Metabolic risk and cardiovascular disease: insights from large biobanks with genetic epidemiological approaches

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CHAPTER 9

Discussion and future perspectives

The overall aim of this thesis was to gain additional in-depth insights into the metabolic risk assessment and management of cardiovascular disease (CVD), based on multiple omics data sources in large population studies and biobanks. The studies described in this thesis contributed to improved insight into the incidence of CVD in three main research areas: 1) the pathophysiological mechanisms of atherosclerosis (**Part I)**, chapters 2 and 3 aimed to capture distinct metabolomic profiles associated with CVD and to characterize a potential novel therapeutic target; 2) the genetics of CVD risk factors (**Part II)**, chapter 4 examined the age-dependent genetic effects on metabolic risk factors of CVD, and chapter 5 investigated the effects of structural genetic variants on sleep disturbances, which is being increasingly considered an important cardiovascular risk factor; 3) inter-individual variations and corresponding CVD risk (**Part III)**, chapters 6, 7 and 8 addressed the role of metabolic syndrome, Lp(a) and subclinical hypothyroidism in CVD risk. In the current chapter, the implications, limitations and future perspectives derived from these different research areas will be discussed.

1. The roles of HDL - challenges and opportunities

It is well-known that both Mendelian randomization (MR) studies (1) and clinical trials (2, 3) have so far failed to support a causal role for high-density lipoprotein-cholesterol (HDL-C) in cardiovascular disease. However, evidence from previous studies suggested that the HDL particle profile, especially small HDL particles, should be considered to be better able to stratify individuals based on cardiovascular risk (4). Notably, small HDL was found to have atheroprotective effects (5, 6), and very small HDL particle number was also found to be strongly associated with lower cardiovascular risk in patients with type 1 diabetes (7). Consistent with these previous findings, our studies in **Chapter 2** and **Chapter 3** suggest that the specific HDL-subclass distribution, independent of ApoB concentration, characterised by higher levels of small HDL particles and lower levels of large HDL particles, may have a potential role in the prevention of cardiovascular disease. Overall, these findings suggest that the single measure HDL-C does not fully capture the role of HDL in CVD. In line, the focus of HDL research has gradually shifted to assessment of HDL function, especially its roles in atherosclerosis, such as reverse cholesterol transport, and inhibition of inflammation and oxidative stress (8-10).

HDL-based therapy in the field of CVD

Reverse cholesterol transport, being the most extensively studied function of HDL, involves several multi-step dynamic processes, including cellular cholesterol efflux to nascent HDL particles, cholesterol esterification, maturation of HDL and cholesterol clearance via the liver.

Cholesterol efflux is the initial step in reverse cholesterol transport, and previous studies indicated that cholesterol efflux capacity was inversely associated with cardiovascular events, independent of HDL-C (11-13). In addition, it has long been suggested that increasing the plasma levels of ApoA1, the main protein in HDLs, could result in an increased level of small HDL particles, increased cholesterol efflux capacity and reduced cardiovascular risk (11). Therefore, HDL or ApoA1 has been suggested as an attractive therapeutic target to combat CVD (14). Although the recent AEGIS-II trial found that weekly four infusions of CSL112 (composed of human plasma–derived ApoA1) did not significantly reduce the risk of recurrent cardiovascular events after acute myocardial infarction (15), the results did suggest a potential trend toward benefit. The lack of a significant effect may be attributable to the short 90-days follow-up period and the advanced stage of atherosclerotic cardiovascular disease in this secondary disease prevention trial. In addition, achieving clinical benefit may require not only increased efflux of cholesterol from atherosclerotic plaques to HDL, but also an increased flux of cholesterol from large HDL particles to the liver. The scavenger receptor class BI (SR-BI) promotes selective hepatic uptake of cholesterol, primarily from large cholesterol-enriched HDL particles (16), and hepatic SR-BI deficiency was associated with an increased cardiovascular risk despite increased HDL-C levels (17). Presumably, this increased HDL-C is caused by the accumulation of cholesterol loaded large HDL particles that cannot be cleared via SR-BI by the liver.

