Diabetes and Nontraumatic Lower Extremity Amputations

Incidence, risk factors, and prevention—a 12-year follow-up study in Nauru

A.R.G. HUMPHREY, MB, CHB
G.K. DOWSE, MB, BS, MSC
K. THOMA, DSM
P.Z. ZIMMET, MD, PHD

OBJECTIVE — To measure the 12-year incidence (1982–1994) of nontraumatic lower extremity amputations (LEAs) in Nauruans, a population at high risk for NIDDM, and to determine the risk factors for amputation in Nauruans with diabetes.

RESEARCH DESIGN AND METHODS — Amputation data were abstracted from operating theater records in Nauru, hospital databases in Australia, and Nauru government records. Baseline characteristics of a cohort of 1,564 Nauruans aged ≥20 years examined during a population-based survey in 1982 were used to determine risk factors for first LEAs.

RESULTS — Over this 12-year period, 46 first LEAs were performed on people with NIDDM, of whom 30 were members of the 1982 study cohort. The incidence of first LEAs in Nauruans aged ≥25 years with NIDDM was 8.1 per 1,000 person-years in the study cohort and an estimated 7.6 per 1,000 person-years nationally. Amputations were associated significantly with lower BMI, lower blood pressure, higher fasting plasma glucose (FPG) level, and longer mean duration of diabetes at baseline, but levels of other risk factors, including cigarette smoking, plasma triglycerides, and plasma cholesterol, were also elevated in amputees. There were no amputations among individuals with baseline FPG levels <7.8 mmol/l, irrespective of diabetes duration. FPG, baseline diabetes duration, and male sex were independent risk factors for first amputation using the Cox proportional hazards model. There was a decrease in the incidence of amputations after the commencement of a national foot care health education and prevention campaign in June 1992.

CONCLUSIONS — The incidence of LEAs in diabetic Nauruans was higher than in other populations after adjusting for age and duration. Given the apparent success of the Nauruan footcare program in reducing amputation rates, other populations with high rates of NIDDM and LEAs should consider population-wide prevention strategies.

Diabetes is the leading cause of nontraumatic lower extremity amputations (LEAs). Of all amputations performed in the U.S., approximately half are on people with diabetes (1). In populations where the prevalence of NIDDM is high, such as the Pima Indians of Arizona (2), the proportion of amputations associated with diabetes is even higher. However, studies of the Oklahoma Indians (3) and other Native Americans (4) have demonstrated that differences in the incidence of amputation are not directly related to the prevalence of diabetes alone but may reflect variation in levels of other factors, including standards of health care, socioeconomic status, and education. There is an epidemic of NIDDM in many developing countries, but we are not aware of any studies that have examined the incidence of amputations in these populations.

From the International Diabetes Institute, Melbourne, Australia.
Address correspondence and reprint requests to Alistair Humphrey, MD, International Diabetes Institute, 260 Kooyong Rd., Caulfield South, Melbourne VIC 3162, Australia. E-mail: zimmet@vaxc.cc.monash.edu.au.
Received for publication 20 October 1995 and accepted in revised form 25 January 1996.
FPG, fasting plasma glucose; 2PG, 2-h plasma glucose; IGT, impaired glucose tolerance; LEA, lower extremity amputation; WHO, World Health Organization.

The present study describes the incidence and risk factors for LEAs in the Republic of Nauru, which has the highest national prevalence of diabetes in the world (5). We also examined the effect of a population-wide footcare health promotion program designed to reduce the incidence of foot complications in Nauru.

RESEARCH DESIGN AND METHODS

Background and study population

Nauru is an isolated island in the Central Pacific Ocean with a population, according to the 1992 census, of 6,831 ethnic Nauruans. The prevalence and incidence of diabetes (exclusively NIDDM) and its complications have been studied in Nauru since 1975 (5–8). The present study is limited to the period since January 1982, when a baseline survey (8) was attended by an estimated 83% (n = 1,564) of Nauruans aged ≥20 years, of whom 375 had diabetes. The incidence density of LEAs was studied in subjects with NIDDM from this study cohort. In addition, the incidence of LEA for all diabetic Nauruans in this age-range was estimated. The denominators for the latter were calculated by applying age-specific NIDDM prevalence data from 1982 and 1994 surveys to the census-derived population structure. The age-adjusted prevalence of NIDDM did not change between 1982–1994 (5,9), and age-specific prevalence has remained relatively constant over the same period. In addition, a postsurvey questionnaire in 1994 revealed no difference between attendees and nonattendees, with the exception of a slightly higher prevalence of smokers in nonattendees. The same detail was not available for the 1982 survey, but there was no difference in age distribution between attendees and nonattendees. We are confident, therefore, that prevalence rates of diabetes in the survey populations can be applied to the general population.

