-MB (63) and troponin I (0.62) increased in 50 mg/L PS MPs group ($p < 0.05$), but not in the 0.5 and 5 mg/L PS MPs groups compared to control group ($p > 0.05$).	Compared to the control group, the IOD of Bax significantly increased in 5 and 50 mg/L PS MPs groups, by 24 and 36, respectively ($p < 0.05$). In contrast, the IOD of Bcl-2 significantly decreased (by 22) in the 50 mg/L PS MPs group ($p < 0.05$), while there were no significant differences in Bax and Bcl-2 expressions in 0.5 mg/L compared to that of the control group ($p > 0.05$)

Table 3 (continued)

Author and year	Study design	Sample size	Findings	Conclusion
Sun, Mengqi et al. (2021) [47]	Experimental study	30 zebrafish embryos in each experimental group	The results showed that, after treatment to 48 hpf, the zebrafish embryos heart rates of the 25, 50, 100, and 200 µg/mL groups were 172, 172, 173, and 172 beats/minute, respectively, there was no statistical difference compared with the control (171 beats/min), $p > 0.05$. And atrial rates of zebrafish embryos in concentration group were the same as their respective ventricular rates, suggesting that the nanoplastics had no effect on heart rates of zebrafish embryos under the experimental conditions, and did not induce atrioventricular block (A/V block) in zebrafish embryos. After treatment with 96 hpf, compared with the control, the pericardium edema area of zebrafish embryos in 25, 50, 100 and 200 µg/mL concentration groups was 14,904, 15,309, 16,016 ($p < 0.01$) and 16,715 ($p < 0.01$) pixels respectively, and the pericardial edema inducing effects were 5%, 8%, 13% and 18% .The results indicated that pericardial edema could be induced in zebrafish embryos at concentrations of 100 and 200 µg/mL under the experimental conditions. Compared with the control (41,021 pixels), the subintestinal vascular areas of 25, 50, 100 and 200 µg/mL were 40,856, 35,233, 33,767 ($p < 0.05$), and 25,274 ($p < 0.01$) pixels, and the inhibitory effect of subintestinal angiogenesis were 0%, 14%, 18%, and 38%, respectively. It is suggested that nanoplastics can inhibit the angiogenesis of zebrafish embryos under the concentration of 100 and 200 µg/mL	The incidence of thrombosis in 25, 50, 100 and 200 µg/mL groups was 17%, 20%, 20% and 23%, respectively.The results demonstrated that the fluorescence signal intensity of ROS was 1,618, 1,620, 2137 ($p < 0.05$), and 2687 ($p < 0.01$), and ROS induction was 0%, 0%, 32%, and 66% in the 25, 50, 100, and 200 µg/ mL, separately, as compared with the control (1617), indicating that nanoplastics could induce ROS in zebrafish embryos at the concentration of 100 and 200 µg/mL. . Fluorescence images showed that the chemotaxis and recruitment of neutrophils in the tail vein of zebrafish embryos were significant with the increase of exposure dose. The number of neutrophils in the 25, 50, 100, and 200 µg/mL was 166, 172, 175 and 196 ($p < 0.01$), and the inflammatory induction was 1%, 4%, 6%, and 19%, respectively , compared with the control (165). It is suggested that nanoplastics can induce systemic inflammation of zebrafish embryos at the concentration of 200 µg/mL.

Table 3 (continued)

Author and year	Study design	Sample size	Findings	Conclusion
Roshanzadeh, Amir et al. (2021) [7]	Laboratory-based experimental study	Neonatal rat hearts	Surface charge-dependent translocation of nanoplastics into neonatal cardiomyocytes and their subsequent impact on cardiac performance under electrical stimulation intended to mimic the electrical synchronization of the mammalian heart was demonstrated. The higher internalization of positively charged nanoplastics during the acute exposure resulted in decreased myocardial contractility due to highly correlated alterations in intracellular calcium levels.	-
Dhakal, Bikalpa et al. (2024) [48]	Experimental study	Pigs (Porcine coronary artery and its endothelial cells)	Enavogliflozin (ENA) significantly reduced the NP-induced increase of SA-β-gal activity in Porcine Coronary Artery (PCA) and PCAECs. In addition, ENA prevented the NP-induced up-regulation of senescence markers, p53, and p21 that promoted the inhibition of EC proliferation. ENA also prevented the NP-induced oxidative stress and up-regulation of NOX2 and p22phox in ECs. Exposure of coronary artery rings to NPs blunted endothelium-dependent relaxation and decreased the expression level of endothelial nitric oxide synthase level, and both of these effects were prevented by ENA.	NPs were internalized in ECs in a time- and concentration-dependent manner. Exposure of porcine coronary artery endothelial cells (PCAECs) to NPs significantly up-regulated SGLT2 expression and increased SA-β-gal activity, one of the prominent senescence markers.

