The 14-Year Incidence of Lower-Extremity Amputations in a Diabetic Population

The Wisconsin Epidemiologic Study of Diabetic Retinopathy

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OBJECTIVE — To estimate the cumulative 14-year incidence of lower-extremity amputations (LEAs) and evaluate risk factors for LEA.

RESEARCH DESIGN AND METHODS — Study subjects consisted of population-based cohorts of younger-onset (diagnosed before age 30 years and taking insulin, *n* = 906) and older-onset (diagnosed after age 30 years, *n* = 984) individuals with diabetes. Subjects participated in baseline (1980–1982), 4-year, 10-year, and 14-year examinations or interviews. LEAs were determined by history.

RESULTS — The cumulative 14-year incidence of LEA was 7.2% in younger- and 9.9% in older-onset patients. In multivariable analyses based on the discrete linear logistic model, LEA in the younger-onset group was more likely for males (odds ratio [OR] 5.21 [95% CI 2.50–10.88]), older age (OR for 10 years 1.71 [1.30–2.24]), higher glycosylated hemoglobin (OR for 1% 1.39 [1.22–1.59]), higher diastolic blood pressure (OR for 10 mmHg 1.58 [1.20–2.07]), history of ulcers of the feet (3.19 [1.71–5.95]), and more severe retinopathy (OR for one step 1.16 [1.08–1.24]). In younger-onset patients aged ≥18, pack-years smoked (OR for 10 years 1.20 [1.03–1.41]) was also associated with LEAs, and daily aspirin use was inversely associated (OR 0.11 [0.01–0.83]). In the older-onset group, LEA was more likely for men (2.66 [1.49, 4.76]) and if the subject had higher glycosylated hemoglobin (OR for 1% 1.25 [1.09–1.43]), higher pulse pressure (OR for 10 mmHg 1.19 [1.04–1.37]), history of ulcers (3.56 [1.84–6.89]), and more severe retinopathy (OR for one step 1.07 [1.00–1.13]).

CONCLUSIONS — There are several risk factors for LEA with potential for modification and preventive strategies.

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Estimates of the proportion of lower-extremity amputations (LEA) occurring in people with diabetes center around one-half (1–6). In addition, it has been estimated that people with diabetes are 10–24 times more likely to have a LEA than people without diabetes (1–4,6–8). However, several programs for education and diabetic foot care have demonstrated that amputations are not an inevitable consequence of diabetes (9–12). Knowing risk factors for amputations is important both for targeting education programs toward people at high risk and for suggesting modifiable factors that might be explored in clinical trials of prevention programs.

We have previously reported the incidence of LEA in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) cohort after 4 and 10 years of follow-up (13,14). Now, after 14 years of follow-up, we have more data with which to evaluate relationships of variables from baseline and from examinations later in the study. Thus, the purpose of this article is to estimate the 14-year incidence of LEA and to investigate risk factor relationships.

RESEARCH DESIGN AND METHODS

— Details of the case identification methods and the population have been published (15–21). Briefly, the study area is composed of 11 counties in southern Wisconsin. From 1 July 1979 through 30 June 1980, all patients with diabetes were identified in the practices of 452 of 457 primary care physicians in the area (*n* = 10,135). Estimates of the extent of underreporting have been described in a previous publication (15). A two-part sample of this population was invited to participate in the baseline examination from 1980 to 1982. The first part consisted of all patients who were diagnosed as having diabetes before 30 years of age and who were taking insulin (*n* = 1,210), referred to as the younger-onset group. The second part consisted of a probability sample, stratified on duration of diabetes, of people who were diagnosed at or after 30 years of age whose diagnosis was confirmed by a casual or postprandial serum glucose of at least 11.1 mmol/l or a fasting serum glucose of at least 7.8 mmol/l on at least two occasions at least 1 month apart (*n* = 1,780). This group is referred to as the older-onset group. Of the younger-onset group, 996 (82.3%) participated in the baseline examination, and of the older-onset group, 1,370 (77.0%). Younger-onset nonparticipants had not had diabetes as long as participants. Otherwise, they did not differ significantly with respect to age, blood pressure, or recent blood glucose control (16). Among older-onset patients, nonparticipants were older, were diagnosed at a later age, had had diabetes longer, and were more likely to be women than participants. They did not differ with respect to blood pressure or recent blood glucose control (17). Surviving patients were invited to

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Abbreviations: LEA, lower-extremity amputation; OR, odds ratio; RR, relative risk; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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

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participate in 4-year (1984–1986) and 10-year (1990–1992) follow-up examinations and a 14-year (1995–1996) follow-up examination (younger-onset group) or interview (older-onset group). Comparisons of participants and nonparticipants in the follow-up examinations have appeared elsewhere (18–21).

