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## Relationship between plasma plasminogen activator inhibitor-1 and hypertension in American Indians: findings from the Strong Heart Study

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### Abstract

**Objectives**—Deficient plasminogen activator inhibitor-1 (PAI-1) prevented hypertension in mice. Plasma PAI-1 was associated with hypertension in cross-sectional analyses, but the prospective association of PAI-1 with incident hypertension in large epidemiological studies is scarce.

**Methods**—Leveraging two longitudinal cohorts of American Indians in the Strong Heart Study (SHS,  $N = 1019$ ) and the Strong Heart Family Study (SHFS,  $N = 1502$ ), we examined the prospective association of plasma PAI-1 with incident hypertension by multivariate logistic regression, adjusting for age, sex, study site, smoking, drinking, dietary sodium, obesity, lipids, fasting glucose, kidney function, inflammation, and follow-up years. Family relatedness in the SHFS was accounted for using the GLIMMIX procedure. Plasma PAI-1 level at baseline was measured by immunoassay. All participants were free of hypertension, cardiovascular diseases, and chronic kidney disease at baseline.

**Results**—A total of 305 and 258 participants, respectively, from the SHS ( $57 \pm 7$  years) and the SHFS ( $33 \pm 13$  years) developed incident hypertension during follow-up. In the SHS, higher level of log-transformed PAI-1 was associated with 1.35-fold increased risk of hypertension [odds ratio (OR) (95% confidence interval): 1.35 (1.06–1.72)]. Analysis using categorical PAI-1 (in tertiles) showed that participants in the highest tertile ( $> 58$  ng/ml) had 63% increased risk for hypertension [OR = 1.63 (1.12–2.37)] compared with those in the lowest tertile ( $< 33$  ng/ml). This association

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#### Conflicts of interest

There are no conflicts of interest.

was confirmed in the SHFS with similar effect sizes [OR = 1.41 (1.11–1.81) for log-transformed PAI-1; OR = 1.64 (1.08–2.50) for categorical PAI-1: 58 vs. <33 ng/ml].

**Conclusion**—A higher level of plasma PAI-1 is significantly associated with hypertension in American Indians, independent of established risk factors. The potential causality warrants further investigation.

### Keywords

American Indians; hypertension; plasminogen activator inhibitor-1; prospective association; the Strong Heart Study

## INTRODUCTION

Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor mainly produced by endothelial cells, vascular smooth muscle cells, and hepatocytes [1]. In vascular tissue, PAI-1 promotes accumulation of extracellular matrix and regulates vascular remodeling and perivascular fibrosis [2]. In plasma, PAI-1 promotes clot formation, thereby contributing to myocardial infarction, stroke, and other cardiovascular diseases (CVD) [3]. Accumulating evidence suggests that PAI-1 may be implicated in the pathogenesis of hypertension [4]. For instance, recent experimental studies have demonstrated that PAI-1 deficiency prevented hypertension and vascular fibrosis in mice [2,5–7]. Associations of plasma PAI-1 with hypertension [8–14] and its related conditions, such as arterial stiffness [15] and atherosclerosis [16], have been reported in human studies. However, these results were largely derived from cross-sectional analyses and thus raising a question as to whether increased plasma PAI-1 is a cause or consequence or just an accompanied manifestation of hypertension. To date, we are aware of only one study investigating the prospective association of plasma PAI-1 with incident hypertension in the Framingham Offspring Study [17]. The prognostic effect of plasma PAI-1 on hypertension risk has not been well studied, and no study has investigated the possible role of PAI-1 in hypertension among American Indians, a minority group with high rates of CVD, diabetes, hypertension, and related conditions [18]. The goal of this study is to examine the prospective association of plasma PAI-1 with risk of hypertension in two longitudinal cohorts of American Indians participating in the Strong Heart Study (SHS) and the Strong Heart Family Study (SHFS).

