HHS Public Access
Author manuscript
Circulation. Author manuscript; available in PMC 2026 March 03.

Published in final edited form as:
Circulation. 2026 March 03; 153(9): 613–615. doi:10.1161/CIRCULATIONAHA.125.077882.

Micro- and Nanoplastics – A New Perspective in Cardiovascular Prevention

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Perspective

Plastic-related pollution has long been recognized as an environmental threat with increasing urgency due to a globally rising production of plastics. The possible consequences for the human organism receive attention and are subject of intensive scientific debate[1]. A recent study by Marfella et al. provided compelling evidence that micro- and nanoplastics (MNPs) may act as a direct risk factor for cardiovascular disease[2]. Specifically, the study found that patients with MNPs detected in their carotid artery plaques had a significantly higher risk for a composite major adverse cardiovascular event outcome (MACE – myocardial infarction, stroke, or death from any cause – at 34 months of follow-up) than those without MNPs. This finding is underscored by the reported hazard ratio of 4.53 (95% confidence interval, 2.00 to 10.27; $p<0.001$). In effect, this landmark analysis has moved the topic from environmental science to the limelight of clinical cardiology and cardiovascular prevention.

MNPs (particles below 5 µm and 1 µm, respectively) can be found in consumer goods or result from the breakdown of common plastic products like packaging, tires, and textiles.

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Disclosures
None

Since they are detectable in the air, food, and drinking water, there are primary, unavoidable routes of human exposure, including ingestion, inhalation, and dermal contact. Of note, growing evidence strongly suggests that particles smaller than 200 nm can enter and cross barrier organs. Consequently, they have been found in numerous human tissues, including atherosclerotic plaques. We currently believe that smaller plastics (nanoplastics) may be particularly hazardous because they can more easily penetrate cells and subcellular compartments. This biological finding is consistent with recent research, incuding the study from Marfella et. al[2]. Plastic pollution also is the source of plastic chemicals and MNPs may release plastic chemicals within human tissues.

Preclinical *in vitro* and *in vivo* models have already begun to provide strong biological plausibility of MNP-mediated vascular injury. These initial findings are comparable to the evidence concerning ambient air pollution particles, which are already implicated as a causal risk factor for cardiovascular morbidity and mortality[3]. Experiments suggest that MNPs foster inflammation and oxidative stress by inducing reactive oxygen species and activating inflammatory pathways, such as the Nucleotide-binding and Leucine-rich repeat-rich Pyrin domain-containing 3 (NLRP3) inflammasome. MNPs may promote a pro-coagulant state, platelet activation, and hemolysis through direct endothelial damage. They may also modify macrophage function and phenotype by impairing the cell’s ability to clear cellular debris, which could lead to the growth of a necrotic core and thus foster unstable lesions[4]. Crucially, MNPs may act as a ”Trojan Horse” by carrying absorbed environmental toxins and release plastic chemicals e.g. plasticizers such as phthalates and bisphenol A directly into the tissue and the plaque microenvironment[5].

It is important to distinctly acknowledge, however, the current uncertainty on this topic given the complexity of the issue. MNPs have a wide range of sources and different chemical compositions and their surface is modified by environmental and metabolic factors. To date, controlled experimental studies, dose-response relationships, and clear biological mechanisms in human tissues are needed to infer causality. While the magnitude of the reported hazard ratio (HR of 4.53) is extremely high - suggesting an effect size comparable to, or even greater than, many accepted cardiovascular risk factors – exclusion of potential confounding factors may be crucial: MNPs could be mere markers for another high-risk lifestyle or environmental exposure, such as traffic-related air pollution or diets high in processed foods. Furthermore, artefactual contaminants are major concerns as today’s clinical and laboratory equipment is likely to be a source of MNPs. Therefore, establishment of molecular mechanisms, and proof of direct causation remain important outstanding issues.

It is therefore important to address these considerations and learn from the early associated evidence that ultimately allowed airborne fine particulate matter (PM2.5) to be definitively linked to cardiovascular disease. This comparison, however, highlights another major hurdle the field currently faces: to dissect the components, specifically PM2.5 and MNPs, and clearly distinguish their respective contributions to atherogenesis. There remains a critical need to advocate for rigorous and dispassionate hypothesis testing, which will inform and enable evidence-based action. This research will transform potentially the understanding of plaque development and guide treatment options for those already burdened with MNPs.

What could such a roadmap look like? A clear, forward-thinking agenda should include the following (Figure). First, we must identify which MNP properties - polymer type, size, shape, weathering, and/or plasticizer content - promote toxic effects, either in isolation or jointly. Second, we must clearly elucidate the specific molecular pathways by which they enter the body, traffic to the vasculature, and cause cardiovascular injury. Third, we should develop and standardize measurements and quantitative biomarkers of MNP burden, ensuring data are not impacted by technical artifact. Fourth, we should utilize geographically diverse biobanks to analyze historical samples, allowing us to examine associations over decades and map exposure trends against long-term health data. In parallel, we should establish "contamination-free" biobanks for direct comparison to historical samples. Finally, we should call for large prospective cohort studies to quantify exposures, provide means to counteract potential contaminations, link these exposures to incident events, and establish causality via innovative deep molecular phenotyping. Crucially, these studies must determine whether MNP accumulation begins in infancy, whether specific age groups are more vulnerable, and how co-existing cardiovascular risk factors might amplify the damage. These findings will ultimately help to incorporate evidence into public health discussions related to plastic exposure and inform policy-level changes driven by the data.

