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Review

Mendelian Randomization Studies in Atherosclerotic Cardiovascular Diseases

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The authors have no conflicts of interest to declare.

ABSTRACT

This review aimed to highlight the pivotal role of Mendelian randomization (MR) in advancing atherosclerotic cardiovascular disease (ASCVD) research—a field often hindered by the complexities and limitations of traditional studies. MR, which uses genetic variants as instrumental variables, provides a robust mechanism for inferring causality, offering insights untainted by the confounding factors and biases often prevalent in observational and randomized controlled trials. We explored the significant contributions of MR for elucidating the causal relationship between low-density lipoprotein cholesterol and ASCVD, and analyzed its assumptions and methodological nuances. We discussed issues surrounding instrumental variable selection, pleiotropy, and ethical considerations, in an effort to offer a balanced and insightful analysis. We highlighted the promising integration of MR with emerging technologies and global data sharing, as well as its potential to drive personalized medicine. This review provided a concise yet comprehensive journey into MR's transformative impact on ASCVD research, offering a blend of current insights and challenges, in addition to future prospects. We aimed to serve a valuable resource for those seeking to navigate the intricate pathways of causality and intervention in ASCVD, to aid the development of enhanced understanding and targeted treatment strategies in the future.

Keywords: Mendelian randomization analysis; Atherosclerosis; Cardiovascular disease

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), characterized by the buildup of plaque in the arteries, is the leading cause of death worldwide.[1,2] It includes conditions such as coronary artery disease, stroke, and peripheral arterial disease. The morbidity, mortality, and economic burden associated with ASCVD make it a critical area for medical research. The development and progression of atherosclerosis involves several factors, including lipid metabolism, inflammation, and endothelial function.[3-5] Understanding this intricate interplay may lead to improved preventive and therapeutic strategies.

Data Availability Statement

Data sharing is not applicable to this article because no new datasets were generated or analyzed in the study.

Author Contributions

Conceptualization: Ko DS, Kim YH; Writing - original draft: Ko DS; Writing - review & editing: Ko DS, Kim YH.

1. Challenges in ASCVD research

ASCVD results from a combination of genetic, environmental, and lifestyle factors.[6] However, disentangling these various contributors in observational studies can be challenging. Atherosclerosis develops over decades, and studying its progression requires long-term follow-up, which makes it both time-consuming and expensive.[7] Traditional observational studies are susceptible to confounding factors that can distort true associations.[8] Moreover, biases such as selection and information biases can further complicate interpretations. In many observational studies, determining whether a risk factor leads to ASCVD or whether the presence of early ASCVD influences the risk factor is challenging, creating the dilemma of reverse causality. Conducting randomized controlled trials (RCTs) for ASCVD also presents several unique challenges.[9,10] First, given the chronic nature of atherosclerosis and its long latency period, RCTs would require extended durations to observe meaningful clinical outcomes, which is resource-intensive.[11] Second, ethical considerations can present challenges, particularly when withholding potentially beneficial treatments from control groups in the face of life-threatening conditions such as ASCVD.[12] Furthermore, ensuring adherence to interventions—particularly lifestyle modifications—over extended periods is challenging, and can affect the validity of results.[13] Finally, the multifactorial etiology of ASCVD means that isolating the effects of a single intervention can be complex, and a large sample sizes may be required to achieve statistical significance.[14]

2. The need for Mendelian randomization (MR) analyses for ASCVD research

MR leverages genetic variants as instrumental variables to infer causality, helping researchers determine whether a risk factor genuinely contributes to ASCVD or is merely associated with it.[15] Since genetic variants are randomly allocated at conception, they are generally not influenced by lifestyle or environmental confounders.[16] This makes MR a more reliable approach for studying ASCVD risk factors. The genetic foundation of MR ensures that genetic variants precede disease onset, which may clarify the direction of causality and bypass the challenge of reverse causality.[17] With the popularization of genome-wide association studies (GWASs), a wealth of genetic data has become available. MR can harness these data to draw robust conclusions regarding the risk factors and their impact on ASCVD. By providing a clear picture of the causative factors behind ASCVD, MR can guide the development of targeted therapeutic and preventive strategies, potentially leading to more effective interventions.[18]

Although the significance of ASCVD research is undeniable, given the global impact of the disease, the challenges inherent in studying this complex disease necessitate innovative approaches. MR has emerged as a powerful tool in this context, promising to reshape our understanding of ASCVD and guide future therapeutic endeavors. In this review, we provided a thorough overview of MR, exploring its principles, applications in ASCVD research, inherent challenges, and promising future prospects. Through this review, we aimed to highlight the pivotal role of MR in shaping the future of cardiovascular research, offering new possibilities for targeted and more effective future interventions.

