

Environmental Micro-Nanoplastics and Musculoskeletal Disorders: Current Research and Insights

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Abstract: In recent years, micro-nanoplastics, as globally prevalent emerging environmental pollutants, can enter the human body through oral ingestion, respiratory inhalation, and dermal contact, and widely distribute in diverse tissues including blood, placenta, lung, bone marrow, and bone, thereby arousing widespread concern regarding their health risks. As an essential functional system of the human body, the skeletal system is involved in mechanical support, metabolic homeostasis, and immune regulation. Disruption of skeletal homeostasis may induce a series of musculoskeletal diseases, such as osteoporosis, rheumatoid arthritis, intervertebral disc degeneration, and osteoarthritis. Accumulating evidence has verified that micro-nanoplastics can accumulate in human bone, cartilage, intervertebral disc, and bone marrow, and destroy skeletal homeostasis via multiple mechanisms, including inflammatory response, oxidative stress, pyroptosis, ferroptosis, cellular senescence, and epigenetic regulation, thus participating in the occurrence and development of musculoskeletal diseases. This paper systematically reviews the sources, classification, environmental distribution, human exposure pathways, and systemic toxic effects of micro-nanoplastics. It emphatically expounds the impacts and potential molecular mechanisms of micro-nanoplastics on osteoporosis, intervertebral disc degeneration, rheumatoid arthritis, osteoarthritis, lupus-related musculoskeletal lesions, and osteosarcoma progression. Furthermore, we summarize the detection methods and research limitations of micro-nanoplastics in skeletal tissues, and prospect future directions in environmental prevention and control, clinical translation, and high-risk population monitoring. This review is expected to provide novel ideas for mechanistic investigation, risk assessment, and clinical translation of micro-nanoplastic-associated skeletal diseases.

Plain Language Summary: 1. This review systematically summarizes the association between environmental micro-nanoplastics and skeletal homeostasis, as well as the latest research evidence in musculoskeletal disorders.

2. This review elucidates the core mechanisms of skeletal system damage induced by micro-nanoplastics, including inflammatory responses, oxidative stress, pyroptosis, ferroptosis, cellular senescence, and epigenetic regulation.

3. This review proposes future research directions and potential strategies for micro-nanoplastics in skeletal disease studies.

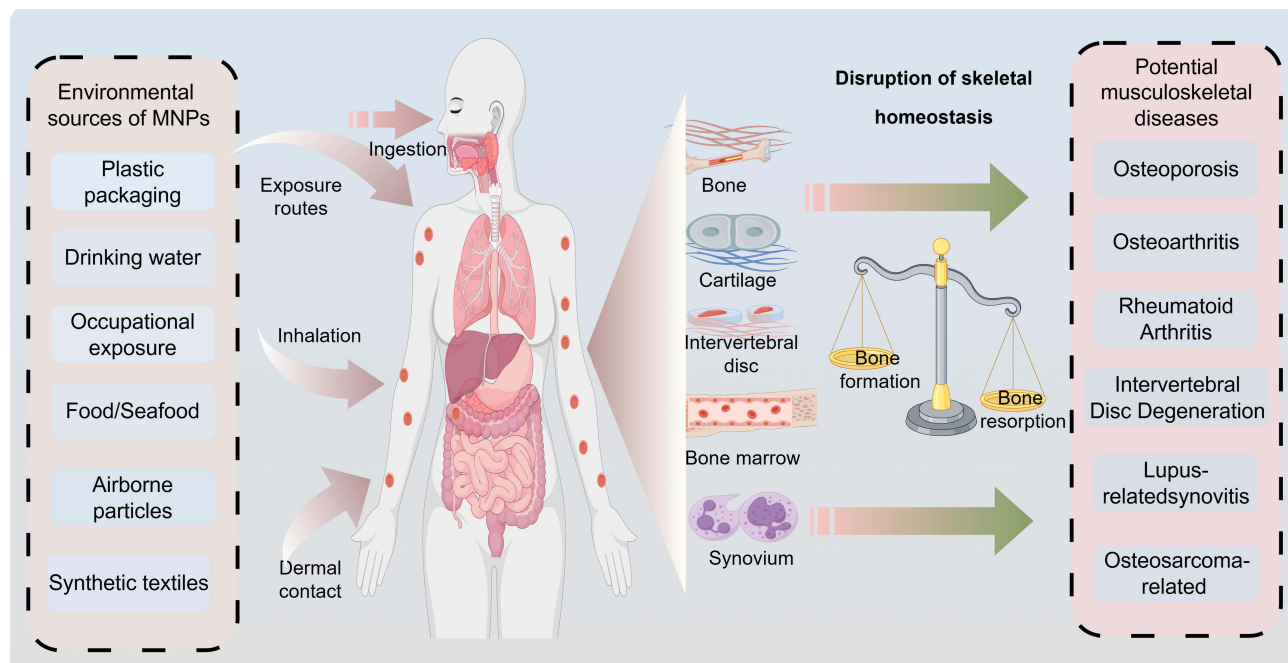
Keywords: microplastics, nanoplastics, skeletal homeostasis, musculoskeletal diseases, ecological environment pollution

Introduction

Microplastics, defined as plastic particles, films, and fibers with diameters less than 5 mm, whereas nanoplastics generally refer to plastic particles within the nanoscale range; however, their size thresholds have not been fully standardized across studies. Together, they have become ubiquitous environmental contaminants.¹⁻³ Over the past few decades, the rapid increase in plastic production, coupled with the strong environmental persistence of plastic waste, has led to the widespread occurrence of micro- and nanoplastic pollution.⁴⁻⁶ Research has documented the presence of



Graphical Abstract



Micro- and nanoplastics in soil, freshwater, sediments, plants, animals, the atmosphere, aquatic ecosystems, and even human bodies.^{7–9} Humans are exposed to micro- and nanoplastics mainly through oral ingestion, inhalation, and potential dermal contact. A growing body of evidence shows that micro- and nanoplastics are present in human blood, placenta, lung tissue, breast milk, liver, spleen, colon, urine, testes, and semen, suggesting that they may cross biological barriers and undergo systemic distribution.^{9–11} The health risks associated with micro- and nanoplastics have therefore attracted considerable global concern, and these pollutants are regarded as important contributors to ecological degradation and potential threats to human health.^{12,13} The skeletal system comprises bones, joints, tendons, ligaments, and other components and is essential for mechanical support, mineral storage, hematopoiesis, endocrine regulation, and immune modulation.^{14–16} Skeletal homeostasis refers to the dynamic equilibrium that maintains bone mass, bone microarchitecture, cartilage integrity, intervertebral disc function, mineral metabolism, and motor function. This process depends on coordinated regulation among osteoblasts, osteoclasts, osteocytes, bone marrow stromal cells, chondrocytes, nucleus pulposus cells, synovial fibroblasts, immune cells, and endocrine factors. Under physiological conditions, osteoblast-mediated bone formation and osteoclast-mediated bone resorption remain dynamically coupled during bone remodeling, whereas cartilage and intervertebral disc tissues preserve joint and spinal homeostasis by maintaining extracellular matrix metabolism and biomechanical function. Disruption of skeletal homeostasis—triggered by inflammation, foreign body exposure, degenerative changes, or metabolic abnormalities—can lead to osteoporosis, fractures, intervertebral disc degeneration, arthritis with motor dysfunction, and immune/inflammatory cascades. These pathological alterations significantly impair human health and quality of life, imposing substantial economic burdens on both society and individuals.^{17–20} Therefore, investigating the adverse effects of microplastics on the skeletal system is crucial for public health, and exploring potential strategies to mitigate microplastic pollution warrants urgent attention.

The skeletal system may be a potential target of long-term micro- and nanoplastic exposure. After entering the human body, micro- and nanoplastics can access the bloodstream and may be transported to highly vascularized or immunologically active tissues, such as bone marrow and synovium. Skeletal homeostasis is closely coupled with immune and inflammatory regulation, and bone remodeling is jointly influenced by cytokines, oxidative stress,

macrophage activation, and osteoimmune signaling. Tissues such as cartilage and intervertebral discs have limited regenerative capacity; therefore, sustained inflammatory stimulation and oxidative injury may increase the risk of structural degeneration and functional impairment. Recent studies have detected microplastics in human bone, cartilage, and intervertebral discs, providing direct evidence of skeletal system exposure.^{21,22} Another study of human bone marrow samples also showed that microplastics can be present in the bone marrow microenvironment, suggesting that their potential effects may not be confined to bone tissue itself.²³ On the basis of these findings, the potential effects of micro- and nanoplastics on skeletal homeostasis and the progression of musculoskeletal diseases warrant further investigation.

Although the body of evidence is increasing, the relationship between micro- and nanoplastic exposure and skeletal system diseases remains insufficiently characterized. Most current studies are based on *in vitro* experiments, animal models, or cross-sectional observations in humans, which are not sufficient to establish a direct causal relationship in the human body. In addition, analytical methods for detecting micro- and nanoplastics in skeletal system samples have not yet been fully standardized. Previous studies have mainly focused on the environmental distribution, systemic toxicity, or general health risks of micro- and nanoplastics, with limited systematic synthesis of their effects on skeletal homeostasis and musculoskeletal diseases. Existing reviews have begun to address the potential effects of microplastics on bone and bone marrow and have suggested possible links with skeletal disorders such as osteoporosis; however, the field still lacks a comprehensive synthesis centered on skeletal homeostasis, disease-related evidence, mechanisms of action, and detection methods.^{22,24} Therefore, this review summarizes the current evidence on the relationship between micro- and nanoplastics and skeletal and musculoskeletal diseases, with a focus on osteoporosis, rheumatoid arthritis, intervertebral disc degeneration, osteoarthritis, lupus-related musculoskeletal involvement, and osteosarcoma progression. It further discusses potential mechanisms, including inflammatory responses, oxidative stress, pyroptosis, ferroptosis, cellular senescence, and epigenetic regulation; compares methods for detecting micro- and nanoplastics in biological samples and skeletal system tissues; and outlines future directions for clinical translation, exposure monitoring, and public health prevention and control.