Downloaded from http://diabetesjournals.org/care/article-pdf/19/7/710/515521/19-7-710.pdf by guest on 20 January 2022

Table 1—*Age- and sex-specific incidence of first lower extremity amputation in diabetic Nauruans ≥25 years of age*

Age-group	Person-years at risk	No. of amputations	Incidence in study cohort	Incidence in whole population
Men				
25–44	488	5	10.2	6.48
45–64	857	11	12.84	11.10
65+	163	1	6.13	9.00
All ages	1,508	17	11.3	8.69
Women				
25–44	735	4	5.44	4.91
45–64	1,067	8	7.50	8.45
65+	261	1	3.83	6.80
All ages	2,063	13	6.30	6.50
Combined sexes				
25–44	1,225	9	7.41	5.67
45–64	1,923	19	9.88	9.80
65+	424	2	4.72	8.03
All ages	3,571	30	8.40	7.58

Person-years ≥25 contributed to each age-group by diabetic Nauruans aged ≥20 years at baseline (January 1982). Age-group in which amputation occurred is shown. Incidence in study cohort is based on cases per 1,000 person-years at risk. Incidence in whole population was the estimated rate in all diabetic Nauruans (see METHODS for explanation).

The Nauru Love Your Feet campaign
In response to a clinically perceived increase in the number of amputations, a dedicated footcare clinic was established in Nauru in March 1992 staffed by two local nurse aides who had received training in the management of the diabetic foot from the Podiatry Department at Caulfield General Medical Centre, Melbourne. At the same time, the Nauru Love Your Feet health promotion program was commenced, during which posters, leaflets, and bumper stickers explaining five basic principles of foot care (foot hygiene and examination; correct toenail trimming; wearing correct footwear; regular clinic attendance for people with diabetes; and early presentation for foot care problems) were distributed in clinics, retail outlets, and schools throughout the island. In addition, a 5-min video containing the same information was screened on the nationwide television channel daily for 2 out of every 10 weeks for 6 months.

Ascertainment of amputations
Medical treatment in Nauru is free at point of service and funded by the government, even when treatment is carried out overseas. Operating theater records were examined in the two hospitals in Nauru to determine the number of nontraumatic amputations carried out in the country between 26 January 1982 and 31 May 1994. All patients requiring overseas treatment were referred to hospitals in Melbourne, Australia. Nauru welfare office data were used to determine the number of amputations carried out in Melbourne. Sources used to validate Nauru theater records were survey questionnaire data from 1987 and 1994 and clinical information; Nauru welfare office data were validated using Melbourne hospital records and referral data from Nauru. The Nauru government had no record of any amputations performed elsewhere during the study period.

Amputations were defined according to the Global Lower Extremity Amputation Study (10). In brief, a minor LEA was any amputation distal to the ankle joint; a major LEA was any amputation through or proximal to the ankle joint. Individuals whose first amputation in the theater records was major were followed back in their medical records to confirm that previous amputations had not occurred.

Baseline measurements
As described previously (5,8), characteristics measured at the 1982 survey included height and weight, systolic and diastolic blood pressure, fasting plasma glucose (FPG), 2-h plasma glucose after an oral glucose challenge (75 g dextrose monohydrate dissolved in 250 ml water), total plasma cholesterol, and fasting plasma triglycerides. Weekly alcohol and daily cigarette consumption were determined from a brief health questionnaire. Diabetes was defined according to 1985 World Health Organization (WHO) criteria (11). Briefly, subjects reporting a history of diabetes had known diabetes if they were currently taking oral agents or insulin or if they had a FPG ≥7.8 mmol/l or a 2-h plasma glucose (2PG) ≥11.1 mmol/l. New diabetic subjects were those without a history who had 2PG ≥11.1 mmol/l or, if the latter was missing, FPG ≥7.8 mmol/l.

