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# Polygenic risk score and age: an extra help in the cardiovascular prevention of the young?

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All major guidelines recommend assessing the risk of atherosclerotic cardiovascular disease (ASCVD) using risk scores. In fact, it has been shown that their use at the population level increases the accuracy of event prediction and facilitates the choice of strategies to be adopted in primary prevention. In fact, their use in clinical practice is far from optimal and their predictive ability on an individual level is not excellent. Our genetic heritage is substantially stable from birth and determines a 'baseline risk' on which external influences act. Genetic information therefore has the potential to be an early predictor of risk. Common diseases such as diabetes mellitus, ASCVD and neurodegenerative diseases are conditioned by different genetic variants with small individual effects, so that a reliable risk prediction requires careful examination of the aggregate impact of these multiple variants. The polygenic risk score (PRS) is a tool that potentially enables this complex assessment and provides a new opportunity to explore our risk of developing common diseases, including coronary artery disease (CAD). In the future, it is possible that a specific PRS could be used as an independent CAD screening tool, but this requires a detailed assessment of the practical implications, including the population to be investigated, and the consequent interventions that would then be offered.

'Prediction is very difficult, especially if it's about the future'. Niels Bohr

## Advantages and limitations of current risk models in primary cardiovascular prevention

It is now widely accepted that age, sex, smoking, dyslipidemia, hypertension, obesity, lack of physical activity, and diabetes are the main risk factors for the development of atherosclerotic cardiovascular disease (ASCVD).[1] It is also recognized that these risk factors interact in a multiplicative way to increase the vascular risk of the single individual. This knowledge has led to the development of models incorporating such risk factors to be used in primary prevention to assess the individual risk of developing ASCVD, including coronary heart disease (CHD). Following the success of the Framingham Heart Study, many other risk scores have been proposed and validated in the USA, Europe, and other parts of the world. Some of the most popular currently used are the SCORE (Systematic Coronary Risk Evaluation) algorithm in Europe,[2] QRISK3 in England and Wales and the "pooled cohort equation" (PCE) of the American College of Cardiology/American Heart Association (ACC/AHA).[3]

All major guidelines recommend ASCVD risk assessment using risk scores. In fact, it has been shown that their use at the population level increases the accuracy of event prediction and facilitates the choice of strategies to be adopted in primary prevention. However, their use in clinical practice is far from optimal.

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Moreover, despite having been validated, their predictive ability on an individual level is not excellent. Furthermore, some parameters have a disproportionate weight: age, for example, plays an excessive role in the assessment of risk, so much so that it has led to the inclusion of age limits for the application of these models in order to avoid that the estimate risk is too influenced by this parameter.

The need to improve traditional models is also highlighted by the incidence of heart attacks that escape risk assessment. In fact, up to 27% of cases of myocardial infarction do not have the risk factors used in classic predictive models.[4] Again, a not negligible proportion of CHD patients experience early infarct relapses despite optimal medical therapy, configuring a 'residual risk' not easy to identify. Hence, the risk prediction scores for ASCVD have room for improvement. For example, PCE has been shown to substantially overestimate the risk of ASCVD in a contemporary and ethnically diverse population followed for a period of 5 years, suggesting that additional diagnostic information may be needed (beyond what traditional risk scores represent) for a better understanding of one's 'real' risk of events.

## The role of heredity of atherosclerotic cardiovascular disease

Studies in families and twins have estimated that the heritability of atherosclerotic CHD varies between 40 and 60%.[5] The Framingham Offspring Study has shown that, after adjustment for traditional risk factors, a history Parental history of premature CAD was associated with twice the likelihood of cardiovascular disease, thus suggesting an independent hereditary basis for CHD.[6] Studies on the genetic determinants of ASCVD have made it clear that distinct patterns of inheritance exist. In some situations, the risk follows a classic Mendelian inheritance model, in which the disease occurs at a young age and often with a more severe clinical phenotype, such as in the now well-known familial hypercholesterolemia (FH). In FH, the genetic risk of ASCVD is due to a rare mutation in a single gene. The most common pathogenic variants for FH occur in genes encoding the LDL cholesterol receptor (LDLR), proprotein convertase subtilisin/kexin type 9 (PCSK9), and apolipoprotein B (APO B). These mutations can be identified thanks to sequencing with new generation technologies and bioinformatics analysis, whose pathogenicity is then confirmed by the geneticist. Identifying carriers of pathogenic mutations in the genes that cause FH is extremely important as these patients have an approximately three-fold increased risk of developing CHD.

