Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events

Running Title: Genetic, lifestyle, and cardiovascular risk

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Abstract

Background: High blood pressure (BP) is a major risk factor for cardiovascular diseases (CVD), the leading cause of mortality worldwide. Both heritable and lifestyle risk factors contribute to elevated BP levels. We aimed to investigate the extent to which lifestyle factors could offset the effect of an adverse BP genetic profile, and its effect on CVD risk.

Methods: We constructed a genetic risk score for high BP using 314 published BP loci in 277,005 individuals without previous CVD from the UK Biobank study, a prospective cohort of individuals aged 40 to 69 years, with median 6.11 years of follow-up. We scored participants according to their lifestyle factors including body mass index, healthy diet, sedentary lifestyle, alcohol consumption, smoking, and urinary sodium excretion levels measured at recruitment. We examined the association between tertiles of genetic risk and tertiles of lifestyle score with BP levels and incident CVD using linear regression and Cox regression models respectively.

Results: Healthy lifestyle score was strongly associated with BP ($P<10^{-20}$ for systolic and diastolic BP and CVD events regardless of the underlying BP genetic risk. Participants with favorable compared to unfavorable lifestyle (bottom vs. top tertile lifestyle score) had 3.6, 3.5, and 3.6 mmHg lower systolic BP in low, middle and high genetic risk groups respectively ($P$ for interaction= 0.0006). Similarly, favorable compared with unfavorable lifestyle showed 30%, 31%, and 33% lower risk of CVD among participants at low, middle and high genetic risk groups respectively ($P$ for interaction= 0.99).

Conclusions: Our data further support population-wide efforts to lower BP in the population via lifestyle modification. Advantages and disadvantages of disclosing genetic predisposition to high BP for risk stratification needs careful evaluation.
Keywords: genetic risk, blood pressure, cardiovascular disease, healthy lifestyle, genetic predisposition to disease
What is new?

- We show that adherence to a healthy lifestyle (including healthy diet, limited alcohol consumption, low urinary sodium excretion, low body mass index, and increased physical activity) is associated with lower blood pressure regardless of the underlying BP genetic risk.
- Adherence to a healthy lifestyle is also associated with lower risk of myocardial infarction, stroke and composite cardiovascular disease at all levels of underlying blood pressure genetic risk.
- Healthy compared with unhealthy lifestyle showed 30%, 31%, and 33% lower risk of CVD among participants at low, middle and high genetic risk groups respectively

What are the clinical implications?

- Genetically predetermined rise in BP and its complications can be offset at least to some extent by healthy lifestyle.
- Our results further support population-wide efforts to lower BP and subsequent CVD risk through lifestyle modification.
Introduction

High blood pressure (BP) is the leading single risk factor for mortality and global burden of disease (9.4 million deaths in 2010) \(^1\). There is a strong graded relationship between BP and cardiovascular disease (CVD) with even small increments in BP associated with an increased risk of CVD, the leading cause of death and disease burden worldwide \(^2\).

In the last four decades, efforts to detect and treat elevated BP have been vigorous. However, there is a need for improved primary prevention of high BP. Heritable and environmental/lifestyle risk factors both contribute to elevated BP levels \(^3, 4\). There is well established evidence for independent unfavorable additive effects on BP of excess sodium intake, unhealthy dietary patterns or adverse calorie balance (body mass), excess alcohol use, and physical inactivity \(^5-11\). At the same time, more than 314 genetic variants are known to affect BP levels and could have a cumulative effect of up to 10mmHg higher systolic BP level by age 50\(^3\). The mechanism through which these genetic variants affect BP levels is largely unknown\(^3\).

We aimed to investigate the associations between healthy lifestyle adherence and blood pressure levels and cardiovascular risk in different subgroups of genetic BP risk. We examined the role of lifestyle in individuals predetermined to have higher BP levels based on their genetic profile in relation to both BP and future CVD events within UK Biobank.
Methods

Additional material is provided in the Online Supplement. Approval for this research was obtained from the UK Biobank Research Ethics Committee and Human Tissue Authority and the participants gave informed consent. The calculated genetic risk score will be made available to other researchers on the UK Biobank website for purposes of reproducing the results or replicating the procedure.

Study population

The UK Biobank is a national long-term cohort in the UK that recruited 502,638 individuals aged between 40 and 69 years. The present study is based on a subset of unrelated individuals with GWAS data\textsuperscript{12-14} and of European ancestry following quality measures and exclusions (sex discordance, high missingness/heterozygosity, 1st- and 2nd-degree relatives, and non-European ancestry excluded) (Supplementary Figure 1).

