Rising Tide of Cardiovascular Disease in American Indians
The Strong Heart Study

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Background—Although cardiovascular disease (CVD) used to be rare among American Indians, Indian Health Service data suggest that CVD mortality rates vary greatly among American Indian communities and appear to be increasing. The Strong Heart Study was initiated to investigate CVD and its risk factors in American Indians in 13 communities in Arizona, Oklahoma, and South/North Dakota.

Methods and Results—A total of 4549 participants (1846 men and 2703 women 45 to 74 years old) who were seen at the baseline (1989 to 1991) examination were subjected to surveillance (average 4.2 years, 1991 to 1995), and 88% of those remaining alive underwent a second examination (1993 to 1995). The medical records of all participants were exhaustively reviewed to ascertain nonfatal cardiovascular events that occurred since the baseline examination or to definitively determine cause of death. CVD morbidity and mortality rates were higher in men than in women and were similar in the 3 geographic areas. Coronary heart disease (CHD) incidence rates among American Indian men and women were almost 2-fold higher than those in the Atherosclerosis Risk in Communities Study. Significant independent predictors of CVD in women were diabetes, age, obesity (inverse), LDL cholesterol, albuminuria, triglycerides, and hypertension. In men, diabetes, age, LDL cholesterol, albuminuria, and hypertension were independent predictors of CVD.

Conclusions—At present, CHD rates in American Indians exceed rates in other US populations and may more often be fatal. Unlike other ethnic groups, American Indians appear to have an increasing incidence of CHD, possibly related to the high prevalence of diabetes. In the general US population, the rising prevalence of obesity and diabetes may reverse the decline in CVD death rates. Therefore, aggressive programs to control diabetes and its risk factors are needed. (Circulation. 1999;99:2389-2395.)

Key Words: cardiovascular diseases ■ heart disease ■ mortality ■ Indians, North American ■ risk factors

American Indians were long thought to have inherent protection from cardiovascular disease (CVD),1 A review of Indian Health Service (IHS) records from the 1960s showed very low rates,2 and coronary heart disease (CHD) mortality rates in Pima Indians from 1965 to 1980 were lower than those in the Framingham Study.3 More recent IHS data, however, indicate that CVD is now the leading cause of death among American Indians.4,5

Mortality data from 1980s IHS records also showed that CVD mortality rates varied: Some tribes had substantially higher (eg, the Northern Plains Indians) or lower (eg, Navaho, Pima) rates than those of the general US population.4 Interpretation of these data is difficult, however, because of the variation in quality of death certificate data and limitations in the determination of the population at risk. Moreover, American Indians have been undergoing rapid changes in lifestyle, with alterations in traditional patterns of activity and diet that might be expected to increase their risk of CVD. Furthermore, the prevalence of diabetes, a strong determinant of CVD, has been rising in American Indians.

The Strong Heart Study was initiated in 1988 to investigate CVD and its risk factors in geographically diverse groups of American Indians. Prevalence data from the initial examination suggested that American Indians had somewhat lower rates of myocardial infarction (MI) and CHD than other US groups2,6 and a lower prevalence of MI and CHD in certain Arizona Indians compared with those in South/North Dakota or Oklahoma. A 1984 to 1988 mortality survey, however,
showed fewer differences in CVD mortality rates among geographic areas. CVD mortality rates in these tribal groups were somewhat higher than the respective state rates in Arizona and Oklahoma and almost 2 times higher than rates in South/North Dakota. These findings suggested that CVD incidence rates are increasing and that CVD more often may be fatal in American Indians. This report presents the results of a 7-year surveillance of CVD morbidity and mortality rates in the 4549 members of the original Strong Heart Study cohort and assesses the association of major risk factors with CVD incidence.

Methods

The study design, survey methods, and laboratory techniques of the Strong Heart Study have been reported previously. The study population included resident members of the following tribes: Pima/Maricopa/Papago Indians of central Arizona who live in the Gila River, Salt River, and Ak-Chin Indian communities; the 7 tribes of southwestern Oklahoma (Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita); and the Oglala and Cheyenne River Sioux in South Dakota and the Spirit Lake Tribe in the Fort Totten area of North Dakota.

The study cohort consists of 4549 individuals aged 45 to 74 who were seen at the first (phase I) examination, conducted between July 1989 and January 1992. Participation rates of all age-eligible tribal members were 72% in the Arizona center, 62% in the Oklahoma center, and 55% in the South/North Dakota center. Nonparticipants were similar to participants in age and self-reported frequency of diabetes. Reexamination rates for those alive at the second (phase II) examination (July 1993 to December 1995) averaged 88%.