However, carriers of this mutation are rare, with a prevalence of around 0.5%, and are often detected in routine controls due to very high LDL levels.[7]

Although the impact of monogenic risk for ASCVD is significant, for the majority of the population the hereditary risk is due to the cumulative impact of many common genetic variants, known as single-nucleotide polymorphisms (SNPs), each of which has a modest effect on risk because it is not able to determine an alteration of the gene.[8] However, when these variants are added together they determine a significant increase in the genetic risk of developing a particular phenotype. When polymorphisms of a single nucleotide add up within an individual, they configure his 'polygenic risk'.

Common diseases are believed to be affected by many genetic variants with small individual effect sizes, such that meaningful risk prediction requires examining the aggregate impact of these multiple variants. Polygenic scores or polygenic risk scores are a tool that allows for this complex assessment. Large-scale studies carried out in recent years have allowed the development of polygenic scores based on polymorphisms, commonly called 'Poligenic Risk Scores' (PRSs).

## The birth and development of the polygenic score as a predictor of risk

Our genetic heritage is substantially stable from birth and determines a 'baseline risk' on which external influences act. Genetic information therefore has the potential to be an early predictor of risk. This is the case with some rare inherited diseases, where knowledge of the single underlying variant has led to the development of highly predictive genetic tests. Instead, as reported above, common diseases such as diabetes mellitus and many neurodegenerative diseases are conditioned by different genetic variants with small individual effects, so that a reliable risk prediction requires a careful examination of the aggregate impact of these multiple variations. The PRS is a tool that enables this complex assessment and provides a new opportunity to explore our risk of developing common diseases.

The nature of the risk information provided by the PRS differs from that obtained through genetic variant testing for inherited diseases. The risk information provided by the analysis of high-penetrance rare genetic variants is often dichotomous (i.e. a high probability of disease or not) and is supported by knowledge of the biological impact of these variants. Conversely, the PRS provides a wider range of probabilistic risks, similar to other biomarkers such as cholesterol and blood pressure. Furthermore, the risk of developing disease is not so strongly linked to the presence of particular variants and is significantly modulated by environmental influences. Coupled with the fact that each individual variant is passed on to different family members in different ways, this means that they do not have the same familiarity implications as the high-penetrance variants. Consequently, their predictive ability will differ substantially for different pathologies, depending on the genetic architecture underlying the disease, as well as on different public health conditions and individual behavioural habits.

Early versions of PRS assumed that each genetic variant included in the score had an equal weight of.[9] However, since each risk variant tends to differ in its strength of association with ASCVD, the performance of these scores was limited. Subsequently, genome-wide

association studies (GWASs) analysed SNPs in the genome and identified those that are found more frequently in people with a particular disease than in people without the disease. Early PRSs based on this approach and which included 13–50 SNPs were strongly associated with history of CHD but did not significantly improve risk reclassification compared with traditional risk factors or family history.[10]

Gradually, we went from studying relative small numbers of SNPs to analysing hundreds of thousands of SNPs. Advances in easy-to-use chip design have further increased the economic efficiency of GWASs by using high-speed sequencing technologies capable of sequencing multiple DNA molecules in parallel, enabling the sequencing of hundreds of millions of DNA molecules at a time[11] Through the use of software that can explain linkage imbalance or non-random assortment of alleles, it is now possible to make a PRS include millions of SNPs from across the genome. The PRS of an individual is therefore a single value that quantifies the cumulative genetic risk conferred by the genetic variants of that individual.[12] Also for the estimate of the risk of CHD, the PRSs have progressively passed from the inclusion of a few SNPs to millions of variants. The construction of a polygenic score is depicted in *Figure 1*.

