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Polygenic scores, risk and cardiovascular disease

UNIVERSITY OF CAMBRIDGE

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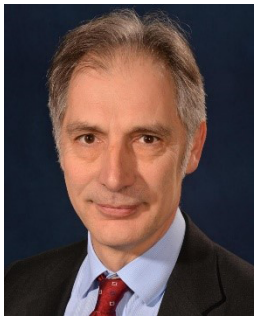


Foreword

The potential of genomics to personalise and thereby improve diagnosis, prognosis and treatment of individuals with disease has long been recognised, but so far evidence of the scope for genomics to drive prevention remains more limited. However, rapid technological developments are making it increasingly feasible that genomics could be used alongside other sources of information to improve population-level as well as individual prevention of disease.

This is why PHE are looking into ways of delivering more 'intelligent' public health, as outlined in the recent Green Paper *Advancing our health: prevention in the 2020s*, ensuring that we make the most of new science and any new sources of data to refine our current approaches. The evidence is rapidly evolving and the expert work of the PHG Foundation in examining the potential of genomics for personalised prevention is clearly invaluable in helping policy-makers keep pace with this fast-moving field.

The use of polygenic scores for common disease risk assessment is an important area of development for public health and warrants close attention. This report, *Polygenic scores, risk and cardiovascular disease*, provides an excellent summary of the basis, use and appraisal of polygenic scores for disease risk that anyone working in common disease prevention will find helpful. It also summarises the current state of evidence for the possible application of polygenic scores within cardiovascular disease prevention efforts, and makes constructive recommendations on addressing gaps in knowledge and preparing for the development of evidence-based changes to practice.

Looking ahead, predictive prevention may well become an increasingly important part of our wider efforts to prevent disease and preserve health. It seems likely that polygenic scores will have a role to play in these approaches at some point, but there is still a good deal to learn about how to maximise benefits for public health. We need to be very clear about the nature of the evidence so far for using such scores and the implications of doing so.

I strongly commend this report as a timely analysis of the potential future utility of polygenic risk scores for cardiovascular disease prevention

Professor John Newton
Director of Health Improvement, Public Health England

Executive summary

It is widely recognised that common diseases have a genetic component, but for the vast majority of the population this information is not currently used in preventive approaches. However, recent advances in research on polygenic scores and their application to risk stratification have created renewed interest about the use of genetic information in prevention of common diseases. The debate thus far has been largely polarised, with strong proponents and critics about the utility of such information. This report examines the field from the perspective of cardiovascular disease prevention, to assess evidence and readiness for clinical implementation.

Polygenic scores as a predictor of risk

Our genetic make-up is largely stable from birth and dictates a 'baseline risk' on which external influences act and modulate. Genetic information therefore has the potential to act as an early risk predictor. This is the case with many heritable disorders, where knowledge of underlying variants has led to the development of highly predictive genetic tests. Common diseases, in contrast, are thought to be influenced by many genetic variants with small individual effect sizes, such that meaningful risk prediction necessitates examining the aggregated impact of these multiple variants. Polygenic scores or polygenic risk scores (PRS) are a tool that enable this assessment and provide an avenue for exploring this baseline risk for common diseases.

The nature of risk information provided by polygenic scores is different from that obtained through genetic testing of variants for heritable disorders. The risk information provided by analysis of rare, high penetrance 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.

In contrast, polygenic scores provide a wider range of probabilistic risks, similar to other biomarkers such as cholesterol and blood pressure. Furthermore, disease manifestation and risk are not as strongly linked with the presence of particular variants and will be significantly modulated by environmental influences. This, together with the fact that each individual variant passes to different family members in different ways, also means they do not have the same familial implications as high penetrance variants. Consequently, the capacity in which this risk information is likely to be used will differ substantially for different conditions, depending on the underlying genetic architecture of the disease, as well as current clinical and public health practice.

Polygenic scores for cardiovascular disease

Appraisal of the literature in the area of polygenic scores for coronary artery disease (PRS-CAD) reveals that although there is indeed potential in the field, it remains under development. This is because research is still in a discovery phase and has been designed in such a way as to explore different mechanisms to generate a polygenic score and stratify individuals; the implications of stratification for clinical practice have not yet been investigated.

The main areas where further work is needed include the development of robust and validated mechanisms to generate and evaluate a polygenic score, and development of a validated test for use in clinical practice. An implementation-ready clinical test is not yet available; development would require the explicit use of a defined assay in a particular population and for a particular purpose, but most studies examining PRS-CAD to date lack a clearly defined clinical purpose.

Evidence of clinical utility of polygenic scores for CVD

Analysis confirms that there is currently no evidence for the clinical utility of PRS for cardiovascular disease prevention but this in itself does not mean that such evidence may not emerge in future years. Rather it may reflect the absence of a purpose or clear clinical application for PRS, at this stage. The evidence base required for potential clinical uptake will vary for different applications. For example, where PRS-CAD is to be included as part of an existing risk tool, improved performance and limited cost are likely to be sufficient to consider implementation. This is because such risk prediction tools are already a part of established clinical practice, used in prioritising and planning primary prevention interventions, and are already regarded as having clinical utility. Utilising PRS outside of this very specific context may require consideration of what additional clinical utility may be offered.

Current narratives around genetics include strong themes of patient empowerment and control; however, there is currently a lack of empirical evidence to suggest that the inclusion of PRS in prevention efforts would make important differences to patient behaviours. This is reinforced by theoretical models of behaviour change suggesting that, whilst the addition of PRS may itself be enough to motivate a small subset of the population to change their behaviour under specific conditions, crucially, provision of PRS needs to be combined with other forms of support to be more generally effective.

The future of polygenic scores and disease prevention

There is considerable interest in the potential use of polygenic scores as a biomarker for earlier identification of those at increased risk prior to the manifestation of clinical disease. For example, in cardiovascular disease there is evidence that plaque build-up in the vasculature (atherosclerosis) can begin at an early age (pre-teen) and stay with individuals for life. Individual genetic information could provide the earliest indication of a predisposition to such build-up, allowing preventative action to be taken in high-risk individuals from a younger age, perhaps even before plaques begin building in childhood. Interventions in these high-risk individuals could be close monitoring, lifestyle adaptation or use of therapeutics. In the future, it is possible that once an individual has been genotyped, multiple polygenic scores could be generated for numerous diseases, traits and subtypes of disease.

This scenario could enable a move towards predictive prevention, but would also require careful consideration of interventions to be offered to individuals identified at elevated risk and demonstration of beneficial health impacts. As many primary prevention interventions rely on behaviour change (whether addressing lifestyle factors or compliance with medications), further research is also needed on techniques that support achieving these goals, including in younger populations. On-going research to determine the public acceptability of programmes with a focus on prevention (as opposed to early detection) are also needed, together with research and evaluation to determine potential wider societal impacts.

Conclusion

Thorough assessment of the application of polygenic scores for cardiovascular disease risk suggests that this is a promising area of development; a polygenic score for CAD can improve stratification, and hence potentially support more effective prevention. Nevertheless, there are still considerable gaps in knowledge, such that polygenic scores are not likely to be ready for implementation in clinical practice in the next three years.

1 Introduction

1.1 Context

Attempts to harness knowledge on common SNPs associated with diseases for the purposes of predicting disease risk have been ongoing for several years. Initial efforts to develop predictive tests based on analysis of polygenic scores met with limited success. This landscape is now changing, due to concomitant developments in the understanding of the genetic basis of many common diseases, developments in methods to generate risk scores and the availability of datasets in which to validate them. Polygenic or genetic scores that combine information from multiple common SNPs are an attractive biomarker, as they are a stable variable across the lifetime of an individual that can be used to stratify populations into different levels of risk.

Recent advances in this field have led to considerations around the potential of polygenic scores to be used as a method of risk assessment, either by themselves or as part of existing risk assessment tools. This field has now reached a critical stage, with discussions moving towards potential clinical implementation. However, prior to discussions around implementation, it is important to have a careful and critical assessment of the readiness of polygenic scores as a clinical tool.

This report examines the readiness for clinical implementation of polygenic scores that have been developed to predict risk of cardiovascular disease.

1.2 Aims and objectives

The aim of this report is to review the literature on polygenic scores, specifically in the field of cardiovascular disease and ascertain their readiness for incorporation into primary and secondary prevention of cardiovascular disease.

Specific objectives are to:

1. Describe what polygenic scores are, how they are generated and mechanisms used to assess their scientific and clinical validity
2. Describe the landscape with respect to currently available polygenic scores for cardiovascular disease
3. Describe risk tools for cardiovascular disease, their uses and the contribution of polygenic scores to these risk tools
4. Provide an analysis of the scientific validity of available polygenic scores for cardiovascular disease
5. Provide an analysis of the evidence base with respect to clinical utility of polygenic scores for cardiovascular disease
6. Provide an independent assessment of the use of polygenic scores for cardiovascular disease prevention

1.3 Methodology

1. Desk based literature review using peer-reviewed literature, grey literature, and official publications
2. Identification of domain specific experts based on mapping key players in this field and harnessing our existing networks
3. In depth interviews (telephone or in person) with experts and relevant stakeholders
4. Synthesis and analysis of information gathered from desk and interview based research
5. Analysis of gaps in the evidence and assessment of the considerations around the use of polygenic scores as part of cardiovascular disease prevention programmes

2 Polygenic scores and their applications

This section begins with a brief background on current understanding of the role of genetics in common diseases. We then provide an overview of terminology and approaches to construction of polygenic scores (PRS) along with a description of the key components in developing them. This is followed by a description of the potential clinical applications of polygenic scores.

Key points

- Numerous methodologies exist for the development of a polygenic score model
- Evidence shows that polygenic scores are useful for the stratification of individuals and proof-of-principle studies demonstrating potential applications have been published
- This is a field still in flux, and the validity and utility of polygenic scores are likely to differ for different diseases and contexts

2.1 Genetics of common diseases

Finding genetic causes that underlie common diseases has been a research focus for many years. Initially this was done through examining associations between a limited number of single nucleotide polymorphisms (SNPs) – which can be also referred to as genetic variants – and the disease of interest. As genomic analysis advanced and became cheaper, research moved to Genome Wide Association Studies (GWAS) (Box 1), where the association between thousands to millions of SNPs and diseases/traits of interest could be investigated simultaneously.

Box 1: Genome Wide Association Studies (GWAS)

Genome wide association studies aim to determine the genetic differences that correlate with a trait or disease of interest. The most common approach is through a case-control design, which compares two large groups of individuals - one healthy control group and one group with the disease or trait of interest. All individuals in each group are genotyped for common known SNPs using a SNP array. SNP arrays are a type of DNA microarray used to detect known common genetic variants within a population. A number of SNP arrays are commercially available. They can be custom made and have <5,000 to over 2 million SNPs[1]. Studies are often accompanied with summary statistics providing the association data for all the variants analysed across the genome in a given study.

GWAS demonstrated that the genetic component of common diseases was more complex than initially envisaged. As opposed to identifying variants with large effect sizes associated with disease, many common SNPs (i.e. present in >1% of the population) were found to have small effects on disease risk. This led to the common disease-common variant hypothesis (Box 2)[2].

Box 2: Common disease-common variant (CD-CV) Hypothesis

- Hypothesis that common genetic variants (such as SNPs) of modest effect make an important contribution to common human diseases
- Predicts that common variants (not necessarily disease-causing) will be found in all human populations which manifest a given disease or trait
- According to this hypothesis, some of those variants influence susceptibility to common diseases

Given that common diseases could be influenced by many SNPs with small effect sizes, methods were developed to examine the impact of multiple SNPs on disease risk. This involved aggregating the impact of multiple SNPs into a single score. Methods to examine the aggregated impact of multiple SNPs have been in existence for some time, recent advances in statistical techniques and the availability of large datasets have led to rapid developments in this area over the past five years.

2.2 Overview of terminology and approaches to score construction

The terminology related to polygenic scores is inconsistent and evolving as the methodologies advance. Table 1 provides an overview of the different terms that are used to describe scores generated by combining multiple SNPs. These terms (allelic risk score, genetic/polygenic risk score (PRS), and GRS/GPS) are often used interchangeably. For the purpose of this report we will use either the term 'polygenic score' or the commonly used abbreviation 'PRS'. In essence, the terminology reflects changes in the scale of SNP information that is aggregated to derive the final score.

Initially, polygenic scores were based on relatively few SNPs that were identified through candidate gene studies. As GWAS were initiated and grew in size, the number of SNPs found to be associated with disease increased, and enabled inclusion of a greater number of SNPs in polygenic scores. Common practice is to include the top hits i.e. those above a chosen threshold of statistical significance. The small size of the studies meant that only a relatively small number of SNPs were associated with disease and there was less precision around the effect size of the association with disease.

Table 1: Types of polygenic scores

Term	Type of polygenic scores
Basic/simple/genetic/ allelic risk score	Based on combination of a few SNPs. Uses SNPs that have been identified in association studies and may include effect sizes derived from previous publications. Sometimes simply additive - counts the number of risk alleles each person carries, ignoring their estimated effect size.
Polygenic/genetic risk score	Larger number of SNPs are included into the PRS calculation than in basic genetic risk scores (above). Uses SNP effect sizes from the GWAS to develop the score. Polygenic hazard score (PHS) is where SNP weights use hazard ratios rather than odds ratios. It is now common practice to designate a PRS by the number of SNPs incorporated to distinguish them from one another, e.g. PRS-313 has 313 SNPs in the calculation.
Genome-wide polygenic risk score (GRS)	A score developed by incorporation of hundreds of thousands to millions of SNPs across the genome. The term metaGRS[3] has been used when multiple scores are combined into a single score.

As GWAS sizes grew and included analysis of a broader range of SNPs, more SNPs were identified and precision in estimates increased. It was also realised that SNPs that do not meet highly stringent significance thresholds for genome-wide association could also be predictive of disease. The inclusion of more SNPs means that additional considerations are required, such as the possible correlation of the SNPs with each other (due to linkage disequilibrium, LD) (Box 3) and the signal to noise ratio. To try and control for these aspects, statistical models are employed to assist in SNP selection, weightings and to make adjustments which enable better performance of the score.

Most commonly, polygenic scores are calculated as a weighted sum of the number of risk alleles carried by an individual, where the risk alleles and their weights are defined by the SNPs and their measured effects as detected by GWAS[4]. However, there has been a recent proliferation of methods to develop scores. The evolving terminology in this field reflects the fast pace of development.

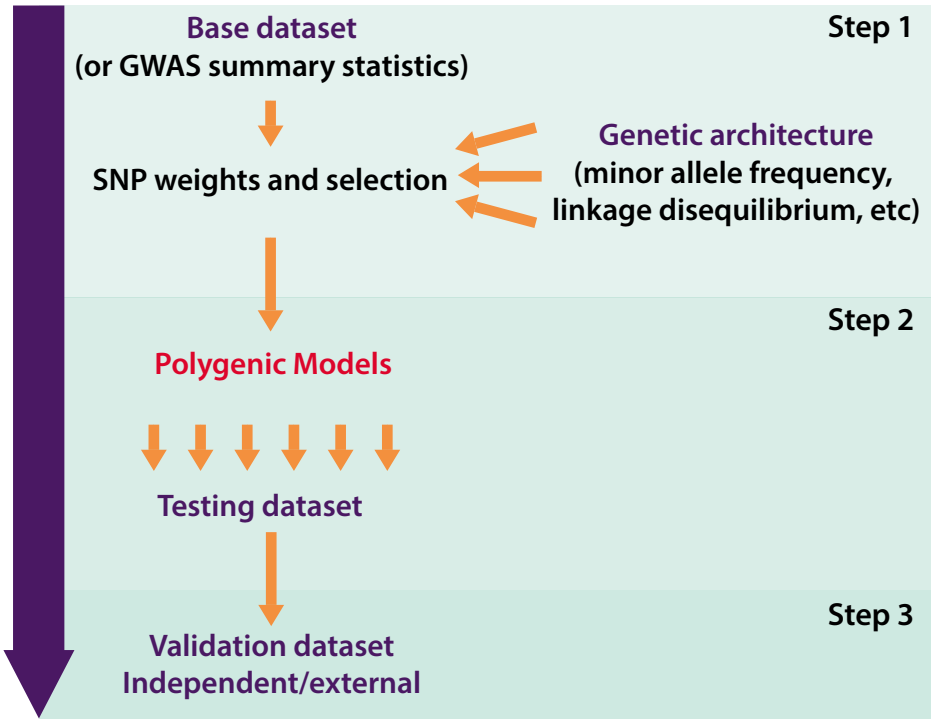
Box 3: Linkage Disequilibrium and imputation

Linkage disequilibrium (LD) describes the non-random association between alleles at different loci on the same chromosome. Alleles in LD appear together more or less often than expected by chance. From the SNPs included on an array it is also possible to infer the genotype of other SNPs through imputation. Imputation describes the process of predicting genotypes that have not been directly genotyped in a sample of individuals, but are statistically inferred (imputed) based on haplotype blocks (i.e. areas of high LD) from a reference sequence.

2.3 Steps in the construction of polygenic models

Polygenic scores are calculated utilising statistical models, the model construction process involves three essential steps: selecting the SNPs and their weightings (often done in a discovery/base dataset), selection of the best polygenic model using a testing dataset, and validation of the score in an external dataset (Figure 1).

Figure 1: Construction of a polygenic score. In the process of developing a polygenic score, numerous models are tested and then compared. The model that performs best (as determined by one or more measures) is then selected for validation in the external dataset.



The main challenge in developing a polygenic score is in determining which SNPs to include and the disease-associated weighting to assign to these. Model development is reliant on processes of SNP selection for inclusion and optimisation of assigned weightings. Researchers may use a number of methodological approaches which vary in complexity to develop initial models. These are tested to assess which approach will ultimately work best within the disease of interest. Measures of predictive accuracy, performance or applicability to external datasets may contribute to determining which model is selected. Below, each component of score development is examined in more detail.

Datasets

Development of a polygenic score is reliant on use of different datasets. Terminology varies but comprises three levels: the base (or discovery or training) dataset, the testing (or internal validation) dataset, and the external validation (or application) dataset (Figure 1). A base dataset is used for identification of SNPs associated with the disease state and their effect sizes. The weighting parameters assigned to a SNP impact the calibration and predictive ability of the final model - these parameters are determined in the base dataset. The information required from a base dataset comprises summary statistics (beta/odds ratios, p-values) and the set of SNPs selected for inclusion in the score. If the SNPs are preselected and their associated weightings predetermined (normally through use of evidence in the literature), it is possible to start the development of a polygenic score in the testing dataset. Finally an external dataset is used to validate the selected model, and to assess its performance in accurately predicting the trait of interest.