Hypertension was defined according to WHO criteria (12) as a mean diastolic blood pressure ≥95 mmHg, mean systolic blood pressure ≥160 mmHg, or a self-reported history with current use of antihypertensive medication.

Statistical analysis
Patient-year amputation rates in the study cohort for ages ≥25 years were calculated using survival time from 26 January 1982 until either the first amputation or 31 May 1994, the date of completion of the study. People who died during the follow-up period were censored at the date of death. Age-specific person-years were calculated by summing the number of years contributed to each age stratum across all subjects. The contribution of diabetic person-years was taken from the date of diagnosis. Mortality rates were calculated by the same method.

Analyses of risk factor associations were confined to those subjects who attended the 1982 survey and who were classified as having diabetes at that time. Proportions were age standardized by the direct method (13) using the 1992 Nauru Census as the standard population. The age-standardized prevalence of baseline risk factors in amputees and nonamputees was compared using a variation of Cochrane's test, as described by Armitage and Berry (13). Mean values for continuous variables were compared using analysis of covariance after adjusting for age and duration using SPSSPC+ software (14). Crude incidence density rate ratios and associated *P* values were calculated using density follow-up methods (15).

Multivariate analysis of risk factors was performed using a forward stepwise procedure with the Cox propor-

Downloaded from http://diabetesjournals.org/care/article-pdf/19/7/710/515521/19-7-710.pdf by guest on 20 January 2022

Table 2—*Age-standardized prevalences and age/duration-adjusted means of risk factors at baseline among diabetic Nauruans with and without amputations, 1982–1994*

Risk factor at baseline	Amputee	Nonamputee	*P* value
n	29	346	
Age (years)	45.9	46.5	0.73
Duration (years)	7.2	3.4	<0.01
Male sex (%)	58.7	44.1	0.28
Hypertension (%)	1.0	26.0	0.03
Alcohol consumption per day (g)	24.8	24.6	0.99
Current smoker (%)	67.6	46.0	0.07
BMI (kg/m^2)	31.9	34.9	0.03
Systolic blood pressure (mmHg)	121	135	<0.01
Diastolic blood pressure (mmHg)	75	79	0.2
Plasma cholesterol (mmol/l)	5.11	5.02	0.68
Fasting plasma triglycerides (mmol/l)	1.60	1.36	0.20
FPG (mmol/l)	14.3	10.9	<0.01

tional hazards model (16) and BMDP software (17). Variables tested for inclusion in the models were chosen on the basis of results of preliminary analyses and of studies in other populations. The proportionality assumption was verified using survival plots of those variables that were significant. Interactions were tested between significant variables.

RESULTS— There was a total of 46 first nontraumatic LEAs (26 men, 20 women) performed on Nauruans during the follow-up period, a national incidence for all Nauruans aged ≥25 years (both diabetic and nondiabetic) of 2.37 per 1,000 person-years in men and 1.75 per 1,000 person-years in women. The youngest amputee was 33 years old at the time of amputation. Of the 46 people who had amputations, 18 had a single minor amputation, 18 had a single major amputation, 7 had a major and a minor amputation, and 3 had more than one major amputation. All nontraumatic amputees had diabetes. The estimated national incidence rate of first LEA among men and women diabetic Nauruans aged ≥25 years was 8.69 and 6.50 per 1,000 person-years, respectively (Table 1). There were 30 first LEAs performed on members of the 1982 cohort, of whom 29 had diabetes in 1982 and 1 developed diabetes after the survey but before their first amputation. Table 1 shows the incidence of amputations in diabetic members of the 1982 study cohort; the incidence density ratio of diabetic men to women was 1.8 ($P = 0.05$).

The mean duration of diabetes at baseline in incident amputees was 7.2 years compared with 3.4 years in nonamputees ($P < 0.01$), but mean age did not differ significantly between the two groups (Table 2). When adjusted for both age and duration of diabetes, amputees had significantly higher levels of FPG and significantly lower levels of systolic blood pressure and BMI. Plasma cholesterol, triglyceride levels, and frequency of cigarette smoking were nonsignificantly elevated in amputees. When stratified by sex, comparisons of risk factors between amputees and nonamputees were similar to those for combined sexes (data not shown).