The phase I and phase II clinical examinations consisted of a personal interview and a physical examination. Fasting blood samples were obtained for measurements of lipids and lipoproteins, insulin, plasma creatinine, plasma fibrinogen, and glycohemoglobin, and a 75-g oral glucose tolerance test was performed as described previously. Laboratory methods were published previously.

Weight, height, and waist and hip circumferences were measured and percent body fat was estimated as described previously. Blood pressure measurements were obtained and electrocardiograms were taken, read, and coded as described previously. Percentage of Indian heritage was computed from reported degree of Indian heritage for each parent and grandparent. Participants were classified as diabetic according to World Health Organization criteria. Participants were considered hypertensive if they were taking antihypertension medication or if they had a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg. Urinary albumin excretion was estimated by the ratio of albumin (mg) to creatinine (g). Microalbuminuria was defined as a ratio of urinary albumin (mg/mL) to creatinine (g/mL) of 30 to 299 mg/g and macroalbuminuria as a ratio >300 mg/g.

Deaths among the original Strong Heart Study cohort between the participants’ first examination and December 1995 were identified through tribal and IHS hospital records and by direct contact by study personnel with participants and their families. Copies of death certificates were obtained from state health departments and ICD-9 coded centrally by a nosologist. Possible CVD deaths were initially identified from death certificates as described previously. Cause of death was investigated through autopsy reports, medical record abstractions, and informant interviews, as described previously. All materials were reviewed independently by physician members of the Strong Heart Study Mortality Review Committee to confirm the cause of death. Criteria for fatal CHD and stroke were as described previously.

Medical records were reviewed at the second examination to identify any nonfatal cardiovascular events that had occurred since the phase I examination. Records of those who did not participate in the second examination (n=498; 2 died in 1996) also were reviewed. New MI and new CVD events were defined as in the first examina-

### TABLE 1. Strong Heart Study Population, Age 45 to 74 Years at Baseline Examination

<table>
<thead>
<tr>
<th>Center</th>
<th>Total</th>
<th>No Definite CVD at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>546</td>
<td>532</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>642</td>
<td>589</td>
</tr>
<tr>
<td>South/North Dakota</td>
<td>658</td>
<td>608</td>
</tr>
<tr>
<td>Total</td>
<td>1846</td>
<td>1729</td>
</tr>
</tbody>
</table>

Data Analysis

Incidence rates for fatal and nonfatal events were calculated per 1000 person-years after elimination of individuals in the cohort who had definite CHD or stroke at baseline. Person-years were calculated from the date of the phase I examination to diagnosis or time of the first event. Statistical significance of center-specific differences was evaluated by $\chi^2$ test. Univariate assessment of associations of risk factors at baseline with incident CVD was performed by univariate logistic regression analysis, adjusted for age and center, in those with and those without events. A Cox proportional hazards model was used for computing age- and center-adjusted hazard rate ratios and 95% confidence intervals. All variables examined in the univariate analyses, plus sex and center, were then used in the model for examination of CVD risk factors. Stepwise Cox regression analysis, with entry and retention criteria of 5%, was used to compute hazard rate ratios for the multivariate analysis.

Results

The population at risk for CVD mortality or morbidity in the follow-up interval (7 years; average 4.2 years) was 4380 individuals (Table 1). In both women and men, CHD mortality rates (Table 2) did not differ significantly between centers. In all 3 centers, fatal CHD rates were significantly higher in men than in women ($P<0.0001$). Rates for fatal stroke were lower than those for fatal CHD. Rates for fatal stroke did not differ significantly between centers.

Incidence rates for nonfatal CVD (Table 3) were similar for nonfatal CHD in Arizona and South/North Dakota women, with rates in Oklahoma women being somewhat but not significantly lower. Among men, rates for nonfatal CHD were highest in South/North Dakota and lowest in Arizona ($P=0.17$). In all 3 centers, rates for nonfatal CHD were higher among men than among women ($P<0.01$). As was observed for fatal stroke, rates for nonfatal stroke were much lower than for nonfatal CHD. Rates for nonfatal stroke were somewhat but not significantly higher among both men and women in South/North Dakota compared with the other 2 centers. In all 3 centers, rates for nonfatal stroke were similar in men and women.
Figure 1 shows composite incidence rates of CVD (morbidity plus mortality) in men and women in the three geographic areas. In men, combined rates were lowest in Arizona, highest in South/North Dakota, and intermediate in Oklahoma ($P = 0.09$). In women, the combined rates also were highest in South/North Dakota but lowest in Oklahoma ($P = 0.11$). The differences in men are largely due to differences in nonfatal events, with mortality rates being very similar in all 3 centers.