The genotyping data can either be in a raw format or provided as summary statistics. The availability of raw data allows for different models; however, computational issues arise because of the size of the data. Summary statistics from GWAS are commonly made available but there are no standards for publicly available files, meaning some processing and quality control steps are required. Awareness of these steps is valuable in understanding which SNPs are ultimately used in a polygenic score model. Individual level genomic data are often not available to researchers due to privacy concerns, so the focus has been on ways to improve risk prediction using well powered summary statistics.

Careful consideration is required around the context in which data used was collected as it will impact on the performance of the final score. For example, data collected from a screening population may not be suitable as a base dataset for the development of a polygenic score that will be used for disease prediction in the general population. Allele frequency and LD (Box 3) patterns can vary between populations and, if used inappropriately, can translate into poor performance of the polygenic model in populations different to that in the base dataset.

The most common source of base data is from GWAS, where currently individuals have been genotyped using SNP arrays (Box 1). In the future, this may move towards whole genome (WGS) or whole exome (WES) sequencing, which could reduce reliance on imputation (Box 3). The size of the dataset is an important factor in developing polygenic scores – larger datasets are needed to ensure there is sufficient power to detect SNPs with small effect sizes and to accurately estimate the small effect sizes associated with these SNPs.

SNP selection

The number of SNPs included in the calculation of a polygenic score can range from a few to tens, hundreds, thousands, or all SNPs with information available. The number that can be included may be limited by the available dataset and how the genotyping and corresponding processing of collected data have been performed in it. Selection of SNPs to include in a polygenic model can be done in a number of ways:

- Using SNPs associated with the disease or trait of interest identified in candidate gene studies
- On the basis of the significance of the individual SNP associations with disease in a GWAS, where a p-value threshold or a number of thresholds are defined prior to analysis. This can be done on either filtered or unfiltered SNPs

- Through a process of LD thinning/filtering. Essentially SNPs correlated with other SNPs in a region are removed, by either pruning or clumping, resulting in at least one SNP remaining as a marker in a region of high LD
- Statistical approaches such as stepwise regression where SNPs are selected based on how much they improve the models predictive performance (ignoring knowledge of LD)

The importance of SNP selection is to ensure that the model based on these SNPs provides the best discriminative ability. The above steps can ensure that only the relevant SNPs are included, avoids double-counting of loci and minimises the issue of overfitting, where a model mistakes noise for signal. If overfitting occurs, it typically manifests as good performance in the testing dataset but poor performance upon external validation [5]. Additionally, poor performance may result from imperfect tagging with the underlying causal SNP [6]. This is because the causal SNP that is associated with disease might not be in LD with the SNP in the model (i.e. the tag SNP) but in LD with another SNP, in particular this can occur where the LD can vary between populations.

SNP weightings

A major component of the polygenic score calculation is to determine the disease-specific weightings of a SNP based on the effect size of the association or GWAS-derived statistics. Previously, when simple genetic risk scores were calculated using only a few SNPs, the effect sizes associated with SNPs were ignored. Estimating weightings is now acknowledged to be an important component in the development of a polygenic score and the standard is now to use GWAS effect sizes as a weighting parameter.

Numerous methodologies have been developed to improve weighting and to enhance the discriminative power of a polygenic score, ranging from basic weighting schemes to complex statistical measures which can include reweighting. Each method has its advantages, disadvantages and limitations; consequently, selecting which method is most appropriate needs careful consideration. When calculating a polygenic score, the resulting units of measurement depend on which measurement is used for the weighting [7]. The weights can be given as a log odds ratio (log OR) for discrete traits or linear regression coefficient (β) in continuous traits from univariate regression tests.

Some methods do not involve selection of SNPs but instead optimise weights for all SNPs that have been genotyped using their overall GWAS weights, LD and an estimate of the proportion of SNPs that are expected to contribute to the risk [8]. An additional method of weighting is to embed non-genetic information (for example age specific odds ratios) which could improve the weighting [9].

2.4 Implications of methodologies

The development of a model to calculate a polygenic score involves refinement of parameters, and selection of the best of several models. This can be an iterative process that relies on the data, methodology chosen for SNP inclusion and weights, as well as the context of the development of the polygenic score. Testing of the model(s) with refinement - balancing between the SNPs included, weightings assigned and the data available - allows for more accurate discrimination. The goal is also to find a model that generalises to an external validation dataset.

It is a significant challenge to derive a methodology that performs well across several diseases – i.e. for all types of genetic architecture. It is currently clear that each disease has its own complexities and needs to be handled individually.

Due to there being a number of different methodologies to generate a score, numerous models may exist for the same condition and each of the resulting scores could perform differently e.g. Willoughby *et al* report 29 polygenic score models for breast cancer from 22 publications [10]. It may be that scores perform differently because the measured outcome or context applied in discovery datasets used to generate models is also different e.g. developing a polygenic score for risk of breast cancer versus a particular subtype of breast cancer [11, 12]. This diversity, alongside the lack of established best practice and standardised reporting in publications, makes comparison and evaluation of polygenic scores for use in clinical settings more challenging [13, 14]. Currently, each polygenic score needs to be individually examined to determine suitability, applicability and performance, and determine which may be most appropriate for the clinical question being addressed.

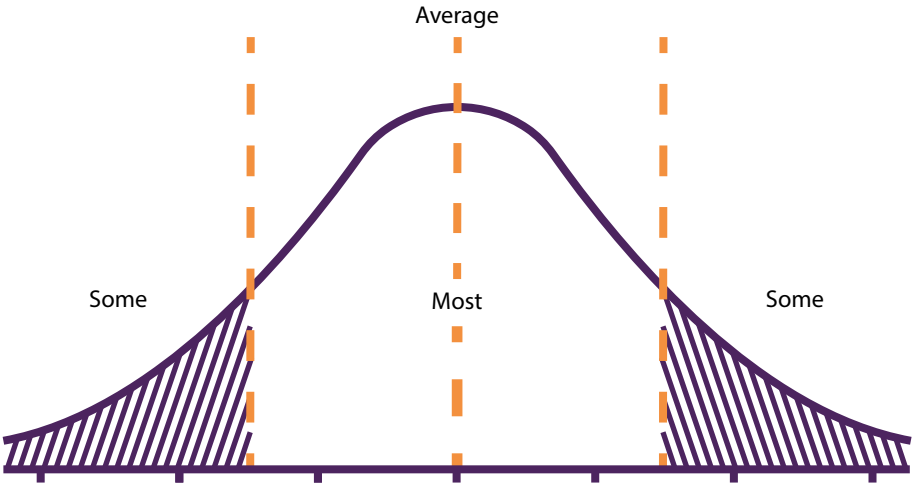
Genotyping technology has improved through time with the number and variety of SNPs examined in GWAS increasing. As the size of GWAS increase, both in study size and SNP numbers, as well as the improvement of statistical methods, identification of SNPs that provide information on disease risk has improved, as demonstrated earlier (Table 1). It is estimated that there are between 4.1 and 5 million SNPs in any one individual [15]. Current GWAS do not cover every single known SNP. GWAS use SNP arrays (Box 2) which only have a subset of known common SNPs included. There is interest in a move towards whole genome sequencing (WGS) to obtain SNP information. There have been limited studies of polygenic scores developed from WGS data, due to limitations in data availability [16]. If in the future WGS becomes the main method of genotyping in healthcare this could allow for the use of a polygenic model on this type of data. Use of WGS will also allow for identification of monogenic variations that contribute to disease risk [16].

2.5 Potential applications of polygenic scores in healthcare

Polygenic scores, much like other biomarkers, are normally distributed across a population and hence can theoretically provide a risk distribution from 0-100% (Figure 2). This means that for the majority of a population, their score will fall in the middle of this distribution - the average, or population, risk level.

Again, much like other biomarkers, the scores can be used to identify a subset of individuals at the ends of the distribution who have either increased or decreased risk. In research, individual-level polygenic score values are often used to stratify populations into distinct groups of risk based on percentile cut-off values (i.e. top 1% etc.). These risk-thresholds can be determined by pre-existing clinical guidelines. Clinical guidelines will often also recommend cut-off values for when an individual is considered to be at increased risk and can be recommended for further screening, treatment or referral to specialists.

Figure 2: Example distribution of polygenic scores across a population.



Similar to other applications of genomic information, a polygenic score can inform healthcare in multiple ways. In the future, it is possible that once an individual has been genotyped with WGS or a SNP array, that multiple polygenic scores could be generated for numerous diseases, traits and subtypes of disease. It is unlikely that scores will be used on their own, rather they will be combined with other risk factors and incorporated within existing risk prediction models. The building of comprehensive risk models including polygenic scores is already underway in research [17]. However, the exact clinical application of polygenic scores will differ substantially for different diseases, depending on underlying genetic architecture of the disease as well as current clinical and public health practice. Below we provide some potential applications of polygenic scores.

Aiding disease diagnosis

Genetic testing is already an option for mendelian sub-sets of common diseases. Polygenic scores to aid diagnosis of coeliac disease[5] and familial chylomicronemia syndrome [18] have been developed but are not yet evaluated. Polygenic scores could also aid diagnosis of certain Mendelian disorders which have an underlying polygenic architecture. For example, familial hypercholesterolemia where a single pathogenic mutation has not been identified but multiple pathogenic SNPs contribute to the disease [18, 19], or to further refine diagnosis e.g. for people already diagnosed with diabetes [20].

Informing selection of therapeutic intervention

Better targeting of treatment strategies is a key area in which genomics can contribute to healthcare. It is recognised that polygenic scores can provide additional discrimination or risk stratification which could enable more precise targeting of therapies in clinical trials as well as clinical care. The most widely cited example of this is in primary prevention of coronary artery disease (CAD) where studies have shown that polygenic scores may help better refine identification of individuals who are at greater risk and are therefore more likely to benefit from statin therapy [3, 21-23].

Improvement of risk prediction

Polygenic scores could be incorporated into existing risk prediction tools. As many diseases are known to have both a genetic and an environmental contribution, the incorporation of a polygenic score as an additional biomarker may improve the predictive ability of risk tools. This requires proper assessment of the polygenic score prior to incorporation followed by suitable validation, evaluation and assessment of the comprehensive tool as well as determination of whether the polygenic score adds value. The tool can then be used to better stratify individuals. It has already been demonstrated that prediction is improved with incorporation of polygenic scores in breast cancer [24, 25].

Our genetic make-up is to a large extent stable from birth and dictates a "baseline risk" on which external influences act upon and modulate. Thus, genetic information could act as standalone risk predictor, as is the case for a vast majority of heritable disorders. Polygenic scores could provide an avenue for exploring this baseline risk for common diseases, and could enable early risk prediction in situations where other biomarkers are lacking.

Informing disease screening

A polygenic score may have utility in terms of informing the decision to initiate screening recommendations. For example, in breast cancer, current mammography-based screening programmes have an age-based criterion for initiation of screening. This is based on consideration of the balance between risk of breast cancer at various age thresholds and the harms of false-positive results from mammography. The use of polygenic scores as part of integrated risk models could identify a proportion of 40 year old women who are at the equivalent (or increased) level of risk as an average 50 year old woman and therefore could benefit from earlier screening. Therefore, polygenic scores may contribute to improving cancer screening programmes such as breast and colorectal cancer [12, 26] via risk-stratified screening programs. There is already some evidence that adopting a risk-stratified screening strategy could improve cost-effectiveness and the benefit-to-harm ratio of breast screening programs [27], and reduce overdiagnosis in prostate cancer [28].

Informed life planning

Polygenic scores may have utility at a personal level even if they do not yet have utility at the population level. They could provide information on risk of developing a disease that may not yet have a clinical intervention. For example, some people may want to know if they are at increased risk of diseases such as Alzheimer's disease for the purposes of life-planning, e.g. informing financial, legal or care planning.

2.6 Summary

There is rapid progress in the development of polygenic scores both due to the availability of larger datasets, primarily from GWAS and concomitant developments in statistical methodologies. As understanding and knowledge develops, the usefulness and appropriateness of polygenic scores for different diseases and contexts are being explored. Nevertheless, this is still an emerging field, with a variable evidence-base. Prior to clinical implementation, each disease-specific polygenic score will need to be carefully and thoroughly tested and validated as well as assessed for clinical utility.

3 Concepts related to critical appraisal of polygenic scores

As described in the previous section, polygenic scores are of particular interest as a potential method of risk assessment, either by themselves or as part of existing risk assessment tools. In this section, we give a brief overview of frameworks and concepts that inform critical appraisal of emerging applications of polygenic scores.

Key points

- Genetic test evaluation frameworks along with frameworks for evaluation of risk prediction models can be used for the appraisal of polygenic scores
- There is still debate as to the details of the evaluation required for risk prediction tools
- Key parameters require description at the outset to enable evaluation specific to the context and population in which polygenic scores are to be applied

3.1 Evaluation of genetic tests

Rapid developments in genetic testing technologies led to the need for frameworks to assess the benefits, risk and limitations of using these tests in clinical practice and public health. These frameworks enable assessment of the available evidence base, ensure responsible implementation of tests with proven benefits, and can guide translation into clinical practice.

The most widely used framework is the ACCE (referring to Analytic validity, Clinical validity, Clinical utility and Ethical, legal and social implications) model developed by the US Centers for Disease Control and Prevention [29, 30], which examines key parameters of test performance and wider implications of the use of the test. These are outlined below.

- **Analytic validity** defines the ability of a test to accurately and reliably measure the genotype of interest. Evaluation measures include analytical sensitivity and specificity
- **Clinical validity** defines the ability to detect or predict the presence or absence of the phenotype, clinical disease or predisposition to disease. Evaluation parameters include clinical sensitivity and specificity, positive predictive value and negative predictive value
- **Clinical utility** refers to the likelihood that the test will lead to an improved outcome - it considers the risks and benefits of testing. Parameters that may be examined include: consideration of the effectiveness of interventions available for those who test positive; the implications of a positive or negative finding for individuals; and economic evaluation. Evaluations of clinical utility vary due to differing views of what constitutes an improved outcome

- Examination of **ethical, legal and social implications** also form an important aspect of evaluation. This includes considering wider factors that impact on or are impacted by the availability of the test, such as access to testing and treatment, risk of discrimination and legal issues regarding consent and ownership of data

The evaluation of genetic tests is the same as for any other medical test and aims to enable objective assessment of the evidence prior to implementation. An important consideration for evaluation is clear definition of the disease or trait, population and purpose [31]. Context and purpose are particularly important in test evaluation, as these parameters affect interpretation of the test performance characteristics as well as wider considerations around implementation.

3.2 Congruence of genetic testing and risk prediction

It is well established that genetics is an important contributor to biological risk and hence knowledge of genetic factors can contribute to risk prediction. There are three broad approaches that could be applied to assessing risk for common diseases using genetic information:

- Analysis of a limited number of genes – this approach is usually useful where there are a limited number of known high-penetrant variants that have a significant impact on risk. Testing for variants in genes that significantly increase susceptibility to common disease is established practice in management of certain conditions e.g. *BRCA1/2* testing in management of those considered to be at high risk of breast cancer

- Analysis of multiple genetic loci – polygenic scoring methods that bring together information on multiple low penetrance loci that individually have a minimal impact on risk. This approach is yet to be established and is in its early days

- Integrated risk prediction – integration of genetic information along with other risk factors to inform risk assessment. This approach is used to a limited extent in the context of management of high risk individuals e.g. in the integration of genetic information with risk tools such as BOADICEA and Tyrer-Cuzick [17, 25]

Genetic test evaluation frameworks have largely been used in the context of tests developed for Mendelian disorders. The high penetrance and the rarity of the genetic variants assessed in tests for Mendelian diseases, or hereditary forms of common diseases, mean that in this context genetic testing is usually diagnostic or very highly predictive, as the assumption is that the presence of the variant is likely to be indicative of current or future disease. This assumption is supported by knowledge of the biological impact of these variants, which is often deleterious and sufficient by itself for disease manifestation. Hence they are usually evaluated using metrics that assess their ability to discriminate between diseased and non-diseased individuals.

Individuals with hereditary forms of common disease are often managed on the basis of their familial risk. Analysis of specific genes can provide additional information that can be used in assessing risk and informing subsequent management. In this context, possession of certain deleterious germline variants in key genes (e.g. DNA repair genes in the case of hereditary cancers) substantially increases susceptibility to disease. The biological impact of variants in these genes in most instances (but not all) will have been elucidated. Thus genetic testing although not diagnostic on its own, can by itself inform risk assessment; however, it is recognised that integration of this information with other risk factors can better inform risk assessment. The most well-known example is mutations in the *BRCA1* and *BRCA2* genes, both tumour suppressor genes, and risk of developing breast cancer in individuals with a family history of cancer.

In contrast, most common complex disorders are influenced by multiple low penetrance variants and by environmental factors. In addition, the mechanisms whereby these variants contribute to disease risk are largely unknown [32-34]. As such, polygenic scores in such contexts cannot be considered a diagnostic marker, but as a predictive measure that provides a wider range of probabilistic risk information. This together with the fact that common diseases result from an interplay between genetic and environmental factors, mean that disease manifestation is not as strongly linked with the presence of particular variants. Thus their evaluation requires considering parameters that are applied to risk prediction models.

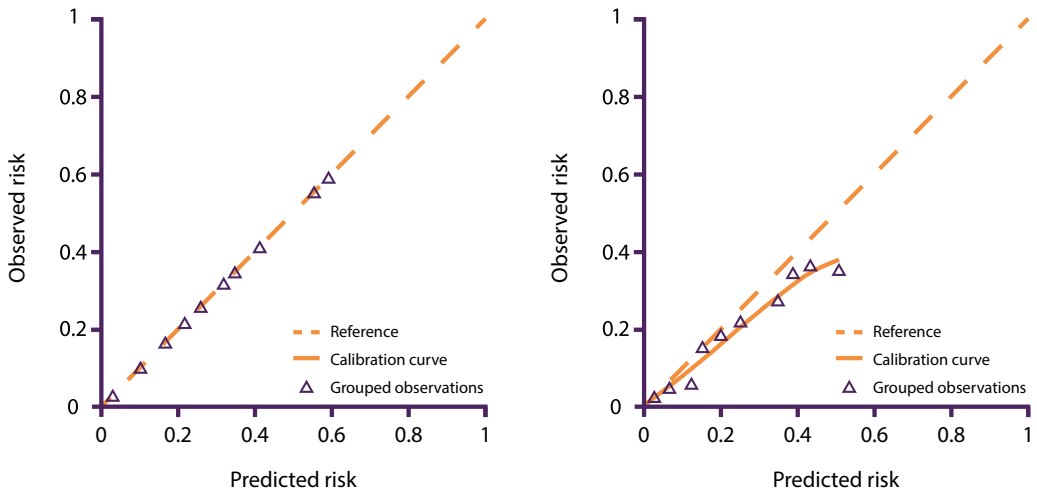
3.3 Evaluation of risk prediction models

Evaluation of risk prediction models involves examining both statistical validity (model performance) as well as clinical validation. Statistical validation involves comparison of predictions from the model with true outcomes in order to assess how well the model functions in predicting risk. Clinical validation is usually assessed using the same statistical measures but with particular clinical contexts in mind – i.e. is the prediction accurate enough for its purpose? The same principles are applied to evaluating polygenic scores, either by themselves or when necessary as part of a risk tool. Below we provide an overview of the key questions the evaluation process aims to answer and the metrics used in the evaluation process.