Table 3 (continued)

Author and year	Study design	Sample size	Findings	Conclusion
Shiwakoti, Saugat et al. (2022) [40]	Laboratory-based experimental study	Pig hearts - included tissues procured postmortem from a local commercial slaughterhouse (Mokpo, South Korea)	NPs were internalized and accumulated in ECs time-dependent manner and increased the SA-β-gal activity in a concentration-dependent manner not only in porcine coronary artery endothelial cells (PCAEC) but also in porcine left anterior descending coronary artery, suggesting that premature ECs senescence was induced by NPs. NPs with concentrations below 10 μg/mL showed no significant toxic effects on porcine coronary artery endothelial cell viability. Exposure to NPs reduced ECs proliferation in a concentration-dependent manner reaching 90.48%, 69.04%, and 56.62% in response to 0.1, 1, and 10 μg/mL NPs, respectively, compared to control PCAECs treated with 10% Fetal Bovine Serum. NPs affect preferentially the endothelium rather than the vascular smooth muscle cells and promote premature endothelial dysfunction.	NPs exposure strongly increased the formation of ROS leading to premature senescence and subsequent endothelial dysfunction. Oxidative stress-induced excessive ROS formation involves the NADPH oxidases/Sirt1 pathway and might be involved in NP-induced premature senescence. The antioxidant, the NADPH oxidase inhibitor, and the Sirt1 activator prevented NP-induced EC senescence and dysfunction.

Table 3 (continued)

Author and year	Study design	Sample size	Findings	Conclusion
Zhang, Tianyi et al. (2023) [41]	Experimental study	72 mice (4 groups of 6 mice; control, low dose, medium dose, high dose over 1 week, 4 weeks, and 12 weeks, respectively)	IVIS imaging showed that PS-NPs aggregated in the chest and abdomen of mice after exposure for 4 weeks and 12 weeks. Compared to the control group, the cardiac fluorescence signal was stronger in the 4-week and 12-week groups, and it appeared that more PS-NPs aggregated in the heart as the exposure duration increased On Respiratory exposure, There were no changes in body weights, heart weights, or heart organ coefficients after 1 week and 4 weeks of exposure. However, 12 weeks of exposure resulted in significant body and heart weight loss in mice, with no change in the heart/body weight index. There was no change in ejection fraction (EF) or short axis fractional shortening (FS) after 1-week exposure. However, the values of EF and FS significantly decreased in a dose-dependent manner after 4 weeks and 12 weeks of exposure. Notably, mice exposed to LD and MD for 4 weeks showed lower EF and FS values than the same dose group exposed for 12 weeks. PS-NPs dramatically activated the inflammatory response in heart tissues among all exposure duration groups. The levels of inflammation in serum were also significantly elevated in a dose-dependent manner compared to the corresponding control groups	The control group exhibited well-organized myocardium, while exposure to high doses of nanoparticles for 4 weeks led to disorganized myofilament arrangement and myocardial fragmentation. Even the low-dose group showed significant cardiac structural damage after 12 weeks, with the extent of damage increasing with higher exposure doses. Cardiac fibrosis, indicative of persistent myocardial damage, was significantly elevated after 12 weeks of exposure. Ultrastructural analysis revealed disrupted myocardial fibers, swollen mitochondria, and disappearing cristae, with more pronounced damage observed with longer exposure times.

Table 3 (continued)

Author and year	Study design	Sample size	Findings	Conclusion
Li, Jingyan et al. (2024) [43]	Experimental study	Human embryonic stem cells and zebrafish embryo	PS-NPs not only caused cytotoxicity in hESCs in a dose- and time-dependent manner, but also impeded cardiac differentiation as revealed by the low efficiency of differentiation, malformation, and weak contraction at both cardiomyocytes and Cardiac Organoids levels. The influence of embryonic exposure of PS-NPs on cardiac development was further verified by reduced cardiac contraction and blood flow in the zebrafish model.	-
Liu, Ling et al. (2024) [44]	Laboratory-based experimental study	Adults Marine medaka	Both PS-MP5 (5 μm) and PS-NP50 (50 nm) were found to adhere to the embryo's surface. Additionally, PS-NP50 could passively enter the interior of the embryo, accumulating in the intestine and head, whereas PS-MP5 could not enter the body in a passive manner. Regarding active ingestion, both PS-MP5 and PS-NP50 were ingested by the larvae, primarily accumulating in the intestine.	PS-MNPs and TPT influenced embryonic development by affecting the complement and coagulation cascade pathways

disappearing cristae were revealed on ultrastructural analysis.