PRINCIPLES OF MR

MR is a groundbreaking approach in epidemiological research that is fundamentally rooted in the principles of Mendelian inheritance. This concept hinges on the random assortment of genetic variants (or alleles) during gamete formation, ensuring their general independence from confounding factors that often compromise conventional observational studies. By

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capitalizing on this inherent randomness, MR establishes a quasi-randomized experiment.[19] In this framework, genetic variants act as instrumental variables, offering a unique lens through which to discern the causal effects of risk factors or interventions on health outcomes. There are three pivotal assumptions at the heart of MR.[20,21]

1. Association with exposure

The genetic variant chosen as an instrumental variable must be robustly associated with the exposure of interest (**Fig. 1A**). This ensures that the variant can effectively serve as a proxy for the exposure, allowing researchers to draw inferences regarding the causal effect of the exposure on the outcome.

2. Independence from confounders

A pivotal assumption in MR is that the genetic variant is not associated with any confounders of the exposure-outcome relationship (**Fig. 1B**). Given that genetic variants are randomly allocated at conception, they are typically free from the biases that plague observational studies, such as confounding.

3. Exclusivity of pathway

The genetic variant should influence the outcome solely through its effect on the exposure (**Fig. 1C**). Therefore, no alternative pathways (often termed "pleiotropic" pathways) through which the variant affects the outcome should be present, bypassing the exposure.

KEY STUDIES USING MR IN ASCVD RESEARCH

Recently, a number of MR studies have firmly established causal relationships between ASCVD and risk factors such as blood lipids and inflammatory markers.

1. Low-density lipoprotein cholesterol (LDL-C)

The relationship between LDL-C and ASCVD has been a focus of cardiovascular research. LDL-C is not only a biomarker, but also a causal agent in the development of atherosclerosis. Elevated levels of LDL-C are directly associated with an increased risk of coronary artery disease.[22] This association has been confirmed by a wealth of evidence from genetic, observational, and clinical intervention studies. A comprehensive analysis of over 200 prospective cohort studies, MR studies, and randomized trials has provided compelling evidence of the link between LDL-C and ASCVD.[23] The studies surveyed included more than

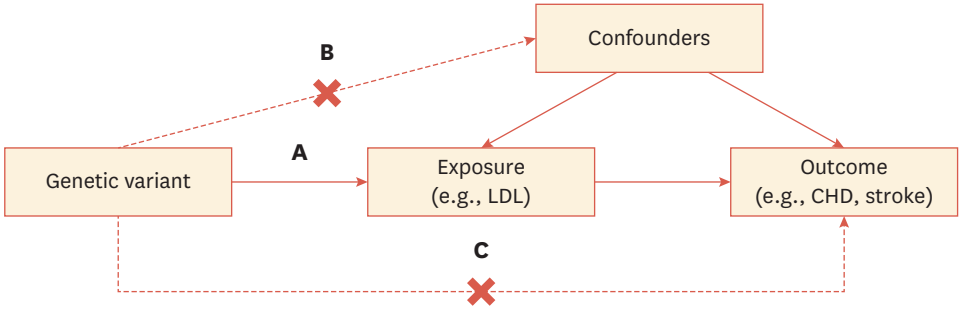

Fig. 1. Graphical representation of the MR assumptions. (A) association with exposure, (B) independence from confounders, and (C) exclusivity of pathway.
MR, Mendelian randomization; LDL, low-density lipoprotein; CHD, coronary heart disease.

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two million participants, with over 20 million person-years of follow-up, and documented over 150,000 cardiovascular events. These findings highlight a consistent, dose-dependent, log-linear association between the extent of vascular exposure to LDL-C and the risk of developing ASCVD. Notably, this risk increases with prolonged exposure to LDL-C.

