Prediction of Blood Pressure and Blood Pressure Change With a Genetic Risk Score

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The authors investigated whether a genetic risk score (GRS) constructed of 32 single nucleotide polymorphisms would predict incident hypertension and blood pressure (BP) change over time in a population cohort during an 11-year follow-up (n=5402 at baseline, 3266 at follow-up). In multivariable models, GRS was associated with higher systolic/diastolic BP values at baseline (β±standard error [SE], 1.04±0.14/1.11±0.13 mm Hg; $P<.0001$ for both) and at reinvestigation (β±SE, 0.84±0.18/0.79±0.16 mm Hg; $P<.0001$ for both). Among participants who were normotensive at baseline (n=2045), GRS was not independently associated with systolic/diastolic BP change over time (β±SE, 0.16±0.18/0.20±0.18 mm Hg; $P\geq.28$ for both). In participants in the top tertile of the GRS, as compared with the bottom tertile, the predicted increase in systolic/diastolic BP was 1.18±0.78/0.70±0.49 mm Hg ($P=.046/.15$) greater and the odds ratio for incident hypertension was 33% higher ($P=.03$). These data show that GRS is strongly associated with BP but weakly associated with BP increase and incident hypertension in a late middle-aged population. *J Clin Hypertens (Greenwich).* 2016;18:181–186. © 2015 Wiley Periodicals, Inc.

High blood pressure (BP) is not only the leading risk factor for global disease burden, accounting for 7% of disability-adjusted life years, but also a classical complex genetic trait.[1] Data from family and twin studies suggest that BP is moderately heritable, with heritability estimates at 40% to 60%.[2,3] In addition to rare genes for Mendelian forms of hypertension, several recent genome-wide association studies have identified more than 40 single nucleotide polymorphisms (SNPs), which have been shown to be convincingly associated with essential hypertension.[4] In addition, genetic risk score (GRS) values of the combined effects of these variants have been shown to be even more strongly associated with BP and hypertension at baseline in multiple populations,[5–7] including in the current study.[8]

Despite a large number of studies demonstrating the applicability of hypertension-related GRSs in a cross-sectional setting, only a handful of studies have assessed their value as a prognostic marker for future cardiovascular events[8–10] and incident hypertension among children[11] and middle-aged patients.[12] Furthermore, several of these studies have provided inconclusive results, especially regarding whether a GRS provides any meaningful incremental value in risk prediction over and above models encompassing only the traditional cardiovascular risk factors.

To elucidate the association between a BP-related GRS and incident hypertension, we genotyped 32 genetic variants that have been previously reported to be associated with BP at genome-wide significance. After an 11-year follow-up, we investigated whether GRSs constructed of these variants were associated with cross-sectional BP and hypertension prevalence at baseline and at reexamination, and whether they could be useful in predicting BP changes and hypertension incidence over time.

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METHODS

Study Population

The study sample was a stratified two-stage cluster sample of 8028 patients drawn from the population register to represent the whole adult population aged 30 years and older in Finland (Health 2000 Survey). A total of 6771 patients participated in the baseline examination (attendance rate of 84%). Participants with missing information on baseline BP (n=429), body mass index (n=68), education (n=35), leisure-time exercise (n=231), or GRS genotypes (n=973) were excluded from the analyses. After excluding participants with one or more exclusion factors, 5402 individuals were included in the cross-sectional baseline analyses.

Of the individuals who participated in the baseline examination, 1226 had died or were lost to follow-up for other reasons. A total of 5545 of the eligible individuals were invited for a reexamination and 3903 participated (participation rate of 70%). Participants with missing information on follow-up BP (n=21), body mass index (n=8), leisure-time exercise (n=179), or GRS genotypes (n=469) were excluded from the analyses. After excluding participants with one or more exclusion factors, 3266 individuals were included in the cross-sectional follow-up analyses.

Of these 5402 individuals who were included in the baseline analyses, those with hypertension at baseline

(n=2447) or missing information on follow-up BP (n=910) were excluded and 2045 participants were included in the longitudinal analyses.