All examinations followed a similar protocol, which was approved by the institutional Human Subjects Committee. Pertinent parts of the examination included explaining the nature of the procedures and obtaining informed consent, measuring blood pressure, administering a medical history questionnaire, taking stereoscopic color fundus photographs of seven standard fields, determining urine protein level by means of a reagent strip (Labstix; Ames Division of Miles Laboratories, Elkhart, IN), and determining glycosylated hemoglobin concentration.

The incidence of LEA was determined by history and included amputations of toes, feet, or legs. Traumatic amputations and those unrelated to diabetes were excluded. Any question concerning whether an amputation was a result of diabetes was referred to the subject's physician. Incidence is based on patients who had not had an amputation at baseline. The incidence reported is for the first amputation.

Severity of retinopathy was determined by grading of the fundus photographs by means of a modified Airlie House classification scheme as further adapted for the WESDR follow-up examinations (18). A 15-step scale was used for multivariable analyses.

Hypertension is defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or a history of hypertension with current use of antihypertension medications. Pulse pressure is defined as systolic minus diastolic blood pressure. Proteinuria is defined as a urinary protein level ≥0.30 g/l. BMI is defined as weight (kilograms) divided by height (meters) squared. A history of ulcers of the feet or ankles is defined as a breakdown in the skin caused by diabetic peripheral neuropathy or vascular disease. Patients are classified as nonsmokers if they reported having smoked <100 cigarettes in their lifetime, ex-smokers if they had smoked >100 cigarettes but had stopped smoking before the baseline examination, and current smokers if they had not stopped. Pack-years smoked is defined as the number of packs (1 pack = 20 cigarettes) smoked per day multiplied by the number of years smoked. Metabolic control was measured by glycosylated hemoglobin level using a microcolumn technique (22).

Several variables were first measured at the 1984–1986 examination. Plasma C-peptide was measured on a casual sample using the method described by Faber et al. (23). The lower limit of detectability is 0.03 nmol/l. Average daily consumption of absolute alcohol, in milliliters, was calculated as $(0.04 \times 360 \times A + 0.15 \times 120 \times B + 0.45 \times 45 \times C)/7$, where A, B, and C are the average numbers of portions consumed each week of 360 ml beer, 120 ml wine, and 45 ml distilled spirits, respectively. A nondrinker had not consumed any alcoholic beverages in the past year; a light drinker had consumed ≤6.3 ml absolute alcohol per day; a moderate drinker had consumed >6.3 but <30 ml per day; and a heavy drinker had consumed ≥30 ml per day. Information on claudication and physical activity was collected by history. The question regarding claudication reads, "Do you have (or had) any of these problems that may be related to your diabetes? Pain in legs on walking, relieved by resting (not due to arthritis)?" A person is said to be active if he or she engaged in a regular activity long enough to work up a sweat at least three times per week; otherwise, the person is said to be sedentary. Total cholesterol and HDL cholesterol were measured in a subset of the 1984–1986 examination participants (24–26).

Some participants in the 1984–1986 examination did not participate in later follow-up examinations; thus, these are censored observations. To compute 14-year cumulative incidence while still using the information contained in these censored observations, the product-limit method was used (27). To test for trends in incidence, the Mantel-Haenszel test of non-zero correlation, stratified on follow-up period, was used (28). Multivariable analyses were based on the discrete linear logistic model (29).

