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Opinion

Ancestry, ethnicity, and race: explaining inequalities in cardiometabolic disease

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Population differences in cardiometabolic disease remain unexplained. Misleading assumptions over genetic explanations are partly due to terminology used to distinguish populations, specifically ancestry, race, and ethnicity. These terms differentially implicate environmental and biological causal pathways, which should inform their use. Genetic variation alone accounts for a limited fraction of population differences in cardiometabolic disease. Research effort should focus on societally driven, lifelong environmental determinants of population differences in disease. Rather than pursuing population stratifiers to personalize medicine, we advocate removing socioeconomic barriers to receipt of and adherence to healthcare interventions, which will have markedly greater impact on improving cardiometabolic outcomes. This requires multidisciplinary collaboration and public and policymaker engagement to address inequalities driven by society rather than biology *per se*.

Highlights

Use of the terms 'ethnicity,' 'race,' and 'ancestry' to distinguish populations must recognize their distinct definitions and how these definitions associate with environmental risk factors that determine cardiometabolic risk.

The role of gene variants that co-segregate with population groups in determining both cardiometabolic risk and response to cardiometabolic medication is limited.

By contrast, the role of societally imposed socioeconomic disadvantage on risk of cardiometabolic disease is underresearched and poorly appreciated but critical to social policy interventions.

Risk prediction scores should differ by ethnicity if they equally predict disease and thus drive equitable intervention.

Disease outcomes would be better served by ensuring equitable intervention and adherence to established medication rather than pursuit of personalized medicines.

Us and them: should cardiometabolic disease prevention and treatment differ by population group?

Our knowledge of cardiometabolic disease, its pathogenesis, and choice of intervention is largely driven by studying European origin populations. Yet, overwhelmingly, and increasingly, most of the global population with cardiometabolic disease does not share these origins [1], nor does it exhibit similar disease characteristics. This has prompted investigation of diverse populations and promotion of different population-specific screening thresholds and different treatment guidelines based on race or ethnicity. A central assumption, explicitly or implicitly, is that population differences are largely or solely driven by biological, specifically genetic factors. By contrast, implementing population stratification for treatment has been challenged [2] as being based on flawed science and resulting in inequitable care.

In this opinion article, we aim at clarity on the use of the terms 'ethnicity,' 'ancestry,' and 'race' in the context of cardiometabolic disease. We consider candidate explanations for population differences in both disease incidence and outcomes. We explore stratification for either disease prediction or drug responsiveness. Finally, we propose future directions for understanding and addressing population inequalities in cardiometabolic disease.

Disambiguating ancestry, ethnicity, and race from an epidemiological perspective

The widely used term 'ancestry' refers to the degree to which individuals are related [3]. Categorization into discrete groups overlooks the degree of relatedness between individuals that exists on a continuum [4]. Furthermore, categorizations are subjective, often depending on the reference populations against which ancestral distances are compared. Additionally, an individual's

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genetic ancestry can vary markedly from one chromosomal segment to another due to the ubiquity of human migration and **admixture** (see Glossary) [5]. Ancestry-related variants can have biological influences. However, clustering of genetic factors based on ancestral distance can be closely coupled with, and correlated to, clustering of environmental factors due to confounding by demographic history (Figure 1). In terms of their association with disease or other traits, **ancestry informative markers** and other more sophisticated measures of genetic population structure are often more likely capturing differential environmental exposures rather than population-specific biology [6].

Ethnicity refers to culture: customs, language, history, and religion that are often tied to geographical regions. These can manifest in environmental exposures (e.g., diet, physical environment) that an individual experiences due to the social groups with which they self-identify and self-select but to which they can also be assigned by others. These categorizations are subjective and mutable. Parents may categorize the ethnicity of their children differently from how the children come to see themselves. Additionally, association of these categories with exposures will differ over time, by place, and by generation.

