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STATE-OF-THE-ART REVIEW

Polygenic Risk Scores for Atherosclerotic Cardiovascular Disease in the Asia-Pacific Region

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ABSTRACT

Approximately one-half of the phenotypic susceptibility to atherosclerotic cardiovascular disease (ASCVD) has a genetic basis. Although individual allelic variants generally impart a small effect on risk for ASCVD, an emerging body of data has shown that the aggregation and weighting of many of these genetic variations into "scores" can further discriminate an individual's risk beyond traditional risk factors alone. Consistent with the theory of population genetics, such polygenic risk scores (PRS) appear to be ethnicity specific because their elements comprise single-nucleotide variants that are always ethnicity specific. The currently available PRS are derived predominantly from European ancestry and thus predictably perform less well among non-European participants, a fact that has implications for their use in the Asia-Pacific region. This paper describes the current state of knowledge of PRS, the available data that support their use in this region, and highlights the needs moving forward to safely and effectively implement them in clinical care in the Asia-Pacific region. (JACC: Asia 2021;1:294–302) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide. Dyslipidemia, diabetes, and hypertension are well-known cardiometabolic risk factors contributing to the development of ASCVD. ASCVD and these cardiometabolic risk factors are also heritable traits (1). Accordingly, researchers have long been working to determine the heritable elements underscoring cardiometabolic disease.

Early studies identified familial hypercholesterolemia (FH) as a monogenic disorder, mainly caused by mutations of genes regulating expression of the low-density lipoprotein (LDL) receptor and accounting for ~7% of premature ischemic heart disease (2).

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In addition to monogenic disorders affecting LDL receptor expression, other examples exist, including adenosine triphosphate-binding cassette sub-family G member 5 (*ABCG5*), adenosine triphosphate-binding cassette sub-family G member 8 (*ABCG8*), lipoprotein lipase (*LPL*), and lipoprotein A (*LPA*), in which rare mutations elevate serum lipid levels, thereby leading to the development of ASCVD (3-6).

In parallel, increasing evidence suggests that ASCVD events can be predicted by using polygenic risk scores (PRS), comprising common single-nucleotide variants (SNVs) associated with ASCVD risk (7). Although part of such genetic variations comprises those associated with hyperlipidemia, hypertension, diabetes, and inflammation, the specific role played by the majority of components of PRS in the pathogenesis of ASCVD remains uncertain (8). Importantly, ASCVD PRS associate with clinical events, independently of cardiometabolic risk factors (9). This has the potential to not only identify individuals at a higher ASCVD risk, even in the absence of established risk factors, but also to identify new avenues for research to develop new therapeutic targets. However, established scores are typically ethnicity specific (10,11), in distinction to other classical cardiometabolic risk factors. In this sense, most data have thus far been derived from European ancestries; therefore, accumulation of such data in the Asia-Pacific region is required to establish a PRS for ASCVD in this region.

The present review summarizes the current status and future perspective of personalized medicine, especially PRS, in predicting ASCVD in the Asia-Pacific region.

IMPORTANCE OF UNDERSTANDING THE RISK AMONG INDIVIDUALS IN THE ASIA-PACIFIC REGION

Given that the Asia-Pacific region has the world's largest population, it is important to understand the risk for ASCVD among its citizens. We know that risk estimation equations for particular populations can underperform in different populations (12,13). Although some of these differences may be attributed to variable lifestyles, genetic factors may also play an important role. To date, genome-wide association studies (GWAS) conducted on different ethnicities have identified unique loci associated with ASCVD and its related risk factors (14-16), suggesting that genetic risk underscoring ASCVD development may vary in different populations. The degree of contributions by those genetic factors may also differ according to ethnicities. There are also a number of indigenous groups living in these regions in which unique genetic variations associated with ASCVD may exist. In fact, South Asian subjects are known to have a higher risk for ASCVD, possibly in part due to their genetic backgrounds, compared with other populations, including East Asian subjects (17,18).

