Incidence of Lower-Extremity Amputation in American Indians

The Strong Heart Study

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OBJECTIVE — To define incidence and predictors of nontraumatic lower-extremity amputation (LEA) in a diverse cohort of American Indians with diabetes.

RESEARCH DESIGN AND METHODS — The Strong Heart Study is a study of cardiovascular disease and its risk factors in 13 American-Indian communities. Data on the presence/absence of amputations were collected at each of three serial examinations (1989–1992, 1993–1995, and 1997–1999) by direct examination of the lower extremity. The logistic regression model was used to quantify the relationship between risk of LEA and potential risk factors, including diabetes duration, HbA_{1c}, peripheral arterial disease, and renal function.

RESULTS — Of the 1,974 individuals with diabetes and without prevalent LEA at baseline, 87 (4.4%) experienced an LEA during 8 years of follow-up, and a total of 157 anatomical sites were amputated among these individuals. Amputation of toes was most common, followed by below-the-knee and above-the-knee amputations. Age-adjusted odds of LEA were higher among individuals with unfavorable combinations of risk factors, such as albuminuria and elevated HbA_{1c}. Multivariable modeling indicated that male sex, renal dysfunction, high ankle-brachial index, longer duration of diabetes, less than a high school education, increasing systolic blood pressure, and HbA_{1c} predicted LEA risk.

CONCLUSIONS — The 8-year cumulative incidence of LEA in American Indians with diabetes is 4.4%, with marked differences in risk by sex, educational attainment, renal function, and glycemic control.

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Data from the baseline examination of the Strong Heart Study (SHS) show that lower-extremity amputation (LEA) due to diabetes was present in 3% of the cohort and 6.3% of individuals with diabetes (1), findings that are generally consistent with previous studies (2–4) in other American-Indian tribes. Rates of incident LEA have been reported for several American-Indian tribes (5–8). Previous studies have shown that hyperglycemia (5,6,9,10), duration of diabetes (5,6), male sex (2,5,6,10), and prevalent microvascular disease (5,6,10) contribute to LEA risk in American Indians.

The purpose of this study is to define the incidence of first LEA due to diabetes in a diverse, population-based cohort of American Indians with diabetes. We hypothesized that among SHS participants with diabetes, increasing age, diabetes duration, glycemic control, smoking, peripheral arterial disease, renal dysfunction, and male sex would predict incident LEA and that combinations of risk factors, such as poor glycemic control and renal dysfunction, would interact to increase LEA risk.

RESEARCH DESIGN AND METHODS

— The SHS was initiated in 1988 to investigate cardiovascular disease and its risk factors in American Indians (11). The design, methods, and laboratory techniques of the SHS have been previously reported (12,13). The SHS cohort consists of 4,549 participants aged 45–74 years from 13 American-Indian communities in Oklahoma, the Dakotas, and Arizona who were seen at the baseline examination conducted between 1989 and 1992. The second and third examinations were conducted from 1993 to 1995 and 1997 to 1999, respectively. Within the study population, nonparticipants were similar to participants in age, BMI, and self-reported frequency of diabetes and hypertension (13).

Evaluation of LEA

At each of the three SHS examinations, trained examiners collected amputation data from direct observation of both legs. These data included the presence/absence of portions of lower limbs and the cause of missing extremities. Missing extremities were coded by study personnel as toe/foot, below-the-knee amputation (BKA), or above-the-knee amputation (AKA).

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Abbreviations: ABI, ankle-brachial index; AKA, above-the-knee amputation; BKA, below-the-knee amputation; LEA, lower-extremity amputation; SHS, Strong Heart Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Participants were asked to attribute each missing extremity to a specific factor. These attributions were coded as diabetes (LEA), trauma, congenital, other, and unknown.

Definition of diabetes

Participants were categorized as having diabetes if they had a fasting glucose ≥126 mg/dl (14), reported use of hypoglycemic medications, or reported that they had been told by a health care professional that they had diabetes. Diabetes duration among participants who reported having previously been diagnosed with diabetes was assessed by questionnaire at the baseline examination.