Calibration – how well does the model fit the data?

'Model fit' examines discrepancies between predicted and observed values and is usually examined by plotting observed risk against predicted risk. Well-calibrated prediction models have a slope = 1, with predicted risk falling along the reference line (Figure 3). If predictions are higher or lower than observations, there is deviation from the reference line indicating over and under estimation, respectively. Calibration in an external dataset (external validation) is important to assess if the model functions as well outside of datasets in which it was developed.

Figure 3: Calibration plots (adapted from Janssens & Martens[35])

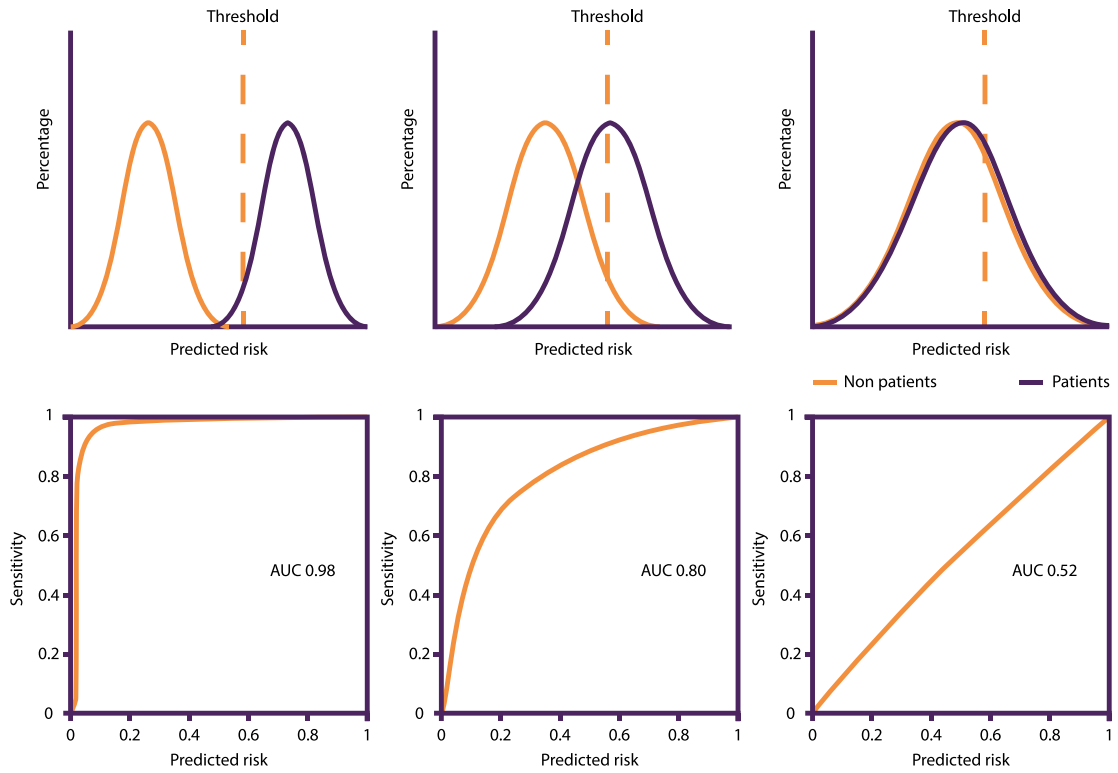


What is the discriminative accuracy of the model?

The discriminative ability of a model indicates the ability of the model to distinguish between those who will develop the disease or not develop the disease. The risk distribution will vary in cases and controls (Figure 4), with cases having a higher risk than controls. Nevertheless, some people at high risk will not develop the disease and some at low risk will develop the disease. The separation between these two curves indicates ability to discriminate between future cases and controls. This is measured by the area under the receiver operating curve (AUC) – also known as the C-statistic or C-index – which ranges from 0.5 (no discriminative ability) to 1 (perfect discriminative ability). Models which produce risk distributions for cases and controls with less overlap (so better discrimination) result in a higher AUC.

The receiver operating curve (ROC) presents sensitivity (true positive rate) against 1-specificity (false positive rate), for different risk thresholds. Combinations of sensitivity and specificity at different thresholds could be examined to see if they are favourable. This is useful as clinical decisions are often made in categorical or dichotomous ways and have thresholds, hence it can be useful to know the number of people above or below particular thresholds.

Figure 4: Risk distributions and area under the ROC curve (AUC) (adapted from Janssens & Martens[35])



Importantly AUC provides information of the discriminative capacity and does not summarise the clinical impact of the model, as there is no set threshold for AUC that can be considered optimal. The optimal AUC is dependent on the intended use of the model. Situations where accurate disease classification is needed – e.g. diagnosis or identification of sub-groups for an expensive intervention – will require a higher AUC. Conversely, population stratification into risk categories for differential management where interventions are inexpensive or have little harm may not require as high an AUC.

What is the predictive ability of the model?

The predictive ability of a model is assessed by examining the distribution of predicted risks in the population. Larger variation in predicted risk (i.e. greater spread) is needed for higher predictive ability. As the variance of the risk distribution defines its spread, it is a key determinant of performance. Larger variation in predicted risk is needed to distinguish between individuals.

As described above, AUC is the most commonly used measure of predictive ability of a model. Increases in AUC are often examined to assess improvements in predictive ability of models when new predictors are added or to compare two models. However, this metric has been criticised as being an insensitive measure that is not able to fully capture all aspects of predictive ability [36]. This is because increases in AUC are usually small when predictors with small effect size are added, especially if the existing model is already able to discriminate between cases and controls effectively.

This has led to the development of alternative metrics to evaluate model performance such as increase in risk difference or integrated discrimination improvement (IDI). IDI compares the difference in average predicted risk for cases and controls for two prediction models. For example, average risks in models with and without genetic factors can be compared. If the addition of genetic factors results in better separation of cases and controls, this would result in a positive IDI value. If there is an increase in risk differences between the two models, this serves to indicate improved discriminative capacity has been achieved.

The above measures examine improvements in predictive performance of a model; model performance may also be evaluated by examining impact on reclassification of individuals across thresholds. Examination of reclassification using measures such as net reclassification index (NRI) can allow assessment of whether the addition of predictors results in differential classification of individuals across thresholds. For example, the addition of predictors (e.g. polygenic score) to an existing model (e.g. QRISK) can lead to changes in risk distribution and predicted risks, this in turn can lead to re-classification of events across thresholds, which in turn can lead to different treatment decisions. Measures such as the NRI assess the improvement in discrimination for specific risk thresholds, but are influenced by the value and number of thresholds.

What is the model performance in external datasets?

As model fit and performance are usually better in the dataset the model was developed in, external validation in an independent dataset enables further assessment of performance. Internal validation uses a different subset of data from the same dataset used to derive the model, whereas external validation utilises an independent dataset. External validation is important to assess generalisability of the model.

Does the model lead to a change in clinical practice?

The clinical utility of a risk model depends first on its ability to accurately and correctly stratify a population. Correct stratification then allows for division into categories with sufficiently distinct risks that there is an impact on provision of interventions. Division into various risk categories can be done for a number of reasons. This depends on various factors, including the absolute risk of disease, the available strategies for disease prevention in the population and the risk-benefit implications of the interventions.

Adequacy of these models is often assessed using metrics of diagnostic performance such as sensitivity and specificity, which fail to account for clinical utility of a specific model. Further evaluation methods are widely used when assessing utility, such as use of decision curve analysis (DCA). In this framework, a clinical judgment of the relative value of benefits (treating a true positive case) and harms (treating a false positive case) associated with prediction models is made. As such, the preferences of patients or policy makers are accounted for by using a metric called threshold probability. A decision analytic measure called net benefit is then calculated for each possible threshold probability, which puts benefits and harms on the same scale [37].

3.4 Gaps in evaluation of risk prediction models

Similar to other healthcare practices, evaluation and assessment of predictive models are required prior to their clinical translation and implementation. Measures for clinical utility include: decision curve analysis, net benefit, impact on decision making and cost effectiveness. However, clinical outcome measures are not always necessary and will rely on the context in which risk prediction is being done. Poor discrimination and calibration result in poor clinical utility but excellent discrimination and calibration does not always result in good clinical utility.

The lack of data, methodological limitations and resources to comprehensively evaluate prediction models act as bottlenecks to effective translation, especially given the lack of clarity on criteria that need to be met by risk prediction models [38]. Attempts are being made to address this issue, and several academic papers have explored the different phases of model development and methods of assessing model performance. In addition, criteria for reporting of studies developing, validating or updating predictive models have also been produced [39]. The TRIPOD statement was released in 2015 with the aim of improving transparency in the development and validation of prediction models through better reporting. It is a checklist of 22 items deemed essential for the transparent reporting of a prediction model study.

These have been produced in order to enable relevant experts to more easily critically appraise and identify appropriate models for use in clinical practice. Whilst these existing efforts provide some guidance to researchers on parameters that need evaluating and to decision makers on selecting particular tools, a number of issues still remain in relation to the evaluation process. In particular, more clarity is needed on when risk prediction models can be considered to be valid or validated sufficiently for incorporation into a clinical risk calculator and how they can be implemented into a clinical pathway.

3.5 Summary

Evaluation of risk prediction models and assessment of whether it is clinically useful to incorporate genetic information in the form of polygenic scores into prevention programmes requires consideration of available evidence. Existing frameworks for evaluation of risk prediction models provide mechanisms for evidence appraisal. However, there is still debate as to the appropriate degree of evaluation required for risk prediction tools and the extent to which this can be fulfilled, especially in research settings. Nevertheless, key parameters that require description at the outset to enable evaluation are specific to the context and population in which polygenic scores are to be applied [39]. This enables clarification of the clinical changes that are expected as a result of using this information, thereby providing assessment of the clinical utility associated with the use of the tool.

Knowledge of intended use can also guide assessment of whether the improvement in predictive ability is sufficient to be useful in clinical care. For example, modest increases in predictive ability could still be useful in certain contexts, e.g. risk stratification to inform mammographic screening. In other instances it may not be enough to inform practice where more certainty is required, for example informing decisions to undertake prophylactic mastectomy. In practice these decisions may also be individualistic and heavily influenced by individual patient preferences. This suggests that contextual issues surrounding the delivery of the polygenic score may be particularly important. Some of these issues are explored in section 7. Furthermore, exploration of contextual issues can also enable decision makers to assess whether investment in obtaining genetic information can add value to specific prevention programmes and the mechanisms through which this will be achieved.

4 Cardiovascular disease

This report examines the readiness for clinical implementation of polygenic scores developed for cardiovascular disease. In the previous sections we set out key background information on polygenic scores and their evaluation. In this section and the next we provide an overview of cardiovascular disease (CVD) in England, its risk factors and their relevance to disease prevention. Understanding this landscape is useful in appraising the value of polygenic scores for prevention.

Key points

- CVD is not a single disease. It is a collective term for a set of heterogeneous diseases with different but frequently overlapping pathogeneses, all affecting the heart and/or blood vessels
- Rare monogenic conditions account for a small proportion of the morbidity and mortality burden of CVD, which are in the majority common complex diseases
- The genetic and environmental influences on CVD risk are many, overlapping and complex; meaning that determining and measuring risk for specific forms of CVD requires careful consideration

4.1 Introduction

Cardiovascular disease is a broad term for a group of conditions affecting the heart and/or blood vessels, which can negatively impact on the function and efficiency of the circulatory system.

Major forms of CVD are outlined below:

- **Ischaemic heart diseases**, also referred to as **coronary heart disease (CHD)** or **coronary artery disease (CAD)**, are diseases caused by narrowing of the coronary arteries due to atherosclerotic plaques. Complete blockage can lead to myocardial infarction (heart attack)
- **Cerebrovascular disease** is a collection of conditions affecting the blood vessels supplying the brain; this includes: stroke (ischaemic and haemorrhagic), cerebral atherosclerosis, cerebral infarction, and transient ischemic attack
- **Hypertensive diseases** result from chronic high blood pressure, these include hypertensive heart disease (heart failure, left ventricular hypertrophy) and chronic kidney disease
- **Peripheral arterial disease**, or peripheral vascular disease, results from fatty build up in the blood vessels and restricts blood supply to the arms and legs
- Other diseases of the peripheral vascular system include **clotting disorders** such as deep vein thrombosis, which describes the formation of blood clots in the leg veins; clots can dislodge and move to organs such as the lungs, resulting in pulmonary embolism
- **Rheumatic heart disease** is caused by damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria

Other forms of CVD include rare diseases, congenital heart diseases and cardiovascular components of clinical syndromes affecting multiple systems. Major preventable forms of CVD include CHD and cerebrovascular diseases. These share similar pathophysiological features and underlying risk factors.

4.2 Epidemiology of cardiovascular disease in England

In 2014, CVD was the second most common cause of mortality in England [40, 41]. Furthermore, it has been identified as one of the main causes of premature mortality (i.e. mortality in those under 75 years). A proportion of these premature deaths are preventable through addressing risk factors for the major cardiovascular diseases, such as stroke and CHD. Trend data show that the number of people dying from CVD has fallen markedly over the past several decades and increasing numbers of people are living with CVD due to improvements in survival rates following CVD-related events [41].

Table 2 shows mortality associated with different types of CVD in England. The primary causes of CVD-related death are coronary heart disease and stroke (including all cerebrovascular disease). These are responsible for nearly 85,000 deaths per year in England, around 24,000 of which are in people under the age of 75 (Table 2). These diseases also carry notable morbidities - interrupted blood flow can cause significant damage to tissues deprived of oxygenated blood and, in the case of stroke, may lead to brain damage and associated consequences such as paralysis and difficulties with communication. More generally, poor cardiovascular health can also lead to chronic kidney disease, peripheral arterial disease and the onset of vascular dementia. Large numbers of deaths are also associated with 'other heart diseases'; this group encompasses a broad range of conditions including pulmonary diseases, valve disorders and cardiomyopathies.

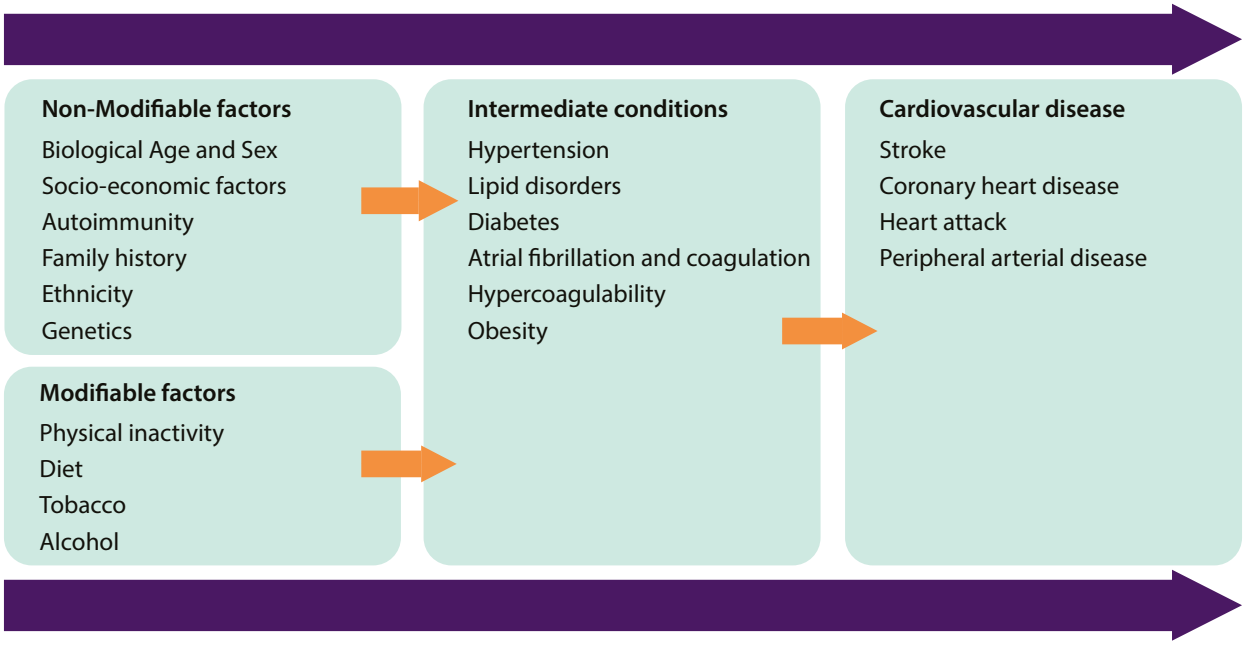
Table 2: Mortality associated with different forms of CVD, England, 2016. Source: British Heart Foundation [40]

Condition (ICD Code)	Deaths all ages	Deaths under 75
All cardiovascular disease (I00-I99)	124615	33812
Coronary heart disease (I20-I25)	53668	17922
Stroke (I60-I69)	30439	6187
Other heart diseases (I26-I52)	23047	4827
Diseases of arteries, arterioles and capillaries (I70-I79)	7633	1938
Hypertensive diseases (I10-I15)	6296	1359
Diseases of veins, lymphatic vessels and lymph nodes (I80-I89)	2764	1368
Chronic rheumatic heart disease (I05-I09)	747	209

4.3 Overview of risk factors for cardiovascular disease

Many risk factors are common across cardiovascular disease, with both inherited and acquired factors contributing to risk of developing pathology or intermediate disease states that influence the likelihood of an adverse event (Figure 5).

Figure 5: Summary of major risk factors for cardiovascular disease



Adapted from Health Hub: Healthy Living www.healthhub.sg/live-healthy/16/screening_heart_disease

The common pathophysiological feature of most cases of preventable CVD is atherosclerosis, whereby plaques consisting of fatty deposits, inflammatory white blood cells and smooth muscle cells develop inside the lumen of an affected artery. Continual rupture and healing of atherosclerotic plaques progressively reduces the lumen diameter, which limits blood flow through the artery and reduces its capacity to meet tissue-oxygen demands. Temporary oxygen deprivation (hypoxia) of organs supplied by atherosclerotic arteries can result in symptomatic CVD, such as angina pectoris and transient ischaemic attacks. Formation of a blood clot (thrombosis) at the site of plaque rupture can lead to complete occlusion of the artery and acute cardiovascular events such as myocardial infarction and stroke [42, 43].

Numerous factors are known to increase the likelihood of developing atherosclerosis. These include non-modifiable factors such as age, sex, family history, socio-economic factors and ethnicity, and modifiable risk factors such as other conditions (e.g. hypertension and diabetes) and lifestyle behaviours (e.g. tobacco and alcohol use).

