Prehypertension, Diabetes, and Cardiovascular Disease Risk in a Population-Based Sample
The Strong Heart Study

Ying Zhang, Elisa T. Lee, Richard B. Devereux, Jeunliang Yeh, Lyle G. Best, Richard R. Fabsitz, Barbara V. Howard

Abstract—There are few data about the impact of the recently-defined category of prehypertension (systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg) on cardiovascular disease incidence. It is also unknown whether this association differs between individuals with or without diabetes. A total of 2629 Strong Heart Study participants free from hypertension and cardiovascular disease at baseline examination were followed for 12 years to observe incident cardiovascular disease. Approximately 42% of the 2629 participants had diabetes. We assessed the prevalence of prehypertension and the hazard ratios of incident cardiovascular disease associated with prehypertension. Prehypertension was more prevalent in diabetic than nondiabetic participants (59.4% versus 48.2%, \( P < 0.001 \) adjusted for age). Compared with nondiabetic participants with normal blood pressure, the hazard ratios of cardiovascular disease were 3.70 (95% confidence interval: 2.66, 5.15) for those with both prehypertension and diabetes, 1.80 (1.28, 2.54) for those with prehypertension alone and 2.90 (2.03, 4.16) for those with diabetes alone. Impaired glucose tolerance or impaired fasting glucose also greatly increased the cardiovascular disease risk in prehypertensive people. Clinical investigation of more aggressive interventions, such as drug treatment for blood pressure control for prehypertensive individuals with impaired fasting glucose, impaired glucose tolerance, or diabetes is warranted. (Hypertension. 2006;47:410-414.)

Key Words: cardiovascular disease ■ cohort study ■ diabetes mellitus ■ prehypertension

Morbidity and mortality from cardiovascular disease are common in individuals with elevated blood pressure.1 According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7),2 prehypertension is defined as systolic blood pressure between 120 to 139 or diastolic blood pressure between 80 to 89 mm Hg. However, the relative risk of cardiovascular disease in individuals with prehypertension has not been thoroughly studied either in diabetic or nondiabetic adults, nor has the prevalence of prehypertension been established in diverse populations.

The aims of this observational study are: (1) to estimate the prevalence of prehypertension in a population with a high prevalence of diabetes and (2) to assess hazard ratios for cardiovascular disease with prehypertension in diabetic and nondiabetic individuals.

Methods

Study Population
The Strong Heart Study is a cohort study of cardiovascular disease in 13 American Indian tribes/communities conducted in southwestern Oklahoma, central Arizona, and North and South Dakota. Participants (n=4549) aged 45 to 74 years underwent baseline examination from 1989 to 1992. The design, survey methods, and laboratory techniques were described previously.3-8 After excluding those who were hypertensive or who had previous cardiovascular disease at baseline examination, there were 2629 participants in this analysis. Participants were followed for an average of 12.6 years by the end of 2001. The first quartile, the median, and the third quartile of follow-up are 9.0, 10.7, and 11.6 years. Indian Health Service Institutional Review Board, Institutional Review Boards of the participating institutions, and the participating tribes approved the study. Informed consent was obtained from all participants.

Measurements
During a personal interview, information was collected on demographic factors, medical history, medication use, and personal health habits (physical activity, smoking, alcohol consumption). A physical examination was conducted in the morning, which included collecting blood samples for laboratory tests and a 75-g oral glucose tolerance test. Anthropometric measurements were performed, and sitting blood pressure (first and fifth Korotkoff sounds) was measured 3 times consecutively using standard mercury sphygmomanometer (WA Baum Co) after 5 minutes rest.6 The average of the 2nd and 3rd systolic and diastolic blood pressure measurements were used in the analysis.
According to JNC 7 criteria,2 hypertension was defined as systolic blood pressure $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, or use of antihypertensive medication. Prehypertension was defined as systolic blood pressure between 120 to 139 mm Hg or diastolic blood pressure between 80 to 89 mm Hg. Normal blood pressure was defined as $<120/80$ mm Hg. According to the 1998 Provisional World Health Organization Report,7 diabetes was defined as use of an oral hypoglucose agent or insulin, fasting glucose $\geq 7.0$ mmol/L or postchallenge glucose $\geq 11.1$ mmol/L (75-g oral glucose tolerance test). Impaired glucose tolerance was defined as fasting glucose $<7.0$ mmol/L with postchallenge glucose between 7.8 to 11.0 mmol/L. Impaired fasting insulin, fasting glucose $<7.0$ mmol/L with postchallenge glucose $<7.8$ mmol/L. Normal glucose tolerance was defined as fasting glucose $<6.1$ mmol/L with postchallenge glucose $<7.8$ mmol/L.