The details of the stratification and sampling procedures have been previously reported.[13]

Baseline and Reexamination

The Health 2000 Survey cohort was examined with mostly identical methods in the years 2000–2001 and 2011–2012. Information on background, sociodemographics, lifestyles, health and illnesses, and use of medication was gathered by centrally trained interviewers at the participant's home in 2000–2001 and at the study site in 2011–2012. A physical examination was performed on each participant 1 to 6 weeks later at a local health center by centrally trained doctors and nurses. Each participant's height and weight were measured, and fasting blood samples for serum lipids and glucose were taken from the participants. BP was measured by a nurse with a conventional calibrated mercury sphygmomanometer on the right arm with the patient in a seated position after a 10-minute rest. The mean of two measurements performed at 2-minute intervals were used to determine BP. Similar to recent genome-wide association studies (GWAS), based on the known average treatment effects, fixed increments of 15 mm Hg systolic BP and 10 mm Hg diastolic BP were added to the BPs of treated patients.[14] Details of the methodology of the Health 2000 Survey examinations have been published elsewhere.[13]

SNP Selection, Genotyping, and GRSs

We selected 32 SNPs that have been associated with systolic or diastolic BP in GWAS[5,6,15–17] and previously described in detail.[8] For the most part, the samples were genotyped with the Sequenom platform (iPlex MassARRAY, San Diego, CA). In addition to Sequenom genotyping, we extracted the SNPs from a subset of 2123 Health 2000 participants, which was genotyped with Illumina HumanHap 610k array and imputed with IMPUTE software using 1000 Genomes interim phase 1 (June 2011) release data as the reference panel.[18,19] We calculated the GRSs using the reported effect sizes from the reference studies as weights per copy of the coded allele for each individual SNP. Different SNPs thus contribute different weights, as opposed to an alternate approach in which no weighting of effects is used, and each SNP allele counts equally in the score. The coded allele is the allele coded 0, 1, or 2 according to the number of copies of the allele. A single unit increase in the GRS corresponds to a 1-mm Hg increase in the predicted systolic or diastolic BP, as a result of the aggregated predicted effects of all 32 SNPs. In addition, the analyses were also performed using the unweighted GRSs. Missing genotype data for each SNP were imputed using the average coded allele frequency. However, if >60% of the SNP genotypes were missing for a given individual, the GRS was set as missing for that individual. Two GRSs were calculated, one for systolic BP and one for diastolic BP. Details of the genotyping have been previously published.[8]

Statistical Analysis

Continuous variables are presented as mean±standard deviation. Multiple linear and logistic regression analyses were used in the models with BP and hypertension status as the dependent variables. The independent variables in the three models were: model 1: GRS; model 2: model 1 + age + sex; and model 3: model 2 + smoking (daily use of tobacco products), diabetes (fasting serum glucose ≥7.0 mmol/L or use of antidiabetic medication), education (primary, secondary, tertiary), hypercholesterolemia (fasting serum cholesterol ≥7.0 mmol/L or use of lipid-lowering medication), leisure-time exercise (scale from 1 to 4 with the highest two grades combined[20]), and body mass index. The covariates were selected based on previous literature on factors associated with incident and prevalent hypertension. In the longitudinal analyses, patients already diagnosed as hypertensive at baseline (BP ≥140/90 mm Hg and/or antihypertensive medication) were not included, and mean arterial pressure at baseline was included as a covariate in model 3. Systolic GRS was used for the analyses involving systolic BP and diastolic GRS for analyses involving diastolic BP. Systolic GRS was the independent variable when hypertension status was used as the dependent variable. The incremental value of adding GRS to predict prevalent and incident hypertension was estimated with C statistics by calculation of the area under the receiver operating characteristic curve, the net reclassification improvement, and the integrated discrimination index.[21] Participants were assigned to one of four categories (<5%, 5%–10%, 10%–20%, and >20%) according to their risk for prevalent or incident hypertension as estimated by the various prediction models. Model calibration was tested by the Hosmer-Lemeshow χ^2 test. All tests were two-tailed, and P values <.05 were considered statistically significant. All data were analyzed with SAS version 13.0 (SAS Institute, Cary, NC).

RESULTS

The characteristics of the study population at baseline and at follow-up are reported in Table I.