PERSONALIZED MEDICINE BASED ON HUMAN GENOME INFORMATION

The use of human genetic information to personalize the care of individuals at risk for ASCVD is attractive for a number of reasons. First, ASCVD is a highly heritable trait, and thus genetic information ought to provide useful insight, particularly because up to one-quarter of patients may present with ASCVD in the absence of traditional risk factors. Second, human genome information need only be assessed once, and it can be performed early in life, allowing preventive intervention to be adopted. Third, understanding the contributions from, and interaction between, heritable and nonheritable ASCVD risk may inform the basis of observed "residual risk," permitting us to refine predictive algorithms and develop individual treatment approaches.

WHAT IS A PRS?

Approximately one-half of the phenotypic heterogeneity observed in ASCVD susceptibility may be explained by genetics (19). Although some monogenic abnormalities such as those observed in FH clearly link diagnosis with prognosis (20), the individual contribution from most genetic variants, including the 9p21 locus, is generally small (21-23). Thus, although searching for monogenic abnormalities has an established clinical role in the screening and diagnosis of conditions such as FH, there has been considerable interest in aggregating these large numbers of smaller effect-size genetic variants into PRS as a way of determining an overall "barometer" of genetically determined ASCVD risk. Currently, there are several risk scores in the field of cardiology that have undergone varying degrees of performance assessment and external validation. Although seminal work using PRS with as few as 13 common genetic variants was unable to significantly influence risk discrimination or net reclassification of ASCVD (24), subsequent scores using variants of higher orders of magnitude have been shown to complement traditional risk factors and offer incremental risk prediction (25). Obtaining the necessary genetic information with a genotyping array is relatively inexpensive and

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

FH = familial hypercholesterolemia

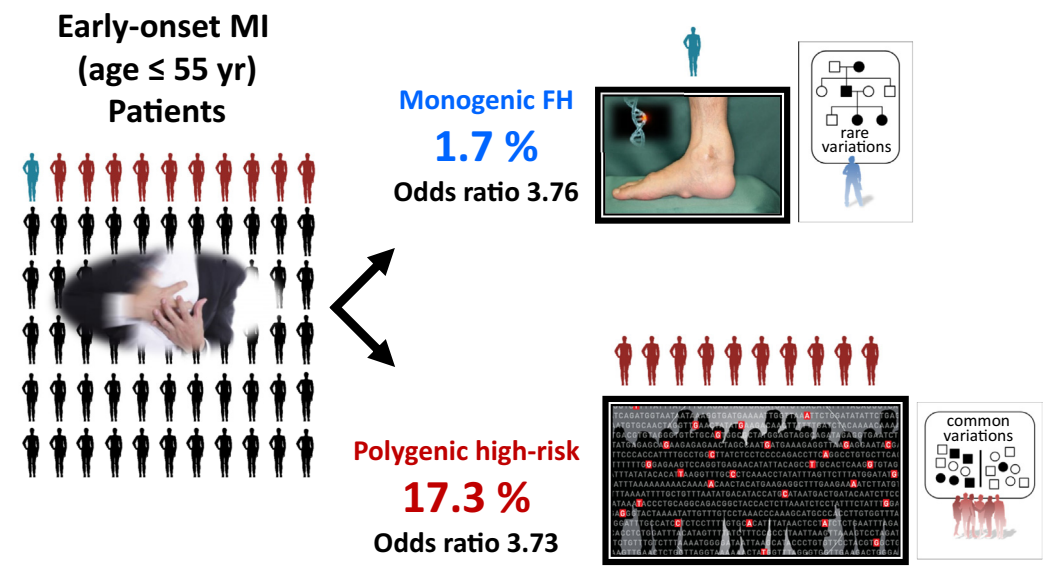
GWAS = genome-wide association studies

LDL = low-density lipoprotein

PRS = polygenic risk score(s)

SNV = single-nucleotide variant

FIGURE 1 Monogenic Versus Polygenic Contribution to Early-Onset MI



Among patients with early onset of myocardial infarction (MI), ~1.7% were monogenic familial hypercholesterolemia (FH), whereas 17.3% were considered as polygenic high risk.

has become less costly than many routine clinical laboratory tests. This reflects a major change as the technology has advanced. Moreover, the procedure of calculating a PRS is straightforward and is less demanding than handling clinical whole-genome sequencing data. Indeed, one of the attractive features of a PRS is that it may be feasible to deploy it across the entire population, perhaps at the time of birth.