## MATERIALS AND METHODS

### Study population

The SHS is a multicenter, population-based longitudinal study of CVD, diabetes, and associated risk factors in American Indians in tribes and communities residing in Arizona, North/South Dakota, and Oklahoma. The study design, survey methods, and laboratory techniques of SHS have been described previously [19]. Briefly, the SHS first clinical examination was conducted in 1989–1991 (Phase I) by enrolling 4549 tribal members aged 45–74 years. All surviving participants were re-examined in 1993–1995 (Phase II) and 1998–1999 (Phase III). The SHFS, a component of SHS, enrolled 3665 participants from 94 families of the original SHS cohort members in 2001–2003 (Phase IV). All living SHFS participants were re-examined in 2006–2009 (Phase V) and are currently being followed

through 2018. The SHS and SHFS protocols were approved by the Institutional Reviews Boards from the Indian Health Service and the participating institutions.

Figure 1 described the selection of study participants included in the current analysis. In the SHS, given that plasma PAI-1 was only available in Phase II, we studied 3638 participants who attended this clinical visit. Of these, 643 participants from one community were excluded due to withdraw of consent. Participants were further excluded if they met one or more of the following: missing plasma PAI-1 ( $N=289$ ); prevalent hypertension ( $N=1202$ ); overt CVD ( $N=109$ ); chronic kidney disease ( $N=205$ ); or loss of follow-up ( $N=171$ ). Our final data analysis in the SHS included a total of 1019 participants. In the SHFS, we excluded participants who withdrew their consent ( $N=874$ ), had no plasma PAI-1 data ( $N=89$ ), had prevalent hypertension ( $N=880$ ), CVD ( $N=19$ ) or chronic kidney disease ( $N=36$ ), also attended the SHS ( $N=67$ ), or lost to follow-up ( $N=198$ ). A total of 1502 participants were included in the final data analysis of the SHFS. We excluded participants with prevalent CVD or chronic kidney disease because they might have received medications that could affect blood pressure (BP) or plasma PAI-1 levels [20].

### Measurement of plasma plasminogen activator inhibitor-1

Plasma PAI-1 concentrations were measured using ELISA according to standard protocols as described previously [21]. All antibodies and reagents were obtained from the Center for Thrombosis and Vascular Research, University of Leuven, Belgium. The assay coefficient of variation was less than 5%.

### Definition of incident hypertension

BP was measured three times by trained staff using a standard mercury sphygmomanometer and a cuff of appropriate size according to a standard protocol [22], after the participants had been resting for at least 5 min. The first and fifth Korotkoff sounds were recorded as SBP and DBP. The mean of the last two measurements was used in statistical analyses. Hypertension was defined as SBP at least 140 mmHg and/or DBP at least 90 mmHg or under antihypertensive medications [22]. Incident hypertension was defined as participants who were free of hypertension at baseline but initiated antihypertensive medications during follow-up or had an SBP at least 140 mmHg or an DBP at least 90 mmHg in the last follow-up examination. Incident cases of hypertension were identified through follow-up of participants in examinations conducted in 1998–1999 (SHS, Phase III) or 2006–2009 (SHFS, Phase V) and verified by review of medical records as previously described [23].

### Assessment of hypertension risk factors

Cigarette smoking was classified as current smoking, past smoking, and never smoking. Current smoking was defined as having smoked at least 100 cigarettes in the entire life, having smoked cigarettes regularly, and smoking currently. Past smoking was defined as having smoked at least 100 cigarettes in the entire life, having smoked cigarettes regularly in the past, but not smoking currently. Never smoking was defined as never smoked or having smoked fewer than 100 cigarettes in the entire life. Alcohol consumption was classified as current drinkers, former drinkers, and never drinkers as previously described [24]. Current drinkers were those who had consumed any alcohol during the past year, former drinkers

