Why are there ethnic differences in cardio-metabolic risk factors and cardiovascular diseases?

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Abstract
Europe’s population is becoming increasingly ethnically diverse, and epidemiological studies indicate that there are remarkable differences in cardio-metabolic risk factors between ethnic groups living in the same area. Variations observed in the distribution of cardiovascular risk factors in these communities may therefore help explain—at least in part—the different burdens on cardiovascular diseases. So far, the underlying pathophysiology leading to ethnic variations in the prevalence of cardio-metabolic risk factors is still poorly understood but it is likely to represent the complex interactions from several innate and environmental factors. Tailored prevention and treatment strategies should therefore be implemented in those “high-risk populations,” but data derived from randomized clinical trials are still limited. This article will provide an overview on the role of ethnicity on cardio-metabolic risk factors and cardiovascular diseases, focusing on type 2 diabetes and dyslipidemia based mainly on Dutch and British data.

Keywords
Ethnicity, type 2 diabetes, dyslipidemia, epidemiology

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Introduction
Europe’s population is becoming increasingly ethnically diverse. In the Netherlands, an estimated 11.1% of the total inhabitants are categorized as foreign-born, with 8.5% of them born outside of the European Union. This percentage is considerably higher in metropolitan areas like Amsterdam and it is further projected to rise to 20% by the year 2060.¹ Similar findings are reported across other European countries, including the United Kingdom where non-White-British residents account for 55% of London’s urban population.² Such rising epidemiological figures will inevitably have an impact on the national health systems, as the disease risk profiles of ethnic minorities differ to that of the host population.³

In general terms, ethnic minorities reflect health characteristics that are a composite of their native countries; exposure to specific influences occurred during the migration process and environmental factors of the host countries. Variations observed in the distribution of cardiovascular (CV) and cardio-metabolic risk factors in these communities may therefore help to explain a different burden on CV diseases (CVD).³ At the same time, increasing amounts of evidence have highlighted that traditional CV and metabolic risk factors (such as dyslipidemia, central adiposity, or insulin resistance) measured in midlife do not fully explain the observed variability in CVD.⁴ In order to address this issue, additional elements have been advocated including early life exposures to risk factors (e.g. low birth weight) as well as socioeconomic circumstances—an umbrella term that includes dietary habits, psychosocial factors, marginalization, and access to care.⁵

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Given the close association between risk factors and CVD, it is of crucial importance to identify and address the role of ethnicity in the pathophysiology of these elements, thereby developing tailored strategies targeting specific ethnic groups. However, despite an unquestionable impact of ethnicity on CV health, ethnic minorities are often still underrepresented in clinical and health research, and as a consequence, recommendations on primary and secondary prevention are still extremely limited.6

Cardiovascular risk factors in ethnic minorities: Genes or lifestyle?

Compared to resident populations, ethnic minorities in Europe appear to be disproportionately affected by CV risk factors including hypertension, type 2 diabetes (T2DM), and dyslipidemia.3 This higher incidence seems to be the result of complex interactions between genetic and environmental elements that influences the pathophysiology of CVD.3

Using obesity as paradigm, it is well recognized that lifestyle factors including diet and socioeconomic status make a relatively large contribution to higher prevalence of obesity in some ethnic groups in comparison to resident populations.7 At the same time, ADMIRE (Analysis of DNA Methylation In genomic Regions) studies in the USA have also observed an inverse relationship between body mass index (BMI) and percentage of European ancestry genes present in individuals, thereby highlighting the impact of genetic variations in acquiring the condition.8 Similarly T2DM, which will be described in detail in the following section, is thought to develop from an interplay between genetic and lifestyle elements, and the extensive between-individual variability in susceptibility to lifestyle risk factors has often been explained by the single genomic characteristics. However, the interaction between common genetic variants and environmental factors is still incompletely understood. As an example, the results of the EPIC InterAct study9 on a cohort of 340,234 European participants showed that the association with T2DM of a genetic risk score comprised of 49 loci was greatest in the younger and leaner subjects; however, the study also demonstrated that the absolute risk of T2DM was dominated by modifiable factors, particularly obesity. This “genetic approach” may also help to understand why traditional risk factors measured in midlife do not always fully characterize the risk profile of some populations; however, in those individuals, early signs of “organ damage” can be potentially identifiable at very early stages of life.10