Clinical studies

As the potential implications of nanoplastic exposure on CVS pathologies become a growing concern, numerous studies are presently underway to elucidate the presence and impact of nanoplastics on CVS. Marfella et al. [33] conducted a prospective, multicenter, observational study to collect carotid plaque specimens from patients undergoing carotid endarterectomy and study them for the presence of NPs with the use of pyrolysis–gas chromatography–mass spectrometry, stable isotope analysis, and electron microscopy. Out of the 257 patients, 150 patients (58.4%) exhibited detectable quantities of polyethylene (PE) within the excised carotid plaque while Polyvinyl chloride (PVC) was found in measurable quantities in 31 (12.1%) of these individuals. A positive correlation was found between the presence of NPs and levels of inflammatory markers, suggesting NP's role in inducing the proinflammatory pathways. Notably, it was observed during the 34 month follow-up period, within the cohort demonstrating evidence of NPs, 30 out of 150 patients (20.0%) experienced nonfatal myocardial infarction, nonfatal stroke, or succumbed to mortality from any cause. Conversely, in the subgroup lacking detectable NPs, 8 out of 107 patients (7.5%) experienced such adverse events. These findings establish that patients with higher levels of NPs in the carotid plaque are at greater risk of developing adverse cardiovascular outcomes.

An ACS cohort study suggested an association between prolonged PM2.5 exposure and increased risk of death from arrhythmias, heart failure, and cardiac arrest (relative risk 1.13, 95% confidence interval 1.05 to 1.21 per 10 $\mu g/m^3$), though the effect was weaker than for ischemic heart disease mortality [22].

Another study conducted by Yang et al. [45] focused on the detection of NPs within human cardiac tissues and adjacent structures. The study involved the collection of five distinct types of normal tissue samples from patients undergoing various cardiac surgical procedures. These tissue types comprised pericardium, epicardial adipose tissue (EAT), pericardial adipose tissue (PAT), myocardium, and the left atrial appendage (LAA). NPs were detected in all five types of samples, ranging from 20 to 469 μm in diameter. However, particles smaller than 20 μm could not be identified due to limitations in the methods used.

Nine different types of MPs were found in the tissue samples, with the most common being polyethylene terephthalate (PET) constituting 77% and polyurethane (PU) making up 12%, accounting for approximately 90% of the total MPs detected. PE was present in all tissue types, although it comprised only 1% of the total MP count. The investigation also extended to the examination of venous blood samples obtained prior to and following surgical procedures. Notably, NPs were detected in all blood samples, with sizes ranging from 20 to 184 μm. Concerningly, alterations in the composition of NPs were noted between pre- and post-surgery blood samples. These findings suggest the possibility of the introduction of NPs into the bloodstream during the invasive medical procedures and surgery.

To study the presence of NPs in the arterial system, Liu et al. [46] collected samples of carotid arteries, coronary arteries, and aorta from patients undergoing vascular surgeries. NPs were found in each of the 17 arterial samples, with concentrations varying between 52.62 and 225.23 μg/g of tissue, and averaging at 118.66 ± 53.87 μg/g of tissue. Mainly four kinds of NPs were found in the arterial samples, of which PET was predominant (73.70%), followed by PA-66 (15.54%), PVC (9.69%), and PE was the least (1.07%). The study also investigated the demographic characteristics of the donors, including factors such as age, body mass index, and blood pressure, along with their daily habits related to plastic use, such as smoking, consumption of bottled water, take-out food, and prepackaged food. Additionally, the ambient air quality of their residence was examined for its potential effect on NPs concentrations in arterial tissues. However, the results of Spearman's correlation analysis indicated no significant correlation between these factors and microplastic concentrations within arterial tissues.

Current challenges in studying nanoplastics

Studying NPs presents a multifaceted challenge that demands meticulous attention and innovative solutions [43, 44, 48]. With plastic production surging to unprecedented levels, concerns regarding environmental contamination and potential health risks have escalated proportionally [43, 48]. A primary obstacle in studying NPs lies in their interactions with biological systems and their diverse routes of exposure [43, 48]. While efforts have focused on identifying their presence in organs like the intestine and placenta, direct in vivo evidence remains limited [43, 48]. Moreover, the methods used for detection, such as the Laserdirect infrared (LDIR) chemical imaging system, may underestimate their prevalence, necessitating the development of more sensitive techniques [43, 48]. Additionally, correlating exposure to health outcomes poses challenges due to limited sample sizes and the absence of robust epidemiological data [43, 48].