In detail, we excluded participants who were pregnant or unsure of their pregnancy at baseline (N=372) as well as those withdrawn consent (N=19). Genetic data were available for 487,409 individuals. After merging genetic and phenotype data, 487,048 individuals remained. We excluded 147,637 individuals being related to at least one individual in the genotype data. We further excluded 30,464 individuals of non-European ancestry, 21,134 individuals with CVD events at or before baseline and 10,808 individuals with missing values on the main covariates of the current study. The final sample for analysis comprised 277,005 participants.

Lifestyle factors and physical measurements

Following informed consent, participants completed a standardized questionnaire on life course exposures, medical history and treatments and had a range of physical measurements. We assessed diet based on a self-completed food frequency questionnaire. Participants ranked their daily intake of dietary consumption including alcoholic products, fruits and vegetables, oily and non-oily fish, processed and unprocessed meat, using touch-screen multiple choice
questions. We defined smoking based on self-reported information on current (“most of days” and “occasional” smokers), past smokers and never smokers. Sedentary behavior was defined by the sum of three questions about the hours per day participants spent (i) driving, (ii) using a computer and (iii) watching television. We calculated alcohol intake from the self-reported alcohol drinking information on the touch-screen questionnaire. The quantity of each type of drink (red wine, white wine, beer/cider, fortified wine, spirits) was multiplied by its standard drink size and reference alcohol content. Drink-specific alcohol intake during the reported drinking period (a week for frequent drinkers or a month for occasional drinkers) was summed up and converted to grams per day for participants with complete response to the quantitative drinking questions. Grams per day of alcohol consumption for participants with incomplete response was imputed by bootstrap resampling from the complete responses, stratified by drinking frequency (occasional or frequent) and sex.

Two BP measurements were taken seated after two minutes rest using an appropriate cuff and an Omron HEM-7015IT digital BP monitor. Systolic (SBP) and diastolic blood pressure (DBP) were analyzed. We calculated mean SBP and DBP from two automated (N= 253,419) or two manual readings (N=15,454) BP measurements. For individuals with one manual and one automated BP reading (N=7,886), we used mean of these two values. For individuals with single BP measurement (one manual or one automated BP reading, N=246), we used that single measurement. For individuals reported to be taking BP-lowering medication (N=47,438 of individuals), we added 15 and 10 mmHg to SBP and DBP respectively.

Standing height was measured using a Seca 202 device. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²) with weight measured using electronic weighing scales (Tanita BC-418).
Sodium and potassium concentrations were measured in stored urine samples by the Ion Selective Electrode method (potentiometric method) using Beckman Coulter AU5400, UK Ltd. Analytical range for sodium was 2-200mmol/L and for potassium 10-400 mmol/L. Details of quality control and sample preparation have been published previously 16.

Healthy Lifestyle Score

A composite healthy lifestyle score adapted from American Heart Association cardiovascular health recommendations was constructed 17. A healthy lifestyle score was defined by BMI below median, sedentary hours below median, alcohol intake below median, meat intake (processed and unprocessed) below median, urinary sodium excretion below median, fruit and vegetable intake above median, fish intake (oily fish and non-oily) above median, and never smoking. One point was given for each favorable lifestyle factor (range 0 to 8).

We additionally performed a sensitivity analysis using cut-offs of the American Heart Association (AHA) for healthy lifestyle 18, 19 presented in Supplementary Table 1.

Cardiovascular events

For all participants, retrospective and prospective linkage to electronic health data is available, including Hospital Episode Statistics (HES) and Office for National Statistics cause of death data. HES provide detailed information for participants admitted to hospital and includes coded data on diagnoses and procedures. CVD was defined as an event of coronary artery disease (CAD), or stroke or myocardial infarction classified using an in-house algorithm comprising codes from International Classification of Disease (ICD) 9 and 10 codes and Classification of Interventions and Procedures (OPCS) codes (Supplementary Table 2).

