# Prediction of Blood Pressure Changes Over Time and Incidence of Hypertension by a Genetic Risk Score in Swedes.

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**PREDICTION OF BLOOD PRESSURE CHANGES OVER TIME AND INCIDENCE OF HYPERTENSION BY A GENETIC RISK SCORE IN SWEDES.**

**Short title: GRS and hypertension**

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**Abstract**

Recent Genome Wide Association Studies (GWAS) have pinpointed different single nucleotide polymorphisms (SNPs) consistently associated with blood pressure (BP) and hypertension prevalence. However, little data exist regarding SNPs predicting BP variation over time and hypertension incidence. The aim of this study was to confirm the association of a genetic risk score (GRS), based on 29 independent SNPs, with cross sectional BP and hypertension prevalence and to challenge its prediction of BP change over time and hypertension incidence in more than 17,000 middle-aged Swedes participating in a prospective study, the "Malmö Preventive Project" (MPP), investigated at baseline and over a 23-year average period of follow-up. The GRS was associated with higher systolic and diastolic BP values both at baseline (ß±SEM 0.968±0.102mmHg and 0.585±0.064mmHg; p<1E-19 for both) and at reinvestigation (ß±SEM 1.333±0.161mmHg and 0.724±0.086mmHg; p<1E-15 for both) and with increased hypertension prevalence (OR [95%CI] 1.192 [1.140-1.245] and 1.144 [1.107-1.183]; p<1E-15 for both). The GRS was positively associated with change (Δ) in BP (ß±SEM 0.033±0.008mmHg/year and 0.023±0.004mmHg/year; p<1E-04 for both) and hypertension incidence (OR 95%CI 1.110 (1.065-1.156) p=6.7 E-07), independently from *traditional risk factors*. The relative weight of the GRS was lower in magnitude than obesity or pre-hypertension, but comparable to diabetes mellitus or a positive family history of hypertension (PFH). A C-statistics analysis does not show any improvement in the prediction of incident hypertension on top of *traditional risk factors*. Our data from a large cohort study show that a GRS is independently associated with BP increase and incidence of hypertension.

**Key words:** genetic risk score, blood pressure, incidence, variation, hypertension, genetics.

**Abbreviations list**

AHT, antihypertensive treatment

BMI, body mass index

BP, blood pressure

DBP, diastolic blood pressure

GRS, genetic risk score

GWAS, genome wide association study

MPP, Malmö Preventive Project

SBP, systolic blood pressure

## INTRODUCTION

Hypertension is the major risk factor for stroke and one of the most important factors for other cardiovascular events. Small increases in blood pressure (BP), even within the normal range, are associated with an increased risk of morbidity and mortality.[1,2]

BP and hypertension are highly heritable traits[3] but the search for genetic variants associated with these traits has only recently brought consistent results. Two Genome Wide Association Studies (GWAS) have shown 13 loci associated with BP/hypertension and an extensive meta-analysis of GWAS data, with a total sample size of nearly 200,000 people of European descent, have identified 16 novel loci associated with systolic blood pressure (SBP) and diastolic blood pressure (DBP).[4-6] Indeed, a genetic risk score (GRS) with aggregate genetic information from 29 SNPs have been shown to be associated with the prevalence of hypertension and the incidence of coronary events and strokes.[6] Fewer data exist on the impact of genetic variants or GRS on hypertension incidence and BP variation over time.[7,8] Other recent GWAS, in Caucasian, Asian and African American populations have focused their attention especially on cross-sectional data (that is prevalence of hypertension) and none produced data on BP change over time or hypertension incidence.[9-15] The possibility to predict future hypertension onset could allow the adoption of individual preventive measures, such as decreasing the salt content in foods, adopting a healthier diet, decreasing alcohol consumption, and implementation of aerobic exercise, which are well-known to impact BP,[16,17] even if it has yet to be proven whether the result of a genetic test could help to change people's behavior.[18] The aim of the present study was to confirm that a GRS, consisting of the un-weighted (count) and weighted allele sum of 29 SNPs, is associated with cross-sectional BP and hypertension prevalence and to test if it could be useful in predicting hypertension incidence and changes in BP over time using the Malmö Preventive Project (MPP) study, including more than 17,000 people.

## MATERIALS AND METHODS

An extended version of the Methods section is reported in the "Online Methods and Results" section. All study participants provided written informed consent. The procedures were in accordance with the institutional guidelines. The Ethics Committee of the Medical Faculty of Lund University approved the study.

### Subjects

The MPP is an urban-based prospective study that screened 33,346 Swedish participants from the city of Malmö during 1974–1992 (attendance rate 71%). Of the individuals participating in the initial screening, 4,931 have died and 551 were lost after follow-up for other reasons. Twenty-five thousand of the eligible individuals were invited for a re-screening visit from 2002–2006, including a physical examination with BP measurement (participation rate was 70.5%). DNA was obtained from 18,240 individuals participating in the re-screening.

*Blood pressure*

We treated BP as a continuous variable before and after adjustment of the measured BP values (see below) and as a dichotomized trait (hypertension vs. normotension).
Details about BP measurements, BP adjustments in subjects with antihypertensive treatment, hypertension and pre-hypertension definitions are presented in the Online Methods section.

*Laboratory analysis*

After an overnight fast, blood samples were drawn for the determination of whole blood glucose, lipids and creatinine. Samples were analyzed by standard methods at the Department of Clinical Chemistry, Malmö University Hospital.[19]

**Genotyping**

Information about the different SNPs included in the GRS is reported in the Supplementary Methods Section. The SNPs were genotyped using IPLEX on a MassARRAY platform (Sequenom, San Diego, CA, USA) according to the manufacturer's standard protocols. Nearly 30% of the samples were run in duplicate. All genotypes were called by two different investigators. We pre-specified a threshold call rate of 90% per individual SNP (that is SNPs would be excluded if its call rate is<90%). A threshold of $p<10^{-07}$ was first established for excluding SNPs, according to Hardy-Weinberg equilibrium calculation. A SNP, *FES* rs2521501, that we found to be outside the threshold for Hardy-Weinberg equilibrium, was anyhow included in the GRS to adhere to the previously validated GRS.

*Genetic risk score*

Two methods were used to create the multivariable GRS, a simple, unweighted count method (count GRS, cGRS) and a weighted method (weighted GRS, wGRS) according to the β-coefficient attributed to the tested SNPs in previous studies.[4-6] Details about the construction of different GRSs are presented in the Online Methods.

***Statistics***

Continuous variables are presented as means±SD. All data were analyzed with SPSS statistical software (version 20.0; SPSS Inc. Chicago, Illinois, USA). The chi-square test (Pearson) was used to compare group frequencies and to test for deviations from the Hardy-Weinberg equilibrium. Multiple linear and logistic regression analyses were used in the multivariate models with BP and hypertension status as the dependent variables. The independent variables were either basic demographic and anthropometric data (model A; see also Online Methods), or covariates as in model A plus gluco-lipid parameters and CKD-EPI estimated-glomerular filtration rate (GFR; model B) or covariates as in model A plus B plus anamnestic, socio-economic and life-style data (model C). Subjects already

diagnosed as hypertensive at baseline were not included in the longitudinal analysis. We assessed the improvement in discrimination by comparing the area under the receiver operator characteristic curves (AUC) with or without the cGRS in models with all the non-genetic covariates significantly associated with the incidence of hypertension. ROC curves were developed using a probability-weighted Cox model. All tests were two-sided and *p* values less than 0.05 were considered statistically significant.

## RESULTS

The clinical characteristics of the individuals included in the study are summarized in Table 1. Hardy-Weinberg equilibrium data and details about individual markers are presented in Online Table S2, whereas the number of missing genotypes per subjects in Online Table S3. Histograms showing the distribution of subjects with different cGRS and wGRS before standardization are presented in Online Figure S1-4. Results about the association of different SNP with BP-related traits is presented in the Online Results section.

### *Cross sectional analysis*

In the simplest regression model (model A: adjusting for age, sex, BMI and HR), the GRS was independently and highly significantly associated with systolic and diastolic BP and hypertension prevalence both at baseline and reinvestigation (table 2-3, see also Figure 1a and b). When other variables, such as gluco-lipid parameters and other anamnestic elements (including a positive family history of hypertension) were included in the model the association was somewhat attenuated but remained highly significant (model B and C). An increase of one standard deviation (SD) in the GRS implies an increase of nearly 1.0 or 1.3 mmHg in the predicted systolic and 0.6 or 0.7 in the predicted diastolic BP at baseline and reinvestigation, respectively. Among individuals in the top quartile of the GRS, the predicted increase in BP with respect to the bottom quartile was 2.6 or 3.5 mmHg systolic

and 1.6 or 2.0 mmHg diastolic BP and the odds ratio (O.R.) for hypertension was 61% or 47% higher respectively at baseline and reinvestigation, respectively.

***Longitudinal analysis***

In linear regression (model A), the GRS was independently associated with BP change over time and the incidence of hypertension (table 4; see also figure 1c). When the other covariates were added in the model (model B and C), including baseline blood pressure, the association remained substantially unaltered. In the regression model C an increase of 1 SD of the GRS imply an increase of 0.033 mmHg/year in predicted systolic BP and 0.023 mmHg/year in diastolic BP and an increase in the O.R. for hypertension of nearly 10%. Between subjects in the top quartile of the GRS, the predicted increase in BP with respect to the bottom quartile was 0.082 mmHg/year for systolic and 0.063 mmHg/year for diastolic BP and the O.R. for incident hypertension was 28% higher. When the GRS score was added to the regression models for Δ systolic/diastolic BP and hypertension incidence the proportion of variance explained increased by 1.0% and 0.7% and 2.9%, respectively, with respect to the proportion explained by the *traditional risk factors* alone.

***Comparison of GRS magnitudes with respect to well-known predictors of hypertension incidence***

In table 5, all the covariates included in the logistic regression (model C), that associate with hypertension incidence, are presented. As could be expected, the highest O.R. was obtained for dichotomous *traditional risk factors* such as obesity and pre-hypertension status at baseline. However, the effect of the GRS ($1^{st}$ quartile vs. $4^{th}$ quartile) was independent and comparable in magnitude to that of positive family history, and diabetes mellitus.

**Discrimination**

The area under the curve (AUC) for all the non-genetic variables as included in model C was only marginally and not significantly improved after the addition of the cGRS (see Online Figure S5) shifting the AUC (95%CI) from 0.662 (0.651-0.672) to 0.664 (0.653-0.675).

**Stratification by gender and sensitivity analysis**

Sex-stratified analysis is presented in Online tables S6a-b, S7a-b and S8a-b. No major differences between associations of the GRS with hypertension-related traits are evident. In the sensitivity analysis, we verified that our results are not substantially modified by different type of BP adjustment (adding either 10 or 20 mmHg to the treated Systolic BP and 5 or 15 mmHg to the treated diastolic BP or using stepped addition; Online Tables S9, S10 and S11). Also using only supine or standing BP measurements at baseline did not substantially change the results (Online Table S12).

## DISCUSSION

The issue of what extent genetics can predict the incidence of future hypertension or cardiovascular events is stimulating, but remains unanswered. Recent GWAS found genetic loci and SNPs constantly associated with hypertension but the proportion of variance explained by individual SNPs is very limited.[4-6, 20] The aggregation of genetic information, obtained from many markers, into a single GRS variable, permits to condense this information into a statistical metric of low dimensionality. Thus, a GRS was proposed by the ICBP consortium to sum up the effects of these SNPs on hypertension prevalence and cross sectional data.

We hereby furnish the validation of the same genetic score for hypertension prevalence and show an association of the GRS with hypertension incidence with highly significant results

in a large Swedish sample. This approach confirms the validity of the tested GRS, indicating that the sum of the SNPs is independently associated with hypertension incidence, but discrimination analysis shows that the information added by the GRS on top of non-genetic risk factors is marginal. Indeed, the magnitude of the association of the GRS with hypertension incidence is substantially lower when compared with obesity and pre-hypertension status, and compatible with the magnitude of either a positive family history of hypertension or the presence of diabetes. The reason for this low magnitude is unclear but most likely reflects the fact that only a subset of the SNPs included in the GRS, when taken singularly, were significantly associated with BP-related traits in our population. Thus, the non significant SNPs most likely contributed to the dilution of the magnitude of the results. In our opinion, this is, at the same time, a major weakness but also a strength of the present GRS; which, in contrast to other studies, has not been obtained and validated from the same population sample, which would potentially cause over-fitting of the data and inflation of the p-value. For the same reasons as above, the weighted GRS were sometimes inferior to the count GRS because the applied β-coefficients were taken from the results obtained in other populations. Our results regarding the GRS are in line with the ICBP, where it was concluded that the GRS could explain nearly 1.6 mmHg and 1.1 mmHg increases in cross-sectional systolic and diastolic BP, respectively, as well as 23% of the hypertension prevalence.[6] Differences in BP of this magnitude should not be disregarded because it has been shown that modest increments in population SBP and DBP, even if based on a single BP measurement, are associated with substantial increases in cardiovascular disease risk.[1,2,21,22] Recently, another longitudinal study in Finns validated a GRS with 13 SNPs in people followed longitudinally from childhood to early adulthood, confirming the independence from positive family history.[7] Indeed, with a more complex approach using genome wide association data and different p-value thresholds, Taal and

colleagues, analyzed the predictivity of different GRSs and found that, even including thousands of SNPs the maximum explained variance arrives at 1.2%, which is consistent with our data and our much simpler and feasible design.[8]

When looking at single SNP results, fibroblast growth factor 5 (*FGF5*), despite being a known oncogene, was confirmed to be one of the most interesting genes for hypertension[4-6, 23-26] putatively through effecting salt sensitivity.[27] FGF family members possess broad mitogenic and cell survival activities, and are involved in a variety of biological processes, including embryonic development, cell growth, morphogenesis, tissue repair, tumor growth and invasion. Interestingly also *FGF1*, another member of the same family, has been shown to segregate with higher BP values and to be highly expressed in the kidney with its binding protein.[28,29] Mutations in *CYP1A2*, a gene implicated in the metabolism of several xenobiotics, including polycyclic aromatic hydrocarbons, caffeine and other methyl xanthines,[30,31] was the only gene that remained positively associated to both prevalent and incident BP measures. It has already been shown that some polymorphisms in this gene could help explain the controversial association between coffee intake and BP.[32,33] In particular, in non-smokers, *CYP1A2* variants were associated with higher reported caffeine intake, which in turn was associated with lower odds of hypertension and lower BP.[32] Moreover, the induction of CYP1A2 has been associated with the presence of an estrogen metabolite, 16alpha-hydroxyestrone, which is related to lower BP values in post-menopausal women.[33,34] By contrast, it is currently unknown via which pathway the other associated SNPs, transmembrane protein 133 (*TMEM133*) and early B-cell factor 1 (*EBF1*), could be involved in BP homeostasis.