Race, by contrast, is typically an externally imposed societal construct, often based on physical characteristics. The concept emerged in the 17th century, partly to justify enslavement of African people and oppression of others through European colonialism [7]. From an epidemiological perspective, race invokes cultural, social, and environmental exposures that an individual experiences due to this categorization. As an indicator of such factors, the inferential value in epidemiological studies of racial categorization is potentially substantial. Race and ethnicity are often correlated with ancestry, but the structure of human genetic diversity is far more complex than any racial or ethnic categorization, and thus these categories poorly proxy for genetic homogeneity [8].

These terms are socially sensitive, related, and often used interchangeably in error. Critically, they speak to different causal processes influencing cardiometabolic disease. Researchers must use them responsibly; inaccurate use can lead to invalid inferences and can also perpetuate harmful ideas predicated on the notion that humans naturally divide into biologically distinct populations.

We aim to keep these terms and the distinctions between them clear. However, to the extent that they overlap, such as in describing cultural and social categorizations that affect disease risk, we preferentially use the term 'ethnicity,' which is more often self-defined, as opposed to 'race.' At times when referring to published work, we use the term used by the authors. Where no causal structure is implied, we default to the term 'population'.

Population differences in cardiometabolic disease: findings in people of European ancestry may not generalize to other groups

On the basis of knowledge of cardiometabolic disease in people of European ancestry, we begin by highlighting discordances within and between populations. European ancestral populations have one of the lowest risks of type 2 diabetes mellitus (T2DM) globally. Rates in many other populations are far higher, from the isolated Pima and Nauruans to people of, for example, South Asian, Middle Eastern, and African ancestry. T2DM is associated with adverse cardiovascular risk factors, and populations with elevated T2DM risks are likely to have elevated risks of coronary heart disease (CHD) and stroke. Low CHD risks in people of African descent in some settings are a notable exception.

Disease phenotype and associations between risk factors and disease also differ by population. For example, ketosis, as the initial presentation of T2DM, is frequent in African ancestral

Glossary

Admixture: the phenomenon of gene flow between populations, following which the genomes of some or all individuals in these populations will contain chromosomal segments representing a combination of ancestries.
Ancestry informative markers: SNPs that correlate with genetic population structure and are sometimes used to distinguish population groups and inform on admixture
Embodiment: the biological incorporation of the environment in which we live. The environment in which we live is shaped by the way the dominant social groups have structured society (e.g., the siting of major roadways through diverse neighborhoods). Our environment elicits biological responses (e.g., traffic pollution elicits airway inflammation), which have biological consequences (e.g., chronic airway inflammation leads to lung disease). Thus, the way that our society is structured can lead to health inequities between social groups.
Linkage disequilibrium (LD): where alleles at different genetic variants are nonrandomly associated because of those variants being in close physical proximity to each other on a chromosome. Such patterns of association between variants are relatively well conserved within ancestral groups. LD is typically represented as the correlation coefficient in a sample of individuals within that ancestral group. Patterns of LD can differ substantially as ancestral distance between individuals increases.
Minor allele frequency: allele frequency is the proportion of all chromosomes in a sample that have that specific allele at that specific genomic position. When a genomic position has two or more alleles in the sample, the minor allele frequency is the frequency of the least common allele and will take a value between 0 and 0.5.