The convergence of insights from MR studies, preclinical models, and observational epidemiology has been instrumental in drug development, particularly for lowering LDL-C and apolipoprotein B levels. An essential example of this is the recent MR analysis that focused on the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene. The study revealed a dose-dependent log-linear association between PCSK9-mediated reduction in LDL-C levels and decreased risk of myocardial infarction or death due to coronary artery disease (CAD).[24] This pivotal study catalyzed the development of PCSK9 inhibitors, which have proven to be highly effective at mitigating the risk of ASCVD among high-risk individuals. Clinical trials involving monoclonal PCSK9 antibodies have confirmed the effectiveness of this intervention in significantly reducing cardiovascular events.[25,26] Furthermore, the role of ezetimibe, an inhibitor of cholesterol absorption in the small intestine, has been highlighted in the context of LDL-C reduction.[27] This drug works by inhibiting the activity of the Niemann-Pick C1-like 1 (NPC1L1) protein. Multiple MR analyses have consistently shown significant associations between variations in NPC1L1 levels with serum LDL-C levels and CAD risk, emphasizing the causal link between the two and opening new avenues for targeted therapeutic interventions.[28]

2. High-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs)

The potential protective effects of elevated HDL-C and reduced TGs in coronary heart disease (CHD) have been of considerable interest. However, the outcomes of randomized trials targeting these lipid fractions have yet to provide conclusive evidence.[29,30] One pivotal MR study constructed LDL-C genetic risk scores from specific single nucleotide polymorphisms (SNPs) associated with HDL-C, LDL-C, and TGs.[31] The analysis confirmed a causal link between LDL-C levels and carotid intima-media thickness (CIMT), a subclinical marker of atherosclerosis. However, it did not establish a similar causal relationship between CIMT and HDL-C or TG levels. A number of MR meta-analyses that analyzed a total of 17 studies involving 62,199 participants and 12,099 CHD events, were instrumental in delineating these associations.[32] Both unrestricted and restricted allele scores for LDL-C were associated with CHD. The unrestricted allele score for HDL-C indicated an association with CHD; however, this association was not observed when the score was restricted or adjusted for TGs, LDL-C, or statin use. In the context of TGs, both unrestricted and restricted allele scores were associated with CHD. However, this association was attenuated when the unrestricted score was adjusted for HDL-C, LDL-C, and statin use—highlighting the intricate interplay between these lipid fractions and their collective impact on CHD risk. While interventions aimed at elevating HDL-C or reducing TG levels are theoretically promising, empirical evidence from MR analyses and randomized trials remains inconclusive. The causal pathways linking these lipid fractions to CHD are complex and warrant further investigation. Unraveling these pathways is essential, as they have the potential to inform targeted therapeutic interventions and enhance the precision and efficacy of CHD management.

3. Lipoprotein (a) (Lp[a]) and remnant cholesterol

Lp(a) has emerged as a significant focal point in cardiovascular disease (CVD) research. It is formed by the covalent attachment of apolipoprotein A to apolipoprotein B via disulfide bonds.[33] Notably, the concentration of Lp(a) is inversely related to that of apolipoprotein A,

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and is mainly determined genetically, as the genetic factor accounts for approximately 90% of its levels.[34] The importance of Lp(a) levels as a recognized risk factor for CVD has been highlighted in various studies. Notably, when LDL-C levels were 104 mg/dL, Lp(a) exhibited a stronger association with CVD that positioned it as a residual risk factor.[35] A two-sample MR study, primarily based on the inverse variance weighted (IVW) method, unveiled a causal link between elevated Lp(a) levels and aortic aneurysms (AA), CHD, and ischemic stroke.[36]

In parallel with insights into Lp(a), the role of remnant cholesterol (RC) in ASCVD has also recently been elucidated. RC, which encompasses cholesterol content in chylomicrons, chylomicron remnants, very low density lipoproteins, and intermediate density lipoproteins, has been identified as a significant independent contributor to ASCVD risk, particularly following reductions in LDL-C levels.[37] This notion emphasizes the concept of residual risk and highlights the persistence of clinical events despite intensive lipid-lowering therapies.[38] In a recent large-scale MR study, the causal effects of RC on the risks of CAD, myocardial infarction (MI), and stroke were established, independent of LDL-C.[39]