had stopped consuming alcohol for at least 12 months, and never drinkers were those who reported never drinking alcohol in their life time. Dietary intake was assessed using a 24-h dietary recall in the SHS and a Block food frequency questionnaire and an American Indian supplemental foods questionnaire that collected data regarding reported 'usual' intake of 119 foods over the past year in SHFS [25]. Dietary sodium (mg/day) was extracted from the dietary records. Body weight (kg) and height (cm) were measured when participants wore light clothes and no shoes by trained staff. BMI was calculated by dividing weight in kilograms by the square of height in meters ( $\text{kg}/\text{m}^2$ ). Obesity was defined as a BMI at least  $30 \text{ kg}/\text{m}^2$ , and overweight was defined as a BMI over  $25 \text{ kg}/\text{m}^2$  but less than  $30 \text{ kg}/\text{m}^2$  [26]. Fasting glucose, serum creatinine, C-reactive protein, and blood lipids, including total cholesterol, triglycerides, LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C), were measured by standard laboratory methods [19]. Estimated glomerular filtration rate (eGFR) was estimated on the basis of serum creatinine by using the Modification of Diet in Renal Disease Study equation [27]. Chronic kidney disease was defined as an eGFR less than  $60 \text{ ml}/\text{min}$  per  $1.73\text{m}^2$ .

### Statistical analysis

Baseline characteristics were presented according to plasma PAI-1 levels in the SHS participants and the SHFS participants, respectively. PAI-1 levels were categorized into three levels in both cohorts – low: less than  $33 \text{ ng}/\text{ml}$ , intermediate:  $33\text{--}57 \text{ ng}/\text{ml}$ , and high: at least  $58 \text{ ng}/\text{ml}$  (in tertiles in the SHS participants). Log-transformation was applied to maximal normality of plasma PAI-1. A two-tailed *P* value less than 0.05 was considered statistically significant. All statistical analysis was conducted using SAS statistical software (version 9.4; Cary, North Carolina, USA).

### Analysis in the Strong Heart Study

To examine the prospective association between baseline plasma PAI-1 and incident hypertension, we constructed a multivariate logistic regression model, in which incident hypertension was the dependent variable and baseline plasma PAI-1 (continuous log-transformed PAI-1 or categorical PAI-1 levels in tertiles: low vs. intermediate vs. high) was the independent variable, adjusting for conventional risk factors, including age, sex, study site, current smoking, current drinking, dietary sodium, obesity, fasting glucose, LDL-C, HDL-C, eGFR, C-reactive protein at baseline as well as follow-up years. Missing data were imputed by multiple imputations using the Markov Chain Monte Carlo (MCMC) method.

### Replication in the Strong Heart Family Study

To confirm the prognostic role of plasma PAI-1 in predicting incident hypertension identified in the SHS, we constructed a similar multivariate logistic regression model in the SHFS. In this model, incident hypertension was the dependent variable and baseline plasma PAI-1 (continuous log-transformed PAI-1 or categorical PAI-1 levels as defined above: low vs. intermediate vs. high) was the independent variable, adjusting for age, sex, study site, current smoking, current drinking, dietary sodium, obesity, fasting glucose, LDL-C, HDL-C, eGFR, C-reactive protein, and follow-up years. Multiple imputations were conducted to impute missing data using the MCMC method. Family relatedness of study participants was accounted for using the GLIMMIX procedure implemented in SAS.

## Sensitivity analyses

To examine whether potential misclassification of incident hypertension influences our results, we considered more restrictive definitions of incident hypertension that included participants who initiated antihypertensive medications during follow-up or had an SBP at least 160 mmHg or an DBP at least 95 mmHg by the end of follow-up. To examine whether baseline BP affects the relationship between plasma PAI-1 and risk of hypertension, we additionally adjusted for baseline SBP. To examine whether diabetes affects our results, except for adjusting for fasting glucose in the above-described models, we also conducted separate analysis by excluding participants with prevalent diabetes at baseline. To examine whether plasma PAI-1 improves prediction performance over conventional risk factors, such as age, sex, smoking, drinking, dietary sodium, obesity, fasting glucose, LDL-C, HDL-C, eGFR, and C-reactive protein, we calculated and compared area under the receiver operating characteristic curves for two prediction models (conventional risk factors only vs. conventional risk factors plus log-transformed PAI-1) using logistic regression.