To add more complexity to the issue, it should also be considered that the interpretation of epidemiological figures is susceptible to several pitfalls. Data relating to ethnicity are affected by a plethora of methods used to define the term and information collected in one country may not be readily applicable to similar ethnic groups in other geographical locations. In other words, the concept of ethnicity itself is difficult to define, as the majority of studies are based on self-reported ethnicity which is not sufficient to protect against population stratification. For the purpose of this review, our data will focus on T2DM and dyslipidemia and will be mainly restricted to Dutch and British data.

Role of ethnicity in T2DM

The prevalence of T2DM continues to increase, and some ethnic minority groups have been disproportionately affected by T2DM compared to the resident populations.5

Measures of body composition (i.e. BMI, body fat percentage, waist-to-hip ratio) can only partially explain that difference, whereas the “residual risk” is still not well characterized.11 Studies analyzing genetic background relative to T2DM have established that migrant populations do not reflect the same pattern of T2DM incidence as those residing in their country of origin.11 This suggests that other mechanisms—like different migration history and/or effects of environmental and lifestyle factors in the host country—may be involved. For example, in Netherlands, the higher prevalence of T2DM in specific ethnic minority groups can be ascribed to their socioeconomic circumstances although the latter does not seem to play a role in other minority communities.12

A recent meta-analysis conducted in Europe5 also showed that the risk of developing T2DM is non-homogenous between various ethnic groups. Individuals of South East Asian (SA) origin were approximately three to five times more likely to develop T2DM compared to Europeans; a greater risk ratio compared to Black African (BA) populations who showed a two to three greater risk of diabetes compared to European peers.

Focusing on the BA group, the precise reasons for the “excess” of T2DM incidence and prevalence are still unknown, but it is likely that environmental factors can at least partially explain this variation. A multicenter cross-sectional study conducted in more than 5000 BA subjects found obesity and T2DM to be more common in individuals living in Europe compared to those residing in Africa.13 Their higher prevalence of diabetes can be partially attributed to the significant level of obesity observed in Europe, given the well-established relationship between body weight and glucose intolerance. However, even after adjustment for “body fat,” the prevalence of T2DM in BA subjects...
living in Europe was still significantly higher for a given level of BMI and waist circumference. Of note, in the same population, there was an inverse relationship found between T2DM and educational level of subjects suggesting that socioeconomic factors play an important part in disease incidence.\textsuperscript{14} Similarly, SA populations show an equal, if not comparatively higher, prevalence of T2DM in comparison to BA individuals as confirmed in both UK- and Dutch-based cohorts.\textsuperscript{15} Of note, increased risk of diabetes in SA populations is recorded at much lower levels of BMI and at a significantly younger age compared to their European peers.\textsuperscript{16} Early manifestation of risk factors (e.g., higher body fat percentage and visceral fat deposition or insulin-resistant phenotype) is also consistent with the epidemiological figures reflecting the higher prevalence of T2DM in this community\textsuperscript{17,18} and might be at least partially explained by the “thrifty genotype” hypothesis.\textsuperscript{16} According to this hypothesis, undernutrition in fetal and infant life favors visceral storage of fat later on in life particularly in the presence of abundant food and calorie availability.\textsuperscript{16} Longitudinal data have also consistently reported a rapid yearly deterioration of HbA1c in SA individuals, despite greater prescription of oral glycemic drugs\textsuperscript{19} when compared to other ethnic groups or the resident population. As a result, SA with early-onset T2DM have significantly more risk of complications at diagnosis compared to Europeans, including established macrovascular disease, retinopathy, and nephropathy.\textsuperscript{20}

