In this thesis, I investigated the influence of environmental and genetic factors on blood pressure (BP) across the lifespan by leveraging multiple data sources from the Netherlands and other countries. Figure 1 presents a graphical overview of the thesis chapters and how their content represents different periods of the lifespan.

This chapter is the general discussion of my findings. First, I interpret the main findings and their implications in a broader context (e.g. prevention and public health), then I give some comments regarding methods used in the thesis, finally, I discuss future research directions.

Figure 1. Graphic representation of the chapters and how they map to different periods of the lifespan. Color represents the content of the chapters: blue indicates the focus of environmental factors of BP, orange the focus of genetic factors of BP, and a mixture of blue and orange represents an investigation of both environmental and genetic factors and their interactions in the same chapter.
Main findings and interpretation

Part 1 Environmental factors influencing BP over the life course

Prenatal, perinatal, and postnatal factors influence childhood BP at age 6

There is still much uncertainty in the field of developmental origins of BP largely due to complex interrelationships between early risk factors. In chapter 2, we explored the effects of a comprehensive set of potential determinants before, at, and after birth. We found that higher maternal prepregnancy BMI, maternal hypertension, relatively lower birth weight for gestational age, shorter gestational age, limited duration of breastfeeding, and more rapid early BMI gain are associated with higher childhood BP at the age of 6 years after adjustment for the child’s own BMI at age 6.

Because both intrauterine growth restriction and prematurity can lead to low birth weight, most previous studies could not clearly distinguish the effects of these two factors.\(^1\) Therefore, we standardized birth weight for sex and gestational age to create a proxy for intrauterine growth which is independent of gestational age, and our results showed that intrauterine growth has a relatively larger effect than gestational age on BP. This is one useful method to disentangle the respective roles of intercorrelated factors in BP regulation. Other statistical methods such as structural equation models\(^2\) and Mendelian randomization\(^3\) may also help to understand the complicated relationship between early determinants and BP.

These findings contribute to our understanding of the developmental origins of BP and also provide evidence for starting BP prevention as early as the prenatal period, e.g. improving maternal health, closer BP monitoring of children born prematurely or with low birth weight, and children with excessive postnatal growth.

Physical activity is associated with lower systolic BP in puberty

In chapter 5, we observed that physical activity was associated with lower SBP independent of adiposity in puberty (age 8-14 years). Children who were active had on average 1.84 mmHg lower SBP than inactive children. This suggests that higher physical activity during childhood may reduce BP levels at an early age thus also reducing BP levels attained in adulthood. In addition, previous evidence shows that physical activity is likely to track from childhood to adulthood, so early physical activity may also benefit adulthood health through indirect effects resulting from adult physical activity.\(^4\)

Taken together, promotion of physical activity should start as early as possible, especially for those at higher risk of developing hypertension, e.g. children with intrauterine growth
restriction or prematurity, offspring of women with hypertension, and children with a higher genetic predisposition to hypertension. WHO recommends that children aged 5–17 years old should accumulate a minimum of 60 minutes of moderate to vigorous-intensity physical activity daily to improve cardiovascular and metabolic health biomarkers.\textsuperscript{5} But how to effectively promote physical activity, e.g. improving accessibility and increasing compliance to an exercise regime requires further investigation.

**Spousal pairs show similarities in BP levels and hypertension**

In chapter 6, we observed that spousal pairs showed similarities in BP levels and hypertension in both Dutch and Japanese populations. The age-adjusted spousal correlation for SBP is 0.123 in Dutch pairs and 0.086 in Japanese pairs. Men were at 45\% and 20\% increased risk of hypertension if their wives had the same condition in Dutch and Japanese populations, respectively. In line with previous studies\textsuperscript{6,7}, our findings support spousal similarities for BP and hypertension in diverse populations regardless of region, ethnicity, or culture.