RESULTS — Of the 996 younger-onset patients participating in the baseline examination, 891, 765, and 634, respectively, participated in the 4-year, 10-year, and 14-year examinations. An additional 27, 50, and 65, respectively, provided information concerning LEA by interview at the same time as the 4-, 10-, and 14-year examinations. Among the younger-onset patients who participated in the 4-year follow-up by examination or interview, 906 were at risk of a first LEA. Of the 1,370 older-onset patients participating in the baseline examination, 987, 533, and 306, respectively, participated in the 4-year and 10-year examinations and the 14-year interview. An additional 27 and 37, respectively, provided information concerning LEA by interview at the same time as the 4- and 10-year examinations. Among the older-onset patients who participated in the 4-year follow-up by examination or interview, 984 were at risk of a first LEA. Table 1 presents baseline characteristics for younger- and older-onset patients at risk for amputation.

In the younger-onset cohort, 59 first LEA have occurred, resulting in a cumulative 14-year incidence of 7.2% (95% CI

Table 1—*Baseline characteristics of younger- and older-onset diabetic patients*

	Younger-onset		Older-onset	
Characteristic	*n*	Value	*n*	Value
Age at diagnosis (years)	906	14.4 ± 7.5	984	53.5 ± 12.3
Duration of diabetes (years)	906	13.5 ± 9.6	984	10.9 ± 7.8
Age at examination (years)	906	27.9 ± 12.2	984	64.4 ± 11.1
Glycosylated hemoglobin (%)	865	10.8 ± 2.1	910	9.6 ± 2.0
Blood pressure (mmHg)				
Systolic	900	123 ± 19	983	145 ± 23
Diastolic	898	78 ± 11	980	79 ± 11
BMI (kg/m^2)	904	23.4 ± 4.2	984	29.2 ± 5.7
Male	906	50.4	984	43.6
White	906	99.0	984	98.5
Proteinuria	876	19.4	948	10.9
Undetectable C-peptide	828	85.4	914	11.2

Data are *n*, means ± SD, or %. C-peptide levels were first measured in 1984–1986.

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5.4–9.0). In the older-onset group, 59 first LEA have occurred, resulting in an incidence of 9.9% (7.3–12.5).

Figures 1 and 2 present the 14-year incidence of LEA in younger- and older-onset patients by age and duration of diabetes, respectively. Incidence increased significantly ($P < 0.001$) with age in the younger-onset group but not in the older-onset group. In both groups, incidence increased significantly with duration of diabetes ($P < 0.001$).

Additional univariate relationships between baseline characteristics of the younger-onset group and 14-year cumulative incidence of LEA are presented in Table 2. Significantly higher incidence was present in patients with higher systolic and diastolic blood pressure, pulse pressure, glycosylated hemoglobin, retinopathy severity level, and pack-years smoked. Also, men, subjects with hypertension, proteinuria, or a history of ulcers of the feet and ankles, and former and current smokers were more likely to have had a LEA. Patients who had taken aspirin in the month before the baseline examination or who had regularly taken a daily aspirin for at least a 3-month period experienced significantly fewer amputations.

The results of similar univariate analyses of the older-onset group are presented in Table 3. Patients with higher pulse pressure, glycosylated hemoglobin, and retinopathy severity level were at greater risk of amputation. In addition, men and subjects with proteinuria or a history of ulcers of the feet or ankles were more likely to have had an amputation. There was an inverse association between diastolic blood pressure and incidence of amputations.

Information regarding some variables was first collected at the first follow-up examination in 1984–1986. We examined the relationships of these variables with incidence of LEA over the 10-year period to 1995–1996. In the younger-onset group, subjects with a higher C-peptide level (relative risk [RR] 1.95 [95% CI 0.88–4.36] for detectable C-peptide <0.3 nmol/l; RR 3.41 [1.12–10.32] for detectable C-peptide ≥0.3 nmol/l compared with undetectable C-peptide) were more likely to experience amputations. While the joint association of microalbuminuria (RR 2.34 [0.88–6.20]) and gross proteinuria (RR 6.17 [3.04–12.53]) was significant ($P < 0.001$), the comparison of subjects with microalbuminuria to those who were normoalbuminuric did not reach statistical significance. The associations between 10-year incidence of amputations and alcohol consumption, physical activity, total cholesterol, HDL cholesterol, and total-to-HDL cholesterol ratio were not significant. In the older-onset group, there was an inverse relationship between total cholesterol (RR 0.70 [0.25–1.93] for 5.10–6.10 mmol/l; RR 0.10 [0.02–0.48] for 6.15–17.00 mmol/l compared with 2.60–5.05 mmol/l) and 10-year incidence of amputations. The relationships with the remaining variables did not reach statistical significance.