Measurement of known and potential LEA risk factors

SHS methods and protocols have been described (11,12). Age, diabetes, smoking, hypertension, loss of protective sensation, and male sex have been associated with increased LEA risk in other studies (4,5,9–11,15). Participants were considered hypertensive if they had a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or if they were taking antihypertensive medication. Smoking history was determined by questionnaire and coded as ever versus never. At-risk drinking was defined as report of either ≥5 drinks on one occasion in the past month or ≥14 drinks in a typical week (1,16). Cholesterol, triglycerides, and fasting glucose were determined by enzymatic methods using a Hitachi chemistry analyzer and consistent standardized reagents (Boehringer Mannheim Diagnostics, Indianapolis, IN). Fasting insulin and fibrinogen were measured by established methods (17,18). Microalbuminuria was defined as a ratio of urinary albumin (in milligrams per milliliter) to creatinine (grams per milliliter) of 30–299 mg/g and macroalbuminuria as a ratio of ≥300 mg/g.

An ankle-brachial index (ABI) of <0.90 ("low") is 95% sensitive and 99% specific for angiographically documented peripheral arterial disease (19,20) and has been used in previous work (21) in the SHS. Data from the SHS show that an ABI >1.40 ("high") is associated with a similar level of cardiovascular disease and mortality risk as low ABI (22). Baseline ABI was used to identify three groups of individuals: those with low ABI (<0.90), those in the normal range of ABI (0.90 ≤ ABI ≤ 1.40), and those with high ABI (>1.40). Monofilament data and other measures of neuropathy were not collected at the baseline examination, and information on history of foot ulcers was unavailable.

Statistical methods

χ^2 and Student's *t* tests were used to examine differences in proportions and means between categorical and continuous variables, respectively. Because the purpose of this report is to understand risk factors for a first amputation, comparisons focused on differences in baseline risk factors between participants with diabetes who did and did not experience a first (incident) LEA during the follow-up period. We report selected supplemental data on recurrent amputations among individuals with incident LEA. We were also interested in the effects of combinations of LEA risk factors, particularly duration of diabetes, HbA_{1c}, ABI, and renal function. Accordingly, we created dummy variables for these factors and examined their age-adjusted joint effects on LEA risk. We then used the logistic regression model to identify risk factors that were independently associated with increased odds of incident LEA. Variables chosen for inclusion in the logistic regression models were based on findings from univariate analysis and previous studies.

Following examination of main effects in the logistic models, we explored the interaction of elevated HbA_{1c} and renal dysfunction to test the hypothesis that this combination of risk factors acted synergistically to increase LEA risk. Despite our interest in other key interactions, sparse cells prevented testing of the interactions between ABI × HbA_{1c} and ABI × renal function in the logistic models. In some analyses, we examined LEA risk factors separately in relation to minor (toe/foot) and major (BKA+AKA) amputation. We employed the Hosmer-Lemeshow test to evaluate the goodness of fit of the models and examined receiver-operating characteristic curves to assess how well the models predicted an incident LEA.

RESULTS — Of the 4,549 participants in the SHS cohort, 1,974 (43.4%) had diabetes and no LEA at baseline. This group constitutes the analysis sample in this report. Of these 1,974, 87 (4.4% of individuals with diabetes; 6% of men and 3.5% of women) experienced an incident LEA during a mean of 7.9 years of follow-up (Table 1). Among both men and women, amputation of toes was most common, followed by BKA and AKA. Compared with women, a slightly larger proportion of men had incident LEA above the knee: 14 vs. 11%. The difference in proportions was somewhat larger for BKA: 35% in men vs. 25% in women. Conversely, among women with incident LEA, amputation of toes was somewhat more common than among men. A total of 159 anatomical sites were amputated among the 87 individuals with incident LEA, yielding ~1.8 amputated sites per individual. However, men with incident LEA had more amputated sites than women. The 43 men with incident LEA had 85 sites, yielding ~2.0 sites per man, whereas the 44 women had 74 sites, yielding ~1.7 sites per woman. Twenty-five participants with incident LEA (29% of all LEAs) had more than one amputation during follow-up. Among participants with incident LEA at the second examination, eight individuals had ipsilaterial LEA at the third exam. Two participants had an incident LEA at exam 2 and a contralateral LEA at exam 3, seven participants had a bilateral LEA ascertained at exam 2, and nine participants had a bilateral LEA ascertained at exam 3. One participant had both ipsilateral and contralateral LEAs between exams 2 and 3.