Besides BP levels and hypertension, we also observed significant spousal similarities for many other traits/lifestyles/diseases such as BMI, lipid traits, smoking, and metabolic syndrome. Interestingly, we found an increasing trend of spousal concordance with age for an important lifestyle factor of BP: physical activity. Throughout their relationship, spouses interact with each other and share some environmental factors (e.g., access to resources for exercise), thus their physical activity may be associated, i.e. people are more likely to be active if their partners are avid exercisers. This may inform the strategies of promoting physical activity which then may benefit BP control.

All these findings suggest that couple-based prevention and interventions strategies may be more effective in hypertension management than those aimed at individuals. Examples include hypertension screening for people whose spouses have hypertension and promotion of healthy lifestyles in spouses\textsuperscript{8}. Future studies that evaluate the effectiveness of couple-based interventions are still needed.

**Part 2 Genetic factors influencing BP over the life course**

**BP loci identified in children**

Although there has been much progress in discovering genetic markers for BP in adults\textsuperscript{9}, only one previous study conducted a genome-wide association study (GWAS) of BP in children (N\textasciitilde10,000)\textsuperscript{10}. Therefore in chapter 3, we performed a meta-analysis of GWAS in 28,425
children of European ancestry and identified 8 loci genome-wide significantly associated with childhood BP traits. We also performed meta-GWAS of HR in over 22,000 European children and identified 3 loci for childhood HR.

These loci have been previously reported to be associated with adult BP suggesting a shared genetic background between childhood and adulthood BP, as demonstrated in a longitudinal twin study that found that about 60% of the genetic influence on BP was shared between childhood and early adulthood. To our knowledge, this is the largest GWAS of childhood BP, but it is still relatively small compared the sample size of one million individuals in adult GWAS of BP. Further expanding sample size in genetic studies of childhood BP may help to discover more loci including those that influence BP uniquely during childhood. Multi-trait GWAS analyses such as GenomicSEM and MTAG can also boost power and may identify more SNPs than single-trait GWAS.

**Adult-based GRSs/PRSs predict BP levels and trajectories at an early age**

As most SNPs were identified from meta-GWAS in adults, we explored if adult-based allelic scores can predict BP levels and trajectories at an early age in chapters 4 and 5, respectively.

In chapter 4, we generated genetic risk scores (GRSs) of SBP and DBP based on over 900 significantly associated SNPs identified in adults by Evangelou et al. We found that adult-based GRSs could predict BP levels and hypertension at age around 16.

Furthermore, in chapter 5, we improved the scores for BP by calculating polygenic risk scores (PRSs) based on the summary statistics from the largest BP GWAS in adults we conducted in chapter 7. Using longitudinal data, we explored if these PRSs could also predict BP trajectories. Our findings demonstrated that higher PRSs were associated with elevated BP levels starting from as young as 5 years and were also linked with faster SBP/DBP changes in puberty/postpuberty, respectively.

Our efforts in these chapters show the potential of applying genetic risk prediction in preventing hypertension at an early age. For example, closer BP monitoring and lifestyle interventions such as dietary advice and physical activity could be targeted to individuals who are identified with a high genetic predisposition to hypertension in childhood/adolescence, thus reducing BP levels attained in adulthood. Future expansion of the sample size of GWASs in adults or children and improved approaches for calculating genetic predictors will likely further improve genetic risk prediction of hypertension from a young age.
Chapter 8

Novel BP loci identified in adults and more accurate risk prediction of hypertension

In chapter 7, we performed a single-stage meta-analysis of over 1 million individuals of European ancestry and identified 113 genome-wide significant novel loci for SBP, DBP, and PP. Together with 1,723 pairwise independent genetic signals which have been previously reported for BP traits and 267 additional secondary SNPs, a total of 2,103 independent genetic signals have now been identified to be associated with all three BP traits.

