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A blood pressure genetic risk score is a significant predictor of incident cardiovascular events in 32,669 individuals

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Abstract

Recent genome-wide association studies (GWASs) have identified genetic variants associated with blood pressure (BP). We investigated whether genetic risk scores (GRSs) constructed of these variants would predict incident cardiovascular disease (CVD) events. We genotyped 32 common single nucleotide polymorphisms (SNPs) in several Finnish cohorts, with up to 32,669 individuals after exclusion of prevalent CVD cases. The median follow-up was 9.8 years, during which 2,295 incident CVD events occurred. We created GRSs separately for systolic (SBP) and diastolic BP (DBP) by multiplying the risk allele count of each SNP by the effect size estimated in published GWASs. We performed Cox regression analyses with and without adjustment for clinical factors including BP at baseline in each cohort. The results were combined by inverse variance-weighted fixed-effects meta-analysis. The GRSs were strongly associated with SBP and DBP and baseline hypertension (all $p<10^{-62}$). Hazard ratios comparing the highest quintiles of SBP and DBP genetic risk scores with the lowest quintiles after adjustment for age, age squared and sex, were 1.25 (1.07–1.46, p = 0.006) and 1.23 (1.05–1.43, p = 0.01), respectively, for incident coronary heart disease; 1.24 (1.01–1.53, p = 0.04) and 1.35 (1.09–1.66, p = 0.005) for incident stroke; and 1.23 (1.08–1.40, $p = 2\times10^{-6}$) and 1.26 (1.11–1.44, $p = 5\times10^{-4}$) for composite CVD. In

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conclusion, BP findings from GWASs are strongly replicated. GRSs comprised of bona fide BP SNPs predicted cardiovascular disease risk, consistent with a life-long effect on BP of these variants collectively.

Keywords

Hypertension; blood pressure; genetics; cardiovascular disease; prospective cohort study; genetic risk score

Introduction

Elevated blood pressure (BP) is a strong, independent and modifiable risk factor for stroke and heart disease.[1,2]BP is a heritable trait with estimated heritability of 0.4-0.5,[3] and recent well-powered genome-wide association studies (GWAS) have identified several genetic loci which are associated with systolic (SBP), diastolic blood pressure (DBP) or commonly both.[4-8] While the variants have modest effects on BP, their presence may act over the entire life course and therefore lead to substantial increases in risk of cardiovascular and cerebrovascular disease. For example, it was recently found that common genetic variants are associated with preclinical blood pressure traits even in childhood.[9]The intra-individual and measurement variability of BP is high[10] and therefore several measurements are optimally needed over time to reliably determine a person's BP level. In principle, genetic background is stable and could, in borderline cases, help clinicians decide whether BP treatment is needed or alter the intensity of BP treatment.

We genotyped 32 genetic variants which have been previously reported to be associated with BP at genome-wide significance and investigated whether genetic risk scores (GRSs) constructed of these variants would be significant predictors of incident cardiovascular (CVD) events in prospective, population-based cohorts from Finland.

Methods

An expanded description of the Methods section is available in the online-only Data Supplement.

Study Populations

FINRISK surveys are cross-sectional, population-based studies conducted every 5 years since 1972 to monitor the risk of chronic diseases. For each survey, a representative random sample was selected from 25–74 year old inhabitants of different regions in Finland. The survey included a questionnaire and a clinical examination, at which a blood sample was drawn, with linkage to national registers of cardiovascular and other health outcomes. The study protocol has been described elsewhere.[11] Study participants were followed up through 31 December 2010. The current study included eligible individuals from FINRISK surveys conducted in 1992, 1997, 2002, and 2007 (total n=27,838).

Health 2000 was based on a stratified two-stage cluster sampling from the National Population Register to represent the total Finnish population aged 30 years and over. The Mini-Finland Health Survey was originally conducted between 1978 and 1980 in similar manner to the Health 2000 Study. Of the Mini-Finland participants, 985 living in seven large cities participated in a follow-up study in 2001 at which DNA was collected. Health 2000 and Mini-Finland cohorts were analyzed pooled, adjusting for study cohort. The survey included an interview about medical history, health-related lifestyle habits, and a clinical examination at which a blood sample was drawn. A detailed description of the study

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protocol is available at: http://www.terveys2000.fi/doc/methodologyrep.pdf. Study participants were followed up through 31 December 2010.After restricting the study to participants aged ≤80 years at baseline, there were 6,731 individuals eligible for the current study.

