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

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Abstract—Recent Genome-Wide Association Studies (GWAS) have pinpointed different single nucleotide polymorphisms consistently associated with blood pressure (BP) and hypertension prevalence. However, little data exist regarding single nucleotide polymorphisms 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 single nucleotide polymorphisms, with cross-sectional BP and hypertension prevalence and to challenge its prediction of BP change over time and hypertension incidence in >17 000 middle-aged Swedes participating in a prospective study, the Malmö Preventive Project, 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 (β±SEM, 0.968±0.102 mm Hg and 0.585±0.064 mm Hg; *P*<1E-19 for both) and at reinvestigation (β±SEM, 1.333±0.161 mm Hg and 0.724±0.086 mm Hg; *P*<1E-15 for both) and with increased hypertension prevalence (odds ratio [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 (β±SEM, 0.033±0.008 mm Hg/y and 0.023±0.004 mm Hg/y; *P*<1E-04 for both) and hypertension incidence (odds ratio [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 prehypertension, but comparable with diabetes mellitus or a positive family history of hypertension. 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. **(*Hypertension*. 2013;61:00-00.)** ● **Online Data Supplement**

Key Words: genetic risk score ■ blood pressure ■ incidence ■ variation ■ hypertension ■ genetics

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 BP (SBP) and diastolic BP (DBP).[4–6] Indeed, a genetic risk score (GRS) with aggregate genetic information from 29 single nucleotide polymorphisms (SNPs) has 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 white, Asian, and black populations have focused their attention especially on cross-sectional data (ie, 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 is yet to be proven whether the result of a genetic test could help change people's behavior.[18] The aim of the present study was to confirm that a GRS, consisting of the unweighted (count) and weighted allele sum of 29 SNPs, is associated with cross-sectional BP and hypertension prevalence and to test whether it could be useful in predicting hypertension incidence and changes in BP over time using the Malmö Preventive Project (MPP) study, including >17 000 people.

Received July 24, 2012; first decision August 17, 2012; revision accepted November 12, 2012.

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.202655/-/DC1.

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Materials and Methods

An extended version of the Methods section is reported in the Methods and Results section in the online-only Data Supplement. 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, 4931 have died and 551 were lost after follow-up for other reasons. Twenty-five thousand of the eligible individuals were invited for a rescreening visit from 2002 to 2006, including a physical examination with BP measurement (participation rate was 70.5%). DNA was obtained from 18 240 individuals participating in the rescreening.

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 versus normotension).

Details about BP measurements, BP adjustments in subjects with antihypertensive treatment, hypertension, and prehypertension definitions are presented in the Methods section in the online-only Data Supplement.

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 Methods Section in the online-only Data Supplement. The SNPs were genotyped using IPLEX on a MassARRAY platform (Sequenom, San Diego, CA) according to the manufacturer's standard protocols. Nearly 30% of the samples were run in duplicate. All genotypes were called by 2 different investigators. We prespecified a threshold call rate of 90% per individual SNP (ie, 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 Methods in the online-only Data Supplement.

Table 1. Anthropometric, Anamnestic, and Metabolic Features of the Investigated Subjects With ≥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, y	17 688	45.2±7.4	17 688	68.2±5.8
Systolic blood pressure, mm Hg	17 352	126.8±14.1	17 491	144.9±20.0
Diastolic blood pressure, mm Hg	17 352	85.3±8.7	17 491	83.6±10.6
Δ-Systolic blood pressure, mm Hg/y			11 303	1.1±0.9
Δ-Diastolic blood pressure, mm Hg/y			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 per 1.73 m^2	17 616	84.9±14.1		
Chronic kidney disease (GFR<60 mL/min per 1.73 m^2)	17 616	2.5		
Hypertension (prevalence), %	17 375	34.2	17 561	72.3
Hypertension (incidence), %			11 334	63.3
Diabetes mellitus, %	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 nonmanual 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

MPP indicates Malmö Preventive Project; GFR, glomerular filtration rate; and HDL, high-density lipoprotein.

Statistics

Continuous variables are presented as mean±SD. All data were analyzed with SPSS statistical software (version 20.0; SPSS Inc, Chicago, IL). The χ^2 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 Methods in the online-only Data Supplement), or covariates as in model A plus gluco-lipid parameters and CKD-EPI estimated-glomerular filtration rate (model B) or covariates as in model A plus B plus anamnestic, socioeconomic, and lifestyle 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 with or without the cGRS in models with all the nongenetic covariates significantly associated with the incidence of hypertension. Receiver operating characteristic curves were developed using a probability-weighted Cox model. All tests were 2-sided, and P values <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 Table S2 in the online-only Data Supplement, whereas the number of missing genotypes per subjects in Table S3. Histograms showing the distribution of subjects with different cGRS and weighted GRS before standardization are presented in Figure S1–S4. Results about the association of different SNP with BP-related traits are presented in the Results section in the online-only Data Supplement.