These findings improve the understanding of the BP genetic architecture and help to detect novel pathways in BP regulation, thus may benefit drug development. In addition, the richness of results enabled us to develop more accurate genetic predictors for BP levels and hypertension. For example, for SBP, variance explained increased from 6.77% for the GRS of 1723 previously published SNPs to 7.17% for the full optimal PRS. Compared with individuals at the bottom decile of the PRS, those at the top decile had on average 12.9 mm Hg higher SBP and 5.4-fold increased odds of hypertension. Including the optimal PRS for SBP and DBP in the predictive model for hypertension also significantly improved the discrimination and calibration of the model. This study is therefore an important step toward improving genetic risk prediction for hypertension.

Data sources and methodological considerations

General comments

The use of multiple data sources allowed me to explore BP at different ages from childhood to adulthood. I also used several analytic approaches to investigate the influence of environmental and genetic factors on BP: traditional epidemiological methods in chapter 2 and 6, GWAS meta-analyses in chapters 3 and 7, genetic risk score applications in chapters 4 and 5.

Data sources

Here I discuss data sources that contributed to the thesis with the focus on the three most important cohorts - the Groningen Expert Center for Kids with Obesity (GECKO) Drenthe study\textsuperscript{15}, the Tracking Adolescents’ Individual Lives Survey (TRAILS) cohort\textsuperscript{16}, and the Lifelines Cohort Study and Biobank\textsuperscript{17}. I also briefly discuss other data sources involved.

GECKO Drenthe study

Data from the GECKO Drenthe study was used for chapters 2 and 5, and it was also included in meta-GWAS of childhood BP and HR in chapter 3. This population-based birth cohort includes 2842 ever actively participating children born between April 2006 and April 2007.
in Drenthe, a northern province of The Netherlands. Data collection started from the last trimester of pregnancy and all children are followed up from birth to adulthood. A wide range of information for the children and their parents has been collected, including genetic, biomedical, social, and environmental data. BP was measured by healthcare professionals when children were around 6 years old. Comprehensive data collected throughout perinatal periods and early childhood permitted us to investigate early determinants of BP at age 6 (chapter 2). Recently BP data at the age of 10-11 years has become available, which provided us with the opportunity to explore factors influencing BP trajectories in childhood (chapter 5). Around a thousand children’s DNA samples in GECKO Drenthe have been genotyped using a high-throughput genotyping array, thus we were able to perform GWAS (chapter 3) and PRS analyses (chapter 5) for these children.

**TRAILS**

Data from TRAILS was used for chapters 3 and 4. TRAILS is an ongoing prospective population-based cohort in the Netherlands. At baseline in 2001, 2,230 children aged about 11 years were included and have been followed up every 2.5 to 3 years since then. TRAILS provides information on a wide range of disease-related traits such as BP during adolescence (aged around 16 years). Genotype data is available for ~1300 participants, which were included for GWAS meta-analyses in chapter 3 and GRS analyses in chapter 4.

**Lifelines**

The Lifelines cohort is another important data source, which was used in four chapters. This large prospective population-based cohort included 167,729 individuals living in the North of the Netherlands at baseline and has been shown to broadly represent the general Dutch population. Extensive biomaterials and data have been collected including genomics and follow-up assessments are ongoing. With a unique three-generation design, Lifelines includes both children and adults, as well as spouses or partners. Children with genetic data and BP measurements were included in meta-GWAS of childhood BP in chapter 3 and analyses of PRS on BP trajectories in chapter 5. Data of eligible adults were used to perform GWAS of BP and GRS analyses in adults in chapter 7. Over 28,000 couples from Lifelines were included in the spousal similarity study in chapter 6.

**Other data sources**

The ABCD (Amsterdam Born Children and Their Development) study is a population-based birth cohort from Amsterdam, which was used for replication analyses in chapter 2.
The Tohoku Medical Megabank Organization (ToMMo)\(^{20}\) is a population-based prospective cohort performed in Miyagi and Iwate Prefectures, Japan. More than 5,000 spousal pairs from ToMMo were included in spousal similarity analyses in chapter 6.