Major limitations of our GRS are that the included SNPs have been obtained without taking into account possible interaction with other genetic variants or with other demographic or environmental factors. Moreover, the included SNPs do not consider the physiology or

biology of BP homeostasis. Indeed, it is possible that other SNPs coming from either newer GWAS, or candidate gene approach or related-pathway strategies could be implemented in a better-suited GRS, improving its predictivity. Future studies will clarify if the different scores are needed in people with different ethnicities or if other confounders have to be taken into account before applying the GRS. Evidence is accumulating that rarer variants, in genes responsible for Mendelian forms of hyper- and hypotension account for major differences in BP in carriers with respect to wild type subjects.[35,36] Thus, also implementing these rare variants in a GRS could substantially augment the prediction of a genetic score. The main aim of complex disease genetics remains the identification of new genes that can help further our understanding of pathways and possible new pharmacological targets for treatments, but the issue of the prediction is both relevant and intriguing.[37]

We have to acknowledge some specific limitations of our sample, the first being that our findings cannot be generalized to populations with genetic backgrounds different from that of our population. We could only obtain DNA from subjects who survived from the first to the final examination (nearly 23 years of follow-up). Thus, people at greater risk for cardiovascular disease (i.e., carriers of deleterious polymorphisms) could have died at a higher frequency than did subjects not carrying a deleterious polymorphism. Our adjustment for antihypertensive medications is a relatively simple and widely adopted way to use data coming from treated patients, and it has proven to augment familial genetic and shared environmental signals without increasing the noise from individual-specific sources of variation.[38] Our sensitivity analysis confirms that different manners of adjusting for antihypertensive medications, or even exclusion of treated subjects, do not substantially influence the results.

Finally, to increase the power of our analysis, we decided to impute the genotypes of people with SNPs with 5 failed SNP genotypes or less. We underline that, a different

approach, based on an averaged GRS (that is by summing up the effects of the single SNPs and dividing them for the effective number of valid SNPs) gave similar results (data not shown).

To be adherent to the ICBP where the GRS was first tested, we included in this GRS the SNPs that deviated from the Hardy-Weinberg equilibrium. When evaluating the expected and observed heterozygosity the difference is nearly 2.3% but these results are statistically significant for the large sample size. We rerun nearly 6,000 samples and found a very high agreement between the call rates of different genotypes (Online Table S2). However, we cannot exclude that this discrepancy could be due to some technical errors. We are aware that these could have further diluted the effect of the GRS and by excluding this SNP form the GRS, we obtained an even lower p-value for associations with approximately the same magnitude (data not shown).

**PERSPECTIVES**

In conclusion, we validated a previously reported GRS for prevalent hypertension in a large urban-based sample, and demonstrated its independent association with hypertension incidence and BP change over time.

The low percentage of BP/hypertension variance that was explained by the GRS, when compared to other well-known predictors, along with the non significant improvement in discrimination on top of non-genetic risk factors, suggests that it is not yet ready to be considered for a clinical use. On the other hand, when future knowledge about different SNPs and their complex interactions both with genetic and environmental factors become clearer, and when rare genetic variants are included in different GRS versions, better suited GRSs could become applicable in a clinical setting.

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**Novelty and Significance: 1) What Is New, 2) What Is Relevant?**

**What Is New?**

- A genetic risk score based on 29 SNPs is associated with blood pressure change over time and hypertension incidence.
- The effect of the GRS is independent of other well-known traditional risk factors including a family history of hypertension.

**What Is Relevant?**

- A comprehensive GRS could help physicians to estimate the risk of future hypertension in normotensive people.

**Summary - of the conclusions of the study.**

- The relatively low effect of the GRS suggests that it is not yet ready for clinical application.
- Either many common SNPs related to BP remain to be discovered, or rarer variants with a higher effect on BP have a major impact also at the population level.

**Figure legend:**

Crude associations between the weighted GRS (in quartiles) and hypertension prevalence at baseline (a), re-examination (b) and incidence (C) over 23 years of follow-up.

**Table 1. Anthropometric, anamnestic and metabolic features of the investigated subjects with at least 24 valid genotypes in the MPP (at baseline and reinvestigation).**

| Variables | Data available (n) | MPP at baseline | Data available (n) | MPP at follow-up |
|---|---|---|---|---|
| **Gender, male (%)** | 17,688 | 63.3 | 17,688 | 63.3 |
| **Age, years** | 17,688 | 45.2±7.4 | 17,688 | 68.2±5.8 |
| **Systolic blood pressure, mmHg** | 17,352 | 126.8±14.1 | 17,491 | 144.9±20.0 |
| **Diastolic blood pressure, mmHg** | 17,352 | 85.3±8.7 | 17,491 | 83.6±10.6 |
| **Δ-Systolic blood pressure, mmHg/year** | | | 11,303 | 1.1±0.9 |
| **Δ-Diastolic blood pressure, mmHg/year** | | | 11,297 | 0.2±0.5 |
| **Heart rate, bpm** | 17,681 | 68.3±9.6 | 17,625 | 70.6±12.0 |
| **Body mass index, kg/m$^2$** | 17,681 | 24.3±3.4 | 17,589 | 27.2±4.2 |
| **Obesity, %** | 17,681 | 5.6 | 17,688 | 21.7 |
| **Estimated GFR, ml/min/1.73m$^2$** | 17,616 | 84.9±14.1 | | |
| **Chronic Kidney disease (GFR<60 ml/min/1.73m$^2$)** | 17,616 | 2.5 | | |
| **Hypertension, (prevalence) %** | 17,375 | 34.2 | 17,561 | 72.3 |
| **Hypertension, (incidence) %** | | | 11,334 | 63.3 |
| **Diabetes, %** | 17,573 | 3.2 | 17,443 | 13.3 |
| **Antihypertensive therapy, %** | 17,658 | 4.4 | 17,685 | 38.3 |
| **Positive family history of hypertension, %** | 17,324 | 33.5 | | |
| **Current smoker, %** | 17,251 | 38.2 | | |
| **Married or cohabiting as a couple, %** | 17,677 | 72.5 | | |
| **Manual work or low-level non manual work, %** | 17,627 | 61.5 | | |
| **Problematic alcohol behavior, %** | 17,688 | 19.5 | | |
| **Prevalently sedentary in spare time, %** | 16,796 | 37.7 | | |
| **Total cholesterol, mmol/L** | 17,655 | 5.61±1.05 | 17,680 | 5.6±1.1 |
| **HDL-cholesterol, mmol/L** | | | 17,670 | 1.4±0.4 |
| **Triglycerides, mmol/L** | 17,649 | 1.28±0.80 | 17,678 | 1.3±0.8 |
| **Glucose, mmol/L** | 17,623 | 4.9±0.75 | 17,666 | 5.84±1.4 |

AHT, antihypertensive therapy, GFR, glomerular filtration rate; HDL, high-density lipoprotein.

**Table 2. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP baseline.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=17,337) | | Model B (n=17,190) | | Model C (n=16,553) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| SBP (+ 15 mmHg if treated) | cGRS | 1.090 (0.103) | 3.3 E-26 | 1.089 (0.103) | 2.8 E-26 | 0.968 (0.102) | 2.8 E-21 |
| | wGRS | 1.119 (0.103) | 1.6 E-27 | 1.109 (0.103) | 3.6 E-27 | 1.004 (0.102) | 8.1 E-23 |
| | 1 vs. 2 | 0.983 (0.287) | 0.001 | 0.915 (0.286) | 0.001 | 0.970 (0.285) | 0.001 |
| | 1 vs. 3 | 1.879 (0.289) | 7.9 E-11 | 1.840 (0.288) | 1.8 E-10 | 1.666 (0.287) | 6.7 E-09 |
| | 1 vs. 4 | 2.883 (0.292) | 7.2 E-23 | 2.833 (0.291) | 3.0 E-22 | 2.592 (0.290) | 4.2 E-19 |
| DBP (+ 10 mmHg if treated) | cGRS | 0.663 (0.064) | 8.8 E-25 | 0.655 (0.064) | 2.9 E-24 | 0.585 (0.064) | 6.7 E-20 |
| | wGRS | 0.691 (0.064) | 8.0 E-27 | 0.679 (0.064) | 5.6 E-26 | 0.625 (0.064) | 1.7 E-22 |
| | 1 vs. 2 quart. | 0.615 (0.181) | 0.001 | 0.597 (0.181) | 0.001 | 0.559 (0.180) | 0.002 |
| | 1 vs. 3 quart. | 1.161 (0.180) | 1.1 E-10 | 1.149 (0.180) | 1.6 E-10 | 1.011 (0.179) | 1.6 E-08 |
| | 1 vs. 4 quart. | 1.816 (0.18) | 5.1 E-23 | 1.784 (0.183) | 2.7 E-22 | 1.638 (0.182) | 3.0 E-19 |
| | | OR (95%CI) | P-value | OR (95%CI) | P-value | OR (95%CI) | P-value |
| Prevalence of Hypertension | cGRS | 1.163 (1.124-1.203) | 2.9 E-18 | 1.166 (1.126-1.206) | 1.7 E-18 | 1.192 (1.140-1.245) | 5.9 E-15 |
| | wGRS | 1.173 (1.134-1.214) | 2.5 E-20 | 1.154 (1.120-1.190) | 3.1 E-20 | 1.201 (1.150-1.255) | 3.2 E-16 |
| | 1 vs. 2 quart. | 1.173 (1.064-1.293) | 0.001 | 1.230 (1.088-1.390) | 0.001 | 1.207 (1.063-1.371) | 0.004 |
| | 1 vs.3 quart. | 1.324 (1.202-1.459) | 1.3 E-08 | 1.339 (1.185-1.513) | 2.8 E-06 | 1.300 (1.146-1.476) | 4.6 E-05 |
| | 1 vs. 4 quart. | 1.545 (1.404-1.701) | 6.1 E-19 | 1.6386 (1.453-1.846) | 5.9 E-16 | 1.607 (1.420-1.818) | 5.5 E-14 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; Quart., quartiles; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure. Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles. Please refer to the "Methods" section for details about different covariates in different regression models.

**Table 3. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP reinvestigation.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=17,480) | | Model B (n=17,306) | | Model C (n=16,375) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| SBP (+ 15 mmHg if treated) | cGRS | 1.494 (0.158) | 5.8 E-21 | 1.472 (0.158) | 9.9 E-21 | 1.333 (0.161) | 1.6 E-16 |
| | wGRS | 1.459 (0.159) | 4.9 E-20 | 1.445 (0.158) | 5.2 E-20 | 1.304 (0.161) | 7.1 E-16 |
| | 1 vs. 2 quart. | 1.387 (0.448) | 0.002 | 1.356 (0.444) | 0.002 | 1.137 (0.455) | 0.012 |
| | 1 vs. 3 quart. | 2.281 (0.440) | 2.2 E-07 | 2.200 (0.436) | 4.6 E-07 | 1.884 (0.446) | 2.4 E-05 |
| | 1 vs. 4 quart. | 3.924 (0.450) | 3.4 E-18 | 3.830 (0.446) | 1.1 E-17 | 3.531 (0.458) | 1.4 E-14 |
| DBP (+ 10 mmHg if treated) | cGRS | 0.815 (0.084) | 3.6 E-22 | 0.792 (0.084) | 3.7 E-21 | 0.724 (0.086) | 3.9 E-17 |
| | wGRS | 0.806 (0.084) | 1.0 E-21 | 0.780 (0.084) | 1.3 E-20 | 0.722 (0.086) | 4.3 E-17 |
| | 1 vs. 2 quart. | 0.715 (0.238) | 0.003 | 0.690 (0.237) | 0.004 | 0.529 (0.242) | 0.029 |
| | 1 vs. 3 quart. | 1.371 (0.234) | 5.2 E-09 | 1.313 (0.233) | 1.9 E-08 | 1.147 (0.239) | 1.6 E-06 |
| | 1 vs. 4 quart. | 2.187 (0.238) | 4.6 E-20 | 2.145 (0.237) | 1.6 E-19 | 1.973 (0.243) | 5.1 E-16 |
| | | OR (95%CI) | P-value | OR (95%CI) | P-value | OR (95%CI) | P-value |
| Prevalence of Hypertension | cGRS | 1.178 (1.138-1.219) | 1.4 E-20 | 1.179 (1.138-1.221) | 4.1 E-20 | 1.144 (1.107-1.183) | 1.5 E-15 |
| | wGRS | 1.169 (1.129-1.209) | 7.6 E-19 | 1.168 (1.127-1.209) | 2.3 E-15 | 1.153 (1.115-1.191) | 4.3 E-17 |
| | 1 vs. 2 quart. | 1.175 (1.069-1.291) | 0.001 | 1.156 (1.049-1.273) | 0.003 | 1.134 (1.026-1.253) | 0.014 |
| | 1 vs. 3 quart. | 1.288 (1.171-1.417) | 1.9 E-07 | 1.276 (1.158-1.406) | 9.0 E-07 | 1.245 (1.125-1.376) | 2.0 E-05 |
| | 1 vs. 4 quart. | 1.509 (1.369-1.663) | 1.2 E-16 | 1.494 (1.354-1.649) | 1.5 E-15 | 1.466 (1.324-1.625) | 2.4 E-13 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; Quart., quartiles; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles. Please refer to the "Methods" section for details about different covariates in different regression models.