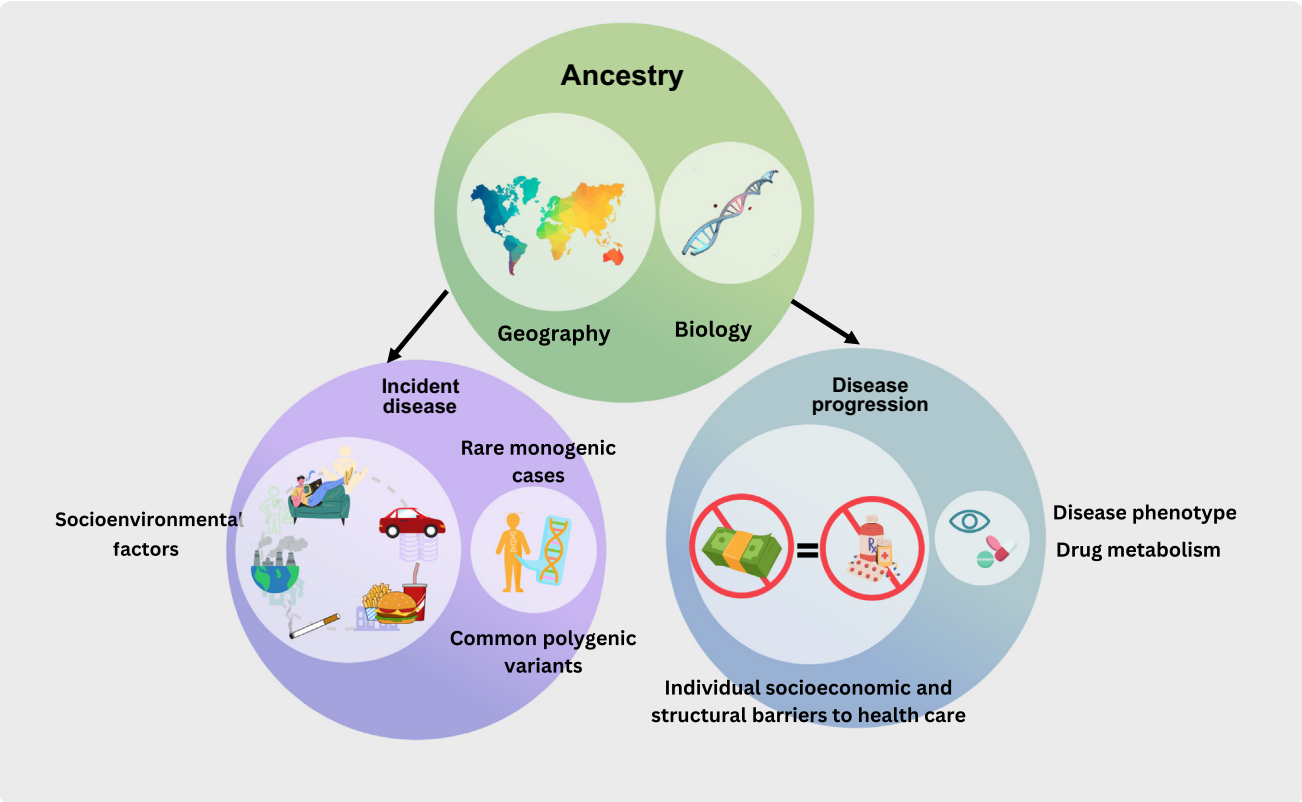

Figure 1. Geographical and biological underpinnings of the association between population ancestry and cardiometabolic disease incidence and progression. Population ancestry includes an intrinsic biological, specifically genetic component, reflecting relatedness. It also has an extrinsic component, based on geographical colocation, including the effects of shared environments, cultures, lifestyle behaviors, and beliefs. Both components influence cardiometabolic disease incidence and progression. For incidence, genes are responsible for infrequent monogenic cases, and polygenic variants for more frequent enhanced susceptibility, and potentially different phenotype. Low- and middle-income countries have been subject to rapid obesogenic environmental change, whereas migrants from these settings to high-income countries often reside in more deprived locations and are of lower socioeconomic position, both contributing to unhealthy lifestyles. It is difficult to be certain of the exact proportionate contribution of intrinsic and extrinsic factors to cardiometabolic risk that must differ by location and population, but evidence suggests that incident disease risk is dominated by extrinsic factors. Similarly, disease progression can be influenced by phenotype; for example, different contributions of pancreatic beta-cell failure and peripheral insulin resistance will influence the incident type 2 diabetes mellitus (T2DM) phenotype and may determine differential drug response. Additionally, certain genes, differentially distributed by biological ancestry, can influence drug metabolism. However, the greater determinant of disease progression is access to health care, specifically timely initiation and modification of medication by the provider and long-term adherence to medication by the patient. Socioeconomic factors, including education and culture, influence individual healthcare seeking and adherence behaviors. These interact with the quality and knowledge of healthcare providers. Structural barriers, more frequent in poorer locations, such as availability and affordability of care, also contribute to disease progression.

populations [9]. Compromised insulin secretion assumes greater importance over insulin resistance in the development of T2DM in many populations, in contrast to Europeans. Body mass index (BMI) is generally lower in South Asians than in Europeans. But BMI does not reflect ectopic fat deposition, and South Asians preferentially deposit fat hepatically [10], itself strongly related to T2DM. Although stroke risks are elevated in South Asians compared with Europeans, blood pressure is not necessarily raised, and associations between blood pressure and stroke may differ [11]. People of African descent do not display the unfavorable atherogenic lipoprotein profile of insulin resistance, characterized by high triglyceride and low high-density lipoprotein (HDL) cholesterol, even in the presence of T2DM, potentially contributing to lower CHD risks [12].