Outcome Variables
Incident cardiovascular disease events included fatal and nonfatal cardiovascular disease events occurring between the baseline examination and December 31, 2001. Fatal cardiovascular disease events included fatal myocardial infarction, sudden death caused by coronary heart disease, other fatal coronary heart disease, and fatal stroke. Deaths occurring between baseline examination and December 31, 2001, were confirmed through tribal and Indian Health Service hospital records and through direct contact with participants’ families or other informants by study personnel, as reported previously.2,9 Nonfatal cardiovascular disease events included definite myocardial infarction, coronary heart disease, and stroke, either identified by participant contact and record review or at the 2nd Strong Heart Study examination in 1993 to 1995 and the 3rd Strong Heart Study examination in 1997 to 1999. During each examination, a 12-lead ECG and medical history, including the Rose Questionnaire for angina pectoris, were obtained. Medical records were reviewed to identify nonfatal cardiovascular disease between examinations until the end of 2001, as reported previously.2,8,9; mortality follow-up was 99.8% complete.

Statistical Methods
Baseline characteristics including age, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were presented as means (standard deviation) for diabetic and nondiabetic participants. The t test was used to compare means between the 2 groups. Triglycerides and physical activity were presented in quartile (first quartile, median, third quartile) and a nonparametric rank sum test was used to compare the distribution of these 2 variables between groups because of their skewed distribution. Proportions of prehypertension, smoking, alcohol use, and female gender are presented in diabetic and nondiabetic participants, and the $\chi^2$ test was used to compare the proportions between groups. Two-tailed $P<0.05$ was considered to be statistically significant.

The prevalence of prehypertension was presented by age group (45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74 years) and diabetes status. The Mantel-Haenszel $\chi^2$ test was used to compare prevalence of prehypertension in diabetic and nondiabetic individuals adjusted for age.

The incidence of cardiovascular disease was calculated by dividing the number of participants who had had cardiovascular disease events by the end of 2001 by the total number of person-years of follow-up for all eligible participants. Kaplan-Meier plots and the log-rank test were used to compare the cumulative incidence of cardiovascular disease among the following 4 groups: participants with diabetes and prehypertension, participants with diabetes alone or with prehypertension alone, and participants with neither diabetes nor prehypertension. The Cox proportional hazard model was used to compute the hazard ratios of cardiovascular disease among these 4 groups of participants. Hazard ratios for cardiovascular disease were also calculated for participants with impaired fasting glucose, impaired glucose tolerance, or diabetes, with or without the presence of prehypertension, and these hazard ratios were compared with participants with normal glucose tolerance and normal blood pressure. The trend analysis was done for cumulative incidence rate of cardiovascular disease associated with prehypertension and glucose metabolic status using $\chi^2$ test for trend. All Cox proportional hazard models were adjusted for potential confounders including baseline age, gender, body mass index, waist circumference, LDL cholesterol, HDL cholesterol, triglyceride, physical activity, smoking, and alcohol use.

Results
Baseline Characteristics
Baseline characteristics by diabetes status are given in Table 1. Participants with diabetes were older, had higher body mass index and waist circumference, higher systolic blood pressure and triglyceride levels, but lower LDL and HDL cholesterol levels than nondiabetic participants, with no difference for diastolic blood pressure. Diabetic participants were also significantly less physically active than nondiabetic participants. Prehypertension was significantly more prevalent at baseline among diabetic participants (59.4%) than among nondiabetic participants (48.2%). Diabetic participants were more likely to be women and less likely to be current smokers and alcohol users. A high proportion of the participants with diabetes had stopped smoking and using alcohol as compared with those without diabetes.

In all age groups from 45 to 49 to 70 to 74 years, diabetic participants had higher prevalence of prehypertension at baseline than nondiabetic participants (Figure 1, overall $P<0.001$ adjusted for age). The prevalence of prehypertension increased continuously with older age in the entire population and among those with diabetes but remained level after age 60 among nondiabetic participants.