The recorded “Episode date” was considered as the date of the event. For individuals with missing of “Episode date”, “admission date” was used as the date of event. For individuals
with multiple CVD hospitalizations in HES, the date of the earliest event was used as date of event. Fatal CVD events were searched in mortality data and were added to the main CVD variable. We additionally used the algorithmically derived definitions of myocardial infarction (MI) and stroke as coded by UK Biobank. History of CVD at baseline was defined based on self-reported data and/or on HES data with episode date preceding the date of the visit in the study assessment center. CVD events occurring prior to assessment date and self-reported CVD events were considered as existing CVD events at baseline. Fatal CVD events with pre-existing CVD from HES occurring before assessment or self-reported CVD were considered as existing CVD events at baseline. Individuals with CVD events occurring before assessment were excluded. Follow-up time was calculated as the time starting from assessment date for each individual until 31st March 2015. Individuals who died during follow-up were censored.

Our primary traits and outcomes were a) SBP and DBP measured at baseline and b) the composite measure of CVD events (See Supplementary Table 2), and separately MI and stroke (non-fatal and fatal) during follow up (2006-2016). The main exposures studied included: a) genetic risk score for BP (tertiles), b) lifestyle score (tertiles), and c) the 3×3 matrix of the genetic risk and lifestyle scores.

Genotyping and Imputation

Detailed information about genotyping and imputation in the UK Biobank study has been provided elsewhere. Briefly, DNA samples of the UK Biobank study participants were genotyped using a custom Affymetrix UK Biobank Axiom array (designed to optimize imputation performance). Genotype imputation used a special reference panel comprising a merged sample of UK10K sequencing and 1000 Genomes imputation reference panels to maximize using of haplotypes with British and European ancestry for imputation. Imputation
was carried out centrally by the UK Biobank using an algorithm implemented in the IMPUTE2 program. Genetic principal components to account for population stratification were computed centrally by the UK Biobank.

Genetic Risk Score for BP

A weighted genetic risk score was calculated based on previously reported genetic variants (Supplementary references 1 and 2) for SBP, DBP, and pulse pressure (PP): (i) 267 SNPs with weights (β coefficients) reported by Warren et al. \(^1\) (we extracted weights from replication cohorts for novel signals and from UK Biobank for known signals as described in Warren et al.\(^1\)) and (ii) 47 SNPs identified and replicated from Hoffmann, et al.\(^23\) with weights (β coefficients) from the International Consortium for Blood Pressure (ICBP)+ Genetic Epidemiology Research on Adult Health and Aging (GERA) meta-analysis. We calculated a standardized BP genetic risk score for each of SBP, DBP, and PP loci and combined them into a single BP genetic risk score by averaging the three standardized SBP, DBP and PP genetic risks. Pairwise-independent, LD filtered (\(r^2 < 0.2\)) variants were used for the analysis (Supplementary Table 3).

Statistical Analysis

Genetic risk and lifestyle scores (and their combination) were analyzed with respect to a) SBP and DBP considered separately using multiple linear regression and b) CVD events using Cox Proportional Hazards regression with duration of follow-up as the time metric. Proportional hazards assumptions were tested using Schoenfeld residuals implemented in R Package Survival, and risk estimates were presented as Hazard Ratio (HR). Analyses were adjusted for age, sex and, when genetic risk was included in the model, for the first ten genetic principal components. For the statistical analyses, we also adjusted for BMI, sedentary lifestyle, smoking status, and healthy diet score (defined as consumption of fruits and vegetables each \(\geq 3\) servings a day; fish \(\geq 2\) servings a week; processed meat \(\leq 1\) servings a week; and unprocessed
meat ≤ 1.5 servings a week\textsuperscript{17}). We tested for interaction between the genetic risk and lifestyle scores using a likelihood ratio test comparing a model with and without interaction terms (categorized in tertiles).

We calculated standardized 5-year cumulative incidence rates for CVD, MI, and stroke. Standardization was performed using the World Health Organization (WHO) Standard population \textsuperscript{24} and the European Standard population (ESP 2013)\textsuperscript{25}.

As sensitivity analyses, we excluded participants receiving BP (N= 47,438) or lipid lowering (N = 35,155) medication and those with diabetes diagnosis at baseline (N = 10,958) as they may have changed their lifestyle habits due to the diagnosis of their condition (total exclusion, N= 64,555). Also, we examined the association between genetic risk score and each lifestyle variable separately in relation to SBP, DBP and CVD events. Lifestyle variables included BMI (tertiles), healthy diet score (as above), sedentary lifestyle (tertiles), smoking status (present, past or never smoker), urinary sodium and potassium excretion and alcohol intake (tertiles). For sedentary lifestyle, we performed additional sensitivity analysis excluding individuals with an event during the 2 years of follow up since low physical activity could be a marker of subclinical or undiagnosed disease.

