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Review

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Review

Inclusion of Underrepresented Populations in Cardiovascular Genetics and Epidemiology

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Abstract: Novel genetic risk markers have helped to advance the field of cardiovascular epidemiology and refine our current understanding and risk stratification paradigms. Discovery and analysis of variants can help to tailor prognostication and management. However, populations underrepresented in cardiovascular epidemiology and cardiogenetics research may experience inequities in care if prediction tools are not applicable to them clinically. Therefore, the purpose of this article is to outline the barriers that underrepresented populations can face in participating in genetics research, describe current efforts to diversify cardiogenetics research, and outline strategies that researchers in cardiovascular epidemiology can implement to include underrepresented populations. Mistrust, a lack of diverse research teams, improper use of sensitive biodata, and constraints of genetic analyses are all barriers for including diverse populations in genetics studies. Current work is beginning to address the paucity of ethnically diverse genetics research and has already begun to shed light on the potential benefits of including underrepresented and diverse populations. Reducing barriers for individuals, utilizing community-driven research processes, adopting novel recruitment strategies, and pushing for organizational support for diverse genetics research are key steps that clinicians and researchers can take to develop equitable risk stratification tools and improve patient care.

Keywords: cardiovascular epidemiology; cardiogenetics; underrepresented populations; diversity; genetics; genomics

1. Current State of Cardiovascular Genetic Epidemiology for Common Traits and Diseases

Cardiovascular disease is the leading cause of death globally and comprises a group of diseases with widespread impact [1]. While investigating the occurrence and distribution of disease, cardiovascular epidemiology also involves research into the determinants of clinical phenotypes. Among other factors, genetics play a significant role in cardiovascular disease pathophysiology and clinical course [2,3]. Cardiogenetics is a broad and relatively novel field, which includes advancing cardiovascular epidemiology through the ability to identify individuals at risk of cardiac disease and guide their care with risk prediction tools [4–6].

Advancements in population based cardiogenetics have primarily relied on the implementation of large genome-wide association studies (GWAS), which identify genetic variants associated with common traits and clinical phenotypes [4–6]. For example, coronary artery disease (CAD) GWAS have elucidated key associations between genetic loci, discovered new drug targets, and identified new genes important in CAD's pathophysiology [5]. Each variant identified in a GWAS represents a small contribution to a phenotype; however, by aggregating multiple associated variants one can better predict the occurrence of a trait. A polygenic risk score (PRS) is one such method for aggregation—formulated by the sum of risk alleles, identified by a GWAS, for a given phenotype—that has wide-spread and clinically relevant use [7–9]. In cardiovascular epidemiology, PRS development is improving risk-prediction and shaping clinical management in atrial fibrillation [10,11], CAD [12–30], cerebrovascular disease [31–37], hypertension [38–45] and heart failure [46–49].

While providing an applicable risk-prediction tool, a PRS's utility and reliability is not uniform across individuals. For a given PRS derived from a GWAS composed of certain ancestries,

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performance is best when applied to an individual of similar ancestry, and lacks predictive power for different ancestries [50–58]. For example, Duncan et al. (2019) analyzed PRS studies from 2008-2017, finding that PRSs derived from European ancestry have poorer prediction in non-European populations [55]. Gola et al. (2020) illustrate that even within a European ancestry cohort, population specific PRSs for CAD perform best in their respective subdivided population groups [58]. Poor transferability between populations occurs for various reasons including variable degrees of associations comparing ancestries, and differences in linkage disequilibrium that can reduce effect sizes and subsequently decrease predictive power [52].

Reflecting the underrepresentation of diverse populations in cardiovascular trials [59], as of 2021 the vast majority of GWAS, 86%, are composed of participants of European ancestry [60], which is an increase from 81% in 2016 [61]. Improvements in diversity over recent years has largely been driven by the development of East Asian GWAS [61]. GWASs thus far have poorly represented Hispanic/Latino, African, South Asian, and East Asian populations [60–63], and especially Indigenous populations globally [55,64]. Inequities for these populations subsequently arise, as PRSs are not reliably able to predict risk and management cannot be personalized for these individuals.

While the current use of cardiogenetic methods in cardiovascular epidemiology is providing benefits to patients, inequities occur for those populations underrepresented in genetics research. Rectifying this gap is a matter of securing justice and equity for all individuals. At the same time, it is also imperative for the genomes of diverse populations to be studied for optimized clinical management, reduction of health disparities, and understanding both human biology and our history [65]. Although cardiogenetics is a multi-faceted field, the importance of including diverse populations in GWAS and other genetics studies cannot be overstated. To underscore this, the purpose of this review is to answer: What are the barriers contributing to underrepresentation of certain populations in cardiogenetics research? What efforts are researchers making to support diversity in cardiogenetics? What strategies can future cardiogenetics research use to include underrepresented populations?