Cox regression analysis revealed that FPG, diabetes duration, and male sex were independent risk factors for amputation (Table 3). These risk factors were also significant predictors of all cause mortality in the 1982 diabetic cohort using the same model, with the addition of cigarette smoking and age (data not shown). Increasing blood pressure carried a lower risk of amputation. No interaction could be demonstrated between significant variables.

As shown in Fig. 1, at any level of baseline diabetes duration, risk of LEA increased with higher levels of FPG. There were no amputations in the 77 diabetic patients with baseline glucose levels <7.8 mmol/l, even when duration was >10 years.

Compared with the years 1990–1992, the incidence of amputations nationally decreased (incidence density ratio = 0.446, $P = 0.047$) after June 1992, the date of commencement of the national foot care program (Fig. 2). Although nonsignificant at the 0.05 level, the incidence after 1992 was also reduced relative to the longer period of 1982–1992 (incidence density ratio = 0.57, $P = 0.096$).

CONCLUSIONS— The incidence of LEAs in diabetic Nauruans is high compared with rates in diabetic whites, which range from 2.4 per 1,000 person-years in Finnish women (18) to 5.7 and 6.0 per 1,000 person-years in the U.K. (19) and the U.S. (1), respectively. The overall incidence of amputations in Nauruans is lower than rates recorded in Pima (2) and Oklahoma (3) Indians, though this does not take into consideration population differences in age and survival/duration of diabetes. It is impossible to account for every difference among such diverse populations, and five yearly surveys will underestimate diabetes duration more than the two yearly examinations performed on the Pima Indians. However, when stratified for age and duration of diabetes, amputation rates in Nauruans are generally higher than in Pima Indians (Fig. 3).

The risk factors for amputation demonstrated by univariate analysis (duration of diabetes and FPG) and multivariate analysis (duration, FPG, and male sex) in diabetic Nauruans have been found in other populations with both low (20) and high (2,3) prevalence of

Table 3—*Risk factors for first lower extremity amputation (1982–1994) in diabetic Nauruans using the Cox proportional hazards model*

Risk factor	Unit	*P*	Relative risk (95% CI)
FPG	1 mmol/l	<0.001	1.26 (1.14–1.38)
Diabetes duration	1 year	<0.001	1.15 (1.07–1.23)
Female sex	yes/no	0.015	0.34 (0.18–0.83)
Systolic blood pressure	10 mmHg	0.010	0.78 (0.76–0.80)

Risk factors not entering the model were age, BMI, total plasma cholesterol, fasting plasma triglycerides, mean daily alcohol intake, and cigarette smoking.

Downloaded from http://diabetesjournals.org/care/article-pdf/19/7/710/515521/19-7-710.pdf by guest on 20 January 2022

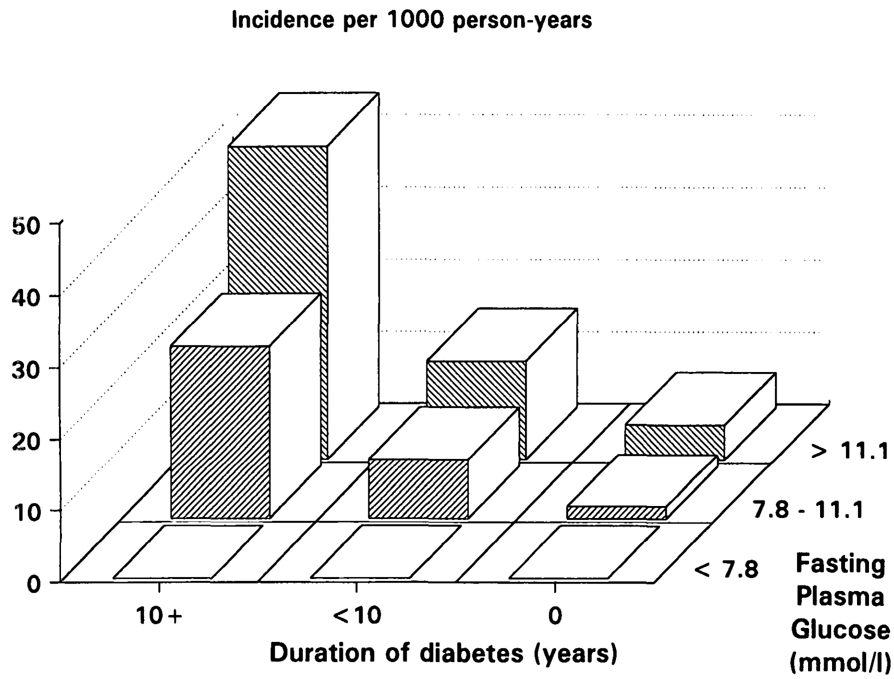

Figure 1—*Incidence (1982–1994) of first LEAs stratified by baseline FPG and baseline duration in diabetic Nauruans aged ≥20 years at baseline.*