4.4 Non-modifiable risk factors

Biological sex and age

Men and women are differently susceptible to certain types of CVD. Premenopausal women are generally at lower risk due to the protective effects of circulating oestrogen. However, in post-menopausal women, factors such as increased blood pressure and change in composition of lipoproteins contribute to higher risk of certain types of CVD such as stroke. Men are at increased risk of developing CVD when compared to women across all but the older age groups; overall, risk of developing CVD increases with age [44]. Mortality rates differ between the sexes for different types of CVD; each year in the UK, more men are recognised as having died as a result of CHD than women, whilst the reverse is true for stroke. Sex and age may also influence the predictive value of some modifiable risk factors.

Socio-economic factors

People of lower socio-economic status (SES), as determined by education level, employment status and income, are at greater risk of CVD and are likely to have poorer outcomes following disease. This has previously been attributed primarily to differences in diet across the spectrum of socio-economic status and its impact on the pathogenesis of CVD. However, it is likely that a number of other mediating factors such as smoking are involved in modifying risk [45, 46], suggesting a more complex relationship with cardiovascular health. Exclusion of other major risk factors has suggested an independent role for SES in CVD risk, showing that measures of SES capture influencing forces in ways that other major risk factors do not. It has been suggested that current interventions do not adequately account for SES as an independent risk factor for CVD and do little to mediate its impact [47]. The extent to which SES impacts CVD risk may differ geographically [47].

Autoimmunity

Autoimmunity describes conditions in which the body's immune system attacks and damages healthy tissue. People with autoimmune conditions such as lupus and rheumatoid arthritis are at greater risk of developing CVD due to autoimmune-driven tissue damage, greater systemic inflammation, and as a consequence of chronic use of steroid-based medications. Joint/muscle pain and fatigue may also lead people with autoimmune conditions to lead more sedentary lifestyles, which additionally increases the risk of CVD [48].

Family history

Individuals with relatives who have suffered from cardiovascular disease before the age of 55 for male relatives, or 65 for female relatives, are considered to be at higher risk of CVD themselves. Family history of CVD can indicate inherited genetic risk. It can alter risk of CVD independently or through their influence on conditions that increase risk such as high cholesterol or high blood pressure [44].

Ethnicity

Ethnicity is a recognised risk factor for CVD; for example, people with South Asian heritage are at greater risk of CHD and other types of CVD, and people of African-Caribbean heritage are at an increased risk of stroke, compared to ethnically European populations. Increased risk is likely due to a mixture of biological, environmental and cultural factors. For example, there is an increased prevalence of diabetes in these populations and, in some, presence of higher-than-average blood pressure [44]. However, these factors do not fully explain perceived differences in CVD morbidity and mortality between ethnic groups [49].

Genetic architecture of cardiovascular disease

Genetic factors contributing to CVD risk range from rare high penetrance variants responsible for inherited cardiovascular conditions (e.g. familial hypercholesterolemia, hypertrophic cardiomyopathy) to common low penetrance SNPs that modulate risk of CVD in those with common forms of disease. There is considerable genetic heterogeneity underlying many inherited cardiac conditions. Disease may be caused by mutations that impact on the functioning of components of the electrical and contractile system of the heart or its vasculature, or as a result of mutations in genes that impact on cholesterol metabolism [50].

This complexity and heterogeneity is also reflected in common forms of CVD. GWAS have led to identification of a large number of SNPs associated with CVD. This relates both to SNPs that are associated with sub-types of CVD (e.g. CAD) as well as traits that increase risk of CVD overall (e.g. hypertension, high blood cholesterol etc.) [51]. In CAD, common SNPs (present in >1% population), have been reported to explain approximately 30-40% of heritability, whilst rare variants, which have a more substantial impact on individual risk, explain a much smaller proportion of heritability of CAD [32, 52, 53]. It is expected that some of the 'missing heritability' of CAD will also be accounted for by common SNPs yet to be associated with the disease [52].

The exact role of these SNPs in physiological pathways is yet to be elucidated [32], however many have been linked with risk factor pathways pertinent to CVD. For example: SNPs in the *CHN2* gene have been associated with altered carotid intima-media thickness (measurement of the innermost walls of the carotid artery); SNPs in *APOA5* are associated with altered blood lipid levels [54, 55]. Loci identified through GWAS have also been linked to lipid metabolism and blood pressure. There is considerable overlap between loci identified through GWAS and those identified through studies in families. However, studies indicate that different SNPs within the same gene/loci may be associated with, or known to be responsible for, consequences of markedly different magnitude. For example, rare mutations in the *FBN1* gene cause thoracic aortic aneurisms whereas common SNPs in some non-protein-coding regions within a gene (known as introns) of *FBN1* are associated with spontaneous, non-syndromic thoracic aortic aneurism [32, 55, 56].

The clinical relevance of knowledge of genes implicated in common forms of CVD is still a point of debate. A better understanding of their physiological function may lead to new therapeutic targets. With respect to risk of CVD, variants associated with increasing risk of CVD are thought to be comprised of a mixture of common, low frequency and rare variants. Individually, many of these gene variants do not have a large impact on disease risk, but in combination can contribute to risk – i.e. as with many other complex diseases, CVD risk is believed to have polygenic architecture.

4.5 Modifiable risk factors

Physical inactivity

Individuals who are physically inactive are more susceptible to developing CVD. An increase in physical activity through exercise is associated with reduced blood pressure, lower LDL levels, and lower resting heart rate, and ultimately with reduced risk of CVD. Increasing activity levels is especially effective in reducing CVD risk in those who are physically inactive. Although physical inactivity is strongly tied to obesity, it remains an important independent contributor to CVD risk [57, 58].

Diet

Certain dietary components can influence CVD risk. Diets high in saturated fats, sugars and low in fibre have been linked to increased risk of hypertension and abnormal cholesterol levels. These in turn contribute to risk of CVD [59]. Recommendations around 'healthy eating' change frequently. However, a diet low in saturated fats, sugar and sodium, but high in fibre and polyunsaturates, are often recommended for reducing risk of CVD.

Tobacco

Chronic tobacco smoking results in damage to the arteries, promoting atherosclerosis. Components of tobacco smoke, such as carbon monoxide and nicotine, increase stress on the heart and reduce blood-oxygen levels, respectively. In addition, smoking is contributory to many other factors associated with increased risk of CVD. A global study published in 2005 suggests that in the year 2000, over one in ten deaths from CVD were attributable to smoking [60]. Cessation of smoking significantly reduces risk of many forms of CVD, including stroke and heart attack [44].

Alcohol

It is broadly acknowledged that high levels of alcohol consumption increase individual risk of CVD. High levels of consumption are linked to high blood pressure and tissue damage, and contribute to weight gain. Light consumption of alcohol has been associated with a reduced risk of developing CVD compared with those who abstain - this is thought to be due in part to associated anti-coagulant effects of alcohol. However, interacting genetic factors mean that for some groups, reduction in alcohol consumption across all levels of consumption is associated with reduced CVD risk [61].

4.6 Intermediate conditions

Hypertension

Hypertension is defined as persistently high blood pressure and can be classified into different stages of severity. Hypertension is associated with stiffening and thickening of vascular and ventricular walls, increasing the risk of CVD types such as CHD, stroke, arrhythmias and vascular dementia [62]. Blood pressure medications and lifestyle changes (including diet and exercise) may be prescribed to those with consistently high blood pressure. Hypertension is more prevalent in people who are older, either male or post-menopausal women, or of African-Caribbean descent.

Hypertension itself is influenced by other factors including high dietary sodium intake, obesity, insulin resistance, physical inactivity and heavy alcohol consumption [63]. Obesity and abdominal obesity are major independent contributors to hypertension [64, 65]. In a minority of cases, hypertension can occur secondary to other diseases such as chronic kidney disease, or as a result of rare monogenic hypertensive syndromes [66].

Lipid disorders

There are several different lipid disorders which contribute to increased risk of CVD. These include conditions such as hypercholesterolemia and hyperlipidaemia – which come in differing forms and have differing contributing risk factors, such as alcohol consumption, obesity, and type 2 diabetes, in addition to non-modifiable genetic and demographic risk factors [67]. Abnormal levels of low-density lipoproteins, cholesterol and other circulating lipids promote formation of atherosclerotic plaques, and consequently the risk of developing CVD. Lipid disorders may be treated with statins or other medications, and lifestyle modifications, which can reduce the risk of CVD [68].

Diabetes

Diabetes is a condition in which chronically elevated levels of blood glucose (hyperglycaemia) results from insulin deficiency or resistance. Type 2 diabetes (T2D) is the only preventable form of diabetes, and is most common in older adults, individuals who are obese, who have experienced gestational diabetes and in people of South Asian, African or Caribbean descent [69]. Individuals with T2D have a two-fold higher relative risk of developing CVD, which is the predominant cause of morbidity and mortality in people with the condition [70]. T2D can be altered through lifestyle modifications e.g. weight loss, smoking cessation and physical activity, and the use of anti-diabetic drugs.

Atrial fibrillation and coagulation

Atrial fibrillation (AF) is an irregular heartbeat that may be periodic or persistent. One in five of all strokes is attributed to atrial fibrillation [65]. Obesity, high blood pressure and excessive alcohol consumption influence AF risk, which in turn increases risk of serious cardiovascular events such as stroke and heart failure [71, 72]. AF is more prevalent in those over the age of 65, in people with other heart conditions, and a selection of other medical conditions [73]. Morbidity and mortality risk from AF comes from the increased risk of clot formation, which itself has several contributing risk factors, including readiness of blood clot formation.

Hypercoagulability

Increased readiness of clot formation or thrombosis is an independent risk factor for CVD and can exist as a result of inherited or acquired defects that impact on the clotting process. Inherited genetic variants that increase the likelihood of clotting, such as in Factor V Leiden thrombophilia where absence of an anti-clotting protein leads to hypercoagulability, are associated with a modest increase in risk of some types of CVD. However, inherited bleeding disorders such as haemophilia are protective provide some protection against certain types of CVD. A wide range of factors can increase risk of developing acquired hypercoagulable conditions, these include: advancing age, smoking, pregnancy, undergoing orthopaedic surgery, and more [74].

Obesity

Obesity contributes substantially to the prevalence and severity of other risk factors for CVD. Being overweight is strongly associated with increased blood pressure, abnormal blood-lipid levels and development of type 2 diabetes [75]. Obesity can also lead to insulin resistance and hyperglycaemia, which in turn increase risk of CVD. The relationship between obesity and the many associated mediators of CVD risk is complex, however overall increased levels of obesity are strongly associated with increased risk of CVD. Dietary changes and changes to exercise regimes are recommended to reduce CVD risk associated with obesity and accompanying disorders.

Other risk factors

There are many additional risk factors for CVD for which either research on impact returns inconsistent conclusions, or there is severely limited actionability (for external factors). Examples of these factors include air pollution and HIV positive status. Some studies have suggested that HIV positive status is associated with an increased risk of CVD, with people living with HIV up to twice as likely to develop cardiovascular disease [76]. Where found, increased risk has been attributed to either or both of the consequences of viral infection, such as increased inflammation, and consequences of the use of anti-retroviral drugs, such as dyslipidaemia. However, results have been inconsistent [77]; other work has seen associations between HIV and CVD-linked pathologies such as increased carotid intima-media thickness, but not CVD itself. Others linked use of anti-retroviral drugs to increased CVD risk, but not HIV infection.

The increased concentration of particulate matter, a subset of pollutants produced by both transportation and industry, has been associated with increased risk of CVD and other risk factors for CVD. The extent of adverse health effects has been seen to vary with the size and type of pollutant [78] but is not fully understood. There is little practical advice regarding management of personal exposure to common air pollutants in order to moderate CVD risk.

4.7 Summary

CVD encompasses a number of different conditions for which morbidity and mortality rates differ substantially and for which various factors influence risk. These risk factors can be environmental and/or genetic, may be modifiable or non-modifiable, and may impact risk directly or indirectly. Many risk factors actually alter the risk of developing intermediate conditions to CVD, such as high salt intake leading to higher blood pressure, or certain genetic variants leading to altered lipid metabolism which increases circulating cholesterol. Many known risk factors interact with or influence other risk factors – diet and exercise both contribute to obesity, and smoking reduces levels of high-density lipoproteins which have protective effects against CVD. These examples highlight the interplay between different risk factors in the pathogenesis of CVD. Genetic factors play a large part in CVD risk; both common and rare variants have been shown to impact rates of CVD, accounting for different proportions of heritability. However, in many cases a larger part of risk has been attributed to environmental factors, many of which are modifiable.

5 Prevention of cardiovascular disease

Cardiovascular disease is a common cause of mortality and thus is a focus for public health prevention strategies. Approaches to prevention are varied and involve both broader public health initiatives as well as a focus on identification and management of high risk individuals. In this section we give a brief overview of the approach to prevention in England.

Key points

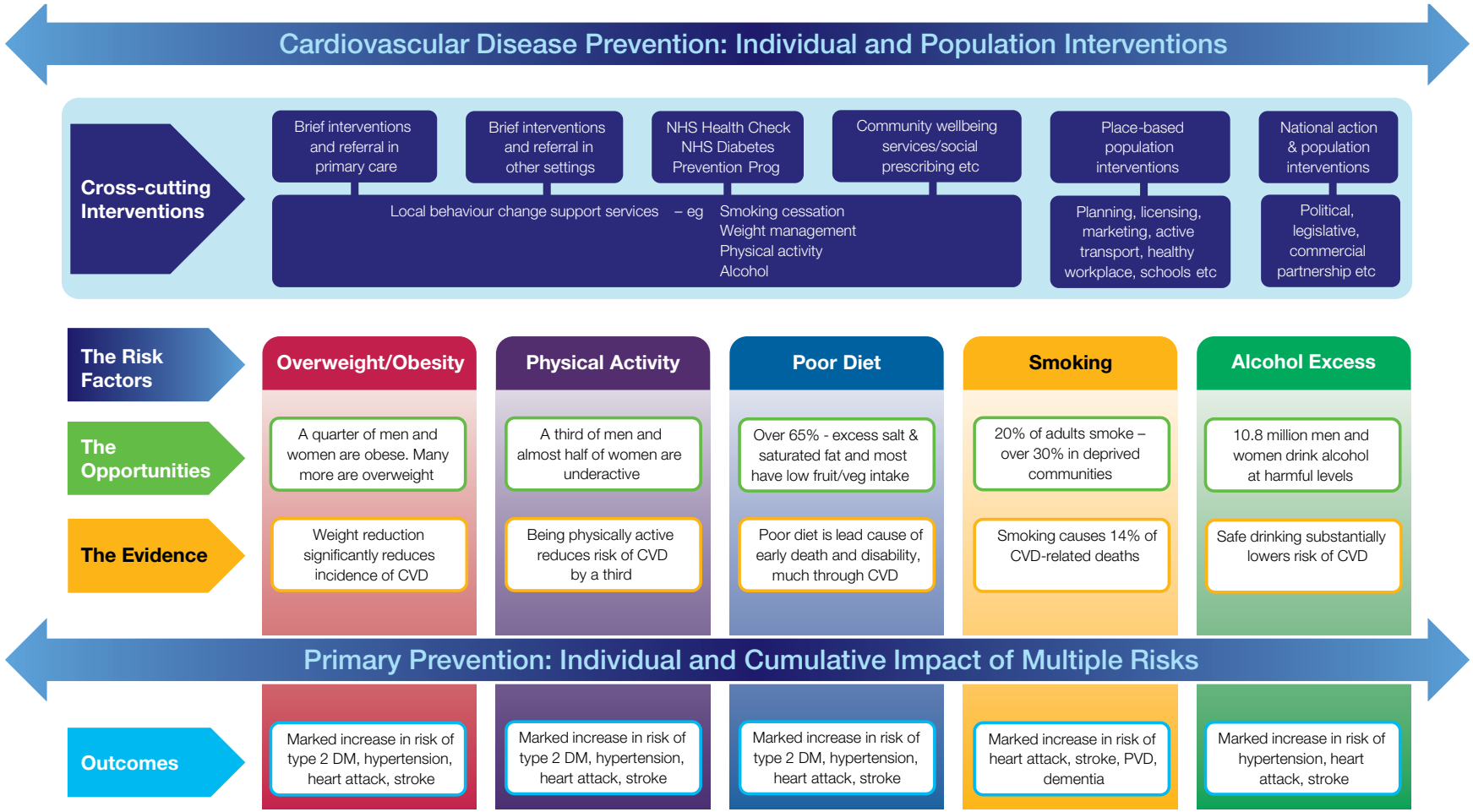
- CVD is a common cause of death and as such a number of interventions and prevention strategies already exist
- The goal of prevention programmes is identification of individuals at risk through multiple approaches, both systematic and opportunistic
- Risk assessment tools play an important role in prioritising and planning primary prevention interventions for CVD

5.1 Overview

Cardiovascular disease (CVD) prevention programmes aim to reduce the occurrence of adverse cardiovascular events that can lead to increased morbidity and mortality. This involves focusing both on high-risk-groups as well as population-wide strategies that address lifestyle risk factors, along with better diagnosis and management of conditions that increase risk of a CVD event. This approach to CVD prevention is believed to enable healthy people to maintain their health and for those at high risk or already diagnosed with CVD to engage in behaviours that reduce risk and/or receive optimal medical management to meet risk factor targets.

Given the wide variety of risk factors that influence cardiovascular disease, their shared influence on other chronic diseases and the impact of wider social determinants, the approach to prevention of cardiovascular disease is holistic. Policy and interventions to address prevention of CVD are multi-sectoral involving a range of different organisations, such as PHE, NHS local government, local communities, professional bodies and health charities. The aim is for a concerted effort with interventions working at different life stages and at a number of different levels including population, community and individual level. Consequently, CVD prevention programmes can be broad ranging and overlap with programmes and initiatives focussed on other conditions or risk factors shared with other diseases (Figure 6).

Figure 6: NHS Right Care CVD risk prevention pathway providing a summary of individual and population prevention interventions (Source: NHS RightCare, CVD Prevention pathway [79])



5.2 Interventions for primary prevention

Interventions to reduce CVD risk include population-wide health promotion initiatives across the life course, provision of timely and sustained lifestyle interventions as well as drug treatments (e.g. statins or anti-hypertensives) for the management of health conditions that can increase risk.

Population-wide health promotion

Population level efforts that encourage healthy lifestyles throughout life are a key part of prevention efforts, given that healthy lifestyles can not only prevent the onset of conditions that increase risk of CVD but also CVD itself. As described above, lifestyle factors such as diet, physical activity and smoking can impact directly on CVD risk as well as indirectly via their impact on health conditions such as hypertension that increase risk of CVD. Population-wide health promotion includes efforts to decrease smoking (e.g. ban on smoking in public places), reduce salt and sugar in foods (e.g. the tax on sugar sweetened beverages), as well as efforts to improve diet and increase physical activity [80].

