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A novel healthy blood pressure phenotype in the Long Life Family Study

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Abstract

Background—Hypertension tends to run in families and has both genetic and environmental determinants. We assessed the hypothesis that a novel healthy blood pressure (BP) phenotype is also familial and sought to identify its associated factors.

Methods—We developed a healthy BP phenotype in the Long Life Family Study, a cohort of two-generation families selected for longevity. Participants from the offspring generation ($n =$

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Conflicts of interest

There are no conflicts of interest.

2211, ages 32–88) were classified as having healthy BP if their age-adjusted and sex-adjusted SBP z-score was between -1.5 and -0.5 . Offspring on antihypertensive medications were classified as not having healthy BP. Families with at least two offspring ($n = 419$ families) were defined as meeting the healthy BP phenotype if at least two and at least 50% of their offspring had healthy BP.

Results—Among 2211 offspring, 476 (21.5%) met the healthy BP phenotype. When examining the 419 families, only 44 (10.5%) families met the criteria for the healthy BP phenotype. Both offspring and probands from families with healthy BP performed better on neuropsychological tests that place demands on complex attention and executive function when compared with offspring and probands from remaining families. Among families with the healthy BP phenotype compared with families without, a higher proportion of offspring met the American Heart Association definition of ideal cardiovascular health (10.8 versus 3.8%, respectively; driven by BP, smoking status, and BMI components).

Conclusion—In this cohort of familial longevity, few families had a novel healthy BP phenotype in multiple members. Families with this healthy BP phenotype may represent a specific pathway to familial longevity.

Keywords

aging; familial longevity; healthy blood pressure

INTRODUCTION

Hypertension is familial with known genetic and environmental determinants [1]. The prevalence of hypertension among American older adults (aged ≥ 60) is 65% [2], with the prevalence increasing with age [3,4]. The Framingham Heart Study estimated a 90% life time risk of developing hypertension for those normotensive at age 55 [5]. Clinical research on blood pressure (BP) is generally focused on hypertension and treatment to reduce BP [6,7]. The American Heart Association has begun shifting its focus to promoting cardiovascular health and disease prevention [8]. To address the American Heart Association goals, the focus of research on hypertension should be shifted to the factors contributing to healthy BP [9]. Not becoming hypertensive, that is, having healthy untreated BP throughout old age, is a rare phenotype [10] that may have unique determinants that influence health and longevity.

The Long Life Family Study (LLFS) recruited long-lived individuals and their siblings, offspring, and siblings' offspring. Such a cohort, where families were selected for longevity, may be useful in: identifying a healthy BP phenotype, examining whether healthy BP is familial, and determining its environmental and behavioral associations. It has been shown that LLFS participants are healthier than other older adult cohorts; specifically they perform better on physical function tests and have fewer cardiovascular risk factors [11]. Participants in the LLFS proband generation also have a delayed onset of aging-related diseases [12]. Typically, SBP increases with age and has been shown to be a stronger predictor of age-related outcomes than DBP or pulse pressure [13–15]. Thus, individuals with BP, especially SBP, that is healthier than expected for their age may represent an endophenotype explaining

a biological pathway, influencing health and longevity in the LLFS cohort. Families with this phenotype might have novel genetic variants or shared environments that promote longevity.

We previously developed a healthy memory phenotype in the LLFS [16]. Similarly, in this report, we used SBP to classify participants in the offspring generation of the LLFS as having healthy BP to identify families with exceptional cardiovascular health. Our specific aims were to assess the hypothesis that healthy BP is common in LLFS families and to examine whether families with healthy BP are healthier in other domains when compared with remaining LLFS families.

METHODS

The Long Life Family Study

The LLFS recruited families demonstrating clustering for longevity, with the objective to examine familial and non-familial environmental, behavioral, and genetic determinants of healthy aging and exceptional survival. Families were recruited from four centers; three in the United States: Boston, New York, and Pittsburgh, and one in Denmark. Family eligibility criteria were: first, long-lived individual (proband) aged at least 90, second, at least one enrolled sibling of the proband, third, at least one enrolled offspring of either the proband or their sibling(s), and fourth, the proband generation demonstrated clustering of exceptional survival (Family Longevity Selection Score [17] = 7). The LLFS protocol was approved by the Human Research Protection Office of the coordinating center at Washington University, the Regional Scientific Ethical Committees for Southern Denmark, and the institutional review boards at the University of Pittsburgh, Boston University, and Columbia University. More information on study recruitment has been published elsewhere [11]. All participants provided informed consent.

The LLFS cohort is primarily white (>99%) and includes two generations: the proband generation and the offspring generation. The proband generation includes the proband and many of their siblings. The offspring generation includes as many offspring of participants in the proband generation as possible. The LLFS also recruited as many spouses as possible from both generations, but information from these participants was not included in this analysis. Among the offspring, there were 86 excluded from the analysis because they were missing SBP. Families included in the analysis had at least two offspring in the study. Thus, the analysis sample size was 419 families comprised of 2211 offspring and 1164 probands.

Examination

The initial phenotypic data and blood sample collection were performed in the participant's home near the time of enrollment which occurred during 2006–2009. The in-home visit measured BP as an average of three measurements while the participant was sitting with their feet flat on the floor and conversation kept to a minimum (BpTRU blood pressure monitor 300; VSM MedTech, Coquitlam, British Columbia, Canada). BP cuffs were applied to the upper right arm (or left if there was a medical reason) in a relaxed position at their side. Cuffs were available in five sizes: extra-large, large, regular, small, or child. If the

largest cuff did not fit the upper arm, BP was measured on the forearm. Technicians measuring BP went through a stringent certification procedure to minimize observer variations. If BP was out of the normal range, participants were advised to see their physician.

Participants self-reported sex, race, ethnicity, smoking status, and years of education. History or presence of disease(s) was based on a self-report of a physician's diagnosis. The category of heart disease included prior myocardial infarction and/or coronary artery bypass surgery; stroke included stroke or transient ischemic attack; and hypertension included SBP at least 140 mmHg, DBP at least 90 mmHg, or history of hypertension confirmed by the use of antihypertensive medication(s). Lung function was assessed by spirometry (EasyOne; ndd Medical Technologies, Andover, Massachusetts, USA) following American Thoracic Society guidelines. Gait speed [18] and grip strength were determined with standardized measures. The Activities of Daily Living Questionnaire was also administered. Participants were asked to fast for at least 8 h prior to a blood draw (though phlebotomy was still performed if they did not fast). Glucose, total cholesterol, HDL and LDL cholesterol, triglycerides, creatinine, and cystatin C were measured in the blood by the LLFS central laboratory at the University of Minnesota. Glomerular filtration rate was estimated using the following equation [19]: $186.3 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if women})$.