However, significant barriers have limited translation of PRS to the clinic. First, multiple PRS exist that have been derived and validated in specific cohorts, and thus their generalizability to populations with varying ethnicities is unknown. Second, although a number of loci can be mapped to biologically plausible disease processes associated with ASCVD, a number cannot, and while this represents opportunity for discovery, it currently limits our linkage to mechanism, specifically whether there are certain components that are driving polygenic risk (eg, inflammation) that may respond to specific therapies (eg, anti-inflammatories). Third, no prospective study has been performed to show that treatment based on a PRS-based approach improves outcomes. Although iterative technological advances will reduce the cost of performing genotype arrays, a compelling need exists to understand the comparative performance of PRS in varying ethnicities and across regions, in particular the Asia Pacific, which has generally been underrepresented in both derivation and validation cohorts (26).

MONOGENIC AND POLYGENIC RISKS OF ASCVD

When we think about monogenic and polygenic risks of ASCVD, the polygenic risk framework is a "continuous trait" normally distributed, whereas monogenic risk is usually a "dichotomous trait," which has a certain threshold. According to this difference, comparing these risks has been difficult. However, these risk factors are not always mutually exclusive but, rather, it appears that both are important elements for preventive cardiology. We know that a single pathogenic variant of FH confers 3- to 4-fold odds of developing ASCVD (20). Alternatively, Thériault et al (27) have suggested that polygenic states may make a more substantial contribution to early onset of coronary artery disease than FH to ASCVD risk. Subsequently, using a PRS comprising 6.6 million genetic variants, Khera et al (28) found that there are as many as 8% of individuals who have an extreme polygenic risk of ASCVD that approximates the risk conferred by a pathogenic FH mutation. Furthermore, they found that even among patients with FH whose ASCVD risk is elevated substantially by a rare genetic variation,

TABLE 1 Studies of PRS for the Prediction of ASCVD

First Author (Ref. #)	Year of Publication	PRS	Population	Outcomes	Main Results
Talmud et al (21)	2008	9p21 locus only	UK cohort (Caucasian)	Coronary heart disease	HR: 1.60; 95% CI: 1.12-2.28
Horne et al (22)	2008	9p21 locus only	U.S. cohort (most Caucasian)	Coronary heart disease	OR: 0.95; 95% CI: 0.83-1.09
Kathiresan et al (34)	2008	9 SNV (associated with lipids)	Swedish cohort (Caucasian)	Coronary heart disease	HR: 1.63; 95% CI: 1.21-2.19 Genotype score: ≥11 vs ≤9
Paynter et al (23)	2009	9p21 locus only	U.S. cohort (Caucasian)	Coronary heart disease	HR: 1.25; 95% CI: 1.04-1.51
Ripatti et al (24)	2010	13 SNVs	Finnish and Swedish cohorts (Caucasian)	Coronary heart disease	HR: 1.66; 95% CI: 1.35-2.04 Top vs bottom quintile (PRS)
Ganna et al (25)	2013	395 SNVs	Swedish cohorts (Caucasian)	Coronary heart disease	HR: 1.54; 95% CI: 1.25-1.92 Top vs bottom quartile (PRS)
Tada et al (37)	2014	12 SNVs	Swedish cohort (Caucasian)	Ischemic stroke	HR: 1.23; 95% CI: 1.04-1.46 Top vs bottom quintile (PRS)
Mega et al (35)	2015	27 SNVs	Swedish cohort (Caucasian) Primary/secondary prevention groups in the United States (most Caucasian)	Coronary heart disease	HR: 1.81; 95% CI: 1.22-1.47 Top vs bottom quintile (PRS)
Tada et al (36)	2016	27 and 50 SNVs	Swedish cohort (Caucasian)	Coronary heart disease	HR: 1.70 (95% CI: 1.48-1.94) for: 27-SNV-PRS HR: 1.92 (95% CI: 1.67-2.20) for: 50-SNV-PRS Top vs bottom quintile (PRS)
Thériault et al (27)	2018	182 SNVs	UK Biobank (Caucasian)	Coronary heart disease (early onset)	OR: 1.84; 95% CI: 1.52-2.24 1 SD increase of PRS
Khera et al (28)	2018	6.6 million SNVs	UK Biobank (Caucasian)	Coronary heart disease	OR: 4.53; 95% CI: 3.95-5.17 Top 1% vs remaining 99%
Inouye et al (38)	2018	1.7 million SNVs	UK Biobank (Caucasian)	Coronary heart disease (life course)	HR: 4.17; 95% CI: 3.97-4.38 Top vs bottom quintile (PRS)
Hachiya et al (41)	2020	>350,000 SNVs	Japanese cohort (East Asian)	Ischemic stroke	HR: 2.44; 95% CI: 1.16-5.12 Top vs bottom quintile (PRS)
Wang et al (42)	2020	6.6 million SNVs	UK Biobank (South East Asian) Case-control study in Bangladesh and India (South East Asian)	Coronary heart disease	OR: 2.46-4.16 Top 5% vs middle quintile (PRS)
Koyama et al (43)	2020	~1 million SNVs	Biobank Japan (East Asian) UK Biobank (Caucasian) CardiogramC4D consortium (Caucasian)	Coronary heart disease	OR: 2.65; 95% CI: 2.30-3.05 Top 10% vs remaining 90%