Population differences in cardiometabolic disease: the role of time and place

Migration studies aid understanding of the role of time and place and thus socioenvironmental factors in determining disease incidence. An early example is of Japanese migrants to Hawaii who accrued risks of T2DM and CHD that were comparable with those of 'Caucasians' living in Hawaii and much higher than risks in individuals of Japanese ancestry living in Japan [13]. This rapid change in cardiometabolic risk was ascribed to adoption of American diets. Since then, many report rapid escalation of cardiometabolic risk in diverse populations migrating from low- or middle- to high-income countries [14] and on migration from rural to urban settings within countries [15,16], a consequence of adopting unhealthy lifestyles. Durability of migration effects depends on place; second-generation Japanese Americans have higher rates of obesity and diabetes than the first generation, likely due to whole-of-life rather than adulthood-only exposure to unhealthy lifestyles [17], whereas, by contrast, second-generation South Asians and African Caribbeans in the UK have lower risks than the first generation, correlated with improvement in neighborhood socioeconomic position [6]. Although these examples illustrate impacts and mutability of recent rapid environmental change, such change has occurred frequently throughout history. Investigation of skeletal remains spanning ~11 000 years indicate a marked height reduction in South Asia on adoption of agricultural living and suggest that the low lean mass for height, characteristic of these populations, is a durable effect of ecological pressures [18].

Determinants of population differences in cardiometabolic disease

The speed at which incident cardiometabolic disease is accelerated by within- and between-country migration strongly supports the role of environmental factors in driving population differences in disease. Box 1 introduces the term **embodiment** [19] to articulate the interplay between extrinsic environments and intrinsic biology and distinguishes between factors that determine incidence and those that drive progression. Incidence is determined by dose and combination of extrinsic exposures and their interplay with intrinsic susceptibility, specifically biological differences, in capacity to respond.

Population differences in biomarkers of cardiometabolic disease are evident in early life [20]. Developmentally disordered organ structure and function compromise capacity to respond. Examples include the kidney, resulting in poor sodium handling and increasing susceptibility to hypertension [21], and the pancreas, resulting in suboptimal insulin productive capacity, contributing to a younger age of T2DM incidence [22].

Timing of disease emergence is influenced by the interplay between exposures and susceptibility. For example, the contribution of maldeveloped kidneys to hypertension becomes evident only

Box 1. A framework to understand population differences in cardiometabolic disease

Cardiometabolic disease is a consequence of societally determined distribution of extrinsic environmental exposures impacting intrinsic biology, including gene expression. This concept, termed '**embodiment**' [19], highlights both the need to consider environments and genes in tandem and the role of societal structures in promoting health equity.

Building on work by colleagues on health inequalities [81], we distinguish between disease incidence and disease progression. For the former, we further differentiate between societally driven extrinsic exposures, including density of fast-food outlets, walkability of neighborhoods, and air pollution, which influence individual health behaviors, including smoking, dietary choices, and physical activity. These impact intrinsic factors, including susceptibility genes, developmentally determined target organ reserve, and psychological factors to determine risks of disease and between-ethnicity differences in disease.

Disease progression is also strongly influenced by extrinsic socioeconomic factors, including cost and availability of healthcare services, patient education status and trust in healthcare providers, and clinician factors including experience and discriminatory behaviors. Biological factors determining progression include preexisting comorbidity (itself a consequence of embodiment) and genetic factors determining drug response.

when exposure to salt intake is high, and the contribution of the pancreas to diabetes becomes evident only in the presence of obesogenic diets.