Ideal cardiovascular health was classified using the American Heart Association definition [8]. A participant had ideal cardiovascular health if they met the following criteria: first, smoking status: never or quit >12 months ago; second, BMI less than 25 kg/m²; third, physical activity: at least 150 min/week of moderate intensity or at least 75 min/week of vigorous intensity, or a combination of both at least 150 min/week; fourth, untreated total cholesterol less than 200 mg/dl; fifth, untreated BP less than 120/80 mmHg; and sixth, untreated fasting plasma glucose less than 100 mg/dl. A diet consisting of fruits, vegetables, fish, fiber-rich whole grains, nuts, legumes, seeds, and minimal: sodium, sugar-sweetened beverages, processed meats, and saturated fats is also a component of this definition; however, these components of diet were not measured in the LLFS.

Cognition was assessed using the mini-mental state examination [20] (range: 0–30), and a battery of other cognitive tests. The digit symbol substitution test [21] measured information processing speed, working memory, and visuospatial scanning (range: 0–100). Semantic fluency (range: 0–154) was the sum of animals and vegetable fluency tests [22] (both tests range from 0 to 77), where participants named as many animals and vegetables as possible, respectively, in 60 s. Attention/working memory (range: 0–24) was the sum of digit span forward and backward [23] (both tests range from 0 to 12), where participants heard number sequences of increasing difficulty and were asked to repeat the sequences forward and backward, respectively. Episodic memory was assessed by participants' ability to recall a short passage immediately and 30 min after hearing the story (both tests range from 0 to 25) [23], where overall memory was the sum of the two (range: 0–50). Higher scores on all neuropsychological tests were favorable. Cognitive performance was also represented as a single measure in the form of an endophenotype (based on tests of animal and vegetable

recall, digit forward and backward, and immediate and delayed memory) developed using factor analysis by Singh *et al.* [24].

Healthy blood pressure phenotype

Individual-level healthy blood pressure phenotype—Measurements from participants in the offspring generation (ages 32–88) were used to develop a healthy BP phenotype. We initially defined a healthy BP phenotype using a simple cutoff of less than 120 mmHg SBP and less than 80 mmHg DBP, as in the American Heart Association definition of ideal BP, but we noted that this identified younger individuals and families. To identify individuals across a wide age range, we changed our approach to use SBP *z*-scores that were age-adjusted and sex-stratified. Offspring on antihypertensive medication ($n = 610$, 27.6%) were excluded and SBP from the remaining $n = 1601$ offspring was used to calculate the age-adjusted, sex-stratified SBP *z*-scores. Offspring were defined as meeting the individual-level healthy BP phenotype if their SBP *z*-score was between 1.5 and 0.5. In other words, if they had a SBP lower (better) than average for their age and sex, but not too low. Because both high and low BP is associated with poor health and adverse outcomes in older adults, offspring with an adjusted SBP *z*-score outside the range of -1.5 to -0.5 , or who were taking antihypertensive medication, were classified as not meeting the individual-level healthy BP phenotype.

Family-level healthy blood pressure phenotype—A family was defined as meeting the healthy BP phenotype if at least 2 and at least 50% of their offspring met the individual-level healthy BP phenotype. The healthy memory phenotype that was developed in the LLFS cohort [16] classified families as having healthy memory if they had at least two offspring with healthy memory. However, we were concerned that this definition may be biased toward selecting larger families. To address this issue when identifying families with healthy BP, we added a second criterion on to the definition that also required at least 50% of offspring in a family had healthy BP.

Statistical analysis—Distributions of all variables were assessed for normality. The distribution of SBP was confirmed to be normal in offspring who were not taking antihypertensive medication. Linear regression models of SBP on age, while stratifying by sex were applied using measurements from offspring who were not taking antihypertensive medication. The predicted SBP values and the standard error (SE) of prediction (root mean squared error) were used to calculate a SBP *z*-score for each offspring by subtracting their predicted value from their observed SBP and dividing by the respective sex-specific SE. This gave us a standardized value for each offspring describing how far their SBP deviated from the average for their sex and age.

Mean (SD) or frequency (%) were used to describe differences in demographic, health status, physical performance, and neuropsychological test performance measured at enrollment in offspring who met the individual-level healthy BP phenotype versus offspring who did not. Effect sizes were used to quantify the magnitude of the differences between offspring who met the healthy BP phenotype versus offspring who did not relative to the amount of variability among the two groups. An effect size is interpreted as a *z*-score from a

standard Normal distribution, thus, it illustrates how many SDs above or below the average individual among those who met the healthy BP phenotype is compared with the average individual among those who did not meet the healthy BP phenotype. Effect sizes were calculated using Cohen's *d* for continuous measures and phi coefficient for categorical measures. Differences in the two groups were tested using generalized estimating equations, which adjusted for relatedness of individuals and differences in family size. All differences, except for neuropsychological test performance, were also tested while additionally adjusting for age and sex. Differences in neuropsychological test performance were examined while adjusting for age and education instead. The same descriptive statistics and tests were performed when comparing offspring and probands from families with the healthy BP phenotype versus offspring and probands, respectively, from remaining families. As a sensitivity analysis, we compared results using our adjusted *z*-score approach to the results using a simpler approach of a standard BP cutoff of 120/80 mmHg.

RESULTS

Individual-level healthy blood pressure phenotype

Out of the 1601 offspring who were not on antihypertensive medication, 476 had a SBP *z*-score between -1.5 and -0.5 , thus meeting the individual-level healthy BP phenotype. Figure 1 shows the actual SBP for an adjusted *z*-score between -1.5 and -0.5 versus age for men and women and the equations used to calculate the *z*-scores. For a *z*-score between -1.5 and -0.5 for less than 55 years of age, the range of observed SBP was 91–112 mmHg for women and 94–116 mmHg for men and for 75 and older observed SBP ranged from 118–138 mmHg for women and 118–132 mmHg for men. The 610 offspring on antihypertensive medication were classified as not meeting the individual-level healthy BP phenotype.