The Helsinki Birth Cohort Study (HBCS) is composed of 8,760 individuals born between the years 1934-44 in one of the two main maternity hospitals in Helsinki, Finland. Between 2001 and 2004, a randomly selected sample of 928 males and 1,075 females participated in a clinical follow-up study with a focus on cardiovascular, metabolic and reproductive health, cognitive function and depressive symptoms. The participants were followed up through 31 December 2010, and 1,676 participants were eligible for the present study.[12]

The Oulu Project Elucidating Risk of Atherosclerosis (OPERA) is a population-based, epidemiological study examining risk factors and disease end points of atherosclerotic cardiovascular diseases. The hypertensive cohort (cases) consisted of 600 subjects (300 men and 300 women, aged 40 to 59 years at the time of selection) from the town of Oulu randomly selected from the national register of medication reimbursements for moderate or severe hypertension. For each year of birth (1931 to 1950), 15 hypertensive men and 15 hypertensive women were selected. For each hypertensive subject, an age- and sex-matched control was randomly selected from all inhabitants of Oulu excluding subjects with reimbursement for hypertension medication.[13] Study participants were followed up through 31 December 2009. For the present study, 1,000 participants were eligible.

Blood pressure measurement methods for each of the cohorts are described in the online-only Data Supplement.

Follow-up

During follow-up, hospitalization and mortality data were obtained from the Finnish National Hospital Discharge Register and the National Causes-of-Death Register. These registers cover all cardiovascular events that have led either to hospitalization or death in Finland. The cardiovascular diagnoses in these registers have been validated.[14,15]Coronary heart disease (CHD) was defined as non-fatal myocardial infarction, unstable angina pectoris, coronary revascularization (coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty), or death due to CHD. Cardiovascular disease (CVD) included CHD and ischemic stroke events. The clinical outcomes were linked to study subjects using their unique national social security ID, which is assigned to every permanent resident of Finland. Events prior to baseline were traced back to 1970 when computerized records first became available in Finland. In the OPERA study, however, register data was available only from the baseline onwards, and events prior to baseline were determined by a detailed interview of a physician. All study subjects provided written informed consent. The local institutional ethical review boards approved each study.

SNP Selection, Genotyping and Genetic Risk Scores

We selected 32 single nucleotide polymorphisms (SNP; Table S1) which have been associated with SBP or DBP in GWAS.[4-8] Details of the genotyping are provided in the online-only Data Supplement. We calculated the GRS 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 one unit increase in the GRS corresponds to a 1 mm Hg increase in the predicted SBP or DBP as a result of the aggregated predicted effects of all 32 SNPs. Missing genotype data

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for each SNP was imputed using the average coded allele frequency within each study cohort. However, if more than 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 SBP and one for DBP.

Statistical Analyses

Associations of the GRSs and, as a secondary analysis, individual SNPs with SBP or DBP with imputation for use of antihypertensive therapy (+15mmHg for SBP; +10mmHg for DBP as an estimate of the expected BP off antihypertensive therapy)[16] was performed using linear regression, adjusting for baseline age and its square, sex, and geographic region (eastern vs western Finland).The analysis was repeated with further adjustment for BMI, alcohol consumption (grams/week), and leisure time physical activity (moderate to high vs low). Association of the GRSs and individual SNPs with baseline hypertension (HTN, defined as SBP ≥140 mmHg or DBP ≥ 90 mmHg or use of antihypertensive therapy) was analyzed using logistic regression adjusted for the same covariates as above.

Associations of the GRSs and secondarily individual SNPs with incident CVD outcomes were analyzed using Cox proportional hazards regression with age as the time scale. All models were stratified by sex and adjusted for geographic region. As a secondary analysis we included also prevalent CVD cases, i.e., using the first event since birth. In these analyses we used time from birth as the time scale except in HBCS, which used elapsed time from the first date of eligibility, 1 January 1970. Power analysis for detecting a single SNP effect in the Cox regression for incident CVD is provided in Figure S1.

The incident outcome associations were then analyzed using two further adjustments. First, we adjusted for the following Framingham Risk Score risk factors: total cholesterol, high-density lipoprotein cholesterol, current smoking and baseline diabetes, plus lipid-lowering treatment. The last covariate is not part of the Framingham Score, but it was significant in most models, improving model fit and validity of the proportional hazards assumption. Second, we adjusted additionally for SBP or DBP (in the case of the DBP GRS) and for antihypertensive treatment. In addition to the analyses of the primary CVD endpoint, we performed secondary Cox regression analyses using ischemic stroke and CHD events as the outcomes with the same covariate adjustments as in the primary analyses.