## RESULTS

### Baseline characteristics

Our analyses included 1019 SHS participants (mean age  $57 \pm 7$  years, 61% women) and 1502 SHFS participants (mean age  $33 \pm 13$  years, 62% women). The median levels of plasma PAI-1 in the two cohorts were similar [44 ng/ml [interquartile range (IQR): 29–68] in the SHS, 44 ng/ml (IQR: 26–69) in the SHFS]. Baseline characteristics of study participants in the two cohorts are shown in Tables 1 and 2, respectively. Participants with higher plasma PAI-1 had significantly higher BP at baseline than those with lower plasma PAI-1 in both cohorts (all  $P < 0.05$ ). Compared with participants with lower level of plasma PAI-1, those with higher plasma PAI-1 were older and had higher levels of BMI, fasting glucose, blood lipids, eGFR, and C-reactive protein in both cohorts (all  $P < 0.05$ ). No significant difference in dietary sodium or cigarette smoking was found across PAI-1 levels in both studies.

### Prospective association of plasma plasminogen activator inhibitor-1 with incident hypertension in the Strong Heart Study

Of the 1019 SHS participants, 305 developed new hypertension during a median 4.0 years of follow-up. The incidence density of hypertension was 75.1 per 1000 person-years. The prospective association of baseline plasma PAI-1 with incident hypertension in the SHS was shown in Table 3.

Logistic regression using log-transformed PAI-1 as a continuous variable showed that a higher level of plasma PAI-1 was significantly associated with an increased risk of hypertension [odds ratio (OR) = 1.35, 95% confidence interval (CI): 1.06–1.72,  $P = 0.014$ ], after adjusting for age, sex, study site, current smoking, current drinking, dietary sodium, obesity, fasting glucose, LDL-C, HDL-C, eGFR, C-reactive protein, and follow-up years. Results of logistic regression based on plasma PAI-1 tertiles (low vs. intermediate vs. high) detected an association in the same direction. Compared with participants with low PAI-1, those with intermediate and high PAI-1 had a 46% (OR = 1.46, 95% CI: 1.02–2.09,  $P =$

0.039) and 63% (OR = 1.63, 95% CI: 1.12–2.37,  $P = 0.011$ ) increased risk for developing hypertension, respectively.

### Results of replication in the Strong Heart Family Study

During a median 5.3 years of follow-up, 258 of the 1502 SHFS participants developed new hypertension. The incidence density of hypertension was 31.2 per 1000 person-years. The prospective association of baseline plasma PAI-1 with incident hypertension in SHFS participants was similar to that observed in SHS participants (Table 3).

After adjusting for age, sex, study site, current smoking, current drinking, dietary sodium, obesity, fasting glucose, LDL-C, HDL-C, eGFR, C-reactive protein, and follow-up years, logistic regression using log-transformed PAI-1 as the independent variable revealed a significant and positive association between plasma PAI-1 and risk of hypertension (OR = 1.41, 95% CI: 1.11–1.81,  $P = 0.007$ ). Logistic regression using categorical PAI-1 level (low vs. intermediate vs. high) as the independent variable found that participants with high PAI-1 had a 64% extra risk for developing hypertension (OR = 1.64, 95% CI: 1.07–2.50,  $P = 0.023$ ) but those with intermediate PAI-1 had a marginally increased risk for incident hypertension (OR = 1.37, 95% CI: 0.90–2.08) compared with those with low PAI-1.

### Results of sensitivity analysis

The use of more restrictive definitions for incident hypertension did not attenuate the observed association between plasma PAI-1 and hypertension risk. Specifically, the multivariate-adjusted ORs for hypertension restricted to individuals who initiated treatment during follow-up, or had a SBP at least 160 mmHg, or DBP at least 95 mmHg at the end of follow-up for higher log-transformed PAI-1 were 1.45 (95% CI: 1.09–1.94,  $P = 0.012$ ) in SHS participants and 1.40 (95% CI: 1.05–1.87,  $P = 0.023$ ) in SHFS participants (Supplementary Table S1, <http://links.lww.com/HJH/A769>). Additional adjustment for baseline SBP did not change the association between plasma PAI-1 and incident hypertension in both cohorts (Supplementary Table S2, <http://links.lww.com/HJH/A769>). Exclusion of participants with prevalent diabetes did not change the observed association between plasma PAI-1 and incident hypertension in SHFS participants, but results became statistically nonsignificant in SHS participants (Supplementary Table S3, <http://links.lww.com/HJH/A769>). Adding plasma PAI-1 to the prediction model did not significantly increase prediction performance for hypertension compared with the model including conventional risk factors only in either cohort (Supplementary Fig. S1, <http://links.lww.com/HJH/A769>).