4. Causality between inflammation and ASCVD

The intricate relationship between inflammation and ASCVD has been the focus of a number of studies, with C-reactive protein (CRP) often highlighted. CRP, an acute-phase protein produced in the liver, has been studied extensively as a systemic marker of inflammation.[40] Observational epidemiological studies have demonstrated a log-linear relationship between CRP concentration and the subsequent risk of CHD; however, this association is significantly influenced by conventional risk factors as well.[41] CRP not only binds to low-density lipoproteins, but is also found in atherosclerotic plaques, which has sparked interest regarding its potential causal relevance to CHD.[42] However, the causal role of CRP with regard to CHD remains unclear. Despite the observational correlations that have been described, human genetic data suggest that CRP concentration is unlikely to be a significant causal factor for CHD. Randomized trials specifically targeting CRP in relation to vascular disease outcomes are yet to be conducted. In one MR study, the risk ratio for CHD was neutral per every 1 standard deviation (SD) increase in genetically-elevated natural log concentrations of CRP.[43]

Interleukin 6 (IL-6), another inflammatory marker, has also been associated with an increased risk of CHD events in prospective observational studies, in a similar manner to CRP and fibrinogen.[44,45] Using a novel approach, genetic proxies for the IL-6 receptor (IL-6R)-mediated downregulation of IL-6 signaling were identified and associated with decreased CRP levels. CRP, a downstream molecule of IL-6 signaling, serves as a clinically useful biomarker for assessing residual inflammatory cardiovascular risk.[46] In conclusion, while inflammatory markers such as CRP and IL-6 are associated with ASCVD, their causal roles are yet to be established definitively. The complex relationship between inflammation and ASCVD merits further investigation, particularly through randomized trials and advanced genetic studies, to unravel the underlying mechanisms and inform targeted therapeutic interventions.

LIMITATIONS AND CHALLENGES

MR has undeniably created a niche in cardiovascular research, offering insights that are less susceptible to confounding and the biases inherent to observational studies. However, like any scientific method, MR is not without its limitations and challenges, which are crucial to acknowledge for a balanced perspective and informed application.

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1. Instrumental variable selection

The selection of appropriate instrumental variables is a primary challenge in MR studies. Genetic variants should be robustly associated with the exposure of interest, but not with confounders—a condition that can be difficult to satisfy.[47] The risk of weak instrument bias, wherein genetic variants explain only a small proportion of the variance in the exposure, can lead to imprecise and biased estimates of causal effects.[48] For example, a study on the genetics of smoking and its relationship with ASCVD highlights the issue of potential bias due to the use of weak genetic instruments. This study identified genetic liability to smoking as a risk factor for hypertension and increased body mass index but faced challenges due to conflicting results from previous studies and potential bias towards observational estimates. These findings underscore the importance of selecting strong and appropriate genetic instruments in MR studies to avoid biased conclusions.[49]

2. Measurement error in MR studies

An additional crucial aspect often overlooked is the impact of measurement error in both exposure and outcome variables. Inaccuracies in measuring these variables can lead to biased estimates, influencing the reliability of causal inference in MR studies. These errors may stem from various sources, including genetic variant measurement, phenotypic variability, and data collection inaccuracies. For instance, errors in dietary factor measurements or physical activity assessments can significantly skew MR results. To mitigate this, improved data collection methods and advanced statistical techniques that account for measurement error are essential. The consequence of ignoring measurement error is the potential attenuation or exaggeration of the estimated causal effect, as evidenced in several MR studies where measurement inaccuracies significantly impacted the findings.[50]

3. Binary exposures

Complications can arise when dealing with binary exposures, which are dichotomizations of continuous risk factors (e.g., hypertension as a dichotomization of blood pressure). Such dichotomizations can lead to violations of the exclusion restriction assumption, where the genetic variant might influence the outcome through a continuous risk factor, even if the binary exposure remains unchanged.[51]