Table 1—*Summary of incident LEA among American Indians with diabetes and without a history of LEA by sex: the SHS*

Sex and most proximal site of LEA	Individuals	Anatomical sites
Men		
n	712	—
Toe/foot	22 (51)	61 (72)
BKA	15 (35)	18 (21)
AKA	6 (14)	6 (7)
Total	43	85
Women		
n	1,262	—
Toe/foot	28 (64)	55 (74)
BKA	11 (25)	14 (19)
AKA	5 (11)	5 (7)
Total	44	74
Grand total	87	159

Data are *n* (%). *N* = 1,974.

Table 2 compares the baseline characteristics of SHS participants with and

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Table 2—*Baseline characteristics of American Indians with diabetes without a history of LEA by LEA status at follow-up: the SHS*

Characteristic	Incident LEA	No LEA	Difference in means or crude relative risk (95% CI)*	*P*
n	87	1,887	—	—
Age (years)	56.2	57.1	−0.9 (−2.6 to 0.8)	0.31
Sex [*n* (% male)]	43 (49)	669 (35)	1.7 (1.2–2.6)	<0.01
Center				
North/South Dakota	17 (20)	497 (26)	1.0	—
Oklahoma	14 (16)	546 (29)	0.8 (0.4–1.5)	0.43
Arizona	56 (64)	844 (45)	1.9 (1.1–3.2)	0.02
Duration of diabetes (years)†	14.8	11.7	3.1 (1.1–5.1)	<0.01
Undiagnosed diabetes‡	2 (2)	478 (25)	—	NA
HbA_{1c} (%)	9.8	8.4	1.5 (0.9–2.0)	<0.01
Hypertension§	42 (48)	851 (45)	1.1 (0.8–1.7)	0.56
Systolic blood pressure (mmHg)	138	131	7.1 (2.7–11.5)	<0.01
Diastolic blood pressure (mmHg)	78	77	1.2 (−1.0 to 3.3)	0.29
Total cholesterol (mg/dl)	184	190	−5.8 (−15.6 to 3.9)	0.24
Triglycerides (mg/dl)	174	178	−3.9 (−46.2 to 38.4)	0.81
HDL cholesterol (mg/dl)	43	43	−0.2 (−2.7 to 2.3)	0.88
LDL cholesterol (mg/dl)	106	111	−4.7 (−12.1 to 2.6)	0.21
Fibrinogen (mg/dl) (ln)	5.8	5.7	0.1 (−0.01 to 0.11)	0.09
BMI (kg/m^2)	29.8	32.3	−2.5 (−1.1 to −3.9)	<0.01
Ever smoker	59 (69)	1,264 (67)	1.1 (0.7–1.7)	0.78
High school education or higher	24 (28)	905 (48)	0.43 (0.27–0.68)	<0.01
At-risk drinking‖	23 (26)	396 (21)	1.3 (0.8–2.1)	0.22
Albuminuria				
Normal	13 (16)	958 (53)	1.0	—
Microalbuminuria	44 (54)	545 (30)	5.6 (3.0–10.3)	<0.01
Macroalbuminuria	25 (30)	319 (17)	5.4 (2.8–10.5)	<0.01
Peripheral arterial disease				
ABI (low)	8 (9)	112 (6)	1.8 (0.9–3.8)	0.09
ABI ≥0.9 to ≤1.4 (normal)	58 (67)	1,542 (83)	1.0	—
ABI >1.4 (high)	20 (23)	210 (11)	2.4 (1.5–3.9)	<0.01

Data are *n* (%), unless noted otherwise. $N = 1,974$. *Data represent differences in mean baseline values (95% CI) for continuous variables between participants with and without incident LEA or relative risks (95% CI) for categorical variables, both over 7.9 years of follow-up; †data were available for 126 participants with diabetes and LEA and for 1,423 participants with reported diabetes and no LEA; ‡no reported diabetes and fasting glucose ≥126 mg/dl; §systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or taking antihypertensive medication; ‖report of ≥5 drinks on one occasion or ≥14 drinks in a single week.

without incident LEA during follow-up. Participants with diabetes who experienced incident LEA were more likely to be male; to be from the Arizona center; to have longer duration of diabetes; to have renal disease, abnormal ABI, and/or higher systolic blood pressure; and to lack a high school education ($P < 0.01$, for all). Compared with participants with normal albuminuria, risk of LEA was increased 5.6 and 5.4 times among those with micro- and macroalbuminuria, respectively. Participants with high ABI had an LEA risk 2.4 times that of those with normal ABI, and the risk was marginally elevated among those with low ABI. Baseline BMI was lower in participants who experienced an incident LEA compared with those who did not.

