The evolving landscape of cardiometabolic diseases

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The epidemic of cardiometabolic diseases

Cardiometabolic diseases (CMDs), a group of interconnected disorders including metabolic diseases, like obesity and type 2 diabetes mellitus (T2DM) coupled with cardiovascular complications such as ischemic heart disease (IHD) and heart failure (HF), are now recognized as the leading cause of death globally[1] with almost 18 million cardiovascular deaths reported in 2019.[1]

Significant advancements in therapeutics for IHD have led to improved survival rates and better clinical outcomes. However, advancements in treating obesity and metabolic disorders have not kept pace. The increasing prevalence of overweight/obesity, T2DM, and metabolic syndrome—particularly in low- and middle-income countries—has exacerbated CMD burden.

We propose that two key conditions within the CMDs spectrum—heart failure with preserved ejection fraction (HFpEF) and metabolic dysfunction-associated steatotic liver disease (MASLD)—are likely to play a substantial role in shaping cardiometabolic research and healthcare priorities in the near future. HFpEF now accounts for over half of all HF cases, and its causal association with obesity and metabolic dysfunction has redefined it as a systemic, multi-organ disease, rather than simply a cardiac-centric condition.[2]

Similarly, MASLD, which affects an estimated 30% of the global population, is emerging as a major metabolic disease with severe cardiovascular consequences.[3] The recent reclassification of MASLD, moving beyond its former characterization as non-alcoholic fatty liver disease (NAFLD), reflects a growing understanding of its metabolic roots and its connection with other cardiometabolic conditions. Both HFpEF and MASLD share common risk factors—such as insulin resistance, obesity, and systemic inflammation.

As CMDs evolve, HFpEF and MASLD became key contributors to cardiovascular morbidity and mortality. Addressing these conditions will require a shift in research focus towards understanding inter-organ crosstalk, the shared metabolic pathways that link these diseases, and the development of novel therapies targeting these mechanisms. As healthcare systems struggle with the rising burden of these conditions, both research and clinical strategies must evolve to integrate CMDs management into comprehensive, multidisciplinary care models.

Canonical and emerging risk factors for cardiometabolic diseases

CMDs have long been considered to be driven by well-established risk factors, including age, family history, obesity, hypertension, diabetes, dyslipidemia, and smoking.[1] These classical drivers, along with non-cardiac comorbidities such as liver disease and chronic kidney disease (CKD), continue to play a major role in CMDs progression. The global epidemic of obesity and T2DM, driven largely by unhealthy dietary patterns and physical inactivity has significantly amplified the global CMDs burden.[1] "Obesogenic" diets—characterized by oversized portions, low fruit and vegetable intake, and high consumption of sodium, processed meats, and trans fats—fuel the increasing prevalence of these diseases.

Beyond these traditional risk factors, emerging environmental, and lifestyle-related threats demand attention. Pollution, including air pollution and particularly fine particulate matter (PM2.5), has been shown to contribute to systemic inflammation and endothelial dysfunction trough immune cells activation and production of pro-inflammatory cytokines.[4] This is accompanied by oxidative stress, reactive oxygen species (ROS) production and dysregulated lipid metabolism, including the release of free fatty acids.[5] For example, an increase in oxidized lipid species, such as 7-ketocholesterol, has been observed in aortic plaques and macrophages isolated from PM2.5-exposed mice. This suggests that similar derangements in circulating metabolites and related alterations in immune cells may occur in humans exposed to air pollution. These

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findings imply a common mechanistic pathway through which air pollution could contribute to cardiometabolic dysfunction. Along these lines, recent studies have shown that microplastics and nanoplastics (MNPs) detected in arterial plaques are associated with significantly higher rates of cardiovascular events, including myocardial infarction and stroke.[6] Climate change and the global warming crisis also have the potential to exacerbate CMDs through increased heat exposure, food insecurity, and migration-related stress.[1] Our knowledge of the interplay between genetic risk factors and the exposome in CMDs is rapidly evolving[7] requiring more research effort to understand their full impact on CMDs development and progression. Considering that the precise mechanisms by which these emerging risk factors impact cardiometabolic health are not yet fully understood, framing translational research questions around these pathways will help identifying novel therapeutic targets.

Despite growing recognition of these risk factors, the critical importance of prevention through lifestyle interventions remains underappreciated. Regular physical activity is a key pillar in the prevention of CMDs, yet it remains insufficiently practiced. Data on physical activity before the 2000s were sparse, but global inactivity levels increased from 23.4% in 2000 to over 31% in 2022.[8] Although the benefits of healthy diets and exercise are well documented, challenges such as weight cycling and persistent adiposopathy can complicate prevention efforts. While prevention through lifestyle changes must remain a cornerstone of CMD management, research must also expand to address the obesity pandemic and emerging threats such as pollution, consequences of climate change, and the MNPs. The future of CMD research and management depends on a comprehensive approach that integrates both traditional and novel risk factors. Public health strategies must adapt by implementing targeted measures such as stricter air quality regulations, monitoring pollution exposure, and promoting urban planning that reduces pollution sources. Additionally, public health initiatives should focus on increasing awareness of the health risks associated with pollution and MNPs, integrating environmental health into cardiometabolic disease prevention programs. These strategies should aim to reduce exposure to harmful pollutants, improve early detection of pollution-related health effects, and promote lifestyle changes, such as physical activity and dietary interventions, that can mitigate the adverse metabolic impacts of pollution. By addressing these specific needs, public health policies can more effectively reduce the growing global burden of cardiometabolic diseases linked to pollution.