## DISCUSSION

In two longitudinal cohorts of American Indians participating in the SHS (1993–1995) and the SHFS (2001–2003), we found that baseline plasma PAI-1 significantly predicted risk of hypertension, independent of many known risk factors. Specifically, a higher level of plasma PAI-1 was associated with over 35% increased risk of developing hypertension in this high-risk population. Our results suggest that plasma PAI-1 may contribute to the development of hypertension through pathways beyond traditional risk factors.

The observed association between plasma PAI-1 and incident hypertension in our study is in line with previous animal and human studies. For example, experimental research has demonstrated that PAI-1 deficiency induced by either *PAI-1* gene knockout [2,5,7] or pharmacological inhibition [6,7] was protective against the development of hypertension, cardiac hypertrophy, and vascular fibrosis in mice. In human study, individuals carrying the 4G allele of *PAI-1* gene exhibited a higher level of plasma PAI-1 than those carrying the 5G allele [28], and carrying two copies of the 4G allele was associated with higher SBP, DBP, and mean arterial BP in a population comprising 194 elderly women [29]. The association of plasma PAI-1 with BP or hypertension was also reported in several other cross-sectional and case-control epidemiological studies [8–14]. Although these studies clearly demonstrated an association between plasma PAI-1 and hypertension, the prospective relationship between plasma PAI-1 and incident hypertension in large, community-based longitudinal cohorts is still lacking. We are aware of only one prospective study examining the association of plasma PAI-1 with incident hypertension among 1456 European whites in the Framingham Offspring Study [17]. The authors reported that participants with higher level of plasma PAI-1 was associated with an increased risk of hypertension (OR = 1.28, 95% CI: 1.05– 1.57 for per SD increment). Our study confirms this association with similar effect size and provides initial evidence for a potential prognostic effect of plasma PAI-1 on hypertension risk in American Indians. The prospective relationship between plasma PAI-1 and incident hypertension was also in agreement with previous studies demonstrating that plasma PAI-1 significantly predicted risk of arterial stiffness [15], atherosclerosis [16], and cardiovascular events [3], all of which have been associated with hypertension.

Plasma PAI-1 was found to be associated with several risk factors of hypertension, such as obesity [30,31], insulin resistance [31,32], and inflammation [33]. However, the observed association between plasma PAI-1 and hypertension in our study was unlikely to be confounded by these chronic conditions because these factors were adjusted in our statistical models. Moreover, our sensitivity analysis indicated that the observed prospective association was robust to potential confounding by possible misclassification of incident hypertension and prevalent diabetes (at least in the SHFS). Although the mechanism underlying the relationship between PAI-1 and hypertension remains to be determined, it is possible that PAI-1 may affect hypertension risk through its effect on vascular remodeling [2], because overproduction of PAI-1 has been shown to accelerate perivascular and medial fibrosis through plasmin inhibition and inhibition of vascular smooth muscle cell migration in mice [34]. Vascular remodeling may increase peripheral resistance and reduced elasticity, which in turn contribute to risk for hypertension [35].

Although we identified that baseline plasma PAI-1 significantly predicted the risk of incident hypertension, it did not significantly increase the prediction performance over conventional risk factors. Thus, the clinical utility of PAI-1 in risk prediction for hypertension warrants further investigation. Despite that a number of PAI-1 inhibitors have been used to examine the pharmacological effect of PAI-1 inhibition *in vitro* and *in vivo* [36], large-scale clinical trials are clearly needed to evaluate the potential clinical utility of PAI-1 inhibitors in disease prevention or intervention.