NIDDM. Risk factors that we were unable to investigate included insulin treatment, since very few members of our 1982 cohort were treated with insulin, and markers of peripheral neuropathy, which were not measured.

The association between lower BMI and LEA by univariate analysis may reflect weight loss due to poor glycemic control, but BMI and FPG were not significantly correlated, and BMI was not retained in multivariate models. The association of LEA with lower blood pressure is hard to explain; it is unlikely to be due to antihypertensive treatment in diabetic Nauruans, since only 1% of amputees were hypertensive and/or on antihypertensive treatment. It is possible that the complications of hypertension (such as stroke and myocardial infarction) causes death before the necessity for an amputation arises. The Framingham Study (21) found hypertension to be a risk factor for peripheral vascular disease, but blood pressure has not been a consistent risk factor for amputation in other studies (2,3,20).

Cox regression revealed that the risk factors for death among diabetic Nauruans were the same as risk factors for amputations, with the addition of age and smoking. Given the high rate of mortality in diabetic Nauruans, even in young adults (22), it is likely that in many cases, death precludes amputation. Mortality in diabetic Nauruans is considerably higher than in Pima Indians (23) irrespective of age (A.R.G.H., unpublished observations), and the effect of mortality in reducing average duration of diabetes is likely to be in large part responsible for the lower crude incidence of LEA in Nauruans. However, as shown earlier, age- and duration-stratified amputation rates in Nauruans are higher than those of the Pima Indians. Poorer glycemic control in Nauru may account for at least some of the higher amputation rates, since baseline FPG levels of ≤7.8 mmol/l accounted for only 24% of follow-up in the Nauruan cohort, compared with 32% of person-years follow-up in the Pima Indians (2).

It is not known whether differences in medical management of diabetic sepsis and gangrene might confound comparison of amputation rates between Nauruans, Pima, and other populations, but we have no reason to believe amputations in Nauru are performed unnecessarily. In fact, over 60% of deaths in diabetic Nauruans attributed to septicemia during the follow-up period were secondary to gangrene. This suggests that gangrene was managed conservatively in Nauru. By contrast, gangrene is an obligatory indication for amputation in the U.S. (2). Given the validation procedures used and the distinctive nature of amputation as an endpoint, a difference in reporting or ascertainment of LEA is unlikely to account for the difference in the amputation rate between the Pimas and the Nauruans.

There were no amputations among the 20.8% of diabetic Nauruans who had FPG levels <7.8 mmol/l at baseline, irrespective of disease duration. Although only a single fasting glucose measurement was used, this is generally accepted as a good indicator of long-term