Major risk factors for fatal and nonfatal CVD were evaluated with the use of Cox regression analysis, adjusting for age and center (Table 4). Hypertension, HDL cholesterol (inverse), albuminuria, and fibrinogen were each associated with CVD in both men and women. Diabetes was strongly associated with disease in both men and women, with diabetic men having a 2.2-fold increased risk of CVD and diabetic women having a 3.5-fold increased rate compared with nondiabetic individuals. The other strong risk factor in both sexes was albuminuria, with men with macroalbuminuria having a 3.8-fold increase in CVD risk and women with macroalbuminuria having a 5.4-fold increase in risk. LDL cholesterol was a significant predictor in men but not in women. Obesity, as measured by percent body fat, was a significant inverse predictor in women but not in men, and body fat distribution, determined by waist circumference, was not related to CVD in either sex. Triglyceride concentration...
was a significant predictor in women but not in men. Insulin concentration was a significant predictor in men but not in women. When full-blooded Indians were compared with those with non-Indian admixture, there was no association with CVD risk. There was no association between smoking and CVD in either men or women.

In a multivariate stepwise Cox proportional hazards analysis (Table 5), the significant independent predictors of CVD in women were albuminuria, age, diabetes, obesity (inverse), LDL cholesterol, triglycerides, and hypertension. In men, age, albuminuria, LDL cholesterol, diabetes, and hypertension were independent predictors.

CVD rates in the Strong Heart Study were compared with other US populations (Figure 2), as measured by the Cardiovascular Health Study (CHS) \(^{14}\) and the Atherosclerosis Risk in Communities (ARIC) Study, \(^{15}\) which used similar methods of ascertainment. Rates for stroke are similar in women and lower in American Indian men than in the general US population, but rates for CHD in American Indian men and women are almost 2-fold higher than the US population.

**TABLE 4. Age- and Center-Adjusted Hazard Rate Ratios for Fatal and Nonfatal CVD by Major CVD Risk Factors: Strong Heart Study**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Women Hazard Rate Ratio 95% CI</th>
<th>Men Hazard Rate Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (Y/N)</td>
<td>2.48 (1.75–3.52)</td>
<td>1.67 (1.37–2.64)</td>
</tr>
<tr>
<td>Current smoking (Y/N)</td>
<td>1.18 (0.81–1.73)</td>
<td>1.20 (0.88–1.63)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.43 (0.94–2.17)</td>
<td>2.13 (1.45–3.13)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.52 (0.32–0.84)</td>
<td>0.55 (0.36–0.84)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.58 (1.33–1.88)</td>
<td>1.09 (0.97–1.22)</td>
</tr>
<tr>
<td>Diabetes (DM vs IGT + NGT)</td>
<td>3.50 (2.34–5.23)</td>
<td>2.16 (1.58–2.95)</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.13 (0.94–1.36)</td>
<td>1.24 (1.06–1.45)</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Micro vs normal 2.38 (1.55–3.67)</td>
<td>1.65 (1.12–2.43)</td>
</tr>
<tr>
<td>Macro vs normal</td>
<td>5.36 (3.48–8.27)</td>
<td>3.81 (2.54–5.71)</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>0.46 (0.32–0.72)</td>
<td>0.64 (0.57–1.25)</td>
</tr>
<tr>
<td>Waist</td>
<td>0.94 (0.61–1.46)</td>
<td>0.97 (0.66–1.43)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2.38 (1.64–3.46)</td>
<td>1.84 (1.35–2.50)</td>
</tr>
<tr>
<td>Full-blooded Indian (Y/N)</td>
<td>1.06 (0.70–1.59)</td>
<td>0.94 (0.66–1.32)</td>
</tr>
</tbody>
</table>

Mean of the lowest quartile group vs mean of the upper quartile group: 156 vs 74 mg/dL in women, 158 vs 74 mg/dL in men for LDL cholesterol; 66 vs 34 mg/dL in women, 61 vs 30 mg/dL in men for HDL cholesterol; 276 vs 66 mg/dL in women, 306 vs 61 mg/dL in men for triglycerides; 42.29 vs 7.31 μU/mL in women, 39.90 vs 5.24 μU/mL in men for insulin; 50% vs 32% in women, 37% vs 21% in men for percent body fat; 127 vs 88 cm in women, 120 vs 88 cm in men for waist; and 216 vs 222 mg/dL in women, 387 vs 205 mg/dL in men for fibrinogen. DM indicates diabetes; IGT, impaired glucose tolerance; and NGT, normal glucose tolerance.