Formation, Classification, and Environmental Distribution of Microplastics and Nanoplastics

Classification, Sources, and Formation of Micro- and Nanoplastics

Microplastics can be classified into five major categories: fragments, fibers, foams, particles, and films. Based on their chemical composition, microplastics are divided into six types: polyethylene (PE), polystyrene (PS), polypropylene (PP), polyurethane (PUR), polyvinyl chloride (PVC), and polyethylene terephthalate (PET).^{25,26} In terms of origin, microplastics are categorized as primary or secondary. Primary microplastics consist of small synthetic polymers intentionally manufactured for use in exfoliating agents, chemical formulations, abrasive products, plastic product maintenance, and synthetic textile production.^{27,28} Secondary microplastics originate from the fragmentation of larger plastic items or mesoplastics, primarily driven by environmental processes such as biodegradation, photodegradation, thermo-oxidative degradation, thermal degradation, and hydrolytic decomposition. Ultraviolet irradiation, temperature fluctuations, wave action, and abrasion by sand and gravel can all promote the fragmentation of plastic waste and represent important sources of secondary microplastics in the environment.^{29–31} We illustrate the formation and classification of microplastics in [Figure 1](#) (All figures were drawn by Figdraw). Nanoplastics are generally defined as plastic particles within the nanoscale range. In this review, nanoplastics are operationally defined as plastic particles measuring 1–1000 nm, although some studies and regulatory frameworks adopt a narrower upper size limit of 100 nm.^{32,33} Compared with microplastics, nanoplastics have smaller particle sizes, larger specific surface areas, and greater reactivity, properties that may enhance their interactions with biological membranes and facilitate translocation across the blood–brain barrier and other biological barriers, thereby conferring higher bioavailability and potential toxicity.^{34–37} Over the past 70 years, global plastic production has surged from 1.5 million metric tons to approximately 359 million metric tons. Large quantities of plastic waste are incinerated, landfilled, or discharged directly into the environment, further exacerbating micro- and

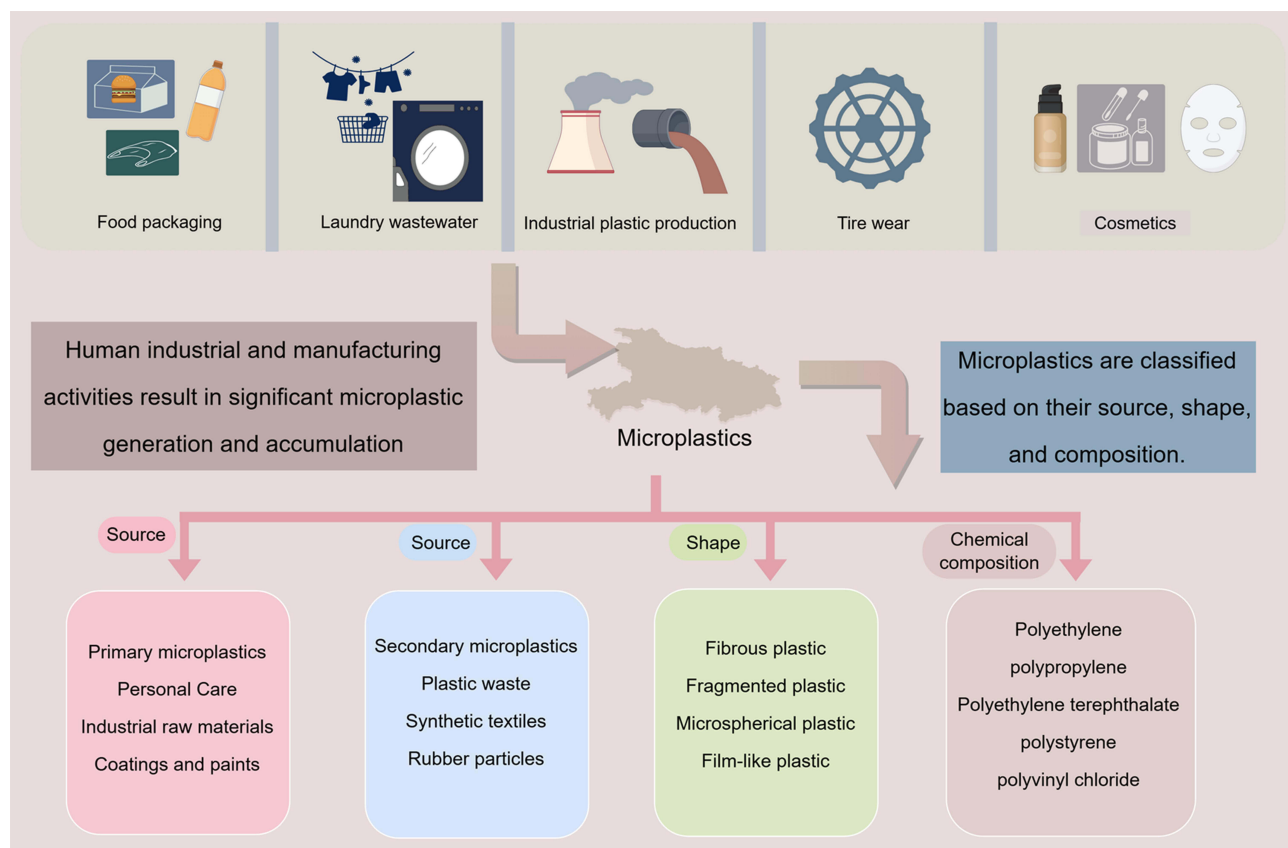


Figure 1 The production of micro-nanoplastics is closely linked to human activities, and micro-nanoplastics can be classified based on their source, shape, and composition.

nanoplastic pollution. Owing to their persistence and resistance to degradation, microplastics and nanoplastics have become a major concern in global environmental health.^{38–40}

Environmental Distribution and Ecological Basis of Exposure to Micro- and Nanoplastics

Micro- and nanoplastics are widely distributed across environmental media, including marine waters, freshwater, soil, the atmosphere, sediments, and glaciers. In recent years, the production of microplastics has significantly increased, with concentrations reaching thousands of particles per cubic meter detected in coastal areas of certain marine regions. These minute particles exert substantial environmental impacts, particularly on aquatic organisms, as they accumulate and leach toxic organic and inorganic contaminants.^{41,42} Furthermore, microplastics are renowned for their stability and resistance to degradation, implying a persistence in the environment for decades.⁴³ Owing to their stability and slow degradation, microplastics can persist in the environment for extended periods and migrate and accumulate across trophic levels through the food chain.^{44,45} After ingestion by aquatic organisms, microplastics may induce adverse effects such as disrupted feeding behavior, gastrointestinal injury, immune dysfunction, oxidative stress, and growth inhibition.^{46–49} Their ecotoxicity is closely related to the route of exposure, particle size, morphology, polymer type, and adsorbed contaminants. Direct exposure is typically characterized by acute or localized injury resulting from particle–organism contact, whereas indirect exposure mainly causes chronic toxicity through food-chain transfer and co-exposure to associated contaminants.^{50–52} These patterns of environmental distribution and ecological accumulation provide an important basis for continuous human exposure to micro- and nanoplastics. Microplastics have been found to exert multiple adverse effects on the environment and organisms (Figure 2).

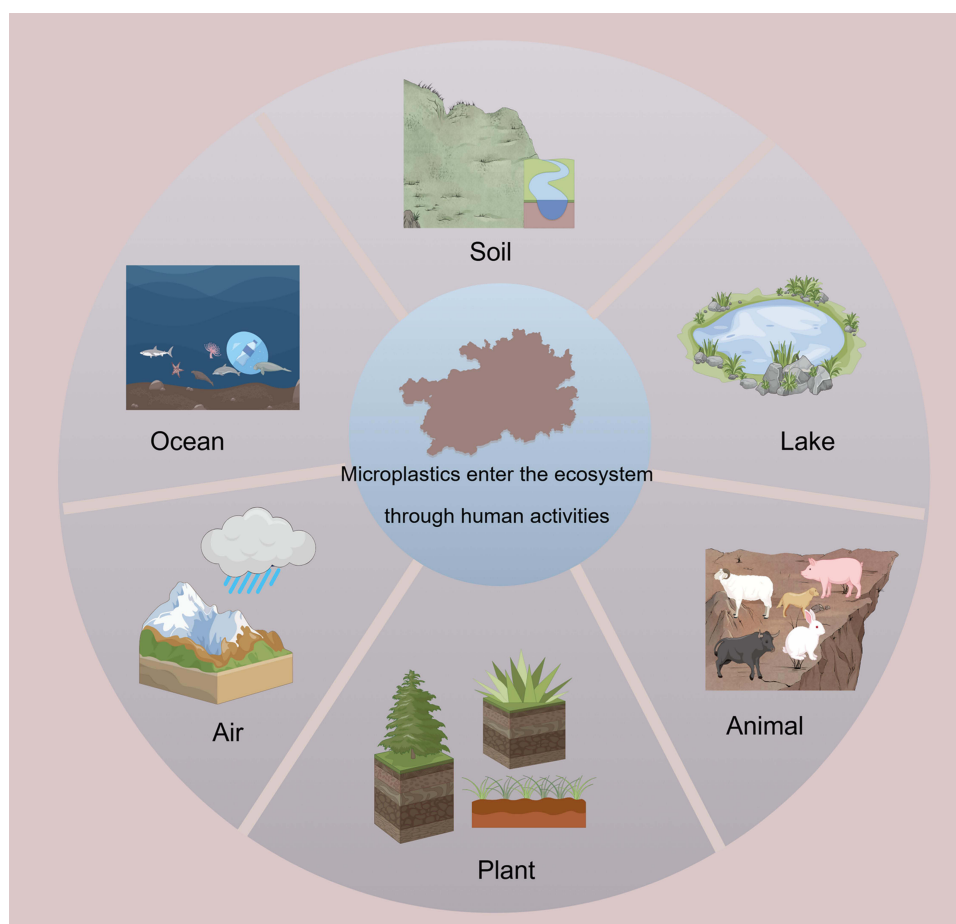


Figure 2 The release of micro-nanoplastics severely impacts ecosystems.

Human Exposure Routes and in vivo Distribution of Micro- and Nanoplastics

Microplastics and nanoplastics have been detected across diverse human samples, with particle sizes ranging from ≥ 800 nm to 5 mm, exhibiting varied colors and dimensions. These contaminants have been identified in critical biological matrices including lungs, breast milk, liver, spleen, placenta, blood, sputum, colon, saliva, facial tissues, urine, testes, and semen.^{46,48,53} Humans are exposed to micro- and nanoplastics mainly through oral ingestion, inhalation, and potential dermal contact. Because air, water, soil, and food can all serve as carriers of micro- and nanoplastics, humans may be subject to long-term, low-dose, and multi-route exposure risks.

The Hazards to Human Health from Drinking Water and Food Sources

Aquatic ecosystems are particularly vulnerable to plastic pollution and high-density plastic particle contamination, with approximately 10–20% of microplastics discharged into aquatic environments originating from marine sources.^{47,54} Reports reveal that over 5.25 trillion particles, totaling 268,940 metric tons, float in the world's oceans. These alarming figures have raised scholarly concerns regarding the survival and mutagenic potential of aquatic organisms.^{55–57} Within urban systems, microplastics are released into aquatic environments through urban/industrial wastewater (eg, water treatment facilities, washing machines) runoff or the breakdown of larger debris via physical, biological, and chemical degradation processes. They have been detected in numerous rivers, oceans, and even in polar snow and Antarctic ice layers worldwide.^{58–60}

Drinking water is also an important source of exposure. Previous studies have detected microplastics in tap water, bottled water, and mineral water, with possible sources including contamination of water sources, packaging processes,

and pollution along the water supply chain.^{61–63} Food packaging materials can likewise release microplastics, particularly under high-temperature conditions involving items such as tea bags, plastic kettles, and infant feeding bottles, where particle release may be more pronounced.^{64–66} During contact between food and plastic packaging, packaging constituents and micro- and nanoplastics may migrate into food, and the gastrointestinal tract is considered an important entry route for nanoplastics into the human body.^{67–69} After entering the digestive tract, micro- and nanoplastics may affect the intestinal barrier, gut microbiota, and local immune responses, thereby inducing systemic biological effects.