Cross-Sectional Analyses

In the crude model without other covariates (model 1), the GRS was strongly associated with systolic and diastolic BP and hypertension prevalence both at baseline and at reexamination (P<.0001 for all, Tables II and III). The association between GRS and BP at baseline and at reexamination remained strongly significant after adjusting for age and sex (model 2) and in the fully adjusted model 3 (P<.0001 for all, Tables II and III). Compared with participants in the lowest tertile of GRS, participants in the highest tertile had a 4.8±0.6/2.9±0.4 mm Hg and 3.9±0.8/2.2±0.5 mm Hg higher systolic/diastolic BP at baseline and at re-investigation,

TABLE I. Characteristics of the Study Population at Baseline and at Reinvestigation for Patients With GRS Available

Characteristic	Ye ar 2000	Year 2011
Participants, No.	5402	3266
Male sex, %	45.5	45.4
Age, y	52.7±14.8 (51 [30–98])	60.0±11.8 (59 [41–97])
Systolic BP, mm Hg[a]	137.5±23.5 (134 [89–255])	138.3±20.8 (136 [80–240])
Change 2001–2011	NA	5.0±18.9 (6 [−101 to 80])[b]
Diastolic BP, mm Hg[a]	83.6±12.4 (83 [35–136])	83.0±11.5 (83 [41–123])
Change 2001–2011	NA	−0.1±12.2 (1 [−66 to 43])[b]
Systolic GRS	0.0±1.8 (0.0 [−5.8 to 7.0])	0.0±1.8 (0.1 [−5.8 to 7.0])
Diastolic GRS	0.0±1.2 (0.0 [−3.9 to 4.2])	0.0±1.2 (0.0 [−3.9 to 4.2])
AH treatment,%	18.2	26.9
BMI, kg/m^2	26.9±4.6 (26.3 [12.3–53.7])	27.4±4.9 (26.7 [17.0–60.9])
Current smokers, %	26.7	17.7
Diabetes, %	6.5	10.2
Education, %		
Primary	38.8	30.6
Secondary	32.3	30.7
Tertiary	28.8	38.7
Hypercholesterolemia, %	22.7	24.7
Leisure-time exercise, %		
Low	27.4	29.2
Moderate	55.2	53.2
High	17.4	17.6

Abbreviations: AH, antihypertensive; BMI, body mass index; BP, blood pressure; NA, not available; GRS, genetic risk score. Continuous variables are reported as mean±standard deviation (median [minimum−maximum]). [a]+15/10 mm Hg if treated. [b]Data available for 3239 participants.

respectively ($P<.0001$ for all, model 3 in Tables II and III). In addition, the highest tertile of GRS had 67% and 83% greater odds of having hypertension than the lowest tertile at baseline and at reexamination, respectively ($P\leq.0001$ for both, model 3 in Tables II and III, Figure). When the cross-sectional analyses at baseline and at follow-up were performed using the unadjusted GRS instead of the adjusted GRS, all analyses were significant ($P\leq.02$ for all analyses, Tables S1 and S2).

Longitudinal Analyses

The systolic and diastolic GRSs, as continuous or categorical variables, were not associated with BP change from baseline to reexamination in any of the fully adjusted regression models ($P\geq.23$ for all, Table IV). However, participants in the highest tertile of GRS had 33% greater odds for developing hypertension during follow-up than the lowest tertile ($P=.03$, model 3 in Table IV, Figure). When the longitudinal analyses were performed using the unadjusted GRS instead of the adjusted GRS, the borderline significant associations became nonsignificant as a result of the reduction in precision of the GRS (Table S3).

Discrimination

When we added GRS as a covariate to a model that predicted prevalent hypertension and already included all the other covariates in model 3 of Table I, the C-index was increased from 0.800 to 0.803 ($P=.002$), yielding a net reclassification improvement of 3.3% ($P<.001$) and an integrated discrimination index of 0.6% ($P<.001$).

The addition of GRS to a model that already included all the other covariates in model 3 of Table IV for the incidence of hypertension did not result in a significant increase in the C-index (0.731–0.733, $P=.22$). Furthermore, the resulting net reclassification improvement (0.5%, $P=.46$) and integrated discrimination index of 0.08% ($P=.17$) were nonsignificant.