Figure 1 shows the age-adjusted effects of HbA_{1c} and renal function on odds of incident LEA. In general, as HbA_{1c} increased and renal function diminished, risk of LEA increased, with the combination of high HbA_{1c} and poor renal function having stronger effects than either characteristic alone. Similarly, the combination of unfavorable ABI and increasing HbA_{1c} was also associated with substantially increased age-adjusted odds of incident LEA (Fig. 2), and the combination of abnormal ABI and diminishing renal function was also associated with increased risk of LEA (Fig. 3). Of note in these analyses is the unexpectedly lower risk of LEA in some categories of macroalbuminuria. Twenty-two percent of participants with baseline macroalbuminuria (compared with 11% in the microalbuminuria and 8% in the normal groups) had died by the second SHS examination, when incident LEA was first ascertained.

Logistic regression models are based on data for 81 participants with an LEA and 1,799 participants without an LEA who had complete data for all covariates of interest. Table 3 shows that men were

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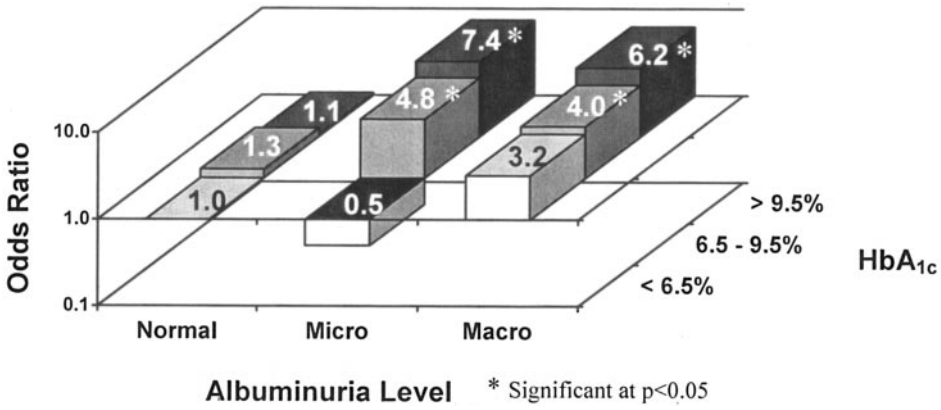

Figure 1—*ORs of incident LEA by categories of HbA_{1c} and albuminuria: the SHS. Comparisons are between each vertical bar and the reference group (those with normal albuminuria and HbA_{1c} <6.5%), which is indicated by an OR of 1.0.*

twice as likely as women to experience an incident LEA and having a high school education reduced the risk by >50%. Increasing diabetes duration and HbA_{1c} both influenced risk of incident LEA. The effect of poor glycemic control on risk of LEA was considerable: compared with participants with HbA_{1c} <6.5%, LEA risk was increased two- and threefold among participants with HbA_{1c} between 6.5 and 9.5% and among those with HbA_{1c} >9.5%, respectively. Microalbuminuria (odds ratio [OR] 2.67, 95% CI 1.48–4.84) was associated with increased LEA risk, as was a high baseline ABI (1.80, 1.02–3.17). The Hosmer-Lemeshow test suggested that the model fit the data well ($P = 0.88$), and inspection of a receiver-operating characteristic curve indicated that in this sample the model correctly identified LEA cases 80% of the time. We observed no significant interactions between pairs of risk factors and LEA risk in the adjusted models. Although stratification of our models according to major/minor LEA reduced statistical power considerably, these analyses did not result in meaningful differences in the results with respect to the direction or magnitude of point estimates.

We also examined the association of baseline risk factors with risk of multiple (more than one) incident LEA. We defined participants as having multiple LEAs if they were missing portions of extremities on both legs or feet at a single SHS examination or if they had missing extremities at the second examination, followed by additional LEAs at the third examination. Forty-four percent of participants with more than one LEA had macroalbuminuria at baseline compared with 25% of those with one LEA and 18% among those without LEA ($P < 0.0001$).

CONCLUSIONS — This report presents a systematic analysis of incident LEA in a diverse, population-based sample of American Indians with diabetes and indicates that the 8-year cumulative incidence of a first LEA was 4.4%. The adjusted risk of LEA in men was twice that of women, and increasing diabetes duration, poor glycemic control, low educational attainment, renal disease, and ABI >1.40 were all significantly associated with increased LEA risk.