Airborne Sources

Airborne microplastics have recently been detected globally, indicating their ubiquitous presence in the atmosphere and associated inhalation risks to humans.^{70,71} Studies have reported residual microplastic particles in lung tissue samples of non-smoking adults.⁷² Jenner et al identified microplastics across all pulmonary regions, predominantly as fibers and fragments.⁷³ Microplastics isolated from bronchoalveolar lavage fluid (BALF) pose a severe concern, as inhaled microplastics have been confirmed to translocate to placental and fetal tissues.^{74,75} The respiratory epithelium serves as the primary target for inhaled nanoplastics (NPs), with biological reactivity dependent on their physicochemical properties. Atmospheric sources of NPs and microplastics include textiles, dried sludge, agricultural residues, and tire rubber dispersed through mechanical abrasion during vehicle operation.^{76,77} The pulmonary alveolar surface, spanning approximately 150 m², features tissue barriers thinner than 1 μm. This barrier enables NP penetration into capillaries, facilitating systemic distribution.⁷⁸ Autopsy analyses of human lung tissues have confirmed microplastics presence, with polymer particles and fibers detected in 13 out of 20 samples.⁷² In occupational settings such as plastic production and processing, monitoring of related monomers and metabolites, in addition to particles themselves, may provide useful exposure information. In styrene-related biomonitoring, urinary styrene (StyU) represents styrene itself, whereas mandelic acid (MA) and phenylglyoxylic acid (PGA) are the major urinary metabolites of styrene and can be used to assess human styrene exposure levels.⁷⁹

Direct Contact

Dermal contact is generally considered a relatively minor route of exposure to microplastics; however, under specific conditions, nanoscale particles may still enter local tissues through sweat glands, hair follicles, or sites of skin barrier disruption.^{80–82} The stratum corneum serves as an important barrier that prevents particulate matter and chemicals from entering the body, and particle size, surface properties, and skin integrity are key factors influencing transdermal penetration.^{83,84} Nanoplastics derived from cosmetics and textiles may increase the risk of dermal exposure. Gopinath et al found that nanoplastics extracted from cosmetics exerted cytotoxic effects on keratinocytes, inducing oxidative stress, inhibiting cell proliferation, and promoting cellular senescence.⁸⁵

Following absorption, microplastics can enter the circulatory system and undergo systemic distribution, potentially harming various organs or tissues. A study by Han et al demonstrated that intratracheally instilled polyethylene (PE)-microplastics accumulated predominantly in mouse lungs, followed by the heart, liver, and gastrointestinal tract.⁸⁶ Other migration pathways involve the lymphatic system and neural fibers, which contribute to microplastics distribution. In zebrafish, research indicated microplastics accumulation in brain regions of embryos, leading to oxidative DNA damage.⁸⁷ The transport and distribution of microplastics depend not only on blood flow, tissue affinity, and diffusivity but also on exposure routes and particle characteristics. Yong et al observed the highest bioaccumulation rate of orally administered microplastics in the gut, with an average residence time of ~17 days.⁸⁸ Additionally, individual health status influences microplastics counts in identical tissues; compared to healthy individuals, higher microplastics levels were detected in the livers of patients with cirrhosis. Thus, the ubiquitous exposure to microplastics and their subsequent systemic adverse effects warrants rigorous attention.⁸⁹

Systemic Toxic Effects of Micro- and Nanoplastics and Their Relevance to Skeletal Homeostasis

After entering the human body, the health effects of micro- and nanoplastics are not confined to the initial sites of exposure. Current evidence indicates that micro- and nanoplastics may affect the nervous, respiratory, gastrointestinal, reproductive, and immune-related systems through mechanisms involving oxidative stress, inflammatory responses, mitochondrial dysfunction, immune dysregulation, endocrine disruption, and metabolic abnormalities.^{90–94} For example, particulate exposure can activate neuroinflammatory responses through direct translocation or the systemic release of pro-inflammatory mediators, thereby inducing microglial activation, oxidative stress, and neuronal injury.^{95,96} Population-based studies suggest that microplastic exposure may be associated with mild cognitive impairment, the risk of Alzheimer's disease progression, and the incidence of dementia.^{97,98} Animal studies have also shown that microplastics can affect neurotransmitter metabolism, oxidative stress levels, and behavioral outcomes.^{99,100}

The respiratory system is one of the major entry sites for micro- and nanoplastic exposure. Inhaled microplastics can deposit in the respiratory tract and lung tissue and may disrupt pulmonary homeostasis through local inflammatory responses, epithelial barrier injury, and activation of inflammation-related genes.^{101,102} The gastrointestinal tract is the primary target site after oral ingestion of micro- and nanoplastics. Previous studies have reported higher fecal microplastic concentrations in patients with inflammatory bowel disease than in healthy individuals, with concentrations correlated with disease severity.^{103,104} Animal experiments further suggest that exposure to microplastics such as PVC can cause intestinal barrier injury, gut microbiota dysbiosis, metabolic disturbances, and systemic inflammatory responses.^{105,106} These alterations may further affect the homeostasis of distant organs through disruption of the intestinal barrier, changes in microbial metabolites, and dissemination of immune-inflammatory signals.

Studies on reproductive and developmental toxicity have shown that nanoplastics can impair reproductive capacity across generations, induce abnormal gonadal development, and increase the risk of translocation across the placental barrier.^{107,108} After pregnant mice were exposed to 20 nm polystyrene nanoplastics, particles were detected in multiple maternal organs as well as in the liver, lungs, heart, kidneys, and brain of fetuses, accompanied by reduced fetal body weight and placental weight.⁷⁴ These findings suggest that smaller nanoplastics may have greater barrier-penetrating capacity and pose higher developmental toxicity risks.

These systemic effects are linked to skeletal homeostasis at multiple levels. Chronic inflammation and oxidative stress can enhance osteoclast activity, impair osteogenic differentiation, and promote extracellular matrix degradation in cartilage and intervertebral disc cells. Intestinal barrier dysfunction and gut microbiota dysbiosis may affect bone metabolism through the gut–bone axis, while abnormalities in endocrine and energy metabolism may also alter the local and systemic regulatory environment required for bone remodeling. These mechanisms provide a biological basis for understanding the potential skeletal toxicity of micro- and nanoplastics. Given these links, it is necessary to further synthesize the available evidence on the potential effects of micro- and nanoplastics on osteoporosis, rheumatoid arthritis, intervertebral disc degeneration, osteoarthritis, lupus-related musculoskeletal involvement, and osteosarcoma progression. The major systemic toxic effects of micro- and nanoplastics and their potential links with skeletal homeostasis are summarized in [Figure 3](#).

In conclusion, the multi-system issues caused by microplastics in the human body cannot be ignored.

Micro- and Nanoplastics in Skeletal and Musculoskeletal Diseases

The skeletal system is not merely a structural support system; rather, it is a dynamic organ system closely linked to immune, metabolic, endocrine, and inflammatory regulation. In recent years, evidence of microplastics in human bone, cartilage, intervertebral discs, and bone marrow has drawn increasing attention to the potential effects of micro- and nanoplastics on skeletal homeostasis and musculoskeletal diseases. At the disease level, current evidence is mainly concentrated in osteoporosis, rheumatoid arthritis, intervertebral disc degeneration, osteoarthritis, lupus-related musculoskeletal involvement, and osteosarcoma progression. It should be noted that most existing studies are based on cross-sectional human observations, animal experiments, or *in vitro* mechanistic investigations. Further long-term cohort studies and clinical validation are therefore needed to clarify the potential relationship between micro- and nanoplastic

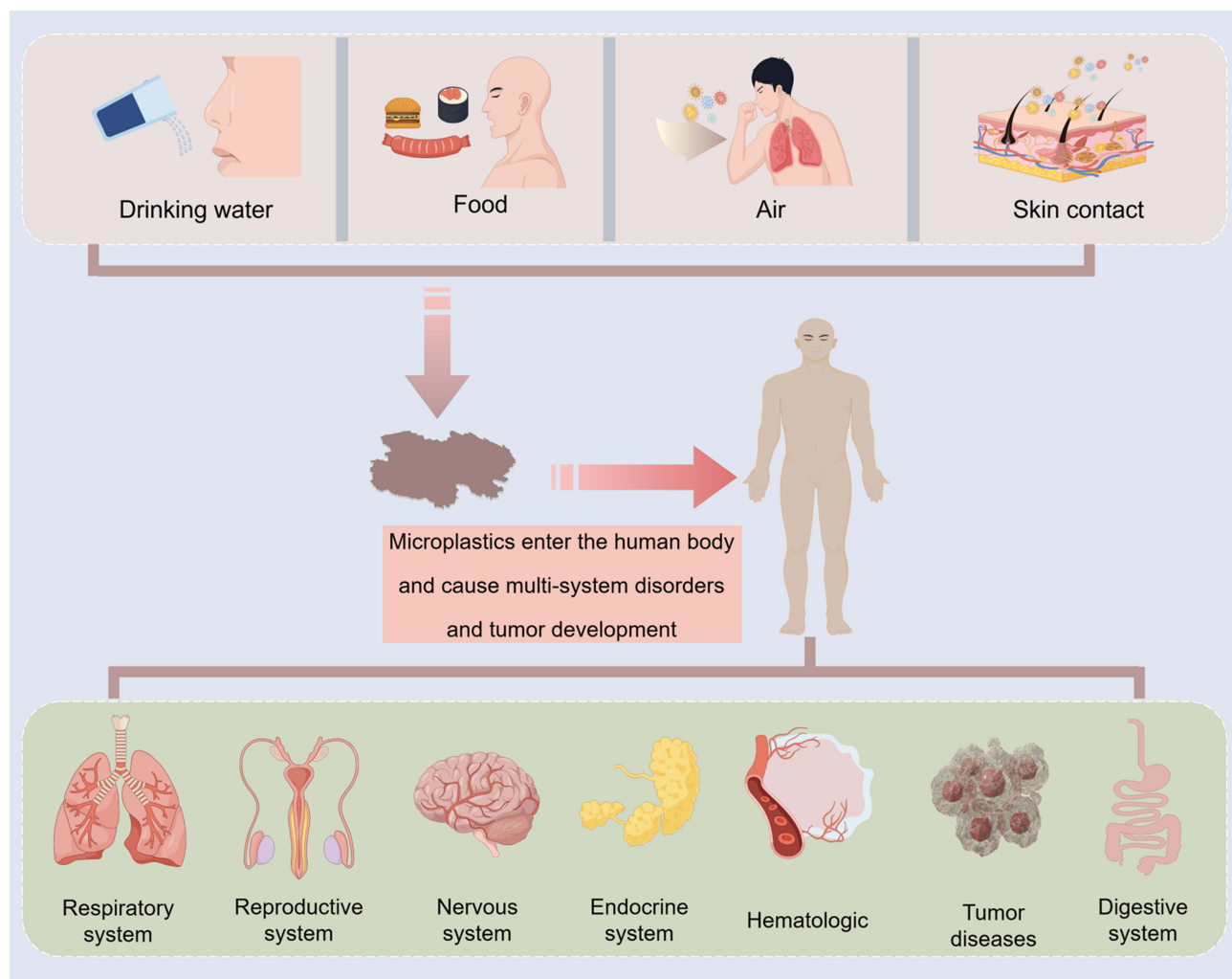


Figure 3 Plastics enter the human body through drinking water, food, air, and skin contact, and pose adverse effects on multiple body systems.

exposure and skeletal diseases. To provide an overview of the current evidence, representative studies linking micro- and nanoplastics to skeletal and musculoskeletal disorders are summarized in [Table 1](#).