Notably, a recent paper identified a protective effect of medium HDL against atherosclerosis by examining associations of NMR-based (apo)lipoprotein profile with carotid intima-media thickness and coronary artery disease, and provided evidence from multi-omics data that the *PSRC1* gene is a potential drug target for medium HDL with therapeutic potential also for coronary artery disease (18). In line with this observation, in **Chapter 2**, we found that the rs12740374 genetic variant mapping to *PSRC1* was genome-wide significantly associated with the profile characterised by HDL-subclass distribution. Although emerging evidence indicates the potential of HDL-based therapies to improve cardiovascular disease prevention, there are currently no clinical trials that have successfully demonstrated the beneficial effects of HDL-based therapy on cardiovascular disease. In the future, perhaps a reconceptualization (19) is needed that focuses on developing better assays for characterizing HDL functions that can be used in conjunction with genomics, metabolomics, proteomics, and transcriptomics to identify novel targets (8) and the correct (sub)population of patients in which to test therapies to improve cholesterol efflux and the functionality of HDL.

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HDL - beyond lipid metabolism

Emerging evidence suggests that HDL exerts a wide range of pleiotropic effects beyond lipid metabolism (8, 9). First, HDL has been shown to play a significant role in modulating coagulation pathways (20). One of the key mechanisms by which HDL influences coagulation is through its interaction with endothelial cells. HDL inhibits the expression of tissue factor, a critical initiator of the coagulation cascade, thereby reducing thrombogenicity and the risk of arterial thrombosis (20). Additionally, HDL enhances the production of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, further contributing to its antithrombotic properties (20). A study showed that patients with high levels of both ApoA1 and HDL-C have a lower risk of recurrent venous thromboembolism (21). In addition, evidence from preclinical data supports a protective role of HDL in preventing hyperglycaemia (22). A prior study showed that CETP inhibitors could reduce the incidence and progression of diabetes, which may have been related, at least in part, to the increase in HDL-C concentration (23). Another study reported that infusing discoidal reconstituted HDL into patients with type 2 diabetes increased plasma insulin levels and reduced plasma glucose levels (24). Although these specific therapies have not been translated to clinical use, they underscore the merit of investigating whether interventions that target HDL metabolism may be used for the prevention and treatment of diabetes. A previous study showed that patients with diabetes have decreased antioxidant and anti-inflammatory functions of HDL (25). Importantly, both antithrombotic and antidiabetic effects of HDL could further decrease the risk of CVD development.

Furthermore, HDL may play a protective role in sepsis, which is a life-threatening condition characterized by systemic inflammation and organ dysfunction. HDL particles have a number of properties that are relevant to sepsis, including their ability to bind and inactivate pathogen-associated lipids such as lipopolysaccharide, as well as their anti-inflammatory and antithrombotic actions and their ability to enhance inflammatory responses in macrophages (26). In addition, a population-based cohort study showed that HDL levels were lower in patients with sepsis, and this reduction was associated with worse clinical outcomes (27, 28). Early-phase preclinical trials have also suggested that HDL-based therapies could be beneficial for the treatment of sepsis and other inflammatory conditions (29). These findings highlight the potential of HDL-based therapies for the treatment of sepsis and other inflammatory conditions.

The diverse roles of HDL beyond lipid metabolism underscore the need for a broader understanding of its biology and therapeutic potential. Future research could leverage advanced omics technologies, such as proteomics and metabolomics, to unravel the molecular mechanisms underpinning pleiotropic effects of HDL. Integrating these omics data

with advanced computational methodologies, like machine learning approaches, may further reveal novel biomarkers of HDL functionality, moving beyond traditional HDL-C measurements to assess its protective capacity. Such advancements could pave the way for more personalized interventions tailored to individual risk profiles, particularly in complex diseases.

2. Lifecourse genomics studies

Genome-wide association studies (GWASs) have so far identified thousands of variants associated with biological traits and diseases (30). However, studies commonly quantify the impact of genetic variation on a single trait statistically corrected for age, but for most traits it not fully clear whether the genetic variants have similar or different effects on the studied outcome at different time periods over the life course within a population. Previous studies have observed some age-dependent genetic effects for cardiometabolic risk factors (31-36), including lipids, blood pressure and body mass index (BMI). In addition, a study based on UK Biobank (UKB) participants aged 40 to 70 years found that polygenic risk scores (PRS) for coronary artery disease (CAD) are more predictive for cardiovascular risk in younger individuals, with the proportion of myocardial infarction risk attributable to the CAD PRS declining from 30% to less than 10% over the 30-year age range (37). Therefore, based on these findings, it could be concluded that specific genetic factors contribute to disease risk in an age-dependent manner across the lifespan.