**Table 4. Association of the GRS with Delta-Systolic and Diastolic BP and Hypertension incidence between MPP baseline and reinvestigation.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=11,290) | | Model B (n=11,200) | | Model C (n=10,781) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| ΔSBP/year (excluding subjects with Ht at baseline) | cGRS | 0.038 (0.008) | 3.8 E-06 | 0.040 (0.008) | 1.1 E-06 | 0.033 (0.008) | 3.3 E-05 |
| | wGRS | 0.036 (0.008) | 1.1 E-05 | 0.038 (0.008) | 4.0 E-06 | 0.031 (0.008) | 8.2 E-05 |
| | 1 vs. 2 quart. | 0.039 (0.023) | 0.086 | 0.040 (0.023) | 0.074 | 0.027 (0.022) | 0.22 |
| | 1 vs. 3 quart. | 0.077 (0.022) | 0.001 | 0.078 (0.022) | 4.9 E-04 | 0.062 (0.022) | 0.005 |
| | 1 vs. 4 quart. | 0.092 (0.023) | 5.3 E-05 | 0.094 (0.023) | 4.0 E-05 | 0.082 (0.022) | 2.7 E-04 |
| ΔDBP/year (excluding subjects with Ht at baseline) | cGRS | 0.025 (0.005) | 2.9 E-08 | 0.026 (0.005) | 1.7 E-08 | 0.023 (0.004) | 3.5 E-07 |
| | wGRS | 0.025 (0.005) | 3.5 E-08 | 0.026 (0.005) | 3.0 E-08 | 0.023 (0.004) | 3.6 E-07 |
| | 1 vs. 2 quart. | 0.025 (0.013) | 0.050 | 0.025 (0.013) | 0.052 | 0.017 (0.012) | 0.17 |
| | 1 vs. 3 quart. | 0.058 (0.013) | 6.2 E-06 | 0.057 (0.013) | 8.6 E-06 | 0.049 (0.012) | 9.2 E-05 |
| | 1 vs. 4 quart. | 0.073 (0.013) | 2.2 E-08 | 0.072 (0.013) | 3.0 E-08 | 0.063 (0.013) | 6.2 E-07 |
| | | OR (95%CI) | P-value | OR (95%CI) | P-value | OR (95%CI) | P-value |
| Hypertension Incidence | cGRS | 1.127 (1.083-1.172) | 2.6 E-09 | 1.118 (1.074-1.163) | 5.5 E-08 | 1.110 (1.065-1.156) | 6.7 E-07 |
| | wGRS | 1.122 (1.078-1.167) | 9.9 E-9 | 1.110 (1.066-1.155) | 3.4 E-07 | 1.105 (1.061-1.151) | 1.7 E-06 |
| | 1 vs. 2 quart. | 1.119 (1.005-1.247) | 0.04 | 1.109 (0.993-1.237) | 0.065 | 1.092 (0.976-1.222) | 0.12 |
| | 1 vs. 3 quart. | 1.265 (1.134-1.411) | 2.4 E-05 | 1.243 (1.112-1.389) | 1.2 E-04 | 1.229 (1.097-1.377) | 3.6 E-04 |
| | 1 vs. 4 quart. | 1.344 (1.203-1.502) | 1.8 E-07 | 1.301 (1.162-1.456) | 5.1 E-06 | 1.284 (1.143-1.441) | 2.4 E-05 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; Quart., quartiles; ΔSBP, delta Systolic Blood Pressure; ΔDBP, delta Diastolic Blood Pressure. Estimates of SBP and DBP effects (beta and SEM) are in mmHg/year per coded allele; HT, hypertension. Units

are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles. Please refer to the "Methods" section for details about different covariates in different regression models.

**Table 5. Odds Ratio (95% confidence interval) as found in logistic regression (multivariate model) for hypertension incidence at reinvestigation (n=10,781 as in model C).**

| COVARIATES | OR (95%CI) | P-value |
|---|---|---|
| **Sex, M** | 1.379 (1.244-1.528) | 9.9 E-10 |
| **Age, year** | 1.122 (1.058-1.189) | 1.1 E-04 |
| **Age$^2$, year$^2$** | 0.999(0.998-1.000) | 0.002 |
| **Sex times age, year** | 1.004 (1.002-1.006) | 0.001 |
| **Heart rate, bpm** | 1.012 (1.007-1.017) | 1.7 E-14 |
| **Obesity at baseline** | 2.276 (1.698-3.053) | 1.9 E-09 |
| **Diabetes mellitus at baseline** | 1.376 (1.038-1.824) | 0.026 |
| **Hypertriglyceridemia* at baseline** | 1.452 (1.282-1.645) | 4.4 E-09 |
| **Pre-hypertension at baseline** | 2.379 (2.173-2.603) | <1.0 E-36 |
| **Positive family history of hypertension** | 1.307 (1.191-1.434) | 1.6 E-08 |
| **Sedentary in spare time** | 1.110 (1.013-1.217) | 0.025 |
| **Problematic alcohol behavior** | 1.116 (1.002-1.242) | 0.045 |
| **Married or living as a couple** | 0.879 (0.802-0.964) | 0.006 |
| **High level non manual work** | 0.826 (0.759-0.899) | 1.0 E-05 |
| **Current smokers** | 1.422 (1.304-1.550) | 1.3 E-15 |
| **GRS for trend** | | 5.1 E-05 |
| **GRS, 2$^{nd}$ quartile vs. 1$^{st}$ quartile** | 1.092 (0.976-1.222) | 0.12 |
| **GRS, 3$^{rd}$ quartile vs. 1$^{st}$ quartile** | 1.229 (1.097-1.377) | 3.6 E-04 |
| **GRS, 4$^{th}$ quartile vs. 1$^{st}$ quartile** | 1.284 (1.143-1.441) | 2.4 E-05 |

GRS, Genetic Risk Score. Both Chronic Kidney Disease and hypercholesterolemia at baseline were discarded from the model. The sex of the participant was coded as 1 male and 0 female. *Hypertriglyceridemia: serum triglycerides≥1.7 mmol/L

**Prediction of blood pressure changes over time and incidence of hypertension by a genetic risk score in Swedes.**
**Short title: GRS and hypertension**

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**Online supplements**
**Methods and results**

## METHODS

### Equation used for the calculation of the count and weighted GRS

For each genotype subjects with two non coded alleles were computed as 0, heterozygous subjects as 1 and homozygotes for the coded/risk allele as 2. The beta coefficient was obtained by previous studies.[1-3]

**cGRS:**
+rs17367504 + rs633185 + rs6015450 + rs1799945 + rs381815 + rs2681492 + rs10850411 + rs1173771 + rs11953630 + rs13082711 + rs13107325 + rs13139571 + rs1327235 + rs17608766 + rs12946454 + rs3184504 + rs1378942 + rs2521501 + rs11191548 + rs2932538 + rs3774372 + rs419076 + rs4373814 + rs7129220 + rs805303 + rs932764 + rs16998073 + rs1530440 + rs16948048

**wGRS for Systolic BP:**
+0.547 x rs17367504 +0.565 x rs633185 + 0.896 x rs6015450 + 0.627 x rs1799945 + 0.840 x rs381815 + 1.26 x rs2681492 + 0.354 x rs10850411 + 0.504 x rs1173771 + 0.412 x rs11953630 + 0.315 x rs13082711 + 0.981 x rs13107325 + 0.312 x rs13139571 + 0.34 x rs1327235 + 0.556 x rs17608766 + 0.210 x rs12946454 + 0.448 x rs3184504 + 0.416 x rs1378942 + 0.65 x rs2521501 + 0.464 x rs11191548 + 0.388 x rs2932538 +0.067 x rs3774372 + 0.409 x rs419076 + 0.373 x rs4373814 + 0.619 x rs7129220 + 0.376 x rs805303 + 0.484 x rs932764 + 0.740 x rs16998073 + 0.43 x rs1530440 + 0.410 x rs16948048.

**wGRS for diastolic BP:**
+0.903 x rs17367504 +0.328 x rs633185 +0.557 x rs6015450 + 0.457 x rs1799945 + 0.510 x rs381815 +0.62 x rs2681492 + 0.253 x rs10850411 + 0.261 x rs1173771 +0.281 x rs11953630 +0.238 x rs13082711 +0.684 x rs13107325 + 0.260 x rs13139571 + 0.302 x rs1327235 + 0.129 x rs17608766 + 0.447 x rs12946454 + 0.598 x rs3184504 + 0.613 x rs1378942 + 0.359 x rs2521501 + 0.646 x rs11191548 + 0.240 x rs2932538 +0.367 x rs3774372 + 0.241 x rs419076 + 0.218 x rs4373814 + 0.299 x rs7129220 + 0.228 x rs805303 + 0.185 x rs932764 + 0.650 x rs16998073 + 0.51 x rs1530440 +0.400 x rs16948048.

**wGRS for hypertension:**
+0.103 x rs17367504 +0.07 x rs633185 +0.110 x rs6015450 + 0.095 x rs1799945 + 0.090 x rs381815 + 0.14 x rs2681492 + 0.045 x rs10850411 + 0.062 x rs1173771 +0.052 x rs11953630 +0.035 x rs13082711 +0.105 x rs13107325 + 0.042 x rs13139571 + 0.034 x rs1327235 + 0.025 x rs17608766 + 0.051 x rs12946454 + 0.056 x rs3184504 + 0.073 x rs1378942 + 0.059 x rs2521501 + 0.097 x rs11191548 + 0.049 x rs2932538 +0.017 x rs3774372 + 0.031 x rs419076 + 0.046 x rs4373814 + 0.045 x rs7129220 + 0.054 x rs805303 + 0.055 x rs932764+ 0.100 x rs16998073 +0.05 x rs1530440 +0.06 x rs16948048.

**Imputation of missing genotypes**

In the attempt to not exclude subjects with few missing genotypes from the analysis we decided to impute missing genotypes. Briefly, missing genotypes were replaced by random genotypes that had to respect the proportion of the allele frequency in the remaining of the population where genotypes were available.[4] Briefly, a series of randomly generated numbers (at www.random.org) corresponding to subjects with missed genotypes were assigned to the genotypes with the established proportion of wild type homozygotes, heterozygotes and mutated homozygotes. However, to avoid inclusion of people with too little genetic information available we excluded subjects (N=552) with less than 24 valid genotypes. Thus, for all the presented analysis only subjects with at least 24 out of 29 genotypes were included. In Table S4, the number of subjects with missing genotypes is presented.

**Blood pressure**

We treated BP as a continuous variable before and after adjustment of the measured BP values (see below) and as a dichotomized trait (hypertension vs. normotension). Hypertension was defined as being on antihypertensive treatment or a SBP/DBP equal or greater than 140/90 mmHg (according to current diagnostic criteria) whereas normotension was defined as a SBP/DBP less than 140/90 mmHg. Pre-hypertension was defined as SBP >130 mmHg but ≤140 mmHg and DBP >85 mmHg but ≤90 mmHg.
In both studies, BP was measured by specially trained nurses on the right brachial artery using a mercury sphygmomanometer. The SBP was defined by the 'phase I' and the DBP was defined by the 'phase V' Korotkoff sounds.
At baseline, the first BP reading was taken after 1 minute of rest in the supine position. The participants were asked to stand up and a second BP measurement was taken in an upright standing position after one minute. This procedure was then repeated following an initial 10-minute rest in the supine position. The average BP of all subjects with at least three valid measurements were used in the present study. At reinvestigation, BP was measured twice in the supine position and all of the measurements were recorded. The average BP of all the subjects with at least two valid measurements was used in the present study.

*Blood pressure adjustment*

To overcome the possibility that a biased selection might result from selecting only individuals who were free of antihypertensive treatments, we conducted an analysis adjusting the systolic BP and diastolic BP of hypertensive individuals who were taking antihypertensive drugs at the time of investigation. Similarly to recent GWAS, based on the known average treatment effects, fixed increments of 15 mmHg systolic BP and 10 mmHg diastolic BP were added to the pressures of

treated subjects.[1-3] In sensitivity analyses also different fixed and stepped increments were tested as suggested by Cui and colleagues.[5]

**Laboratory analysis**

After an overnight fast, blood samples were drawn for the determination of whole blood glucose, lipids and creatinine. Samples were analyzed by standard methods at the Department of Clinical Chemistry, Malmö University Hospital.[6] Laboratory analyses were performed according to standard methods; triglyceride, cholesterol and glucose were measured enzymatically and creatinine was determined with Jaffe's alkaline picrate method. For estimation of the glomerular filtration rate (eGFR), the *Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)* equation was applied for creatinine in mg/dL.[7]

Information about medical history, anthropometric data, lifestyle and socio-economic factors, and family history of hypertension in first-degree relatives was derived from the baseline questionnaire. Diabetes mellitus was defined as a fasting whole blood glucose >6.1 mmol/L or self-reported history of a physician´s diagnosis of diabetes. Body mass index was calculated as weight (in kilograms) divided by the square of height (in meters).

**Genotyping**

Information about the different SNPs included in the GRS is reported in the Supplementary Section. The SNPs were genotyped using IPLEX on a MassARRAY platform (Sequenom, San Diego, CA, USA) according to the manufacturer's standard protocols. Nearly 30% of the samples were run in duplicate. All genotypes were called by two different investigators. We pre-specified a threshold call rate of 90% per individual SNP (that is SNPs would be excluded if its call rate is<90%). A threshold of $p<10^{-07}$ was first established for excluding SNPs, according to Hardy-Weinberg equilibrium calculation. A SNP, *FES* rs2521501, that we found to be outside the threshold for Hardy-Weinberg equilibrium, was anyhow included in the GRS to adhere to the previously validated GRS.

**Genetic risk score**

Two methods were used to create the multivariable GRS, a simple, unweighted count method (count GRS, cGRS) and a weighted method (weighted GRS, wGRS) according to the β-coefficient attributed to the tested SNPs in previous studies.[1-3] Both methods assumed each SNP to be independently associated with risk. The additive genetic model was assumed: weightings of 0, 1, and 2 were given according to the number of coded (risk) alleles present. The count method assumed that each SNP contributed equally to hypertension risk and was calculated by summing the number of risk alleles across the panel of SNPs tested. The weighted GRS was calculated by multiplying the β-coefficient for systolic, diastolic BP or hypertension, as estimated in previous studies by the number of corresponding coded alleles (0, 1, or 2), and then summing the products. The GRS was modeled as a continuous variable and as quartiles. Details about the equation utilized to calculate the wGRS are presented in the Supplementary method section along with a frequency histogram for all the GRS. Both the cGRS and wGRS were standardized.

***Statistics***

The independent variables were either genotype, age, sex, age times sex, age$^2$, BMI or obesity (defined as BMI >30 kg/m$^2$), heart rate, follow-up years (when appropriate; model A), or covariates as in model A plus gluco-lipid parameters: either total cholesterol or hypercholesterolemia (total serum cholesterol >5.17 mmol/L or specific treatment); either triglycerides or hypertriglyceridemia (serum triglycerides≥1.7 mmol/L or specific treatment);

either HDL-cholesterol or hypo-HDL-cholesterol (serum HDL-cholesterol < 1.03 mmol/L in males and <1.29 mmol/L in females); fasting blood glucose or diabetes mellitus (fasting blood glucose≥6.1 mmol/L or antidiabetic treatment or answering yes at specific question on a questionnaire); CKD-EPI estimated-glomerular filtration rate (GFR) or chronic kidney disease (eGFR<60 ml /min/1.73 $m^2$); baseline BP or pre-hypertension (BP ≥130/85 and <140/90; when appropriate; model B) or as in model A plus B plus a positive family history of hypertension in at least one 1$^{st}$ degree relative; smoking habit; problematic alcohol behavior; civil state (married or cohabiting as a couple vs. single); physical activity (mostly sedentary in spare time vs. mostly non sedentary); socio-economic status (either manual worker or low-level non manual worker vs. either moderate to high level non manual worker or entrepreneur; model C). Subjects already diagnosed as hypertensive at baseline were not included in the longitudinal analysis. An unbiased estimate of the variance explained by the GRS was obtained by evaluating the increase in explained variance of the trait when adding the GRS to the model C tested in linear and logistic regression (Nagelkerke $r^2$).