Micro- and Nanoplastics and Osteoporosis

Osteoporosis (OP) is a systemic metabolic bone disease characterized by microarchitectural changes in bone tissue and reduced bone density, which subsequently increase fracture risk, leading to pain, decreased mobility, and deterioration of quality of life, with severe cases posing life-threatening risks.^{121,122} As the most common skeletal disorder, over 200 million individuals worldwide are affected by OP. Indeed, due to population aging and increasing life expectancy, its incidence continues to rise annually, positioning OP as an increasingly severe global public health concern.¹²³

Bone remodeling is a fundamental process for maintaining bone mass, bone strength, and mineral homeostasis. Under physiological conditions, osteoblast-mediated bone formation and osteoclast-mediated bone resorption remain dynamically coupled. When this balance is disrupted by factors such as aging, menopause, inflammatory responses, endocrine disorders, nutritional deficiency, or metabolic abnormalities, relatively enhanced bone resorption or insufficient bone formation can promote the onset and progression of osteoporosis. Therefore, any exogenous factor capable of affecting osteoblast–osteoclast coupling, the bone marrow microenvironment, or osteoimmune regulation may represent a potential environmental risk factor in osteoporosis research.^{124–126} Blood samples from 37 OP patients were analyzed for microplastic composition, revealing significantly elevated levels of PVC and PET particles compared to non-

Table 1 Summary of Studies Linking Microplastics and Nanoplastics to Skeletal and Musculoskeletal Disorders

Disease/Pathological Condition	Study Model/Evidence Type	Particle Type and Exposure Condition	Main Findings	Potential Mechanisms	Ref.
Accumulation in human skeletal tissues and bone marrow	Human bone, cartilage, intervertebral disc, and bone marrow samples	Various MPs; 25.44–407.39 μm in bone/cartilage/disc samples; most bone marrow particles <100 μm	MPs were detected in human bone, cartilage, intervertebral discs, and bone marrow, providing direct evidence of skeletal exposure	Potential effects on local inflammation, osteogenic factors, bone marrow immune microenvironment, and bone metabolism	[21,23]
Osteoporosis/bone loss	Human blood association study; long-term mouse exposure; BMSC experiments	PVC, PET, and PS-MPs; long-term low-dose PS-MP exposure in drinking water; BMSC treatment	PVC/PET particles were increased in patients with osteoporosis; PS-MPs reduced bone mass, impaired trabecular structure, suppressed bone formation, and enhanced osteoclast activation	NF- κB activation, BMSC senescence, impaired osteogenesis, RANKL-mediated osteoclastogenesis, oxidative stress, and inflammation	[109,110]
Rheumatoid arthritis	RA synovial fluid detection; RA-FLS experiments; arthritis animal models	MPs or 5 μm PS-MPs; RA-FLS exposure; CFA-induced arthritis and humanized SCID models	PS-MPs were detected in RA synovial fluid; MPs promoted RA-FLS proliferation, migration, invasion, inflammatory mediator release, joint inflammation, and cartilage erosion	Mitochondrial dysfunction, NF- κB /MAPK activation, JNK/p38 signaling, and upregulation of IL-6, IL-8, CCL2, MMP3, and MMP9	[111,112]
Intervertebral disc degeneration	Human disc samples; mouse IVDD model; NPC and macrophage-derived exosome experiments	PE-MPs; human cervical, lumbar, and thoracolumbar disc samples; NPC and macrophage models	MPs were detected in human intervertebral discs, with PE as a major polymer; PE-MPs promoted NPC senescence, ferroptosis, ECM degradation, and IVDD-like changes	TLR4/NOX2/ROS axis, oxidative stress, macrophage-derived exosome transport, NAT10/SLC7A11, ac4C modification, ferroptosis, and senescence	[113,114]
Osteoarthritis	Translational review; network toxicology; DMM mouse OA model; chondrocyte experiments	MPs/MNPs; 20 nm PS-NPs; PET-MP mechanism prediction and validation	MNPs may accelerate OA progression, cartilage matrix loss, chondrocyte inflammatory injury, and joint microenvironment disruption	Lysosomal destabilization, cathepsin B release, NLRP3 inflammasome activation, GSDMD-mediated pyroptosis, and PTGS2-related inflammation	[115–117]
SLE-related synovitis/musculoskeletal involvement	MRL/lpr SLE mouse model; C57BL/6 lupus-like model	5 μm MPs; 0.5 and 5 mg/kg by gavage, 5 times/week for 9 weeks; systemic mouse exposure models	MPs aggravated synovial injury, oxidative stress, synovial fibrosis, inflammatory cytokine release, pyroptosis, and lupus-like manifestations	Upregulation of NLRP3, caspase-1, GSDMD, IL-1 β , and IL-18; NF- κB activation; NRF2/KEAP1 dysregulation	[118,119]
Osteosarcoma progression	Human osteosarcoma tissue detection; osteosarcoma cell experiments; tumor animal model	PE-MPs; human tumor samples; in vitro and in vivo exposure models	MPs were detected in human osteosarcoma tissues; PE-MPs were internalized by osteosarcoma cells and promoted malignant phenotypes and tumor growth	ITGA5 upregulation and formation of the ITGA5/FAP α /LGMN cancer-promoting complex	[120]

Notes: The summarized mechanisms are based on available evidence and do not establish causality. Most human studies remain observational or detection-based.

Abbreviations: MPs, microplastics; NPs, nanoplastics; MNPs, microplastics and nanoplastics; PS, polystyrene; PE, polyethylene; PVC, polyvinyl chloride; PET, polyethylene terephthalate; BMSCs, bone marrow mesenchymal stem/stromal cells; RA-FLS, rheumatoid arthritis fibroblast-like synoviocytes; NPCs, nucleus pulposus cells; IVDD, intervertebral disc degeneration; SLE, systemic lupus erythematosus; OA, osteoarthritis; ECM, extracellular matrix.

osteoporotic individuals. In cellular experiments, the phagocytic capacity of MC3T3 cells incubated with PET or PVC increased over time. Additionally, PET- or PVC-treated cells exhibited higher apoptosis rates, upregulated pro-inflammatory cytokines (IL-1 β , TNF- α , and IL-6), and enhanced reactive oxygen species (ROS) responses.¹⁰⁹ This human study mainly suggests a potential association between microplastic burden and osteoporosis, but does not establish that PVC or PET microplastics directly cause osteoporosis.

In vivo studies demonstrated that long-term low-dose PS-MP exposure suppressed bone formation, promoted osteoclast activation, caused significant damage to trabecular bone structure, and elevated senescence markers in mice, potentially contributing to OP development. Bone marrow stromal cells (BMSCs) cultured with varying PS-MP concentrations displayed reduced expression of osteogenic markers (Osterix and RUNX2) and increased adipogenic differentiation markers. Mechanistically, the NF- κ B pathway played a pivotal role in PS-MP-induced BMSC senescence and osteoclastogenesis, as targeting this pathway reversed MP-mediated BMSC aging.¹¹⁰ In summary, prolonged microplastic accumulation disrupts bone homeostasis by altering the balance between osteogenesis and osteoclasticity, triggering cellular and microenvironmental inflammation, oxidative stress, and impaired osteoblast migration while enhancing osteoclastogenesis.¹²⁷ Future prospective cohort studies are still needed to further validate the relationships between microplastic exposure levels, reductions in bone mineral density, changes in bone turnover markers, and fracture risk.

Micro- and Nanoplastics and Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease primarily affecting joints. RA can occur in individuals of any age, with higher incidence observed in populations over 40 years old. Women are affected at a frequency 2–3 times greater than men.¹²⁸ Currently, the pathogenesis of RA is complex, involving abnormal immune cell function, cytokine release, and microbiome-joint axis interactions as key mechanisms. It is characterized by inflammatory changes in synovial tissues, cartilage, and bone, along with less frequent extra-articular inflammation.¹²⁹

Genetic susceptibility plays a pivotal role, with first-degree relatives of RA patients exhibiting a 2- to 5-fold increased risk compared to the general population.¹³⁰ Multiple alleles have been associated with elevated RA risk, most notably those related to rheumatoid factor (RF), antibodies targeting post-translationally modified proteins, and T/B lymphocyte migration to synovium. Additionally, environmental factors such as cigarette smoke and dust exposure significantly contribute to aberrant immune system activation, highlighting critical crosstalk between adaptive and innate immune components. Clinically, RA manifests as synovial joint pain, swelling, stiffness, and cartilage/bone destruction.^{131,132} Fibroblast-like synoviocytes (FLS) in the synovial lining layer have been demonstrated to play a central role in RA pathogenesis. When incubated with varying concentrations of microplastics (0–1.0 mg/mL) for 60 minutes, fluorescently labeled microplastics were internalized into FLSs in a dose- and time-dependent manner. Microplastic stimulation enhanced proliferation markers and migratory capacity of RA-FLSs. Furthermore, microplastic exposure promoted FLS migration in RA and stimulated release of inflammatory cytokines IL-6, IL-1 β , and TNF α . In vivo, intra-articular injection of microplastics in mouse knees and paws significantly exacerbated cartilage damage and accelerated arthritis progression.¹¹¹ It should be noted that the concentrations of microplastics used in some in vitro experiments were higher than realistic environmental exposure levels; therefore, these findings are more appropriate for elucidating potential mechanisms than for directly extrapolating exposure risks to the general population.

Recent studies have further strengthened disease-level evidence linking microplastics to RA. PS-MPs have been detected in the synovial fluid of patients with RA, and 5 μ m PS-MPs were shown to be taken up by RA-FLS, activate the NF- κ B/MAPK signaling pathways, promote the expression of inflammatory and matrix-degradation-related molecules such as IL-6, IL-8, CCL2, MMP3, and MMP9, and exacerbate joint inflammation and cartilage erosion in animal models.¹¹² Notably, the microplastic concentration range used in these FLS in vitro experiments was 0–1.0 mg/mL, which is higher than most realistic environmental or general population exposure levels. Accordingly, such experimental findings are more suitable for revealing the inflammatory and migratory mechanisms that may be triggered after microplastics are internalized by synovial cells, rather than for directly inferring the risk of RA onset under environmental exposure conditions in the general population.

Overall, current evidence suggests that microplastics may act as environmental particulate stimuli that exacerbate synovial inflammation and joint structural damage in RA. However, direct evidence for their role in RA initiation remains lacking, and these conclusions require further validation using larger patient samples, realistic exposure assessment, and long-term follow-up studies.

Micro- and Nanoplastics and Intervertebral Disc Degeneration

Intervertebral disc degeneration (IDD) is a prevalent cause of joint-related chronic disability in the elderly worldwide. It severely impacts quality of life and imposes substantial socioeconomic burdens. With the aging population and accelerating life pace alongside persistent stress from daily work routines, IDD has become a common underlying pathology for age-related joint dysfunction. As the primary source of low back pain, it serves as the shared pathological basis for multiple spinal disorders including lumbar disc herniation and spinal stenosis.^{133,134} The intervertebral disc (IVD) comprises the nucleus pulposus (NP), annulus fibrosus (AF), and cartilaginous endplate (CEP), playing critical roles in spinal motion and load bearing. The NP, located centrally within the IVD, contains abundant water and extracellular matrix (ECM) essential for maintaining disc functionality. Key characteristics of IDD include reduced disc height, diminished hydration capacity, and impaired pressure absorption capability. During IVD degeneration, multiple phenotypic changes occur, including decreased NP cell (NPC) quantity, ECM degradation, disorganization of NP and AF tissues, CEP calcification, and microfractures.^{135,136} Extensive studies demonstrate close associations between inflammation and various pathological processes of IDD, including sustained ECM loss, cell apoptosis, and senescence. Genetic predisposition, aging, obesity, smoking, trauma, and abnormal mechanical loading are generally recognized as contributing factors.^{20,137}

With the widespread use of microplastics, emerging research reveals intimate correlations between microplastic exposure and IDD progression. Raman spectroscopy analyses have detected diverse polymeric microplastic in human cervical, thoracic, and lumbar discs. Animal experiments demonstrate that polyethylene microplastic (PE-MP) exposure induces significant disc degeneration in mice, manifesting as reduced NP thickness, irregular morphology, and decreased cellular density. Mechanistically, microplastic promote disc aging and degeneration by activating the TLR4/NOX2 signaling axis to induce oxidative stress, thereby promoting NP cell senescence and the degenerative disc phenotype.¹¹³ Other studies suggest that microplastics may further affect the intervertebral disc microenvironment through intercellular transport and regulated cell death. PE-MPs can be transported to NP cells via macrophage-derived exosomes and induce lipid peroxidation, ferroptosis, cellular senescence, and ECM degradation through NAT10/SLC7A11- and ac4C modification-related pathways, thereby promoting IDD progression.¹¹⁴ In addition, network toxicology and molecular docking analyses further identify AKT1, SRC, CASP3, KDR, PTGS2, PIK3CA, and MAPK14 as key genes mediating PET-MP-driven IVDD progression.¹³⁸ Overall, IDD is currently one of the areas in skeletal system research on microplastics with relatively direct tissue-level evidence; however, further population-based studies are needed to clarify the relationship between microplastic burden in intervertebral discs and the clinical severity of disc degeneration.