DISCUSSION

Our study confirms the highly significant association of a GRS constructed of common genetic variants with BP and hypertension prevalence. However, only a nonexisting to weak association was observed between our GRS and BP change over time in the more aged general adult population.

Numerous studies have demonstrated the significant association between GRS and BP in a cross-sectional setting.[5–7] However, in aggregate, the proportion of BP variation explained by these GRSs is only 1% to 1.5% after accounting for the other major nongenetic determinants of BP. The findings of our study are in line with these results. Although our GRS was strongly associated with systolic and diastolic BP, the 32 variants tested explained only approximately 1% of the variance in systolic and diastolic BP (data not shown). Considering the heritability estimates of 40% to 60% found in twin studies,[2,3] this highlights the need for new experiments to capture additional trait variability with more refined

TABLE II. Association of the GRS With BP and Hypertension Prevalence at Baseline (n=5402)

		Regression Model					
		Model 1		Model 2		Model 3	
BP Variable	GRS Variable	β±SE	*P* Value	β±SE	*P* Value	β±SE	*P* Value
Systolic BP (+15 mm Hg if treated)	GRS	1.03±0.17	<.0001	1.07±0.15	<.0001	1.04±0.14	<.0001
	Tertile 1 vs 2	2.24±0.78	.004	2.56±0.66	<.0001	2.55±0.64	<.0001
	Tertile 1 vs 3	4.49±0.78	<.0001	4.92±0.66	<.0001	4.83±0.63	<.0001
Diastolic BP (+10 mm Hg if treated)	GRS	1.11±0.14	<.0001	1.13±0.14	<.0001	1.11±0.13	<.0001
	Tertile 1 vs 2	1.78±0.41	<.0001	1.74±0.40	<.0001	1.71±0.37	<.0001
	Tertile 1 vs 3	2.78±0.41	<.0001	2.90±0.40	<.0001	2.86±0.37	<.0001
	GRS Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Prevalence of Hypertension	GRS	1.09 (1.06–1.12)	<.0001	1.12 (1.08–1.16)	<.0001	1.12 (1.08–1.16)	<.0001
	Tertile 1 vs 2	1.20 (1.05–1.37)	.02	1.29 (1.11–1.50)	.001	1.31 (1.12–1.53)	.001
	Tertile 1 vs 3	1.44 (1.26–1.64)	<.0001	1.63 (1.41–1.89)	<.0001	1.67 (1.43–1.95)	<.0001

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error. Values are reported per 1-unit increase in genetic risk score (GRS), or as comparison between tertiles. Model 1 is the crude model with only GRS as the covariate; model 2 is model 1 + age + sex; model 3 is model 2 + smoking, diabetes, education, hypercholesterolemia, exercise, and body mass index. Systolic GRS was used for the analyses involving systolic blood pressure (BP) and diastolic GRS for analyses involving diastolic BP. Systolic GRS was the independent variable when hypertension status was used as the dependent variable. Systolic GRS tertile cutoffs: <−0.78, −0.78 to 0.83, and >0.83. Diastolic GRS tertile cutoffs: <−0.48, −0.48 to 0.51, and >0.51.

TABLE III. Association of the GRS With BP and Hypertension Prevalence at Reinvestigation (n=3266)

		Regression Model					
		Model 1		Model 2		Model 3	
BP Variable	GRS Variable	β±SE	*P* Value	β±SE	*P* Value	β±SE	*P* Value
Systolic BP (+15 mm Hg if treated)	GRS	0.87±0.20	<.0001	0.88±0.19	<.0001	0.84±0.18	<.0001
	Tertile 2 vs 1	1.31±0.87	.14	1.66±0.85	.05	1.75±0.82	.03
	Tertile 3 vs 1	3.80±0.87	<.0001	3.91±0.82	<.0001	3.90±0.81	<.0001
Diastolic BP (+10 mm Hg if treated)	GRS	0.83±0.17	<.0001	0.83±0.17	<.0001	0.79±0.16	<.0001
	Tertile 2 vs 1	1.49±0.49	.003	1.36±0.48	.005	1.37±0.47	.003
	Tertile 3 vs 1	2.20±0.49	<.0001	2.21±0.48	<.0001	2.20±0.46	<.0001
	GRS Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Prevalence of hypertension	GRS	1.12 (1.07–1.16)	<.0001	1.13 (1.08–1.17)	<.0001	1.13 (1.09–1.18)	<.0001
	Tertile 2 vs 1	1.24 (1.05–1.47)	.01	1.29 (1.09–1.54)	.004	1.34 (1.11–1.61)	.002
	Tertile 3 vs 1	1.67 (1.41–1.98)	<.0001	1.75 (1.47–2.08)	<.0001	1.83 (1.53–2.20)	.0001