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; HR = hazard ratio; OR = odds ratio; PRS = polygenic risk score; SNV = single-nucleotide variant.

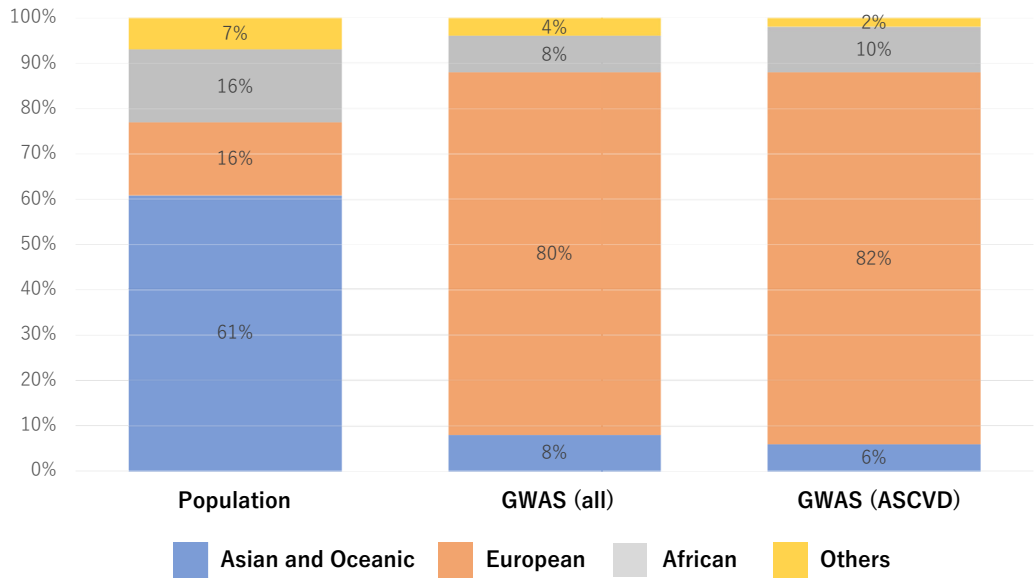
there is a significant trend of association between a PRS comprising multiple common genetic variations independent of a rare FH mutation and ASCVD risk (29).