To assess the independent association of risk factors with the incidence of amputations in the presence of other variables, we performed multivariable analyses based on the discrete linear logistic model. The results of those analyses, which include the odds ratio (OR) for amputation associated with a specified increment in the independent variables, are summarized in Table 4. In the younger-onset group, age was included in every model because it was highly correlated with several other factors, including blood pressure, BMI, and pack-years smoked. In the younger-onset group, those factors associated with a higher incidence of amputations included older age, male sex, higher glycosylated hemoglobin, higher diastolic blood pressure, a history of ulcers of the feet and ankles, and more

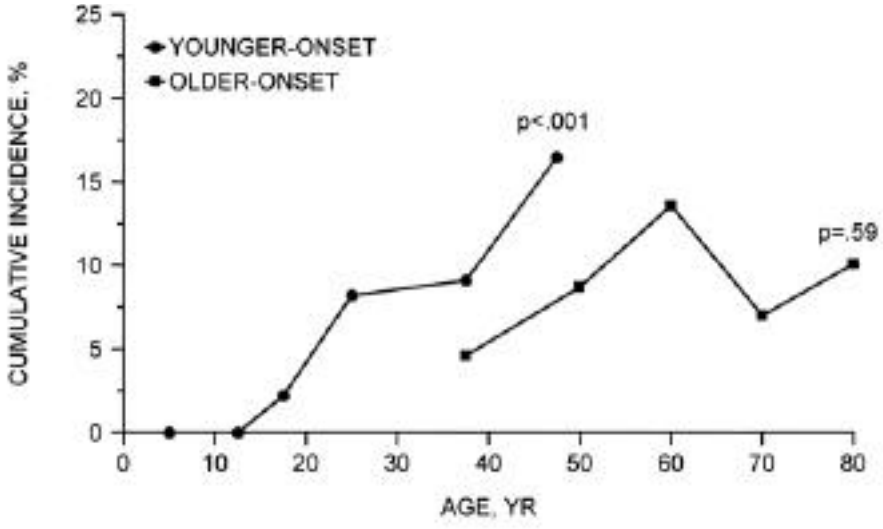

Figure 1—*The 14-year cumulative incidence of LEA by age at baseline in younger- and older-onset diabetic patients. Annotated* P *values are for a test of trend.*

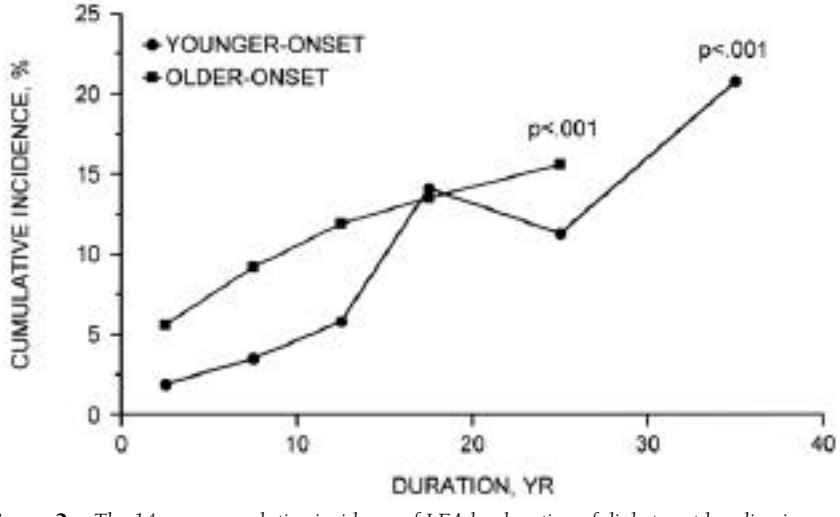

Figure 2—*The 14-year cumulative incidence of LEA by duration of diabetes at baseline in younger- and older-onset diabetic patients. Annotated* P *values are for a test of trend.*