Micro- and Nanoplastics and Osteoarthritis

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by articular cartilage degeneration, subchondral bone remodeling, synovial inflammation, and pain. Aging, obesity, abnormal mechanical loading, joint injury, and low-grade chronic inflammation can all contribute to the onset and progression of OA.^{139,140} Although clinical evidence regarding the relationship between micro- and nanoplastics and OA remains limited, this area is receiving increasing attention.

Existing translational reviews and mechanistic studies suggest that micro- and nanoplastics may contribute to OA progression through inflammatory responses, oxidative stress, chondrocyte injury, and disruption of the joint microenvironment.^{115,116} Network toxicology and molecular docking studies also indicate that PET-MPs may affect shared targets and inflammatory pathways related to OA and RA, with molecules such as PTGS2 potentially playing a role in microplastic-associated joint toxicity.¹¹⁷

A recent experimental study further suggested that exposure to 20 nm PS-NPs can accelerate OA progression in mice and promote cartilage matrix loss through lysosomal destabilization, Cathepsin B release, NLRP3 inflammasome

activation, and GSDMD-mediated chondrocyte pyroptosis.¹¹⁵ These findings suggest that nanoplastics may act as potential pathological amplifiers within the OA joint microenvironment. However, evidence from human samples and long-term exposure studies remains lacking in the context of OA, and the role of nanoplastics in OA onset and progression requires further validation.

Micro- and Nanoplastics and Lupus-Related Musculoskeletal Involvement

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the presence of autoantibodies targeting nuclear antigens and immune complex deposition. The organs most severely affected by SLE are the kidneys, nervous system, joints, and skin, with persistent inflammation potentially leading to irreversible organ damage. Although SLE can occur at any age, it predominantly affects women of reproductive age. Most patients may develop arthralgia, myalgia, synovitis, or other musculoskeletal manifestations during the disease course. Although SLE is a systemic autoimmune disease, musculoskeletal manifestations such as arthralgia, myalgia, and synovitis are common; therefore, lupus-related osteoarticular involvement may be discussed as extended evidence for the effects of micro- and nanoplastics on the musculoskeletal system.^{141,142}

The pathogenesis of SLE is complex, involving interactions between genetic, environmental, hormonal, and immunological factors, including both innate and adaptive immune dysregulation. A hallmark feature of SLE is the production of autoantibodies forming immune complexes that precipitate in vasculature, driving organ injury. Biological mechanisms involve self-antigens triggering T cell dysfunction, subsequently causing B cell hyperactivation and excessive antibody production.^{143,144} Given that SLE-associated synovitis and joint involvement are closely related to immune inflammation, pyroptosis, and oxidative stress, the potential effects of micro- and nanoplastics on SLE-related musculoskeletal injury warrant attention.

Chronic microplastic exposure has been shown to significantly exacerbate synovial inflammation in SLE mouse models, evidenced by increased inflammatory cell infiltration, enhanced angiogenesis, and elevated TUNEL-positive cells. These pathological changes correlate with microplastic dosage, with apoptotic rates increasing by 5% after low-dose exposure and 10% after high-dose exposure.¹¹⁸ Mechanistically, microplastics can upregulate the expression and phosphorylation of NF- κ B signaling pathway-related proteins in a dose-dependent manner and promote the expression of pyroptosis-related molecules, including NLRP3, CASPASE-1, GSDMD, IL-1 β , and IL-18, thereby amplifying synovial inflammation and pyroptotic responses. Dysregulation of the NRF2/KEAP1 antioxidant pathway may also be involved in this process.¹¹⁹

Additionally, microplastic exposure upregulates NF- κ B signaling pathway-related protein expression and phosphorylation in a dose-dependent manner. Microplastic may amplify synovial inflammation and pyroptosis by modulating NF- κ B pathways, thereby worsening structural and functional synovial damage. Prolonged high-dose microplastic exposure further aggravates renal structural injury in mice, induces lupus-like symptoms, and potentiates pre-existing lupus manifestations. These include abnormal elevations in splenic double-negative T cells, plasma cells, serum autoantibodies, and pro-inflammatory cytokines.¹¹⁹

However, these findings are mainly derived from animal models and do not directly demonstrate that microplastics are an inducing factor for human SLE. Current evidence more strongly supports the possibility that microplastics may exacerbate lupus-related inflammatory responses and musculoskeletal involvement, whereas their role in the onset of human SLE requires further validation.

Micro- and Nanoplastics and Osteosarcoma Progression: Emerging Evidence

Beyond degenerative and inflammatory osteoarticular diseases, the relationship between microplastics and bone tumor progression has also begun to receive attention. Osteosarcoma is one of the most common primary malignant bone tumors and is characterized by high aggressiveness, a strong tendency for metastasis, and a high risk of recurrence. Whether environmental pollutants contribute to remodeling of the bone tumor microenvironment and malignant progression has emerged as an important area of investigation.

A recent study detected microplastics in human osteosarcoma tissues and further showed that PE-MPs can be internalized by osteosarcoma cells, promoting malignant cellular phenotypes and tumor growth. Mechanistic analyses

suggested that PE-MPs can upregulate ITGA5 and promote the formation of the pro-tumorigenic ITGA5/FAP α /LGMN complex; blockade of this complex partially reversed the microplastic-mediated pro-tumor effects.¹²⁰ This study provides emerging evidence for a potential link between microplastics and bone tumor progression. However, research in osteosarcoma remains at an early stage, and the available evidence is mainly derived from a single human tissue-detection study and experimental models. Whether microplastics participate in osteosarcoma initiation, progression, or remodeling of the tumor microenvironment requires further validation in independent cohorts, different plastic particle models, and long-term exposure studies.

Current Mechanisms of Micro- and Nanoplastics Harm to the Skeletal System

Research on the effects of micro- and nanoplastics on the skeletal system is still at an early stage. However, existing evidence suggests that their injurious effects are not mediated by a single pathway, but instead involve multiple processes, including particle uptake, activation of inflammatory signaling, oxidative stress, mitochondrial dysfunction, pyroptosis, cellular senescence, ferroptosis, and disruption of osteoblast–osteoclast coupling. Bone, cartilage, synovium, intervertebral discs, and the bone marrow microenvironment differ in cellular composition and metabolic characteristics; therefore, the modes of action of micro- and nanoplastics may also vary across tissues. Overall, inflammatory responses and oxidative stress are currently the two shared mechanisms with the strongest body of evidence.

Particle Uptake, Tissue Accumulation, and Disruption of the Skeletal Microenvironment

The ability of micro- and nanoplastics to reach skeletal tissues and interact with local cells is a prerequisite for their effects on the skeletal system. Recent studies of human samples have detected microplastics in bone, cartilage, intervertebral discs, and bone marrow, providing direct evidence of skeletal system exposure.^{21,23} At the cellular level, micro- and nanoplastics can be taken up by osteoblast-like cells, bone marrow stromal cells, synovial fibroblasts, macrophages, and nucleus pulposus cells, potentially affecting lysosomal function, mitochondrial homeostasis, and cellular stress responses. Particle uptake and the resulting disturbance of the local microenvironment represent a common starting point for subsequent mechanisms such as inflammatory responses, oxidative stress, pyroptosis, cellular senescence, and matrix degradation.

Activation of TLR4/NF- κ B- and MAPK-Mediated Inflammatory Signaling

Activation of inflammatory signaling is one of the key mechanisms by which micro- and nanoplastics induce skeletal system injury. After entering local tissues, micro- and nanoplastics may activate pattern-recognition receptors through particle stimulation, surface-adsorbed contaminants, cellular stress responses, or the release of damage-associated molecules, among which the TLR4/NF- κ B pathway has received considerable attention.^{145–148} In the canonical inflammatory response, lipopolysaccharide (LPS) is a typical ligand of TLR4 and can activate IRAK, TRAF6, and the IKK complex through the TLR4/MyD88 axis, promoting I κ B α degradation and nuclear translocation of NF- κ B p65, ultimately inducing the expression of IL-1 β , IL-6, TNF- α , COX-2, and various chemokines. Unlike LPS, whether micro- and nanoplastics directly act as TLR4 ligands remains unclear. They are more likely to indirectly amplify TLR4/NF- κ B-mediated inflammatory cascades through particle surface properties, adsorbed endotoxins or organic pollutants, oxidative injury, and the release of cellular danger signals.

In skeletal system-related studies, the TLR4/NF- κ B pathway is closely associated with impaired osteogenesis, enhanced osteoclastogenesis, synovial inflammation, and extracellular matrix degradation. In osteoporosis models, PS-MPs can activate NF- κ B signaling, promote BMSC senescence, and enhance RANKL-related osteoclastogenesis, thereby disrupting the dynamic balance between bone formation and bone resorption.¹¹⁰ In studies of rheumatoid arthritis, PS-MPs have been detected in the synovial fluid of patients with RA, and 5 μ m PS-MPs can be taken up by RA-FLS, activate the NF- κ B/MAPK signaling pathways, promote the expression of inflammatory and matrix-degradation-related molecules such as IL-6, IL-8, CCL2, MMP3, and MMP9, and aggravate joint inflammation and cartilage erosion in

animal models.¹¹² These findings suggest that the NF- κ B/MAPK pathways may serve as important signaling nodes through which microplastics promote synovial inflammation, cartilage destruction, and osteoarticular structural damage.

Similar inflammatory pathways may also participate in lupus-related synovitis and other forms of musculoskeletal injury. Studies using SLE models have shown that microplastic exposure can increase the expression and phosphorylation of NF- κ B-related proteins in synovial tissue, accompanied by inflammatory cell infiltration, synovial injury, and upregulation of pyroptosis-related molecules.^{118,119} Collectively, these findings suggest that micro- and nanoplastic-induced inflammatory responses are not confined to a single skeletal disease, but may represent a shared pathological basis across osteoporosis, inflammatory arthropathies, and degenerative diseases. However, most current studies remain limited to animal models and in vitro cellular systems. Whether micro- and nanoplastics drive inflammatory responses in the human skeletal system through a specific TLR4-recognition mechanism requires further validation.

Oxidative Stress, NOX2/ROS, and NRF2/KEAP1 Antioxidant Imbalance

Oxidative stress is one of the more consistent mechanistic signals implicated in micro- and nanoplastic-induced skeletal system injury. After entering cells, micro- and nanoplastics can promote the generation of reactive oxygen species (ROS) through mitochondrial dysfunction, activation of NADPH oxidases, recruitment of inflammatory cells, and contaminants adsorbed onto particle surfaces. Excessive ROS can cause oxidative damage to lipids, proteins, and DNA, while further amplifying inflammatory responses, cellular senescence, and cell death. In the skeletal system, oxidative stress can inhibit osteogenic differentiation of osteoblasts and BMSCs, promote osteoclast activation, and accelerate degeneration of chondrocytes and nucleus pulposus cells.

In osteoporosis-related studies, PET or PVC microplastics were shown to increase ROS levels in MC3T3 cells, accompanied by elevated expression of inflammatory cytokines such as IL-1 β , TNF- α , and IL-6.¹⁰⁹ In studies of intervertebral disc degeneration, PE-MPs enhanced ROS production through the TLR4/NOX2 signaling axis and induced nucleus pulposus cell senescence and degenerative phenotypes.¹¹³ These findings suggest that NOX2-mediated oxidative stress may be an important mechanism by which microplastics impair nucleus pulposus cell function and disrupt intervertebral disc homeostasis.