The evolving management of cardiometabolic diseases: therapies and prevention

Historically, cardiovascular treatments primarily targeted the heart and vasculature, aiming to manage symptoms and prevent further organ damage. For decades, medications like beta-blockers, renin-angiotensin-aldosterone system (RAAS)-targeting agents, and statins were developed to directly address heart function, blood pressure, and cholesterol levels. These therapeutic strategies have substantially improved clinical outcomes in patients with IHD and cerebrovascular diseases. However, it has become increasingly clear that CMDs are not confined to the cardiovascular system but are interconnected with metabolic and multi-organ processes. This growing understanding has shifted research and clinical strategies towards therapies that treat CMDs as systemic conditions, focusing on multi-organ crosstalk, metabolic dysfunction, and inflammatory pathways.

In this direction, emerging therapies, such as sodium-glucose cotransporter 2 inhibitors (SGLT2i), have demonstrated broad benefits beyond glucose control, improving outcomes in HFpEF, MASLD, and CKD. Similarly, incretin-based therapies, initially developed for diabetes, are now recognized for their ability to treat obesity and provide cardiovascular protection. The success of these drugs highlights the importance of a systemic treatment approach to CMDs, opening new avenues for therapies that target the metabolic, renal, and inflammatory components of the disease.

Despite these advances, drug therapies remain expensive, and their long-term accessibility is limited. Therefore, prevention remains the most cost-effective and sustainable strategy for addressing CMDs. Integrating lifestyle interventions such as exercise and dietary improvements alongside pharmacological therapies offers the best chance of reducing cardiometabolic risk factors early, before the onset of irreversible organ damage. Focusing on prevention through public health initiatives and encouraging healthier living, particularly in high-risk populations, is essential to reducing CMDs prevalence and improving long-term outcomes.

Future directions

The growing burden of CMDs demands a concerted effort to develop innovative risk assessment, detection, and treatment methods that move beyond traditional approaches. The complexities of CMDs—driven by behavioral, environmental, and metabolic factors—call for a more personalized and systemic strategy. The heterogeneity of risk factors across populations highlights the inadequacy of a one-size-fits-all model, pushing the need for precision approaches that integrate cutting-edge technologies.

In this context, the integration of metabolic biomarkers, anthropometric measurements, and artificial intelligence (AI)-driven models shows great promise for personalizing CMDs risk assessments. AI, in particular, is poised to revolutionize diagnostics by enhancing the predictive accuracy of non-invasive imaging tools like ECG, echocardiography, cardiac CT, and MRI. Machine learning (ML) algorithms can reduce operator

variability, automate complex analyses, and even reclassify diagnostic parameters, such as coronary stenosis severity in CT angiography, with greater precision. AI-powered echocardiographic analyses have demonstrated the ability to classify phenotypes and predict adverse events in HFpEF, offering detailed patient stratification that could reshape both clinical decision-making and research.

Beyond diagnostics, AI also plays a crucial role in drug discovery and translational research. Organoids and patient-specific models enable more precise drug testing while AI-guided insights from electronic health records, digital pathology, and imaging data are driving new discoveries in CMDs. For instance, AI tools such as SteatoSITE are enhancing clinical stratification of patients and biomarker identification in MASLD, marking significant strides in precision medicine for CMDs.[9] In addition, ML/AI tools have the potential to personalize treatment. For example, while many HF patients are referred for cardiac resynchronization therapy (CRT), this treatment is ineffective in up to 40% of these patients. An ML model has improved the ability to predict outcomes after CRT, showing an eight-fold difference in survival between those with the highest and lowest predicted probabilities of death compared to the traditional method.[10] As research progresses, these AI-driven methods are expected to contribute to creating tailored treatment plans that address systemic metabolic dysfunction across multiple organs.

Furthermore, emerging technologies such as wearable devices, mobile health apps, and telemedicine are expanding the possibilities for continuous CMDs monitoring, allowing for real-time tracking of risk factors and treatment responses. These tools hold promise to improve early detection and intervention, shifting the focus from managing advanced disease to preventing CMDs. However, significant gaps remain in validating these AI-driven interventions in real-world clinical settings. To fully realize the potential of these technologies, a coordinated effort is required from researchers, clinicians, and technologists to integrate clinical, genomic, and imaging data effectively into daily practice.

Conclusion

The future of CMDs research and healthcare must embrace this systemic approach, where innovative technologies not only enhance diagnostics and treatment but also enable preventive strategies that tackle the root causes of CMDs. By fostering collaboration and leveraging advances in AI and precision medicine, we are confident in our ability to transform the management of CMDs and ultimately reduce their global burden.

Contributors

All three authors contributed equally to the literature review, design, and writing.

Declaration of interests

None.

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