2. Barriers to Inclusion of Diverse Populations

Difficulties in recruiting diverse population pools is a persistent problem in medical research [66–68]. Thus, in a similar vein, these obstacles are inherent in genetic and genomic research, and above and beyond with the addition of field-specific issues. Barriers occur at multiple points in the research process, presenting at the individual level, in communities, in research teams, and at the organizational level.

Mistrust

Starting at the individual level, one barrier commonly facing recruitment of underrepresented populations is fear of harm and a lack of trust in researchers [69–76], a finding prominent in genetic research [76–80]. For minority individuals and communities that have experienced significant trauma through unethical research practices, participating in research studies can be perceived as harmful and decrease participation [76,81,82]. A pertinent example is the Tuskegee Study of Untreated Syphilis, in which African American participants with HIV were observed and studied but not treated, which has resulted in long-standing mistrust of the healthcare system for African Americans [75,76]. Similarly, Indigenous populations have experienced harm through the medical system in various ways—one example being forced sterilization of Native American Women via tubal ligations while under surgical anesthetic [83]. When considering genetic research, the Havasupai Tribe in Arizona, was subject to significant harm when researchers misused their DNA samples originally meant for Type 2 Diabetes research, instead using it for studies on highly stigmatized topics including schizophrenia and migration theory [84]. Another example is exploitation of blood samples given by the Nuu-chah-nulth tribe in British Columbia, Canada for investigation of rheumatoid arthritis prevalent in their community—producing no findings, researchers instead conducted different research with the samples, including work on infectious spread of viruses via intravenous drug use

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[85]. Given these occurrences, minority populations have valid concerns in participating in research projects that may harm by increasing stigma with potential for discrimination.

In addition to fearing harm through the research process, many underrepresented populations have experienced little benefit from participating in research. Historically, researchers have performed research on minority communities, rather than with them [86,87]. Extracting data from populations without proper consent and consultation may prevent relevant research important to communities being carried out [84,85]. Given previous and ongoing research work that benefits the investigator and may harm the minority participant, communities may not engage with contemporary research efforts and subsequently become underrepresented in data sets.

Identifying and Reaching Populations

Identifying underrepresented populations and ensuring outreach is targeted effectively is another barrier in research recruitment. Self-identification is typically used to collect ethnic data; however, the categorization researchers or participants choose may reflect socially defined ethnicity rather than the ancestral population targeted, where the latter is particularly relevant in genetics research [69,88]. Additionally, underrepresented populations may be genetically and ethnically heterogeneous, as is the case between different Indigenous communities [64]. Therefore, broad categorizations may not reflect clinically relevant cohorts and obscure important associations [64]. In addition to identification, out-reach to specific target populations can also come with difficulties. Underrepresented populations may face obstacles in accessing healthcare services for a variety of reasons—including time constraints [71–74], transportation difficulties [70–72], and financial burden [70,71]— decreasing opportunities to participate in research endeavors and the ability to attend research appointments. Differences in health literacy, language, and exposure to the healthcare system can also lead to miscommunication and a lack of opportunity to meaningfully engage in research [71].

Organizational Constraints: Diversity and Funding

A lack of diverse representation in research teams is another barrier to inclusion of underrepresented populations [64,69]. Diversity in the medical research workforce has been improving compared to previous measures but is still disproportionate to the general population [89–91]. Without input from population stakeholders, research goals may be misaligned from participant goals, leading to dissatisfaction and a lack of engagement in research. Health-literacy and language barriers are another factor not easily overcome without representation of culturally congruent and linguistically appropriate team members [70,71]. Difficulties in retaining minority researchers center around cultural safety and support for ensuring diverse teams are formed, which requires dedicated policies and funding [92]. Similarly, system pressures and resource limitations may make intensive strategies necessary to recruit underrepresented populations difficult to implement [93]. Ultimately, poor recruitment and retention of minority researchers coupled with a need for significant institutional funding are key barriers to including diverse populations in genetics research.