All statistical analyses were performed in R software, version 3.3 (R Project for Statistical Computing).
Results

The sample of 277,005 individuals (Supplementary Figure 1) comprised 152,121 (55%) women and 124,884 (45%) men (Table 1). Median follow-up for CVD was 6.11 years. During follow-up, 9,278 CVD events occurred (incidence rate 5.55 per 1000 person-years), of which 2,984 were MI (incidence rate 1.53 per 1000 person-years) and 1919 were stroke (incidence rate 1.00 per 1000 person-years). Supplementary Table 4 shows the distribution of various risk factors of CVD per subgroups of genetic risk and healthy lifestyle.

Genetic risk score as a continuous variable (Supplementary Table 5) was significantly associated with all outcomes examined (HR \( \text{CVD} = 1.11; 95\% \ CI = 1.09 \text{ to } 1.14; P<10^{-320} \)) per unit increase in the genetic risk score. Healthy lifestyle score (per unit) as a continuous variable was also strongly and inversely associated with both SBP (Beta= -0.88mmHg, 95% CI, -0.92 to -0.85, \( P<10^{-320} \)) and DBP (Beta= -0.71mmHg, 95% CI, -0.73 to -0.69, \( P<10^{-320} \)) (Supplementary Table 5). Similarly, strong inverse associations were observed between lifestyle score (per unit increase) and incident CVD (HR= 0.92; 95% CI=0.92 to 0.93; \( P<10^{-320} \)). Figures 1 and 2 show a significant risk gradients between tertiles of healthy lifestyle or tertiles of genetic risk score in relation to SBP levels and incident CVD.

With the exception of alcohol, which was associated with BP, MI, and stroke but not with CVD (Supplementary Table 5), all other the individual healthy lifestyle factors (diet, BMI, sedentary lifestyle) were associated with both BP and all CVD events.

Within combined subgroups of healthy lifestyle and genetic risk, healthy lifestyle was associated with lower SBP and DBP within each teritle of genetic risk (Figure 2). Among participants at low genetic risk, the estimated mean SBP was 140 mmHg (95% CI 102 to 177) for participants with unfavorable lifestyle and 134 mmHg (95% CI 95 to 172) with a favorable lifestyle (Figure 2). For those at high genetic risk, the estimated mean SBP was
146 mmHg (95% CI 106 to 186) among those with an unfavorable lifestyle and 142 mmHg (95% CI 100 to 184) among those with a favorable lifestyle. An unfavorable lifestyle as compared with a favorable lifestyle, was associated with 4.9 mmHg higher SBP among participants at low genetic risk, 4.3 mmHg higher SBP among participants at intermediate genetic risk, and 4.1 mmHg higher SBP among participants at high genetic risk (Supplementary Table 6). There was modest statistical evidence for interaction between genetic risk and healthy lifestyle scores in relation to SBP (P for interaction=0.0006) but not for DBP (P for interaction=0.8).

Regarding CVD events, participants with favorable compared with unfavorable lifestyle showed 30%, 33%, and 31% lower relative risk of CVD among participants at low, intermediate, and high genetic risk groups respectively (Supplementary Table 7). Participants with less favorable genetic and lifestyle profiles (top tertile of BP genetic risk, bottom tertile of healthy lifestyle score) had nearly two-fold greater risk of CVD (HR= 1.75; 95% CI=1.59, 1.93) compared with participants with favorable genetic and lifestyle profiles (the reference group; Figure 3; Supplementary Table 7). Genetic risk and healthy lifestyle score were statistically independent of each other and there was no statistically significant interaction (P for interaction=0.99). Among participants at low genetic risk, the standardized 5-year CVD rates based on WHO World and Europe standard populations were 2.77% and 3.22% respectively among those with an unfavorable lifestyle and they were 1.46% and 1.75% respectively among those with a favorable lifestyle. Among participants at high genetic risk, the standardized 5-year coronary event rates were 3.53% and 4.11% respectively among those with an unfavorable lifestyle and 1.76% and 2.09% respectively among those with a favorable lifestyle. Similar pattern of associations was observed for MI and stroke (Supplementary Table 8).
Sensitivity analyses with exclusion of participants with self-reported diabetes or taking blood pressure and/or lipid lowering medication, and the individual lifestyle components, showed similar associations for BP and CVD events (Supplementary Table 6 & 7, Supplementary Figure 2). Sensitivity analysis for healthy lifestyle score using AHA cut-offs as well as sensitivity analysis for sedentary lifestyle excluding participants with an event within the first two years of follow-up did not materially change the results (Supplementary Table 9 & 10).
Discussion