Cross-Sectional Analysis

In the simplest regression model (model A: adjusting for age, sex, body mass index, and heart rate), the GRS was independently and highly significantly associated with SBP and DBP and hypertension prevalence both at baseline and reinvestigation (Tables 2 and 3, see also the Figure, panels A 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 1 SD in the GRS implies an increase of nearly 1.0 or 1.3 mm Hg in the predicted SBP and 0.6 or 0.7 in the predicted DBP 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 mm Hg SBP and 1.6 or 2.0 mm Hg DBP and the odds ratio 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 the Figure, panel C). When the other covariates were added in the model (model B and C), including baseline BP, the association remained substantially unaltered. In the regression model C an increase of 1 SD of the GRS implies an increase of 0.033 mm Hg/y in predicted SBP and 0.023 mm Hg/y in DBP and an increase in the odds ratio 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 mm Hg/y for SBP and 0.063 mm Hg/y for DBP and the odds ratio for incident hypertension was 28% higher. When the GRS score was added to the regression models for Δ SBP/DBP and hypertension incidence the proportion of variance explained increased by 1.0%, 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 odds ratio was obtained for dichotomous traditional risk factors such as obesity and prehypertension status at baseline. However, the effect of the GRS (1st quartile versus 4th quartile) was independent and comparable in magnitude with that of positive family history, and diabetes mellitus.

Discrimination

The area under the curve for all the nongenetic variables as included in model C was only marginally and not significantly improved after the addition of the cGRS (Figure S5) shifting the area under the curve (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 Tables S6a and S6b, S7a and S7b, and S8a and S8b. No major differences between

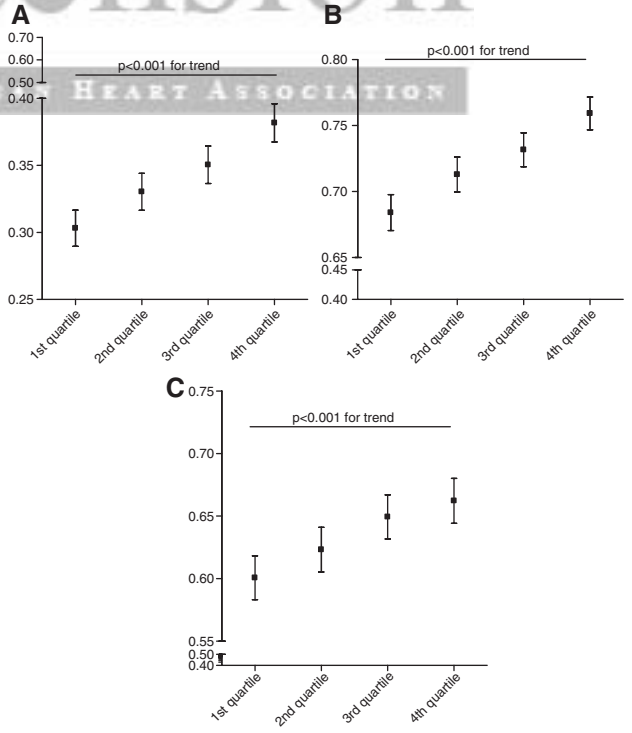

Figure. Crude associations between the weighted genetic risk score (in quartiles) and hypertension prevalence at baseline (**A**) re-examination, (**B**) and incidence, and (**C**) over 23 years of follow-up.

Table 2. Association of the GRS With Systolic and Diastolic BP and Hypertension Prevalence at MPP Baseline

		Regression Model					
		Model A (n=17 337)		Model B (n=17 190)		Model C (n=16 553)	
BP/HT	Type of GRS	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
SBP (+15 mm Hg 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 mm Hg 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 vs3 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

GRS indicates Genetic Risk Score; BP, blood pressure; MPP, Malmö Preventive Project; HT, hypertension; SBP, Systolic Blood Pressure; cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; Quart., quartiles; and 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.

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 types of BP adjustment (adding either 10 or 20 mm Hg to the treated SBP and 5 or 15 mm Hg to the treated DBP or using stepped addition; Tables S9, S10, and S11). Also using only supine or standing BP measurements at baseline did not substantially change the results (Table S12).