Such efforts are important in preventing events in those who are at low/moderate risk, reducing the number of cases by slowing down the development of atherosclerosis in young people and by supporting individual level health promotion in those at high risk.

Individual level health promotion

Lifestyle interventions addressing modifiable risk factors may also be offered to those individuals considered to be at higher risk. NICE guidelines recommend providing advice and support in line with national recommendations with respect to alcohol intake, physical activity, weight management, diet and smoking to those at high risk. Support may also be available in the form of smoking cessation programmes and referral to lifestyle services such as weight management and exercise referral programmes [80].

Medical treatment

Statins are the only medical treatment recommended for primary prevention of CVD. Atorvastatin (20mg) is recommended by NICE in those under 85 years who have a 10% or greater estimated 10-year risk of developing CVD [81]. This is due to demonstration of benefit through lowering risk in this population [82]. NICE guidelines recommend the use of the QRISK®2 assessment tool, which enables risk assessment on the basis of multiple factors. Healthcare professionals are also reminded that interpretation of risk scores should always reflect informed clinical judgement. The QRISK®2 tool has been updated (QRISK®3), however, NICE guidelines have not as yet been updated to include QRISK®3. The NICE surveillance report does state that 'The new evidence and topic expert feedback indicates that the inclusion of additional clinical variables in QRISK®3 has a greater potential value to identify those at most risk of heart disease and stroke' [83].

Guidelines do not define what constitutes a normal range for lipid levels, however, those with total lipid levels >9mmol/L or non-HDL >7.5mmol/L are recommended for referral to specialist services.

Other medical treatments that impact on CVD risk include anti-hypertensives and anticoagulants. Reducing blood pressure to within a recommended target range is seen to have benefits for CVD risk. Anti-hypertensives are recommended for those under 80 years of age with stage 1 hypertension and a 10-year CVD risk equivalent to 20% or greater, and those with stage 2 hypertension [84].

The reduction of this risk threshold to 10% is currently being considered. It is recommended that those with stage 1 hypertension under 40 years of age be referred for specialist evaluation, as cardiovascular risk assessment tools can underestimate lifetime risk of CVD events in these individuals. Anticoagulants are recommended for people with AF who are assessed as being at risk of stroke. The management of pre-diabetes, diabetes and chronic kidney disease are also important in addressing CVD risk.

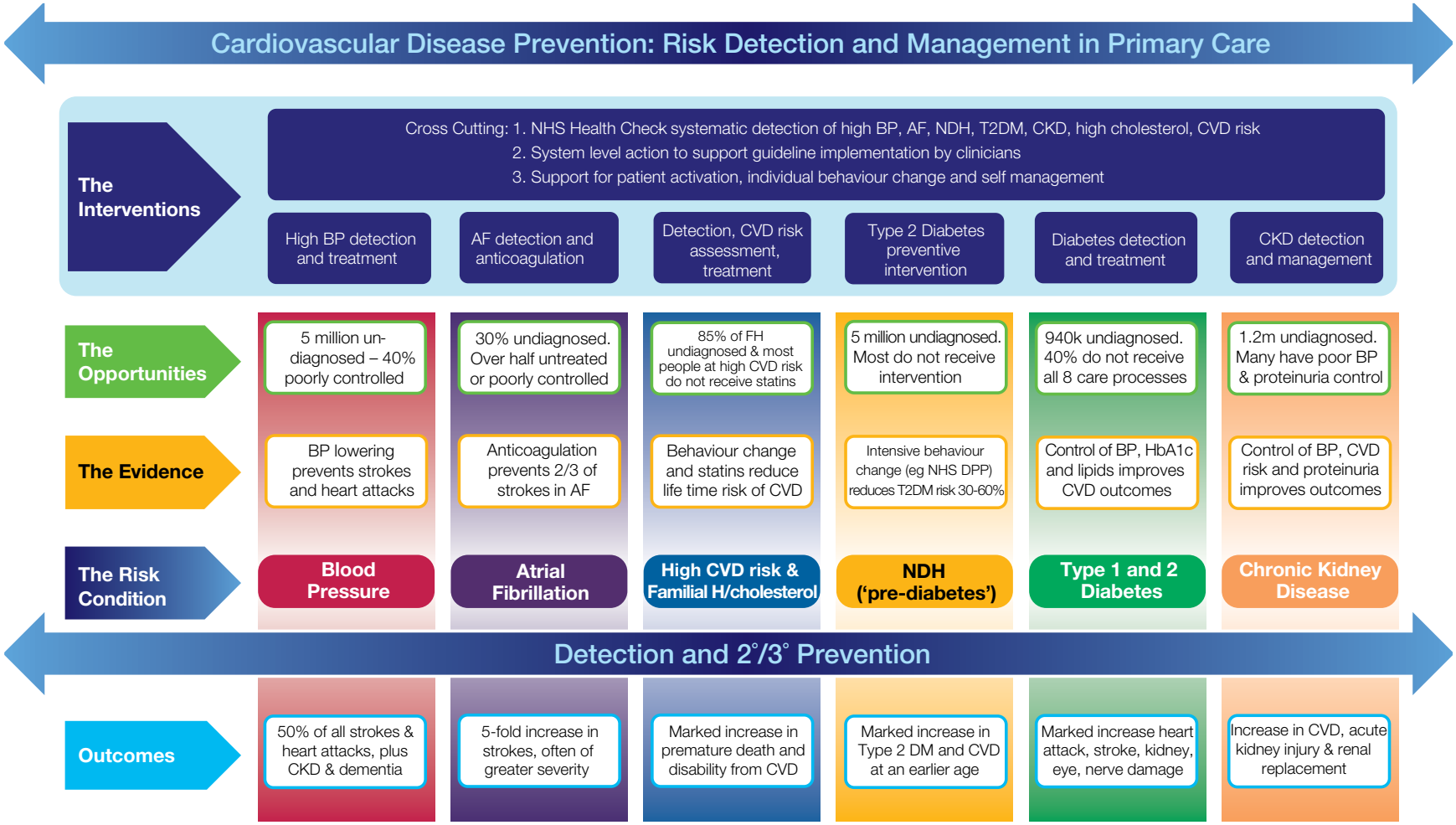
5.3 Identifying individuals eligible for individual-level interventions

A variety of mechanisms are used for identification and management of those at increased risk of CVD. This includes both opportunistic identification of those at high risk during routine visits, for example the 'Making every contact count' initiative encourages GPs to ask about weight, smoking and alcohol in every consultation, as well as more systematic or formal processes. NICE recommends the systematic identification of people who are likely to be at risk of dying early from CVD. This includes those who are disadvantaged due to social circumstances or are considered high risk, defined as having 20% or higher risk of a first CVD event in the next 10 years.

Systematic identification is usually on the basis of CVD risk factors already recorded in primary care electronic medical records. Individuals may then be prioritised for a formal risk assessment for CVD using the QRISK®2 tool. This may also incorporate assessment for signs of conditions known to increase CVD risk, such as diabetes, chronic kidney conditions, or hypertension. The CVD prevention pathway developed by PHE and NHS Right Care outlines initiatives which are focused on improving detection and management of these key conditions – blood pressure, cholesterol, AF, pre-diabetes, diabetes and chronic kidney disease (Figure 7) – mainly through primary care. These are seen as important in achieving goals set for CVD prevention in England.

The NHS Health Checks is another mechanism by which to identify those at high-risk of CVD. This programme offers a free health check for adults in England aged 40-74, not already diagnosed with the above conditions. It is designed to spot early signs of stroke, kidney disease, heart disease, type 2 diabetes and dementia. Support and advice to address risk factors are also part of the programme. Formal risk assessment of CVD using the QRISK®2 assessment tool is recommended every five years in those without established CVD, type 1 diabetes, chronic kidney disease or familial hypercholesterolemia, and below 84 years of age[81]. It is seen as a preventative programme rather than a screening programme for disease, a key aspect of which is risk assessment and management to support people to stay healthy for longer.

Figure 7: NHS RightCare CVD risk prevention pathway providing a summary of risk factors and how these are detected and managed in primary care (Source: NHS RightCare, CVD Prevention pathway [79]**)**



5.4 The role of risk assessment in CVD prevention

Almost all CVD guidelines recommend some form of risk scoring as a way to prioritise and plan primary prevention interventions. Globally, CVD risk assessment (also known as absolute risk assessment, total risk assessment or risk scoring) is an integrated approach that assesses multiple risk factors to determine the absolute risk of experiencing a CVD event in a given period of time [85]. As described above, crude assessment of absolute risk can enable identification of populations eligible for formal risk assessment. More detailed assessment of risk can inform decisions about individual level health promotion and drug treatments, which are usually offered to those individuals considered to be at high risk of CVD. This is because these individuals have the potential to gain the most from interventions. Also, the risk estimate is generally not used in isolation but in combination with clinical features to determine which intervention path to take. This reflects the fact that a risk score needs to be used in conjunction with clinical judgement.

Thresholds for initiating treatment or an intervention are predominately based on 5- or 10-year absolute risk for CVD or the combination of age and additional CVD risk factors [86]. Thresholds to trigger certain interventions can be problematic, since risk is a continuum and there is no threshold at which, for example, a drug is automatically indicated. While no threshold is universally applicable, the intensity of advice should increase with increasing risk [87]. Common cut-offs are categorised into low risk, moderate risk, high risk and very high risk.

The risk threshold chosen for interventions is dependent on resource availability and consideration of the impact of interventions. This is reflected in considerable discrepancies with respect to thresholds in global CVD prevention guidelines [86]. Treatment thresholds in NICE UK guidelines recommend a 10 year CVD event risk of 10%, whereas in the US American College of Cardiology / American Heart Association guidelines it is 7.5%, and in the Scottish Intercollegiate Guidelines Network (SIGN) the threshold is at 20%. These thresholds have also evolved over time, for example in England, the risk threshold for statin treatment has been lowered from 20% prior to 2014 to 10%, making more people eligible for treatment [88]. Furthermore, the form of risk assessment and/or threshold for an intervention may vary in those populations known to have high risk of CVD.

Alternative guidelines that recommend risk assessments also exist for the purposes of screening in disease-specific populations known to have high risk of CVD, namely: dysglycemia (diabetes) screening, dyslipidea screening, and hypertension screening [86]. Generally, risk assessment is not necessary in these individuals as they are already at high risk, but an assessment may assist in decisions about treatments.

5.5 Available risk prediction models and tools

Guidelines mostly agree on the use of a prediction model to aid clinical decision making, however there is no single tool recommended for use, particularly for total CVD risk. Available risk tools differ in their end points and the risk factors they consider in the risk prediction (Table 3) [86]. Traditionally most models estimated CAD risk only; however, a proportion of models have evolved to estimate the risk of multiple different CVD endpoints [87]. Furthermore, even though the use of a risk assessment tool is recommended, the impact of using total CVD risk assessment on long-term patient outcomes is unknown. This is because there is very limited evidence of the effectiveness with evaluation of clinical events as the outcome in randomised controlled trials. Nevertheless, the evidence suggests that targeting high risk patients is an effective way to allocate resources to reduce CVD events [85].

The choice of model/tool to be used is based on considerations around the population it is to be used in, which will impact on its performance. Most risk assessments perform rather similarly when applied to populations comparable to those from which the risk estimation was derived [87]. In England, for example, NICE concluded that the QRISK®2 and Framingham tools did not show major differences, but QRISK®2 showed better performance in terms of calibration and reclassification than the Framingham tool [89]. The Framingham tool is based on a cohort of people from the USA and the calibration is updated approximately every three years, whereas QRISK is derived from a large database of UK GP records and is updated every year and can therefore be considered to be more appropriate for the UK population.

5.6 QRISK

The risk assessment tool QRISK®2, and more recently QRISK®3, have been developed to estimate CVD risk. The QRISK model was initially developed in 2007 and has been updated and recalibrated through the years. The model has been validated by the developers as well as independent groups and databases, both in the UK and internationally. The tool has also been evaluated in observational studies, cost effectiveness evaluations and clinical trials. QRISK®2 is used by health services across England and appears in a number of guidelines [90]. It is integrated in electronic patient record systems which allows for many fields of data entry to be automatically completed for quick assessment.

QRISK®3, a recent update and expansion of QRISK®2, was developed and validated in a prospective open cohort study which used 981 GP practices with 7.89 million patients to develop the risk scores, and 328 practices with 2.67 million patients to validate the scores [90]. CVD, defined as 'a composite outcome of coronary heart disease, ischaemic stroke, or transient ischaemic attack', was the primary outcome assessed.

The various models developed appeared to be well calibrated, and the mean predicted risks and observed risks correspond closely within each model and in each age group, except in those aged 25–39 where mean observed risks were marginally lower than the predicted risks. Overall performance of the updated QRISK®3 algorithms was found to be non-inferior to the QRISK®2 algorithms [90]. The decision to use QRISK®2 in guidelines can be extrapolated to the updated version QRISK®3. In addition, QRISK®3 has been expanded and considers a number of conditions which are already known to cause high risk of CVD, such as diabetes and chronic kidney disease. The inclusion of these conditions means it is possible to achieve a more accurate prediction of CVD risk in these groups.

Table 3: Commonly applied CVD risk prediction tools.

QRISK®2 and recently QRISK®3 (UK) [91] https://qrisk.org/	
Types of risk prediction/ output/ outcomes	Estimate the 10-year risk of CVD in women and men (CHD, stroke, and transient ischemic attack) Fatal CVD
Risk factors	Age, ethnicity, deprivation, systolic blood pressure, body mass index, total cholesterol (high density lipoprotein, cholesterol ratio), smoking, family history of coronary heart disease in a first degree relative aged less than 60 years, type 1 and 2 diabetes, treated hypertension, rheumatoid arthritis, atrial fibrillation (AF), chronic kidney disease (stage 4 or 5) QRISK®3 added; Chronic kidney disease (stage 3), a measure of systolic blood pressure variability (standard deviation of repeated measures), migraine, corticosteroids, systemic lupus erythematosus (SLE), atypical antipsychotics, severe mental illness, erectile dysfunction
Guidelines	NICE guidelines: Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease [92,93] and the Public Health England (PHE) NHS Health Check: best practice guidance [94]

Framingham risk score [95, 96] https://www.framinghamheartstudy.org/fhs-about/	
Types of risk prediction/ output/ outcomes	Estimate (or risk) of developing CVD or a component of CVD (such as coronary heart disease, stroke, peripheral vascular disease, or heart failure) over a fixed time, for example the next 10 years or lifetime risk. Fatal or non-fatal: CHD, CVD, myocardial infarction and stroke Separate calculators for: Atrial fibrillation (AF), CVD, CHD, hypertension, stroke after AF
Risk factors	Sex, age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes status
Guidelines	5-year Framingham risk score in the National Vascular Disease Prevention Alliance guidelines (Australia) Guidelines for the management of absolute cardiovascular disease risk [97] 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [98]

Pooled Cohort Risk Equations (PCE) [99-101] American College of Cardiology (ACA)/ American Heart Association (AHA) USA http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/	
Types of risk prediction/ output/ outcomes	Multivariable Cox proportional hazards regression equations to estimate the 10-year absolute risk for Atherosclerotic Cardiovascular Disease (ASCVD) (includes nonfatal myocardial infarction, nonfatal stroke, and fatal cardiovascular disease)
Risk factors	Sex, ethnicity, age, total and high-density lipoprotein (HDL) cholesterol levels, systolic blood pressure, use of antihypertensive medication, smoking ,diabetes status
Guidelines	2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [98]

Systematic Coronary Risk Evaluation (SCORE) algorithm [102] https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts Interactive online tool: HeartScore http://www.heartscore.org/en_GB	
Types of risk prediction	10-year risk estimate. Cardiovascular mortality from CHD, sudden death, congestive heart failure, peripheral vascular disease. Fatal: CHD, CVD and non-CVD Shows absolute, relative and risk change if lifestyle adapted. Separate scores for high/low risk countries.
Risk factors	Systolic blood pressure, total cholesterol, total cholesterol/high density lipoprotein, smoking, age (age used as a temporal variable)
Guidelines	European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure [71]

Assessing Cardiovascular Risk using Scottish Intercollegiate Guidelines Network (ASSIGN)[103] http://www.assign-score.com/	
Types of risk prediction/ output/ outcomes	10-year risk estimate Fatal and non-fatal cardiovascular event
Risk factors	Age, sex, total cholesterol, systolic blood pressure, high density lipoprotein, diabetes, smoking, family history of myocardial infarction, area based deprivation index
Guidelines	Scottish Intercollegiate Guidelines Network: Risk estimation and the prevention of cardiovascular disease. A national clinical guideline. Guideline 97 [104]

Reynolds[105] http://www.reynoldsriskscore.org/	
Types of risk prediction/ output/ outcomes	10-year risk estimate (targeted to people without diabetes or previous CVD) Acute myocardial infarction, cardiovascular accident (ischemic), Revascularization treatment (coronary), cardiovascular death
Risk factors	Age, smoking, systolic blood pressure, total cholesterol, high density lipoprotein, hsCRP, family history of myocardial infarction (<60), hgba1c (women only)
Guidelines	2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [71]

5.7 Risk assessment to inform secondary prevention

People who already have CVD can benefit from risk factor modification and cardiac rehabilitation. Additional groups of people that can be considered for secondary prevention are individuals already considered to be at high risk of developing CVD, because they have:

- Familial hypercholesterolemia, or other inherited disorders of lipid metabolism
- Age of 85 years or over - age alone, but especially smokers and people with high blood pressure
- Existing CVD condition or event, including atrial fibrillation
- Diabetics
- Chronic Kidney Disease patients
- Hypertension / high blood pressure
- High cholesterol

These groups do not need formal risk assessment to determine risk as they are already considered to be at high risk, but assessment can assist in better care. Generally each condition will have their own guidelines addressing if and how assessments are done.

Evidence regarding the use of tools in these conditions is building and is being incorporated into existing tools (e.g. QRISK®3). A recent study looking at CVD risk prediction in diabetic patients found that no single model performed consistently well and it was difficult to recommend one model over another as none showed outstanding discriminative performance [106]. The authors felt that the inability to reliably use risk stratification in the care of diabetes leads to all patients being aggressively treated to reduce risk [90]. Therefore improvement in models for this group is needed.

NICE does not currently recommend using risk assessment tools for people with type 1 diabetes mellitus, or chronic kidney disease. However, new evidence suggests that QRISK®3 performs well for people with type 1 diabetes and chronic kidney disease, and may help some people with these conditions to make an informed choice about whether to take statins [83].

5.8 Summary

Both population-wide and high-risk-group strategies have been adopted to address key risk factors in prevention of CVD. A first step is to detect those at increased risk of CVD, and a number of mechanisms are recommended for this including systematic identification via primary care records as well as the offer of health screening to those above the age of 40, via the NHS Health Checks programme. Risk assessments form an important component of prevention efforts and facilitate decision making with respect to individual level interventions. However, most tools are only applicable to those between the ages of 40-75.