However, most of the previous study populations primarily consisted of middle-aged to old adults. As a result, this introduced potential survival bias, as individuals with a high genetic risk for the investigated phenotypes may have already developed the condition or experienced adverse health outcomes before enrolment. In addition, middle-aged to older adults have been accumulatively exposed to environmental factors and lifestyle behaviours for a long time, which may play a more dominant role in explaining the later-life risk than genetic factors. Consistent with this hypothesis, in **Chapter 4**, we investigated the genetic risk for common metabolic cardiovascular risk factors over a 30-year period spanning middle age, and observed age-dependent effects for only a few genetic variants. Future studies should prioritize extensive longitudinal designs that follow individuals from birth to old age, allowing for a more comprehensive understanding of how genetic risk evolves over the life course.

Another limitation is the overrepresentation of European-ancestry individuals in previous genetic research. This lack of diversity limits the generalizability of findings to other population groups, particularly given the heterogeneous genetic architecture of

cardiometabolic traits across ancestries (38, 39). Studies have shown that genetic risk scores derived from European populations often perform poorly when applied to non-European groups (40-42). For example, African populations have diverse genetic backgrounds, and a genomic architecture with smaller haplotype blocks compared to European genomes (43). In this context, the majority of the existing PRS developed from European data not only showed limited transferability, but also showed large variation, like PRS prediction on LDL-C varying greatly between the South African Zulu (R^2 = 8.14%) and Ugandan cohorts (R^2 = 0.026%) (42). Additionally, participation bias in large cohorts such as the UK Biobank, where participants tend to be healthier and have higher socioeconomic status than the general population, may further skew results in studies (44). This bias has profound implications for understanding gene-age-environment interactions, as individuals from deprived backgrounds often face worse environmental conditions, limited access to healthy food, and higher levels of chronic stress, which may affect disease risks. Therefore, inclusion of diverse populations in studies is important to ensure that findings are broadly applicable and to better capture the interplay between genetic and environmental factors.

In addition, exploring the interplay between genetic predispositions and environmental factors, including modifiable lifestyle factors, throughout the lifecourse could provide actionable insights for disease prevention and intervention strategies. Research has consistently shown that while genetic predisposition plays a significant role in determining cardiometabolic risk, lifestyle modifications can substantially mitigate long-term health risks (45-48). For example, individuals with high genetic risk for abdominal obesity who adhere to a healthy lifestyle may have a lower risk of developing coronary heart disease compared to those with low genetic risk but an unhealthy lifestyle (45). Moreover, studies have shown that childhood risk factors, including elevated LDL-C and BMI, are associated with adult CVD, independent of adulthood levels of these factors (49), suggesting that early intervention is crucial. Additionally, integrating genetic risk information with personalized lifestyle interventions may enhance the effectiveness of prevention strategies, particularly in underserved populations (50). Taken together, this evidence highlights the need to integrate genetic risk information with personalized lifestyle interventions from an early age, particularly for high-risk individuals.

Furthermore, several methodological challenges must be addressed when conducting life course genetic studies to ensure robust and reliable findings. First, investigating gene-environment interactions requires high statistical power, which is often limited by sample size and the complexity of interactions. Second, selection and survival bias are particularly problematic in older populations, as individuals with the highest genetic risk may have already died or dropped out of the study, leading to an underestimation of genetic effects (51). In summary, while life course genetic studies hold great promise for understanding the

interplay between genetics and environment, addressing these existing limitations and challenges is critical to ensure the validity and generalizability of findings.