## RESULTS

In Table S1, baseline characteristics of subjects with available DNA, compared with subjects who died or did not attend the reinvestigation survey, are presented.

***Cross sectional analysis for different SNPs***

Associations between individual SNPs and cross sectional data on BP/hypertension both at baseline and reinvestigation are presented in the Online table S4. Only 4 SNPs in the *FGF5*, *EBF1*, *TMEM133* and *CYP1A2* genes were significantly associated with systolic, diastolic BP and hypertension prevalence both at baseline and at reinvestigation. The lowest p-value was reached for diastolic BP using the *FGF5* rs16998073A>T SNP (β±SEM: 0.485±0.095; P=3.8 E-07).

***Longitudinal analysis for different SNPs***

The associations between individual SNPs and longitudinal data about BP change over time (Δ-BP) and hypertension incidence at reinvestigation are presented in Online table S5. A few SNPs were significantly associated with Δ-systolic and Δ-diastolic BP/year including the rs633185 C>G near *TMEM133* and the rs1378942 C>A nearby *CYP1A2* (borderline significant for Δ-systolic BP), already associated with BP in the cross-sectional analysis. For the rs1378942 C>A nearby *CYP1A2*, a borderline significant association was evident also for incident hypertension.

## Reference List


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**Table S1. Baseline Anthropometric, anamnestic, socio-economic, lifestyle and metabolic features of subjects with available DNA as compared with subjects who died or did not attend the reinvestigation survey.**

| Variables | Subjects without DNA (n=9,118) (not participating at reinvestigation) | Death before reinvestigation (N=5,988**) | Subjects with DNA (n=18,240) (participating at reinvestigation) | Post-hoc |
|---|---|---|---|---|
| **Gender, male (%)** | 66.0 | 81.3 | 63.4 | A,B,C |
| **Age, years** | 45.3+7.8 | 47.8+6.6 | 45.2+7.4 | A,C |
| **Systolic blood pressure, mmHg ⌠** | 126.9+15.8 | 130.6+17.6 | 124.5+14.3 | A,B,C |
| **Diastolic blood pressure, mmHg ⌠** | 84.5+9.7 | 87.0+10.7 | 83.2+9.1 | A,B,C |
| **Heart rate, bpm** | 71.4+11.8 | 72.5+11.2 | 70.0+10.4 | A,B,C |
| **Body mass index, kg/m$^2$** | 24.8+3.9 | 25.1+3.9 | 24.3+3.4 | A,B,C |
| **Manual work or low level non-manual work** | 64.2 | 65.3 | 61.5 | |
| **Problematic drinking behaviour** | 22.1 | 25.8 | 19.6 | A,B,C |
| **Civil (married/cohabiting)** | 65.6 | 61.6 | 72.6 | A,B,C |
| **Prevalently sedentary in spare time, %** | 42.3 | 52.5 | 37.3 | A,B,C |
| **Smoke** | 48.3 | 61.2 | 37.2 | A,B,C |
| **Creatinine (median)** | 87 | 88 | 87 | A,C † |
| **Glucose (median)** | 4.9 | 4.9 | 4.8 | A,B,C † |
| **Triglycerides (median)** | 1.2 | 1.33 | 1.1 | A,B,C † |
| **Cholesterol** | 5.7+1.1 | 5.8+1.1 | 5.6+1.0 | A,B,C |
| **Diabetes, % ‡** | 5.5 | 8.0 | 3.2 | A,B,C |
| **Antihypertensive therapy, %** | 6.1 | 7.8 | 4.4 | A,B,C |

‡ ≥6.1 mmol/L or diabetes according to questionnaire

**death before 2003-03-01 (n=5449) or lost to follow-up (emigrated)
$p<0.01$ for A: $1^{st}$ vs. $2^{nd}$ group, B: $1^{st}$ vs. $3^{rd}$ group, and C: $2^{nd}$ vs $3^{rd}$ group.
a $p<0.05$ for $1^{st}$ vs. $2^{nd}$ group.
† log-transformed values were used for the analysis.
⌠values are based on a single measure in supine position after 10 minutes rest.

**Table S2. Hardy-Weinberg equilibrium for all the SNPs in MPP.**

| Gene | SNP | Chr. | Position | % of valid genotypes | C.A. | A.A. | MAF | Observed heterozigosity | Expected heterozigosity | HWE p-value | Kappa* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***MTHFR-NPPB*** | rs17367504 | 1 | 11,862,778 | 99.6 | A | G | 0.152 | 0.26 | 0.258 | 0.3099 | 0.976 |
| ***MOV10*** | rs2932538 | 1 | 113,216,543 | 96.6 | G | A | 0.264 | 0.398 | 0.389 | 8.8 E-04 | 0.966 |
| ***SLC4A7*** | rs13082711 | 3 | 27,537,909 | 96.6 | C | T | 0.22 | 0.346 | 0.343 | 0.2384 | 0.974 |
| ***ULK4*** | rs3774372 | 3 | 41,877,414 | 97.4 | C | T | 0.156 | 0.262 | 0.263 | 0.6369 | 0.974 |
| ***MECOM*** | rs419076 | 3 | 169,100,886 | 90.8 | T | C | 0.454 | 0.492 | 0.496 | 0.2827 | 0.971 |
| ***FGF5*** | rs16998073 | 4 | 81,184,341 | 98.8 | T | A | 0.343 | 0.452 | 0.451 | 0.6815 | 0.974 |
| ***SLC39A8*** | rs13107325 | 4 | 103,188,709 | 97.6 | C | T | 0.048 | 0.091 | 0.091 | 1 | 0.970 |
| ***GUCY1A3-GUCY1B3*** | rs13139571 | 4 | 156,645,513 | 96.2 | C | A | 0.22 | 0.35 | 0.343 | 0.0082 | 0.967 |
| ***NPR3-C5orf23*** | rs1173771 | 5 | 32,815,028 | 94.9 | G | A | 0.404 | 0.499 | 0.481 | 2.0 E-06 | 0.954 |
| ***EBF1*** | rs11953630 | 5 | 157,845,402 | 95.6 | C | T | 0.344 | 0.456 | 0.451 | 0.1555 | 0.966 |
| ***HFE*** | rs1799945 | 6 | 26,091,179 | 92.5 | G | C | 0.115 | 0.201 | 0.203 | 0.2423 | 0.924 |
| ***BAT2-BAT5*** | rs805303 | 6 | 31,616,366 | 96.0 | G | A | 0.37 | 0.476 | 0.466 | 0.0057 | 0.977 |
| ***CACNB2(5')*** | rs4373814 | 10 | 18,419,972 | 94.9 | C | G | 0.428 | 0.499 | 0.490 | 7.7 E-03 | 0.955 |
| ***c10orf107*** | rs1530440 | 10 | 63,524,591 | 98.9 | C | T | 0.188 | 0.305 | 0.305 | 0.9709 | 0.967 |
| ***PLCE1*** | rs932764 | 10 | 95,895,940 | 96.9 | G | A | 0.446 | 0.490 | 0.494 | 0.2687 | 0.971 |
| ***CYP17A1-NT5C2*** | rs11191548 | 10 | 104,846,178 | 89.7 | T | C | 0.108 | 0.191 | 0.193 | 0.1239 | 0.971 |
| ***ADM*** | rs7129220 | 11 | 10,350,538 | 97.0 | A | G | 0.104 | 0.189 | 0.186 | 0.0456 | 0,976 |
| ***PLEKHA7*** | rs381815 | 11 | 16,902,268 | 96.4 | T | C | 0.274 | 0.392 | 0.398 | 0.0645 | 0.970 |
| ***FLJ32810-TMEM133*** | rs633185 | 11 | 100,593,538 | 95.9 | C | G | 0.297 | 0.412 | 0.417 | 0.1296 | 0.969 |
| ***ATP2B1*** | rs2681492 | 12 | 90,013,089 | 97.3 | T | C | 0.145 | 0.249 | 0.248 | 0.1902 | 0.971 |
| ***SH2B3*** | rs3184504 | 12 | 111,884,608 | 97.0 | T | C | 0.48 | 0.495 | 0.499 | 0.579 | 0.961 |
| ***TBX5-TBX3*** | rs10850411 | 12 | 115,387,796 | 96.4 | T | C | 0.289 | 0.413 | 0.411 | 0.6181 | 0,961 |
| ***CYP1A2-ULK3*** | rs1378942 | 15 | 75,077,367 | 92.1 | C | A | 0.321 | 0.436 | 0.435 | 0.7069 | 0.976 |
| ***FES*** | rs2521501 | 15 | 91,437,388 | 95.6 | T | A | 0.327 | 0.462 | 0.439 | 7.1 E-07 | 0,968 |
| ***PLCD3*** | rs12946454 | 17 | 43,208,121 | 99.1 | T | A | 0.246 | 0.373 | 0.371 | 0.5117 | 0.969 |
| ***GOSR2*** | rs17608766 | 17 | 45,013,271 | 97.4 | C | T | 0.14 | 0.243 | 0.241 | 0.2908 | 0.966 |
| ***ZNF652*** | rs16948048 | 17 | 47,440,466 | 98.3 | G | A | 0.383 | 0.471 | 0.473 | 0.6711 | 0.970 |
| ***JAG1*** | rs1327235 | 20 | 10,969,030 | 95.1 | G | A | 0.494 | 0.508 | 0.500 | 0.0418 | 0,963 |
| ***GNAS-EDN3*** | rs6015450 | 20 | 57,751,117 | 92.5 | G | A | 0.132 | 0.229 | 0.229 | 0.7999 | 0.976 |

SNP, Single Nucleotide polymorphism; Chr., chromosome; C.A., coded allele; A.A. alternative allele; MAF, Minor Allele Frequency; HWE, Hardy Weinberg equilibrium. *Kappa indicates the agreement between genotypes as calculated on more than 6,000 samples run in duplicate.

**Table S3. Number of missing genotypes per subject.**

| Number of missing genotypes | Number of subjects |
|---|---|
| **No missing genotypes** | 10,202 |
| **1 missing genotype** | 4,858 |
| **2 missing genotypes** | 1,685 |
| **3 missing genotypes** | 593 |
| **4 missing genotypes** | 528 |
| **5 missing genotypes** | 92 |
| **6 or more missing genotypes** | 552 |

Subjects with 6 or more missing genotypes were excluded from the analysis.

**Table S4. Summary association statistics based on all data for 29 independent SNPs in MPP at baseline and reinvestigation. Estimates of SBP and DBP effects (beta and SEM) are in mmHg per coded allele; HTN effects (beta, SEM) are in (OR) units per coded allele.**