Appropriate Handling of Biodata

Collection, analysis, storage, and ownership of biodata is particularly relevant in genetics research. Some cultures view biological samples as incredibly important pieces of information, representing extensions of themselves and connections with relatives and belief systems [82,94]. As such, a significant amount of trust is needed to provide biodata to researchers; considering the previous and ongoing harm that research has caused, an individual or community may feel the risk is too great. Questions of ownership and how results of research are disseminated is another pertinent issue when including underrepresented populations in genetics research [64,95–97].

Constraints of Genetic Analysis

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As Bentley et al. (2017) describes, the propensity for research focusing on European ancestry cohorts can be attributed to their greater relative availability of large open-access datasets. Given that a genomic study's validity is evaluated with sample size being a key factor in revealing associations, researchers may find it prudent to utilize these cohorts over others [65]. A higher level of linkage disequilibrium in European ancestries relative to other cohorts can make analysis in European populations more efficient through discovery of more variant associations [65]. An additional barrier is the higher genetic diversity in certain populations such as African ancestries compared to European, making discovery of variant associations more difficult, and analysis more complicated without subdivision [98]. Available technologies may also not be suitable for analysis in genetically diverse cohorts given lack of inclusion in current models—for example, the genomic reference panel derived from the 1000 Genomes Project dataset does not represent many South Asian and African population genomes [99]. Addition of diverse ancestries allows for discovery of risk variants that would be otherwise unearthed. This is also true for single-gene disorders such as hypercholesterolemia, cardiomyopathy, and inherited arrhythmias [100,101] where large multi-gene panels are used for diagnoses. The knowledge of which variants are common or rare in a population, improves the ability to confirm a precise diagnosis. Endeavors such as the "Silent Genomes Project" in Canada [102] and the "Aotearoa Variome" in New Zealand [103] are building Indigenous background variant databases to further genetics research and care for these chronically underserved and heterogeneous communities [64]. Other multi-ethnic, non-European platforms, such as the "All of Us" research program [104], Million Veteran Program [105], the UK Biobank [106], and Biobank Japan [107], are providing researchers a more diverse pool to draw from for equitable genomic research. Evidence shows that dedicated research programs working towards diversity in genetic research can improve representation of historically underrepresented populations [108].

3. Increasing Diversity in Cardiogenetics Studies

Despite the numerous barriers present to including diverse populations in research endeavors, early diversification efforts in cardiogenetics studies are underway to include underrepresented populations. For cardiogenetic prediction tools to be calculated, large genetic databases must be available for a given population. Recognizing this, a major step in increasing representation has been addressing the paucity of diverse genetic biobanks. For example, Legget et al. (2021) detail a large-scale project, The Multi-Ethnic New Zealand Study of Acute Coronary Syndromes (MENZACS), which comprises a large diverse biobank for future prospective study of the genetic factors influencing ACS [109]—represented populations include Māori, Pacific, Indian, and NZ European.

As further genetic data from underrepresented populations is collected, analyses can draw on them to incorporate in future efforts towards PRS development. As has been detailed previously, PRSs created from primarily European cohorts tend to perform poorly in non-European populations. Work being performed now illustrates the strength that diverse genetic backgrounds can provide to PRS performance. Martin et al. (2019) demonstrated that prediction tools form ancestry-matched GWAS summary statistics had improved accuracy in predicting anthropometric measures and disease endpoints [52]. Wojcik et al. (2019) discuss the Population Architecture using Genomics and Epidemiology (PAGE) study and its efforts of conducting genetic epidemiological research in diverse populations; authors found evidence of heterogeneous effect-size across different ancestries for BMI and height, and demonstrated how fine-mapping of gene loci with diverse populations increases association discovery [110]. Mahajan et al. (2022) demonstrated how utilizing a meta-analysis of multi-ancestry GWAS studies allowed for greater transferability of predicting Type 2 Diabetes across various populations. Authors additionally elucidated specific genetic mechanisms via fine-mapping that provided the basis for functional investigations, made possible by greater population diversity [111].

There is also evidence that the incorporation of diverse ancestral backgrounds is being considered in cardiac epidemiology as researchers begin to address this gap and unmet need. Kullo & Dikilitas (2020) describe a framework for using coronary heart disease PRSs in a specific population, entailing the determination of where an individual's score falls in an ancestry matched distribution