3. Genetic risk beyond SNPs - structural variants and epigenetics

Extensive GWAS with many thousands or even millions of individuals have identified loci that explain a sub-portion of the hereditability, and provided insight into the underlying biological mechanisms of CVD and its risk factors (52, 53). However, the proportion of heritability explained by these loci remains limited, suggesting that genetics alone cannot fully account for the risk of complex diseases. This "missing heritability" underscores the importance of exploring additional factors, such as epigenetic modifications, which may play critical roles in shaping disease risk (54). Epigenetic changes, such as deoxyribonucleic acid (DNA) methylation and histone modification, accumulate over time and can modify the expression of genes associated with cardiovascular risk. For example, a study summarized the evidence of altered DNA methylation associated with cigarette smoke (55), and a study on physical activity found that a physically active lifestyle is associated with a 40% reduction in the genetic predisposition to common obesity (56). In addition, in **Chapter 4** of this thesis, we observed that rs429358 (mapped to *APOE*) showed interactions with age on both ApoB and TG, and three additional lead variants were identified for ApoB: rs11591147 (R46L in *PCSK9*), rs34601365 (near *APOB*), and rs17248720 (near *LDLR*). Effect sizes of the identified lead genetic variants were closer to the null with increasing age. Considering the well-known roles of all identified genes (*APOE4*, *PCSK9*, *APOB* and *LDLR*) in lipoprotein metabolism, and in particular their effects on LDL receptor (LDLR) numbers or LDLR activity (57-60), it is reasonable to assume that the age-related decrease in *LDLR* expression could partially explain the attenuated genetic effects with aging in our study. Our hypothesis is supported by previous evidence from population and animal studies on the increase in LDL-C with age, which is attributed to the reduced hepatic *LDLR* expression leading to a reduced capacity to remove LDL-C (61, 62). All these lines of evidence suggest a potential role for epigenetic modifications to serve as a bridge between genetic predisposition and environmental influences and triggers.

Beyond well-characterized and common types of genetic variations, like single nucleotide polymorphisms (SNPs), other forms of genetic variation, such as copy number variations (CNV) or repetitive sequences and retroviral insertions, also play important roles in disease risk but are less frequently investigated. It is well-known that certain diseases are associated with the expansion of trinucleotide repeats beyond normal thresholds. For instance, Huntington's disease is linked to a cytosine-adenine-guanine (CAG) codon repeat expansion

in the *HTT* gene, leading to neurodegeneration (63). Notably, recent studies have revealed that the CAG repeat expansion below the pathogenic threshold is also associated with other metabolic phenotypes, such as plasma lipids and BMI (64, 65). Previous evidence showed that CAG repeat variations could account for 0.75% of the total BMI variation (65). In **Chapter 5**, we observed a (non-linear) association between CAG repeats and sleep disorders in two Dutch cohorts, and the explained variance of CAG repeats for sleep disorders could even be up to 12%. In addition, human endogenous retroviruses (HERVs) constitute a significant portion of the human genome and have been implicated in various diseases. Recent research has highlighted extensive HERV expression and regulation in the adult cortex, including associations with psychiatric disorder risk (66). Addressing the impact of these poorly measured genetic variations requires advanced genomic technologies, such as long-read sequencing and comprehensive bioinformatics analyses, to detect and interpret complex structural variations. Incorporating these approaches into genetic studies can enhance our understanding of the full spectrum of genetic contributions to cardiovascular risk.

4. Personalized prevention for cardiovascular risk

Although the age-standardized global mortality related to CVD showed a 27% decline between 2000 and 2019 (67), CVD still remains a leading cause of death, and contributes substantially to morbidity and associated healthcare costs (68-70). One of main challenges in CVD prevention is that the individual variations among populations (e.g., age, sex, family history, ethnicity, lifestyle) could result in heterogenous effects on disease development and treatment response (71). First, a growing amount of evidence has revealed the importance of including sex differences in prevalence and presentation of cardiovascular conditions. Previous studies suggested that while women and men mostly share traditional risk factors (like diabetes, hypertension, obesity, and smoking) for CVD, the relative impact of risk factors is greater in women compared to men (72). In **Chapter 6** of this thesis, we found that (middle-aged and older) women with an unfavourable dyslipidaemia profile have higher risk of developing CAD compared to men with a similar dyslipidaemia profile. Moreover, two large guidelines have incorporated premature menopause as a "risk-enhancing" or "risk-modifying" factor for atherosclerotic CVD to guide patient risk assessment (73, 74). It has been suggested that premature natural and surgical menopause is not only an emerging risk factor for adverse cardiovascular outcomes in women, but also may increase the risk of developing additional cardiovascular risk factors (72, 75). Furthermore, in **Chapter 5**, we observed that non-pathogenic CAG repeat sizes are associated with sleep health, especially for women and postmenopausal women with severe depression status. The complex interplay between estrogen and dopamine (76) may explain the sex- and menopause-specific