| *Genetic variants* | | BASELINE | | | | | | REINVESTIGATION | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SBP | | DBP | | HT | | SBP | | DBP | | HT | |
| ***Gene*** | **Index SNP** | **Beta (SEM)** | **p-value** | **Beta (SEM)** | **p-value** | **Beta (SEM)** | **p-value** | **Beta (SEM)** | **p-value** | **Beta (SEM)** | **p-value** | **Beta (SEM)** | **p-value** |
| ***MTHFR-NPPB*** | rs17367504 | 0.846 (0.202) | 2.8 E-05 | 0.513 (0.127) | 5.0 E-05 | 0.092 (0.035) | 0.009 | 0.939 (0.319) | 0.003 | 0.467 (0.170) | 0.006 | 0.062 (0.036) | 0.090 |
| ***MOV10*** | rs2932538 | 0.331 (0.166) | 0.046 | 0.159 (0.104) | 0.127 | 0.018 (0.029) | 0.533 | 0.889 (0.262) | 0.001 | 0.314 (0.139) | 0.024 | 0.077 (0.030) | 0.010 |
| ***SLC4A7*** | rs13082711 | -0.092 (0.175) | 0.596 | -0.058 (0.109) | 0.595 | 0.019 (0.030) | 0.527 | 0.214 (0.276) | 0.437 | 0.282 (0.147) | 0.055 | 0.084 (0.032) | 0.008 |
| ***ULK4*** | rs3774372 | 0.035 (0.199) | 0.859 | 0.322 (0.125) | 0.010 | 0.072 (0.034) | 0.034 | -0.507 (0.314) | 0.106 | 0.504 (0.167) | 0.003 | -0.025 (0.036) | 0.479 |
| ***MECOM*** | rs419076 | -0.095 (0.145) | 0.509 | 0.034 (0.091) | 0.706 | 0.003 (0.025) | 0.899 | 0.010 (0.228) | 0.965 | -0.005 (0.121) | 0.965 | -0.017 (0.026) | 0.522 |
| ***FGF5*** | rs16998073 | 0.749 (0.152) | 8.9 E-07 | 0.485 (0.095) | 3.8 E-07 | 0.101 (0.026) | 1.2E-04 | 0.681 (0.241) | 0.005 | 0.420 (0.128) | 0.001 | 0.066 (0.028) | 0.017 |
| ***SLC39A8*** | rs13107325 | 0.810 (0.339) | 0.017 | 0.761 (0.212) | 3.4 E-4 | 0.212 (0.060) | 4.5E-04 | 0.271 (0.537) | 0.614 | 0.335 (0.285) | 0.240 | 0.087 (0.061) | 0.153 |
| ***GUCY1A3-GUCY1B3*** | rs13139571 | 0.498 (0.176) | 0.005 | 0.393 (0.110) | 3.7 E-4 | 0.062 (0.031) | 0.042 | 0.269 (0.278) | 0.333 | 0.106 (0.148) | 0.471 | 0.083 (0.032) | 0.009 |
| ***NPR3-C5orf23*** | rs1173771 | 0.410 (0.150) | 0.006 | 0.226 (0.094) | 0.016 | 0.052 (0.027) | 0.050 | 0.793 (0.236) | 0.001 | 0.285 (0.126) | 0.023 | 0.032 (0.027) | 0.236 |
| ***EBF1*** | rs11953630 | 0.395 (0.153) | 0.010 | 0.201 (0.096) | 0.035 | -0.064 (0.026) | 0.014 | 0.773 (0.241) | 0.001 | 0.420 (0.128) | 0.001 | 0.097 (0.028) | 4.6 E-04 |
| ***HFE*** | rs1799945 | 0.142 (0.226) | 0.531 | 0.099 (0.142) | 0.486 | 0.018 (0.039) | 0.638 | 0.631 (0.357) | 0.077 | 0.293 (0.190) | 0.123 | 0.015 (0.041) | 0.722 |
| ***BAT2-BAT5*** | rs805303 | 0.363 (0.151) | 0.016 | 0.209 (0.095) | 0.027 | 0.058 (0.026) | 0.027 | 0.283 (0.239) | 0.235 | 0.088 (0.127) | 0.487 | 0.065 (0.027) | 0.017 |
| ***CACNB2(5')*** | rs4373814 | 0.117 (0.148) | 0.428 | 0.174 (0.093) | 0.061 | 0.022 (0.026) | 0.381 | 0.246 (0.234) | 0.293 | 0.192 (0.124) | 0.122 | 0.019 (0.027) | 0.489 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***C10ORF107*** | rs1530440 | 0.529 (0.185) | 0.004 | 0.307 (0.116) | 0.008 | 0.089 (0.032) | 0.006 | 0.428 (0.292) | 0.143 | 0.275 (0.155) | 0.077 | 0.066 (0.033) | 0.048 |
| ***PLCE1*** | rs932764 | 0.382 (0.145) | 0.008 | 0.056 (0.091) | 0.539 | 0.007 (0.025) | 0.774 | 0.479 (0.228) | 0.036 | 0.235 (0.121) | 0.053 | 0.056 (0.026) | 0.033 |
| ***CYP17A1-NT5C2*** | rs11191548 | -0.060 (0.231) | 0.795 | -0.106 (0.145) | 0.466 | -0.037 (0.040) | 0.350 | -0.306 (0.366) | 0.402 | -0.391 (0.194) | 0.044 | 0.017 (0.042) | 0.680 |
| ***ADM*** | rs7129220 | 0.636 (0.237) | 0.007 | 0.322 (0.149) | 0.030 | 0.090 (0.041) | 0.027 | 1.201 (0.375) | 0.001 | 0.410 (0.199) | 0.040 | 0.084 (0.044) | 0.052 |
| ***PLEKHA7*** | rs381815 | 0.026 (0.161) | 0.873 | 0.118 (0.101) | 0.242 | 0.019 (0.028) | 0.484 | 0.668 (0.253) | 0.008 | 0.294 (0.135) | 0.029 | 0.060 (0.029) | 0.040 |
| ***FLJ32810-TMEM133*** | rs633185 | 0.453 (0.157) | 0.004 | 0.344 (0.098) | 4.7 E-04 | 0.077 (0.027) | 0.005 | 0.827 (0.248) | 0.001 | 0.517 (0.132) | 8.6E-05 | 0.061 (0.028) | 0.030 |
| ***ATP2B1*** | rs2681492 | 0.248 (0.206) | 0.230 | 0.009 (0.129) | 0.945 | 0.049 (0.036) | 0.169 | -0.533 (0.327) | 0.103 | -0.178 (0.174) | 0.306 | -0.023 (0.037) | 0.532 |
| ***SH2B3*** | rs3184504 | 0.276 (0.144) | 0.055 | 0.195 (0.090) | 0.031 | 0.030 (0.025) | 0.225 | 0.446 (0.227) | 0.049 | 0.386 (0.121) | 0.001 | 0.082 (0.026) | 0.002 |
| ***TBX5-TBX3*** | rs10850411 | -0.046 (0.159) | 0.774 | -0.060 (0.100) | 0.549 | 0.008 (0.028) | 0.768 | 0.028 (0.252) | 0.911 | 0.007 (0.134) | 0.957 | -0.017 (0.029) | 0.556 |
| ***CYP1A2-ULK3*** | rs1378942 | 0.395 (0.154) | 0.010 | 0.199 (0.097) | 0.039 | 0.079 (0.027) | 0.003 | 0.650 (0.243) | 0.008 | 0.392 (0.129) | 0.002 | 0.087 (0.028) | 0.002 |
| ***FES*** | rs2521501 | 0.369 (0.156) | 0.018 | 0.152 (0.098) | 0.120 | 0.059 (0.027) | 0.020 | 0.748 (0.247) | 0.003 | 0.363 (0.131) | 0.006 | 0.073 (0.029) | 0.011 |
| ***GOSR2*** | rs17608766 | 0.535 (0.209) | 0.010 | 0.168 (0.131) | 0.200 | 0.026 (0.036) | 0.478 | -0.450 (0.330) | 0.173 | -0.098 (0.175) | 0.576 | 0.098 (0.038) | 0.011 |
| ***ZNF652*** | rs16948048 | 0.195 (0.148) | 0.188 | 0.107 (0.093) | 0.249 | 0.075 (0.026) | 0.003 | 0.251 (0.234) | 0.285 | 0.218 (0.125) | 0.080 | 0.054 (0.027) | 0.043 |
| ***JAG1*** | rs1327235 | 0.091 (0.146) | 0.534 | -0.090 (0.091) | 0.325 | -0.025 (0.025) | 0.315 | -0.096 (0.230) | 0.677 | -0.132 (0.122) | 0279 | -0.006 (0.026) | 0.827 |
| ***Dovr + GNAS-EDN3*** | rs6015450 | 0.672 (0.214) | 0.002 | 0.512 (0.134) | 1.4 E-4 | 0.108 (0.037) | 0.003 | 0.295 (0.338) | 0.383 | 0.306 (0.180) | 0.089 | 0.029 (0.039) | 0.449 |
| ***PLCD3*** | rs12946454 | 0.109 (0.168) | 0.515 | 0.117 (0.105) | 0.268 | -0.007 (0.029) | 0.819 | 0.344 (0.265) | 0.195 | 0.004 (0.141) | 0.978 | 0.002 (0.030) | 0.947 |

After full adjustment (regression model B). SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HT, Hypertension.

**Table S5. Summary association statistics based on all data for 29 independent SNPs for BP change and incidence of hypertension between baseline and reinvestigation. Estimates of SBP and DBP effects (beta and SEM) are in mmHg/year per coded allele; HT effects (beta, SEM) are in (OR) units per coded allele.**

| *Genetic variants* | | Δ-Systolic BP/year | | Δ-Diastolic BP/year | | HT | |
|---|---|---|---|---|---|---|---|
| ***Gene*** | **Index SNP** | **Beta (SEM)** | **p-value** | **Beta (SEM)** | **p-value** | **Beta (SEM)** | **p-value** |
| ***MTHFR-NPPB*** | rs17367504 | 0.000 | 0.979 | 0.004 | 0.633 | 0.013 | 0.741 |
| | | (0.016) | | (0.009) | | (0.041) | |
| ***MOV10*** | rs2932538 | 0.023 | 0.081 | 0.008 | 0.290 | 0.068 | 0.044 |
| | | (0.013) | | (0.007) | | (0.034) | |
| ***SLC4A7*** | rs13082711 | 0.026 | 0.084 | 0.021 | 0.005 | 0.090 | 0.012 |
| | | (0.016) | | (0.008) | | (0.036) | |
| ***ULK4*** | rs3774372 | -0.027 | 0.154 | 0.013 | 0.152 | -0.052 | 0.197 |
| | | (0.013) | | (0.009) | | (0.041) | |
| ***MECOM*** | rs419076 | 0.002 | 0.878 | -0.003 | 0.664 | -0.017 | 0.561 |
| | | (0.011) | | (0.006) | | (0.029) | |
| ***FGF5*** | rs16998073 | 0.013 | 0.273 | 0.013 | 0.056 | 0.033 | 0.285 |
| | | (0.012) | | (0.007) | | (0.031) | |
| ***SLC39A8*** | rs13107325 | 0.010 | 0.709 | 0.020 | 0.158 | 0.039 | 0.559 |
| | | (0.026) | | (0.014) | | (0.067) | |
| ***GUCY1A3-GUCY1B3*** | rs13139571 | 0.008 | 0.540 | 0.000 | 0.956 | 0.049 | 0.167 |
| | | (0.014) | | (0.008) | | (0.036) | |
| ***NPR3-C5orf23*** | rs1173771 | 0.018 | 0.119 | 0.009 | 0.182 | 0.017 | 0.568 |
| | | (0.012) | | (0.007) | | (0.030) | |
| ***EBF1*** | rs11953630 | -0.004 | 0.710 | -0.001 | 0.848 | 0.049 | 0.111 |
| | | (0.012) | | (0.007) | | (0.031) | |
| ***HFE*** | rs1799945 | 0.017 | 0.337 | 0.013 | 0.199 | 0.021 | 0.650 |
| | | (0.018) | | (0.010) | | (0.047) | |
| ***BAT2-BAT5*** | rs805303 | 0.006 | 0.634 | 0.007 | 0.323 | 0.040 | 0.194 |
| | | (0.012) | | (0.007) | | (0.031) | |
| ***CACNB2(5')*** | rs4373814 | 0.014 | 0.209 | 0.008 | 0.189 | 0.034 | 0.259 |
| | | (0.012) | | (0.007) | | (0.030) | |
| ***C10orf107*** | rs1530440 | 0.004 | 0.784 | 0.000 | 0.961 | -0.005 | 0.901 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | (0.014) | | (0.008) | | (0.037) | |
| ***PLCE1*** | rs932764 | 0.012 | 0.278 | 0.011 | 0.071 | 0.038 | 0.195 |
| | | (0.011) | | (0.006) | | (0.029) | |
| ***CYP17A1-NT5C2*** | rs11191548 | 0.008 | 0.669 | 0.000 | 0.989 | 0.043 | 0.366 |
| | | (0.018) | | (0.010) | | (0.047) | |
| ***ADM*** | rs7129220 | 0.028 | 0.138 | 0.005 | 0.669 | 0.026 | 0.593 |
| | | (0.019) | | (0.011) | | (0.049) | |
| ***PLEKHA7*** | rs381815 | 0.018 | 0.157 | 0.000 | 0.969 | 0.061 | 0.064 |
| | | (0.013) | | (0.007) | | (0.033) | |
| ***FLJ32810-TMEM133*** | rs633185 | 0.026 | 0.036 | 0.016 | 0.020 | 0.047 | 0.137 |
| | | (0.012) | | (0.007) | | (0.032) | |
| ***ATP2B1*** | rs2681492 | -0.022 | 0.163 | -0.001 | 0.940 | -0.010 | 0.990 |
| | | (0.016) | | (0.009) | | (0.042) | |
| ***SH2B3*** | rs3184504 | 0.010 | 0.361 | 0.016 | 0.010 | 0.084 | 0.004 |
| | | (0.011) | | (0.006) | | (0.029) | |
| ***TBX5-TBX3*** | rs10850411 | 0.001 | 0.911 | 0.003 | 0.619 | -0.017 | 0.609 |
| | | (0.012) | | (0.007) | | (0.033) | |
| ***CYP1A2-ULK3*** | rs1378942 | 0.023 | 0.060 | 0.015 | 0.023 | 0.082 | 0.009 |
| | | (0.012) | | (0.007) | | (0.032) | |
| ***FES*** | rs2521501 | 0.031 | 0.011 | 0.014 | 0.043 | 0.047 | 0.143 |
| | | (0.012) | | (0.007) | | (0.032) | |
| ***GOSR2*** | rs17608766 | 0.006 | 0.701 | -0.016 | 0.089 | 0.093 | 0.031 |
| | | (0.016) | | (0.009) | | (0.043) | |
| ***ZNF652*** | rs16948048 | 0.011 | 0.322 | 0.010 | 0.107 | 0.033 | 0.274 |
| | | (0.012) | | (0.007) | | (0.030) | |
| ***JAG1*** | rs1327235 | -0.001 | 0.902 | -0.004 | 0.443 | -0.017 | 0.579 |
| | | (0.011) | | (0.006) | | (0.030) | |
| ***GNAS-EDN3*** | rs6015450 | 0.001 | 0.937 | 0.001 | 0.823 | 0.019 | 0.669 |
| | | (0.017) | | (0.006) | | (0.044) | |
| ***PLCD3*** | rs12946454 | 0.011 | 0.407 | -0.002 | 0.736 | -0.018 | 0.588 |
| | | (0.013) | | (0.007) | | (0.034) | |

After full adjustment (regression model C). SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HT, Hypertension.

**Table S6a. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP baseline in males.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=11,170) | | Model B (n=11,087) | | Model C (n=11,053) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| SBP (+ 15 mmHg if treated) | cGRS | 0.871 (0.117) | 1.2 E-13 | 0.876 (0.117) | 8.2 E-14 | 0.830 (0.116) | 8.2 E-13 |
| | wGRS | 0.958 (0.117) | 2.8 E-16 | 0.964 (0.117) | 1.7 E-16 | 0.914 (0.115) | 2.6 E-15 |
| | 1 vs. 2 quart. | 0.664 (0.329) | 0.044 | 0.557 (0.329) | 0.091 | 0.585 (0.325) | 0.072 |
| | 1 vs. 3 quart. | 1.809 (0.336) | 7.4 E-08 | 1.804 (0.336) | 8.0 E-08 | 1.605 (0.331) | 1.2 E-06 |
| | 1 vs. 4 quart. | 2.396 (0.335) | 9.4 E-13 | 2.341 (0.333) | 2.5 E-12 | 2.193 (0.330) | 3.1 E-11 |
| DBP (+ 10 mmHg if treated) | cGRS | 0.615 (0.078) | 4.8 E-15 | 0.607 (0.078) | 1.1 E-14 | 0.580 (0.077) | 6.3 E-14 |
| | wGRS | 0.667 (0.078) | 2.0 E-17 | 0.658 (0.078) | 5.1 E-17 | 0.631 (0.077) | 2.8 E-16 |
| | 1 vs. 2 quart. | 0.530 (0.222) | 0.017 | 0.502 (0.222) | 0.024 | 0.506 (0.219) | 0.021 |
| | 1 vs. 3 quart. | 1.228 (0.221) | 3.0 E-08 | 1.227 (0.221) | 1.6 E-10 | 1.107 (0.217) | 3.4 E-07 |
| | 1 vs. 4 quart. | 1.832 (0.222) | 2.2 E-16 | 1.798 (0.222) | 6.7 E-16 | 1.723 (0.219) | 3.9 E-15 |
| | | OR (95%CI) | P-value | OR (95%CI) | P-value | OR (95%CI) | P-value |
| Prevalence of HT | cGRS | 1.136 (1.091-1.183) | 8.2 E-10 | 1.141 (1.095-1.189) | 2.9 E-10 | 1.140 (1.094-1.189) | 8.4 E-10 |
| | wGRS | 1.149 (1.103-1.197) | 2.0 E-11 | 1.153 (1.107-1.202) | 1.9 E-11 | 1.154 (1.107-1.203) | 1.9 E-11 |
| | 1 vs. 2 quart. | 1.132 (1.008-1.272) | 0.037 | 1.121 (0.997-1.261) | 0.056 | 1.129 (1.002-1.272) | 0.047 |
| | 1 vs. 3 quart. | 1.318 (1.174-1.480) | 3.1 E-06 | 1.321 (1.175-1.485) | 3.3 E-06 | 1.295 (1.150-1.459) | 2.1 E-05 |
| | 1 vs. 4 quart. | 1.464 (1.305-1.642) | 8.2 E-11 | 1.469 (1.308-1.650) | 8.1 E-11 | 1.461 (1.298-1.645) | 3.2 E-10 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; Quart., quartiles; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HT, hypertension. Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles.