Comparisons of offspring who met the individual-level healthy BP phenotype versus offspring who did not are listed in Tables 1–4. Offspring with healthy BP had a slightly younger average (SD) age when compared with remaining offspring [59.5 (7.8) and 60.8 (8.4), respectively] and were more highly educated. Adjusting for age and sex, offspring with healthy BP had significantly lower average BMI, fasting glucose, triglycerides, and cystatin C; and significantly higher HDL cholesterol, forced vital capacity, ankle-arm index, and gait speed. In addition, they presented with a significantly (adjusting for age and sex) smaller proportion of heart disease, stroke, diabetes, and taking lipid-lowering medication when compared with offspring who did not meet the individual-level healthy BP phenotype. Offspring with healthy BP had an average grip strength that was slightly less than remaining offspring [31.6 kg (11.2) and 32.5 kg (11.4), respectively].

Among those who met the individual-level healthy BP phenotype, 13.4% (16.4% for those ages 40–59 and 10.2% for those ages ≥ 60) also met the American Heart Association definition of ideal cardiovascular health for the six measured components; whereas among those who did not meet the individual-level healthy BP phenotype, only 1.8% (3.3% for those ages 40–59 and 0.5% for those ages ≥ 60) had ideal cardiovascular health. This difference was driven by a higher proportion of offspring meeting the American Heart Association ideal definition of BP, BMI, cholesterol, and fasting glucose among those who met the individual-level healthy BP phenotype versus those who did not.

Offspring who met the individual-level healthy BP phenotype also performed modestly (but significantly) better on most neuropsychological tests: overall episodic memory and semantic fluency were 1.5 and 1.7 points higher, respectively, than remaining offspring (Table 4). Offspring who met the individual-level healthy BP phenotype had an average cognitive endophenotype score that was 0.39 SDs better than offspring who did not meet the individual-level phenotype.

Family-level healthy blood pressure phenotype

There were 44 (10.5%) families (195 offspring and 112 probands) with healthy BP because they had at least 2 and at least 50% of their offspring meeting the individual-level healthy BP phenotype (Fig. 2). The remaining 375 families (2016 offspring and 1052 probands) were defined as not having healthy BP.

Offspring from the 44 families with the healthy BP phenotype tended to be healthier on some measures than offspring from the 375 remaining families (Tables 5–8). Adjusting for age and sex, offspring from families with healthy BP had a significantly lower average BMI when compared with offspring from remaining families. There were 7% more offspring who met the American Heart Association definition of ideal cardiovascular health among families with healthy BP versus remaining families, where the difference was driven by BP, smoking, and BMI. On average, offspring from families with healthy BP performed 0.37, 0.29, and 0.23 SDs higher than offspring from remaining families on the digit symbol substitution test, attention/working memory, and semantic fluency, respectively (average differences of 4.6, 1.2, and 2.1 points, respectively).

Probands from the 44 families with healthy BP also tended to be healthier on some measures compared with probands from remaining families (Tables 5–8). Adjusting for age and sex, probands from families with healthy BP had a better average HDL cholesterol and healthy aging index [25] score when compared with probands from remaining families. Even though families were not selected based on proband BP, probands from families with the healthy BP phenotype had lower BP and less hypertension. Probands from families with healthy BP had an average SBP and DBP that was 5.4 and 2.2 mmHg lower, respectively, and 12.2% fewer with hypertension than probands from families without the healthy BP phenotype. Probands from families with healthy BP also performed better, on average, on all neuropsychological tests, although only digit symbol substitution and digit span backward were statistically significant. On average, probands from families with healthy BP performed about a quarter of a SD higher on both the digit symbol substitution and the digit span backward than probands from remaining families.

Blood pressure of 120/80 mmHg versus our adjusted z-score approach

In a sensitivity analysis, we used the American Heart Association definition of ideal BP to develop the individual-level healthy BP phenotype. This method identified more of the younger individuals and families as having healthy BP when compared with our adjusted z-score approach (Supplementary Fig. 1, <http://links.lww.com/HJH/A828>). The adjusted z-score approach defined a more stringent healthy BP for women 63 and younger and for men 59 and younger than the American Heart Association definition of ideal BP (Fig. 1). Our

adjusted *z*-score approach also tended to select families with healthier probands. Though, patterns of associations between these two phenotype definitions and health factors were similar (Supplementary Tables 1 and 2, <http://links.lww.com/HJH/A828>).

DISCUSSION

We developed a healthy BP phenotype in the LLFS by classifying families as having healthy BP if they had at least two and at least 50% of their offspring with healthy BP. We found that healthy BP did not cluster greatly within families; only 10.5% ($n = 44$) of families met our criteria for healthy BP. Within these families, a higher proportion of offspring met the American Heart Association definition of ideal cardiovascular health when compared with offspring from remaining families (driven by BP, smoking status, and BMI components). Participants in the offspring and proband generation from families with healthy BP performed modestly, but significantly better on tests that measure multiple cognitive abilities, but also share a common reliance on aspects of executive function than offspring and probands from remaining families.

Notably, our adjusted *z*-score approach had a threshold of classifying participants with healthy BP that was less than 120 mmHg for women 63 and younger and for men 59 and younger. Although, the American Heart Association uses a single cutoff of 120 mmHg, the association of SBP and mortality is continuous with the nadir of risk at approximately 110 mmHg for adults without impaired function from the Atherosclerosis Risk in Communities study [26]. Conversely, LLFS offspring in their 80s would still be classified as having healthy BP if their SBP was above the American Heart Association cutoff of 120 mmHg, specifically they would be classified as having healthy BP if their SBP was around 115–140 mmHg. Our adjusted *z*-score approach also tended to identify families that had healthier probands, on average, than simpler methods. This gave us a multigenerational phenotype, that is, a phenotype that identified families that had healthy probands in addition to their offspring. Using our adjusted *z*-score approach to develop a phenotype based on relative health (rather than a simple cutoff identifying younger participants) that is also multigenerational may be more successful when it comes to identifying genetic variants associated with healthy BP. Our *z*-score approach did classify 50 offspring as meeting the individual-level healthy BP phenotype who had a DBP characterized as unhealthy (>80 mmHg) based on the American Heart Association definition, though the majority of these participants' DBP was marginally unhealthy (44/50 had a DBP between 80 and 85 mmHg). In addition, we want to emphasize our *z*-score approach was *not* intended to suggest BP targets with age, but instead was intended to identify individuals in the LLFS who had relatively healthy BP and LLFS families who had a clustering of members with healthy BP.