associations between CAG repeat length and sleep health. However, gaps in our understanding of sex-related diversity in cardiovascular health over the life course still persist. Importantly, despite the fact that CVD is a leading cause of female deaths, the CVD risk in women remains underestimated and understudied, leading to underdiagnosis and undertreatment of CVDs in women (77).

In addition, aging is a large non-modifiable risk factor for CVD, and other common CVD risk factors, including obesity, dyslipidaemia and diabetes, are also closely associated with increased age (78, 79). Notably, compared to younger populations, older populations have a relatively high prevalence of subclinical hypothyroidism (which is biochemically characterised by elevated circulating TSH concentrations, while circulating concentrations of thyroid hormones are within the population reference range). In previous observational studies, subclinical hypothyroidism has been associated with increased risk of CVD, and it has been suggested that the impact of subclinical hypothyroidism may vary depending on the magnitude of TSH elevation and on age (80). Up to this date, randomised clinical trials have failed to identify any benefit of treatment of (mild) subclinical hypothyroidism with synthetic thyroid hormone (levothyroxine) on CVD incidence (81). As CVD develops over a long period of time, in **Chapter 8** of this thesis, we investigated the 1-year levothyroxine treatment response effects using ^{1}H-NMR based cardiometabolic biomarkers in older people aged 65 years and over with subclinical hypothyroidism. We observed favourable effects of levothyroxine therapy on several atherogenic lipid measures only in participants with TSH> 10 IU/ml, and in interaction with statin use. These findings highlight the importance of personalised prevention strategies in older adults, suggesting that potential cardiovascular benefits of levothyroxine therapy in subclinical hypothyroidism may depend on individual factors such as baseline TSH levels and concurrent statin use. Tailoring interventions based on these characteristics could enhance the effectiveness of preventive approaches and guide treatment decisions in this heterogenous population.

5. MR - developments and limitations

Randomized controlled trials (RCTs) are regarded as the gold standard for assessing causal associations between exposures and health outcomes. By randomly allocating participants into treatment and control groups, RCTs effectively minimize confounding factors and biases that could obscure causal inferences. However, RCTs are often expensive and time-consuming, requiring substantial financial and logistical resources. Ethical concerns may also arise, especially when randomization could withhold beneficial treatments from certain participants. Furthermore, RCTs may not always be feasible for longer-term or large-scale population studies. With the emergence of large-scale cohorts and biobanks, researchers have

gained access to vast amounts of genetic and phenotypic data, enabling them to explore potential causal associations in observational studies. Therefore, advanced statistical methodologies based on genetics have been developed to strengthen causal inference in observational studies, reducing biases that typically arise from confounding and reverse causation. By leveraging genetic variants as instrumental variables to infer causal associations between risk factors and disease outcomes, MR, especially two-sample MR, is becoming a prominent approach in genetic epidemiology, which could provide insights into causal effects and unravel complex biological mechanisms underlying diseases. In addition, benefitted from the ongoing large number of GWAS with large-scale sample and a more cost-effective alternative to RCTs, MR has become highly popular in research.