In our study, the adjusted risk of LEA associated with male sex was 2.06, a consistent finding in at least two previous prospective studies of incident LEA in American Indians. In the Oklahoma Indian Diabetes Study (5) ($n = 875$), men's risk of incident LEA was twice that of women's, and in a study of 4,399 Pima Indians (6), the rate of LEA in men was 2.6 times higher than in women, adjusted for age and diabetes duration. However, the observation that men are at higher risk of LEA is not a universal finding. In a national study of 20-year risk of LEA, sex did not predict incident LEA (15). One reason for the absence of a sex effect in the latter study may be due to the fact that it included a mix of individuals with and without diabetes, potentially masking an important sex effect in studies exclusively of individuals with diabetes.

Several factors might explain the persistent observation that men with diabetes experience more LEAs than women with diabetes. First, this observation may be due to anatomical differences predisposing to diabetic neuropathy, a known LEA risk factor. Insensate neuropathy likely reflects severe underlying nerve damage and is a known risk factor for LEA (23). A twofold sex difference in insensate neuropathy reported in one study (24) is consistent with twofold sex differences in LEA risk in the current report and other LEA studies in American Indians with diabetes (5,6). The SHS did not collect measures of sensory neuropathy at the baseline examination that would have permitted direct examination of whether men had more neuropathy than women. However, a number of studies support the key role of neuropathy as a risk factor for LEA, including one report (25) that showed that South Asians with diabetes have about one-quarter the risk of LEA of Europeans with diabetes, a difference attributable to lower rates of neuropathy and peripheral arterial disease.

It is also possible that men experience more minor trauma to the foot that ultimately results in LEA. Sex differences in type of employment rather than biological differences between men and women may be one way that Indian men are exposed to potentially high-risk foot trauma. Unfortunately the SHS does not have information that permits testing of this hypothesis. A third explanation might be related to the tendency for men to have less contact with the health care system or different attitudes toward self-care than women. A small study of the influence of sex among individuals with diabetes and severe foot lesions indicated that women were active in self-care and preventive care and actively sought information. In contrast, men more often sought care only for acute problems, had a passive attitude toward foot care, and frequently sought

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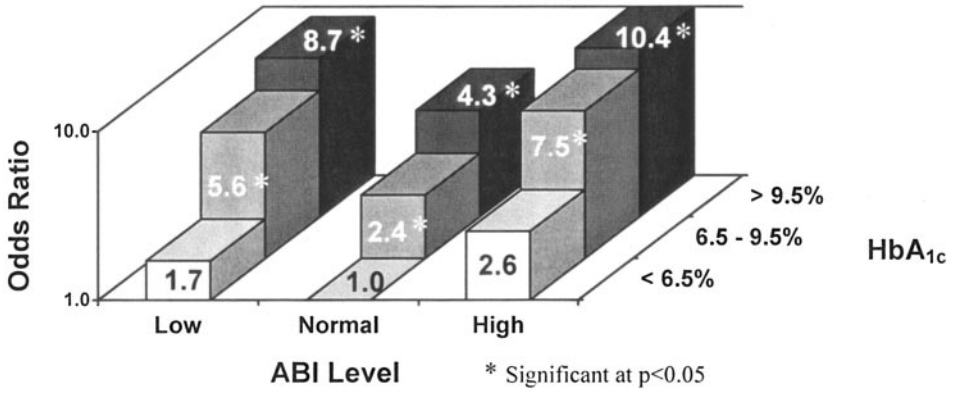

Figure 2—*ORs of incident LEA by categories of HbA_{1c} and ABI: the SHS. Comparisons are between each vertical bar and the reference group (those with HbA_{1c} <6.5% and normal ABI), which is indicated by an OR of 1.0.*

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complementary care from their wives (26). Although the latter study was not conducted in American Indians, it is possible that attitudes and beliefs about foot care among Indian men, rather than sex per se, may contribute to the persistent association between male sex and LEA risk.

Peripheral arterial disease, defined in various studies as absent or diminished lower-extremity pulses (ABI <0.90 or <0.80), has been shown to predict incident LEA in individuals with diabetes (5,24,26). Our models showed an elevated (OR 1.50, 95% CI 0.66–3.40) but nonsignificant risk associated with ABI <0.90. Among participants with an LEA, 9.2% were in the low ABI group, compared with 6% in the no LEA group. However, there were only eight LEAs in the low ABI group, and this small number limited precision in the low ABI point estimate for LEA risk. Despite the absence of statistical significance, both the magnitude and direction of the point estimate are consistent with previous studies.