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error. Values are reported per 1-unit increase in genetic risk score (GRS) or as comparison between tertiles. Model 1 is the crude model with only GRS as the covariate; model 2 is model 1 + age + sex; and model 3 is model 2 + smoking, diabetes, education, hypercholesterolemia, exercise, and body mass index. Systolic GRS was used for the analyses involving systolic blood pressure (BP) and diastolic GRS for analyses involving diastolic BP. Systolic GRS was the independent variable when hypertension status was used as the dependent variable. Systolic GRS tertile cutoffs: <−0.78, −0.78 to 0.84, and >0.84. Diastolic GRS tertile cutoffs: <−0.48, −0.48 to 0.53, and >0.53.

BP phenotyping and next-generation sequencing, such as whole exome and genome sequencing.

We found only two previous studies that have examined the association between a GRS and incident hypertension in a longitudinal setting. In a study from Malmö, Sweden, of more than 10,000 individuals with a mean age of 45 years at baseline, the GRS was positively associated with the change in BP independent of traditional risk factors.[12] In this study, the predictive power of the GRS was lower in magnitude than that of obesity or prehypertension but comparable with diabetes or a positive family history of hypertension. The Young Finns Study, which included 2625 individuals aged 3 to 18 years at baseline and a 21- to 27-year follow-up, found a high GRS to be an independent risk factor for adult hypertension.[11] However, the GRS did not provide incremental predictive value as compared with parental hypertension history. In both studies, the GRS did not show any significant improvement in the prediction of incident hypertension. In our study, the

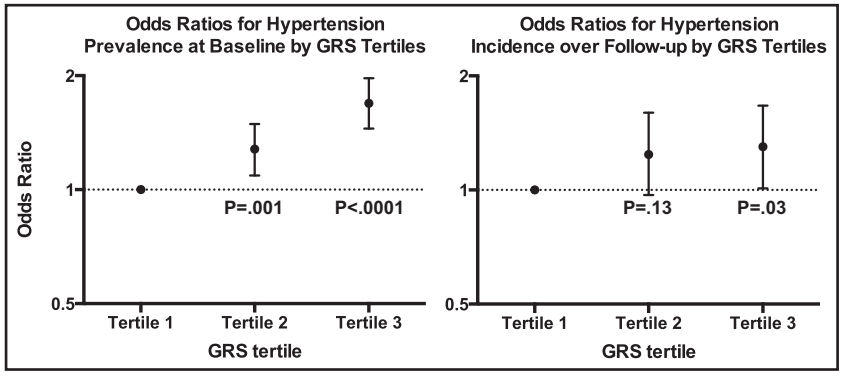

FIGURE. Adjusted odds ratios for prevalent and incident hypertension by tertiles of genetic risk score (GRS).

TABLE IV. Association of the GRS With BP Change and Hypertension Incidence Between Baseline and Reinvestigation (n=2045)

		Regression Model					
		Model 1		Model 2		Model 3	
BP Variable	GRS Variable	β±SE	*P* Value	β±SE	*P* Value	β±SE	*P* Value
ΔSystolic BP (+15 mm Hg if treated)	GRS	0.03±0.18	.85	0.05±0.18	.79	0.16±0.18	.36
	Tertile 2 vs 1	1.06±0.78	.17	1.14±0.77	.14	1.33±0.77	.08
	Tertile 3 vs 1	0.95±0.79	.23	1.06±0.79	.18	1.18±0.78	.046
ΔDiastolic BP (+10 mm Hg if treated)	GRS	0.08±0.20	.66	−0.04±0.19	.83	0.20±0.18	.28
	Tertile 2 vs 1	0.59±0.54	.36	0.35±0.51	.50	0.67±0.48	.17
	Tertile 3 vs 1	0.42±0.54	.44	0.02±0.52	.97	0.70±0.49	.15
	GRS Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Incidence of hypertension	GRS	1.05 (1.00–1.10)	.08	1.06 (1.01–1.12)	.03	1.04 (0.98–1.10)	.23
	Tertile 2 vs 1	1.22 (0.97–1.53)	.09	1.25 (0.99–1.58)	.06	1.21 (0.95–1.55)	.13
	Tertile 3 vs 1	1.33 (1.06–1.67)	.02	1.41 (1.12–1.78)	.004	1.33 (1.03–1.70)	.03