## Clinical applications of the PRS

The potential of the PRS had been circulating among researchers for several years. It was only in 2018, however, that these scores were shown to have a rationale for large-scale clinical use. A study by the Cardiovascular Disease Initiative at the Broad Institute in Cambridge, Massachusetts, identified people at high risk for five common diseases based on their genome.[13] The team used genome-wide data and evaluated millions of common genetic variations associated with CHD, atrial fibrillation, type 2 diabetes, inflammatory bowel disease and breast cancer. For each pathology, they applied an algorithm that combines the information of all variants into one number, or PRS, which reflects hereditary susceptibility to these diseases. When they then tested their PRS for heart disease on 290 000 UKBiobank participants, they found that 8% of the population had a three times the normal risk of a myocardial infarction.

Almost simultaneously, another study generated a PRS of 1.7 million SNPs and demonstrated further improvements in discrimination and risk prediction. When tested in the UK biobank, this PRS discriminated risk better than classic individual risk factors. This study also confirmed the results of previous studies which suggested that the risk identified by these SNPs is independent of clinical risk factors.[14] Subsequently, the use of PRS was proposed to improve the implementation of preventive measures. In fact, the clinical usefulness of a PRS to improve the estimation of CHD risk, beyond the known and established risk factors, and in defining clinical actions to be implemented based on the results of the PRS is still widely debated. In detail, the debate is not about the reproducibility of the study results as the PRS appears to be accurate in a given population, and therefore

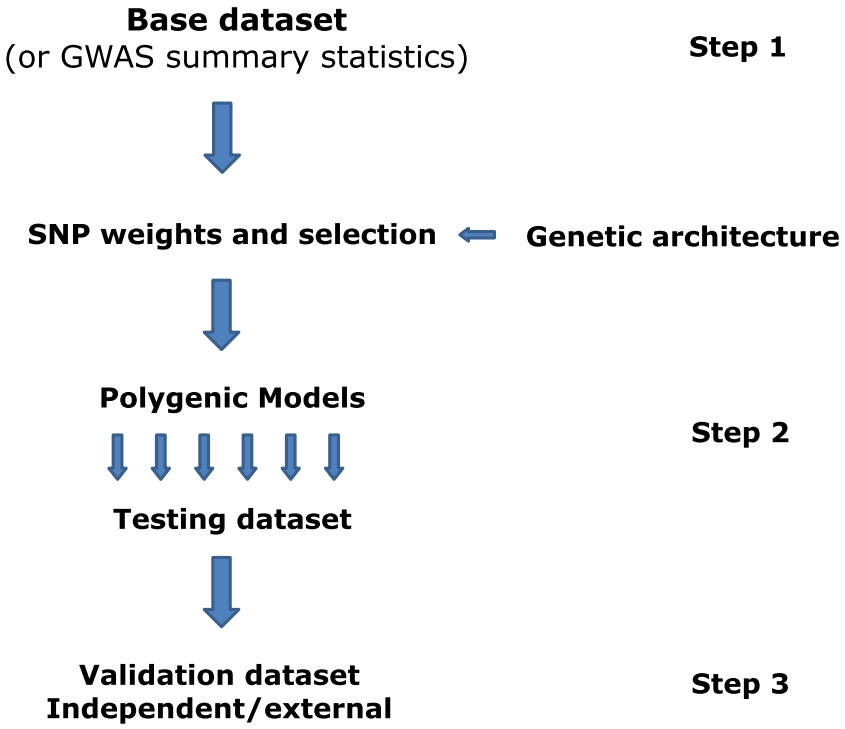


**Figure 1** Construction of a polygenic score. In the process of developing a polygenic score, numerous models are tested and then compared. The best performing model is then selected for validation in an external dataset. GWAS, whole genome association studies; SNP, Polymorphism of a single nucleotide.

reproducible. For example, the increase in risk per standard deviation of a PRS is between 1.3 and 1.7 in the European population.[15] The point is rather: what is the real clinical benefit?