By contrast, disease progression and outcomes are more responsive to healthcare interventions, specifically in identifying risk and offering treatment. Inequitable or inappropriate healthcare interactions can drive disparities in outcomes.

Understanding the role of socioeconomic factors in determining ethnic differences in cardiometabolic disease

Adverse social and environmental conditions, driven by societal structures, impact both cardiovascular [23] and metabolic [24] health. In high-income countries, communities arising from relatively recent migration tend to cluster in socially deprived neighborhoods, with attendant greater exposure to adverse environments [25] (Box 1). The extent to which socioeconomic disadvantage accounts for differences in cardiometabolic disease is unclear, unsurprisingly, given the difficulty of capturing lifetime socioeconomic and biological factors. Additionally, particularly in migrant populations, the contributions of individual and structural discrimination are overlooked.

Racial discrimination, structural racism, and cardiometabolic health

Most of the work on the association between racism and cardiometabolic health has been conducted in the USA. A systematic review observed an adverse association between racial discrimination and cardiovascular health in 86% of 84 studies based in the USA [26]. Mechanisms are unclear, and while stress response pathways are invoked, supportive evidence is scant. However, racial discrimination, potentially via psychological distress, may increase adoption of adverse health behaviors such as smoking initiation [27] and heaviness [28], offering a more obvious mechanism by which discrimination increases susceptibility to cardiometabolic disease (Box 1).

Alongside personal experiences, we should consider unequal societal structuring. Structural racism is defined as the totality of ways in which society discriminates against racially minoritized groups [29] and drives inequitable distribution of health care, education, fresh food, employment opportunities, and toxic exposures such as pollution [30]. This recontextualizes highly correlated factors such as occupation, education, and healthy lifestyles from individually determined choices to societally influenced factors. Structural racism is related to cardiometabolic health. The US Federal Housing Association policy in the 1930s of denying mortgages to people living in predominantly Black or Hispanic neighborhoods adversely impacted both neighborhood investment and individual wealth and had detrimental effects on cardiovascular health [31]. Few reports are available from other migration destinations, but their results tend to concur with this [32].

Known ancestry-associated cardiometabolic genetic variants

While emphasizing the major role of environmental factors, we cannot discount the effect of genetic variations. The relatedness implicit in the definition of ancestry, its correlation with ethnicity, and the observation of long-standing differences in the cardiometabolic phenotype invite speculation regarding the role of genetic variants in determining population differences.

Strength of association of genetic factors with a phenotype can appear to be different across populations for two main reasons. First, the genetic factor has different allele frequencies corresponding to differential exposure. Second, the genetic factor interacts with an environmental or genetic background whose distribution differs across populations. This second mechanism corresponds to the idea of there being a differential susceptibility between populations.

Variants associated with familial hypercholesterolemia strongly predict premature cardiovascular disease (CVD), but they occur infrequently, and neither their effects nor their distributions appear to differ by ancestry [33]. But cardiometabolic traits are both common and complex, influenced by large numbers of genetic factors. Just 15% of the variance in CAD risk in Europeans is explained by 5 000–10 000 common variants across the genome [34]. Some common variants for lipids are being identified that exhibit differential effects across samples clustered by ancestry, although the vast majority of lipid-associated variants have shared effects [35]. A polygenic approach to T2DM subphenotypes may be more fruitful, accounting for an important proportion of the differential risk between East Asians and Europeans, although notably not for other population groups [36]. Although the influence of the complex polygenic component of cardiometabolic disease could be augmented in some populations through ethnic customs of consanguinity, this effect is modest and does not apply to all vulnerable populations [37]. In sum, genetic variation makes a limited contribution to cross-population differences in cardiometabolic disease.