Vascular Health Study (CHS) \(^{14}\) and the Atherosclerosis Risk in Communities (ARIC) Study, \(^{15}\) which used similar methods of ascertainment. Rates for stroke are similar in women and lower in American Indian men than in the general US population, but rates for CHD in American Indian men and women are almost 2-fold higher than the US population.

**Discussion**

The present longitudinal analysis was undertaken to clarify the apparent discrepancy between the initial cross-sectional data\(^{2,6}\) and subsequent reports\(^{7}\) on CVD prevalence and mortality in the Strong Heart Study. The present data showed that whereas incidence rates for nonfatal CVD in Arizona men were lower than those in Oklahoma and South/North Dakota, incidence rates for nonfatal CVD in women and CVD mortality in both men and women were similar in all 3 centers.

The present CVD incidence data were compared with those in the CHS\(^{14}\) and ARIC\(^{15}\) studies: 2 other national population studies with predominantly white (CHS) and 25% black (ARIC) cohorts (Figure 2). Rates for stroke in American Indians appear to be lower for men than in the CHS data but similar for women; rates for CHD in American Indian men and women, however, are almost 2-fold higher than rates in the ARIC Study. These data suggest that rates of coronary disease in American Indians may exceed those of other US populations. In contrast to reports of low CVD rates from earlier data\(^{1,3,16}\) and contrary to other US ethnic groups, American Indians have rates of CVD that appear to be rising. Further, coronary events may be more often fatal, especially in the Arizona communities, as shown by their similar CVD death rates in men despite lower incidence of nonfatal CVD events.

The most likely explanation for the high rates of CVD in American Indians is the high prevalence of diabetes in these communities. Univariate and multivariate analyses show that diabetes was the strongest determinant of CVD, with 56% of the events in men and 78% of the events in women occurring in those with diabetes. Because 70% of the individuals in Arizona and \(>40%\) in the other 2 centers had diabetes, diabetes thus accounts for an extremely high percentage of the population-attributable risk. Although diabetes is well known to increase CVD risk factors, the present analysis, as well as many others, shows a strong independent effect of diabetes after adjustment for other risk factors.
Hyperglycemia may contribute to atherosclerosis by impeding endothelial function\textsuperscript{17,18} and causing advanced glycation end products to form that may promote myocardial dysfunction. This latter effect has been demonstrated in Strong Heart Study echocardiograms that show increases in left ventricular wall thickness and mass, ventricular dysfunction, and evidence of increased arterial stiffness in individuals with diabetes.\textsuperscript{19}

Albuminuria was one of the strongest correlates of CVD both in this longitudinal analysis and the baseline cross-sectional data. Several prospective studies examining risk factors for CVD among individuals with diabetes have observed a relation between albuminuria and CVD.\textsuperscript{20–22} Renal disease may be related to CVD because of its influence on lipoproteins, blood pressure, and other metabolic factors. Albuminuria remains a significant correlate in the multivariate analysis after adjustment for these factors as well as for the presence of diabetes. This suggests that the association between diabetes and CHD may share common determinants with microvascular disease in other organs, of which albuminuria is a marker. Thus microvascular disease is the probable cause of the renal disease, left ventricular dysfunction, and other echocardiographic abnormalities that we have documented in diabetic Strong Heart Study participants. The consistent finding of albuminuria as a major risk factor further emphasizes the importance of measuring urinary albumin in clinical assessments of individuals with diabetes and applying aggressive measures to attempt to retard the progression of microvascular disease as a strategy to control coronary disease.

LDL cholesterol was a significant independent predictor of CVD in American Indian men and women. Total and LDL cholesterol levels in American Indians are lower than the US average,\textsuperscript{16} and this observation has impeded recognition of the potential importance of LDL cholesterol as a cause of coronary disease. The positive relation observed in this study shows that aggressive cholesterol lowering might lower CHD risk and supports the recently suggested target LDL levels of $<100$ mg/dL ($<2.6$ mmol/L) for individuals with diabetes.