In addition, ~20 other studies were used for meta-analyses in chapter 3, such as the Avon Longitudinal Study of Parents and Children (ALSPAC)\(^{21}\) and Generation R Study\(^{22}\). In chapter 7, four large-scale studies were included to optimize the sample size of the metaGWAS, including UK Biobank (UKB)\(^{23}\), the International Consortium for Blood Pressure (ICBP)\(^{24}\), the Million Veteran Program (MVP)\(^{25}\), and Vanderbilt University’s biorepository of DNA linked to de-identified medical records (BioVU)\(^{26}\).

**Collaborations between cohorts, countries, and ethnicities**

A key feature of this thesis is extensive collaborations between cohorts, countries, and ethnicities, which enable us to confirm or compare the results, optimize the sample size and study BP at different ages across the life course.

Chapter 2 performs analyses in the GECKO Drenthe cohort and replicates the results in the ABCD cohort. The same analytic methods such as calculation and standardization of variables were performed in the two cohorts. Although there are large differences between the two cohorts in geography, socioeconomic status, and BP levels, the observed associations between early determinants and childhood BP were generally consistent, which provides strong confirmation of our results.

In chapter 5, by combining GECKO Drenthe and the Lifelines cohort, we were able to examine the associations of PRSs with BP trajectories in prepuberty, puberty, and postpuberty. GECKO Drenthe follows BP of children only from 6 to 10 years i.e., during prepuberty, while Lifelines includes children at older ages. Thus, these two cohorts together cover BP trajectories in childhood, adolescence, and young adulthood.

In chapter 6, we established collaboration with Japanese researchers to quantify and compare spousal similarities in cardiometabolic risk factors and diseases between Dutch and Japanese populations. We defined variables in the same way and ran the same statistical analyses in Lifelines (Dutch) and ToMMo (Japanese) to make our results as comparable as possible between the two populations. It yielded unique results in the field of spousal epidemiology as few researchers have examined and compared spousal concordance of different populations in one paper.
For meta-GWASs of BP and HR in children (chapter 3), we collected the maximum possible sample size by cooperating with Dutch and international cohorts, two of which were from other ethnicities. For meta-GWASs of BP in adults (chapter 7), we combined four large-scale studies to achieve the sample size of over one million.

**Definition of hypertension in children**

Unlike in adults, the definition of hypertension in childhood is statistically derived from normative BP data. Children are categorized as having hypertension if their SBP or DBP $\geq$ 95th percentile for sex, age, and height based on a normative distribution of BP in healthy children. More recently in 2017, the American Academy of Pediatrics (AAP) revised the normative BP tables using the same data but excluded children who were overweight and obese. Since BMI is positively associated with BP, the normative BP values for normal-weight children in the 2017 APP guideline are several mm Hg lower than those using the whole pediatric population in the 2004 Fourth Report. Thus, it is expected that the prevalence of abnormal BP would increase when using the 2017 APP guideline. Indeed, recent studies showed that the use of the 2017 AAP guideline led to an overall increase in the prevalence of hypertension, and children who were reclassified upward were more likely to be overweight or obese and to have adverse lipid profiles as well increased fasting glucose than those with normal BP. Another longitudinal study also found that children who were reclassified to higher BP categories based on the 2017 AAP guideline were at increased risk of developing hypertension, metabolic syndrome, and left ventricular hypertrophy in later life. All of this evidence suggests that the 2017 AAP guideline allows better identification of youth with high risk for cardiovascular disease. Therefore, the 2017 AAP guideline is used in this thesis to define hypertension in children (chapter 2 and 4). This likely caused a high prevalence of hypertension observed in the GECKO Drenthe study in chapter 2.