4. Pleiotropy

Pleiotropy, in which a single genetic variant influences multiple traits, presents a significant challenge that can lead to biased estimates if not adequately addressed. Different forms of pleiotropy, including balanced and unbalanced, can affect the results of MR studies in several ways. Methods such as MR-Egger regression have been developed to detect and correct pleiotropy; however, they have their own sets of assumptions and limitations.[52]

5. Population stratification

MR studies are susceptible to population stratification, a situation in which allele frequencies vary between subpopulations due to systematic differences in ancestry. This can lead to confounding and biased causal estimates if not properly controlled. Techniques such as genomic control and principal component analysis are often applied to mitigate this issue; however, they are not foolproof.[53]

6. Data accessibility and quality

The accessibility and quality of data are crucial for the success of MR studies. Large sample sizes are often required to detect modest causal effects with precision. Although large

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biobanks and consortia have facilitated access to extensive datasets, issues related to data harmonization, quality control, and ethical considerations for data sharing persist.[54]

7. Statistical methods and assumptions

The statistical methods used in MR and their underlying assumptions are subjects of ongoing debates. The violation of MR assumptions can lead to biased results. Various statistical approaches in different studies often lead to biases, including pleiotropy, population stratification, and weak instrument bias, all of which may skew causal estimations. Sensitivity analyses and complementary methods are often used to assess the robustness of findings; however, consensus on best practices is still evolving.[55] Furthermore, the critical role of replication studies is undeniable. They are essential for affirming the validity of MR findings, ensuring both their robustness and the reliability of derived conclusions.

8. Integration with other data types

The integration of MR with other types of data, including functional genomic and epigenetic data, is an emerging frontier. Although this integration promises enriched insights, it also introduces challenges related to data complexity, computational requirements, and methodological development.[56]

9. Ethical and interpretational challenges

Ethical considerations are of paramount importance, particularly those concerning data privacy and consent. The interpretation of MR findings should be done with caution. Establishing causality does not imply clinical actionability, and translating MR findings into preventive and therapeutic interventions necessitates careful consideration of broader clinical, ethical, and societal contexts.[57]

FUTURE DIRECTIONS

As MR continues to evolve, it is expected to play an increasingly important role in ASCVD research. The future of MR is rich in opportunities; however, these are also contingent on addressing existing challenges and adapting to emerging trends in genomics, data science, and clinical research.

1. Advancements in MR techniques

The refinement of MR techniques is a cornerstone for future advancements. Two-sample and multivariate MR are examples of methodologies that have expanded the scope and applicability of MR studies.[58] In particular, two-sample MR allows the use of summary data from different sources, enhancing the feasibility of MR analyses without the need for individual-level data.[59] The ongoing development of more sophisticated statistical methods is expected to mitigate biases, enhance precision, and facilitate the exploration of complex causal pathways.

2. Integration with emerging technologies

Integrating MR with cutting-edge technologies such as machine learning and network analysis is another promising direction. Machine learning algorithms can enhance the identification and validation of instrumental variables, improve the handling of pleiotropy, and facilitate the analysis of high-dimensional data.[60] Network analysis can aid in deciphering the intricate web of causal relationships between multiple exposures and outcomes, offering a holistic view of the etiological landscape of CVDs.[61]

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3. Expanding the genetic instrument repository

The expansion of the repository of genetic instruments is crucial. With the advent of large-scale GWASs, an unprecedented opportunity to identify novel genetic variants associated with multiple exposures has developed. Efforts to curate, harmonize, and make these data accessible to the research community will be pivotal in propelling MR studies to new heights.[62]

4. Translational applications

Translational applications of MR findings are of paramount importance. Causality is a precursor to the development of targeted preventive and therapeutic interventions. An enhanced focus on translating MR findings into clinical trials and, eventually, evidence-based clinical guidelines are possible outcomes in the future. The role of MR in drug repurposing, where existing drugs are tested for new therapeutic applications, is also an area that is ripe for future exploration.[63]

5. Ethical and regulatory considerations

As MR continues to develop, ethical and regulatory considerations have come to the forefront. Issues related to data privacy, consent, and the equitable inclusion of diverse populations in MR studies require careful attention. Developing frameworks that balance scientific advancement with ethical considerations will be crucial to the future of this field.[64]