Cumulative Incidence of Cardiovascular Disease
During the 12 years of follow-up (25,035 person-years), there were a total of 389 incident cardiovascular disease events (16

### Table 1. Baseline Characteristics by Diabetic Status: The Strong Heart Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Diabetes (No. = 1532)</th>
<th>Diabetes (No. = 1097)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mm Hg)</td>
<td>73 (8)</td>
<td>74 (8)</td>
<td>0.14</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.2 (0.8)</td>
<td>3.0 (0.8)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.2 (0.4)</td>
<td>1.1 (0.3)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.2 (0.8–1.6)</td>
<td>1.5 (1.0–2.2)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Physical activity (hours/week)</td>
<td>15.8 (2.5–33)</td>
<td>6.9 (1.2–24.3)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Prehypertension (%)</td>
<td>48.2</td>
<td>59.4</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>45.0</td>
<td>30.8</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Past smoking (%)</td>
<td>27.3</td>
<td>35.4</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Current alcohol use (%)</td>
<td>47.6</td>
<td>37.2</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Past alcohol use (%)</td>
<td>39.6</td>
<td>45.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Female (%)</td>
<td>57.2</td>
<td>66.1</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>
per 1000 person years). Kaplan-Meier plots (Figure 2) show that participants with both diabetes and prehypertension had the highest cumulative incidence of cardiovascular disease during follow-up among the 4 groups. Participants who had diabetes alone or prehypertension alone had lower cumulative incidences, whereas nondiabetic participants with normal blood pressure had the lowest cumulative incidence of cardiovascular disease (log rank tests, \( P < 0.001 \) for all comparisons). The differences between participants with diabetes alone or prehypertension alone were negligible in the first eight years of follow-up.

**Hazard Ratio of Cardiovascular Disease**

After adjusting for potential confounding factors in Cox models, compared with normotensive nondiabetic participants, the hazard ratios for participants with diabetes and prehypertension, with diabetes alone, or with prehypertension alone were 3.70, 2.90, and 1.80, respectively (Table 2). Additional Cox models were fitted with different glucose metabolic status in normotensive and prehypertensive participants. Compared with normotensive participants with normal glucose tolerance, those with prehypertension only, impaired fasting glucose and impaired glucose tolerance also greatly increase cardiovascular disease risk in prehypertensive adults without apparent association with incident cardiovascular disease among normotensive participants.

**Discussion**

Although it is well known that both elevated blood pressure and diabetes are related to higher cardiovascular disease morbidity and mortality, there are no population-based longitudinal data on incidence of cardiovascular disease among individuals with prehypertension by JNC-7 criteria with diabetes or other abnormalities of glucose metabolism. The results of the current analysis show that prevalence of prehypertension is high in nondiabetic (48.2%) and even higher (59.4%) in diabetic nonhypertensive American Indians. Prehypertension is related to an increased subsequent cardiovascular event rate in both diabetic and nondiabetic participants, but this increase is greater in people with diabetes. Impaired fasting glucose and impaired glucose tolerance also greatly increase cardiovascular disease risk in prehypertensive adults without apparent association with incident cardiovascular disease among normotensive participants.

In the Framingham Heart Study population, among those aged \( \geq 65 \) years in pooled groups with normal (systolic blood pressure 120 to 129 mm Hg or diastolic blood pressure 80 to 84 mm Hg) or high normal blood pressure (systolic blood pressure 130 to 139 or diastolic blood pressure 85 to 89 mm Hg) by JNC-6 criteria (which were combined into prehypertension under the JNC-7 guidelines) \( \approx 27\% \) developed hypertension within 4 years. Among those aged \( \geq 65 \) years with normal or high normal blood pressure, \( \approx 42\% \) developed hypertension within 4 years. The Strong Heart Study results revealed that the prehypertension prevalence was very high for all age groups (45 to 74 years) in both diabetic and nondiabetic American Indians, beginning at 43% among the youngest nondiabetic group (45 to 49 years). The situation was even worse in diabetic participants who had a nearly 60% prehypertension prevalence in the youngest group and \( \approx 70\% \) at 65 to 69 or 70 to 75 years of age. Without any intervention, many prehypertensive participants may develop hypertension. This is an important public health issue because of the morbidity
and mortality related to hypertension, especially in a population with a high prevalence of diabetes (42% in current study population). Diabetic participants in this study were far less physically active than nondiabetic participants, making lifestyle intervention (including physical activity and diet change) of especially great value in this population. It has been calculated that optimization of blood pressure in people with normal or high normal blood pressure (systolic blood pressure 120 to 139 mm Hg) could result in more than a one-fourth decrease of blood pressure–related coronary heart disease death.11