The NRF2/KEAP1 pathway is an important protective mechanism by which cells respond to oxidative stress. Under physiological conditions, KEAP1 binds to NRF2 and promotes its degradation. When oxidative stress increases, NRF2 is released from the KEAP1 complex and translocates into the nucleus, where it induces the expression of antioxidant genes such as HO-1, NQO1, and GCLC. If micro- and nanoplastic exposure persistently increases the ROS burden while the NRF2/KEAP1-mediated antioxidant response remains insufficient, oxidative damage may accumulate. In models of SLE-related synovitis, microplastic exposure was associated with NRF2/KEAP1 pathway abnormalities, synovial oxidative stress, and aggravated inflammatory injury.¹¹⁹ Future studies could further incorporate indicators such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), lipid peroxidation products, mitochondrial membrane potential, and antioxidant enzyme activity to determine whether micro- and nanoplastics contribute to skeletal system pathology through oxidative DNA damage and mitochondrial dysfunction.

NLRP3 Inflammasome Activation and Pyroptosis

Pyroptosis is a form of inflammatory programmed cell death that is typically associated with NLRP3 inflammasome activation, caspase-1 activation, GSDMD cleavage, and the release of IL-1 β and IL-18. After entering cells, micro- and nanoplastics may trigger the NLRP3 inflammasome through lysosomal damage, increased mitochondrial ROS production, and disruption of ionic homeostasis. Compared with apoptosis alone, pyroptosis is accompanied by inflammatory cytokine release and cell membrane rupture, making it more likely to amplify local inflammatory responses.

In synovial and cartilage tissues, pyroptosis may promote synovial inflammation, cartilage matrix degradation, and joint structural damage. Studies of SLE-related synovitis have shown that microplastic exposure can upregulate pyroptosis-related molecules, including NLRP3, CASPASE-1, GSDMD, IL-1 β , and IL-18, and aggravate synovial inflammation and tissue injury.¹¹⁹ In the context of osteoarthritis, a recent study suggested that 20 nm PS-NPs can accelerate OA progression and cartilage matrix loss through lysosomal destabilization, Cathepsin B release, NLRP3 inflammasome activation, and GSDMD-mediated chondrocyte pyroptosis.¹¹⁵

These studies indicate that the NLRP3 inflammasome and pyroptosis may represent important mechanisms by which micro- and nanoplastics exacerbate joint inflammation and cartilage injury. However, current evidence is mainly derived from animal models and cellular experiments, and their actual contribution to human osteoarticular diseases requires further validation using patient tissue samples and long-term exposure studies.

Cellular Senescence, SASP, and Disruption of Osteoblast–Osteoclast Coupling

Cellular senescence is an important pathological process in skeletal degeneration and age-related bone diseases. Senescent cells are typically characterized by increased expression of markers such as p16, p21, and SA- β -gal, and can secrete a range of inflammatory cytokines, chemokines, and matrix-degrading enzymes, collectively forming the senescence-associated secretory phenotype (SASP). SASP can persistently alter the local microenvironment and promote chronic inflammation, osteoclast activation, cartilage matrix degradation, and tissue degeneration.

In osteoporosis models, long-term low-dose exposure to PS-MPs can induce BMSC senescence, reduce the expression of osteogenic markers such as Osterix and RUNX2, and enhance RANKL-related osteoclastogenesis.¹¹⁰ These findings suggest that microplastics may alter the balance of bone remodeling by affecting BMSC fate, shifting the bone marrow microenvironment from an osteogenesis-supportive state toward a pro-inflammatory, pro-osteoclastogenic, and low-osteogenic state. In osteoporosis, such changes may lead to reduced bone formation and increased bone resorption. In joint and intervertebral disc tissues, senescence-associated inflammatory mediators and matrix-degrading enzymes may further promote cartilage degeneration and ECM destruction.

Micro- and nanoplastic-induced oxidative stress and inflammatory responses may also feedback to promote cellular senescence, forming a cycle of “increased ROS–amplified inflammation–cellular senescence–disrupted bone homeostasis”. In studies of intervertebral disc degeneration, PE-MPs induced nucleus pulposus cell senescence through the TLR4/NOX2/ROS axis, providing further support for this mechanism.¹¹³ Future studies should clarify differences in senescence responses to micro- and nanoplastic exposure among different skeletal cell types, particularly the specific roles of osteoblasts, osteocytes, BMSCs, chondrocytes, synovial cells, and nucleus pulposus cells in SASP formation and disease progression.

Ferroptosis, Exosome-Mediated Transport, and Extracellular Matrix Degradation

In addition to inflammation, oxidative stress, and pyroptosis, ferroptosis may also contribute to microplastic-mediated skeletal system injury. Ferroptosis is an iron-dependent form of cell death associated with lipid peroxidation and is commonly linked to abnormal glutathione metabolism, reduced GPX4 activity, impaired SLC7A11 function, and lipid ROS accumulation. In tissues that are rich in extracellular matrix and have limited regenerative capacity, such as cartilage and intervertebral discs, ferroptosis and lipid peroxidation may further compromise cell survival and promote disruption of ECM homeostasis.

Studies of intervertebral disc degeneration have shown that PE-MPs can be transported to nucleus pulposus cells via macrophage-derived exosomes and induce lipid peroxidation, ferroptosis, cellular senescence, and ECM degradation through NAT10/SLC7A11- and ac4C modification-related mechanisms.¹¹⁴ This finding suggests that microplastics do not necessarily exert toxicity only through direct contact with target cells, but may also indirectly affect skeletal system cells through macrophages, exosomes, and the local inflammatory microenvironment.

ECM degradation is a shared pathological endpoint in diseases such as RA, OA, and IVDD. In RA studies, PS-MPs have been shown to promote the expression of matrix-degradation-related molecules, including MMP3 and MMP9.¹¹² Studies of OA and IVDD also suggest that micro- and nanoplastic exposure may be accompanied by cartilage or nucleus pulposus ECM destruction. Taken together, ferroptosis, exosome-mediated transport, and ECM degradation may jointly contribute to the progression of micro- and nanoplastic-associated degenerative musculoskeletal diseases, although these mechanisms still require validation in further independent studies.

Epigenetic Regulation and Omics-Based Research Directions

At present, the epigenetic mechanisms by which micro- and nanoplastics affect the skeletal system remain insufficiently investigated, but this area has considerable exploratory value. Chronic inflammation, oxidative stress, and metabolic

abnormalities may alter DNA methylation, histone modifications, non-coding RNA expression, and chromatin accessibility, thereby affecting osteogenic differentiation, osteoclastogenesis, chondrocyte homeostasis, and nucleus pulposus cell degeneration. Bone homeostasis itself is also influenced by epigenetic regulation, with mechanisms such as DNA methylation, histone modifications, and microRNAs participating in the regulation of bone remodeling, osteogenic differentiation, and osteoclast function.¹⁴⁹ Inflammation-related miRNAs, such as miR-146a, miR-155, and miR-21, may be involved in feedback regulation of NF- κ B signaling, macrophage polarization, and osteoimmune responses. However, direct evidence demonstrating a decisive role of these epigenetic factors in micro- and nanoplastic-associated skeletal toxicity is still lacking.

Multi-omics technologies may provide new tools for this field. Single-cell RNA sequencing can help characterize the transcriptional responses of different skeletal cell populations after micro- and nanoplastic exposure and reveal changes in cellular heterogeneity, cell-fate transitions, and intercellular communication; this technology has already been applied in studies of orthopedic diseases such as osteoarthritis, rheumatoid arthritis, intervertebral disc degeneration, and osteosarcoma.¹⁵⁰ Spatial transcriptomics can further preserve tissue spatial information and may be used to examine changes in inflammatory, metabolic, and extracellular matrix microenvironments surrounding regions of particle accumulation; in recent years, its application in musculoskeletal research has also received increasing attention.¹⁵¹ Metabolomics and lipidomics can be used to identify pathways related to oxidative stress, ferroptosis, and energy metabolic abnormalities. In the future, integrating particle detection techniques, animal disease models, patient tissue samples, and multi-omics analyses may help clarify the cell-type-specific mechanisms by which micro- and nanoplastics contribute to osteoporosis, arthritis, intervertebral disc degeneration, and bone tumors. All mechanistic schematics are presented in [Figure 4](#).

Future Perspectives and Clinical Translation

Current evidence suggests that micro- and nanoplastics may affect skeletal homeostasis through inflammatory responses, oxidative stress, immune dysregulation, cellular senescence, and disruption of osteoblast–osteoclast coupling. However, their long-term effects, dose–response relationships, and causal associations in human populations remain to be clarified. Future research should move beyond descriptive toxicological observations and gradually shift toward exposure assessment, disease risk prediction, clinical monitoring, and public health intervention. For the skeletal system, it will be particularly important to integrate biomonitoring of micro- and nanoplastics with clinical outcomes such as bone mineral density, bone turnover markers, indicators of joint inflammation, imaging changes, and fracture risk, in order to determine whether these pollutants have genuine value for disease prediction and intervention.^{21,152}

Environmental Source Control and Public Health Prevention

Reducing the generation and release of micro- and nanoplastics into the environment remains fundamental to lowering the risk of long-term human exposure. Over recent decades, the use of plastic products has continued to increase, whereas the recycling rate of plastic waste remains limited. Large quantities of plastics can enter the natural environment and gradually form microplastics under the effects of light exposure, thermo-oxidation, hydraulic erosion, and mechanical abrasion.¹⁵³ Therefore, future efforts should strengthen whole-chain management of plastic production, use, recycling, and waste disposal, including limiting unnecessary single-use plastics, improving waste sorting and recycling systems, reducing the direct discharge of plastic waste, and promoting the development and application of biodegradable or environmentally friendly alternative materials.

From a public health perspective, assessment of skeletal health risks associated with micro- and nanoplastics should be incorporated into a more systematic exposure-monitoring framework. Future studies could integrate regional levels of environmental contamination, micro- and nanoplastic concentrations in drinking water and food, population exposure levels, and skeletal health indicators to evaluate the potential associations of long-term exposure with reduced bone mineral density, abnormal bone turnover, chronic joint inflammation, and fracture risk. As evidence accumulates, monitoring standards for micro- and nanoplastics in food, drinking water, and key occupational settings may be gradually established to inform public health policy and risk management.