In this large study of more than 277,000 individuals, we observed that unhealthy lifestyle and genetic susceptibility to high BP were associated with higher levels of BP and a greater risk of subsequent incident CVD events (11% higher risk of incident CVD per unit increase of genetic risk). The favorable association of lifestyle with BP and CVD was found across all genetic risk categories, suggesting that the genetically predetermined rise in BP and its complications can be offset at least to some extent by healthy lifestyle. Our results further support population-wide efforts to lower BP and subsequent CVD risk through lifestyle modification.

Consistent with a well-established causal effect of BP on cardiovascular disease\(^\text{27}\) and with a lifelong effect of BP variants on BP levels\(^1,26\), we confirmed that a genetic risk score with 314 BP-associated genetic variants is a strong predictor of CVD events including myocardial infarction and stroke. The association was independent of lifestyle risk factors related to BP and CVD. Indeed, BP is measured with large measurement error due to BP variability whereas BP genotypes can be precisely measured, are constant over time, and therefore capture a fixed component of lifetime BP exposure. Evidence from other areas have shown that, for example, genetic risk scores using lipid or diabetes mellitus genetic variants predict CVD and diabetes mellitus, respectively, more consistently over time than standard clinical biomarkers\(^\text{27, 28}\).

We showed that the detrimental effect of genes on BP and on subsequent CVD risk can be largely offset by a healthy lifestyle in support of previous observations on CVD and obesity\(^\text{29, 30}\). This observation challenges the deterministic interpretation of the genetic risk in individual-based risk assessment. Genetic risk can be known from birth whereas the other conventional CVD risk factors usually appear in midlife and given that genetic risk is non-modifiable, it is aligned with lifelong risk prediction. Our observations raise the possibility of targeting individuals at high genetic risk early in life for lifestyle or pharmacological modification and primordial prevention strategies\(^\text{31}\). Yet, more evidence is needed on the effect of disclosing
genetic information to individuals and risk communication in order to find the most appropriate means to achieve risk modification through lifestyle.

Our study has several strengths including a large sample size and large number of incident CVD events, up to ~8 years follow-up, and rich baseline phenotyping according to a well-defined and standardized protocol. We utilized an updated genetic risk score for BP using latest published results including data on 314 validated BP loci. Limitations include the fact that lifestyle is poorly measured in contradistinction to the genetic information, such that the associations between lifestyle outcome measures may have been underestimated (regression dilution). Also, we limited our analyses to food frequency questionnaire data that lacked information on dairy products, energy intake, and fat consumption. In addition, lifestyle may be influenced by pre-existing conditions and our results may therefore be subject to reverse causality. To account for these limitations, we excluded individuals with a history of CVD and performed sensitivity analyses excluding individuals on treatment for CVD risk factors.

**Conclusion**

In our study of 277,005 individuals, we showed that a healthy lifestyle is associated with low BP levels and a lower risk of subsequent cardiovascular events (i.e. CVD, MI, and stroke) within each category of BP genetic profile. A high genetic risk was largely offset by a favorable lifestyle but also people with low genetic risk could lose their inherent protection if they had an unhealthy lifestyle. While it is possible to modify lifestyle, it is not possible to alter the genetic makeup stressing the importance of population-wide lifestyle approaches to address the pressing BP problem. Our findings highlight the need for timely lifestyle interventions to offset the lifetime risk of future high BP and CVD. Given the importance of population wide lifestyle modification the use of genetic information for risk stratification merits careful evaluation before it is routinely implemented in clinical practice.
Funding sources

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Disclosures

None
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Figure Legends

Figure 1. Cumulative hazard rates according to genetic and lifestyle risk tertiles in the UK Biobank study. The graphs compare different tertiles of genetic risk and lifestyle risk for hazard of CVD (left hand panels), myocardial infarction (middle panels), and stroke (right hand panels) (see Supplementary Table 2 for definition of CVD). Cox regression models were adjusted for age, sex.

Figure 2. Predicted values and 95% CI of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the UK Biobank cohort according to genetic and lifestyle risk tertiles. Predicted values come from linear regression models adjusted for age and sex.