It should be noted that current BP reference values derive from US children which may not be optimal for children in other countries. However, due to the persisting lack of European reference values throughout the entire pediatric age range, the 2016 European Society of Hypertension (ESH) Guidelines recommends using the normative data from US children. Fortunately, The HyperChildNET (Network for BP research in children and adolescents) COST Action is aimed at defining reference values for BP that can be applied all over Europe. These new BP reference tables in the future will allow better identification and follow-up of hypertension in European children.
Conducting meta-GWAS

Meta-analysis of GWASs (meta-GWAS) has been a widely adopted approach to increase power to detect common genetic variants associated with traits or diseases. These meta-GWASs combine summary statistics from GWAS conducted around the world and typically involve a considerable amount of effort and time requiring extensive communication and coordination, standardization of analytical procedures, and rigorous quality control (QC). In this thesis, we performed meta-GWAS of BP in children (chapter 3) and adults (chapter 7). During the process, I have gained some experiences and learned lessons how to successfully and effectively conduct meta-GWAS. First, starting with established consortia helps to include more studies. In meta-GWAS of childhood BP, we started with cohorts from the Early Growth Genetics (EGG) and EArly Genetics and Lifecourse Epidemiology (EAGLE) consortia and then invited additional cohorts we knew might have BP and genetic data for children. Second, a common analysis plan should be distributed to all participating cohorts, which describes the standardized analyses including trait transformation, pre-analysis QC of SNPs and samples, association analysis methods, and format requirements for results uploads. Finally, QC is a crucial step in meta-GWAS to detect potential errors. The GWASInspector R package was used in the thesis to perform a harmonized QC procedure for every GWAS result and final meta-analysis results. It is a powerful and easy-to-use tool for QC in meta-GWAS with its ability to efficiently handle big data, indel and multi-allelic variants and to generate comprehensive graphic reports.

Missing heritability

GWASs have identified a large number of genetic variants associated with traits and diseases but these variants generally only explain a small part of the total heritability estimated from twin and family studies. This is known as the missing heritability problem, which is also observed for BP traits in this thesis. The likely sources of missing heritability can be partitioned into hidden heritability, still-missing heritability, and phantom heritability (Figure 2). In chapter 7, over 2000 identified BP signals in total explained ~7% of the variance of SBP and DBP, while common SNP heritability estimated by GCTA-GREML showed that 17.4% of SBP and 18.8% of DBP can ultimately be explained by common genetic variants captured by GWAS. This gap between the variance explained by GRSs or PRSs and the common SNP heritability is denoted as the hidden heritability. It can be narrowed if more genetic variants are identified by increasing sample sizes as demonstrated in chapter 7, and in theory, hidden heritability could be completely found by GWAS with infinite sample size.
There is still a part of the heritability that cannot be explained by GWAS, which is the still-missing heritability. For instance, in chapter 7, the gap remains between the common SNP heritability and the total heritability of 28%-30% for SBP and DBP recently reported in a family study.\textsuperscript{38} This is caused by rare and structural variants that cannot be measured on or tagged by SNPs on the GWAS array. Future advances of next-generation sequencing\textsuperscript{39} to sequence exomes (i.e. coding regions) or whole genomes enable the discovery of rare variants related to BP\textsuperscript{40}, which helps to reduce still-missing heritability.

Figure 2. Illustration of the likely sources of missing heritability for BP. Dark blue color represents common SNP heritability, i.e. the part of the heritability that can ultimately be explained by GWAS. It contains variance explained by current GWAS through genetic (GRS) and polygenic risk scores (PRS) (green slices) and the hidden heritability (lighter blue color and blue slices). Hidden heritability can be narrowed by larger GWAS and in theory can be completed found by GWAS with infinite sample size. Still-missing heritability is the part of the heritability that cannot be explained by GWAS (red colors) containing rare variants, structural variations, dominance (D), and epistasis (G\text{x}G). The phantom heritability describes the overestimation of the heritability estimates from twin and family studies and includes inadequate accounting for shared environment, dominance effects (D), and epistasis (G\text{x}G). The sum of the hidden, the still-missing, and the phantom heritability is the missing heritability, which is the gap between found heritability by current GWAS and the total heritability estimated from family or twin studies. Adapted from Nolte et al.\textsuperscript{37}
Moreover, heritability estimated from twin and family studies is likely to be overestimated because of inadequate accounting for nonadditive genetic effects, shared environment, and gene-environment interactions and correlations, which is called phantom heritability. This means that part of the missing heritability might simply not be there rather than missing.\textsuperscript{41,42}

