

# Adult Stature and Diabetes Complications in Patients With Type 1 Diabetes

## The FinnDiane Study and the Diabetes Control and Complications Trial

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**OBJECTIVE**—Short adult stature has previously been associated with cardiovascular disease, but its relationship with the microvascular complications of diabetes is uncertain. Therefore, we evaluated the association between adult stature and prevalence and incidence of diabetic microvascular complications.

**RESEARCH DESIGN AND METHODS**—This cross-sectional and longitudinal study comprises 3,968 adult patients with type 1 diabetes from the Finnish Diabetic Nephropathy (FinnDiane) Study and 1,246 adult patients from the Diabetes Control and Complications Trial (DCCT). In FinnDiane, diabetic nephropathy was defined as urinary albumin excretion  $\geq 300$  mg/24 h, dialysis, or renal transplantation. Retinopathy was divided into background and proliferative (laser-treated) retinopathy. In the DCCT, original nephropathy (class 1–6) and retinopathy (Early Treatment of Diabetic Retinopathy Study) classifications were used.

**RESULTS**—In the FinnDiane study, patients in the lowest quartile of adult height had increased risks of prevalent diabetic nephropathy (odds ratio [OR] 1.71, 95% CI 1.44–2.02) and prevalent laser-treated retinopathy (1.66, 1.43–1.93) compared with other patients. Similarly, in the DCCT, patients in the lowest quartile of adult height had increased risks of incident diabetic nephropathy class 4–6 (hazard ratio 2.70, 95% CI 1.59–4.59) and incident proliferative retinopathy (2.06, 1.15–3.71). In the FinnDiane study, the associations were largely explained by childhood exposure to diabetes. However, in the DCCT, where a greater proportion of patients had diabetes onset  $> 18$  years, the association with nephropathy was independent of childhood diabetes exposure.

**CONCLUSIONS**—Short adult stature is associated with microvascular complications in patients with type 1 diabetes. These findings are compatible with either childhood diabetes exposure or “common soil” or both as potential explanations. *Diabetes* 58:1914–1920, 2009

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Despite advances in the treatment of patients with type 1 diabetes, diabetic complications are still a major concern as the main cause of morbidity and mortality in patients with type 1 diabetes. The most devastating complication is diabetic nephropathy, which is associated with a markedly increased risk of end-stage renal failure, cardiovascular disease (1), and premature death (2).

To prevent or delay the development of diabetic complications, the identification of high-risk patients who would benefit from intensive treatment and follow-up is crucial. Established risk factors for diabetic nephropathy include poor glycemic control, duration of diabetes, microalbuminuria, hypertension, male sex, ethnicity, and smoking.

Epidemiological observations indicate that short adult stature is associated with adverse health outcomes, particularly with cardiovascular disease (3). Short stature has also been associated with hypertension and early arterial stiffening (4), impaired glucose tolerance (5), type 2 diabetes (6), gestational diabetes (7), and pre-eclampsia (8). Short stature may be a marker of unfavorable fetal development and subsequent impaired growth in early childhood, factors that are associated with chronic disease in adulthood (9). The pathogenesis of diabetic complications shares several potential mechanisms with these conditions, mainly endothelial dysfunction, chronic low-grade inflammation, and insulin resistance. We recently showed that pre-eclampsia is a risk factor for later development of diabetic nephropathy in women with type 1 diabetes (10). However, the association between short stature and diabetic complications is uncertain (11,12). Therefore, we evaluated this association in two large cohorts of patients with type 1 diabetes: the Finnish Diabetic Nephropathy (FinnDiane) Study and the Diabetes Control and Complications Trial (DCCT).