Mechanisms that may drive spurious differences across ancestries

Generalizing genetic associations with disease from samples of European ancestry to other ancestral groups is not straightforward. Associations discovered in a particular population will be ascertained for being in regions of high **linkage disequilibrium (LD)**. Hence, the genetic effect estimate of a tagging variant in the discovery ancestral group will be systematically larger than in the comparison ancestry group unless fine mapping is used [38]. Additionally, associations in well-powered discovery samples will have high **minor allele frequency** (close to 0.5). Because allele frequencies can differ markedly across ancestral groups, when retesting those same variants in other populations, they will generally have lower minor allele frequencies and therefore lower statistical power, even if effect sizes are consistent. Sample sizes in studies with available genetic data are typically markedly smaller in non-European ancestral groups than European samples [39]. Hence, testing for replication across ancestral groups should focus on comparing the observed replication rate against the expected replication rate to account for power differences [40].

Testing for effect heterogeneity across ancestries is important (e.g., using Cochran's Q) but is sensitive to scale differences. For example, if the relative reduction of low-density lipoprotein (LDL) cholesterol on statins is 40%, the absolute reduction will be greater in populations with overall higher than in populations with overall lower LDL cholesterol levels [41].

The US census category of Asian American, often used in health research, combines people of Far Eastern, Southeast Asian, and South Asian ancestry [42]. But these groups have different cardiometabolic profiles, and combining these risks misses population differences in genetic associations.

Risk prediction by race or ethnicity

Algorithms that include a race or ethnicity term to assess organ function or to predict disease are being challenged [2]. Estimated glomerular filtration rate (eGFR), a measure of kidney function, added a multiplier of ~1.2 for people of Black African heritage [43], justified by higher serum creatinine for a given level of kidney function, supposedly due to greater muscle mass. Referral to specialist services for renal support could occur at much poorer levels of 'true' renal function. Worse still, risks of kidney failure and of total mortality for a given race-adjusted eGFR are higher in people of African descent than in other populations [44] , a difference not observed when the race-unadjusted eGFR is used. The eGFR algorithm is now usually used without its 'race' adjustment [45]. Similarly, the American Heart Association's 'Get with the Guidelines – Heart Failure risk

Clinician's corner

The value of racial and ethnic categorizations in clinical practice should be carefully considered. These are typically based on physical characteristics such as skin color, which are influenced by genetic factors; thus, racial categorizations are often assumed to proxy other biological differences between individuals. But racial and ethnic categorizations are poorly related to genome-wide genetic variation, and genes for skin color do not correspond to those for cardiometabolic disease. Both race and ethnicity are often more an indicator of the different social and economic environments to which an individual has been subjected than a proxy for genetic disease susceptibility.

Correspondingly, the use of ethnicity or race to guide precision medicine initiatives is often inappropriate, and we would advise caution with prediction equations.

Prediction equations to identify high-risk individuals or to assess organ function must be based on robust evidence of equity.

Genetic or subphenotypic measurements to guide treatment, where proved to be of use, should be preferred over using ethnicity or race as a poor proxy for these factors.

Differential quality of care is a key factor impacting population differences in cardiometabolic disease progression. Inequalities in timely initiation of preventative treatment such as statins, as well as lack of appropriate uptitration of treatment in response to suboptimal risk factor control, results in poorly controlled blood pressure, lipids, and glycemia. This in turn partly explains apparent population differences in disease progression and outcomes.

Nonadherence to preventative therapy also varies markedly by population group in the USA and the UK, often being lower in all groups when compared with people of European ancestry. Yet, adherence can markedly improve patient outcomes and reduce public health and economic burdens of cardiometabolic disease. Lack of trust of the medical establishment and poor clinician–patient communication

score' to determine treatment thresholds for patients admitted with acute heart failure disfavors people of African descent. Supporting data suggest that in-hospital mortality is lower in African Americans [46]; yet, risks of heart failure and of all-cause mortality are higher [46]. This paradox is likely due to race-related biases in being admitted to a hospital [47]. The risk calculator is still used but now makes input of 'race' optional (https://www.mdcalc.com/calc/3829/gwtg-heart-failure-risk-score).

Is it always wrong to have population descriptors factored into disease prediction?