The association between high ABI and LEA persisted in multivariable analyses, conferring an adjusted LEA risk of 1.80 (1.02–3.17). Our finding that high ABI predicted LEA risk is consistent with a study showing that radiographically documented medial arterial calcification predicted risk of LEA in Pima Indians (6). A high prevalence of elevated ABI has been reported in the SHS and other studies of American Indians (22,27). The significant association between high ABI and LEA is likely due to the larger number (n = 20) of LEAs in the high ABI group, and the fact that high ABI was more than twice as common among those with an LEA compared with those without (22.9 vs. 11.1%).

One observation relevant to our findings is that among individuals with diabetes, medial arterial calcification is often present in individuals with both neuropathy and poor renal function. In previous work in the SHS, elevated ABI was associated with albuminuria, and both independently predicted mortality (22). In the current report, both ABI >1.40 and albuminuria independently predicted incident LEA. An interesting finding is this work relates to the protective role of education in risk of LEA. In the SHS cohort as a whole, 52% of participants had completed high school, but this proportion differs according to diabetes status: 46% of participants with diabetes completed a high school education compared with 54% of participants without diabetes. Part of the diabetes-associated difference in educational attainment in the cohort is an age effect, with older participants less likely to have completed high school. However, the effect of education persisted in multivariable models that adjusted for age and other LEA risk factors, with a high school education being associated with a reduction in LEA risk of >50%.

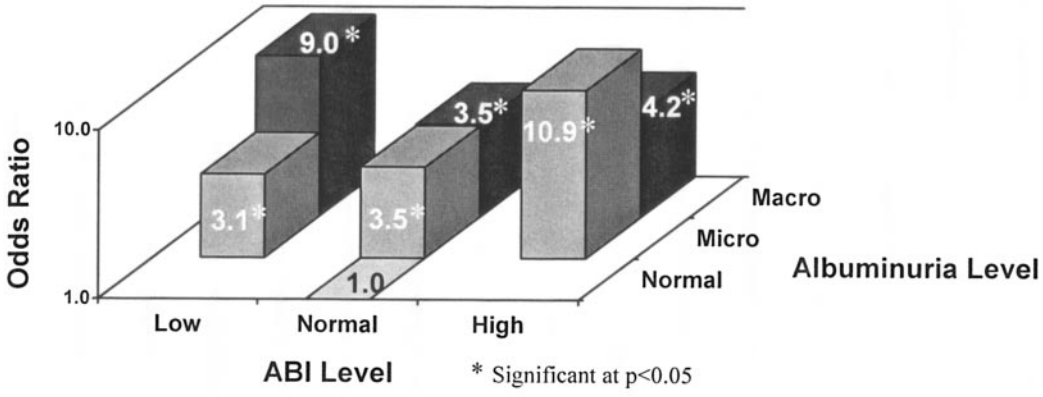

Figure 3—*ORs of incident LEA by categories of albuminuria and ABI: the SHS. Comparisons are between each vertical bar and the reference group (those with normal albuminuria and normal ABI), which is indicated by an OR of 1.0.*

Table 3—*Logistic regression analysis relating baseline characteristics to 8-year risk of LEA: the SHS*

Risk factor	β-Coefficient	OR (95% CI)	*P*
Age	−0.038	0.96 (0.93–0.99)	0.02
Sex (male vs. female)	0.725	2.06 (1.29–3.30)	<0.01
High school education or higher	−0.787	0.46 (0.27–0.76)	<0.01
Center (Oklahoma vs. the Dakotas)	−0.198	0.82 (0.39–1.74)	0.61
Center (Arizona vs. the Dakotas)	0.146	1.16 (0.64–2.11)	0.63
Duration of diabetes	0.030	1.03 (1.01–1.06)	0.01
HbA_{1c} (6.5–9.5 vs. <6.5%)	0.814	2.26 (1.07–4.77)	0.03
HbA_{1c} (>9.5 vs. <6.5%)	1.246	3.48 (1.68–7.20)	<0.01
Systolic blood pressure	0.016	1.02 (1.01–1.03)	<0.01
BMI	−0.063	0.94 (0.90–0.98)	<0.01
Microalbuminuria	0.984	2.67 (1.48–4.84)	<0.01
Macroalbuminuria	0.540	1.72 (0.86–3.41)	0.12
Low ABI (<0.9)	0.405	1.50 (0.66–3.40)	0.33
High ABI (>1.4)	0.586	1.80 (1.02–3.17)	0.04

N = 1,880.