As LLFS families were selected for exceptional survival, we expected a high prevalence of a healthy aging phenotype, that is, healthy BP. We know not all populations experience an increase in BP with age. For example, remote populations with low sodium intake in the INTERSALT study had a 103 mmHg average SBP with little to no change with age [27]. Similarly, a longitudinal study of Tsiamane forager-farmers found a substantially smaller increase in BP with age when compared with the US population [28]. Protective environmental/behavioral factors, such as a protective diet, among multiple family members

in the LLFS cohort may be rare which may be why only a few families had multiple members with healthy BP.

The proportion of offspring who met the American Heart Association definition of ideal cardiovascular health among families with and without the healthy BP phenotype (10.8 and 3.8%, respectively) were both larger than the prevalence in the United States. The US prevalence of ideal cardiovascular health for at least six components is only 0.1% for those 60 and older and 2.9% for ages 40–59 [29]. The Atherosclerosis Risk in Communities study (44% men, all free of cardiovascular disease) reported 3.7 and 2.0% of their participants ages 40–54 and 55–64, respectively, had ideal cardiovascular health for at least six components [30]. Among participants from The Framingham Offspring Study (mean age = 58, 45% men) only 4.6% had ideal cardiovascular health for at least six components [31]. Other studies have reported similarly low proportions of ideal cardiovascular health [32]. LLFS probands (ages 71–110) also had a larger proportion who met the definition of ideal cardiovascular health than the prevalence in the US population 60 and older (1.4 and 0.1%, respectively), specifically, probands from families with healthy BP were more similar to the prevalence in the US population ages 40–59 (2.3 and 2.9%, respectively). By this metric, LLFS participants are quite a bit healthier than the US population, consistent with the study design [11].

Offspring and probands from families with healthy BP performed modestly, but significantly better on measures of psychomotor speed and aspects of executive functioning, including complex attention and working memory when compared with offspring from remaining families. In contrast, there was no significant difference in episodic memory across families. Consistent with this pattern of cognitive findings, previous studies have shown that hypertension is a risk factor for incident cognitive impairment and dementia, specifically declines in executive functioning and processing speed, whereas memory domains are less affected [33]. We also found that only a few LLFS families were classified as having both healthy BP and healthy memory according to the previously developed phenotype in the LLFS [16]. Differences in these two phenotypes may indicate that factors underlying healthy BP and healthy memory may not be on the same biological pathway influencing health and longevity.

Offspring who met the individual-level healthy BP phenotype were healthier in domains other than BP, such as: metabolic health, neuropsychological test performance, respiratory health, and gait speed, as well as they had a lower prevalence of heart disease, stroke, and diabetes. When examining differences among families, we found that families who met the healthy BP phenotype were not healthier on domains other than neuropsychological tests when compared with families who did not meet the healthy BP phenotype. This suggests healthy aging across multiple systems may not cluster within families and that LLFS families may have varying pathways to longevity. This is consistent with findings from other studies showing that there are different patterns of survival to older ages that involve different combinations of environmental and genetic exposures with resultant different combinations of subphenotypes [24,34].

A limitation of this analysis is it does not provide direction of causality for the association detected between families with healthy BP and better performance on tests of executive function. It is possible that individuals with better executive function are equipped with a set of cognitive skills that allow them to gather and evaluate information on their lifestyle and change their behavior and environment in response, thus resulting in a healthier and more stable BP as they age. Conversely, it is also possible that an individual's healthy and stable BP enables the necessary perfusion of prefrontal cortex and/or sub-cortical brain structures that contribute to the integrity of executive function. Future longitudinal assessments in this novel cohort study may provide information indicative of a potential direction of this association. In addition to the limitation of cross-sectional analysis, a second limitation is lack of specific indicators of vascular health such as carotid ultrasound at baseline, though this is currently being measured at follow-up. Lastly, the lack of dietary information and other important risk factors such as uric acid is also a limitation of the study.

In summary, we found that in this cohort of families with longevity, relatively few families had healthy BP in multiple family members. Families and individuals with healthy BP performed better on neuropsychological tests that place demands on complex attention and executive function and have a higher proportion with ideal cardiovascular health when compared with the US population. BP is potentially a key pathway for family longevity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BP	blood pressure
HDL	high-density lipoprotein
LLFS	Long Life Family Study
LDL	low-density lipoprotein
SE	standard error
SD	standard deviation

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FIGURE 1.

SBP versus age by sex and individual-level healthy blood pressure phenotype among participants in the offspring generation.

FIGURE 2.

Diagram comparing the proportion of offspring who met the individual-level healthy blood pressure phenotype and the proportion of offspring from families classified as having healthy blood pressure versus the total sample of offspring.

TABLE 1

Individual-level healthy blood pressure phenotype: comparing demographics of offspring with healthy blood pressure versus remaining offspring

Mean (SD) or number (%) (<i>n</i> if reduced sample)	Offspring who met the individual-level healthy blood pressure phenotype, <i>n</i> = 476	Offspring who did not meet the individual-level healthy blood pressure phenotype, <i>n</i> = 1735	Effect size ^d	Unadjusted <i>P</i> value	Adjusted* <i>P</i> value
Age	59.5 (7.8)	60.8 (8.4)	-0.16	0.003	0.003
Male	195 (41.0%)	756 (43.6%)	-0.02	0.37	0.36
White	476 (100%)	1732 (99.9%)	-0.02	0.99	–
Field center					
Boston	134 (28.2%)	463 (26.7%)	0.01	0.06	0.11
Denmark	111 (23.3%)	510 (29.4%)	-0.06		
Columbia	84 (17.7%)	298 (17.2%)	0.005		
Pittsburgh	147 (30.9%)	464 (26.7%)	0.04		
Education					
Less than high school	16 (3.4%) (<i>n</i> U 475)	120 (6.9%)	-0.06	0.002	0.006
High school or equivalency	27 (5.7%) (<i>n</i> U 475)	153 (8.8%)	-0.05		
More than high school	432 (91.0%) (<i>n</i> U 475)	1461 (84.3%)	0.08		
Height (mm)	1683 (95) (<i>n</i> = 475)	1682 (96) (<i>n</i> = 1729)	0.01	0.87	0.55
Weight (kg)	73.6 (14.9) (<i>n</i> U 473)	79.8 (16.9) (<i>n</i> U 1712)	-0.39	<0.0001	<0.0001

^aEffect size: Cohen's *d* for continuous measures: (mean1 – mean2/pooled SD) and phi coefficient for categorical measures: $\sqrt{\chi^2/n}$.* Adjusted for age and sex. Bold values indicate adjusted *P*-values < 0.05.