Discussion

The issue of to 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 International Consortium for Blood Pressure 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 nongenetic risk factors is marginal. Indeed, the magnitude of the association of the GRS with hypertension incidence is substantially lower when compared with obesity and prehypertension status, and compatible with the magnitude of either a positive family history of hypertension or the presence of diabetes mellitus. 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, was significantly associated with BP-related traits in our population. Thus, the nonsignificant 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 overfitting of the data and inflation of the *P* value. For the same reasons as above, the weighted GRS were sometimes inferior to the cGRS because the applied β-coefficients were taken from the results obtained in other populations. Our results regarding the GRS are in line with the International Consortium for Blood Pressure, where it was concluded that the GRS could explain nearly 1.6 and 1.1 mm Hg increases in cross-sectional SBP and DBP, 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

Table 3. Association of the GRS With Systolic and Diastolic BP and Hypertension Prevalence at MPP Reinvestigation

		Regression Model					
		Model A (n=17 480)		Model B (n=17 306)		Model C (n=16 375)	
BP/HT	Type of GRS	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
SBP (+15 mm Hg 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 mm Hg 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

GRS indicates Genetic Risk Score; BP, blood pressure; MPP, Malmö Preventive Project; HT, hypertension; SBP, Systolic Blood Pressure; cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; Quart., quartiles; and DBP, and 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.

genomewide association data and different *P* value thresholds, Taal et al[8] 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.

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] Fibroblast growth factor 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 nonsmokers, *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, 16 alpha-hydroxyestrone, which is related to lower BP values in postmenopausal 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 whether the different scores are needed in people with different ethnicities or whether 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

Table 4. Association of the GRS With Delta-Systolic and Diastolic BP and Hypertension Incidence Between MPP Baseline and Reinvestigation

		Regression Model					
		Model A (n=11 290)		Model B (n=11 200)		Model C (n=10 781)	
BP/HT	Type of GRS	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
ΔSBP/y (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/y (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)		OR (95% CI)		OR (95% CI)	
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

GRS indicates Genetic Risk Score; BP, blood pressure; MPP, Malmö Preventive Project; HT, hypertension; SBP, Systolic Blood Pressure; cGRS, count Genetic Risk Score; wGRS, weighted Genetic Risk Score; Quart., quartiles; and DBP, and Diastolic Blood Pressure. Estimates of SBP and DBP effects (β and SEM) are in mm Hg/y per coded allele. 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.

years of follow-up). Thus, people at greater risk for cardiovascular disease (ie, 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 include people within 5 failed genotypes, imputing the missing SNPs. We underline that a different approach, based on an averaged GRS (ie, 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 International Consortium for Blood Pressure 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 (Table S2). However, we cannot exclude that this discrepancy could be a result of some technical errors. We are aware that these could have further diluted the effect of the GRS and by excluding this SNP from 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 with other well-known predictors, along with the nonsignificant improvement in discrimination on top of nongenetic risk factors, suggests that it is not yet ready to be considered for a clinical use. On the contrary, 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.

Acknowledgments

The authors acknowledge the Knut and Alice Wallenberg Foundation for its economic support of the SWEGENE DNA extraction facility.

Sources of Funding

This study was supported by grants from the European Research Council (StG-282255) Swedish Medical Research Council, the

Table 5. Odds Ratio (95% CI) 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, y	1.122 (1.058–1.189)	1.1 E-04
Age^2, y^2	0.999 (0.998–1.000)	0.002
Sex times age, y	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
Prehypertension 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 nonmanual 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, 2nd quartile vs 1st quartile	1.092 (0.976–1.222)	0.12
GRS, 3rd quartile vs 1st quartile	1.229 (1.097–1.377)	3.6 E-04
GRS, 4th quartile vs 1st quartile	1.284 (1.143–1.441)	2.4 E-05

OR indicates odds ratio and 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

Swedish Heart and Lung Foundation, the Medical Faculty of Lund University, Malmö University Hospital, the Albert Påhlsson Research Foundation, the Crafoord Foundation, the Ernhold Lundströms Research Foundation, the Region Skane, Hulda and Conrad Mossfelt Foundation, King Gustaf V and Queen Victoria Foundation, and the Lennart Hansson Memorial Fund.

Disclosures

None.

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Novelty and Significance

What Is New?

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

What Is Relevant?

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

Summary

The relatively low effect of the genetic risk score suggests that it is not yet ready for clinical application.

Either many common single nucleotide polymorphisms related to blood pressure remain to be discovered or rarer variants with a higher effect on blood pressure have a major impact also at the population level.