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Table 2—*The 14-year cumulative incidence of LEAs by characteristics of the population in younger-onset diabetic patients*

Characteristic	Number of participants	Incidence (%)	RR (95% CI)	*P*
Sex				<0.001
F	449	2.9	1.00	
M	457	11.4	3.98 (2.23–7.09)	
Blood pressure (mmHg)				
Systolic				<0.001
78–110	225	3.9	1.00	
111–120	250	3.8	1.04 (0.40–2.70)	
121–134	233	4.8	1.26 (0.50–3.16)	
135–221	192	19.4	5.97 (2.97–12.02)	
Diastolic				<0.001
42–71	236	2.8	1.00	
72–78	231	5.8	2.12 (0.82–5.48)	
79–85	210	6.7	2.57 (1.01–6.53)	
86–117	221	14.2	5.84 (2.65–12.85)	
Hypertension				
Absent	662	3.8	1.00	<0.001
Present	239	17.2	5.42 (3.35–8.75)	
Pulse pressure (mmHg)				0.01
8–33	221	7.5	1.00	
34–41	227	3.3	0.44 (0.18–1.04)	
42–52	229	4.4	0.59 (0.26–1.32)	
53–125	221	14.0	2.00 (1.08–3.68)	
BMI (kg/m^2)				0.64
14.4–20.9	233	6.5	1.00	
21.0–23.0	217	7.1	1.08 (0.52–2.24)	
23.1–25.5	230	6.9	1.02 (0.49–2.13)	
25.6–50.8	224	7.9	1.21 (0.60–2.46)	
Glycosylated hemoglobin (%)				<0.001
5.6–9.4	223	2.5	1.00	
9.5–10.5	206	6.7	2.93 (1.10–7.83)	
10.6–12.0	220	7.6	3.21 (1.24–8.33)	
12.1–19.5	216	13.4	5.64 (2.43–13.10)	
Proteinuria				<0.001
Absent	706	5.1	1.00	
Present	170	17.3	3.75 (2.30–6.12)	
History of ulcers				<0.001
Absent	806	5.0	1.00	
Present	100	25.9	6.16 (3.89–10.42)	
Retinopathy				<0.001
None	270	1.6	1.00	
Mild	368	3.1	2.11 (0.68–6.51)	
Moderate	96	8.9	5.61 (1.90–16.51)	
Proliferative diabetic retinopathy	172	27.3	21.35 (10.13–44.98)	
Smoking status				0.003*
Nonsmoker	393	5.8	1.00	
Exsmoker	117	15.3	2.71 (1.46–5.01)	
Current smoker	203	12.3	2.10 (1.17–3.77)	
Pack-years smoked				<0.001
0	394	5.8	1.00	
<5	100	7.5	1.31 (0.56–3.04)	
5–14	92	13.5	2.15 (1.04–4.41)	
≥15	125	18.9	3.52 (1.99–6.23)	
Number of aspirin tablets in last 30 days				0.007
0	269	13.5	1.00	
1–29	366	6.7	0.47 (0.28–0.80)	
≥30	75	5.9	0.44 (0.16–1.20)	
Aspirin tablet/day for 3 months				0.05
No	644	9.9	1.00	
Yes	66	1.5	0.18 (0.03–0.98)	

Smoking and aspirin were assessed only in patients aged ≥18 years. *Test of general association.