**Table S6b. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP baseline in females.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=6,167) | | Model B (n=6,103) | | Model C (n=5,500) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| SBP (+ 15 mmHg if treated) | cGRS | 1.496 (0.196) | 2.3 E-14 | 1.475 (0.195) | 5.0 E-14 | 1.231 (0.201) | 9.6 E-10 |
| | wGRS | 1.420 (0.197) | 6.1 E-13 | 1.370 (0.197) | 3.6 E-12 | 1.166 (0.202) | 7.9 E-09 |
| | 1 vs. 2 quart. | 1.586 (0.543) | 0.004 | 1.552 (0.541) | 0.004 | 1.730 (0.557) | 0.002 |
| | 1 vs. 3 quart. | 1.979 (0.538) | 2.4 E-04 | 1.928 (0.537) | 3.3 E-04 | 1.796 (0.552) | 0.001 |
| | 1 vs. 4 quart. | 3.800 (0.555) | 9.0 E-12 | 3.718 (0.556) | 2.6 E-11 | 3.393 (0.569) | 2.7 E-09 |
| DBP (+ 10 mmHg if treated) | cGRS | 0.767 (0.112) | 7.8 E-12 | 0.751 (0.112) | 2.2 E-11 | 0.595 (0.114) | 1.9 E-07 |
| | wGRS | 0.748 (0.112) | 2.5 E-11 | 0.725 (0.112) | 1.1 E-10 | 0.612 (0.114) | 8.5 E-08 |
| | 1 vs. 2 quart. | 0.810 (0.313) | 0.010 | 0.816 (0.314) | 0.009 | 0.692 (0.318) | 0.030 |
| | 1 vs. 3 quart. | 0.992 (0.310) | 0.001 | 0.967 (0.309) | 0.002 | 0.809 (0.315) | 0.010 |
| | 1 vs. 4 quart. | 1.797 (0.321) | 2.5 E-08 | 1.776 (0.322) | 3.9 E-08 | 1.490 (0.328) | 5.7 E-06 |
| | | OR (95%CI) | P-value | OR (95%CI) | P-value | OR (95%CI) | P-value |
| Prevalence of Hypertension | cGRS | 1.193 (1.126-1.265) | 2.3 E-09 | 1.198 (1.130-1.270) | 1.7 E-09 | 1.178 (1.106-1.256) | 4.3 E-07 |
| | wGRS | 1.191 (1.123-1.262) | 4.2 E-09 | 1.194 (1.126-1.267) | 3.8 E-09 | 1.177 (1.104-1.255) | 5.7 E-07 |
| | 1 vs. 2 quart. | 1.292 (1.095-1.524) | 0.002 | 1.300 (1.099-1.537) | 0.002 | 1.259 (1.050-1.510) | 0.013 |
| | 1 vs. 3 quart. | 1.313 (1.113-1.550) | 0.001 | 1.307 (1.105-1.545) | 0.002 | 1.290 (1.076-1.546) | 0.006 |
| | 1 vs. 4 quart. | 1.614 (1.370-1.901) | 1.0 E-08 | 1.643 (1.392-1.939) | 4.4 E-09 | 1.592 (1.330-1.905) | 4.0 E-07 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; Quart., quartiles; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HT, hypertension. Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles.

**Table S7a. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP reinvestigation in males.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=11,064) | | Model B (n=10,966) | | Model C (n=10,931) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| SBP (+ 15 mmHg if treated) | cGRS | 1.371 (0.200) | 7.5 E-12 | 1.403 (0.193) | 3.6 E-13 | 1.356 (0.192) | 1.9 E-12 |
| | wGRS | 1.348 (0.199) | 1.4 E-11 | 1.374 (0.192) | 9.3 E-13 | 1.332 (0.192) | 4.0 E-12 |
| | 1 vs. 2 quart. | 1.507 (0.564) | 0.008 | 1.314 (0.542) | 0.015 | 1.297 (0.541) | 0.017 |
| | 1 vs. 3 quart. | 2.761 (0.561) | 8.8 E-07 | 2.573 (0.540) | 1.9 E-06 | 2.403 (0.539) | 8.4 E-06 |
| | 1 vs. 4 quart. | 3.846 (0.566) | 1.2 E-11 | 3.730 (0.545) | 8.4 E-12 | 3.663 (0.544) | 1.8 E-11 |
| DBP (+ 10 mmHg if treated) | cGRS | 0.879 (0.109) | 1.1 E-15 | 0.845 (0.105) | 6.8 E-17 | 0.853 (0.105) | 4.0 E-16 |
| | wGRS | 0.865 (0.109) | 3.0 E-15 | 0.868(0.105) | 1.3 E-16 | 0.845 (0.105) | 7.1 E-16 |
| | 1 vs. 2 quart. | 0.846 (0.311) | 0.006 | 0.702 (0.297) | 0.018 | 0.679 (0.297) | 0.022 |
| | 1 vs. 3 quart. | 1.730 (0.307) | 1.9 E-08 | 1.569 (0.292) | 7.9 E-08 | 1.490 (0.292) | 3.4 E-07 |
| | 1 vs. 4 quart. | 2.427 (0.309) | 5.1 E-15 | 2.328 (0.296) | 4.4 E-15 | 2.269 (0.296) | 2.0 E-14 |
| | | **OR (95%CI)** | **P-value** | **OR (95%CI)** | **P-value** | **OR (95%CI)** | **P-value** |
| Prevalence of Hypertension | cGRS | 1.186 (1.134-1.239) | 5.3 E-14 | 1.190(1.137-1.245) | 6.5 E-14 | 1.184 (1.131-1.240) | 3.9 E-13 |
| | wGRS | 1.177 (1.126-1.230) | 5.7 E-13 | 1.178 (1.126-1.232) | 1.3 E-12 | 1.173 (1.121-1.228) | 5.5 E-12 |
| | 1 vs. 2 quart. | 1.158 (1.027-1.307) | 0.017 | 1.125 (0.994-1.272) | 0.062 | 1.120 (0.990-1.268) | 0.072 |
| | 1 vs. 3 quart. | 1.348 (1.191-1.524) | 2.1 E-06 | 1.336 (1.178-1.515) | 6.3 E-06 | 1.310 (1.154-1.486) | 2.9 E-05 |
| | 1 vs. 4 quart. | 1.557 (1.374-1.764) | 3.7 E-12 | 1.546 (1.361-1.756) | 2.2 E-11 | 1.532 (1.3481.742) | 7.2 E-11 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HT, hypertension. Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles.

**Table S7b. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP reinvestigation in females.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=6,416) | | Model B (n=6,340) | | Model C (n=5,444) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| SBP (+ 15 mmHg if treated) | cGRS | 1.717 (0.278) | 7,4 E-10 | 1.641 (0.271) | 1.5 E-09 | 1.335 (0.294) | 5.9 E-06 |
| | wGRS | 1.652 (0.280) | 3.9 E-09 | 1.624 (0.272) | 2.6 E-09 | 1.246 (0.295) | 2.5 E-05 |
| | 1 vs. 2 quart. | 1.821 (0.788) | 0.021 | 1.499 (0.767) | 0.051 | 0.891 (0.835) | 0.286 |
| | 1 vs. 3 quart. | 1.921 (0.767) | 0.012 | 1.604 (0.743) | 0.031 | 0.859 (0.801) | 0.284 |
| | 1 vs. 4 quart. | 4.322 (0.793) | 5.4 E-08 | 4.061 (0.772) | 1.5 E-07 | 3.337 (0.841) | 6.1 E-05 |
| DBP (+ 10 mmHg if treated) | cGRS | 0.718 (0.145) | 0.006 | 0.677 (0.139) | 1.1 E-06 | 0.492 (0.150) | 0.001 |
| | wGRS | 0.688 (0.145) | 0.005 | 0.658 (0.139) | 2.2 E-06 | 0.521 (0.149) | 5.0 E-04 |
| | 1 vs. 2 quart. | 0.904 (0.409) | 0.027 | 0.699 (0.392) | 0.074 | 0.264 (0.422) | 0.531 |
| | 1 vs. 3 quart. | 1.034 (0.405) | 0.011 | 0.943 (0.389) | 0.016 | 0.555 (0.419) | 0.185 |
| | 1 vs. 4 quart. | 1.943 (0.411) | 2.4 E-06 | 1.849 (0.395) | 2.9 E-06 | 1.374 (0.424) | 0.001 |
| | | OR (95%CI) | P-value | OR (95%CI) | P-value | OR (95%CI) | P-value |
| Prevalence of Hypertension | cGRS | 1.165 (1.103-1.231) | 4.5 E-08 | 1.171 (1.107-1.238) | 3.1 E-08 | 1.143 (1.075-1.215) | 2.1 E-05 |
| | wGRS | 1.157 (1.096-1.223) | 1.8 E-07 | 1.157 (1.094-1.223) | 3.6 E-07 | 1.128 (1.061-1.200) | 1.3 E-04 |
| | 1 vs. 2 quart. | 1.173 (1.008-1.366) | 0.039 | 1.183 (1.013-1.382) | 0.034 | 1.124 (0.947-1.334) | 0.181 |
| | 1 vs. 3 quart. | 1.223 (1.051-1.423) | 0.009 | 1.224 (1.048-1.429) | 0.011 | 1.175 (0.991-1.394) | 0.063 |
| | 1 vs. 4 quart. | 1.433 (1.228-1.671) | 4.8 E-06 | 1.438 (1.229-1.684) | 6.2 E-06 | 1.349 (1.134-1.605) | 0.001 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HT, hypertension. Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles.

**Table S8a. Association of the GRS with Delta-Systolic and Diastolic BP and Hypertension incidence between MPP baseline and reinvestigation in males.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=7,014) | | Model B (n=6,963) | | Model C (n=6,940) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| ΔSBP/year (excluding subjects with Ht | cGRS | 0.035 (0.009) | 1.0 E-04 | 0.038 (0.009) | 2.6 E-05 | 0.035 (0.009) | 8.8 E-05 |
| | wGRS | 0.032 (0.009) | 3.6 E-04 | 0.035 (0.009) | 1.1 E-04 | 0.033 (0.009) | 2.5 E-04 |
| | **1 vs. 2 quart.** | 0.034 (0.025) | 0.175 | 0.033 (0.025) | 0.183 | 0.028 (0.025) | 0.26 |
| | **1 vs. 3 quart.** | 0.085 (0.025) | 0.001 | 0.078 (0.025) | 4.8 E-04 | 0.080 (0.025) | 0.001 |
| | **1 vs. 4 quart.** | 0.088 (0.025) | 0.001 | 0.090 (0.025) | 3.9 E-04 | 0.087 (0.025) | 0.001 |
| ΔDBP/year (excluding subjects with Ht | cGRS | 0.026 (0.005) | 4.1 E-07 | 0.027 (0.005) | 2.4 E-07 | 0.025 (0.005) | 1.1 E-06 |
| | wGRS | 0.026 (0.005) | 8.2 E-07 | 0.026 (0.005) | 4.7 E-07 | 0.025 (0.005) | 1.7 E-06 |
| | **1 vs. 2 quart.** | 0.018 (0.014) | 0.202 | 0.017 (0.014) | 0.220 | 0.016 (0.014) | 0.26 |
| | **1 vs. 3 quart.** | 0.060 (0.014) | 3.2 E-05 | 0.060 (0.014) | 3.5 E-05 | 0.056 (0.014) | 1.0 E-04 |
| | **1 vs. 4 quart.** | 0.068 (0.015) | 3.5 E-06 | 0.067 (0.015) | 4.3 E-06 | 0.064 (0.014) | 9.2 E-06 |
| | | **OR (95%CI)** | **P-value** | **OR (95%CI)** | **P-value** | **OR (95%CI)** | **P-value** |
| Hypertension Incidence | cGRS | 1.140 (1.084-1.198) | 3.1 E-07 | 1.150 (1.094-1.210) | 5.9 E-08 | 1.144 (1.087-1.204) | 2.3 E-07 |
| | wGRS | 1.131 (1.076-1.189) | 1.3 E-06 | 1.140 (1.084-1.199) | 3.4 E-07 | 1.136 (1.080-1.195) | 8.8 E-07 |
| | **1 vs. 2 quart.** | 1.101 (0.961-1.261) | 0.165 | 1.108 (0.966-1.271) | 0.142 | 1.093 (0.952-1.251) | 0.209 |
| | **1 vs. 3 quart.** | 1.286 (1.119-1.479) | 4.1 E-04 | 1.294 (1.112-1.389) | 3.4 E-04 | 1.285 (1.115-1.487) | 0.001 |
| | **1 vs. 4 quart.** | 1.405 (1.219-1.619) | 2.6 E-06 | 1.418 (1.229-1.637) | 1.7 E-06 | 1.399 (1.211-1.615) | 5.0 E-06 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; ΔSBP, delta Systolic Blood Pressure; ΔDBP, delta Diastolic Blood Pressure; Estimates of SBP and DBP effects (beta and SEM) are in mmHg/year per coded allele; HT, hypertension. Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles.