### RESEARCH DESIGN AND METHODS

**The FinnDiane study.** The present study includes cross-sectional data from the ongoing FinnDiane study, a comprehensive, nationwide, multi-center study with the aim to identify clinical, biochemical, environmental, and genetic risk factors for diabetic nephropathy in type 1 diabetes. The participating centers represent outpatient clinics at four out of a total of five university central hospitals, all central hospitals ( $n = 16$ ), the majority of all regional hospitals ( $n = 27$ ), and 31 major primary health care centers. At routine outpatient visits, patients with type 1 diabetes (ICD-10 code E10) were asked to participate in the study. Height was measured using a wall-mounted

stadiometer and weight was measured wearing light clothing. Waist and hip circumferences and blood pressure were measured. Based on medical records, the attending physician completed a standardized check-list regarding diabetic complications and medication. Data on smoking (current and previous) and social class (grouped as unskilled/skilled blue collar, unskilled/skilled white collar, farmers, and others) were collected in a self-report questionnaire. Written informed consent was obtained from each patient, and the study protocol was conducted in accordance with the Declaration of Helsinki.

Values for the three most recent urinary albumin excretion rates (UAERs) in timed urine collections were obtained from the study centers. In addition, one 24-h urine collection was completed in which UAER was measured centrally using radioimmunoassay and immunoturbidimetry from 2002. Macroalbuminuria was defined as UAER  $\geq 300$  mg/24 h or  $\geq 200$   $\mu$ g/min in at least two out of three consecutive urine collections. Corresponding UAER values for microalbuminuria were  $\geq 30 < 300$  mg/24 h or  $\geq 20 < 200$   $\mu$ g/min. End-stage renal disease (ESRD) was defined as hemodialysis, peritoneal dialysis, or renal transplantation. Diabetic nephropathy was defined as macroalbuminuria or ESRD. Data on retinopathy were obtained from medical records and classified as background or proliferative (laser-treated) retinopathy. Cardiovascular disease (CVD) was defined as a history of symptomatic coronary heart disease, myocardial infarction, a coronary artery procedure (bypass surgery or angioplasty), stroke, limb amputation, or a peripheral artery procedure.

Renal function (estimated glomerular filtration rate [eGFR]) was calculated with the Cockcroft-Gault formula corrected for body surface area (13). Insulin sensitivity was calculated with the formula for estimated glucose disposal rate (eGDR) (14). The latest A1C value was obtained from the study centers.

In this analysis, the criteria for type 1 diabetes were age at diagnosis of diabetes <35 years and permanent insulin treatment initiation within 1 year of diagnosis. Patients <18 years of age ( $n = 78$ ) were excluded from the analyses because of possible ongoing linear growth. In the FinnDiane database, data on height were available for 3,968 adult patients with type 1 diabetes.

**The DCCT.** To replicate the results from the FinnDiane Study, we used publicly available data from the DCCT, available at <http://www.gcrc.umn.edu/gcrc/downloads/dcct.html>. In brief, the DCCT was a randomized intervention study of 1,441 patients aged 13–39 years designed to compare intensive versus conventional blood glucose management on the development of diabetic complications in patients with type 1 diabetes (15). At baseline, none of the patients had diabetic nephropathy. Renal status was classified as nephropathy class 1–6 as follows: class 1, UAER <40 mg/24 h; class 2, 40–70 mg/24 h; class 3, 70–200 mg/24 h; class 4, 200–300 mg/24 h; class 5, >300 mg/24 h; class 6, >300 mg/24 h plus GFR <70 ml/min per 1.73 m<sup>2</sup>. Progression in renal status was defined according to the highest renal class observed during follow-up. Retinopathy was graded with the abbreviated final version of the ETDRS scale of diabetic retinopathy severity, consisting of step 1–23 for individual persons, which in turn was based on ETDRS level 10–85 for individual eyes (16). Data on height were complete. Patients <18 years of age at study entry ( $n = 195$ ) were excluded because of possible ongoing linear growth, leaving 1,246 patients eligible for the analyses.

**Statistical analyses.** SPSS version 15.0.1 software (SPSS, Chicago, IL) was used for statistical analysis. Height was used both as a continuous variable and as a categorical variable divided into quartiles separately for each decade of birth in the FinnDiane data to minimize the effect of a secular increase in height. Continuous variables were expressed as mean  $\pm$  SD or median (interquartile range). Categorical variables were reported as percentage. Differences between quartiles of height were analyzed by ANOVA for normally distributed continuous variables; otherwise, the Kruskal-Wallis was used. For categorical variables, the  $\chi^2$  test was used. Whenever  $P$  values were adjusted for age or duration of diabetes, ANCOVA and logistic regression were used for continuous and categorical variables, respectively. In cross-sectional data, multiple logistic regression was used as multivariate analysis. Longitudinal data were analyzed by Cox proportional hazard survival regression.