There are several important implications for these studies. First, although FH is one of the most frequent monogenic disorders leading to ASCVD, its prevalence is ~1 in 300 in the general population (30,31). Alternatively, the prevalence of individuals with a high polygenic risk equivalent to FH is much more frequent than FH (**Figure 1**) (32). Second, finding patients with FH is not difficult because of their extremely elevated LDL cholesterol levels and their physical signs, such as Achilles tendon thickness (33). However, pinpointing the individuals whose polygenic risk is as high as that of those with FH has not previously been possible in the clinic. Third, it is important to consider these 2 genetic risk profiles when predicting risk in the clinical setting.

PRS PREDICTING ASVCD

The initial attempt at developing a PRS, focusing on lipid-associated SNVs, was published in 2008 (34). Subsequently, Ripatti et al (24) used a PRS based on 13 SNVs associated with GWAS of European ancestries (case-control design and prospective cohort) and then tested whether the PRS was associated with ASCVD events among independent cohorts. The authors found that the PRS significantly associated with ASCVD events; however, they did not show its usefulness in receiver-operating characteristic and net reclassification improvement analysis at that time. In 2015, Mega et al (35) increased the number of common genetic variations to 27 to determine whether a PRS

FIGURE 2 Proportion of Global Population and GWAS Participants



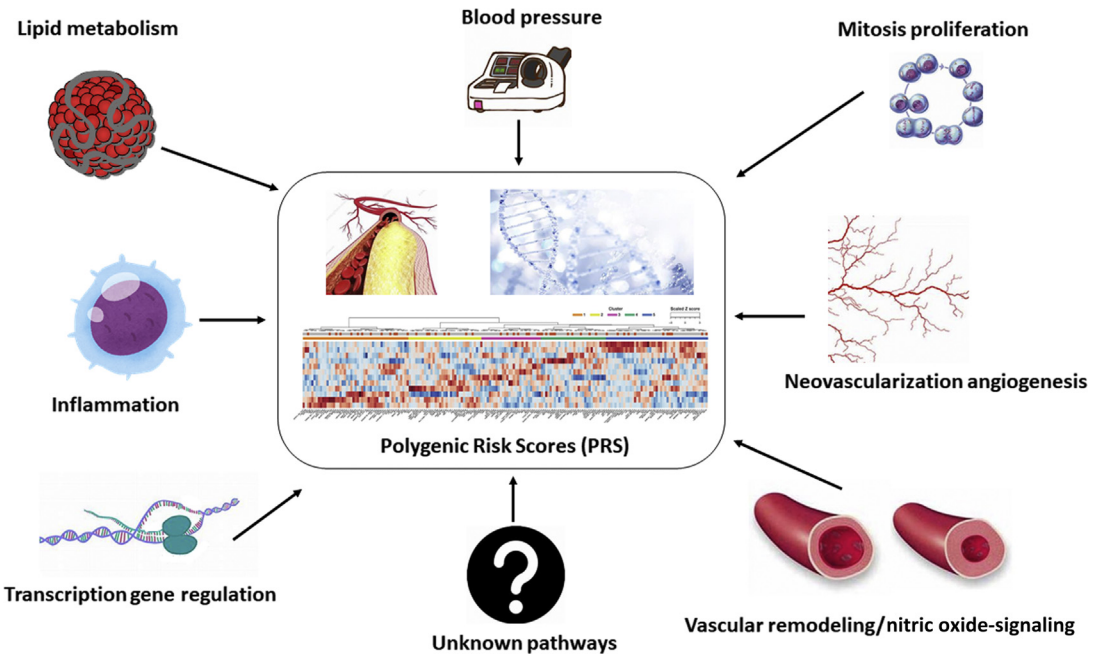
Global population **(left)**, genome-wide association study (GWAS) participants **(center)**, and GWAS participants with atherosclerotic cardiovascular disease (ASCVD) **(right)**. **Blue** indicates Asian and Oceanic, **orange** indicates European, **gray** indicates African, and **gold** indicates others.