Methodological limitations further hinder accurate detection and characterization of NPs [43, 44, 48]. Techniques like pyrolysis–gas chromatography–mass

spectrometry have been employed, but inconsistencies in results and limitations in distinguishing between different types of plastics remain [44, 48]. Moreover, understanding the sources and pathways of these particles in the human body requires longitudinal studies and interdisciplinary collaborations [44, 48]. The complexity of the research is compounded by ethical considerations surrounding human exposure to microplastics and the translation of findings from animal models [46]. Addressing these challenges necessitates collaborative efforts to standardize methodologies, prioritize funding, and develop innovative research approaches [46]. Only through concerted action can we unravel the intricate interplay between nanoplastics, microplastics, and human health [46].

The escalating production of plastics, reaching a staggering 390 million tons in 2021 from 1.5 million tons in 1950, underscores the urgency for robust regulatory measures [2]. Despite efforts, recycling rates in Europe remain low, with only 34.6% recycled in 2020, posing significant ecological risks [3]. Examining the effectiveness of current regulatory frameworks reveals limitations in addressing the proliferation of NPs [45]. While regulations exist, their enforcement and efficacy in curbing plastic pollution remain questionable [45], compounded by the complex nature of NP pollution and its transboundary transport [45].

Advancements in analytical techniques, like laser direct infrared (LDIR) chemical imaging systems, offer promise in detecting NPs in human tissues [22]. However, current regulatory frameworks have yet to adapt to incorporate such innovative methodologies [25], highlighting the critical need to update regulations to encompass emerging technologies [36]. The identification of NPs in the human cardiovascular system underscores the urgency of enhancing regulatory measures [28], especially considering the diverse chemical composition of NPs and their potential health implications [31].

Global regulatory frameworks governing plastic production and disposal vary, with fragmented approaches to addressing the challenges posed by MPs [45]. While some jurisdictions have implemented bans or restrictions on single-use plastics, regulation of nanoplastics remains underexplored [33]. Existing measures primarily focus on macroplastics and microplastics, overlooking the unique hazards associated with NPs [33], exacerbated by the lack of standardized detection methods [33]. Coordinated international efforts are necessary to develop comprehensive regulatory frameworks targeting NPs [33], emphasizing the need for adaptive and proactive approaches [25].

Despite efforts to mitigate macroplastic pollution, limited attention is directed towards NPs specifically [46]. Regulatory measures, such as bans on single-use plastics and initiatives promoting waste management, represent crucial steps [46]. However, challenges in detecting, quantifying, and characterizing nanoplastics hinder the effectiveness of these measures [46]. Standardized methodologies for NPs detection are lacking, complicating risk assessment and management strategies, showing the need for enhanced regulatory capacity and interdisciplinary collaboration [46].

Conclusion and future directions

Studies into NPs research show the interplay between environmental pollutants and human health, particularly cardiovascular well-being. From their initial origins as environmental contaminants to their pathways of exposure and subsequent cardiovascular effects, NPs represent a multifaceted challenge demanding comprehensive investigation and proactive measures. Experimental studies utilizing animal models and clinical observations in human subjects have provided evidence of the cardiovascular risks associated with NPs exposure, ranging from altered heart rate and myocardial fibrosis to structural abnormalities in cardiac valves and endothelial dysfunction. Moreover, the presence of NPs within human cardiovascular tissues, from the arterial system to cardiac tissues and adjacent structures, underscores their pervasive impact on human health. Despite significant progress, numerous challenges persist in studying NPs and addressing their implications for cardiovascular health. Methodological limitations, ethical considerations, and gaps in regulatory frameworks pose substantial hurdles to advancing our understanding and implementing effective mitigation strategies. Moreover, the escalating production and inadequate management of plastics shows the urgent need for robust regulatory measures and interdisciplinary collaborations to safeguard both environmental and human health.

Moving forward, concerted efforts are needed to standardize methodologies, prioritize funding, and develop innovative research approaches to unravel the interplay between NPs and cardiovascular health. Enhancing regulatory frameworks, promoting sustainable plastic management practices, and fostering global cooperation are essential steps toward mitigating the cardiovascular risks posed by NPs.

Abbreviations

MPs	Microplastics
NPs	Nanoparticles
MNPs	Microplastic nanoparticles
POPs	Persistent organic pollutants
CVD	Cardiovascular disease
PM	Particulate matter
ROS	Reactive oxygen species
PS-MPs	Polystyrene microplastics
MeSH	Medical Subject Headings

IVIS	In-Vivo Imaging System
NRVMs	Neonatal rats ventricular myocytes
PET	Polyethylene terephthalate
PU	Polyurethane
PA	Polyamide
PVC	Polyvinyl chloride
PE	Polyethylene
SEM	Scanning electron microscopy
LDIR	Laserdirect infrared
EAT	Epicardial adipose tissue
PAT	Pericardial adipose tissue
LAA	Left atrial appendage

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GO conceptualized the study; all authors were involved in the literature review; GO and NA extracted the data from the reviewed studies; all authors wrote the final and first drafts. All authors read and approved the final manuscript.

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Declarations

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