In order to examine the possibility that the GRS derived for SBP or DBP would not be the optimal GRS for predicting incident cardiovascular events we derived another GRS specifically for CVD, using the Cox regression results of the individual SNPs with incident CVD in the present studies. This CVD GRS used betas or hazard ratios from the meta-analyses (Table S3) as weights for the risk allele counts.

We confirmed that Cox proportional hazards assumptions were met using scaled Schoenfeld residuals (R function cox.zph). The results from individual studies were combined using inverse variance-weighted fixed effect meta-analysis, checking for heterogeneity using the I^2 measure; $I^2 > 0.5$ is considered evidence for significant heterogeneity.[17] This limit was not exceeded in any of the analyses, beyond chance expectation.

Using the Health 2000 and FINRISK 92 and 97 cohorts which have 10 year follow-up, we further assessed the utility of the GRS for 10-year CVD risk prediction by estimating the net reclassification improvement (NRI), clinical NRI for prospective data,[18]integrated discrimination improvement (IDI)[19],and explained relative risk for the GRS. The statistical significance of AUC change between models with and without GRS was tested with the correlated C-index approach.[200] Model calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test.[21]All statistical analyses were performed using R version

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2.15.[22]In general, we considered two-sided p<0.05 statistically significant. For the association tests of individual SNPs with BP/HTN and cardiovascular events, we used Bonferroni correction to account for 32 independent tests.

Results

The baseline characteristics of the study cohorts are given in Table 1. Individually, 23 of the 32 SNPs were associated with SBP or DBP in the same direction as previously reported, after accounting for multiple testing (P<0.0016 = P<0.05/32, Table S1). Directions of effect were consistent for all SNPs but two. Effects on SBP or DBP were highly correlated in the Finnish studies with the original estimated effects reported in the literature (SBP r=0.75, DBP r=0.71). GRSs were strong predictors for SBP, DBP and HTN (Table 2, all $p<10^{-62}$). The average proportion of variance in SBP or DBP explained by each respective score was generally greater than that estimated previously[8]: 1.20% in SBP and 1.18% in DBP using weighted averages across all cohorts. The results for the individual cohorts are provided in Table S4.

After excluding 1,284 individuals with prevalent CVD at baseline, 2,295 incident CVD events occurred during a median follow-up time of 9.8 (IQR 5.1) years. In total, the study participants contributed 347,955 person-years of follow-up. GRSs showed significant, independent and roughly linear associations with CVD risk (Table 2, Table 3, Figure 1). As expected, the observed effects on SBP or DBP of a predicted 1 mm Hg increase in GRS, based on the previously published per-SNP effect estimates, were 1.1 and 1.0 mm Hg, for the SBP and DBP GRSs, respectively (Table 2). A 4% increased hazard for coronary heart disease, stroke or cardiovascular disease was observed for each predicted 1 mm Hg increase in SBP GRS, and 6-8% for each predicted 1 mm Hg increase in DBP GRS, in models adjusting for non-BP clinical risk factors. After further adjustment for antihypertensive treatment and baseline SBP or DBP for their respective GRSs, the hazard ratios were reduced only slightly and for the most part remained statistically significant (Table 2). In models, adjusting for age, age squared and sex, increasing quintile of SBP or DBP GRS was associated with roughly linear increases in BP, HTN prevalence and risk of incident cardiovascular disease, with or without inclusion of prevalent cases (Table 3). For example, the highest compared to lowest quintile of SBP GRS was associated with a hazard ratio for CVD of 1.30 (95% CI 1.17–1.45, $p=1\times10^{-6}$) including prevalent and incident events and 1.23 (95% CI 1.08-1.40, p=2×10-6) including only incident events and the highest quintile of DBP GRS was associated with a hazard ratio of 1.30 (95% CI 1.17–1.45, $p=2\times10^{-6}$) and 1.26 (95% CI 1.11-1.44, $p=5\times10^{-4}$), respectively (Table 3). No individual SNPs were statistically significantly associated with CVD risk after correcting for 32 tests, although some were nominally associated (p<0.05, Table S3).