**Table S8b. Association of the GRS with Delta-Systolic and Diastolic BP and Hypertension incidence between MPP baseline and reinvestigation in females.**

| BP/HT | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=4,276) | | Model B (n=4,237) | | Model C (n=3,841) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| ΔSBP/year (excluding subjects with Ht at baseline) | cGRS | 0.041 (0.015) | 0.007 | 0.043 (0.015) | 0.006 | 0.032 (0.015) | 0.040 |
| | wGRS | 0.041 (0.015) | 0.008 | 0.042 (0.016) | 0.006 | 0.031 (0.015) | 0.047 |
| | 1 vs. 2 quart. | 0.049 (0.044) | 0.261 | 0.054 (0.044) | 0.222 | 0.025 (0.043) | 0.56 |
| | 1 vs. 3 quart. | 0.065 (0.042) | 0.120 | 0.066 (0.042) | 0.116 | 0.042 (0.042) | 0.31 |
| | 1 vs. 4 quart. | 0.103 (0.043) | 0.018 | 0.104 (0.044) | 0.017 | 0.045 (0.083) | 0.083 |
| ΔDBP/year (excluding subjects with Ht at baseline) | cGRS | 0.024 (0.009) | 0.006 | 0.024 (0.009) | 0.006 | 0.019 (0.009) | 0.026 |
| | wGRS | 0.024 (0.009) | 0.005 | 0.024 (0.009) | 0.006 | 0.019 (0.009) | 0.023 |
| | 1 vs. 2 quart. | 0.037 (0.025) | 0.136 | 0.037 (0.025) | 0.138 | 0.020 (0.024) | 0.41 |
| | 1 vs. 3 quart. | 0.053 (0.024) | 0.028 | 0.051 (0.024) | 0.034 | 0.039 (0.023) | 0.092 |
| | 1 vs. 4 quart. | 0.079 (0.025) | 0.001 | 0.079 (0.025) | 0.001 | 0.063 (0.024) | 0.009 |
| | | OR (95%CI) | P-value | OR (95%CI) | P-value | OR (95%CI) | P-value |
| Hypertension Incidence | cGRS | 1.100 (1.033-1.171) | 0.003 | 1.096 (1.025-1.171) | 0.004 | 1.082 (1.011-1.157) | 0.023 |
| | wGRS | 1.096 (1.029-1.166) | 0.004 | 1.090 (1.020-1.166) | 0.011 | 1.080 (1.009-1.156) | 0.027 |
| | 1 vs. 2 quart. | 1.127 (0.948-1.340) | 0.174 | 1.108 (0.920-1.333) | 0.280 | 1.106 (0.916-1.334) | 0.295 |
| | 1 vs. 3 quart. | 1.243 (1.047-1.477) | 0.013 | 1.213 (1.010-1.457) | 0.039 | 1.209 (1.004-1.457) | 0.045 |
| | 1 vs. 4 quart. | 1.247 (1.046-1.488) | 0.014 | 1.230 (1.018-1.485) | 0.032 | 1.195 (0.987-1.447) | 0.068 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; ΔSBP, delta Systolic Blood Pressure; ΔDBP, delta Diastolic Blood Pressure; Estimates of SBP and DBP effects (beta and SEM) are in mmHg/year per coded allele; HT, hypertension. Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as comparison between quartiles.

**Table S9. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP baseline using different types of BP adjustment according to antihypertensive therapy.**

| Different BP adjustment according to antihypertensive therapy | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=17,337) | | Model B (n=17,190) | | Model C (n=16,553) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| **SBP (+10mmHg to treated Hypertensive subjects)** | cGRS | 1.050 (0.100) | 9.4 E-26 | 1.048 (0.100) | 1.1 E-25 | 0.939 (0.099) | 4.2 E-21 |
| **SBP (+15mmHg to treated Hypertensive subjects)** | cGRS | 1.090 (0.103) | 3.3 E-26 | 1.089 (0.103) | 2.8 E-26 | 0.968 (0.102) | 2.8 E-21 |
| **SBP (+20mmHg to treated Hypertensive subjects)** | cGRS | 1.134 (0.106) | 1.2 E-26 | 1.125 (0.106) | 2.5 E-26 | 0.997 (0.105) | 2.9 E-21 |
| **SBP (excluding subjects with antihypertensive treatment)** | cGRS | 0.882 (0.095) | 2.2 E-20 | 0.886 (0.095) | 1.1 E-20 | 0.829 (0.095) | 3.1 E-18 |
| **DBP (+5mmHg to treated Hypertensive subjects)** | cGRS | 0.624 (0.062) | 4.7 E-24 | 0.615 (0.062) | 2.0 E-23 | 0.556 (0.061) | 1.3 E-19 |
| **DBP (+10mmHg to treated Hypertensive subjects)** | cGRS | 0.663 (0.064) | 8.8 E-25 | 0.655 (0.064) | 2.9 E-24 | 0.585 (0.064) | 6.7 E-20 |
| **DBP (+15mmHg to treated Hypertensive subjects)** | cGRS | 0.702 (0.068) | 5.8 E-25 | 0.692 (0.068) | 2.6 E-24 | 0.615 (0.067) | 7.7 E-20 |
| **DBP (excluding subjects with antihypertensive treatment)** | cGRS | 0.543 (0.059) | 6.6 E-20 | 0.522 (0.059) | 1.0 E-18 | 0.502 (0.059) | 2.9 E-17 |

cGRS, count Genetic Risk Score; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure;
Units are the unit of phenotypic measurement, either per SD of genetic risk score.

**Table S10. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP reinvestigation using different types of BP adjustment according to antihypertensive therapy.**

| Different BP adjustment according to antihypertensive therapy | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=17,480) | | Model B ( n=17,306) | | Model C (n=16,375) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| **SBP (+10mmHg to treated Hypertensive subjects)** | cGRS | 1.386 (0.153) | 1.3 E-19 | 1.342 (0.152) | 1.0 E-18 | 1.214 (0.156) | 6.4 E-15 |
| **SBP (+15mmHg to treated Hypertensive subjects)** | cGRS | 1.494 (0.159) | 5.8 E-21 | 1.472 (0.158) | 9.9 E-21 | 1.333 (0.161) | 1.6 E-16 |
| **SBP (+20mmHg to treated Hypertensive subjects)** | cGRS | 1.603 (0.167) | 7.4 E-22 | 1.564 (0.165) | 2.6 E-21 | 1.390 (0.169) | 1.9 E-16 |
| **SBP (stepped addition)*** | cGRS | 1.473 (0.155) | 2.2 E-21 | 1.455 (0.153) | 2.8 E-21 | 1.297 (0.157) | 1.9 E-16 |
| **SBP (excluding subjects with antihypertensive treatment)** | cGRS | 1.329 (0.180) | 1.6 E-13 | 1.378 (0,180) | 2.3 E-14 | 1.289 (0.186) | 4.5 E-12 |
| **DBP (+5mmHg to treated Hypertensive subjects)** | cGRS | 0.705 (0.078) | 1.6 E-19 | 0.707 (0.078) | 1.0 E-19 | 0.650 (0.080) | 4.0 E-16 |
| **DBP (+10mmHg to treated Hypertensive subjects)** | cGRS | 0.815 (0.084) | 3.6 E-22 | 0.792 (0.084) | 3.7 E-21 | 0.724 (0.086) | 3.9 E-17 |
| **DBP (+15mmHg to treated Hypertensive subjects)** | cGRS | 0.924 (0.093) | 4.1 E-23 | 0.890 (0.092) | 7.0 E-22 | 0.807 (0.095) | 1.7 E-17 |
| **DBP (stepped addition)*** | cGRS | 0.807 (0.082) | 6.6 E-23 | 0.794 (0.081) | 2.0 E-22 | 0.736 (0.084) | 1.3 E-18 |
| **DBP (excluding subjects with antihypertensive treatment)** | cGRS | 0.695 (0,093) | 9.4 E-14 | 0.713 (0,094) | 2.9 E-14 | 0.675 (0.097) | 3.1 E-12 |

cGRS, count Genetic Risk Score; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure;
Units are the unit of phenotypic measurement per SD of genetic risk score
*To account for the number of drugs, stepped increments of 8/4, 14/10, 20/16, 26/22 mmHg were added to the measured systolic BP/diastolic BP of treated individuals taking one, two, three and four drug classes at follow-up, respectively.[5]

**Table S11. Association of the GRS with Delta-Systolic and Diastolic BP and Hypertension incidence between MPP baseline and reinvestigation using different types of BP adjustment according to antihypertensive therapy.**

| Different BP adjustment according to antihypertensive therapy | Type of GRS | Regression model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model A (n=11,290) | | Model B (n=11,200) | | Model C (n=10,781) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| **ΔSBP/year (+10 mmHg to treated Hypertensive subjects at follow-up)** | cGRS | 0.036 (0.008) | 6.0 E-06 | 0.029 (0.008) | 1.4 E-04 | 0.037 (0.007) | 6.1 E-05 |
| **ΔSBP/year (+15mmHg to treated Hypertensive subjects at follow-up)** | cGRS | 0.037 (0.008) | 3.8 E-06 | 0.031 (0.008) | 9.8 E-05 | 0.033 (0.008) | 3.7 E-05 |
| **ΔSBP/year (+20mmHg to treated Hypertensive subjects at follow-up)** | cGRS | 0.040 (0.009) | 4.1 E-06 | 0.033 (0.008) | 1.0 E-04 | 0.035 (0.009) | 3.5 E-05 |
| **ΔSBP/year (stepped addiction)*** | cGRS | 0.037 (0.008) | 4.1 E-06 | 0.031 (0.008) | 1.0 E-04 | 0.033 (0.008) | 4.3 E-05 |
| **ΔSBP/year (excluding subjects with antihypertensive treatment)** | cGRS | 0.036 (0.009) | 6.1 E-05 | 0.032 (0.009) | 3.0 E-04 | 0.027 (0.009) | 0.002 |
| **ΔDBP/year (+5mmHg to treated Hypertensive subjects at follow-up)** | cGRS | 0.024 (0.004) | 5.8 E-08 | 0.021 (0.004) | 6.3 E-07 | 0.021 (0.004) | 6.8 E-07 |
| **ΔDBP/year (+10mmHg to treated Hypertensive subjects at follow-up)** | cGRS | 0.025 (0.005) | 2.9 E-08 | 0.023 (0.005) | 3.6 E-07 | 0.023 (0.005) | 3.7 E-07 |
| **ΔDBP/year (+15mmHg to treated Hypertensive subjects at follow-up)** | cGRS | 0.027 (0.005) | 4.3 E-08 | 0.025 (0.005) | 5.0 E-07 | 0.025 (0.005) | 4.9 E-07 |
| **ΔDBP/year (stepped addiction)*** | cGRS | 0.025 (0.004) | 1.5 E-08 | 0.023 (0.004) | 1.7 E-07 | 0.023 (0.004) | 1.9 E-07 |
| **ΔSBP/year (excluding subjects with antihypertensive treatment)** | cGRS | 0.023 (0.005) | 3.0 E-06 | 0.024 (0.005) | 2.0 E-06 | 0.021 (0.005) | 2.2 E-05 |

cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; ΔSBP, delta Systolic Blood Pressure; ΔDBP, delta Diastolic Blood Pressure; estimates of SBP and DBP effects (beta and SEM) are in mmHg/year per coded allele

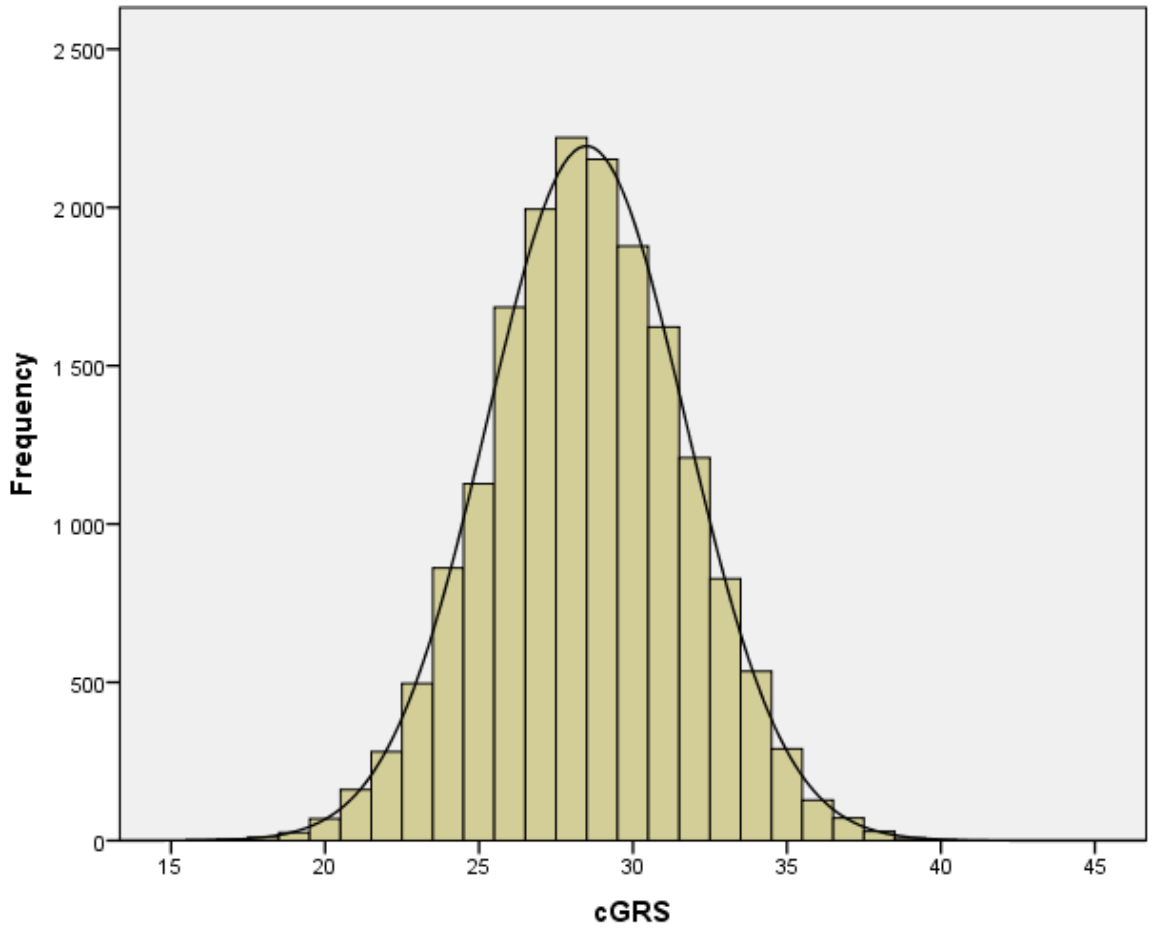
*To account for the number of drugs, stepped increments of 8/4, 14/10, 20/16, 26/22 mmHg were added to the measured systolic BP/diastolic BP of treated individuals taking one, two, three and four drug classes at follow-up, respectively.[5]