TABLE 2

Individual-level healthy blood pressure phenotype: comparing health status and physical performance among offspring with healthy blood pressure versus remaining offspring

Mean (SD) or number (%) (<i>n</i> if reduced sample)	Offspring who met the individual-level healthy blood pressure phenotype, <i>n</i> =476	Offspring who did not meet the individual-level healthy blood pressure phenotype, <i>n</i> =1735	Effect size ^d	Unadjusted <i>P</i> value	Adjusted* <i>P</i> value
Disease prevalence					
Heart disease		81 (4.7%)	-0.09	0.0006	0.002
Stroke	3 (0.6%)	52 (3.0%)	-0.05	0.02	0.04
Hypertension	3 (0.6%)	938 (54.1%)	-0.44	<0.0001	<0.0001
Diabetes	17 (3.6%)	107 (6.2%)	-0.05	0.03	0.08
Cancer	71 (14.9%)	292 (16.8%)	-0.02	0.33	0.67
Emphysema or chronic obstructive pulmonary disease	6 (1.3%) (<i>n</i> = 475)	35 (2.0%) (<i>n</i> = 1725)	-0.02	0.27	0.41
Peripheral artery disease	2 (0.4%)	13 (0.8%)	-0.02	0.45	0.53
Kidney disease	7 (1.5%) (<i>n</i> = 475)	28 (1.6%) (<i>n</i> = 1721)	-0.005	0.81	0.95
Lipid-lowering medication	43 (10.5%) (<i>n</i> = 408)	274 (18.2%) (<i>n</i> = 1503)	-0.08	0.0001	0.003
Markers of disease					
Smoking status					
Never smoked	270 (57.0%) (<i>n</i> = 474)	931 (54.0%) (<i>n</i> = 1724)	0.02		
Former smoker	163 (34.4%) (<i>n</i> = 474)	619 (35.9%) (<i>n</i> = 1724)	-0.01	0.45	0.44
Current smoker	41 (8.7%) (<i>n</i> = 474)	174 (10.1%) (<i>n</i> = 1724)	-0.02		
BMI (kg/m²)	25.9 (4.4) (<i>n</i> = 473)	28.1 (5.3) (<i>n</i> = 1706)	-0.46	<0.0001	<0.0001
Waist circumference (cm)	89.9 (13.1) (<i>n</i> = 464)	96.1 (14.5) (<i>n</i> = 1709)	-0.45	<0.0001	<0.0001
Fasting glucose (mmol/l)	5.03 (0.93) Median = 4.94 (<i>n</i> = 433)	5.30 (1.2) Median = 5.17 (<i>n</i> = 1516)	-0.26	<0.0001	<0.0001
Cholesterol (mmol/l)	11.4 (2.0) (<i>n</i> = 465)	11.5 (2.3) (<i>n</i> = 1662)	-0.04	0.43	0.32
HDL cholesterol (mmol/l)	3.49 (0.96) (<i>n</i> = 465)	3.33 (1.0) (<i>n</i> = 1661)	0.17	0.0009	0.0009
LDL cholesterol (mmol/l)	6.78 (1.7) (<i>n</i> = 458)	6.83 (2.0) (<i>n</i> = 1644)	-0.03	0.56	0.42

Mean (SD) or number (%) (n if reduced sample)	Offspring who met the individual-level blood pressure phenotype, n=476	Offspring who did not meet the individual-level healthy blood pressure phenotype, n=1735	Effect size ^a	Unadjusted P value	Adjusted [*] P value
Triglycerides (mmol/l)	5.70 (4.8) Median = 4.61 (n = 465)	6.63 (4.4) Median = 5.50 (n = 1662)	-0.20	<0.0001	<0.0001
Creatinine (mmol/l)	0.054 (0.01) Median = 0.053 (n = 465)	0.055 (0.02) Median = 0.053 (n = 1662)	-0.09	0.06	0.20
Cystatin C (mmol/l)	0.047 (0.01) Median = 0.048 (n = 464)	0.050 (0.02) Median = 0.046 (n = 1655)	-0.24	<0.0001	<0.0001
Estimated glomerular filtration rate	74.2 (15.4) (n = 465)	73.4 (15.1) (n = 1662)	0.05	0.29	0.63
Forced vital capacity (l)	3.64 (0.94) (n = 456)	3.51 (0.94) (n = 1666)	0.13	0.03	0.003
Forced expiratory volume in 1 s (l)	2.81 (0.75) (n = 456)	2.74 (0.77) (n = 1666)	0.09	0.11	0.08
Ankle-arm index	1.22 (0.13) (n = 355)	1.20 (0.13) (n = 1167)	0.18	0.002	0.002
Difficulty with 1 activities of daily living	11 (2.6%) (n = 427)	66 (4.2%) (n = 1590)	-0.03	0.14	0.26
Healthy aging index [25]	1.36 (1.2) (n = 380)	2.95 (1.6) (n = 1322)	-1.10	<0.0001	<0.0001
Ideal cardiovascular health [8]	57 (13.4%) (n = 425)	27 (1.8%) (n = 1483)	0.24	<0.0001	<0.0001
Physical performance					
Gait speed (m/s)	1.20 (0.22) (n = 474)	1.16 (0.22) (n = 1715)	0.17	0.001	0.01
Average grip (kg)	31.6 (11.2) (n = 475)	32.5 (11.4) (n = 1728)	-0.08	0.15	0.006

^aEffect size: Cohen's d for continuous measures: (mean | - mean| - pooled SD) and phi coefficient for categorical measures: $\sqrt{\chi^2/n}$.