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Table 3—*The 14-year cumulative incidence of LEAs by characteristics of the population in older-onset diabetic patients*

Characteristic	Number of participants	Incidence (%)	RR (95% CI)	*P*
Sex				<0.001
F	555	6.7	1.00	
M	429	14.2	2.36 (1.42–3.91)	
Blood pressure (mmHg)				
Systolic				0.15
80–130	256	8.9	1.00	
131–144	268	7.9	0.81 (0.40–1.64)	
145–160	249	10.3	0.99 (0.49–2.00)	
161–263	210	14.9	1.58 (0.79–3.17)	
Diastolic				0.03
45–70	220	17.3	1.00	
71–78	264	5.4	0.36 (0.18–0.73)	
79–87	263	13.0	0.70 (0.38–1.28)	
88–129	233	5.9	0.33 (0.16–0.68)	
Hypertension				0.44
Absent	263	7.7	1.00	
Present	720	10.9	1.26 (0.71–2.22)	
Pulse pressure (mmHg)				0.03
19–50	249	5.5	1.00	
51–64	240	11.6	1.68 (0.81–3.51)	
65–79	250	9.8	1.63 (0.77–3.47)	
80–153	241	15.6	2.27 (1.09–4.71)	
BMI (kg/m^2)				0.74
17.1–24.6	215	10.0	1.00	
24.7–28.1	244	7.5	0.92 (0.43–1.95)	
28.2–31.7	253	15.3	1.22 (0.61–2.44)	
31.8–56.8	272	7.8	0.81 (0.39–1.68)	
Glycosylated hemoglobin (%)				<0.001
5.4–8.1	244	4.4	1.00	
8.2–9.4	218	8.5	1.98 (0.78–4.99)	
9.5–10.8	223	12.6	2.68 (1.15–6.24)	
10.9–20.8	225	14.6	3.79 (1.72–8.35)	
Proteinuria				0.005
Absent	845	9.4	1.00	
Present	103	17.5	2.60 (1.33–5.07)	
History of ulcers				<0.001
Absent	884	8.1	1.00	
Present	99	26.7	4.24 (2.54–7.08)	
Retinopathy				<0.001
None	465	6.2	1.00	
Mild	357	11.6	1.96 (1.07–3.59)	
Moderate	103	15.3	3.02 (1.42–6.46)	
Proliferative diabetic retinopathy	59	24.0	5.37 (2.61–11.03)	
Smoking status				0.58*
Nonsmoker	552	8.5	1.00	
Exsmoker	292	13.1	1.33 (0.77–2.31)	
Current smoker	140	8.3	1.19 (0.57–2.48)	
Pack-years smoked				0.57
0	553	8.5	1.00	
<5	79	13.6	1.79 (0.84–3.81)	
5–14	62	13.4	1.43 (0.56–3.63)	
15–29	86	4.2	0.64 (0.20–2.02)	
≥30	202	14.0	1.36 (0.73–2.52)	
Number of aspirin tablets in last 30 days				0.17
0	384	13.2	1.00	
1–29	350	8.7	0.82 (0.48–1.42)	
≥30	243	6.3	0.62 (0.30–1.26)	
Aspirin tablet/day for 3 months				0.79
No	741	10.2	1.00	
Yes	239	7.8	0.92 (0.49–1.72)	
Insulin				0.25
Not taking	509	8.8	1.00	
Taking	475	11.0	1.34 (0.81–2.21)	

*Test of general association.

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Table 4—*The 14-year cumulative incidence of amputation for a specified increment in baseline characteristics in multivariate logistic regression*

Characteristic	Increment	*P*	OR (95% CI)
Younger-onset			
Age (years)	10	<0.0001	1.71 (1.30–2.24)
Sex	Male	<0.0001	5.21 (2.50–10.88)
Glycosylated hemoglobin (%)	1	<0.0001	1.39 (1.22–1.59)
Diastolic blood pressure (mmHg)	10	<0.005	1.58 (1.20–2.07)
History of ulcers	Present	<0.0005	3.19 (1.71–5.95)
Retinopathy	One step	<0.0001	1.16 (1.08–1.24)
Younger-onset, age ≥18 years			
Age (years)	10	<0.005	1.56 (1.14–2.12)
Sex	Male	<0.0001	4.56 (2.14–9.70)
Glycosylated hemoglobin (%)	1	<0.0001	1.39 (1.21–1.59)
Diastolic blood pressure (mmHg)	10	<0.005	1.51 (1.14–2.00)
History of ulcers	Present	<0.0005	3.25 (1.71–6.17)
Retinopathy	One step	<0.0001	1.15 (1.07–1.23)
Pack-years smoked	10	<0.05	1.20 (1.03–1.41)
Aspirin/day	Yes	<0.05	0.11 (0.01–0.83)
Older-onset			
Sex	Male	<0.001	2.66 (1.49–4.76)
Glycosylated hemoglobin (%)	1	<0.005	1.25 (1.09–1.43)
Pulse pressure (mmHg)	10	<0.05	1.19 (1.04–1.37)
History of ulcers	Present	<0.0005	3.56 (1.84–6.89)
Retinopathy	One step	<0.05	1.07 (1.00–1.13)