One noteworthy issue is missing heritability due to heterogeneity caused by stronger genetic signals within homogeneous than across heterogeneous populations.\textsuperscript{37} In chapter 3, we used GWAS summary statistics of BP from Evangelou et al\textsuperscript{14} and estimated that common SNP heritability for BP traits in adults was 11%-12%, which is smaller than previous estimates of ~20% in the UK Biobank by Evangelou et al in their paper. Evangelou et al conducted genome-wide discovery analyses of BP traits in European adults from UK Biobank and ICBP which comprises 77 independent studies.\textsuperscript{14} GWAS meta-analysis only captures information about shared genetic associations across populations as it assumes identical genetic effects in all participating cohorts. Thus, if heterogeneity exists across the cohorts participating in meta-GWAS, the estimate of the common SNP heritability using meta-GWAS results is expected to be smaller than that estimated in a single population such as the UK Biobank.

\textbf{Conclusions and future perspectives}

\textbf{Life course perspective of BP studies}

One key feature of the thesis is the life course perspective which emphasizes determinants of BP across the lifespan. The ideal method is to measure BP and collect information on potential determinants in the same individuals across their whole life. However, there is still no single cohort that has done this. Thus, an alternative way is to combine multiple longitudinal cohorts covering different periods of life. For instance, one study modeled life course trajectories of SBP by combining longitudinal data from eight UK cohorts each covering different but overlapping periods spanning from age 7 to >80 years, and this study found four life course phases such as a rapid increase in SBP coinciding with peak adolescent growth.\textsuperscript{43} In chapter 5, we examined the associations of PRSs with BP trajectories in childhood, adolescence, and young adulthood by combining two prospective cohorts. Future studies with a longer duration of follow-up and more collaborations between cohorts can benefit the life course approach to BP. In addition, advances in other fields such as epigenetics\textsuperscript{44} have the potential to understand the underlying biological mechanisms linking early life and later BP.
Future genetic studies of BP

Since the first large GWAS of BP was conducted in 2009, great progress has been made in the discovery of genomic signals underlying BP. As demonstrated in chapter 7 and prior BP GWAS, studies with ever-increasing sample sizes have powered discoveries of BP loci, so future studies of BP traits should continue expanding the sample size to identify more SNPs with smaller effects. This can be facilitated by the development of large biobanks with high homogeneity such as UK Biobank, Lifelines in the Netherlands, the Estonian Biobank, 23andMe, and by using electronic health records which can extend the reach of GWAS to numerous clinical samples.

As GWAS chips mostly measure or tag common SNPs, improving genomic resolution helps to discover novel BP variants with rarer allele frequency. With rapid advances and decreasing cost in sequencing technology, it is expected that next-generation sequencing of exomes or whole genomes will play an increasing role in the discovery of rare variants related to BP. Alternatively, enhancements of the imputation panel also provide opportunities for exploring the contributions of rare variants to BP. Recently, The Trans-Omics for Precision Medicine (TOPMed) program constructed an imputation reference panel including 308,107,085 single-nucleotide variants and indels, which improves imputation of rare variants compared with previous panels such as those from the 1000 Genome and the Haplotype Reference Consortium (HRC).

Currently, GWASs of BP traits have been conducted in predominantly European individuals although genetic architecture differs between populations. This causes difficulties in detecting some BP-related variants if they are rare or even absent in European populations. Also, polygenic risk scores derived in European populations may be less accurate in other ethnicities as we showed in chapter 7, which can widen the existing health disparities between populations. The Population Architecture using Genomics and Epidemiology (PAGE) study conducted a GWAS of 26 phenotypes in 49,839 non-European individuals and showed evidence of effect-size heterogeneity across ancestries for published GWAS associations and substantial benefits for fine-mapping using diverse populations. More studies should be conducted in non-Europeans in the future to maximize genetic discovery of BP and mitigate health disparities such as caused by inequitable access to precision medicine.