The importance of education in reducing risk of LEA was shown in a previous study (15) of black and white Americans in the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study. This study showed that although there were substantially higher age-adjusted rates of LEA in black, compared with white, Americans, this excess risk was eliminated when the presence or absence of a high school education was considered, along with age, diabetes, smoking, and hypertension. Of particular interest in these two reports are the nearly identical adjusted risk estimates associated with having a high school education: in the NHANES Follow-up Study, the adjusted risk estimate for LEA associated with having completed high school was 0.47, and the corresponding risk estimate in the Strong Heart Study was 0.46. Thus, completing high school and/or the complex set of favorable factors that is associated with completing high school reduces the risk of LEA by >50%.

Data concerning the importance of blood pressure as a predictor of LEA in American Indians are conflicting. In the current report, systolic blood pressure was found to be an important predictor of LEA, results that are consistent with findings for men in the Oklahoma Indian Diabetes Study (5) but inconsistent with findings from Pima Indians (6).

Our finding of no association between smoking and LEA risk is consistent with findings from a study of Pima Indians (6). However, smoking is a known risk factor for LEA in other large prospective studies (15). A likely explanation for this finding is that smokers in the SHS cohort smoke fewer cigarettes per day than the national average, with use as low a six cigarettes per day among women in the Arizona center (28). Further, long duration of diabetes among SHS cohort members could overwhelm a weak association between smoking and LEA.

Our data show differences in the cumulative incidence of LEA across the three SHS centers, with the highest rates in Arizona (6.2%) and similar lower incidence in Oklahoma (3.3%) and the Dakotas (2.5%). Although regional differences in physician practice patterns and patient preferences may explain some of the geographic differences in LEA among individuals in the SHS, a more likely explanation for these differences is that participants in the Arizona center had longer duration of diabetes at baseline (13.6 vs. 9.0 and 10.1 years in the Dakotas and Oklahoma, respectively).

Our study has several important limitations. First, information on neuropathy, history of ulcers, or description of foot deformity was not available. If these data had been available at baseline, we expect that we would have observed significant relationships between these factors and incident LEA. To what extent our parameter estimates for risk factors such as sex and HbA_{1c} would have been influenced by inclusion of these factors in the model is difficult to estimate. However, if we had been able to exclude people with a history of foot ulcers from the analysis, it is likely that the number of incident LEAs would have been reduced, and this would have reduced the power of the study. Although we ascertained LEA among participants at each exam cycle by direct examination of the legs and feet, our protocol did not include the use of hospitalization records. We may therefore have missed some LEAs that occurred among participants who died between exams. Addition of these events may have resulted in increased power, which would have added precision to some LEA risk estimates with wide CIs that included 1.0, rendering some relationships statistically significant. Finally, our models were based on data from 81 of the 87 individuals with incident LEA and 1,799 of the 1,887 individuals without LEA who had complete covariate data. Empirical comparison of available risk factor data between the six LEA participants with incomplete covariate data and the 88 non-LEA participants with incomplete data suggested less favorable profiles for those with incident LEA for several important variables, including diabetes duration (19.9 vs. 13.5 years), high ABI (50 vs. 34%), low ABI (16 vs. 7%), and HbA_{1c} (10.9 vs. 8.6%). Although small numbers precluded reliable comparisons, these data suggest that the strength and precision of the associations we report for some LEA risk factors may be underestimated.

Duration of diabetes and baseline HbA_{1c} both appear to contribute important information on LEA risk among individuals with diabetes. Our data show increased risk of LEA associated with worse glycemic control, adjusted for dia-

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betes duration, and the reverse was also true. Despite the importance of diabetes duration in our models of LEA risk, this factor is not one for which interventions can be effectively designed. However, our data suggest that it is possible to identify American Indians at particularly high risk of LEA. LEA prevention efforts may therefore be especially effective in this group. Thus, public health resources for LEA prevention should be focused on designing and implementing effective interventions for modifiable risk factors such as glycemic control, blood pressure, renal disease, and peripheral vascular disease.

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