outperforms reclassification using the traditional risk factors. They found that a PRS comprising 27 common genetic variations has surpassed its threshold. In addition, Tada et al (36) compared the power of a PRS comprising 27 SNVs and that of a PRS containing 50 SNVs and found that the larger number of SNVs increases its predictive power, independent of family history information. Simultaneously, they showed that a PRS comprising 12 SNVs associated with atrial fibrillation was significantly associated with ischemic stroke events (probably cardioembolic stroke) (37). Furthermore, Khera et al (28) have confirmed that a PRS using ~6 million SNVs in predicting ASCVD was significantly associated with actual ASCVD events in a score-dependent manner. Interestingly, they also showed that such PRS comprising common SNVs were significantly associated with ASCVD among patients with FH in whom a rare genetic variation in LDL receptor or its associated gene elevated the risk of ASCVD (29). Inouye et al (38) evaluated the predictive capacity of PRS comprising millions of SNVs compared with conventional risk factors such as smoking, diabetes, hypertension, and cholesterol. Accordingly, genomic screening through PRS appears to add complementary benefit to conventional risk prediction. The attempts at predicting ASCVD events by using a PRS are summarized in **Table 1**.

PRS PREDICTING ASVCD IN THE ASIA-PACIFIC REGION

Currently available PRS are several times more accurate in those of European ancestry than those of other ancestries (39,40). This is not a failure of PRS per se but rather a predictable outcome of the predominantly European GWAS population used to train and derive the PRS. To date, a limited number of studies have been conducted to determine whether a PRS is similarly useful among Asia-Pacific populations. Hachiya et al (41) reported that a genome-wide PRS comprising >350,000 common generic variations was associated with ischemic stroke events among the general Japanese population, independent of other environmental factors. The authors used GWAS summary statistics from the BioBank Japan Project, the Tohoku Medical Megabank Project, the Japan Public Health Center-based prospective study, and Japan Multi-Institutional Collaborative Cohort Study and assessed the ischemic stroke events in the Hisayama Study (a prospective population-

CENTRAL ILLUSTRATION **Pathways Comprising Genetic Risk for Atherosclerotic Cardiovascular Disease**



There are several known and unknown pathways contributing to the individual genetic risk for atherosclerotic cardiovascular disease.

based study started in 1961 investigating the epidemiology of ASCVD in Kyushu Island, a small town in Japan). Wang et al (42) have shown that a genome-wide PRS comprising >6 million common genetic variations was associated with coronary artery disease among South Asian (Indian and Bangladeshi) populations. Interestingly, they essentially used GWAS summary statistics from European ancestry to make a genome-wide PRS and made it ancestry adjusted using a set of whole-genome sequencing data of South Asian subjects. These results indicate that the cumulative impact of common DNA variants, now possible to quantify by using a PRS, is an important driver of risk of coronary artery disease, even among individuals of South Asian ancestry. By optimizing a polygenic score for coronary artery disease in South Asian individuals, the authors observed a 3.22- to 3.91-fold increase in risk comparing the highest versus the lowest quintiles across 3 independent study samples. Moreover, the pattern of disease associations was concordant across individuals of South Asian ancestry living in the United Kingdom, Bangladesh, and India, with an odds ratio/standard deviation increment ranging from 1.58 to 1.66 across the 3 studies. These results suggest feasibility for the transfer of polygenic scores across varying environmental exposures.

More recently, Koyama et al (43) have shown that a trans-ethnic genome-wide PRS outperformed the one that is ethnicity specific in predicting coronary artery disease among Japanese populations. They performed a trans-ethnic meta-analysis combining Japanese GWAS (mainly using BioBank Japan), CardiogramC4D, and UK Biobank and made a trans-ethnic genome-wide PRS. Moreover, most common genetic variations with a nominal significance showed consistent direction of effect between Japanese and European ancestries.

It remains to be determined whether ethnic-specific or trans-ethnic PRS are more effective in risk prediction, with no clear evidence or consensus. Although a generic trans-ethnic PRS may be more useful for application in real-world settings, an ethnic-specific PRS may ultimately perform better, as there are many common SNVs specific to certain ethnicities. Only further investigation will determine how to best implement a PRS in both the clinic and potentially the broader community.