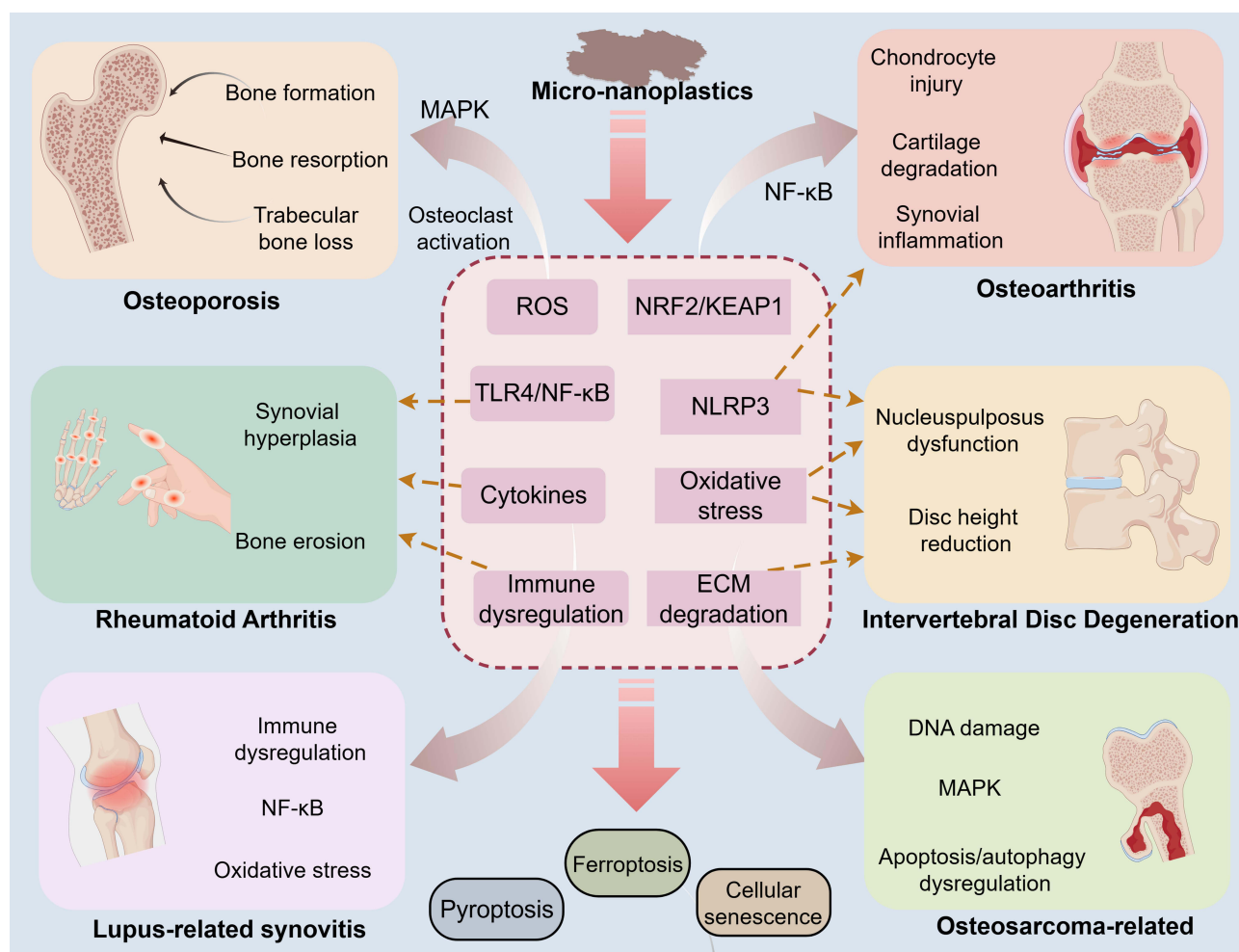


Figure 4 Micro-nanoplastics affect skeletal system health through multiple pathways.

Interventions Targeting Food, Drinking Water, and Daily Exposure

Food and drinking water are important sources of human exposure to micro- and nanoplastics. Plastic packaging materials, bottled water, takeaway containers, tea bags, plastic kettles, and infant feeding bottles may release plastic particles during production, storage, or high-temperature use.^{154,155} Therefore, reducing high-temperature contact between food and plastic materials has practical relevance. In daily life, glass, stainless steel, or ceramic containers may be preferred for food storage and heating, while plastic containers should be avoided for hot foods or microwave heating. For potentially high-risk groups, such as infants, pregnant women, patients with osteoporosis, and patients with rheumatoid arthritis, reducing micro- and nanoplastic exposure from food packaging and drinking water may have preventive value.

Drinking-water filtration technology is another important direction for reducing exposure risk. For micro- and nanoplastic particles that may be present in tap water, bottled water, and household drinking water, future research should further develop efficient, low-cost filtration and adsorption systems suitable for daily use.¹⁵⁶ These technologies should focus on removal efficiency across different particle-size ranges, polymer types, and aged plastic particles, and should establish detection and evaluation standards that reflect real drinking-water scenarios. It should be noted that, at this stage, no single filtration method can be assumed to fully eliminate the risk of micro- and nanoplastic exposure. Source pollution control, optimization of water-treatment processes, and end-point monitoring should therefore be advanced together.

Clinical Translation and Monitoring of High-Risk Populations

As micro- and nanoplastics have been detected in human blood, bone marrow, bone, cartilage, intervertebral discs, and other samples, clinical translational research will become an important direction in this field. Existing reviews have noted that human biomonitoring data for microplastics remain limited, with substantial heterogeneity across studies in sample types, detection methods, and analyses linking exposure to health outcomes; a more standardized exposure-assessment framework is therefore urgently needed.¹⁵⁷ Future research may prioritize prospective cohort studies that combine biomonitoring of micro- and nanoplastics with skeletal health assessment. For example, micro- and nanoplastic burdens in blood, urine, feces, synovial fluid, or bone marrow samples could be measured across populations differing in age, occupation, and disease risk, and then evaluated together with bone mineral density, bone turnover markers, inflammatory cytokines, joint imaging findings, severity of intervertebral disc degeneration, fracture incidence, and joint function scores to assess the relationship between long-term exposure and the onset or progression of skeletal diseases.

For workers in plastic production, textile manufacturing, packaging, waste treatment, and tire- and rubber-related industries, occupational exposure to micro- and nanoplastics and its potential musculoskeletal health effects should be considered. A systematic review of airborne micro- and nanoplastics showed that both indoor and outdoor air can serve as sources of inhalation exposure, with exposure doses varying across age groups and settings, indicating the practical importance of occupational exposure monitoring and protective strategies.¹⁵⁸ Future efforts could establish occupational exposure-monitoring systems that regularly assess airborne particulate levels in workplaces, use of personal protective equipment, blood or urinary exposure biomarkers, and changes in bone mineral density and inflammatory indicators. For patients with established osteoporosis, rheumatoid arthritis, osteoarthritis, or intervertebral disc degeneration, there is currently no evidence to support micro- and nanoplastic testing as a routine clinical screening item. Nevertheless, reducing contact with high-temperature plastic food packaging, drinking effectively treated water, strengthening occupational protection, and lowering exposure to environmental particulates remain feasible recommendations for risk management.

Clinical translation also requires stable and reliable detection workflows. Substantial differences remain across studies in sample collection, tissue digestion, contamination control, particle identification, and quantification methods, limiting the comparability of results. Recent reviews on the detection of micro- and nanoplastics in biological samples have also emphasized that standardization of detection workflows and cross-platform validation are essential prerequisites for future human studies.¹⁵⁹ Future work should prioritize standardized detection procedures for blood, synovial fluid, bone marrow, bone, cartilage, intervertebral disc, and other samples, including the use of non-plastic consumables, procedural blanks, negative controls, spiked recovery experiments, spectral-library matching thresholds, and multi-platform cross-validation. Only when detection methods are sufficiently robust can biomonitoring of micro- and nanoplastics be further applied to disease risk assessment and clinical research.

Emerging Intervention Technologies and Potential Therapeutic Directions

Technologies for clearing micro- and nanoplastics from the body remain at an early exploratory stage. Environmental water-treatment studies have attempted to use magnetic nanomaterials to adsorb and separate microplastics from water. For example, nano-Fe₃O₄ can magnetize various microplastics through surface adsorption and enable their separation under a magnetic field, suggesting that magnetically responsive materials have potential applications in environmental microplastic removal.¹⁶⁰ However, such strategies are mainly used for water purification and cannot be directly extrapolated to *in vivo* clearance in humans.

Research on micro- and nanorobots for microplastic capture and degradation has also mainly focused on environmental water purification. For example, magnetic/enzyme microrobots can capture and degrade target microplastics under an external magnetic field, demonstrating experimental feasibility.¹⁶¹ However, these studies remain at the *in vitro* or environmental-application stage and are still far from achieving safe, controllable, and effective clearance of micro- and nanoplastics in the human body. For these strategies to be translated into biomedical applications, key issues such as tissue targeting, material biosafety, immune responses, metabolic clearance pathways, long-term toxicity, and secondary damage to normal tissues must be addressed.

By contrast, the more practical intervention directions at present remain reducing external exposure, improving environmental governance, strengthening monitoring of drinking-water and food safety, and conducting long-term follow-up of high-risk populations. For skeletal system diseases, future studies may also explore whether antioxidant, anti-inflammatory, gut microbiota-modulating, bone metabolism-improving, and abnormal osteoclast activation-inhibiting strategies can mitigate micro- and nanoplastic-associated skeletal injury. However, these interventions currently lack direct clinical evidence in the context of human micro- and nanoplastic exposure, and their efficacy and safety will need to be validated gradually through animal experiments, organoid models, and population-based studies.

Overall, prevention and control of micro- and nanoplastic-related skeletal health risks require coordinated efforts across environmental governance, exposure reduction, standardized detection, occupational monitoring, and clinical research. As evidence from human skeletal system samples and mechanistic studies continues to increase, this field is expected to move beyond descriptive toxicological observations toward risk assessment, disease prevention, and clinical translational research. To support future studies in this field, commonly used analytical methods for detecting MNPs and their applicability to skeletal system samples are summarized in [Table 2](#).

Research Limitations

Although existing studies suggest that micro- and nanoplastics may affect skeletal homeostasis and may be potentially associated with the progression of various musculoskeletal diseases, this field remains at an early stage. Current evidence still has several limitations regarding human causal inference, exposure models, experimental particle characteristics, detection methods, and clinical extrapolation.

In terms of human evidence, available studies remain limited. Microplastics have been detected in human bone, cartilage, intervertebral discs, and bone marrow, providing direct evidence of skeletal system exposure.^{21,23} Human sample-based or experimental model evidence has also emerged in areas such as osteoporosis, rheumatoid arthritis, and intervertebral disc degeneration. However, most human studies remain cross-sectional observations, tissue-detection studies, or small-sample analyses, making it difficult to determine exposure timing, dose–response relationships, and the temporal sequence between exposure and disease onset. Therefore, current findings are more appropriately interpreted as indicating potential associations and are not sufficient to establish a direct causal relationship between micro- and nanoplastic exposure and human skeletal diseases.

In terms of experimental models, animal and *in vitro* studies provide important mechanistic clues, but caution is needed when extrapolating these findings to humans. Current studies largely rely on mouse, zebrafish, *Caenorhabditis elegans*, or cellular models. These models are useful for elucidating mechanisms such as inflammatory responses, oxidative stress, cellular senescence, pyroptosis, and disrupted osteoblast–osteoclast coupling, but their exposure routes, metabolic characteristics, and disease courses differ from those in humans. Some *in vitro* studies have used micro- and nanoplastic concentrations higher than realistic environmental exposure levels. For example, in RA-FLS-related experiments, the concentration range of microplastics reached 0–1.0 mg/mL. Such conditions are more suitable for observing mechanistic changes such as cellular uptake, inflammatory activation, migration, and invasion, rather than for directly inferring actual exposure risks in the general population.¹¹¹

From the perspective of real-world exposure, experimental particles also differ from environmental particles. Most studies use commercially available plastic microspheres with uniform particle sizes, regular morphology, and single polymer composition, such as PS-MPs or PS-NPs. By contrast, micro- and nanoplastics in the real environment often undergo aging, oxidation, ultraviolet irradiation, and mechanical abrasion, resulting in more complex morphology and surface properties. They may also adsorb exogenous substances such as heavy metals, persistent organic pollutants, pathogens, or endotoxins. Plastic additives, including phthalates, bisphenol A, flame retardants, and plasticizers, may also act together with plastic particles, resulting in mixed exposure and confounding effects.