Figure 3. Risk of cardiovascular events (CVD), myocardial infarction (MI), stroke events in the UK Biobank cohort according to tertiles of genetic risk score (GRS) and lifestyle score. Low GRS corresponds to lowest tertile of the GRS. Favorable lifestyle corresponds to top tertile of lifestyle score. Adjusted HRs and 95% CI were derived from Cox regression models adjusted for age and sex.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All participants (N=277,005)</th>
<th>Males (N=124,884)</th>
<th>Females (N=152,121)</th>
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<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>56.3(8)</td>
<td>56.4(8.1)</td>
<td>56.3(7.9)</td>
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<td>Males, N (%)</td>
<td>124884(45)</td>
<td>NA(NA)</td>
<td>NA(NA)</td>
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<td>High blood pressure*, N, (%)</td>
<td>133786(52)</td>
<td>69098(59)</td>
<td>64688(46)</td>
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<td>Anti-hypertensive medication, N (%)</td>
<td>47438(17)</td>
<td>24332(19)</td>
<td>23106(15)</td>
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<td>Lipid treatment, N, (%)</td>
<td>35155(13)</td>
<td>20120(16)</td>
<td>15035(10)</td>
</tr>
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<td>Diabetes mellitus, diagnosed by doctor, N (%)</td>
<td>10958(4)</td>
<td>6462(5)</td>
<td>4496(3)</td>
</tr>
<tr>
<td>Body mass index mean (SD), kg/m²</td>
<td>27.2(4.7)</td>
<td>27.7(4.1)</td>
<td>26.8(5.1)</td>
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<tr>
<td>Sedentary lifestyle, mean (SD), hours/day</td>
<td>4.4(2.5)</td>
<td>4.9(2.7)</td>
<td>4(2.2)</td>
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<tr>
<td>Smoking, N (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Current</td>
<td>27788(10)</td>
<td>14797(12)</td>
<td>12991(9)</td>
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<tr>
<td>Past</td>
<td>138168(50)</td>
<td>65703(53)</td>
<td>72465(48)</td>
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<tr>
<td>Never</td>
<td>111049(40)</td>
<td>44384(36)</td>
<td>66665(44)</td>
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<td>Alcohol intake, mean (SD), gr/day</td>
<td>17.6(20.9)</td>
<td>25.5(25.5)</td>
<td>11.2(12.9)</td>
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<tr>
<td>Fruit pieces (dry or fresh) daily consumption, mean (SD)</td>
<td>4.8(3.2)</td>
<td>4.5(3.2)</td>
<td>5(3.1)</td>
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<tr>
<td>Vegetable (cooked or raw) consumption, mean (SD)</td>
<td>3(2.5)</td>
<td>2.6(2.5)</td>
<td>3.3(2.5)</td>
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<td>Unprocessed meat consumption frequency, mean (SD)</td>
<td>3.7(1.7)</td>
<td>3.9(1.7)</td>
<td>3.5(1.8)</td>
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<td>Processed meat consumption frequency, mean (SD)</td>
<td>1.9(1.1)</td>
<td>2.2(1)</td>
<td>1.6(1)</td>
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<td>Fish consumption, mean (SD)</td>
<td>3.4(1.4)</td>
<td>3.4(1.4)</td>
<td>3.5(1.4)</td>
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<td>Healthy (DASH) diet score, median[IQR]</td>
<td>3[2.3]</td>
<td>2[2.3]</td>
<td>3[2.4]</td>
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<td>Healthy lifestyle score- mean (SD)</td>
<td>6.1(2.2)</td>
<td>5.3(2.1)</td>
<td>6.8(2.1)</td>
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<td>Genetic risk category- mean (SD)</td>
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<td>Systolic blood pressure, mean (SD), mmHg</td>
<td>140.5(20.5)</td>
<td>144.2(19.3)</td>
<td>137.4(21)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------------</td>
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<td>-----------</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mmHg</td>
<td>84.1(11.2)</td>
<td>86.4(11)</td>
<td>82.2(11)</td>
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</table>

Incident outcomes (non-fatal and fatal)

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
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<tr>
<td>Composite Cardiovascular Disease</td>
<td>9278(3.3)</td>
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<tr>
<td>Myocardial Infarction, N (%)</td>
<td>2984(1.1)</td>
</tr>
<tr>
<td>Stroke, N (%)</td>
<td>1919(0.7)</td>
</tr>
</tbody>
</table>

*Systolic blood pressure >140 or diastolic blood pressure >90 or the use of anti-hypertensive medication. SD: standard deviation; IQR: Inter-quintile range.