Taken together, the discovery of MNPs in atherosclerotic plaques, linked to a higher risk of clinical events, offers a pivotal perspective for cardiovascular prevention. While awaiting full understanding of the phenomena, the confluence of strong clinical signals, biological plausibility, and universal exposure compels the cardiovascular community to act quickly but prudently to better understand MNPs as a potential, emerging, and unaddressed risk for cardiovascular disease. In parallel, this presents a unique opportunity for our community to lead the scientific, clinical, and public health response addressing this new frontier in cardiology.

Funding Sources

Dr. Jarr is supported by Deutsche Forschungsgemeinschaft (JA 2869/3-1), Deutsche Gesellschaft für Innere Medizin, Else Kröner-Fresenius Stiftung (2022_EKEA.91 and 2024_EKES.02), Deutsches Zentrum für Herz-Kreislauf-Forschung (B24-009 SE), and Corona-Stiftung (S0199/10105/2024). Dr. Leeper is supported by grant numbers R35HL 144475 and 176060 from the National Heart Lung and Blood Institute.

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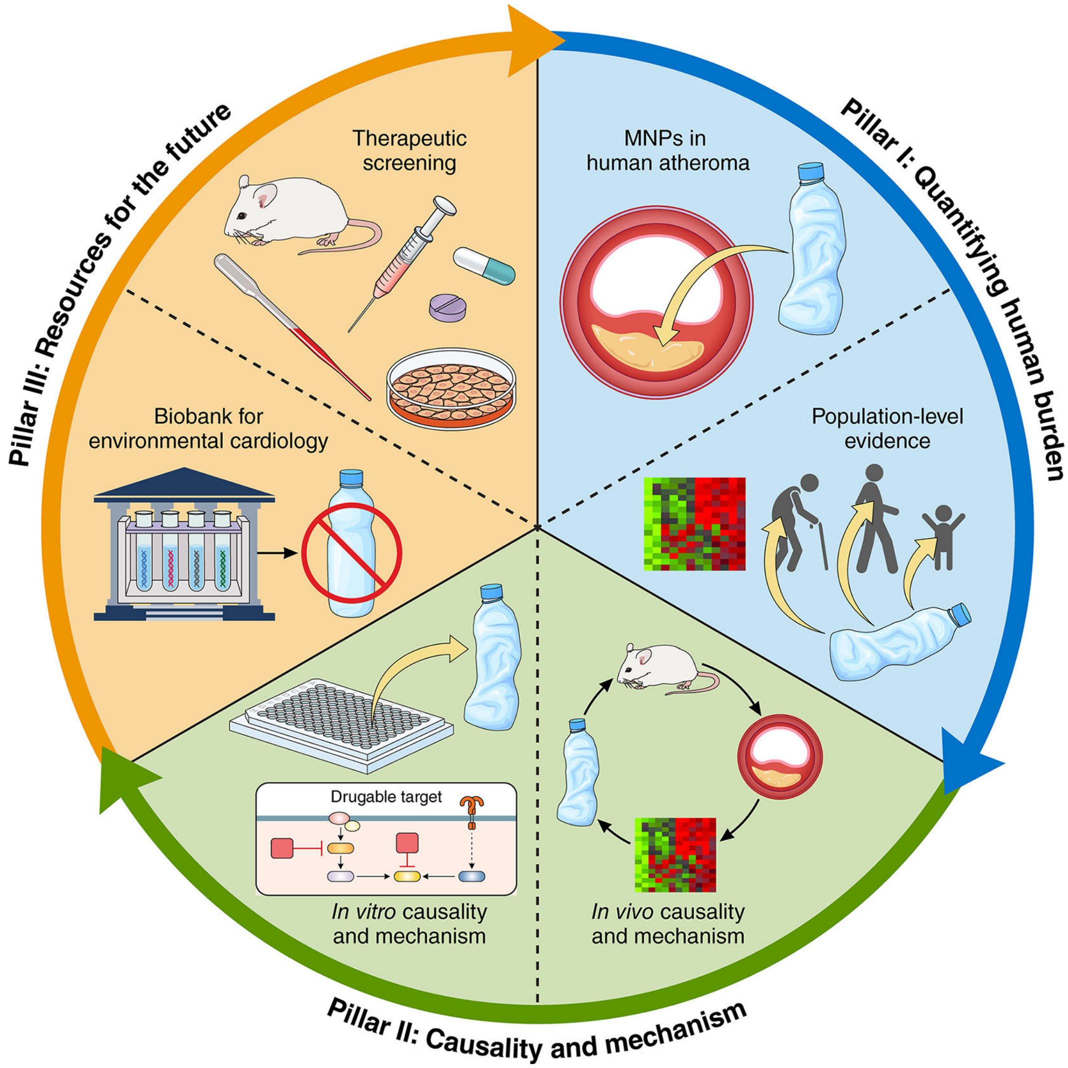

Figure.

An Integrated Translational Research Cycle.

The Figure illustrates the three-stage integrated workflow guiding the progression from clinical observation to bedside implementation. Clinical assessment provides comprehensive data and phenotypes that serve as the foundation for subsequent mechanistic investigation. Causation and mechanistic studies identify underlying biological mechanisms, pathways, and novel targets. The knowledge is then rapidly translated back to clinical practice, thereby completing the cycle.