Focusing on prevention and treatment, trials have shown a significant reduction in T2DM disease progression in high-risk groups irrespective of their ethnic background.\textsuperscript{21} Screening for T2DM at a younger age, in individuals with a low BMI, and screening for complications (such as microalbuminuria in SA population\textsuperscript{22}) may represent useful interventions. In fact, the American Diabetes Association (ADA) and the UK National Institute for Health and Care Excellence (NICE) recommend lowering the BMI threshold for diabetes screening in SA individuals. Strategies to improve metabolic control should also come alongside hypertension management (possibly with a lower threshold for blood pressure values compared to the general population) with an early adoption of Angiotensin converting enzyme inhibitors (ACE-I) and Angiotensin-receptor blockers (ARB) to attenuate excess microvascular risks as well as tailored dyslipidemia management.\textsuperscript{23} However, the efficacy of those interventions still needs to be confirmed in randomized clinical trials (RCTs).

**Role of ethnicity in dyslipidemia**

Dyslipidemia, including high levels of LDL-C ($\geq 130$ mg/dL), total cholesterol ($\geq 200$ mg/dL), and triglycerides (TG; $\geq 150$ mg/dL) along with low levels of high-density lipoprotein cholesterol (HDL-C; $<40$ (men) and $<50$ (women) mg/dL) are all well-established risk factors of CVD including stroke.\textsuperscript{24} Several modifiable risk factors are associated with an increased risk of dyslipidemia—such as high fat diet, physical inactivity, smoking, and obesity and genetic studies suggest an essential role of genetic ancestry in development of specific familial disorders. Despite known heterogeneity in CV risk among various ethnic groups, only a relatively small number of studies have investigated the prevalence of dyslipidemia and treatment effects across different ethnic minorities.

Similar to T2DM, dyslipidemia occurs at lower levels of BMI and body fat in SA individuals than in White peers.\textsuperscript{25} HDL levels are noted to be lower in SA than in Caucasians, especially in women, as confirmed by comparative studies.\textsuperscript{25} Interestingly, SA, and in particular those with high HDL levels ($>40$ mg/dL), exhibit substantial proportions of dysfunctional HDL that has less protective capacities, but rather proinflammatory effects which in turn are linked with the progression of atherosclerosis.\textsuperscript{26} Additionally, SA individuals have a higher prevalence of small, dense LDL-C lipoproteins (a) when compared with White peers.\textsuperscript{25} The high prevalence of increased triglyceride and decreased HDL-C levels together with increased LDL-C form the “atherogenic dyslipidemia phenotype,” which is a major risk factor for CVD.

On the contrary, BA populations that have a higher risk of developing hypertension and T2DM seem to have a more favorable lipid profile. In fact, people of African ancestry often depict high levels of HDL-C and lower levels of serum triglycerides compared to Whites even in the presence of obesity and insulin resistance.\textsuperscript{27} The reasons for this favorable lipid profile among BA are not clear, although genetic variations in hepatic lipase have been advocated to explain this variability.\textsuperscript{27} The data seem to indicate that African individuals have a favorable anti-atherogenic lipid and lipoprotein profile; however, their incidence of CVD, particularly stroke, is disproportionately higher than their White counterparts. This phenomenon is well characterized and is defined as the Insulin Resistance-Lipid Paradox in People of African Ancestry.\textsuperscript{28} There is paucity of data regarding dyslipidemia management in ethnic minorities across Europe. Most of the data come from the US, where African Americans seem less likely than Whites to receive lipid-reduction treatments and are less controlled compared to their White counterparts, although these ethnic inequalities were abolished after differences in healthcare access were taken into account.\textsuperscript{29} This seems to be in line with the results of the ALLHAT
study where pravastatin significantly reduced CV events in BA individuals.  

To summarize, cardio-metabolic risk factors present ethnic variations which contribute—at least in part—to the excess CVD in ethnic minorities. However, the pathophysiological mechanisms for those variations are still partially unexplained and are likely to represent the complex interactions from several innate and environmental factors that are still the subject of ongoing investigations. As a consequence, tailored prevention and treatment strategies should be implemented in those “high-risk populations,” but the efficacy of the interventions would need to be tested in RCTs.

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