To our knowledge, our study represents the first to examine the prospective association of plasma PAI-1 with incident hypertension in American Indians. The strengths of this study include replication in two longitudinal cohorts and comprehensive adjustments of many known risk factors including dietary sodium. However, our study also has several limitations. First, although our statistical analyses adjusted for many covariates, we cannot entirely exclude residual confounding by unknown and/or unmeasured factors. Second, all our study participants are American Indians whose cardiovascular health profiles may be different from those with other racial/ethnic backgrounds. Thus, the generalizability of our results to other populations is uncertain.

In summary, our study demonstrates that elevated plasma PAI-1 is significantly associated with an increased risk of future hypertension among American Indians independent of many known risk factors. More research is needed to establish the causality between PAI-1 and hypertension risk.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

<b>CVD</b>	cardiovascular diseases
<b>eGFR</b>	estimated glomerular filtration rate
<b>HDL-C</b>	HDL cholesterol
<b>IQR</b>	interquartile range
<b>LDL-C</b>	LDL cholesterol
<b>MCMC</b>	the Markov Chain Monte Carlo
<b>OR</b>	odds ratio
<b>PAI-1</b>	plasminogen activator inhibitor-1
<b>ROC</b>	the receiver operating characteristic
<b>SHFS</b>	the Strong Heart Family Study
<b>SHS</b>	the Strong Heart Study



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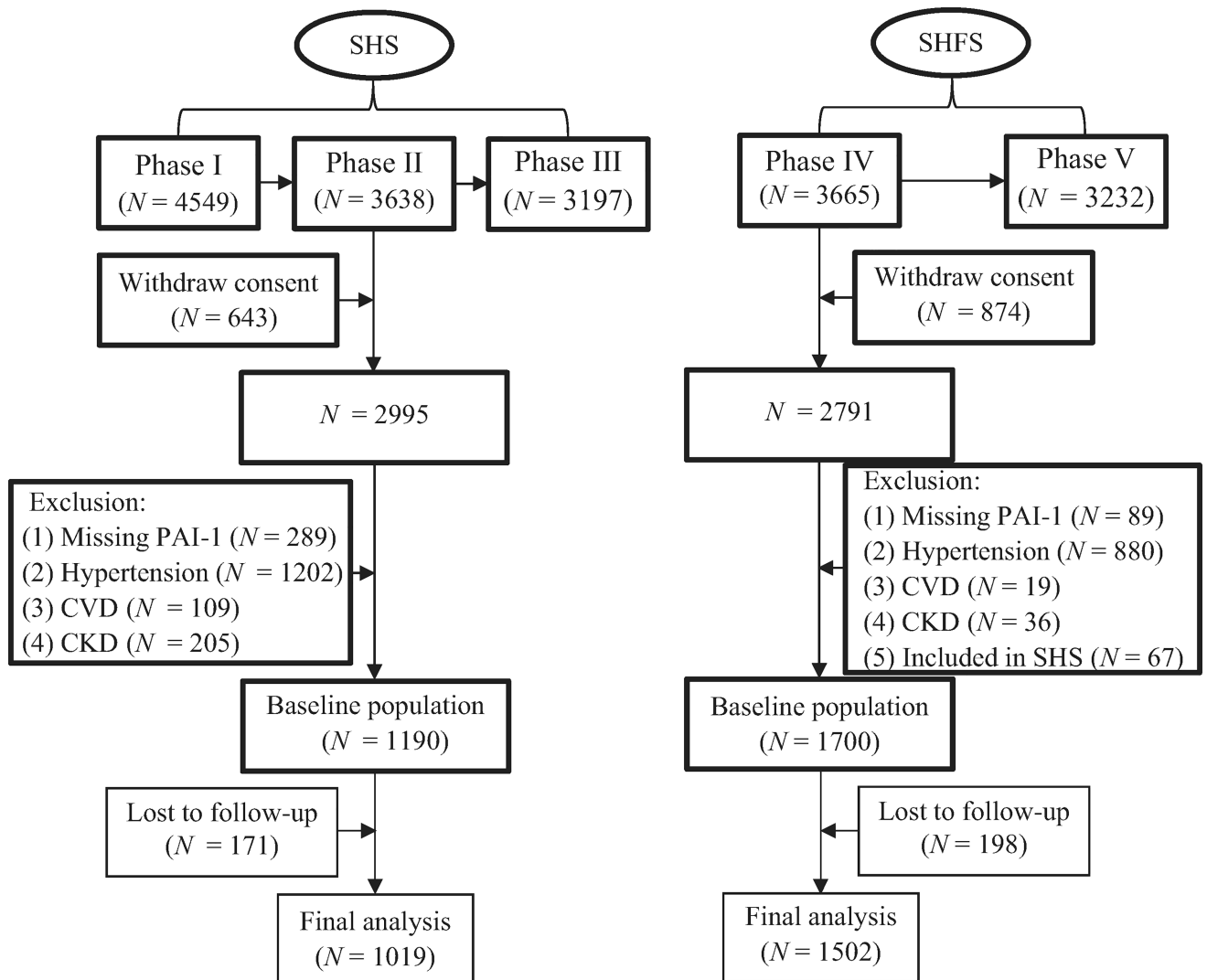
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**FIGURE 1.** Flowchart illustrating the selection of study participants. CKD, chronic kidney disease; CVD, cardiovascular disease; PAI-1, plasminogen activator inhibitor-1; SHFS, the Strong Heart Family Study; SHS, the Strong Heart Study.