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to categorize them into low, medium, and high-risk groups [112]. This strategy allows for contextualized PRSs that better guide an individual's cardiac risk assessment even if their ancestry is relatively underrepresented in GWASs. Wang et al. (2020) illustrate the derivation and validation of an ancestry specific CHD PRS for South Asians from a larger majority-European GWAS and were able to demonstrate improved prediction and ability to risk-stratify individuals [113]. Koyama et al. (2020) provided evidence of a CAD PRS derived from a trans-ancestry meta-analysis outperforming population-matched Japanese and English PRSs [114]. Kurniansyah et al. (2022) similarly developed a PRS based on multiethnic hypertension GWAS data, which had good predictive performance of incident hypertension in follow-up [41]. Tcheandjieu et al. (2022) drew on the Million Veteran Program to report a new GWAS of CAD comprised primarily of White, Black, and Hispanic participant ancestries. In addition to identifying numerous novel loci of interest and providing evidence for disease mechanisms in CAD, authors reiterated how current PRSs, derived from European-ancestry populations, have poor transferability to Black populations—with a new PRS derived from their diverse GWAS, risk prediction was improved across all populations [30]. Authors highlight the importance of data-gathering in non-white populations and refinement of analyses to reduce PRS performance variability between ethnic populations [30]. While some studies show derivation of PRSs from diverse populations does not out-perform population-specific PRSs [30,111], overall the majority of literature to date continues to indicate the value of including underrepresented populations.

4. Strategies for Inclusion of Underrepresented Populations

Including ancestrally diverse populations in cardiogenetics research improves the strength and validity of reported outcomes, while also serving minority populations facing inequitable care. Addressing the gaps underrepresented populations receive in healthcare is an incredibly important undertaking, but not without its challenges. Discussion of key strategies that can be employed by clinicians and researchers can aid in future research endeavors.

Addressing Barriers for Individuals

At the level of the individual, common barriers for those from underrepresented populations to engage with research efforts include time constraints, lack of resources, and a mismatch between language and health literacy [70–72,87]. To counteract these obstacles, recruitment efforts should seek to alleviate individual burdens through appropriate funding and support. For example, Ejiogu et al. (2011) developed a multi-pronged approach to recruiting a socioeconomically diverse cohort of African American and non-Hispanic White participants for a longitudinal age-related study on health disparities. Researchers addressed transportation barriers via mobile data collection centers and free transportation, time and economic constraints via flexible scheduling and financial compensation, and differences in health literacy and language through a culturally-congruent and diverse research team [72]. Transportation interventions in particular have been well-studied, with evidence suggesting no-show rates for appointments decreased with transportation-aid [115,116]. Similarly, a financial support program for cancer clinical trial participation showed an increase in enrollment after implementation [117]. Frameworks for recruitment of minority populations support culturally-congruent research materials and staff to mitigate differences in language and health literacy [118,119]. These interventions can improve trust and comfort of potential participants and enhance enrollment [120,121].

Novel Technological Strategies

Outreach endeavors for underrepresented populations that are hindered by opportunity or sociocultural divides may benefit from the utilization of novel technological strategies and mediums [118,119,122]. For example, outreach via social media can be an effective method of participant recruitment in underrepresented populations, especially when communications are culturally-adapted [123–125]. While not all studies show social media as their most effective outreach strategy,

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these methods still provide a viable and cost-effective method in a well-rounded recruitment approach [126]. Brewer et al. (2018) illustrate how a mobile app paired with a community cardiovascular health program can enhance success in recruitment and utilization of evidence-based health interventions [122]. While technological recruitment strategies offer a promising route, care should be taken when implementing these novel multi-media strategies in underrepresented populations as ethical considerations are still nascent in examination and without specific oversight or official guidelines [127].

Collaborating with Community

Given substantial evidence of harm and perceived lack of benefit for underrepresented populations in research [76,82,84–86], it is necessary, and beneficial, that research be formulated with community-specific guidance from the beginning [128–131]. Community-based participatory research (CBPR) is a widely-used and effective methodology to ensure benefit to the community and meaningful research goals [132]. Collaboration, shared decision-making, and shared ownership of research materials and products are key values of CBPR projects [132]. Cultural differences between participants and researchers may account for underrepresentation in genetics research, where a minority population's motivation for research engagement may for example be focused on benefit for their community rather than publication [133]—this makes CBPR values incredibly important to ensure participant engagement. Trust remains a hallmark of effective collaboration with community; conceptual models, such as a circle of trust, can help guide engagement efforts that include unrepresented and marginalized communities [134]. Communication and relationship-building should be approached in a longitudinal fashion through formal and informal connections [95,119,135]. Collaborating with communities prior to any research activity is key for success, as it can guide design and provide valuable new ideas [129]. Arbour et al. (2008) demonstrated cardiogenetics research driven by CBPR principles, with a Canadian First Nations community, initiating research to investigate high rates of Long QT syndrome in their community and its genetic basis [136]. Ensuring research activities and products are appropriately disseminated to participants and ongoing regular communication with stakeholders is another essential aspect of CBPR [95,129]. Knowledge translation should be enacted in an understandable and transparent manner to ensure meaningful community-involvement [137]. Further recommendations drawing from CBPR principles have been formulated under a genetics and genomics-specific research lens to guide future work [93,138].