GREAT GAPS AMONG ETHNICITIES OF GWAS PARTICIPANTS

Despite concerted efforts, there is still a significant disconnect between global population distribution and its representation in GWAS biobanks. According to the GWAS Catalog, ~80% of GWAS participants are European, whose populations account for ~16% of the global population, whereas only 8% of GWAS participants and 6% of GWAS participants with ASCVD are Asian or Oceanic, despite accounting for ~61% of the global population (44) (**Figure 2**). For PRS to effectively predict ASCVD across a variety of populations, detailed summary statistics that clarify the effect sizes of various SNVs for ASCVD within and across ethnicities and regions are needed. Further PRS performance in each of their intended populations must be studied and validated before widespread implementation.

A CALL TO ACTION IN THE ASIA-PACIFIC REGION

It has been shown that individuals with a high PRS may benefit to a greater degree from statin therapy compared with those with a low PRS (35). Moreover, "healthy" lifestyles have been shown to attenuate the association between PRS and ASCVD (45). These findings suggest that PRS do not necessarily seal the fate of an individual; rather, they suggest potential modifiability of risk. Worldwide, 18.6 million deaths were caused by ASCVD in 2019 (46). Among them, 58% (10.8 million) occurred in Asia, and the percentage of premature deaths in Asia was higher than in other regions. Although this finding may be attributed to acquired factors, such as smoking and obesity, known and unknown genetic factors may also contribute to the high prevalence of premature ASCVD deaths in Asia. PRS-related research and commercial entities have become more prominent in Western countries but are not widely studied in the Asia-Pacific region. We strongly propose that the genetics research community move forward to address this issue in the region for several reasons, including the following: 1) it is important that PRS be useful among individuals in the Asia-Pacific region as well as in other regions; 2) the Asia-Pacific region has the world's largest population; 3) genotyping arrays are now relatively inexpensive, and the procedure of calculating PRS is not difficult; and 4) it would be interesting to investigate the associations between PRS and lifestyles that are specific to the Asia-Pacific region.

FUTURE PERSPECTIVES

Although this review has focused primarily on the ability to develop clinically relevant PRS that are of utility in the Asia-Pacific region, a considerable amount of work will ultimately follow on from this analysis. The ability to use a high PRS to triage individuals to more aggressive preventive strategies may be further enhanced by the ability to tailor that specifically, depending on the specific component driving the PRS and risk, although no evidence exists supporting this concept so far. For example, when we encounter 2 individuals whose PRS appear to be similarly high but the cause of elements is different (eg, individual A has many risk alleles in inflammatory-associated variants, and individual B has many risk alleles in lipid metabolism), anti-inflammatory agents may then be more effective in individual A, whereas lipid modification drugs may be better for individual B. Moreover, a particular behavior may be associated with the offset of elevated PRS, which has been shown previously. Lifestyle and dietary habits differ across the regions and ethnicities; thus, much more data are needed to elucidate the "good" behavior among particular populations according to a PRS and its elements. In addition, most GWAS thus far have used logistic models that cannot capture the interacted associations between genetic variations and an outcome, which may account for the so-called "missing heritability." In this sense, more sophisticated statistical models may be needed to identify such associations, which could result in the development of more robust PRS algorithms. Finally, these concepts should also be applicable not only to common genetic variations but also to rare genetic variations (**Central Illustration**).

HIGHLIGHTS

- Genetic factors should be fully accounted for in the clinical care of atherosclerotic cardiovascular disease.
- A health inequity exists regarding polygenic risk score for atherosclerotic cardiovascular disease in the world.
- We propose a call to action to address this issue in the Asia-Pacific region.

CONCLUSIONS

PRS have generally been shown to offer incremental information for risk prediction of incident ASCVD beyond the use of traditional risk factors. However, their validation, and much less their derivation, has occurred predominantly among European ancestry, thus casting doubt as to their generalizability to other non-European ancestries, particularly Asian subjects and the Asia-Pacific region in general. Further studies are required to evaluate the performance of existing PRS as well as catalogs of rare genetic variations and potentially to derive a risk score specific for the highly populous Asia-Pacific region.

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