TABLE 1

Baseline characteristics of the Strong Heart Study participants according to plasma plasminogen activator inhibitor-1 levels (1993–1995,  $N = 1019$ )

Characteristics	Level of plasma PAI-1 (ng/ml)			P value for linear trend
	Low (4–32)	Intermediate (33–57)	High (58–479)	
<i>N</i>	320	349	350	
Age (years)	56.6 ± 6.4	57.6 ± 7.0	58.6 ± 7.6	<0.001
Male [ <i>n</i> (%)]	147 (45.94)	133 (38.11)	117 (33.43)	0.001
Current smoking [ <i>n</i> (%)]	131 (40.94)	137 (39.26)	153 (43.71)	0.451
Current drinking [ <i>n</i> (%)]	116 (36.25)	112 (32.09)	129 (36.86)	0.840
Obesity [ <i>n</i> (%)]	100 (31.25)	184 (52.72)	217 (62)	<0.001
Dietary sodium (mg/day)	3084.5 ± 1635.2	3114.2 ± 1637.2	3222.3 ± 1709.4	0.293
SBP (mmHg)	115.7 ± 12.5	118.7 ± 11.4	119.1 ± 11.2	<0.001
DBP (mmHg)	70.3 ± 8.3	72.3 ± 7.5	71.8 ± 8.0	0.012
BMI (kg/m <sup>2</sup> )	28.1 ± 5.4	31.0 ± 5.9	31.7 ± 5.6	<0.001
Fasting plasma glucose (mg/dl)	122.3 ± 59.6	141.1 ± 72.0	149.2 ± 75.8	<0.001
Total cholesterol (mg/dl)	193.6 ± 38.6	194.3 ± 37.2	194.9 ± 37.0	0.657
Triglycerides (mg/dl)	125.5 ± 81.5	152.8 ± 107.5	176.6 ± 131.5	<0.001
LDL-cholesterol (mg/dl)	123.7 ± 34.2	124.9 ± 33.0	121.3 ± 31.2	0.362
HDL-cholesterol (mg/dl)	45.2 ± 14.7	40.5 ± 13.0	39.7 ± 12.4	<0.001
eGFR (ml/min per 1.73m <sup>2</sup> )	83.0 ± 21.2	85.4 ± 28.2	87.6 ± 28.1	0.022
C-reactive protein (mg/l)	4.0 ± 6.6	5.4 ± 5.3	7.7 ± 9.3	<0.001

Results were expressed as mean ± SD unless otherwise noted. eGFR, estimated glomerular filtration rate; PAI-1, plasminogen activator inhibitor-1.