The associations of a CVD GRS, created using CVD effects estimated in the Finnish cohorts, with cardiovascular events were stronger than the associations with the BP GRSs with less attenuation after adjustment for Framingham Risk Score components (HR=2.40,$p=6\times10^{-5}$ for incident CHD; HR=2.07, p=0.013 for incident stroke; and HR=2.40,$P=2\times10^{-6}$ for incident CVD; Table S5). However, because the CVD GRS was derived from the same studies in which its association with CVD events was tested, the strength of the association might have been overestimated.

Reclassification analyses in Health 2000, FINRISK 1992 and 1997 showed that the SBP GRS did not improve CVD risk discrimination over and above the standard Framingham risk score (which includes SBP) when assessed using ROC curves and C-statistics, or IDI (Tables S6,S7). There was no net improvement in NRI, either (Tables S6, S7). However, the clinical NRI, i.e., reclassification in the intermediate risk group of 5-20%, was 3.8% and

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statistically significant ($p=5\times10^{-5}$). Model calibration was good in both models with and without the GRS (FigureS2). We found no significant interaction of sex, baseline age, BMI or antihypertensive treatment with the GRS effect on risk of incident CVD.

Discussion

We tested previously established SNPs associated with BP in a large collection of population-based studies in Finland. We replicated 23 SNPs at a stringent Bonferroni-corrected significance threshold and found directional consistency for 30 out of 32 SNPs. Genetic risk scores weighted according to previously reported effect estimates were highly associated with BP and hypertension. An important novel finding of our study was that both SBP- and DBP-based genetic risk scores were strongly associated with risk of incident CVD among those free of CVD at baseline. These associations were largely independent of standard CVD risk factors, including BP measured at baseline.

The field of genetic associations has historically been riddled with irreproducible results, largely due to overly permissive significance thresholds and inadequate power from limited sample sizes.[23] The widespread adoption of stringent p-value thresholds and the development of genotyping platforms allowing the efficient genotyping of scores to millions of variants in tens of thousands of individuals have enabled identification of reproducible associations. We have replicated many of the BP variants identified in GWAS meta-analyses some of which included six times the sample size examined here.

Our findings are consistent with a causal effect of BP on cardiovascular disease. This is well accepted given the broad epidemiologic support for this relationship, the existence of Mendelian syndromes of hypertension and premature cardiovascular disease and the modification of risk by lowering blood pressure through behavioral or pharmacologic means.[24] Most of the SNPs that have been identified lie in chromosomal regions with a heterogeneous set of genes without a single dominant pathway apparent. Despite these heterogeneous effects, when the weak effects of the individual SNPs are considered jointly, a strong and consistent effect on cardiovascular risk is observed.

BP is a highly variable, dynamic measure, with minute-to-minute variation influenced by activity, posture, mental stress, medication, etc. We used the mean of two BP measurements. However, we were limited to the examination of BP at a single time point, which is clearly an imprecise surrogate for the lifetime of exposure to higher BP that contributes to the pathogenesis of cardiovascular disease and could lead to regression dilution of the true impact of BP and other time-varying factors. This, in fact, highlights the potential value of the study of precisely measured genotypes. Genetic variants are fixed and when set against the background of a large dynamic range may capture a fixed component to lifetime BP exposure. Thus, small genetic effects on BP may translate into comparatively large effects when compounded over a lifetime. In the present study, we found no net improvement in NRI due to SBP or DBP GRS over and above the Framingham equation. It should be noted, however, that the Framingham equation estimates ten-year risk only, as risk factors change over time, whereas for BP GRS the estimation of lifetime risk might be more appropriate as genotype is invariant over time.

For decades, investigators have sought to resolve essential hypertension into well-defined subtypes that might benefit from specific therapies, such as low-renin, high-aldosterone hypertension. However, these have not led to widespread adoption or recommendation for specific therapies by most public health guidelines.[24] Given the limited power to detect the weak SNP effects that have so far been found, it is estimated that hundreds of common variants of similarly modest effect will ultimately be found to exist.[8] Assuming as yet

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unidentified effects are as modest as those identified to date, it seems unlikely that common genetic variation will ultimately accomplish this task.

Some SNPs that fall in targets of antihypertensives are potential candidates to modulate the response to antihypertensive therapy. For example, a common BP-associated missense polymorphism lies in *ADRB1* which encodes the β1 adrenergic receptor, a target of beta adrenergic receptor antagonists. Whether such BP-associated variants also influence response to antihypertensive therapy, awaits results from large clinical trials.