6. Global collaboration and data sharing

The future of MR is inherently linked to global collaboration and data sharing. Consortia that facilitate data pooling and collaborative analyses will enhance the power and generalizability of MR studies. Overcoming barriers related to data-sharing protocols, standardization, and interoperability will be key to realizing the full potential of collaborative MR research.[65]

7. Personalized medicine

The role of MR in personalized medicine is a promising frontier. By elucidating the causal pathways underlying CVDs, MR can contribute to the development of personalized risk prediction models and tailored interventions. Integrating MR findings with other -omics data, including transcriptomic, proteomic, and metabolomic data, can offer comprehensive insights into individual disease risks and treatment responses.[66] While these advancements hold significant promise, they also bring forth critical challenges that need careful consideration. The integration of MR with other omics data, such as genomics, transcriptomics, and proteomics, presents a complex landscape of biological interactions and regulatory mechanisms. This complexity raises concerns about the robustness and reliability of the findings. Specifically, the potential for confounding in omics data, which could lead to spurious associations, needs to be rigorously addressed.[67] Furthermore, the application of machine learning techniques in MR studies, although innovative, carries the risk of overfitting. Overfitting occurs when a model is excessively complex and captures noise instead of the underlying biological signal.[68] This can lead to overly optimistic estimates of the model's predictive power and may not generalize well to new datasets. Therefore, while embracing these technological advancements, researchers must employ stringent validation and cross-validation methods, along with sensitivity analyses, to ensure the credibility and generalizability of their findings.

8. Implications of MR studies on clinical practices

In the dynamic field of cardiovascular research, MR studies have not only deepened our understanding of disease mechanisms but are also beginning to shape clinical practices.

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These studies show promise in transforming treatment protocols and preventive strategies in clinical environments. For instance, MR research has shed light on the interplay between cardiometabolic factors and coronavirus disease 2019 (COVID-19). It reveals that higher levels of HDL-C, typically considered protective, do not necessarily reduce COVID-19 risk. Additionally, higher body mass index and LDL-C levels have been linked to increased susceptibility to COVID-19, highlighting them as potential risk factors in the context of the pandemic.[69]

CONCLUSIONS

Supported by the insights presented in this review, MR represents a pivotal methodology in ASCVD research. It has not only enriched our understanding of the complex causal pathways underlying ASCVD, but has also offered a robust mechanism to circumvent the inherent limitations of traditional observational studies. Significant strides have been made in the use of MR to elucidate the causal relationships between various risk factors and ASCVD. By leveraging genetic variants as instrumental variables, MR has provided a more nuanced and reliable lens through which the relationships between exposures and outcomes can be observed. Revelations concerning LDL-C, blood pressure, and other lifestyle factors have been particularly illuminating, offering actionable insights that hold significance for both preventive and therapeutic contexts. However, like any scientific methodology, MR is not without certain challenges. Pleiotropy, the selection of appropriate genetic instruments and the need for large sample sizes are among the obstacles that researchers must overcome when using this technique. However, the evolution of statistical methods and the advent of technologies such as machine learning and network analysis are promising developments that hold the potential to address these challenges effectively.

The future of MR in ASCVD research is marked by immense potential. The integration of MR with emerging technologies, the expansion of genetic instrument repositories, and global collaborations are expected to drive a new wave of discoveries. These advancements will not only refine our understanding of ASCVD, but will also catalyze the translation of these insights into tangible clinical and public health interventions. The prospect of personalized medicine, underpinned by causal inferences drawn from MR studies, promises an era in which interventions are tailored to each individual, maximizing efficacy and minimizing adverse effects.

In conclusion, MR has become a cornerstone of ASCVD research. Its contributions extend beyond the academic sphere and influence policies, clinical practices, and public health initiatives. As we continue to harness the power of genetics, coupled with advancements in technology and data science, MR will play a central role in shaping a future in which the burden of ASCVD has been significantly mitigated. The journey ahead, although marked by challenges, is replete with opportunities for innovation, collaboration, and discovery that will redefine our approach to ASCVD, guiding an era of enhanced understanding, prevention, and treatment.

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