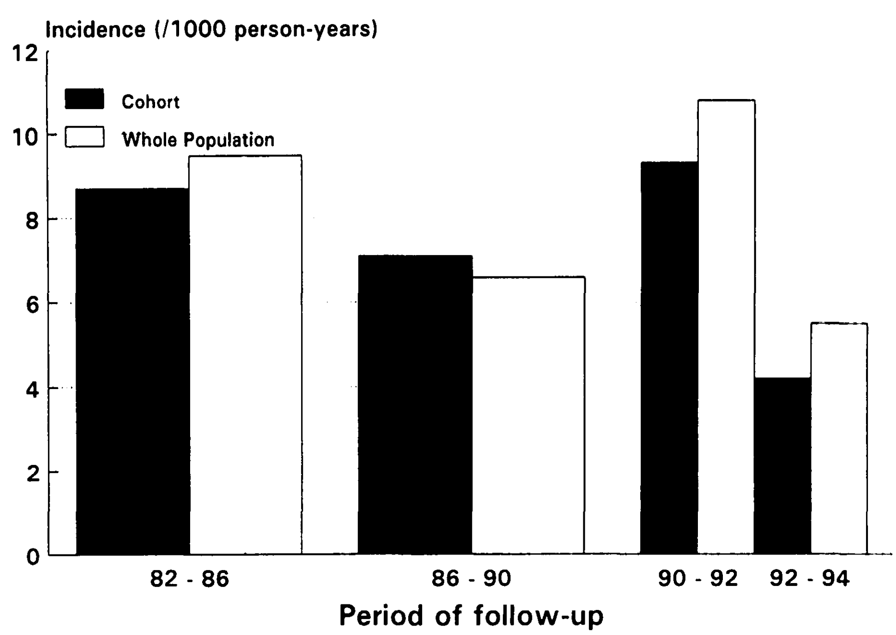

Figure 2—*Incidence (1982–1994) of first LEAs in diabetic Nauruans aged ≥20 years at baseline.*

Downloaded from http://diabetesjournals.org/care/article-pdf/19/7/710/515521/19-7-710.pdf by guest on 20 January 2022

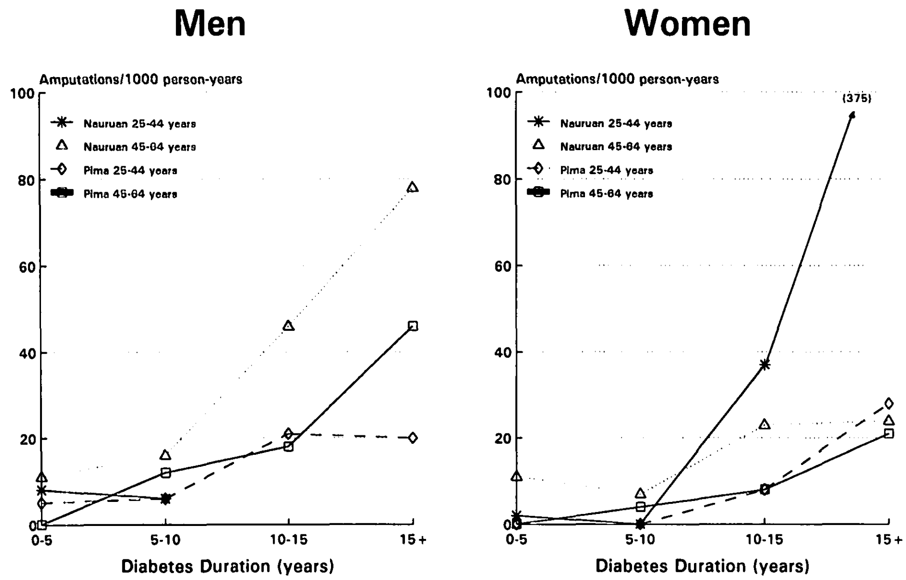

Figure 3—*Incidence of first LEAs by baseline duration of diabetes stratified according to age at amputation and sex in diabetic Pima Indians and Nauruans. Pima data abstracted from Nelson et al. (2).*

control in NIDDM. The results from this study confirm the relationship between poor glycemic control and risk of amputations (2,3,20) but also suggest that a population-based approach towards improving glycemic control is likely to lead to a reduction in the incidence of amputations in diabetic Nauruans and that little or no amputations occur in this population when control is tight.

In conclusion, we have found a high incidence of first LEAs among diabetic Nauruans, which might be higher still were it not for the extremely high (premature) mortality associated with diabetes in Nauru. A decline in the incidence of first LEA has followed the establishment of a dedicated foot care clinic supported by a national health promotion program, though much longer follow-up will be required before the real effect of this program can be established. The Nauru Love Your Feet program may have relevance to other populations with high rates of NIDDM and diabetic amputations. In the meantime, the evidence from this study indicates that, given the high prevalence of diabetes in Nauru, a similar nationwide approach to improved glucose control could help further reduce the incidence of amputations as well as have an impact on other diabetic complications in this population.

Acknowledgments— This study was supported by grant DK-25446 from the National Institute of Diabetes and Digestive and Kidney Diseases.

This study was undertaken in collaboration with the government and health department of Nauru. We also thank Ms. Alison Shaw, Head of Podiatry at Caulfield General Medical Centre; Rina Hartman, nurse for the Nauru Foot Care Clinic; and Ross, Bing, Swallow, and Partners, who helped develop material for the foot care program.