severe retinopathy. Additional significant factors in younger-onset subjects ≥18 years of age included pack-years smoked and a history of taking a daily aspirin for at least a 3-month period (the latter variable having a protective association). In the older-onset cohort, male sex, higher glycosylated hemoglobin, higher pulse pressure, a history of ulcers of the feet and ankles, and more severe retinopathy were associated with greater odds of amputations. For the 10-year period starting in 1984–1986, we also examined the additional effect of the variables first measured at that time. In the younger-onset cohort, C-peptide was significantly associated with the 10-year incidence of amputations (OR 1.36 [95% CI 1.13–1.65] per 0.1 nmol/l). In the subset for whom cholesterol data were available, the ratio of total to HDL cholesterol was inversely related to incidence of amputations (OR 0.64 [0.41–1.00] per 1 unit). Also, in younger-onset subjects who were at least 18 years of age, average alcohol consumption was associated with amputations (OR 6.72 [1.76–25.67] for >30 ml/day). In the older-onset group, only C-peptide was associated with 10-year incidence of amputations (OR 1.61 [1.05–2.47] per 1.0 nmol/l).

CONCLUSIONS — Few studies have followed cohorts for long periods with respect to LEA. Most studies have been short-term, are based on hospital discharge data, are based on ethnic populations, include only older-onset people, or have limited information on potential risk factors (1–7,30–38). The present study has followed population-based younger- and older-onset cohorts at regular intervals for 14 years. Participation in the follow-up examinations has been exceptional. In addition, standardized protocols have been used to examine the population. Data on a variety of potential risk factors are available, including modifiable factors such as glycemic control, blood pressure, and lifestyle factors. These conditions make the WESDR a unique resource for studying the risks for LEA.

Many of the relationships presented herein have also been reported in our previous publications (13,14). These include associations of LEA with age, duration of diabetes, sex, blood pressure, pulse pressure, glycosylated hemoglobin, proteinuria, history of ulcers of the feet and ankles, severity of retinopathy, smoking status, and C-peptide. Some of these relationships have been noted in other studies. The association of age with amputation has not been consistently seen (1–4,6–8,30–32,35–39), which may be due in part to differences in the populations studied. Indeed, even in the present study, the younger- and older-onset cohorts differ with respect to this association. Relationships of amputations with duration of diabetes (31,35,37,38,40), sex (1–3,6,8,30–32,35,38), glycemic control (31,35,37–40), proteinuria (31,35,37, 39–41), retinopathy (31,35,37,39,40), and foot and ankle ulcers (35,39) have been confirmed in other studies. The basis of the increased risk of amputation in men is unknown. It may be a result of occupational and recreational activities that put more stress on the feet, the propensity for men to disregard symptoms until they are at an advanced stage, or the occurrence of more atherosclerotic vascular disease in men. We have no information to test these speculations. Reports of the association between blood pressure and amputations in other studies are difficult to compare because of differences in ethnicity (31,35,38) or because the subjects studied are a mix of insulin-dependent and non-insulin-dependent populations (39,40). One study is consistent with the older-onset group results (37). Smoking as a risk factor for amputation has not been confirmed by other investigations (31,37–40) and has been inconsistent across follow-up examinations in this study (13,14). Thus, it is not likely to be an important risk factor, although there are many other adverse end points for which it is a significant risk. High C-peptide levels are associated with an increased risk of amputation, continuing a trend reported in results from the 10-year follow-up (14). In the older-onset group, this finding, which has not been confirmed by other studies, may be a manifestation of insulin resistance and subsequent hyperinsulinemia. Also known as "syndrome X," this condition is defined by the presence of hypertension, changes in blood lipids, and changes in thrombogenic processes (42). In turn, these conditions may result in macrovascular disease.