**Table S12. Association of the GRS with Systolic and Diastolic BP and Hypertension prevalence at MPP baseline according to different body positions during BP measurements.**

| BP | Type of GRS | Regression model C=all covariates | | | | | |
|---|---|---|---|---|---|---|---|
| | | only supine (n=16,553) | | only standing (n=16,553) | | altogether (n=16,553) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| **SBP (+15 mmHg if treated)** | cGRS | 0.973 (0.104) | 7.4 E-21 | 0.963 (0.107) | 2.9 E-19 | 0.968 (0.102) | 2.9 E-21 |
| **DBP (+10 mmHg if treated)** | cGRS | 0.587 (0.066) | 3.7 E-19 | 0.586 (0.067) | 2.6 E-18 | 0.585 (0.064) | 6.7 E-20 |
| | | only supine (n=10,782) | | only standing (n=10,782) | | altogether (n=10,782) | |
| | | Beta (SE) | P-value | Beta (SE) | P-value | Beta (SE) | P-value |
| **Delta-SBP** | cGRS | 0.031 (0.008) | 1.2 E-04 | 0.035 (0.008) | 1.4 E-05 | 0.033 (0.008) | 3.3 E-05 |
| **Delta-DBP** | cGRS | 0.022 (0.004) | 6.6 E-07 | 0.023 (0.005) | 4.1 E-07 | 0.023 (0.004) | 3.5 E-07 |

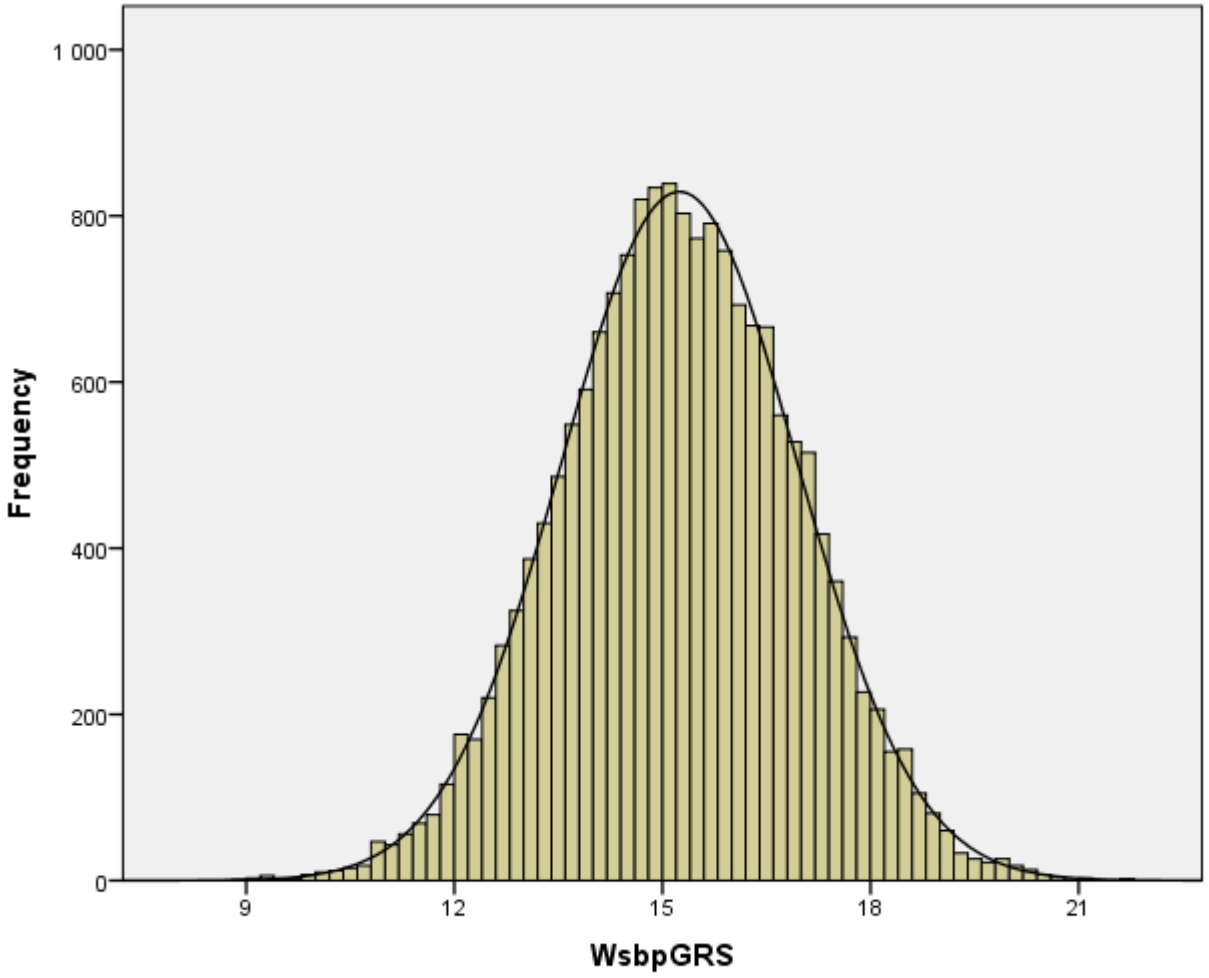
cGRS, count Genetic Risk Score; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; Units are the unit of phenotypic measurement per SD of genetic risk score

**Figure S1. Histogram showing the distribution of subjects with different cGRS before standardization.**



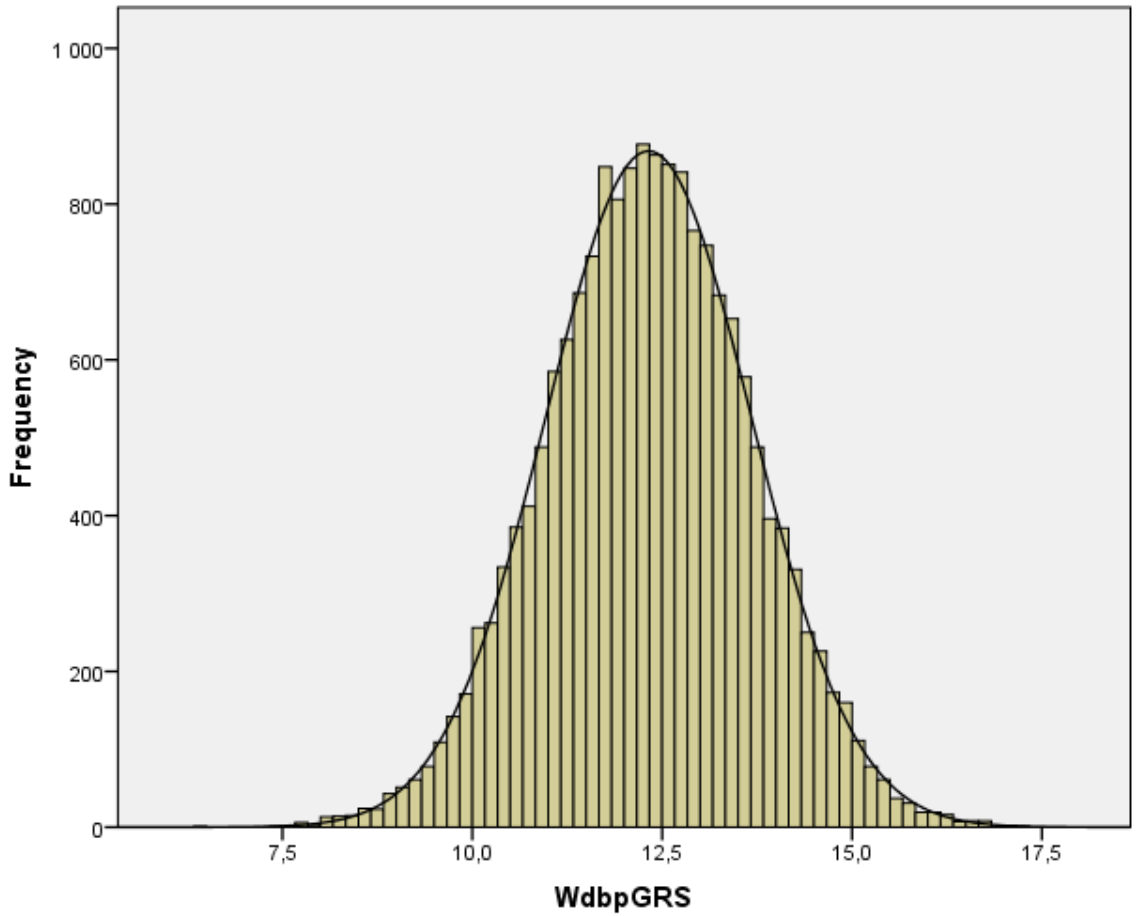

**cGRS, count Genetic Risk Score**
Average: 28.49 SD: 3.216 N=17,688

**Figure S2. Histogram showing the distribution of subjects with different WsbpGRS before standardization.**



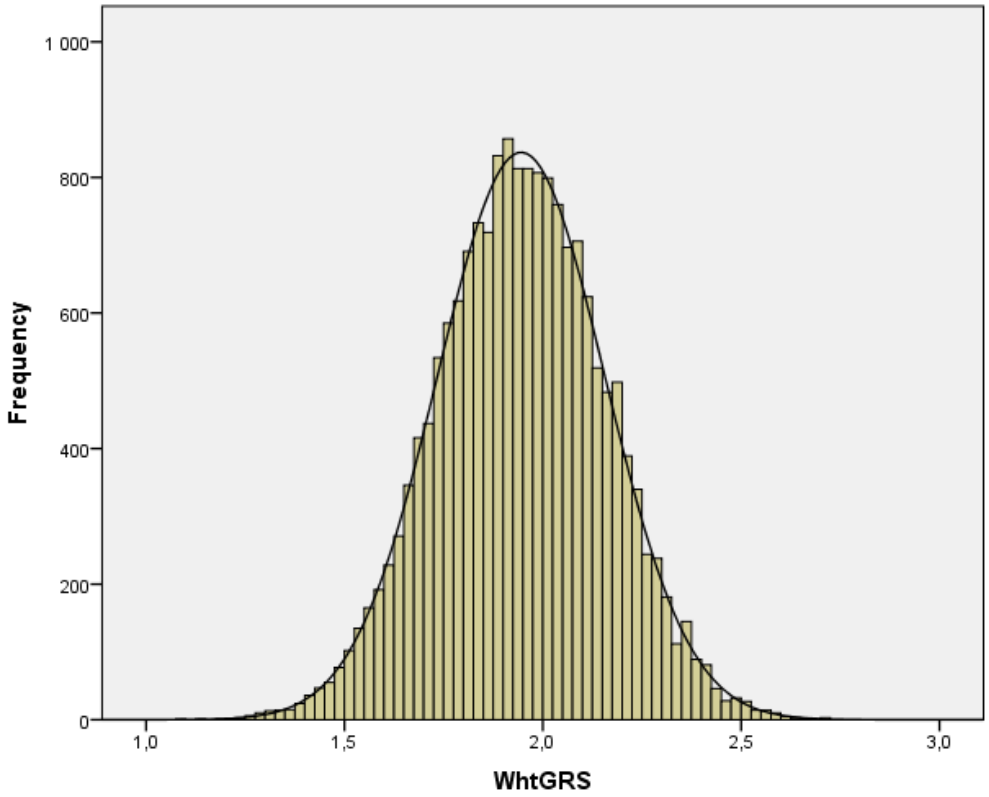

**WsbpGRS, weighted for systolic blood pressure Genetic Risk Score**
Average: 15.24 SD: 1.702 N=17,688

**Figure S3. Histogram showing the distribution of subjects with different WdbpGRS before standardization.**



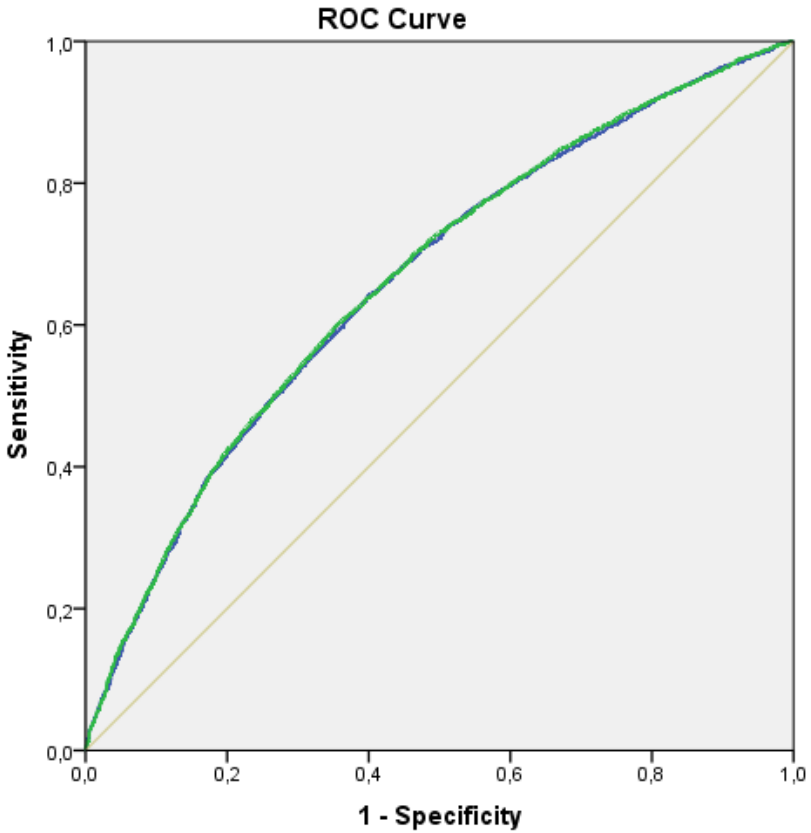

**WdbpGRS, weighted for diastolic blood pressure Genetic Risk Score**
Average: 12.32 SD: 1.354 N=17,688

**Figure 4. Histogram showing the distribution of subjects with different WhtGRS before standardization.**




**WhtRS, weighted for hypertension Genetic Risk Score**
Average: 1.95 SD: 0.211 N=17,688
The boundaries for the inclusion in different quartiles were as follows: 1st quartile: 1.08-1.8020;
2nd quartile: 1.8021-1.9450;
3rd quartile: 1.9451-2.0880;
4th quartile: 2.0881-2.71

**Figure S5. ROC curve for hypertension incidence discrimination using non genetic risk factors and non genetic risk factors plus the cGRS**




…… non genetic risk facttors
…… non genetic risk facttors+cGRS
…… reference line