Strengths of the current study include the large sample size, the population-based sampling of the cohorts examined, the measurement of BP precisely and in a uniform manner, the availability of relevant covariates, the large number of CVD outcomes available for prospective analyses and the single country of origin for all samples. Limitations include the inability to generalize to non-European ancestry groups. We lacked the ability to adjust for time-varying clinical factors that influence BP. The proportion of variation explained by the SNPs remained low, and the level of prediction for events was also relatively small. We lacked power to demonstrate replication even at nominal $p<0.05$ of some of the modest BP effects reported in prior GWAS.

Perspectives

We found that genetic risk scores comprised of 32 SNPs identified in GWAS of BP were strongly associated with risk of incident cardiovascular disease, even after adjustment for baseline BP. While the genetic risk scores were not associated with significant reclassification of CVD risk when added to the Framingham Risk Score, a more complete compendium of genetic variation that reproducibly influences BP will ultimately need to be tested.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New?

- Recent GWAS studies have identified several genetic variants associated with BP.
- The predictive power of BP-associated genetic variants for incident CVD events has not been established

What Is Relevant?

- GRSs comprised of 32 SNPs identified in GWAS of BP were strongly associated with risk of incident CVD, even after adjustment for baseline BP and antihypertensive treatment.
- A more complete compendium of genetic variation that reproducibly influences BP will ultimately need to be tested.

Summary

These findings are consistent with a lifelong effect on BP of these variants and a causal effect of BP on CVD risk.

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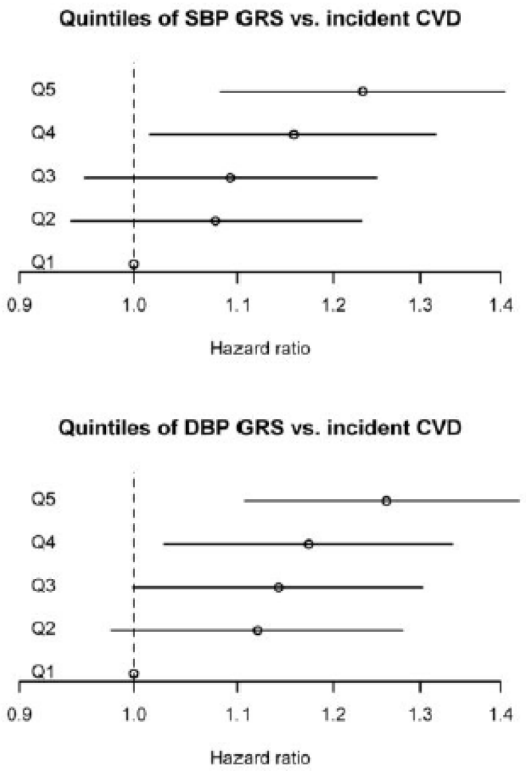

Figure 1.
Association of the SBP and DBP GRS quintiles with incident CVD. Cox regression models were adjusted for sex and study region. Age was used as the time scale and results were combined using inverse variance-weighted fixed-effects meta-analysis.