Consequently, the majority of high risk strategies are targeted at those above the age of 40. Whilst most cardiovascular events are seen in those above the age of 40, pathological processes underlying atherosclerosis tend to begin much earlier in life and develop through adolescence and early adulthood [107]. Rate of progression of atherosclerosis will vary amongst individuals, be influenced by risk factors, and usually remain asymptomatic for a long period. Prevention efforts prior to the age of 40 are mainly in the form of population-wide strategies promoting healthy lifestyles. It is yet to be determined if genetics in the form of a polygenic score could act as a novel biomarker to identify those at increased risk at a younger age, prior to the developments of clinical symptoms.

6 Polygenic scores for cardiovascular disease

Progress in the field of polygenic scores has led to considerations around their implementation in clinical practice. In this section we focus on polygenic scores for coronary artery disease (CAD) and provide an overview of progress in this field and an assessment of their readiness for implementation.

Key points

- A multitude of polygenic scores have been developed that could inform prevention of cardiovascular disease
- Studies indicate that recent polygenic scores developed for CAD could improve the accuracy of risk stratification beyond that provided by use of traditional risk factors alone
- Nevertheless, further investigation is required in order to elucidate their performance in clinical practice and assess if they add value to current prevention pathways

6.1 Progress in developments of polygenic scores for cardiovascular disease

Cardiovascular diseases are recognised as having a strong genetic component, with heritability estimates for diseases such as CAD ranging from 50-60% [108]. A proportion of CVDs result from rare variants that increase risk of disease and present as familial forms of disease (e.g. familial hypercholesterolemia). In such contexts, knowledge of family history and genetic testing can inform management and prevention of adverse events.

However, for the vast majority of the population, the genetic component is polygenic, with many common variants contributing to risk. Efforts to elucidate these genetic determinants and utilise them to improve risk prediction have been underway for some time [109]. Until recently, efforts had focused on utilising information on small numbers of gene variants associated with CVD. However the increasing ease of genetic analysis and the availability of large scale GWAS has led to expansion in identification of genetic variants associated with common forms of CVD. In line with identification of variants associated with disease, efforts have also been underway to utilise this information in risk prediction in the form of polygenic scores.

CVD encompasses a broad group of conditions that affect the heart and circulatory system. Genetic epidemiological research and polygenic score construction for the most part has focussed on specific groups of cardiovascular conditions, such as CAD and stroke, or intermediate conditions such as atrial fibrillation [110], or hypertension [111]. There are a number of large research studies focused on CAD that have allowed for better understanding of the disease and identification of risk factors, including genetic factors, to occur. This, together with the availability of large datasets such as UK Biobank, means that the genetic architecture of CAD is the best studied of all cardiac conditions. This has resulted in polygenic score development being most advanced in this area.

6.2 Overview of existing polygenic scores for CAD/CHD

Polygenic scores for CAD initially incorporated small numbers of associated genetic variants [5-7]. As of 2018, 161 'CAD-associated genetic loci' were reported across the literature, with more than 100 loci discovered within the year prior to publication [112]. Owing to greater availability and scale of data from GWAS and continuing expansion of disease and gene association knowledge, the number of genetic variants being included to determine individual risk has increased; with some models including more than one million genetic variants [3, 21].

There is a large amount of diversity in this field with respect to available scores (Table 4). This is because studies have been designed in such a way as to explore different mechanisms to generate a polygenic score and improve risk prediction. This has shown the ability of polygenic scores to stratify populations, however, the implications of stratification for clinical practice have not been fully investigated. Furthermore, different studies have generated different models and reported different aspects of model performance. Often the context of development, external validation and performance metrics are inconsistently reported, meaning that critical appraisal of models and comparison between models is not possible. Some of the variability we observed between CAD polygenic scores described in the scientific literature are discussed below.

Defining coronary artery disease

Definition of outcome is important in assessing the applicability and generalisability of study findings. In the studies we examined CAD was variably defined and, as in the wider literature, the term was often used interchangeably with coronary heart disease (CHD). This distinction is not strictly necessary in all circumstances since risk factors for both conditions are shared. However, definitions are important to consider as CAD itself comprises several different and more specific conditions [108], and outcomes related to these disease groups vary. Consistent use of definitions is particularly pertinent when using information from several datasets, as studies may be registering different outcomes under the same name. If these different outcomes are being used to develop polygenic scores, the ability to compare between these scores is limited.

Structure of populations used for developing and testing polygenic scores

There is variability in the type of populations used to develop and validate polygenic scores. Some PRS have been developed using data from, or have been tested in, selected groups e.g. CARDIoGRAM [113], West of Scotland Coronary Prevention Study (WOSCOPS) [114] and Atherosclerosis Risk in Communities (ARIC) study [115]. These are made up of specifically recruited individuals already identified as having some form of CVD or intermediate condition alongside a number of control individuals, or have recruited individuals within more narrow demographic groups. As a result the polygenic scores may be more appropriate for risk prediction in particular patient sub-groups than in the general population.

Recent polygenic scores have been developed using large population-based datasets (example UK Biobank) that are more relevant for envisaged applications such as statin prescription or screening at the level of the general population. The population variability reflects the exploratory nature of this field, where researchers are still investigating if genetic information can inform risk assessment either at the general population level or for specific sub-groups. Going forward it is important to consider if populations for which polygenic scores have been developed are clinically relevant populations and, where validation has occurred, whether it is using populations that are representative of those in whom the scores will be used.

The use of different populations is sometimes related to the different purposes for which the polygenic score was developed. For example some earlier models were developed in the context of a clinical trial, where the primary purpose includes: investigating the relative efficacy of benefit of statin therapy [23], for informing prognosis in patient sub-groups [106], as a potential screening tool for primary prevention [3] and for examining off-setting of genetic risk through healthy lifestyle behaviours [116, 117].

The intended use of the polygenic score is generally not the starting point of the research studies. The main focus of these studies has been to demonstrate the model's ability to distinguish between two groups (those with disease and those without) by using a polygenic score. Hence these can be considered proof-of-principle studies which require further investigation in order to elucidate how a polygenic score will perform in clinical practice and the potential role it has in prevention of CVD. Further studies are required that set out the intended use of a polygenic score in a specific population and collect the relevant outcome data, where the clinical endpoint better matches how the polygenic score was developed.

Interpretation of performance metrics

Performance measures reported by studies need careful examination and interpretation. Some studies report performance of the polygenic score in isolation, whilst others include performance measures for PRS with adjustments for other risk factors, e.g. age or gender. Further still, some report performance measures combining the polygenic score with established risk tools in an integrated model. These additional variables can be known traditional risk factors or novel risk factors.

The performance measures of non-genetic risk factors in predicting disease risk may already be high prior to the introduction of the polygenic score, i.e. where the overall performance of the integrated score is high, but the added value of the polygenic score is low. For example, in a study of PRS for CHD the researchers determined that a model with only traditional (non-genetic) risk factors had a C-statistic (a commonly used performance measure) of 0.746, adding the polygenic score increased this to 0.749 [118], a minor improvement. In some cases these metrics are not reported separately, making it difficult to assess the independent or added value of the genetic information.

As stated previously, a model's clinical utility cannot be judged solely on performance metrics. Whilst these are important and useful parameters in assessing the model, they need to be viewed in the context of intended use.

Designation of risk categories using polygenic scores

It is a common practice to place individuals into genetic risk categories on the basis of their polygenic score. Thresholds for allocating individuals into risk categories are sometimes poorly explained. Generally, the test population is divided into three or five groups [116, 119], where the risk categories are defined relative to the tested population e.g. an individual with a risk score that is in the highest 80-100% is considered to be high risk and an individual in the lowest 20% for risk is considered to be low risk. Depending on the goal, the researchers can present the results in a number of different ways. For example, if the goal is to identify individuals at the top end of the distribution, a comparison of the top 10% to the rest could be done. This comparison can be misinterpreted for the potential impact of the polygenic score.

Consequently, the effect sizes alone may not be informative and can be misinterpreted. Furthermore, these thresholds are not always aligned with clinical guidelines. Hence it can be unclear as to whether an individual classified as high risk as a result of their polygenic score would qualify for clinical intervention.

Appropriate validation of polygenic scores

Validation of polygenic scores has been performed to varying degrees. Some studies carry out validation using a subset of the cohort in which they originally developed or tested the polygenic model; fewer models have been subsequently validated in independent external cohorts [3, 120]. External validation does pose difficulties due to the limited availability of genotyped datasets. Validation needs to be carried out in populations independent from discovery or testing datasets that are, in combination, appropriately representative of the population in which a score might be used. For example, if external validation is carried out using the UK Biobank dataset, it will reflect effectiveness of that score in people of 40-69 years of age and primarily of Caucasian ancestry.

Accuracy and utility of polygenic scores in diverse or non-European populations

Polygenic scores have mostly been developed in exclusively or majority European populations. Some preliminary assessments have demonstrated that scores can still discriminate between high and low risk groups in other ethnicities, but that they don't perform as well [121, 122]. There is work underway to determine if recalibration of scores or variant weightings for alternative populations would improve performance [123], and to establish large GWAS projects in more diverse or non-European populations [1,124]. Recalibration has been demonstrated in CVD risk algorithms [125]. It will take time to develop the evidence needed to demonstrate the applicability of polygenic scores in all populations.

Consequently, currently reported studies demonstrate the potential for polygenic scores to stratify individuals but do not provide evidence that these tools are ready to be implemented in clinical practice. Few studies have clearly articulated a clinical need addressed by utilisation of genetic information in the form of polygenic scores or demonstrated the added value of this information within clinical practice. What is currently being demonstrated is the ability to risk stratify individuals by their polygenic score and place them along a continuum of risk in a research context [3, 21].

Table 4: Examples of polygenic risk models that have been developed for CAD/CHD in recent years.

Publication	Purpose	Brief overview of models examined			
		Models	No. of variants in PRS model	Outcome tested by models	Test population
Inouye *et al.* 2018 [3]	Construct a PRS for CAD and estimate its potential as a screening tool for primary prevention	PRS adj. for sex, age, PC, genotyping array Clinical risk factors only (smoking, diabetes, family history, BMI, hypertension, high cholesterol) Combined model (PRS and clinical risk factors)	1,745,180	Prediction of incident CAD	UK Biobank
Khera *et al.* 2018 [21]	Develop and validate PRS for five common diseases (including CAD)	PRS and age, sex and PC	6,630,150	Prediction of CAD	UK Biobank
Natarajan *et al.* 2017 [23]	Examining the impact of statin treatment at different levels of genetic risk	PRS adj. for age, sex, diabetes, smoking, LDL, HDL, BP, antihypertensive use and family history of MI or stroke	38-63	Incident nonfatal MI or death caused by CHD	WOSCOPS
Abraham *et al.* 2016[126]	Construct and externally validate a CHD-PRS, examining lifetime CHD risk and comparison to traditional clinical risk factors	PRS PRS and FRS PRS plus ACC/AHA13 risk score	49,310	Time to CHD event	Three FINRISK cohorts and two FHS cohorts
Khera *et al.* 2016 [116]	Examining the relationship between genetic risk, CAD and healthy lifestyle	PRS	up to 50	Composite of CAD events (MI, coronary revascularization, and coronary cause death)	Tested in ARIC, WGHS, MDCS, BioImage
Tada *et al.* 2016 [118]	Examining improvements in CHD risk prediction by inclusion of more SNPs and relationship with family history of CHD	PRS and age, BP, antihypertensive use, smoking, apolipoprotein A and B, diabetes	27 and 50	Time to first event of CHD	MDCS

Publication	Purpose	Brief overview of models examined			
		Models	No. of variants in PRS model	Outcome tested by models	Test population
Mega *et al.* 2015 [127]	Examining if PRS could ascertain the risk of both incident and recurrent CHD events and identify individuals who derive greater clinical benefit from statin therapy	PRS adjusted for age, sex, diabetes, smoking, family history, HDL and LDL cholesterol and hypertension	27	Incident or recurrent CHD	FINRISK
Krarup *et al.* 2015 [128]	Examine association of PRS with risk and investigate impact on risk prediction	PRS adj. for age and sex PRS incl. age, sex, BMI and smoking	45	MI and CAD	Inter99 study
Tikkanen *et al.* 2013 [129]	Set out to evaluate genetic risk discrimination of CHD, ACS, and combined CHD and stroke events, and estimate the improved risk classification of CHD in a two-stage population screening strategy	Conventional model (conventional risk factors only) Conventional risk factors and family history Conventional risk factors and PRS	28	CHD, CVD and ACS	FINRISK and Health 2000
Ripatti *et al.* 2010 [119]	Establish the external validity of a 13 SNP PRS and examine impact on more precise risk estimates using a prospective cohort design	Conventional risk factors PRS and conventional risk factors	13	CHD, CVD and MI	FINRISK

This is illustrative as opposed to an exhaustive or comprehensive list of available models. Performance metrics for individual models are not included as they are not directly comparable between models/studies due to different intended uses, populations used for evaluation and the specific analysis that has been performed.

Abbreviations: ACS = acute coronary syndrome, BMI = body massindex, BP = blood pressure, CAD = cornory artery disease, CHD = coronary heart disease, CVD = cardiovascular disease, FHS = Framingham Heart Study, FRS = Framingham Risk Score, HDL= high density lipoprotein, LDL = low density lipoprotein, MDCS = Malmö Diet and Cancer Study, MI = myocardial infarction, PC = prinicipal components of genetic ancestry, WOSCOPS = West of Scotland Coronary Prevention Study, incl. = including, adj. = adjusted

6.3 Potential applications of polygenic scores for CAD

The papers we assessed do provide some indications of the potential role of polygenic scores in the prevention of cardiovascular disease. These potential applications are discussed below.

Risk prediction

Genetic contributions to disease risk are defined at birth, and remain stable throughout the life-course. There is evidence that plaque build-up in the vasculature (atherosclerosis) can begin at an early age (pre-teen) and stay with individuals for life [130]. Individual genetic information could provide the earliest indication of a predisposition to such build-up, allowing preventative action to be taken in high-risk individuals from an earlier age, perhaps even before plaques begin building in childhood. Interventions could take place in these high-risk individuals either by close monitoring, lifestyle adaptation or use of therapeutics. CAD development is known to be impacted by environmental risk factors, so assessment of these impacts throughout life would be required in addition to early-stage risk prediction.

Many studies have assessed the predictive ability of polygenic scores as a standalone risk predictor. These studies suggest that polygenic scores can act as a biomarker to identify those at high risk at an earlier time point than traditional risk factors. As discussed above, there are some methodological issues with these studies, and they do not unequivocally support the use of polygenic scores for early identification of those at high risk of CAD at the present time. There is broad agreement that polygenic scores could act as an additional biomarker that could be incorporated with and contribute to current risk prediction efforts in cardiovascular disease.

Incorporation of PRS into existing risk prediction tools

Tools for determining personal risk of developing CVD have existed for many years. For example, as discussed in section 5.5, the Framingham Risk Score calculates CVD risk using non-genetic risk factors such as cholesterol, blood pressure and age. Composite scores combining polygenic scores and traditional risk factors could provide better predictive capability, allowing for better stratification and refinement of risk. This has implications for prescription of therapies such as statins, especially where individuals are reclassified from one intervention threshold to another.

Identify who could benefit from statin therapy

The relative clinical benefit of a treatment may vary by baseline risk of disease. Research has been carried out to assess the clinical benefit of statin therapy in groups of individuals with different CAD disease risk as determined by applying a polygenic score. This work has demonstrated that even though all levels of risk benefited from statin use, people with higher risk scores had the largest relative and absolute reductions in disease risk following statin therapy [23].

6.4 Appraisal of readiness for clinical implementation of PRS-CAD

Our appraisal of the literature in the area of polygenic scores for CAD (PRS-CAD), has led us to conclude that although there is promise and potential in the field, this is an area which is still under development. Implementation within current or future practice will require addressing some key areas, which are outlined below.

Distinction between a PRS assay and PRS-based test

The importance of distinguishing between an assay and a test has been previously discussed with respect to genetic test evaluation [31, 131]. It is worth examining this concept as applied to polygenic scores, as their evaluation is reliant on a clear understanding of the test to be offered. As outlined by Zimmern and Kroese [132], the method used to analyse a substance in a sample is considered the assay, whereas a test is the use of the assay within a specific context. With respect to polygenic scores, the process of developing a model to derive a score can be considered the assay, while the use of this model for a particular disease, in a particular population, for a particular purpose can be considered the test.

With this distinction in mind, it is our view that studies thus far have concentrated on assay development as opposed to test evaluation. Thus the reporting in the studies we examined is most relevant to assay performance as opposed to test performance. Although progress has been made in assay development, our assessment of this field indicates that a polygenic score-based test is yet to be developed and evaluated. The development of a test requires explicit use of an assay in a particular population for a particular purpose. As outlined above, most studies examining PRS-CAD do not have a clearly defined clinical purpose, consequently an implementation ready clinical test is currently unavailable.

Diversity in PRS-CAD models

Available PRS-CAD have been constructed using different methodological approaches, illustrating the variety of models that can be applied to score construction. There is little agreement currently as to the 'best' model for generating a polygenic score, and it is unlikely that consensus will be reached as to a single standardised methodological approach. However, there is likely to be convergence towards an agreed framework to ensure that best practices are followed in the reporting and development of these risk prediction models [133].

Diversity in PRS-CAD models is not a barrier to adoption, provided that the models that are taken forward in test development or implementation are credible and robust and able to produce a score that is considered to be fit for purpose. Model selection will most likely be influenced by practical considerations and trade-offs between obtaining genotype data, processes for score construction and model performance.

Obtaining genotype information

Examination of the literature has shown that the trend in this field is towards inclusion of a greater number of SNPs in score construction. As discussed in section 2, the number of SNPs included in a polygenic model is determined to some extent by genetic architecture of the disease. For cardiovascular disease, experts broadly acknowledged that scores that are constructed using a larger number of SNPs are likely to have greater predictive ability. This is also borne out in the literature where, in general, scores based on a larger number of SNPs appear to have better performance. This hypothesis is valid in light of what is known about the genetic architecture of CAD, where many variants are likely to be involved in risk. However, the additional improvement in predictive ability as a result of adding increasing numbers of SNPs must be balanced against the cost of obtaining this data. The optimal number and specification of which SNPs to include in a polygenic score for CAD is yet to be determined.

Obtaining a polygenic score for an individual requires genotyping, which can impact on the feasibility of score construction. For example, it may currently be more feasible to obtain genotype data on a smaller number (e.g. hundreds) of SNPs as opposed to a larger number (thousands/millions). Microarray technologies are an established part of clinical genetic services, however the high density arrays that would be required to obtain variant information to inform polygenic scores using larger numbers of SNPs are not an established tool. Even in research studies, genotype information across such a large number of SNPs is usually obtained using GWAS arrays followed by imputation to infer variants not genotyped [134]. This may not be ideal for clinical practice, especially where populations are more diverse and imputation is not an appropriate option.