Abbreviations: Δ, change; CI, confidence interval; OR, odds ratio; SE, standard error. Values are reported per 1-unit increase in genetic risk score (GRS), or as comparison between tertiles. Model 1 is the crude model with only GRS as the covariate; model 2 is model 1 + age + sex; and model 3 is model 2 + smoking, diabetes, education, hypercholesterolemia, exercise, body mass index, and mean arterial pressure at baseline. Systolic GRS was used for the analyses involving systolic blood pressure (BP) and diastolic GRS for analyses involving diastolic BP. Systolic GRS was the independent variable when hypertension status was used as the dependent variable. Systolic GRS tertile cutoffs: <−0.93, −0.93 to 0.72, and >0.72. Diastolic GRS tertile cutoffs: <−0.55, −0.55 to 0.44, and >0.44.

association between GRS and incident hypertension was weak and detectable only in the highest tertile of GRS. In addition, the GRS did not improve discrimination. Based on the findings of this study, the Malmö Preventive Project and the Young Finns Study, genetic factors would seem to play a more important role in BP trajectories among the children and the young than in the late middle-aged or older population. This notion is supported by the findings of earlier studies that have demonstrated that the BP of children of hypertensive parents rises more rapidly than that of normotensive children.[22,23]

In addition to incidence of hypertension, GRSs have been shown to predict future cardiovascular events in some, but not all, studies. In a case-cohort study of 2272 patients of European ancestry (1025 cases and 1247 controls) and 39 SNPs, no single SNP was associated with intracerebral hemorrhage although a GRS constructed of these variants was associated with risk of intracerebral hemorrhage.[10] Two follow-up studies from Finland and Sweden, with approximately 30,000 participants each, concluded that the polygenetic component of BP influences risk of cardiovascular morbidity and mortality.[8,9] However, in both studies, the GRSs did not improve cardiovascular risk discrimination above the standard Framingham Risk Score.

STUDY LIMITATIONS

Despite the strengths of our study, such as an unselected nationwide cohort that was examined with identical methods at baseline and reexamination, the results of our analyses must be interpreted within the context of their potential limitations. First, of the 5402 participants examined at baseline and included in the most complex model, only 2045 (38%) were normotensive at baseline and also had follow-up data available, which

reduces the generalizability of the results. However, if the statistically weak associations found in the longitudinal setting of our study had been found to be more robust with an even larger study population, this would not have increased the clinical relevance of the finding. Second, our GRS was based on 32 known SNPs, although recent studies have identified up to 43 SNPs that have been associated with systolic or diastolic BP.[4] Third, our study population consisted of mainly late middle-aged persons from Northern Europe; therefore, our results cannot be generalized to other age groups or to non-Europeans. Fourth, the use of out-of-office measurements could have enabled more accurate BP phenotyping, but home measurements were available for only approximately one third of the population.

CONCLUSIONS

These data show that a GRS based on common SNPs is strongly associated with BP and prevalent hypertension but only a nonexistent to weak association with BP increase and incident hypertension in a late middle-aged adult population. Considering the high heritability of hypertension, our results highlight the need for new research to capture additional trait variability with refined phenotyping and genotyping.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Association of the unweighted genetic risk score with blood pressure and hypertension prevalence at baseline (n=5402).

Table S2. Association of the unweighted genetic risk score with blood pressure and hypertension prevalence at reinvestigation (n=3266).

Table S3. Association of the unweighted genetic risk score with blood pressure change and hypertension incidence between baseline and reinvestigation (n=2045).