Importantly, several limitations must be considered when applying and interpreting MR findings in the field of CVD research. A primary concern is horizontal pleiotropy, where genetic variants influence multiple traits beyond the exposure of interest, potentially biasing causal estimates. In particular, although the increasing availability of multi-omics data, such as metabolomics and proteomics, provides valuable opportunities to dissect the underlying pathophysiology, these highly correlated omics datasets suffer from pleiotropy as a critical issue in MR analyses. In **Chapter 2**, we employed principal component analysis on metabolomic measures to derive independent profiles, which helps mitigate pleiotropy bias caused by correlated traits. However, this approach also introduces limitations in result interpretation, as it may lead to a loss of biological specificity. Some MR methods have been developed to deal with this issue, including the methods of weighted-median and MR-Egger as sensitivity analyses to test for the potential existence of pleiotropy (82, 83), and multivariable MR (MVMR) as an advanced method that accounts for pleiotropy when estimating the effects of the exposure of interest (84). However, the application of these methods to omics data comes with several challenges. First, MVMR can become computationally intensive when applied to high-dimensional omics data (e.g., thousands of proteins or metabolites). Efficient algorithms and high-performance computing resources may be required. Besides, MVMR requires strong genetic instruments for all exposures included in the model. Weak instruments can lead to biased estimates and inflated type I error rates. However, in omics data, it can be challenging to find strong genetic instruments for all traits, especially for traits with low heritability or complex genetic architectures. Previous studies highlight the importance of addressing pleiotropy in omics-based MR studies by combining MR and colocalization evidence (85).

In addition, most MR methods, including two-sample MR, rely on summary statistics derived from independent samples. When the samples used to estimate genetic associations with exposures and outcomes overlap, this can introduce bias due to the winner's curse or overfitting (86). However, many GWAS meta-analyses include shared data sources, such as

the UKB cohort study. Therefore, it is crucial to carefully evaluate not only genetic stratification, which has received attention in research, but also sample overlap when applying open-source GWAS summary statistics to MR analyses. Additionally, the selection of appropriate instrumental variables is crucial, as weak instruments that explain only a small proportion of the variance in the exposure can result in imprecise and biased estimates. Measurement errors in assessing exposures and outcomes further complicate MR analyses, potentially leading to biased causal inferences. Lastly, conventional MR methods often assume linear associations between exposures and outcomes, which may not hold true in all scenarios, necessitating the development of methods to assess non-linear relationships. Taken together, critical evaluation of the best practical MR methodology is needed to infer causality between risk factors and diseases.

6. Clinical application of omics data

In recent years, because of the advent of high-throughput technologies together with the (public) availability of large datasets, omics data, including genomics, transcriptomics, proteomics, metabolomics and epigenomics, have gained popularity in medical research. These data sources, indicating different layers of biological information, are increasingly applied to deepen our understanding of complex diseases and biological pathways, including in the field of CVD research (87, 88). However, despite the growing popularity and application of omics data in research, their translation into clinical practice remains limited and is still evolving. One of the promising futures where omics, particularly genomics, is making progress toward clinical relevance is through the development and implementation of polygenic risk scores (PRS).

PRS - from research to clinical practice

Genomics, referring to the study of the DNA sequences across the entire genome of an organism, has been widely used to explore the genetic contributions to diseases or traits. Besides, advances in technologies, such as next-generation sequencing (NGS), have enabled rapid and cost-effective analyses of entire genomes. Consequently, the increasing amount of genomics data and the increasing availability of large cohort and biobank datasets have facilitated the development and validation of PRS methods across diverse cohorts. Another main reason for the growing popularity of PRS is its ability to aggregate the effects of numerous common genetic variants across the genome into a single risk score, allowing for stratification of individuals based on genetic susceptibility. In addition, unlike traditional risk factors that may fluctuate over time, PRS indicates a stable, lifelong risk estimate that can be

assessed early in life, even before the onset of clinical symptoms, thus providing opportunities for timely interventions and personalized prevention strategies.

Recent studies have demonstrated the potential clinical value of PRS in the CVD field (89). For example, a prior study (90) showed that adding PRS can improve the area under the receiving operating curve of the traditional risk factors by an average of 5.1% (95% CI: 4.9 - 5.2) across all age groups, and in particular by 6.3% (95% CI: 4.8 – 7.8) for those younger than 55 years old. Notably, research also showed that patients in the top 20% of genetic risk for coronary heart disease received the greatest benefit from statin therapy and PCSK9 inhibitors (91, 92). Recently, one study showed that a PRS capturing the dysfunction of endothelial cells identified LDL-sensitive individuals who might benefit most from the LDL-lowering treatment (93). This study emphasises the importance of identifying actionable genotypes that can guide treatment decisions, especially in the context of abundant GWAS data yet to be translated. In general, PRS-based methodology is increasingly recognized for their potential to enhance disease risk prediction and inform personalized prevention strategies. However, there are still some challenges in incorporating PRS into clinical practice.