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Table 1

Characteristics of the study cohorts

Study	FR 19921 (N=5,465)	FR 1997 (N=6,692)	FR 2002 (N=7,951)	FR 2007 (N=4,334)	Health 2000 (N=5,797)	OPERA (N=856)	HBCS (N=1,574)
Follow-up time from baseline, yrs; Median (IQR)	18.8 (0.1)	13.8 (0.1)	8.8 (0.1)	3.9 (0.1)	10.0 (0.3)	17.6 (1.1)	8.0(1.4)
Sex							
Men	2,483 (45.4%)	3,104 (46.4%)	3,611 (45.4%)	1,929 (44.5%)	2,601(44.9 %)	419 (48.9%)	639(40.6%)
Women	2,982 (54.6%)	3,588 (53.6%)	4,340 (54.6%)	2,405 (55.5%)	3,196(55.1 %)	437 (51.1%)	935(59.4%)
Age at baseline, yrs	44.2± 11.3	47.3± 13.0	47.4± 13.0	51.6± 13.5	52.7± 12.8	50.8 ± 5.8	61.4 ± 2.9
Blood pressure							
Systolic (mm Hg)	135.4 ± 19.4	135.4± 19.7	134.7 ± 19.8	136.7 ± 20.5	134.3 ± 20.5	147.9 ± 21.9	145.4± 20.4
Diastolic (mm Hg)	81.2 ± 11.9	82.2± 11.3	79.0 ± 11.4	79.4± 11.2	82.3± 10.9	89.0 ± 12.2	89.1± 10.3
HTN	2,626(48.1 %)	3,256(48.7 %)	3,330 (41.9%)	2,335 (53.9%)	2,857 (49.3%)	655 (76.5%)	1,121(71.2 %)
Antihypertensive medication	481 (8.8%)	802 (12.0%)	1,055 (13.3%)	873 (20.1%)	1,241 (21.4%)	409 (47.8%)	475(30.2%)
Cholesterol(mmol/l)							
Total	5.6 ± 1.1	5.5 ± 1.1	5.6 ± 1.1	5.3 ± 1.1	6.0 ± 1.1	5.7 ± 1.0	6.0 ± 1.1
LDL (Friedewald)	3.6 ± 1.0	3.5 ± 0.9	3.4 ±1.0	3.2 ± 0.9	3.8 ± 1.2	3.5 ± 0.9	3.7 ± 0.9
HDL	1.4 ± 0.3	1.4 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.6 ± 0.4
Body-mass index(kg/m^2)	26.1 ± 4.4	26.6 ± 4.6	26.8 ± 4.7	27.1 ± 4.9	27.0± 4.6	27.6 ± 4.7	27.5± 4.7
Current smoker	1,514(27.7 %)	1,621(24.2 %)	2,073 (26.1%)	772(17.2%)	1,655(28.5 %)	247 (28.9%)	376(23.9%)
Diabetes mellitus	191(3.5%)	342(5.1%)	383(4.8%)	349(8.1%)	392(6.8%)	68 (8.0%)	217(13.8%)
Prevalent cases *							
Coronary heart disease	72(1.3%)	147(2.1%)	210(2.6%)	130(2.9%)	179(3.0%)	117 (11.7%)	79(4.7%)
Ischemic stroke	27 (0.5%)	69(1.0%)	87(1.1%)	68(1.5%)	100(1.6%)	37 (3.7%)	28(1.7%)
Cardiovascular disease	97(1.7%)	204 (3.0%)	284(3.4%)	188(4.2%)	265(4.4%)	144 (14.4%)	102(6.1%)
Incident cases *							
Coronary heart disease	391(7.2%)	411(6.1%)	229(2.9%)	67(1.5%)	360(6.2%)	104 (12.1%)	66(4.2%)
Ischemic stroke	210(3.8%)	231(3.5%)	115(1.4%)	26(0.6%)	154 (2.7%)	49 (5.7%)	30(1.9%)
Cardiovascular disease	555 (10.2%)	599(9.0%)	326(4.1%)	88(2.0%)	495(8.5%)	141 (16.5%)	91(5.8%)

The numbers refer to participants for whom the GRSs are available. Unless otherwise noted, continuous measures are mean±SD and dichotomous measures are N (%). Prevalent CVD cases are excluded from everything else except the prevalent case numbers. Health 2000 was restricted to participants aged ≤80 years. Abbreviations: FR, FINRISK; IQR, Interquartile range; N, number of individuals; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HTN, hypertension. HTN was defined as SBP ≥140 mmHg or DBP ≥ 90 mmHg or use of antihypertensive therapy.

* In the case counts some persons might have both coronary heart disease and ischemic stroke, hence they do not necessary add up to number of persons with cardiovascular disease.

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Table 2

Association of the GRSs with BP and incident cardiovascular disease events.