T2DM diagnostic levels of glycated hemoglobin occur at a lower BMI in people of South Asian and African/African Caribbean than in those of European ancestries [48], informing lower BMI cut points in T2DM screening guidelines [49]. Here, population grouping is substituted for propensity to diabetogenic fat deposition [48] and potentially other, yet unknown, correlated diabetogenic features. A diagnosis of T2DM confers similar absolute risks of any related endpoint by ethnicity [50], indicating that treating an identical glycated hemoglobin diagnostic threshold is equitable. In the absence of low-cost tests for diabetogenic features, using lower BMI cut points to predict an identical hemoglobin A1c (HbA1c) in certain population groups appears to be justified. Risk prediction for CVD includes an ethnicity correction factor, recognizing differential absolute CVD risks [51,52], although performance remains suboptimal [53]. Polygenic risk scores to improve risk prediction have so far not delivered and may never do so [54], even setting aside the challenges of transporting genetic predictors between population groups [55].

Medication by ethnicity – delivering the promise of personalized medicine?

Tailoring medicine to patient characteristics promises optimization of outcomes and reductions in treatment costs [56]. Ethnicity as a stratifier is already employed in antihypertensive [57–59], statin [60], and anticoagulant [61] prescribing guidelines.

Treatment by ethnicity assumes that ethnicity is a valid proxy for biology, be it genetic variants that govern drug response or disease phenotype. Is this true? A prespecified analysis in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [62] informed guidelines recommending first-line antihypertensive treatment with calcium-channel blockers [rather than angiotensin-converting enzyme (ACE) inhibitors] in people of African heritage [57–59], with the low renin phenotype of hypertension in people of Black African descent proffered as the biological rationale. But recent trials contradict ALLHAT [63,64]. More generally, mean responses mask considerable heterogeneity within all population groups [65]. Although randomized trials provide the highest-quality evidence to support clinical decision-making and trial meta-analyses inform on otherwise under-represented populations, these can either be misused, as in the licensing and promotion of BiDil for heart failure in African Americans [66], or remain inconclusive, as in the sometimes contradictory findings of population differences in cardiovascular and renal outcomes in response to the glucagon-like peptide-1 receptor agonists (GLP1Ras) and sodium glucose cotransporter-2 inhibitor (SGLT2i) diabetes medications [67]. Ethnic differences in the T2DM phenotype have been proposed for differences in drug response, although whether different phenotypes respond markedly differently to glucose-lowering agents and whether ethnicity is a valid proxy for phenotype are uncertain [68].

There are pharmacokinetic polymorphisms that do have different frequencies by ancestral group, such as cytochrome p450 family 2 subfamily C member 9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1), key genes relating to warfarin response [69]. These variants correlate well with required warfarin doses, and their effects appear constant between European and African Americans [70]. Similarly, the CYP2C19 gene, relating to clopidogrel

appear to contribute. Initiatives to improve adherence have shown promising results, and sustainable, scalable intervention design and codevelopment with the relevant populations represent a tractable solution.

Collection of data on ethnicity is vital to identification of disadvantage and variations in disease phenotype and to highlight opportunities for intervention.

efficacy, has a higher incidence of loss-of-function alleles in UK Pakistani and Bangladeshi ethnic groups than in Europeans and correlates with higher risk of subsequent myocardial infarction [71]. For variants that influence drug metabolism, it is surely preferable to test for these rather than use ethnicity as a poor proxy. A recent genetically guided study of bucindolol versus metoprolol for heart failure is an example of this approach [72]. Even then, other factors, such as BMI, age, and maybe diet (all of which may differ by ethnicity), are strong determinants of drug response and are often not considered in medication decision-making [73].

The focus on personalized medicine ignores important non-biological factors that threaten optimal response to drugs, specifically timely initiation, dose modification, and adherence [74]. These are often more powerful determinants of outcomes than agent class. While the relative risk of CVD is 1.13 on lisinopril versus amlodipine in African Americans [75], this risk difference is dwarfed by the CVD risk reduction of 0.66 in the most versus least adherent individuals [76]. African Americans are 15%–35% less likely to receive statins for primary prevention than White Americans [77], an inequity apparent even in the UK, where healthcare is nominally free [78]. In sum, healthcare inequalities, rather than population biology, have the more powerful impact on cardiometabolic outcomes.