Promoting Diverse Research Teams

Promoting diversity within research teams is a well-evidenced strategy to improve research outcomes and reach underrepresented populations. Literature shows that diverse groups increase creativity, impact of research, and output of high-quality work that can benefit populations experiencing inequities [139–143]. Blanchard et al. (2017) note how having an Indigenous researcher's perspective allowed for a more culturally-appropriate research design and decreased potential harm in a qualitative study of perceptions on genetic ancestry testing [69]. Promoting diverse teams through community capacity-building is a strategy that can produce competent professionals while aligning research goals with a population's needs [129]. Ultimately, having a diverse team that reflects the culture and languages of prospective study populations can decrease mistrust and promote recruitment [69,72,119–121,135]. Recruiting and retaining a diverse workforce in genetics research is imperative to future work; this fact is highlighted by researcher recommendations [70,93,118] and key organizations such as the National Human Genome Research Initiative including workforce diversity in their strategic vision and recommendations [144].

Safe Research Processes

Research protocols and practices involving underrepresented populations should have safety as a core value in their formulation. Respecting community research protocols and processes is a key step researchers can take in ensuring the safety of research performed with underrepresented

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populations [69]. For example, many Indigenous communities have their own institutional review boards and regulatory bodies to safe-guard their members against potentially harmful projects [129]. Safety is particularly important in the case of genetics research, given more sensitive data consisting of biological samples. Given the previous harms enacted via geneticists in the past [84,85], and the cultural significance of tissue samples inherent to certain populations [82,94], biodata should be collected, stored, and analyzed under community-driven protocols and wishes [95].

Support for Diverse Genetics Studies

Calls for dedicated recruitment of diverse cohorts for genetics research are ongoing given the continuing paucity of underrepresented populations in clinically impactful studies [92,93,145]. Several large-scale endeavors are responding to these recommendations, including the development of multi-ethnic biobanks that can be used for genetics research purposes [102–107,109]. Given the sheer number of data points needed for well-powered genetics studies, the cost-benefit case of large-scale biobank development is evident [146]. Funding is paramount in genetics research, and financial support for genetics studies in underrepresented populations illustrates progress that can be made [60]. Simultaneously, care and culturally-appropriate methods should be implemented in the building of such databases, to ensure harm is not perpetuated and that population-specific contexts and goals are honoured [145,146]. While the addition of underrepresented populations to GWAS and biobank studies progresses, novel strategies in cardiogenetic analysis of multi-ethnic data sets already available should be utilized and developed to begin increasing health and genetic care equity for underrepresented populations [112,113,147].

5. Conclusion

Given the advancement in cardiovascular epidemiology through genetics research and innovation, the importance of equitable implementation of novel care strategies is paramount. Establishing that certain populations are underrepresented in cardiogenetics research, this review found that mistrust, difficulties in reaching certain populations, lack of diversity in the genomics workforce, inappropriate handling of biodata, and constraints particular to genetic analysis all present barriers for increasing diversity in genetics studies. Despite these obstacles, genetics researchers are continuing to make progress in developing large multi-ethnic biobanks that can include underrepresented populations in future analyses. Cardiogeneticists are further engaging in this work by incorporating diverse populations and illustrating the benefits of their results in prediction of cardiovascular disease. To support future genetics work with underrepresented populations, strategies researchers can implement include reducing individual barriers, utilizing community-driven research processes, adopting novel technologies and methods in recruitment, and requesting organizational support and funding.

Future work should aim to incorporate strategies outlined in this review to support and improve future cardiovascular epidemiology genetics studies. Future directions in cardiogenetics research can include the development of guidelines and criteria in using PRSs within a given ancestry to ensure reliability of performance. Similarly, improved methods of analyzing linkage disequilibrium and variant frequencies in non-European populations when using PRSs is a fruitful avenue of inquiry. Future cardiovascular epidemiology work should additionally assess progress made in including underrepresented populations through scoping reviews and meta-analyses. Overall, creating equitable risk prediction tools that benefit all patients with specialized care is an important and necessary step towards advancing cardiovascular epidemiology research and clinical outcomes.

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