Trait	Systolic BP (N=37,176)		Diastolic BP (N=37,168)		HTN (N=37,245)	
Analysis	**mm Hg (95% CI)**	**P**	**mm Hg (95% CI)**	**P**	**OR (95% CI)**	**P**
SBP GRS *	1.1 (1.0;1.2)	1×10^{-87}	0.6 (0.6;0.7)	4×10^{-77}	1.12 (1.11;1.14)	1×10^{-65}
SBP GRS †	1.1 (1.0;1.2)	4×10^{-90}	0.6 (0.6;0.7)	2×10^{-81}	1.13 (1.12;1.15)	3×10^{-67}
DBP GRS *	1.7 (1.5;1.9)	9×10^{-78}	1.0 (0.9;1.2)	3×10^{-82}	1.20 (1.17;1.22)	1×10^{-62}
DBP GRS †	1.7 (1.5;1.8)	1×10^{-79}	1.0 (0.9;1.2)	9×10^{-87}	1.21 (1.18;1.24)	3×10^{-64}
Trait	**CHD (N=32,953; 2,408 events)** ‡ **(N=32,669; 1,628events)** §,‖,¶		**STR (N=32,953; 1,222events)** ‡ **(N=32,669; 815events)** §,‖,¶		**CVD (N=32,953; 3,294events)** ‡ **(N=32,669; 2,295events)** §,‖,¶	
Analysis	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
SBP GRS ‡	1.05 (1.03;1.08)	3×10^{-6}	1.05 (1.02;1.09)	0.001	1.05 (1.03;1.07)	4×10^{-8}
SBP GRS §	1.04 (1.01;1.07)	0.003	1.03 (1.00;1.07)	0.07	1.04 (1.02;1.06)	5×10^{-4}
SBP GRS ‖	1.04 (1.01;1.07)	0.005	1.04 (1.00;1.07)	0.05	1.04 (1.02;1.06)	6×10^{-4}
SBP GRS ¶	1.03 (1.00;1.05)	0.06	1.02 (0.98;1.06)	0.24	1.03 (1.00;1.05)	0.02
DBP GRS ‡	1.08 (1.04;1.11)	4×10^{-5}	1.08 (1.02;1.13)	0.002	1.08 (1.05;1.11)	8×10^{-7}
DBP GRS §	1.06 (1.01;1.10)	0.01	1.06 (1.00;1.12)	0.06	1.06 (1.02;1.10)	0.001
DBP GRS ‖	1.05 (1.01;1.10)	0.01	1.06 (1.00;1.12)	0.05	1.06 (1.02;1.10)	0.002
DBP GRS ¶	1.04 (1.00;1.08)	0.08	1.04 (0.98;1.10)	0.24	1.04 (1.01;1.08)	0.02

Linear regression, logistic regression and Cox regression (age as the time scale) were used as appropriate. Studies were combined using inverse variance-weighted fixed-effects meta-analysis. HTN was defined as SBP ≥140 mmHg or DBP ≥ 90 mmHg or use of antihypertensive therapy. Effect estimates are shown as increase in blood pressure on the mm Hg scale or hazard ratio for dichotomous outcomes for a one unit increase in GRS. One unit for the SBP GRS is one mm Hg increase in predicted SBP and for the DBP GRS one mm Hg increase in predicted DBP, based on effect estimates derived from the published GWAS. Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; HTN, hypertension; GRS, genetic risk score; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; N, number of individuals; OR, odds ratio; STR, stroke, including ischemic stroke and intracerebral hemorrhages.

*Models adjusted for baseline age and its square, sex and study region. In the linear regressions BP measurements were corrected for the use of antihypertensive therapy (+15mmHg for SBP; +10mmHg for DBP).

†Additionally adjusted for BMI, leisure time physical activity (high/moderate vs. none) and average alcohol consumption (7-day abs. gr. or high vs. low or none depending on the study).

‡Prevalent cases were also included. Models stratified for sex and adjusted for study region. OPERA was excluded from the analyses.

§Only incident cases. Models stratified for sex and adjusted for study region.

‖Only incident cases. Additionally adjusted for log(total cholesterol), log(HDL cholesterol), baseline diabetes and current smoking status.

¶Only incident cases. Additionally adjusted for all above and BP treatment and SBP or DBP depending on the trait.

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Table 3

Blood pressure and cardiovascular outcome risk by quintile of blood pressure GRS.