Concluding remarks

Population group differences in risks and phenotype of cardiometabolic disease are widely acknowledged but poorly understood. A genetic explanation for these differences is often assumed, but, putting it crudely, associating population variance in physical appearance to genetic determinants of cardiometabolic disease has no scientific basis (see Clinician's corner). Clarity in the use and interpretation of terms used to group populations is crucial to elucidating the true contribution of genetic factors to differences in cardiometabolic disease. Both the societally imposed concept of race and the self-determined categorization of ethnicity intersect with genealogical ancestry. Ancestral clustering of variants can contribute to cardiometabolic risk factors and to differences in drug response. However, single variants profoundly impacting cardiometabolic risk are rare and, even in combination with differential distribution or effects of multiple common variants, can only account for a fraction of disease risk. Similarly, only a limited number of variants that determine drug metabolism are genealogically clustered, and there is scant evidence that genes aligned with population grouping alter response to many of the cardiometabolic medications in common use.

But race, ethnicity, and ancestry strongly relate to shared common environments at the national, neighborhood, family, and individual levels and to customs and cultures that profoundly shape cardiometabolic risk, phenotype, and healthcare interactions. Societally determined adverse environments foster stark inequalities between and within countries. We contend that comprehending population differences in cardiometabolic disease hinges on these multifaceted, societally determined adversities and advantages acting throughout life. Yet, definitive proof of this assertion is lacking due to a combination of data insufficiency and a lack of prioritization for analysis in the face of more seductive genetic research.

Eurocentric research on genetic determinants of disease is now being addressed. We make a similar plea for the study of environmental determinants of disease and resulting effects on phenotype, including whether genetic factors interact with environmental exposures. We cannot assume exposures, their associations with each other, and impact on disease will be generalizable across populations.

Recommended actions include adopting the National Academy of Sciences guidelines on population descriptors for scientific research [79]. We resist calls to abandon capture of ethnicity in

Outstanding questions

How do environmental exposures, such as measures of socioeconomic position (education, occupation, wealth), neighborhood environment (housing density and quality, fast versus healthy food outlets, green spaces, transport quality, safety, and walkability), and social factors (familial structures, experiences of discrimination), relate to each other, to health behaviors, and to cardiometabolic traits by population group throughout life?

How do these relationships change in successive generations of migrant populations and in people of mixed ancestry?

Can social policy interventions reduce population adversity in cardiometabolic risk?

Can these different relationships of environmental exposures, either alone or in combination with their effects on genetic variants, explain ethnic differences in cardiometabolic risk and phenotype?

Can we identify rare, highly predictive, population group–specific genetic variants that determine infrequent but nevertheless important subgroups of premature cardiometabolic disease events?

Can we generate more precise disease phenotypes, such as by distinguishing predominance of beta cell failure versus insulin resistance for incident T2DM, which in turn relate to polygenic variants and may contribute to population differences in cardiometabolic disease risk?

How do population group differences in phenotype relate to differences in outcomes?

Which factors, and with what weighting, should we include to ensure equitable and simple risk prediction tools for screening and treatment of cardiometabolic disease?

What explains population inequalities in receipt of and adherence to cardiometabolic medications? What interventions can best improve these?

health records. Although ethnicity-stratified analysis has led to discriminatory distribution of health care, without this, we would be unable to identify inequalities, which are a spur to action. At a time when large and ethnically diverse population biobanks are increasingly available for health-related research, clarity on definitions to categorize populations, their meaning, and analytical approaches requires significant consideration. Ill-judged approaches constrain progress and rightly attract significant criticism [42,80].

To understand differences in disease incidence, an immediate solution lies in the unprecedented availability of dense, detailed, geocoded environmental data, coupled with innovative analytical approaches, although this should not supplant the need for greater investment in data collection throughout life (see Outstanding questions). Equitable interventions should be ensured through risk prediction, potentially involving unequal screening, investigation, and treatment thresholds. The ambition of personalized medicine is a chimera. By contrast, addressing inadequacies in treatment access and medication adherence, which affect all population groups, has the potential to make a significant impact in reducing inequalities in cardiometabolic disease.

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