* Adjusted for age and sex. Bold values indicate adjusted P-values < 0.05.

TABLE 3

Individual-level healthy blood pressure phenotype: comparing blood pressure measures among offspring with healthy blood pressure versus remaining offspring

Mean (SD) or number (%) (<i>n</i> if reduced sample)	Offspring who met the individual-level healthy blood pressure phenotype, <i>n</i> = 476	Offspring who did not meet the individual-level healthy blood pressure phenotype, <i>n</i> = 1735	Effect size ^d	Unadjusted <i>P</i> value	Adjusted* <i>P</i> value
SBP (mmHg)	110.5 (7.2)	132.8 (19.1)	-1.55	<0.0001	<0.0001
DBP (mmHg)	71.4 (6.5)	81.1 (10.7)	-1.10	<0.0001	<0.0001
Antihypertensive medication	0 (<i>n</i> = 408)	610 (40.6%) (<i>n</i> = 1503)	-0.36	-	-

^dEffect size: Cohen's *d* for continuous measures: (mean1 - mean2/pooled SD) and phi coefficient for categorical measures: $\sqrt{(\chi^2/n)}$

* Adjusted for age and sex. Bold values indicate adjusted *P*-values < 0.05.

Individual-level healthy blood pressure phenotype: comparing neuropsychological test performance among offspring with healthy blood pressure versus remaining offspring

TABLE 4

Mean (SD) or number (%) (<i>n</i> if reduced sample)	Offspring who met the individual-level healthy blood pressure phenotype, <i>n</i> = 476	Offspring who did not meet the individual- level healthy blood pressure phenotype, <i>n</i> = 1735	Effect size ^d	Unadjusted <i>P</i> value	Adjusted* <i>P</i> value
Digit symbol substitution test	52.5 (12.4) (<i>n</i> = 439)	50.3 (12.4) (<i>n</i> = 1597)	0.18	0.001	0.07
Attention/working memory	15.9 (4.1) (<i>n</i> = 443)	15.3 (4.0) (<i>n</i> = 1621)	0.14	0.006	0.04
Digit span forward total	8.75 (2.2) (<i>n</i> = 445)	8.56 (2.2) (<i>n</i> = 1621)	0.09	0.09	0.27
Digit span backward total	7.11 (2.4) (<i>n</i> = 444)	6.73 (2.3) (<i>n</i> = 1621)	0.16	0.002	0.02
Mini-mental state exam score	28.9 (2.8) Median = 29.0 (<i>n</i> = 389)	28.9 (2.0) Median = 29.0 (<i>n</i> = 1414)	-0.03	0.55	0.28
Overall episodic memory	26.3 (7.3) (<i>n</i> = 443)	24.8 (7.9) (<i>n</i> = 1613)	0.19	0.0002	0.008
Logical memory IA-immediate total	13.7 (3.7) (<i>n</i> = 444)	13.1 (3.9) (<i>n</i> = 1618)	0.16	0.002	0.04
Logical memory IIA-delayed total	12.5 (3.9) (<i>n</i> = 443)	11.7 (4.3) (<i>n</i> = 1613)	0.21	0.0001	0.004
Semantic fluency	38.8 (8.8) (<i>n</i> = 446)	37.1 (8.6) (<i>n</i> = 1621)	0.20	0.0004	0.009
Category fluency-animals total	23.0 (5.8) (<i>n</i> = 446)	22.0 (5.7) (<i>n</i> = 1622)	0.17	0.004	0.05
Category fluency-vegetables total	15.9 (4.6) (<i>n</i> = 446)	15.0 (4.4) (<i>n</i> = 1621)	0.18	0.001	0.01
Cognitive endophenotype [24]	0.820 (2.4) (<i>n</i> = 384)	-0.172 (2.6) (<i>n</i> = 1374)	0.39	<0.0001	<0.0001

^dEffect size: Cohen's *d* for continuous measures: (mean1 - mean2/pooled SD) and phi coefficient for categorical measures: $\sqrt{(\chi^2/n)}$.

* Adjusted for age and education. Bold values indicate adjusted *P*-values < 0.05.

TABLE 5

Family comparison: comparing demographics of participants from families with healthy blood pressure versus remaining families

	Offspring from 44 families who met the healthy blood pressure phenotype, <i>n</i> = 195			Offspring from 375 families who did not meet the healthy blood pressure phenotype, <i>n</i> = 2016			Offspring comparison			Proband comparison		
	Mean (SD) or number (%) \ (<i>n</i> if reduced sample)	60.5 (8.5)	60.5 (8.3)	0.002	0.99	0.98	Effect size ^a	Unadjusted <i>P</i> value	Adjusted* <i>P</i> value	Probands from 44 families who met the healthy blood pressure phenotype, <i>n</i> = 112	Probands from 375 families who did not meet the healthy blood pressure phenotype, <i>n</i> = 1052	Proband comparison
Age												
Male												
White												
Field center												
Boston												
Denmark												
Columbia												
Pittsburgh												
Education												
Less than high school												
High school or equivalency												
More than high school												
Height (mm)												
Weight (kg)												

^aEffect size: Cohen's *d* for continuous measures: (mean1 – mean2/pooled SD) and phi coefficient for categorical measures: $\sqrt{\chi^2/n}$.* Adjusted for age and sex. Bold values indicate adjusted *P*-values < 0.05.