The protective effect of aspirin use is notable. An effect was observed in earlier examinations, but it was not significant at that time (14). With additional follow-up, we now see a significant association in younger-onset patients and a similar, but nonsignificant, trend in older-onset patients. Aspirin's use as a preventive agent for cardiovascular disease is well established (43,44). An added benefit may be the prevention of LEA in people with dia-

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betes, without any adverse effects on the occurrence of vitreous hemorrhage (45). As the potential benefits are great, whether aspirin has use as a primary preventive measure against LEA deserves further study.

In the younger-onset group, an inverse relationship was observed between the ratio of total- to HDL cholesterol and amputations in a multivariable analysis. An inverse relationship was also seen between total cholesterol and amputations in the older-onset cohort, but the association did not remain after controlling for other risk factors. These associations are not in the expected direction. However, previous reports regarding the association of lipids and amputations have been variable. Some studies have found positive relationships (35,37,46), most have found no relationship (31,35,38,40), and one found an inverse relationship (39). It is possible that differential mortality is a factor in some of these studies or that the differences among studies are random variation about the null hypothesis.

Alcohol use was also found to be a significant risk factor in the younger-onset group but only in the highest consumption category of >30 ml/day. This is inconsistent with results for cardiovascular disease, where moderate alcohol intake has been found to have a beneficial effect (47). However, our highest category may include alcohol abusers in whom the toxic effects of alcohol play a role, including the exacerbation of peripheral neuropathy (48–50). Alternatively, it may also represent a group of people who are noncompliant with health guidelines for diabetes, including proper foot care. Other studies that have examined the association of alcohol consumption with amputations have failed to find one (37–39).

There are some limitations in the present study. Recruitment of surviving members of the cohorts for follow-up examinations has been good. Most of the losses are due to death (18–21). If these subjects had had amputations at a higher rate than surviving participants, then the reported cumulative incidence would be underestimated. Because other studies have reported poorer survival among amputees, this scenario is likely (31,35,51–53). However, we can assess the extent of the underestimate by looking at the amputation rates in a study interval for subjects who did or did not die in the next interval. We found the amputation rate to be 13.5 and 4.5 times more among those who died compared with those who did not die in the subsequent study interval in the younger- and older-onset groups, respectively. If we assume that similar higher amputation rates apply to those who died before they could be observed for the portion of an interval for which they survived, then we can estimate what the incidence of amputations may be in the entire cohort. When we perform these calculations, we estimate an adjusted 14-year cumulative incidence of LEA to be 9.8 and 14.0% in younger- and older-onset patients, respectively. Thus, our original estimated incidence may be underreported by 27 and 29%.

Incomplete follow-up may also affect associations between risk factors and the incidence of amputations. Many of the risk factors, such as age, sex, glycemic control, and blood pressure, are also risk factors for death (54). Thus, the effect of the bias would be toward the null hypothesis or weaker associations. Therefore, the associations reported herein may in fact be more substantial than indicated.

Studies of programs for diabetic foot care have shown that LEA can be prevented (9–12). These programs generally target patients with preexisting foot lesions and emphasize foot examinations, proper footwear, and referrals to specialists. The results of this study offer other potential avenues toward prevention of LEA. Some variables, such as claudication, sex, retinopathy, and proteinuria, may highlight groups at high risk toward whom increased efforts at education and foot care should be directed even before the appearance of foot lesions. Other factors, such as blood pressure and aspirin use, should be subjected to further investigation, including clinical trials. A recent report suggests a positive but inconclusive effect of blood pressure control on the incidence of amputations (55). Also, the benefits of better glycemic control may already be appearing following reports from clinical trials in other complications of diabetes (56–58). However, some of these factors are more important than others. Clearly, a person with claudication or an active foot ulcer will be at higher risk of amputation than one who merely has high blood pressure, since the former person is further along in the disease process. We know from prior studies that efforts to preserve limbs in such patients can be successful. Therefore, the time may be at hand to shift preventive efforts to earlier in the etiologic chain. A small change early in the disease may have as large an effect as heroic efforts later.

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