Methodologically, detection workflows for micro- and nanoplastics in skeletal system samples have not yet been fully standardized. Samples such as bone, cartilage, intervertebral discs, synovial fluid, and bone marrow have complex matrices, and exogenous contamination or matrix interference may occur during sample collection, digestion, filtration, and detection. Raman spectroscopy, μ FTIR, LDIR, Py-GC/MS, SEM-EDS, and fluorescence staining each have

Table 2 Analytical Methods for Detecting Microplastics and Nanoplastics in Biological and Skeletal Tissues

Method	Detectable Information and Typical Range	Applicable Samples	Advantages	Limitations	Ref.
Raman microspectroscopy / Raman microscopy	Particle number, size, morphology, color, spatial distribution, and polymer type; suitable for small MPs, including 5–10 μm particles in some human tissue studies	Placenta, blood, urine, bone, cartilage, intervertebral disc, synovium, tissue sections	Non-destructive; high spatial resolution; suitable for single-particle polymer identification and tissue localization	Susceptible to tissue autofluorescence; relatively slow; requires strict digestion, background correction, and contamination control	[11,21]
μ -FTIR/FTIR imaging	Particle number, size, morphology, and polymer type; commonly used for >10–20 μm particles, with lower limits around 3 μm in some studies	Lung tissue, placenta, feces, thrombi, digested bone, cartilage, and intervertebral disc samples	Mature spectral libraries; suitable for larger particles and fibers; higher throughput than Raman in many settings	Limited ability for small MPs and NPs; water and organic matrices may interfere with spectra	[73]
LDIR/LD-IR imaging	Particle number, size, morphology, and polymer type; generally suitable for particles $\geq 10 \mu\text{m}$; relatively automated	Placenta, endometrium, environmental samples, food samples, selected digested tissues	Rapid and automated; suitable for high-throughput screening; provides particle size and polymer information	Fewer applications in human tissues than Raman/ μ FTIR; limited instrument and library availability; requires careful pretreatment	[162,163]
Py-GC/MS/TED-GC/MS	Polymer type and mass concentration; suitable for total quantification of MPs and some NPs; no single-particle morphology or localization	Blood, placenta, urine, bone marrow, synovial fluid, tissue digests, complex biological matrices	High sensitivity; suitable for polymer-specific mass quantification in complex matrices; useful for small-particle burden assessment	Destructive; cannot provide particle number, morphology, or tissue localization; thermal products from biological matrices may interfere	[9,164,165]
SEM-EDS	Surface morphology, microstructure, and elemental composition; useful for micro- to nanoscale particle morphology	Filters, digested tissue residues, environmental samples, suspicious particles from tissues	High resolution; useful for surface cracks, aging features, attached contaminants, and inorganic elements	Cannot reliably identify polymer type; should not be used alone for plastic confirmation	[166,167]
Nile Red fluorescence staining/ fluorescence microscopy	Rapid screening, fluorescence counting, and preliminary particle identification; suitable for hydrophobic micro-sized particles	Environmental samples, tissue digests, placenta, blood sediments, urine, synovial fluid, bone marrow digests	Low cost, fast, suitable for large-scale screening, compatible with automated image analysis	High false-positive risk; lipids, proteins, and natural organic matter may stain; cannot confirm polymer type	[168]
Combined platform: Raman/ μ FTIR + Py-GC/MS	Integrated information on particle number, size, morphology, polymer type, and mass concentration	Blood, urine, placenta, bone marrow, bone, cartilage, intervertebral disc, synovial fluid, synovium, other tissue digests	Complementary: spectroscopy provides particle-level information, while thermal MS provides polymer-specific mass quantification	Expensive, time-consuming, sample-consuming, and requires strict blanks, spectral matching, and contamination control	[169]

Notes: Detection limits vary depending on instrument configuration, sample pretreatment, spectral matching criteria, and contamination control.

Abbreviations: MNPs, microplastics and nanoplastics; MPs, microplastics; NPs, nanoplastics; μ FTIR, micro-Fourier transform infrared spectroscopy; LDIR, laser direct infrared imaging; Py-GC/MS, pyrolysis-gas chromatography/mass spectrometry; TED-GC/MS, thermal extraction desorption-gas chromatography/mass spectrometry; SEM-EDS, scanning electron microscopy-energy dispersive spectroscopy.

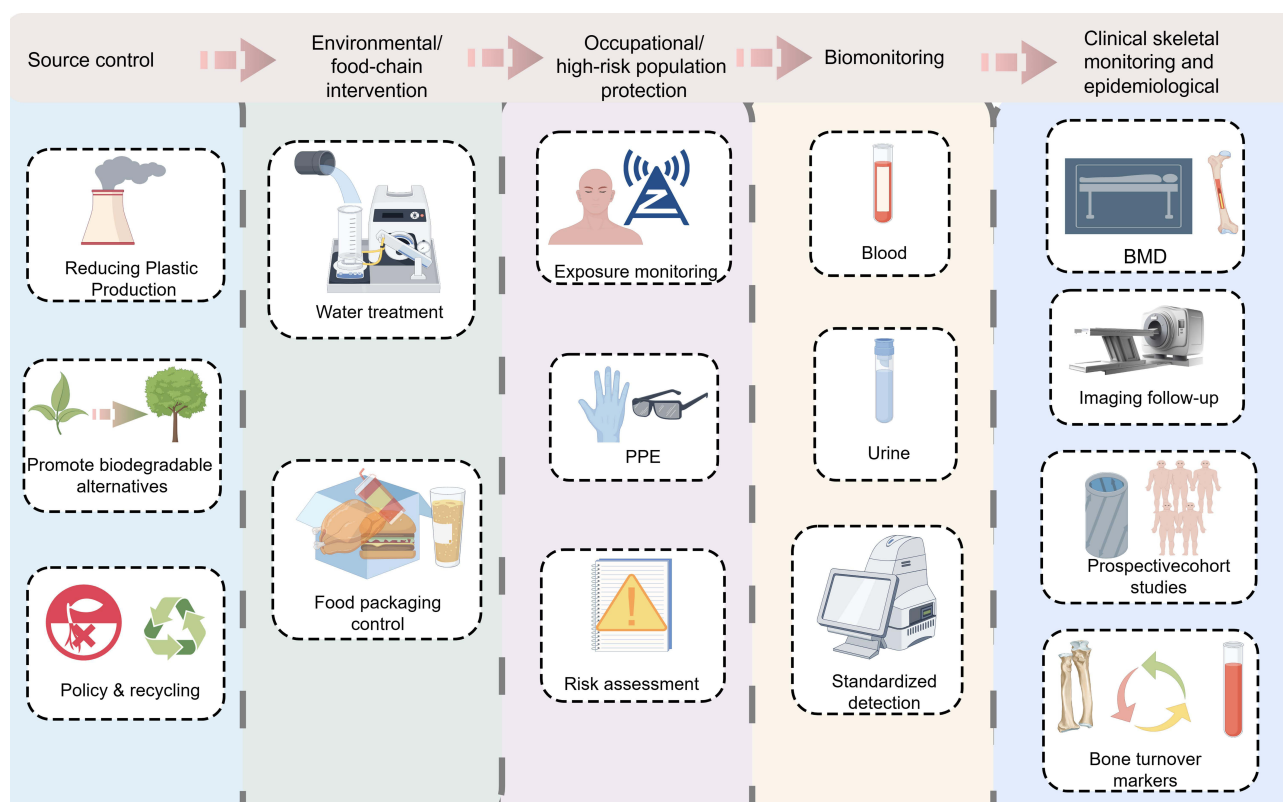


Figure 5 Future applications and research perspectives of micro-nanoplastics.

advantages and limitations, and a single method usually cannot simultaneously provide information on particle number, particle size, morphology, polymer type, spatial distribution, and mass concentration.^{169,170}

Future studies should establish more unified quality-control procedures, including the use of non-plastic consumables, procedural blanks and negative controls, spiked recovery experiments, clearly defined spectral matching thresholds, blinded re-evaluation, and interlaboratory validation. Long-term prospective studies are still needed in potentially high-risk populations, such as older adults, postmenopausal women, patients with osteoporosis, patients with rheumatoid arthritis, and individuals with long-term occupational exposure. These studies should integrate measurements of human micro- and nanoplastic burden with bone mineral density, bone turnover markers, inflammatory indicators, imaging changes, and clinical outcomes to clarify their true significance in the onset and progression of skeletal diseases.

Overall, current evidence suggests that micro- and nanoplastics may contribute to disrupted skeletal homeostasis and the progression of musculoskeletal diseases. However, insufficient causal evidence in humans, limited extrapolation from experimental models, the complexity of real-world exposure scenarios, and the lack of standardized detection methods continue to constrain the strength of existing conclusions. Future research should gradually move from single toxicological experiments toward an integrated research framework that combines standardized detection, realistic exposure modeling, multi-omics mechanistic analysis, and long-term population follow-up. The potential future strategies for micro- and nanoplastic research and risk management are summarized in [Figure 5](#).

Conclusions

Micro- and nanoplastics are widespread emerging environmental pollutants that can enter the human body through oral ingestion, inhalation, and potential dermal contact, and they have been detected in multiple tissues. With emerging evidence of microplastics in human bone, cartilage, intervertebral discs, and bone marrow, the skeletal system has become a new area of interest in research on the health effects of micro- and nanoplastics. Current studies suggest that micro- and nanoplastics may disrupt skeletal homeostasis through mechanisms involving inflammatory responses,

oxidative stress, mitochondrial dysfunction, cellular senescence, pyroptosis, ferroptosis, and disruption of osteoblast–osteoclast coupling, and may be potentially associated with diseases or pathological conditions such as osteoporosis, rheumatoid arthritis, intervertebral disc degeneration, osteoarthritis, lupus-related musculoskeletal involvement, and osteosarcoma progression.

In terms of strength of evidence, osteoporosis, rheumatoid arthritis, and intervertebral disc degeneration are currently supported by relatively more evidence from human samples, animal models, and cellular mechanistic studies. By contrast, osteoarthritis, lupus-related synovitis, and osteosarcoma progression remain emerging research directions, and their related conclusions require further validation in independent studies. It should be emphasized that most current evidence still derives from animal experiments, in vitro studies, or cross-sectional human observations and is not yet sufficient to establish a direct causal relationship between micro- and nanoplastic exposure and human skeletal diseases.

In the future, this field should build on standardized detection methods and integrate realistic exposure modeling, long-term prospective cohorts, multi-omics analyses, monitoring of bone mineral density and bone turnover markers, and imaging assessment of joints and the spine to further clarify the role of micro- and nanoplastics in the onset and progression of skeletal system diseases. At the same time, reducing environmental plastic pollution, lowering exposure from food and drinking water, strengthening occupational protection, and monitoring high-risk populations remain more practical directions for prevention and control at this stage. As direct exposure evidence and mechanistic studies continue to accumulate, assessment of micro- and nanoplastic-related skeletal health risks is expected to gradually expand from basic toxicological research to clinical translation and public health practice.

Abbreviations

MPs, Microplastics; NPs, Nanoplastics; MNPs, Microplastics and nanoplastics; PS, Polystyrene; PE, Polyethylene; PVC, Polyvinyl chloride; PET, Polyethylene terephthalate; OP, Osteoporosis; RA, Rheumatoid arthritis; IDD, Intervertebral disc degeneration; SLE, Systemic lupus erythematosus; BMSCs, Bone marrow mesenchymal stem/stromal cells; FLS, Fibroblast-like synoviocytes; NPCs, Nucleus pulposus cells; ROS, Reactive oxygen species; NF- κ B, Nuclear factor-kappa B; TLR4, Toll-like receptor 4; NOX2, NADPH oxidase 2; NRF2, Nuclear factor erythroid 2-related factor 2; KEAP1, Kelch-like ECH-associated protein 1; SASP, Senescence-associated secretory phenotype; 8-OHdG, 8-hydroxy-2'-deoxyguanosine.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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