In the context of primary prevention, the crucial point is whether the addition of PRS is able to improve risk stratification and the diagnosis of subclinical atherosclerosis on the one hand, and to help doctors and patients improve the prevention of ASCVD on the other. In the light of the lack of overlap with traditional risk factors, the rationale exists for the use of the PRS as a complementary tool. On the contrary, the application of PRSs in the clinical management of patients in secondary prevention with ASCVD or known CHD is less clear. Even less clear is the utility of PRSs in subjects with few traditional risk factors and previous unexplained myocardial infarction, or whether it can be useful in the parents of young patients with a coronary event.[12]

## Current limitations and future prospects of the PRS

Observational studies have shown an association between a high PRS and the benefits of preventive measures or the introduction of statin therapy. However, few studies have investigated the potential benefit of integrating PRSs into clinical practice. For the clinical utility of genomic risk stratification to be fully realized, further work needs to be done to standardize the performance of the PRS and ensure that its implementation leads to equitable improvements in health outcomes. It is imperative to program randomized clinical trials or rigorous studies to evaluate the health benefits for citizens, the potential harms, and the costs of an implementation of the PRS results by the medical profession.

Future clinical trials should seek to identify groups of subjects who would not currently be identifiable at risk of early ASCVD, or those who have a low risk based on risk charts or subclinical atherosclerosis based on imaging, such as calcium score, but who are not eligible for preventive therapies such as statins.[12,16] The primary objective should be the ability to predict major cardiovascular events, but in a first phase of implementation, direct comparisons with current sophisticated coronary imaging methods capable of identifying subclinical atherosclerosis or changes in size and characteristics of the coronary plaque would also be sufficient (for example, latest generation coronary computed tomography angiography (CCTA)).

A major concern with the clinical implementation of PRS is that, so far, scores have largely been calculated from European DNA sequences. The frequency and degree of disease correlation of genetic variants common in African Americans differ from that of European Americans and this reduces the accuracy of PRS. In this context, for example, the potential clinical utility of PRS for CHD was unknown among East Asian populations with significant disparities in both genetics and lifestyle. Only very recently has it been shown that a PRS comprising 540 genetic variants could stratify Chinese individuals into different CHD risk trajectories and further refine CHD risk stratification within each clinical risk category.[17]

Each stage of the construction of the PRS itself must be standardized. Currently, there are a number of different PRSs for ASCVD, diabetes, and obesity, but none of these are standardized or accepted by any of the major cardiovascular guidelines. However, given the challenge of normalizing PRS performance in a population with varying genetic ancestry, it is still unclear whether a single standardized PRS for ASCVD can be applied in all clinical settings.[16] Therefore, work still needs to be done to determine whether one or more PRSs will be needed to generate comparable risk thresholds in a variety of clinical settings (*Table 1*).

## Conclusions

Research in the field of PRS is demonstrating that polygenic scores can help improve CHD risk stratification and provide an indication that may have value in clinical practice. There is broad consensus that this added value can be realized in the short term by incorporating the PRS into existing CHD risk estimation tools. While polygenic scores have mostly been considered in the past as an autonomous tool, current research is investigating the role of the incorporation of the PRS in the classical

**Table 1** Advantages and limitations of the genetic risk stratification of ASCVD

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| *Benefits* |
| The genetic predisposition remains unchanged throughout life |
| Early genetic risk assessment before the development of traditional and environmental risk factors |
| Huge potential in estimating risk trajectories over the course of life |
| Huge potential for improving medical decision making for: |
| Early preventive measures in subjects with high genetic risk |
| Initiation of therapies (e.g. statins) |
| Ability to predict adverse drug effects |
| Simultaneous use for a wide range of other complex diseases |
| *Limitations* |
| Unclear 'accumulation' strategy: whole genome vs. strategy based on millions of SNPs |
| Weaker evidence in non-European ancestry |
| Unclear predictive accuracy beyond traditional risk factors |
| Use of classification vs. dichotomy of the PRS |
| Complete PRS for ASCVD or specific PRS for single pathologies (stroke/CAD/PAD) |
| Unclear target populations for genetic risk stratification |
| Unclear economic value |

ASCVD, atherosclerotic cardiovascular disease; SNP, single-nucleotide polymorphism; PRS, polygenic risk score; CAD, coronary artery disease; PAD, peripheral artery disease.

tools available (such as risk charts). These studies will allow to evaluate the additional benefit of PRS in risk estimation. In the future, it is possible that a CHD-specific PRS could be used as an independent screening tool, but this requires a detailed assessment of how it would work in practice, including the population to be screened, and the consequent interventions that would then be offered.

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