First, it has been known that the performance of polygenic scores in non-European populations is generally poorer than performance in European ancestry samples, particularly for African ancestry samples (40-42). One study investigated PRS studies published in 2008 to 2017, and observed that 67% of studies included exclusively European ancestry participants, only 19% included East Asian ancestry participants, and only 3.8% were among cohorts of African, Hispanic, or Indigenous peoples (40). In addition, a standardized guideline for PRS in clinical applications is necessary and remains unresolved. Clear guidelines can facilitate the integration of PRS into clinical practice by defining roles and responsibilities, establishing best practices for communication, and ensuring consistency in implementation.

Researchers are trying to overcome these limitations to promote the clinical applications. A study (94) conducted by the Electronic Medical Records and Genomics (eMERGE) Network is a recent example aiming to addresses key challenges in PRS application, such as reduced predictive accuracy in non-European populations and the need for effective clinical integration. This study utilized a diverse cohort of 13,475 participants from the All of Us Research Program (95) to calibrate PRS models, adjusting for genetic ancestry to improve accuracy across populations. In addition, in this study, a comprehensive pipeline was established, including PRS transfer to clinical labs, validation, and the creation of a regulatory-compliant framework for returning PRS-based risk assessments to 25,000 participants, including 5000 children (94).

Omics in future practice

Although the above-mentioned developments hold promises for the future application of PRS in clinical practice, PRS alone is an imprecise tool for both clinical practice and medical research. GWAS identify genetic variants associated with disease risk but rarely pinpoint clear causal variants mapping to genes or elucidate the biological mechanisms mediating their effects (30). Many implicated variants reside in genomic regions with poorly understood biology or map to putative drug targets with unclear modulation pathways, complicating the translation of genetic insights into therapeutic development (96). The gap between genotype and phenotype highlights a critical limitation: genomics alone cannot fully capture the complexity of human disease. Disease risk and progression are shaped not only by genetic predisposition, but also by environmental factors, lifestyle, and dynamic physiological states, and the interactions among these.

Benefited from multiple omics data, integrating human genetics with high-throughput, population-scale proteomics and metabolomics offers a potential way to address this problem. While genomics provides a static blueprint of inherited risk, circulating proteins and metabolites serve as dynamic biomarkers that reflect the current state of health and disease (97, 98). For example, based on UKB proteomics profiling and genomics data, research has provided extensive insight into *trans* protein quantitative trait loci (pQTLs) across multiple biological domains, revealing genetic influences on ligand–receptor interactions and pathway perturbations across a diverse collection of cytokines and complement networks (99). Studies on integration of genomic and proteomic data identified protein biomarkers associated with type 2 diabetes risk, such as those involved in insulin signalling and inflammation pathways, providing potential therapeutic targets (100). These insights help clarify the downstream effects of genetic variation and may guide the development of new drug targets or biomarkers.

Nevertheless, there are still some challenges to overcome for the applications of multi-omics. Beyond the ethical concerns of data privacy and the complexities of obtaining informed consent for multi-omics profiling, technical challenges persist. Standardizing omics assays across diverse populations, ensuring cross-platform reproducibility, and managing the computational demands of integrating large-scale datasets are challengeable tasks. Moreover, interpreting these complex data for clinical use requires training for healthcare providers and clear communication strategies. The eMERGE study in establishing a regulatory framework provides an example (94), but broader implementation of omics-based tools in clinical practice will require interdisciplinary collaboration among geneticists, clinicians, bioinformaticians, and health initiatives.

In conclusion, CVD is a chronic and complex condition influenced by a diverse array of risk factors, requiring innovative and multidimensional strategies for effective prevention and management. This thesis highlights the potential of integrating genomics, metabolomics, and personalized approaches to enable more precise and individualized management of metabolic risk associated with CVD over the life course. In the future, with the developing large-scale datasets, multiple omics data, and advanced methodologies, research should not only focus on exploring the underlying disease mechanisms but also aim to translate these insights into actionable strategies that can reduce the CVD burden through more effective prevention and targeted interventions.

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