TABLE 2

Baseline characteristics of the Strong Heart Family Study participants according to plasma plasminogen activator inhibitor-1 levels (2001–2003,  $N=1502$ )

Characteristics	Level of plasma PAI-1 (ng/ml)			<i>P</i> value for linear trend <sup>a</sup>
	Low (5–32)	Intermediate (33–57)	High (58–441)	
<i>N</i>	508	453	541	
Age (years)	31.9 ± 13.0	33.9 ± 13.0	33.6 ± 12.2	0.044
Male [ <i>n</i> (%)]	182 (35.83)	189 (41.72)	191 (35.30)	0.835
Current smoking [ <i>n</i> (%)]	175 (34.45)	182 (40.18)	239 (44.18)	0.002
Current drinking [ <i>n</i> (%)]	315 (62.01)	292 (64.46)	358 (66.17)	0.189
Obesity [ <i>n</i> (%)]	123 (24.21)	202 (44.59)	380 (70.24)	<0.001
Dietary sodium (mg/day)	3726.1 ± 3448.1	3993.2 ± 3593.7	3963.7 ± 4088.3	0.424
SBP (mmHg)	113.4 ± 10.9	116.0 ± 10.2	117.5 ± 10.5	<0.001
DBP (mmHg)	71.7 ± 9.4	73.7 ± 8.6	75.1 ± 8.7	<0.001
BMI (kg/m <sup>2</sup> )	26.6 ± 5.8	30.0 ± 6.8	34.1 ± 7.6	<0.001
Fasting plasma glucose (mg/dl)	94.0 ± 31.6	98.7 ± 33.4	109.2 ± 45.5	<0.001
Total cholesterol (mg/dl)	170.6 ± 30.1	177.6 ± 35.6	184.1 ± 36.6	<0.001
Triglycerides (mg/dl)	113.8 ± 59.5	136.7 ± 84.5	185.6 ± 139.1	<0.001
LDL-cholesterol (mg/dl)	91.7 ± 25.5	99.7 ± 30.0	101.5 ± 29.7	<0.001
HDL-cholesterol (mg/dl)	56.3 ± 14.9	51.1 ± 12.3	46.9 ± 13.0	<0.001
eGFR (ml/min per 1.73 m <sup>2</sup> )	101.5 ± 22.8	100.4 ± 22.8	104.3 ± 22.2	0.084
C-reactive protein (mg/l)	4.3 ± 8.0	5.4 ± 8.6	7.0 ± 7.9	<0.001

Results were expressed as mean ± SD unless otherwise noted. eGFR, estimated glomerular filtration rate; PAI-1, plasminogen activator inhibitor-1.

<sup>a</sup>Using generalized estimating equation models to account for family relatedness among study participants.

TABLE 3

Prospective association between plasma plasminogen activator inhibitor-1 and risk of hypertension in American Indians

Plasma PAI-1 (ng/ml)	No. of incident hypertension	Incidence density <sup>a</sup>	Multivariate adjusted <sup>b</sup>	
			OR (95% CI)	P value
SHS participants (N= 1019)				
Continuous				
Log-transformed PAI-1	305	75.1	1.35 (1.06–1.72)	0.014
Categorical				
Low (<33)	78	59.5	1.00 (reference)	–
Intermediate (33–57)	112	79.9	1.46 (1.02–2.09)	0.039
High ( 58)	115	85.3	1.63 (1.12–2.37)	0.011
SHFS participants (N= 1502)				
Continuous				
Log-transformed PAI-1	258	31.2	1.41 (1.11–1.81)	0.007
Categorical				
Low (<33)	58	20.6	1.00 (reference)	–
Intermediate (33–57)	81	32.5	1.37 (0.90–2.08)	0.133
High ( 58)	119	40.1	1.64 (1.08–2.50)	0.023

CI, confidence interval; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; SHFS, the Strong Heart Family Study; SHS, the Strong Heart Study.

<sup>a</sup>No. per 1000 person-years.

<sup>b</sup>Adjusting for age, sex, study site, current smoking, current drinking, dietary sodium, obesity, fasting glucose, LDL cholesterol and HDL cholesterol, estimated glomerular filtration rate, C-reactive protein, and follow-up years.