Hypertension also was shown to be a predictor of coronary disease. Hypertension is common in American Indian communities except for South/North Dakota, and its prevalence is greater than in the general US population.\textsuperscript{23}

American Indians and most individuals with diabetes have a high prevalence of the insulin resistance syndrome, which is a strong predictor of CHD. The Strong Heart Study data showed high insulin concentrations, high waist-hip ratios, and the typical dyslipidemia characterized by

### Table 5. Stepwise Cox Regression Analysis of Risk Factors for CVD in 45- to 74-Year-Old (at Baseline) American Indians: The Strong Heart Study

<table>
<thead>
<tr>
<th></th>
<th>Women (n=2651)</th>
<th>Men (n=1729)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>Rank</td>
<td>Coefficient</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>4</td>
<td>0.043</td>
</tr>
<tr>
<td>LDL cholesterol (10 mg/dL)</td>
<td>5</td>
<td>0.07</td>
</tr>
<tr>
<td>Macroalbuminuria (mg/g, Y/N)</td>
<td>1</td>
<td>0.612</td>
</tr>
<tr>
<td>Diabetes (Y/N)</td>
<td>7</td>
<td>0.418</td>
</tr>
<tr>
<td>Hypertension (Y/N)</td>
<td>6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Variables included in stepwise analysis are age, center, percent body fat, waist, LDL cholesterol, HDL cholesterol, triglycerides, LDL size, insulin, number of cigarettes per pack-year, degree of Indian admixture, hypertension, diabetes, macroalbuminuria, and microalbuminuria.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** CVD incidence (fatal and nonfatal) in American Indians compared with other US population data from the CHS\textsuperscript{14} and ARIC\textsuperscript{15} studies (rates per 1000 person-years). *3.3-year average follow-up; **5.2-year average follow-up. CHD includes fatal and nonfatal events plus revascularization. SHS indicates Strong Heart Study.
elevated triglycerides; low HDL; and small, dense LDL particles.6–24 In the present data, the univariate analysis showed that plasma insulin concentration was a significant correlate in men, triglycerides were significant in women, and HDL had a strong inverse association in both men and women. In the proportional hazards model, neither insulin nor HDL remained significant, and triglyceride was a significant predictor only in women. In this population, the very high prevalence of diabetes and renal disease may overshadow the atherogenic effects of insulin resistance per se, although the insulin resistance undoubtedly was a strong predisposing factor for the high rate of diabetes.

Rates of smoking are high in many American Indian communities, although numbers of cigarettes smoked per day are less than the US average.16 Although smoking was not a significant independent predictor of CHD, it has been shown to be a significant independent correlate of peripheral vascular disease in American Indians.25

Obesity had a negative association with CVD in both men and women, which was significant in both analyses in women. Body fat distribution showed no relation to CVD in women or men, probably because among obese American Indians, body fat almost always is centrally distributed. On the other hand, it is very difficult to understand the negative relation of obesity with CHD. It is possible that this reflects the fact that individuals with a long duration of diabetes, particularly those with renal disease (who are at high risk for CVD), lose weight, and that this is not completely accounted for in the multivariate analysis. The question of whether there may be ethnic differences in the impact of obesity on CVD needs further investigation.

The prospective surveillance of the Strong Heart Study cohort has shown that incidence rates of fatal CVD in Arizona are actually higher than those in Oklahoma and the Midwest (Fig. 1), and that the low prevalence of coronary artery disease in earlier studies of Arizona Indians, especially the “Pima Paradox,” i.e., the low prevalence and mortality rates of coronary disease documented in earlier studies of Arizona Indians,1,2 This is not surprising, given the high prevalence rates of diabetes in these communities and the existence of several other risk factors such as hypertension and albuminuria. Thus even in populations that may have had innate protection or a lower tendency for atherosclerosis, this protection can be overcome or overridden by diabetes, its associated metabolic abnormalities, and other CVD risk factors. It is entirely possible that similar findings will be observed in other populations throughout the world with traditionally low rates of coronary disease in whom diabetes prevalence is increasing. Further, the rising prevalence of obesity and consequently of diabetes in the general US population may, in the future, lead to rising rates of CVD in the US population. Diabetes prevention programs, coupled with programs aimed at aggressive control of risk factors in diabetic individuals, may help to stem this rising tide of diabetes-associated CHD in American Indians and in other populations with increasing prevalence of diabetes.

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References


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