TABLE 6

Family comparison: comparing health status and physical performance among participants from families with healthy blood pressure versus remaining families

Mean (SD) or number (%) (<i>n</i> if reduced sample)	Offspring from 44 families who met the healthy blood pressure phenotype, <i>n</i> = 195	Offspring comparison			Probands from 44 families who met the healthy blood pressure phenotype, <i>n</i> = 112	Probands from 375 families who did not meet the healthy blood pressure phenotype, <i>n</i> = 1052	Proband comparison			
		Effect size ^d	Unadjusted P value	Adjusted* P value			Effect size ^d	Unadjusted P value	Adjusted* P value	
Disease prevalence										
Heart disease	4(2.1%)	80 (4.0%)	-0.03	0.19	0.17	13 (11.6%)	183 (17.4%) (<i>n</i> = 1051)	-0.05	0.14	0.12
Stroke	5 (2.6%)	52 (2.6%)	-0.0003	0.99	0.98	18 (16.1%)	174 (16.6%) (<i>n</i> = 1051)	-0.004	0.91	0.91
Hypertension	29 (15.0%)	912 (45.2%)	-0.17	<0.0001	<0.0001	61 (54.5%)	701 (66.7%) (n = 1051)	-0.08	0.01	0.02
Diabetes	13 (6.7%)	111 (5.5%)	0.01	0.49	0.52	7 (6.3%)	101 (9.6%) (<i>n</i> = 1051)	-0.03	0.39	0.37
Cancer	25 (12.8%)	338 (16.8%)	-0.03	0.19	0.19	40 (35.7%)	359 (34.2%) (<i>n</i> = 1051)	0.01	0.74	0.84
Emphysema or chronic obstructive pulmonary disease	3 (1.6%) (<i>n</i> = 193)	38 (1.9%) (<i>n</i> = 2007)	-0.007	0.79	0.80	6 (5.4%)	39 (3.7%) (<i>n</i> = 1050)	0.03	0.44	0.49
Peripheral artery disease	0	15 (0.7%)	-0.03	-	-	9 (8.0%)	125 (11.9%) (<i>n</i> = 1051)	-0.04	0.26	0.23
Kidney disease	1 (0.5%) (<i>n</i> = 193)	34 (1.7%) (<i>n</i> = 2003)	-0.03	0.23	0.21	2 (1.8%) (<i>n</i> = 111)	38 (3.6%) (<i>n</i> = 1050)	-0.03	0.32	0.31
Lipid-lowering medications	24 (13.6%) (<i>n</i> = 176)	293 (16.9%) (<i>n</i> = 1735)	-0.03	0.28	0.32	23 (21.1%) (<i>n</i> = 109)	179 (17.7%) (<i>n</i> = 1009)	0.03	0.41	0.42
Markers of disease										
Smoking status										
Never smoked	109 (56.2%) (<i>n</i> = 194)	1092 (54.5%) (<i>n</i> = 2004)	0.01	0.06	0.07	66 (58.9%)	675 (64.4%) (<i>n</i> = 1049)	-0.03	0.34	0.39
Former smoker	77 (39.7%) (<i>n</i> = 194)	705 (35.2%) (<i>n</i> = 2004)	0.03			42 (37.5%)	356 (33.9%) (<i>n</i> = 1049)	0.02		
Current smoker	8 (4.1%) (<i>n</i> = 194)	207 (10.3%) (<i>n</i> = 2004)	-0.06			4 (3.6%)	18 (1.7%) (<i>n</i> = 1049)	0.04		
BMI (kg/m2)	26.5 (4.5) (n = 195)	27.7 (5.2) (n = 1988)	-0.25	0.001	0.0009	26.0 (3.9) (<i>n</i> = 102)	26.0 (4.3) (<i>n</i> = 981)	0.004	0.98	0.88
Waist circumference (cm)	92.5 (14.4) (n = 190)	95.0 (14.5) (n = 1983)	-0.17	0.03	0.01	94.3 (10.2) (<i>n</i> = 104)	94.0(12.4) (<i>n</i> = 972)	0.02	0.87	0.99
Fasting glucose (mmol/l)	5.08 (1.0) Median = 5.00 (<i>n</i> = 174)	5.26 (1.1) Median = 5.11 (<i>n</i> = 1775)	-0.16	0.08	0.06	5.16 (0.84) Median = 5.00 (<i>n</i> = 99)	5.32 (1.2) Median = 5.11 (<i>n</i> = 907)	-0.15	0.15	0.14
Cholesterol (mmol/l)	11.4 (2.1) (<i>n</i> = 186)	11.4 (2.2) (<i>n</i> = 1941)	-0.02	0.83	0.85	10.4 (2.0) (<i>n</i> = 111)	10.5 (2.5) (<i>n</i> = 996)	-0.03	0.76	0.86

Mean (SD) or number (%) (<i>n</i> if reduced sample)	Offspring comparison			Proband comparison		
	Offspring from 375 families who did not meet the healthy blood pressure phenotype, <i>n</i> = 2016	Effect size ^a	Unadjusted P value	Adjusted [*] P value	Probands from 44 families who met the healthy blood pressure phenotype, <i>n</i> = 112	Probands from 375 families who did not meet the healthy blood pressure phenotype, <i>n</i> = 1052
HDL cholesterol (mmol/l)	3.46 (1.0) (<i>n</i> = 186)	0.10	0.17	0.15	3.33 (0.91) (n = 111)	3.09 (0.89) (n = 995)
LDL cholesterol (mmol/l)	6.74 (1.9) (<i>n</i> = 186)	-0.05	0.59	0.58	5.92 (1.6) (<i>n</i> = 111)	6.14 (2.0) (<i>n</i> = 987)
Triglycerides (mmol/l)	6.07 (3.4) Median = 5.17 (<i>n</i> = 186)	-0.10	0.18	0.20	5.74 (2.8) Median = 5.17 (<i>n</i> = 111)	6.18 (3.4) Median = 5.33 (<i>n</i> = 996)
Creatinine (mmol/l)	0.055 (0.01) Median = 0.054 (<i>n</i> = 186)	0.05	0.42	0.38	0.067 (0.02) Median = 0.062 (<i>n</i> = 111)	0.066 (0.02) Median = 0.061 (<i>n</i> = 996)
Cystatin C (mg/l)	0.048 (0.01) Median = 0.046 (n = 186)	-0.15	0.05	0.04	0.078 Median = 0.074 (0.02) (<i>n</i> = 110)	0.080 (0.03) Median = 0.074 (<i>n</i> = 992)
Estimated glomerular filtration rate	72.4 (14.2) (<i>n</i> = 186)	-0.09	0.28	0.15	56.9 (15.1) (<i>n</i> = 111)	58.3 (19.2) (<i>n</i> = 996)
Forced vital capacity (l)	3.60 (1.0) (<i>n</i> = 179)	0.06	0.55	0.64	2.32 (0.74) (<i>n</i> = 93)	2.23 (0.81) (<i>n</i> = 900)
Forced expiratory volume in 1 s (l)	2.76 (0.78) (<i>n</i> = 179)	0.01	0.96	0.80	1.69 (0.60) (<i>n</i> = 93)	1.64 (0.62) (<i>n</i> = 900)
Ankle-arm index	1.23 (0.12) (<i>n</i> = 158)	0.20	0.07	0.09	1.09 (0.15) (<i>n</i> = 76)	1.05 (0.22) (<i>n</i> = 619)
Difficulty 1 activities of daily living	5 (2.9%) (<i>n</i> = 172)	-0.01	0.49	0.52	43 (43.0%) (<i>n</i> = 100)	407 (41.6%) (<i>n</i> = 979)
Healthy aging index [25]	2.03 (1.7) (n = 143)	-0.37	<0.0001	0.0002	5.35 (1.7) (n = 78)	5.72 (1.8) (n = 766)
Ideal cardiovascular health [8]	18 (10.8%) (n = 167)	0.10	<0.0001	<0.0001	2 (2.3%) (<i>n</i> = 89)	11 (1.3%) (<i>n</i> = 835)
Physical performance:						
Gait speed (m/s)	1.19 (0.21) (<i>n</i> = 193)	0.12	0.12	0.14	0.744 (0.27) (<i>n</i> = 105)	0.716 (0.26) (<i>n</i> = 966)
Average grip (kg)	32.7 (11.8) (<i>n</i> = 194)	0.04	0.67	0.95	19.4 (7.5) (<i>n</i> = 107)	19.4 (8.1) (<i>n</i> = 1014)