The current Strong Heart Study findings revealed that in nondiabetic participants, prehypertension increased cardiovascular events 1.8-fold compared with their normotensive counterparts, with an absolute increase of 6 cardiovascular events per 1000 person years. Similar results were also reported by the Framingham Heart Study.18 Diabetes alone increased the risk of cardiovascular disease by 2.9-fold compared with normotensive nondiabetic participants. Diabetes plus prehypertension increased the cardiovascular disease risk 3.7 times, representing an absolute increase of 19 cardiovascular events per 1000 person-years. When the prehypertensive category was stratified into those with blood pressure 120 to 129/80 to 84 mm Hg or blood pressure 130 to 139/85 to 89 mm Hg, hazard ratios for those in the higher group were greater, but there was a significant risk even in those in the lower group. The coexistence of impaired glucose tolerance or impaired fasting glucose and prehypertension also increased cardiovascular disease risk significantly compared with normotensive participants with normal glucose tolerance. The magnitude of the increased cardiovascular disease risk related to the coexistence of prehypertension, glucose intolerance, and diabetes suggests that pharmacological intervention for blood pressure control in these groups may be warranted to prevent cardiovascular disease morbidity and mortality, as suggested by others.15 A clinical trial is needed to confirm this. Increased age, higher body mass index, LDL cholesterol, and triglyceride levels, lower HDL levels, current smoking, ex-alcohol use, and male gender were all related to significantly increased cardiovascular disease risk.

Strengths of this analysis include the large sample size, the long period of follow-up, careful surveillance for cardiovascular disease morbidity and mortality events, and a comprehensive collection of cardiovascular disease risk factors, including laboratory measurements and lifestyle factors. A possible limitation of the analysis would be the use of blood pressure measured at baseline instead of blood pressure during follow-up to estimate the relative risk, possibly underestimating the cardiovascular disease risk.12,14 Nevertheless, our data show strong and persistent associations between prehypertension and cardiovascular disease risk in both diabetic and nondiabetic participants. Because the current study

### TABLE 2. Hazard Ratio for Cardiovascular Disease by Blood Pressure and Status of Glucose Metabolism: The Strong Heart Study

<table>
<thead>
<tr>
<th>Cardiovascular Disease</th>
<th>No. of Events</th>
<th>Events/1000 Person-Years</th>
<th>P for Trend</th>
<th>Hazard Ratio*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>By prehypertension and diabetes status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondiabetes+nornotension</td>
<td>58</td>
<td>7.3</td>
<td>P&lt;0.001</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prehypertension only</td>
<td>97</td>
<td>13.4</td>
<td>1.80</td>
<td>1.28, 2.54</td>
<td></td>
</tr>
<tr>
<td>Diabetes only</td>
<td>79</td>
<td>19.3</td>
<td>2.90</td>
<td>2.03, 4.16</td>
<td></td>
</tr>
<tr>
<td>Diabetes +prehypertension</td>
<td>155</td>
<td>26.5</td>
<td>3.70</td>
<td>2.66, 5.15</td>
<td></td>
</tr>
<tr>
<td>By prehypertension and glucose metabolism status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal glucose tolerance+nornotension</td>
<td>40</td>
<td>7.9</td>
<td>P&lt;0.001</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance+nornotension</td>
<td>11</td>
<td>6.1</td>
<td>0.86</td>
<td>0.43, 1.74</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose+nornotension</td>
<td>7</td>
<td>6.9</td>
<td>0.98</td>
<td>0.44, 2.22</td>
<td></td>
</tr>
<tr>
<td>Normal glucose tolerance+prehypertension</td>
<td>54</td>
<td>12.4</td>
<td>1.54</td>
<td>1.00, 2.38</td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance+prehypertension</td>
<td>27</td>
<td>13.8</td>
<td>2.06</td>
<td>1.23, 3.42</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose+prehypertension</td>
<td>16</td>
<td>18.1</td>
<td>2.12</td>
<td>1.13, 3.98</td>
<td></td>
</tr>
<tr>
<td>Diabetes +nornotension</td>
<td>79</td>
<td>19.3</td>
<td>2.82</td>
<td>1.88, 4.25</td>
<td></td>
</tr>
<tr>
<td>Diabetes +prehypertension</td>
<td>155</td>
<td>26.5</td>
<td>3.61</td>
<td>2.46, 5.31</td>
<td></td>
</tr>
</tbody>
</table>

*The hazard ratio obtained from Cox proportional hazard model was adjusted for age, gender, body mass index, waist circumference, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, physical activity, smoking, and alcohol use.
population had a high risk of diabetes, the results might not be generalizable to all populations. However, it is likely applicable to the many populations in the United States and around the world in which the incidence of diabetes is rapidly rising.

Perspectives
Prehypertension as a clinical category is valuable to guide interventions to prevent cardiovascular disease, the leading cause of mortality in the United States.20 In prehypertensive diabetic people, drug treatment for blood pressure control may be indicated for the prevention of cardiovascular disease. Special attention should be paid to prehypertensive individuals who have impaired glucose tolerance or impaired fasting glucose to reduce cardiovascular disease risks. Univariate analyses showed that prevalence of microalbuminuria and macroalbuminuria are higher in those with prehypertension as compared with people with normal blood pressure. Further studies are needed to understand this and the other correlates of prehypertension.

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