Most genetic studies on BP so far have focused on cross-sectional SBP, DBP, and PP in adults, while further investigations in other BP outcomes may provide additional insights on BP development. For instance, previous findings indicated that GWAS using longitudinal BP can identify variants related to BP trajectories and may outperform the cross-sectional GWAS.
GWAS of childhood BP may also help to discover novel BP loci due to age-dependent genetic effects on BP\textsuperscript{11}.

**Risk prediction and personalized care**

A potential application of BP genetic discovery is risk prediction of raised BP and hypertension. Larger and more inclusive GWAS studies, progress in sequencing technology, and improved approaches to calculating genetic predictors such as PRS\textsuperscript{53}, LDpred\textsuperscript{54}, and SBayesR\textsuperscript{55} offer promise to enhance genetic prediction in the coming years. As germline genetic factors are fixed from birth, genetic predictors can be calculated at an early age before hypertension has developed and high-risk individuals could benefit from more intensive prevention measures. A large Finnish study confirmed that predictive ability of BP PRSs was particularly strong for early-onset hypertension.\textsuperscript{56} Such genomic data together with other omics measurements (e.g. on gene expression, DNA methylation, and proteins) and in combination with environmental factors and clinical data can help to estimate the risk of hypertension more accurately.

In addition, this thesis and earlier literature\textsuperscript{14} suggested the existence of shared biological pathways among BP and other traits/diseases including lipids and cardiovascular diseases as BP SNPs were also associated with these outcomes. This means that BP PRSs may also be useful in prediction of cardiovascular diseases.\textsuperscript{14,56} Beyond BP, genetic predictors can be calculated for a wide range of diseases simultaneously with a one-time cost for genotyping (e.g. Illumina Infinium Global Screening Array cost approximately US $40 per sample\textsuperscript{57}). For example, Khera et al identified individuals with increased risk for five common diseases (e.g. coronary artery disease, type 2 diabetes, and breast cancer) in the UK Biobank using genetic predictors.\textsuperscript{58} Therefore, genetic data can inform the risk for multiple diseases and help to guide personalized prevention and intervention strategies such as lifestyle modifications.

Pioneers such as the Estonian Biobank are making efforts to incorporate personalized genome-based medicine gradually into general health care.\textsuperscript{59} For example, Estonia has passed a special law to govern genome research, which is favorable to the implementation of personalized medicine. To prepare for a nation-wide personalized medicine system, Estonia performed two pilot projects to test the feasibility of different approaches in clinical practice. They expect to provide participants with a report in an clear format and understandable language including information on how risk of disease will increase with age, genetic contribution to the risk, and to what extent it could be altered by lifestyle or medical intervention, together with proper medical support such as genetic counseling,
easy access to medical specialists and follow-up. These experiences will help to ultimately achieve the goal of personalized medicine.

More collaborations

As shown in this thesis, the collaboration between researchers and cohorts will continue to benefit future studies. Also, the trend to share genetic results such as GWAS summary statistics and make them publicly available and build open databases like GWAS Catalog and The Polygenic Score (PGS) Catalog will further facilitate replication and follow-up studies. Moreover, developments in genetics also raise challenges in big data management, data security and privacy, and communications of genetic results to patients or the general public, which calls for interdisciplinary collaborations.

Conclusions

The findings in this thesis provide insights into environmental and genetic influences on BP across the lifespan and thus may benefit early prevention of hypertension. First, early determinants including higher maternal prepregnancy BMI, maternal hypertension, relatively lower birth weight for gestational age, shorter gestational age, limited duration of breastfeeding, and more rapid early BMI gain are all related to higher childhood BP. Second, spouses show similarities for BP and hypertension in diverse populations. Third, adult-based allelic scores can predict BP levels and trajectories at an early age. Finally, larger GWASs in children and adults will help to identify more BP loci and develop more precise genetic predictors.
Reference