BP Quintile	SBP (mm Hg)*	DBP (mm Hg)*	HTN OR (95% CI)*	CHD prev + inc HR (95% CI)‡	CHD inc only HR (95% CI)§	STR prev + inc HR (95% CI)‡	STR inc only HR (95% CI)§	CVD prev + inc HR (95% CI)‡	CVD inc only HR (95% CI)§
SBP GRS Q2	1.4 (0.8;2.1) $P = 1\times10^{-5}$	0.9 (0.5;1.3) $P = 5\times10^{-6}$	1.18 (1.09;1.27) $P = 2\times10^{-5}$	1.09 (0.96;1.24) P = 0.19	1.07 (0.92;1.26) P = 0.39	1.16 (0.97;1.39) P = 0.10	1.22 (0.99;1.50) P = 0.07	1.09 (0.97;1.22) P = 0.14	1.08 (0.94;1.23) P = 0.03
SBP GRS Q3	2.9 (2.2;3.5) $P = 3\times10^{-16}$	1.7 (1.3;2.1) $P = 4\times10^{-18}$	1.37 (1.27;1.48) $P = 2\times10^{-16}$	1.13 (0.99;1.28) P = 0.08	1.15 (0.98;1.34) P = 0.09	1.05 (0.87;1.26) P = 0.63	1.04 (0.84;1.30) P = 0.70	1.10 (0.99;1.23) P = 0.09	1.09 (0.96;1.25) P = 0.05
SBP GRS Q4	3.7 (3.0;4.3) $P = 3\times10^{-29}$	2.1 (1.8;2.5) $P = 5\times10^{-28}$	1.50 (1.39;1.61) $P = 2\times10^{-25}$	1.15 (1.01;1.31) P = 0.03	1.16 (1.00;1.36) P = 0.06	1.16 (0.97;1.39) P = 0.11	1.20 (0.97;1.48) P = 0.09	1.14 (1.02;1.28) P = 0.02	1.16 (1.02;1.32) P = 0.003
SBP GRS Q5	5.8 (5.1;6.4) 1×10^{-69}	3.3 (2.9;3.6) $P = 3\times10^{-62}$	1.82 (1.69;1.96) $P = 2\times10^{-53}$	1.32 (1.16;1.50) $P = 2\times10^{-5}$	1.25 (1.07;1.46) P = 0.006	1.29 (1.08;1.55) P = 0.004	1.24 (1.01;1.53) P = 0.04	1.30 (1.17;1.45) $P = 1\times10^{-6}$	1.23 (1.08;1.40) $P = 2\times10^{-6}$
DBP GRS Q2	1.3 (0.7;2.0) $P = 7\times10^{-5}$	1.0 (0.6;1.4) $P = 1\times10^{-7}$	1.18 (1.10;1.28) $P = 1\times10^{-5}$	1.13 (0.99;1.29) P = 0.07	1.09 (0.93;1.28) P = 0.30	1.20 (1.00;1.44) P = 0.05	1.29 (1.05;1.60) P = 0.02	1.13 (1.01;1.27) P = 0.03	1.12 (0.98;1.28) P = 0.10
DBP GRS Q3	3.1 (2.4;3.7) $P = 1\times10^{-20}$	1.8 (1.4;2.2) $P = 6\times10^{-20}$	1.36 (1.26;1.46) $P = 3\times10^{-15}$	1.15 (1.01;1.31) P = 0.03	1.20 (1.03;1.41) P = 0.02	1.11 (0.92;1.33) P = 0.28	1.14 (0.920;1.42) P = 0.23	1.12 (1.00;1.25) P = 0.05	1.14 (1.00;1.30) P = 0.05
DBP GRS Q4	3.63 (3.0;4.3) $P = 2\times10^{-28}$	2.3 (1.9;2.7) $P = 3\times10^{-31}$	1.49 (1.38;1.61) $P = 5\times10^{-25}$	1.21 (1.06;1.37) P = 0.004	1.20 (1.03;1.41) P = 0.02	1.14 (0.95;1.36) P = 0.18	1.15 (0.925;1.429) P = 0.21	1.18 (1.06;1.32) P = 0.003	1.17 (1.03;1.34) P = 0.02
DBP GRS Q5	5.2 (4.6;5.9) $P = 2\times10^{-57}$	3.3 (2.9;3.7) $P = 4\times10^{-65}$	1.76 (1.63;1.89) $P = 1\times10^{-47}$	1.30 (1.14;1.47) $P = 6\times10^{-5}$	1.23 (1.05;1.43) P = 0.01	1.32 (1.11;1.58) P = 0.002	1.35 (1.09;1.66) P = 0.005	1.30 (1.17;1.45) $P = 2\times10^{-6}$	1.26 (1.11;1.44) $P = 5\times10^{-4}$

Linear regression, logistic regression and Cox regression (age as the time scale) were used as appropriate. Studies were combined using inverse variance-weighted fixed-effects meta-analysis. HTN was defined as SBP ≥140 mmHg or DBP ≥ 90 mmHg or use of antihypertensive therapy. Effect estimates are shown as increase in blood pressure on the mm Hg scale or hazard ratio for dichotomous outcomes for quintiles 2-4 for the SBP and DBP GRS compared to the bottom quintile. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; HTN, hypertension; GRS, genetic risk score; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; OR, odds ratio; STR, stroke, including ischemic stroke and intracerebral hemorrhages.

*Models adjusted for baseline age and its square, sex and study region. In the linear regressions BP measurements were corrected for the use of antihypertensive therapy (+15mmHg for SBP; +10mmHg for DBP).

‡Prevalent and incident cases were included. Models stratified for sex and adjusted for study region. OPERA was excluded from the analyses.

§Only incident cases. Models stratified for sex and adjusted for study region.