References

1. Most RS, Sinnock P: The epidemiology of lower extremity amputations in diabetic individuals. *Diabetes Care* 6:87–91, 1983
2. Nelson RG, Gohdes DM, Everhart JE, Hartner JA, Zwemer FL, Pettitt DJ, Knowler WC: Lower extremity amputations in NIDDM: 12 year follow-up study in Pima Indians. *Diabetes Care* 11:8–16, 1988
3. Lee JS, Lu M, Russell D, Bahr C, Lee ET: Lower-extremity amputation: incidence, risk factors and mortality in the Oklahoma Indian Diabetes Study. *Diabetes* 42: 876–872, 1993
4. Valway SE, Linkins RW, Gohdes DM: Epidemiology of lower-extremity amputations in the Indian Health Service, 1982–1987. *Diabetes Care* 16 (Suppl. 1):349–353, 1993
5. Dowse GK, Zimmet PZ, Finch CF, Collins V: Decline in incidence of epidemic glucose intolerance in Nauruans: implications for the "thrifty genotype." *Am J Epidemiology* 133:1093–1104, 1991
6. King H, Zimmet P, Raper LR, Balkau B: The natural history of impaired glucose tolerance in the Micronesian population of Nauru: a six-year follow-up study. *Diabetologia* 26:39–43, 1984
7. Zimmet P, Taft P, Guinea A, Guthrie W, Thoma K: The high prevalence of diabetes mellitus on a Central Pacific island. *Diabetologia* 13:111–115, 1977
8. Zimmet P, King H, Taylor R, Raper LR, Balkau B, Borger J, Heriot W, Thoma K: The high prevalence of diabetes mellitus, impaired glucose tolerance and diabetic retinopathy in Nauru: the 1982 survey. *Diabetes Research* 1:13–18, 1984
9. Zimmet PZ, Humphrey ARG, Dowse GK: Report on the 1994 Diabetes and Eye Disease Survey: Republic of Nauru. Melbourne, International Diabetes Institute, 1994
10. LEA Study Group: Comparing the incidence of lower extremity amputations across the world: the Global Lower extremity Amputation Study. *Diabetic Med* 12:14–18, 1995
11. World Health Organization: *Diabetes Mellitus: Report of a Who Study Group.* Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
12. World Health Organization: *WHO Expert Committee on Arterial Hypertension.* Geneva, World Health Org., 1978 (Tech. Rep. Ser., no. 628)
13. Armitage P, Berry G: *Statistical Methods in Medical Research.* 3rd Ed. Oxford, England, Blackwell Scientific Publications, 1994, p. 436–441
14. Norušis MJ: *SPSS/PC+ Statistics 4.0.* Chicago, SPSS Inc., 1990
15. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiological Research: Principals and Quantitative Methods.* New York, Van Nostrand Reinhold, 1982, p. 284–288
16. Cox DRX: Regression models and life tables. *J of the Royal Stat Soc of Britain* 34: 187–220, 1972
17. Dixon WJ, Ed: *BMDP Statistical Software Manual* 2. Berkeley, CA, University of California Press, 1988, p. 941–969
18. Siitonen PS, Niskanen LK, Laakso M, Siitonen JT, Pyörälä K: Lower extremity amputations in diabetic and non-diabetic patients: a population based study in eastern Finland. *Diabetes Care* 16:16–20, 1993
19. Deerochanawong C, Home PD, Alberti KGMM: A survey of lower limb amputation in diabetic patients. *Diabetic Med* 9:942–946, 1992
20. Moss SE, Klein R, Klein BEK: The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Int Med* 152:610–616, 1992
21. Kannel WB, McGee DL: Update on some epidemiological features of intermittent claudication: the Framingham Study. *J Am Ger Soc* 33:13–18, 1985
22. Zimmet PZ, Finch CF, Schooneveldt MG, King HO, Thoma K: Mortality from diabetes in Nauru: results of a 4-Yr follow-up. *Diabetes Care* 11:305–311, 1988
23. Sievers ML, Nelson RG, Knowler WC, Bennett PH: Impact of mortality and causes of death in Pima Indians. *Diabetes Care* 15:1541–1549, 1992

Downloaded from http://diabetesjournals.org/care/article-pdf/19/7/710/515521/19-7-710.pdf by guest on 20 January 2022