Processes for score construction

The approach to obtaining genotype information and selecting a polygenic model are linked to some extent. The polygenic model that is taken forward may be selected on the basis of the feasibility of obtaining genotype information or, conversely, the selected polygenic model may determine what genotype information is collected. In either case, as part of assessing the analytical validity of a test, it will be important to elucidate which variants will require robust genotyping in order to inform the score.

The publications that we have examined did not report analytical validity, hence it is unclear to what extent this aspect of score construction has been examined. Nevertheless, for clinical practice, it will be important to ensure that polygenic score construction pipelines are standardised and adequate quality assurance processes are in place to ensure their analytical validity.

Developing a 'PRS-test'

As described above, a 'PRS-test' for clinical use is not yet available. Given the numerous models available, the next steps required are an assessment of available models and their suitability as part of a test. As described in section 3, model performance parameters can provide some guidance, however they may not be optimal. The parameters or guidelines with respect to metrics or aspects of model performance that could assist in choosing a model to take forward as a PRS-test are lacking and need to be addressed. There are already established guidelines such as the TRIPOS statement for the performance assessment of risk prediction models that could be used for the development of PRS specific guidelines [135–137].

Clinical utility

Assessing the clinical utility of PRS-CAD, as with other risk tools, is a complex undertaking, especially given the subjective nature of what could constitute clinical utility. Many consider that a polygenic score should not only improve risk prediction, but also allow for changes in decision making that would not have occurred without it. In understanding the clinical utility of PRS-CAD it will be important to consider the clinical environment in which a tool will be implemented and take into account the current uses and applications of risk stratification for CVD.

Our analysis of the literature and discussion with experts in the field indicate a gap between available research and the current clinical context and need. Current prevention pathways are focussed on early identification of those at risk in order to mitigate against adverse cardiac events. However, preventative efforts tend to be focussed on those above the age of 40. The potential applications of PRS-CAD that have arisen as a result of progress in this field are outlined above.

Thus far polygenic scores have mostly been considered as standalone tools, where they often show improvement in stratification of individuals, but provide only a minor improvement when included alongside other 'traditional' risk factors [118, 126]. This is unsurprising given that PRS have been examined in relatively older populations (i.e. above 40) where age has a large influence on risk and it is possible that these individuals may already be on a disease trajectory. Consequently, polygenic scores may have less utility in these older populations, but could have more value in identification of younger at-risk individuals. If this is the case, it might have significant implications for the structure of prevention programmes.

Small incremental improvements in existing risk prediction tools may still have value, as they can enable better stratification of the population for individualised health promotion or statin therapy. The added value of a polygenic score within existing risk prediction tools is yet to be demonstrated.

Wider implementation

In addition to addressing the gaps outlined above, incorporation into prevention pathways requires detailed consideration of how best to introduce a tool incorporating a polygenic score into practice. This will involve a number of practical considerations such as:

- Who would calculate the polygenic score? Currently within the NHS, the majority of DNA-based testing occurs in clinical genetic laboratories and is carried out for the purposes of supporting care for those with heritable diseases or cancer. The position of a PRS-based test which might be used at scale in this landscape would have to be determined

- What information would be fed back to the patient or be available in the medical record (i.e. just the score or genotyping information)? Genotyping is the first step in generating a polygenic score. However, the output of a PRS-based test is the score. Consideration may need to be given as to whether the NHS would want to store genotype data (allowing for reassessment) in addition to the output. This decision might become increasingly relevant if it becomes the norm for patients to access their electronic patient records in the future

- Informing patients of their scores or genotype information would have implications for health systems; health professionals would need requisite training to enable this information to be provided in a way that maximised the potential benefits and minimised the harms

- Although we have focused on polygenic scores for CAD, developments in polygenic scores for other diseases are likely to impact on implementation plans. Progress is being made in the development of polygenic scores for other common diseases such as cancer and diabetes. It is likely that each score will have a different model supporting it with a different number of SNPs being genotyped. Consideration of the wider landscape and use of polygenic scores is important to ensure the development of implementation plans that are able to adapt to this emerging science

- In addition, as more research and data becomes available, it is likely that existing models will need to be updated. In planning for the future, it is important to ensure a system that is able to incorporate advances in this field as they occur

6.5 Summary

Research in the field of PRS-CAD is showing that polygenic scores can contribute to improvements in risk stratification of individuals and provides an indication that it might have value in clinical practice. There is broad agreement that in the short-term this added value in terms of improved prediction is likely to be realised through incorporation of the polygenic score within existing tools for risk prediction, such as QRISK. Whilst polygenic scores have mostly been considered as a standalone tool until now, research examining incorporation into existing tools (e.g. QRISK) is beginning. Such studies will enable assessment of the added benefit of PRS in predicting risk. In the future it is possible that a PRS-CAD could be used as an independent screening tool, but this requires detailed consideration about how this would function in practice, including the population to be screened and the interventions that would be offered.

This report focuses on CAD, but polygenic scores are also being developed for other CVD-related conditions, such as diabetes, hypertension and hypercholesterolemia. Addition of PRS-CAD into existing models will improve overall CVD risk prediction but inclusion of all the polygenic scores of related conditions or traits could further refine and improve risk prediction of CVD. Therefore, consideration also needs to be given to developments occurring in other disease areas.

To be implementation-ready there is a need for a PRS clinical test to be available, and appropriate evaluation undertaken to develop the required evidence base for clinical use. Implementation will also require consideration of a wide array of practical issues that are likely to influence the nature of the test that is introduced into practice. In considering these issues, further areas of research such as risk communication, professional education, and health economic evaluation will also need to be addressed.

7 The clinical utility of using polygenic scores as part of an integrated risk tool for cardiovascular disease: a behavioural science perspective

Previous sections have outlined the scientific (analytic and clinical) validity of PRS for cardiovascular disease and readiness for clinical implementation. We have also examined potential clinical utility with respect to PRS (section 2) and the evidence base with respect to clinical utility of PRS-CAD (section 6). On the basis of those analyses and in consultation with experts, our assumption is that polygenic scores are likely to increase the accuracy of CVD risk assessment tools such as QRISK®2, and in this regard they therefore have potential value. In this section, we consider the clinical utility of incorporating PRS into CVD risk assessments from a behavioural science perspective.

Key points

- Evidence regarding the clinical utility of current CVD risk assessment tools is limited
- Few studies have been conducted examining the clinical utility specifically of PRS either alone or when incorporated into CVD risk assessment tools
- Overall, there is little empirical evidence to suggest that incorporating genetic risk information has impact on behaviour change beyond conventional risk factors
- If implemented clinically, CVD risk assessment tools incorporating PRS would need to be complemented with personalised risk-reducing resources and interventions to support behaviour change

7.1 Introduction

Evaluation of PRS and risk assessment tools requires analysis beyond the assessment of scientific validity - which is necessary, but not the sole prerequisite for implementing PRS into practice. In addition, evidence based practice also requires that new tests have clinical utility, and that they are also both feasible and acceptable to health professionals and patients. For the purposes of this report, clinical utility is defined as the likelihood that the test will lead to an improved outcome, which incorporates an assessment of the potential benefits and potential harms [31]. This is consistent with definitions of clinical utility adopted in the ACCE framework for the evaluation of new genetic tests [29].

Aspects of feasibility and acceptability, together with other prerequisites such as the assessment of possible patient pathways, ensuring that professionals are competent to deliver risk assessments, and resource considerations will be explored more fully in a separate report to be published in Spring 2020. Here we provide a synopsis of some initial findings.

7.2 The current rationale for use of CVD risk assessment tools

The use of CVD risk tools to help prioritise and guide treatment decisions is recommended in international guidance and has been established in clinical guidance in England [92]. As raised earlier in this report (section 5.4), the rationale for the use of CVD risk assessments tools such as QRISK®2 is to efficiently and accurately prioritise interventions. They can assist clinical practice by enabling objective assessment of individuals and further management of those who are categorised as high risk.

Potential benefits arising from CVD risk assessment include more accurate stratification, potentially resulting in a more targeted distribution of resources (e.g. statins and/or weight loss interventions) to those most likely to benefit in terms of improved health and reduced CVD mortality and morbidity. Implicit in this is that CVD risk assessments will lead to better decision-making and behaviours among healthcare professionals (e.g. improved medication prescribing, lifestyle recommendations) within a given healthcare setting that will lead to beneficial patient behaviours among those most at risk (e.g. taking medication, changing lifestyle behaviours). Conversely, the potential harms associated with using CVD risk assessment include harms to the health system, such as the intervention failing to deliver the anticipated benefits, and opportunity costs associated with implementation. Patient harms include the potential for adverse physical, psychological or social events arising from risk assessment. Psychological harms in response to receiving a high risk result could include depression, anxiety or stress.

Increasing efficiency in the allocation of interventions in itself can be considered as clinical utility if assessment shows that the benefits outweigh any harms, particularly if this is demonstrated to lead to improved individual patient outcomes. However, realising the benefits of interventions relies on patient engagement with these interventions i.e. with recommendations to take statins and/or make lifestyle changes. Evidence suggests patient compliance with CVD risk-reducing recommendations is low [138]. Statins are generally well-tolerated and low adherence negatively impacts clinical outcomes; however, adherence to statins is suboptimal (between 40 and 75% of patients discontinue their statin therapy within one year after initiation [139]).

Motivating healthy behaviours is even more challenging: although 'fear appeals' (informing the public or individuals they are at high risk of disease) have a role to play in health management, this approach is often insufficient to prompt risk-reducing lifestyle changes, particularly if the message is not perceived to be very threatening or is delivered in isolation [140]. We explore this further and examine the existing evidence of behavioural benefits as well as potential harms from current CVD risk assessments in the following section.

7.3 Current CVD risk assessments: empirical evidence on outcomes

Over the last couple of decades, a number of studies have been conducted evaluating the impacts of CVD risk assessments on patient outcomes [141, 142]. A recent overview of systematic reviews of these studies provides a useful synopsis of the evidence base [136]. A total of ten systematic reviews covering 66 studies met the eligibility criteria, making it the largest review of systematic reviews on this topic to date. Based on the evidence from the studies included in the review, the benefits and harms of current CVD risk assessments appear to be minimal. However, it is worth noting that the studies to date are somewhat limited in number and of generally low overall quality. Whilst there are limitations to this review, for example the authors did not formally assess the quality of each study, it does include key papers and gives an indication of the current evidence in this area.

We outline the key primary and secondary findings from the studies reviewed below:

CVD-related health outcomes (benefits):

- **Impact on mortality** – only one review included two original studies from the 1980s examining impact on CVD death [143]. These observed a small reduction in CVD deaths of unreported or insignificant statistical significance
- **Impact on CVD events** – Karmali *et al.* (2017) presented a meta-analysis of three studies on the effect of providing risk assessment on fatal and non-fatal CVD events [144]. It reported no effect compared with conventional care
- **Impact on cholesterol and blood pressure** – results were ambiguous, but a tendency towards slight reduction of blood pressure and total cholesterol was observed, especially in high risk patient groups

Patient (and clinician) behavioural outcomes (benefits):

- **Impact on statin/medication prescribing (clinicians)/taking (patients)** – prescription of anti-hypertensive and lipid-lowering drugs in high CVD risk groups was increased. The effect on patients' medication behaviours was not reported in the majority of reviews
- **Impact on 'lifestyle' behaviours** – there were no changes in diet, alcohol consumption or BMI/obesity, and only small, clinically insignificant, reductions in smoking levels

Psychological outcomes (harms):

- **Impact on adverse psychological effects** – most studies showed no difference in the presence of adverse psychological symptoms in groups with or without a CVD risk assessment. However, a review by Usher-Smith *et al* (2015) observed a small but significant improvement in psychological well-being and in level of anxiety in high CVD risk patients after risk assessment [141]

Current CVD risk assessments have been implemented in clinical practice in the NHS and other healthcare systems despite a lack of compelling empirical evidence that they lead to demonstrable benefits. The limited evidence base suggests minimal benefits, but also minimal harms. As the use of CVD risk assessment tools is already established in the NHS, any improvement in predictive performance created by adding PRS may justify its implementation. This provides a starting point to consider what additional utility, if any, might be gained from integrating PRS into CVD risk assessment tools.

7.4 Potential clinical utility of PRS when incorporated into CVD risk assessment tools

There have been broad statements that genetic risk information will lead to improvements in the health of the public because this will lead to a more 'personalised' health service, more 'tailored' information for patients, and that this type of genomic information will 'empower' people to take more 'control' of their own health [145, 146]. But a more detailed analysis of the actual hypotheses, empirical evidence and theory underpinning these assertions is needed in order to assess whether these optimistic expectations are really justified. Below, we address two ways in which polygenic scores might lead to improved health of the public: (1) via improved accuracy of the risk assessment, which may be viewed as being valuable in and of itself; and (2) via prompting (motivating or 'empowering') high-risk patients to make risk-reducing behaviour changes, specifically statin use and lifestyle improvements. In addition to these potential benefits, we also consider the potential harms, given this is the other component of clinical utility.

Improved accuracy

A critical aspect of the utility of an integrated tool that includes PRS is its impact on clinical management, as risk estimation is vital for therapeutic decision-making. Therefore, improved accuracy of the risk assessment is the first and foremost clear benefit for patients and healthcare professionals. The increased accuracy of a tool containing PRS has been explored earlier in this report. Potential downstream benefits of this improved risk assessment include more effective allocation of resources to those who are most likely to benefit, hopefully leading to reduction/delay in onset of illness. As mentioned before, a key challenge is ensuring developed tools are appropriate to the population, which requires ensuring diverse populations in research and development.

Behaviour change

Although the benefit of improved accuracy of the risk assessment may be justifiable in and of itself, the narrative around the topic of polygenic scores often revolves around the expectation that genetic information 'empowers' patients to act to reduce their risk, in this case their risk of CVD. The two ways in which patients can potentially reduce their CVD risk are both behavioural, i.e. (1) changing lifestyles and (2) taking statins (although taking statins is a medical intervention, it is reliant on patient behaviour for initiation and compliance). Therefore in the next section, we shall assess the currently available empirical evidence on this topic; describe a widely used theoretical framework for behaviour change interventions and a model of human behaviour that are each based on systematic syntheses of multiple prior models; and apply these to consider whether this 'empowerment' hypothesis is justified.

CVD risk assessments that incorporate PRS: empirical evidence on outcomes

Research examining the impact of genetic information on behaviour change has taken different approaches. Early studies examined the behavioural impact of standalone polygenic scores for common complex disease susceptibility. These studies found little evidence to suggest that being categorised as 'high risk' led to significant and sustained behaviour change [147–149]. This lack of behavioural impact has subsequently been reported in several influential systematic reviews and widely cited [150, 151]. These broadly negative findings in part may be due to poor predictive performance of early polygenic scores. Other studies have explored the psychological and behavioural effects of providing patients with results from genetic testing for high penetrance variants that confer increased risk of disease, such as familial hypercholesterolemia[152]. However, these studies may not be directly comparable to behavioural studies of PRS, due to the nature of the information (e.g. more certainty about risk estimates) and the population offered testing (e.g. only families known to have high cholesterol). More recent studies have evolved to incorporate more SNPs, which may have greater predictive performance, and have explored the clinical, behavioural and psychological impact of incorporating genetic risk information into a risk assessment alongside other risk factors.

There are limited studies exploring the clinical utility of polygenic scores for cardiovascular disease. However, a handful of studies to date have explored the clinical, behavioural and psychological impact of incorporating polygenic scores into risk assessments alongside other risk factors. A search for recent studies on online databases revealed two key randomised controlled trials (RCTs) using CVD-related RCTs. MI-GENES [153, 154] was an RCT investigating the impacts of incorporating a polygenic score into Coronary Heart Disease (CHD) risk score estimates in the US. INFORM [155] was an RCT comparing the short-term behavioural impacts of risk information based on phenotypic characteristics against phenotypic plus genetic characteristics in the UK.

In both instances, these RCTs were designed to evaluate whether people are more likely to engage in risk-reducing behaviours when genetic risk information is included in the risk assessment. The MI-GENES trial screened for 28 CHD susceptibility SNPs, and the INFORM trial for 46 SNPs selected from 49 known genomic loci robustly associated with risk of CHD. Participants were not asked whether they viewed genetic information as different to other types of risk information (although there have been qualitative interview studies conducted to explore this question [156]). Rather, the RCT studies were designed to detect between-group differences in behavioural and psychological outcomes assessed at follow-up, comparing between groups with, versus without, genetic information in the risk assessment (as against providing insight into the conscious motivations self-reported by participants). The implications of this limited empirical evidence from research that has incorporated polygenic scores into CVD risk assessments to date [153–155]are discussed below.

CVD-related health outcomes (benefits)

There is no evidence regarding the impact of the incorporation of PRS on primary CVD-related mortality and CVD events. This is due to the fact that only the short term effects were investigated and the duration of follow-up was relatively short for both INFORM (12 weeks) and MI-GENES (6 months). However, there is preliminary evidence from the MI-GENES study to suggest that individuals who received a PRS in addition to a conventional risk estimate for CHD had lower LDL-C levels 6 months after disclosure than participants who received a conventional risk score alone [153].

Behavioural outcomes (benefits)

The results of the few studies to date suggest that there is no clear or consistent evidence that incorporating genetic risk information either raises motivation or translates into actual behaviour change, although further research on this topic is needed. Disclosure of genetic risk did not lead to significant differences in dietary fat intake or physical activity in either study, highlighting an established public health problem that prompting patients to adopt and sustain lifestyle changes remains challenging. However, the MI-GENES study did find that disclosure of risk estimates that included a PRS led to increased information-seeking and information-sharing behaviours [154]. Moreover, it was also reported in the MI-GENES study that the incorporation of genetic risk into shared decision-making sessions with patients and providers led to a modest increase in statin utilisation in those with high genetic risk [153].

Psychological outcomes (harms)

PRS are made up of common variants that confer small incremental risks. There is concern that patients over interpret these variants and perceive the risks as deterministic (genetic fatalism), that disclosure of genetic risk for CVD may be misunderstood by clinicians and patients, and that this might increase stress and anxiety levels in patients with high genetic risk and induce a sense of invulnerability in those at low genetic risk. Therefore the nature and extent of psychological harm is dependent on the clarity and accuracy with which the risk is communicated. This is to be explored in greater depth in a forthcoming report focusing on humanities aspects associated with the use of PRS. However, these and other studies in systematic reviews found that disclosure of genetic risk is not associated with greater anxiety levels or depression and is unlikely to produce lasting emotional harm [138, 153, 155]. This is consistent with other earlier studies on disclosing genetic risk of common complex disorders [151]. There is limited evidence regarding clinician or patient comprehension of the information, and little is known about the harm of confusion or misunderstanding.