^aEffect size: Cohen's *d* for continuous measures: (mean1 - mean2/pooledSD) and phi coefficient for categorical measures: $\sqrt{\left(\chi^2/n\right)}$.

^{*} Adjusted for age and sex. Bold values indicate adjusted *P*-values < 0.05.

Family comparison: comparing blood pressure measures among participants from families with healthy blood pressure versus remaining families

TABLE 7

Mean (SD) or number (%) (<i>n</i> if reduced sample)	Offspring comparison		Proband comparison	
	Offspring from 44 families who met the healthy blood pressure phenotype, <i>n</i> = 195	Offspring from 375 families who did not meet the healthy blood pressure phenotype, <i>n</i> = 2016	Probands from 44 families who met the healthy blood pressure phenotype, <i>n</i> = 112	Probands from 375 families who did not meet the healthy blood pressure phenotype, <i>n</i> = 1052
SBP (mmHg)	117.3 (13.6)	129.0 (19.7)	133.7 (21.7) (<i>n</i> = 109)	139.1 (26.0) (<i>n</i> = 1031)
DBP (mmHg)	74.5 (8.1)	79.4 (10.8)	71.4 (10.9) (<i>n</i> = 109)	73.6 (12.0) (<i>n</i> = 1030)
Antihypertensive medications	22 (12.5%) (<i>n</i> = 176)	588 (33.9%) (<i>n</i> = 1735)	<0.0001	<0.0001
			Effect size ^d	Effect size ^d
			Unadjusted <i>P</i> value	Unadjusted <i>P</i> value
			Adjusted* <i>P</i> value	Adjusted* <i>P</i> value
			0.01	0.02
			0.06	0.06
			0.11	0.11

^dEffect size: Cohen's *d* for continuous measures: (mean1 – mean2/pooledSD) and phi coefficient for categorical measures: $\sqrt{(\chi^2/n)}$.

* Adjusted for age and sex. Bold values indicate adjusted *P*-values < 0.05.

TABLE 8
Family comparison: comparing neuropsychological test performance among participants from families with healthy blood pressure versus remaining families

Mean (SD) or number (%) (n if reduced sample)	Offspring comparison:			Proband comparison:		
	Offspring from 44 families who met the healthy blood pressure phenotype, n = 195	Offspring from 375 families who did not meet the healthy blood pressure phenotype, n = 2016	Effect size ^d	Unadjusted P value	Adjusted* P value	Probands from 375 families who did not meet the healthy blood pressure phenotype, n = 1052
Digit symbol substitution test	54.9 (12.1) (n = 177)	50.3 (12.4) (n = 1859)	0.37	0.005	0.005	27.9 (12.4) (n = 744)
Attention/working memory	16.5 (3.9) (n = 181)	15.3 (4.0) (n = 1883)	0.29	0.01	0.02	12.6 (3.9) (n = 816)
Digit span forward total	9.08 (2.1) (n= 181)	8.55 (2.2) (n = 1885)	0.25	0.03	0.06	7.35 (2.2) (n= 825)
Digit span backward total	7.38 (2.3) (n = 181)	6.75 (2.3) (n = 1884)	0.27	0.009	0.02	5.22 (2.2) (n = 816)
Mini-mental state exam score	29.2 (1.3) Median = 30 (n = 161)	28.9 (2.3) Median = 29 (n = 1642)	0.15	0.02	0.03	25.8 (3.7) Median = 27 (n = 772)
Overall episodic memory	25.7 (6.9) (n = 180)	25.1 (7.9) (n= 1876)	0.08	0.34	0.57	14.2 (8.8) (n = 112)
Logical memory 1A-immediate total	13.5 (3.4) (n = 180)	13.2 (3.9) (n= 1882)	0.06	0.41	0.71	8.09 (4.5) (n= 789)
Logical memory 1A-delayed total	12.2 (3.9) (n = 180)	11.8 (4.3) (n= 1876)	0.08	0.31	0.49	6.02 (4.6) (n= 775)
Semantic fluency	39.4 (9.3) (n = 181)	37.3 (8.6) (n = 1886)	0.23	0.03	0.04	24.2 (7.8) (n = 821)
Category fluency-animals total	23.3 (6.4) (n= 181)	22.1 (5.6) (n= 1887)	0.18	0.11	0.12	14.2 (5.0) (n = 823)
Category fluency-vegetables total	16.1 (4.8) (n= 181)	15.1 (4.4) (n = 1886)	0.21	0.04	0.06	10.0 (3.9) (n = 821)
Cognitive endophenotype [24]	0.780 (2.2) (n = 154)	-0.026 (2.6) (n = 1604)	0.33	0.0006	0.0009	-0.222 (2.8) (n = 515)

^dEffect size: Cohen's *d* for continuous measures: (mean1 – mean2/pooledSD) and phi coefficient for categorical measures: $\sqrt{\chi^2/n}$.

* Adjusted for age and education. Bold values indicate adjusted *P*-values < 0.05.