Overall, there is little empirical evidence to suggest that incorporating genetic risk information has impact on behaviour change beyond conventional risk factors. There is no evidence regarding the impact of PRS on improved CVD health outcomes (due to the lack of long term follow up), and little evidence of impact on lifestyle behaviours such as diet/exercise. However, there is some limited evidence to suggest possibly higher rates of medication use (i.e. statin initiation) in those who receive genetic information relative to conventional risk estimates alone. Crucially, this beneficial impact is not outweighed by harmful impact as there is no evidence to suggest that the harms are more severe for those receiving risk scores that incorporated PRS, compared to those for which PRS was not incorporated.

7.5 Existing evidence gaps

The two CVD-focused trials (MI-GENES and INFORM) described above are part of a 'bigger picture' of studies on the impacts of returning polygenic scores based on only a few SNPs or other common DNA variants to patients or participants. However, significant evidence gaps remain:

- **Outcomes selected for review:** There is a lack of high quality evidence on those people who are particularly likely to benefit from the addition of PRS, namely the small subset of people who might be high risk based on PRS but who are currently undetected based on conventional risk assessments. Similarly, there is limited empirical evidence to demonstrate the impact of adding PRS to existing risk assessment tools

- **Studies needed on participants at high risk:** Studies are needed to test the hypothesis that identifying people at very high (genetic) risk has value through prompting risk-reducing action. For example, the INFORM study was a large well-designed trial, but it is important to note that the study design primarily allowed testing of the hypothesis that (genetic) risk information — regardless of whether low, average or high risk — would motivate risk-reducing action. There is little theory or evidence-based reason to suggest low/average risk information is more motivating than no risk information

- **Studies conducted on representative populations:** Additional studies are needed to study the effects of disclosure of genetic risk for CVD in various ethnic groups and in the 'real world' setting of primary care

- **Duration of longitudinal follow-up:** There is an absence of large-scale clinical trial data with long-term follow-up that is more able to unequivocally demonstrate a clear impact on risk-reducing behaviours and reduction of CVD events among participants whose overall risk and treatment recommendations have been directly informed by both their conventional and genetic risk factors

In the absence of a substantive empirical evidence base from which to assess integrated risk scores for CVD, in the following section we review a key theoretical framework for the development of behaviour change interventions and a model of behaviour change, which provides additional insight into the potential clinical utility of PRS when integrated into CVD risk assessments

7.6 Human behaviour theory and behaviour change intervention frameworks

Models and theories of human behaviour, and frameworks for the development and evaluation of complex behaviour change interventions, can help us interpret existing empirical studies (e.g. understand why behavioural outcomes of an intervention are or are not observed), and inform future research study designs (e.g. develop testable hypotheses and predict potential behavioural outcomes of an intervention). In this section, we provide a brief overview of the most comprehensive of these models and frameworks to date, and apply the framework to understand existing evidence regarding CVD risk assessments with and without PRS.

The Behaviour Change Wheel (BCW): an overview

The Behaviour Change Wheel (BCW) [157] is currently one of the most prominent frameworks for designing and evaluating complex behaviour change interventions. The BCW is a synthesis of 19 behaviour change frameworks that draw on a wide range of disciplines and approaches, and is designed for policy makers, practitioners, intervention designers and researchers [158]. The BCW posits three iterative 'stages' which provide a methodology for developing and implementing effective behaviour change interventions. The theoretical framework provided by the BCW can be applied to evaluate and help understand why current CVD risk assessments appear to have a small impact on statin initiation and little to no impact on lifestyle changes among individuals at high CVD risk.

Stage 1 - Understand the behaviour

In simple terms, this stage involves identifying the specific behaviour or behaviours to be changed, as well as the capabilities, opportunities and motivations (the COM-B model of behaviour) needed in order to help facilitate this change.

Individuals at high CVD risk but who do not know it and have not yet been identified as high risk within the healthcare system, are unlikely to be prescribed or be taking statins, and may also be less likely to be offered support to help them make risk-reducing lifestyle behavioural changes. Thus, we can think of the 'problem' of CVD in behavioural terms, i.e. that at least some high CVD risk individuals are not taking statins and/or are not making lifestyle behavioural changes. Behaviour change theory suggests that in order to help people make these risk-reducing behaviour changes, people identified as being at high CVD risk subsequently need the capability (physical, psychological), opportunity (social, physical) and motivation (reflective, automatic) to enact the behaviour(s) (statin initiation and/or lifestyle change).

Stage 2 - Identify intervention options

This stage involves identifying interventions that might address any missing capabilities, motivations or opportunities (e.g. education, environmental restructuring), and policy strategies to deliver these interventions (e.g. communication/marketing, environmental/social planning, service provision).

Current CVD risk assessments act as an intervention which provides information (education) about the patient's risk status to both the clinician and the patient. Behaviour change theory helps us see that this may impact clinicians' and patients' psychological capability (knowledge) and via this, their reflective motivation to change, but that it is unlikely to directly impact other key aspects required for behaviour change (e.g. automatic motivation, physical opportunity, or social capability).

Stage 3 - Identify intervention content and implementation options

The final step is to identify specific behaviour change techniques and mode/s of delivery for the specified intervention likely to be most feasible in the local context. Behaviour change theory highlights that interventions consisting of individual 'behaviour change techniques' (BCTs) (e.g. education or information about personal disease risks) alone are likely to be ineffective if they are employed in isolation [159]: thus, the theory is consistent with the empirical observation that CVD risk assessments alone do not motivate change in the majority of cases.

However, in individuals who have the motivation, opportunity and physical capability to act on risk information (e.g. people with considerable financial, social and other resources), this type of behaviour change technique may be sufficient to prompt change, even if delivered in isolation. But for most people, other behaviour change techniques such as goal setting, action planning and self-monitoring of behaviour are likely to be needed to accompany the risk information.

However, it is worth noting that clinicians who deliver risk assessments to patients in research and clinical settings also prescribe statins, which can be viewed as a valid BCT designed to act as a form of enablement. Thus, behavioural theory helps explain why CVD risk assessments may lead to prescribing of statins (which is within the clinician's capability to impact) but are unlikely to lead lifestyle behavioural changes (which are most often outside of the clinician's control).

7.7 Using behavioural theory to evaluate CVD risk assessments that incorporate PRS

In the following section, we consider whether the incorporation of PRS into CVD risk assessments might be expected to change any aspect of this BCW theory-driven analysis.

Case 1: Patient who would otherwise remain unidentified is identified as high risk of CVD based on PRS.

The BCW framework methodology suggests that polygenic scores might be viewed relatively simply as an additional type of risk information when incorporated into multi-factor risk assessments for use by clinicians and patients. In the cases where PRS identify at-risk people who would otherwise be un-identified, the PRS provides important additional information about the causes and consequences of ill health, potentially impacting on clinicians' and patients' psychological capability to act (because they now have information they did not have before); and this in turn potentially impacts on both the clinician's and patient's conscious motivation to engage in risk-reducing behaviour.

Just as with conventional risk assessments, because the clinician has the capability to prescribe effective risk-reducing statins, but may not be able to effectively support lasting lifestyle change, they are more likely to successfully enable the patient to start on statins than to make lifestyle changes.

In this context of a PRS identifying high-risk individuals who would otherwise not have been picked up using a conventional assessment, the PRS seems likely to impact on behaviour in a similar way to non-genetic risk information, namely as a form of education rather than as information with 'special' or unique characteristics.

Case 2: Patient is identified as at high risk of CVD based on a combination of conventional and PRS risk factors

CVD risk assessments that include PRS might have a beneficial behavioural impact over and above conventional risk assessments in contexts where patients are identified as being at high risk based on a combination of conventional and PRS based risk factors. For example, currently, NICE guidelines are that patients with elevated LDL cholesterol levels and/or absolute CVD risk greater than 10% should engage in shared decision-making with their clinician, and together the patient and clinician should decide whether the patient will start on a statin and/or try to make lifestyle changes. If a patient is identified as having a high CVD risk based on a combination of conventional risk factors and the PRS, this could impact the clinician's decision-making and prompt them to more strongly recommend that a statin is prescribed; it might also impact the patient by prompting them to adhere to the statin once initiated.

The first stage of the BCW process, in which the behavioural diagnosis is made, is perhaps the most crucial here. The BCW encourages us to define the 'problem' in behavioural terms: whereas previously we were defining the 'problem' as people generically not taking statins and/or not making lifestyle changes, the 'problem' can be defined more specifically in terms of clinicians' behaviour, e.g. as 'clinicians do not recommend statins strongly enough to patients at high risk of CVD.' The 'problem' can also be defined more specifically in terms of patients' behaviour, e.g. as 'patients at high risk of CVD have low initiation of, and/or adherence to, prescribed statins.' Although the intervention functions and content remain largely the same as previously, this re-framing of the behavioural 'problem', can help us see that PRS might have additional motivational impacts above and beyond non-genetic risk factors.

Considerations for future research

It is important to note that these hypotheses about polygenic scores based on the BCW framework are speculative and have not yet been tested in empirical research studies. There are therefore significant research gaps which need to be addressed. This includes research to understand and to determine the optimal ways to communicate risk information and deliver interventions to support risk-reducing actions for patients at differing levels of risk. This research could help to shed light on whether and how different behaviour change methods are effective for different subsets of individuals, whose ability and motivation to enact change may vary depending on their risk profile and the opportunities and capabilities they have. Research should also clarify what additional support is required to enable different types of outcome e.g. distinguishing between the support that will be required for lifestyle change, statin initiation and adherence, as this might vary. However, these research questions are not specific to polygenic scores and apply to other biomarkers and risk scores as well.

7.8 Summary

Current CVD risk assessment tools are considered to be useful despite inconclusive evidence for the clinical utility from research studies. This is because their ability to better stratify patients and therefore enable resources to be better distributed to those who can derive the most benefit is considered sufficient evidence of utility.

The inclusion of polygenic scores into established risk tools has the potential to improve their clinical utility, through more accurate stratification, and potentially by identifying those at high risk who would otherwise not have been identified through conventional risk assessment.

Although dialogues of patient empowerment and control are central to current narratives around genetics, there is currently a lack of empirical evidence to suggest the inclusion of PRS would make important differences to patient behaviours. This is reinforced by theoretical models of behaviour change that suggest that whilst the addition of PRS may itself be enough to motivate a small subset of the population to change their behaviour under specific conditions, crucially provision of PRS needs to be combined with other forms of support. These include communication and system level changes to help address social determinants of health in order to increase medication adherence and motivate healthy behaviour change more widely.

Although clinical utility may not immediately be derived from PRS through motivating risk-reducing behaviours, it is likely to be through improved accuracy of the assessment, and potentially via motivating risk-reducing action among individuals who would not have been identified as high-risk via conventional risk factors. Therefore, as the harms are likely to be minimal, and are likely to be outweighed by the benefits, this suggests that PRS as part of a CVD risk assessment may have clinical utility, but further evidence is needed to establish this.

8 Conclusions

Thorough assessment of the application of polygenic scores for cardiovascular disease risk suggests that this is a promising area of development. Research indicates that a polygenic score for CAD can improve stratification, and hence potentially support more effective prevention. Nevertheless, there are still considerable gaps in knowledge, such that polygenic scores are not likely to be ready for implementation in clinical practice in the next 3 years.

The main areas where further information and evidence are still needed are outlined below:

Clinical grade assays to obtain polygenic scores

Integration of polygenic scores into clinical practice for any application requires robust and validated mechanisms to generate these scores. There are several options for developing a 'polygenic score assay', and practical, clinical-grade assays will most probably have to achieve a suitable trade-off between methods for obtaining genotype data, processes for score construction, and model performance.

Validated tests for use in clinical practice

A polygenic score-based test for cardiovascular disease is yet to be developed and evaluated. Development of such a test requires the explicit use of a defined assay in a particular population and for a particular purpose. Most studies examining PRS-CAD to date lack a clearly defined clinical purpose, and an implementation-ready clinical test is therefore not yet available.

The added value of polygenic information for prevention

There are many potential applications of polygenic score information for the prevention of cardiovascular disease, ranging from standalone risk prediction tools to incorporation alongside other factors as part of an integrated tool. Ascertaining the true worth of polygenic score information to allow development of such a tool will require consideration both of clinical need and where in the existing prevention pathways such information could add value.

Indications are that in the short-term, the greatest added value from polygenic scores is likely to arise from integration with existing disease risk assessment tools. Such tools are already a part of established clinical practice and used in prioritising and planning primary prevention interventions. They are regarded as having clinical utility, even though empirical evidence supporting their use and the impact of cardiovascular risk tools is limited. The addition of PRS could improve the predictive performance of these tools, which may be regarded as beneficial if the cost and effort required to obtain a polygenic score are considered acceptable.

Evidence of additional clinical utility

Analysis confirms that there is currently no evidence for the clinical utility of PRS for cardiovascular disease prevention. This reflects the absence of a clear clinical application for PRS, at this stage. The evidence base required for potential clinical uptake will vary for different applications. For example, where PRS-CAD is to be included as part of an existing risk tool, improved performance and limited cost are likely to be sufficient to consider implementation. This is because, although there is little empirical evidence to suggest that incorporating genetic risk information has any additional beneficial impact on individual behaviours beyond that arising from conventional risk factor information, there is also no evidence of additional harm. Nevertheless, utilising PRS outside of this very specific context may require consideration of what additional clinical utility is offered.

Developing the evidence base

Ideally, a formal evaluation of the use of PRS testing for each potential application within a specified care pathway should be undertaken prior to NHS implementation. This would include determining the analytical validity of each PRS assay, as well as the clinical validity and utility of each test within the relevant pathway. However, this is currently a challenging task due to methodological limitations, the lack of available data and of resources to comprehensively evaluate prediction models. With such barriers in mind, it is important to consider mechanisms that could address knowledge gaps.

At present, datasets containing genomic information on individuals from diverse ethnic backgrounds are scarce. This poses a significant challenge for the development and external validation of polygenic scores. Current initiatives such as plans to sequence the genomes of up to five million individuals over the next few years from UK Biobank and NHS patients, and to develop a cohort of healthy participants as part of these sequencing efforts, are important opportunities to address this need. Going forward, it will be important to ensure these cohorts contain the appropriate population mix for validation of robust polygenic scores.

Whilst existing frameworks for the evaluation of prediction models can act as a guideline for evaluation of risk prediction based on polygenic scores, further refinement of this process is needed to clearly understand which criteria need to be fulfilled. Developing such a framework with appropriate input from experts such as statisticians, clinicians, researchers, decision-makers and model developers will be an important step in addressing this challenge.

Health system readiness

Implementation-ready tools based on polygenic scores for cardiovascular disease prevention are not yet a reality, but are likely to be forthcoming. The logistical and financial impact of a move towards cardiovascular programmes that incorporate genomic information may be significant, requiring careful assessment and planning. The potential effects on services and resources, such as laboratory testing, NHS Health Checks programme and primary care will also need careful consideration, given the potentially large number of individuals that could be tested.

Looking towards the future, if genomic information in the form of polygenic scores is to be more widely used within cardiovascular disease prevention programmes, health systems will need to engage with health professionals and citizens to ensure that they understand the use of genomic information in the context of prevention of common diseases, and that conferred by high-risk disease causing genomic variants, which can have implications for family members.

Addressing the complexities of behaviour change

Education-based interventions such as a CVD risk assessment (with or without PRS) are likely to fail if they only address a small number of the components required for behaviour change to occur. Theoretical models of behaviour change suggest that, whilst the addition of PRS may itself be enough to motivate a small subset of the population to change under specific conditions, it needs to be combined with clear communication and system level changes to address social determinants of health in order to motivate healthy behaviour change more widely, and to increase medication adherence. Consequently, incorporating other elements (e.g. training, environmental restructuring or enablement) that engage other traits (capability, opportunity or motivation) might better facilitate constructive behaviour change at significant levels.

The necessity for horizon scanning

The field of polygenic scores is a dynamic and rapidly advancing research area. Going forward, it is thus important to keep abreast of developments in order to identify emerging applications as early as possible.

Such horizon scanning efforts should consider wider polygenic score developments as well as focusing on specific disease areas. This report has focused on polygenic scores for cardiovascular disease, but research in other diseases may be more advanced. Together with the overlap of cardiovascular disease prevention with other common diseases, this means that integration of genomic information will have to be viewed both from a disease-specific context and from the broader context of prevention of common diseases.

Issues arising from polygenic score development in other disease areas can also inform models of service delivery and integration of genomics into prevention programmes for common diseases. A clearer understanding of possible service delivery models can help shape the collection of evidence of clinical utility.

The future of polygenic scores and disease prevention

Genetic contributions to disease risk are defined at birth, and remain stable throughout the life-course. There is therefore considerable interest in the potential use of polygenic scores as a biomarker for earlier identification of those at increased risk prior to manifestation of clinical disease indicators.

For example, in cardiovascular disease there is evidence that plaque build-up in the vasculature (atherosclerosis) can begin at an early age (pre-teen) and stay with individuals for life. Individual genetic information could provide the earliest indication of a predisposition to such build-up, allowing preventative action to be taken in high-risk individuals from a younger age, perhaps even before plaques begin building in childhood.

Interventions in these high-risk individuals could be close monitoring, lifestyle adaptation or use of therapeutics. In the future, it is possible that once an individual has been genotyped with WGS or a SNP array, multiple polygenic scores could be generated for numerous diseases, traits and subtypes of disease.

This scenario would enable a move towards predictive prevention, but would also require careful consideration of interventions to be offered to individuals identified at elevated risk and demonstration of beneficial health impacts. As many primary prevention interventions rely on behaviour change (whether addressing lifestyle factors or compliance with treatments), further research is also needed on techniques that support achieving these goals, including in younger populations. Ongoing research to determine the public acceptability of programmes with a focus on prevention as opposed to early detection are also needed, together with research and evaluation to determine potential wider societal impact.

It is likely that polygenic scores will be combined with other risk factor information and incorporated within existing risk prediction models in the near future. The use of polygenic scores in isolation to influence prevention efforts has been proposed as a possibility, but the evidence for and possible applications of such an approach remain to be developed.

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making science work for health

About the PHG Foundation

The PHG Foundation is a pioneering independent think-tank with a special focus on genomics and other emerging health technologies that can provide more accurate and effective personalised medicine. Our mission is to make science work for health. Established in 1997 as the founding UK centre for public health genomics, we are now an acknowledged world leader in the effective and responsible translation and application of genomic technologies for health.In April 2018 we became part of the University of Cambridge.

We create robust policy solutions to problems and barriers relating to implementation of science in health services, and provide knowledge, evidence and ideas to stimulate and direct well-informed discussion and debate on the potential and pitfalls of key biomedical developments, and to inform and educate stakeholders. We also provide expert research, analysis, health services planning and consultancy services for governments, health systems, and other non-profit organisations.

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