## RESULTS

**The FinnDiane study.** Data on height were available for 3,968 adult patients with type 1 diabetes (2,032 men, 1,936 women), with a mean age of  $37.8 \pm 11.5$  years (range 18.0–77.9), duration of diabetes  $23.0 \pm 12.0$  years, BMI  $25.0 \pm 3.5$  kg/m<sup>2</sup>, and A1C  $8.5 \pm 1.5\%$ . Mean height was  $177.3 \pm 7.0$  cm in men and  $164.1 \pm 6.3$  cm in women. Mean age at onset of diabetes was  $14.8 \pm 8.5$  years and <18 years in 67.4% of the patients. There was a secular trend of greater adult height in more recent birth cohorts (data not

shown). Of the patients, 56.7% had normal UAER, 12.5% had microalbuminuria, 14.5% had macroalbuminuria, and 6.9% had ESRD. In 9.4% of the patients, renal status could not yet be defined because of an insufficient number of urine collections; 35.3% of patients had laser-treated retinopathy and 9.8% had CVD.

Clinical characteristics according to quartiles of height are presented in Table 1. Shorter stature was associated with worse glycemic control and blood lipid profile, higher prevalence of antihypertensive medication, higher insulin dose per body weight, and importantly a higher prevalence of microalbuminuria, diabetic nephropathy, laser-treated retinopathy, and CVD. There were no differences in age between quartiles of height because of stratification for decade of birth, but there were, however, differences in the duration of diabetes across quartiles of height because of differences in age at onset of diabetes. After further adjustment for duration of diabetes, there were still significant associations between short stature and diabetic nephropathy and retinopathy, but not with CVD. In supplementary Table 1 (available in the online-only appendix at <http://diabetes.diabetesjournals.org/cgi/content/full/db08-1767/DC1>), absolute values for height according to complication status are given for men and women, showing a shorter stature beginning at the level of microalbuminuria compared with normoalbuminuria for both sexes.

The time from diagnosis of diabetes to nephropathy did not differ across quartiles of height ( $P = 0.395$ ). Similarly, there was no difference in time to the first laser treatment for proliferative retinopathy ( $P = 0.675$ ). Height correlated with UAER and eGFR in men (Spearman  $r = -0.11$  and  $0.18$ , respectively,  $P < 0.001$  for both) and in women ( $r = -0.10$  and  $0.13$ , respectively,  $P < 0.001$  for both).

To adjust for possible confounding factors, multiple logistic regression analyses were undertaken (Table 2), in which short stature was independently associated with both diabetic nephropathy and laser-treated retinopathy in addition to the conventional risk factors duration of diabetes, A1C, blood pressure, male sex, smoking, and social class.

To explore the possibility of a cohort effect, we further analyzed the prevalence of nephropathy and retinopathy by height quartile and decade of birth (Fig. 1A and B), showing a consistent association over time. Moreover, there was still an association between higher prevalence of laser-treated retinopathy and short stature after exclusion of patients with diabetic nephropathy (Fig. 1C).

Age at onset of diabetes was associated with adult stature (Table 1). Therefore, we divided the patients based on age at onset of diabetes (Fig. 1D). We observed an association between higher prevalence of nephropathy and a shorter stature in patients who had developed diabetes at <5 and 5–12.9 years of age, whereas no evident association between adult stature and nephropathy was seen in the group of 13–18 years at onset (Fig. 1D). The results for retinopathy were similar as for nephropathy (data not shown). In patients >18 years at diabetes onset, there was a nonsignificant trend toward a higher prevalence of nephropathy in patients with short stature: 17.0 versus 11.9% in 1st quartile versus 2nd–4th quartiles ( $P = 0.058$ ). Furthermore, when we additionally adjusted for years of diabetes exposure during the years of linear growth (i.e., years of diabetes before age 18 years) in the logistic regression model in Table 2, adult stature was no longer associated with nephropathy or retinopathy. Because of possible collinearity between the diabetes dura-

TABLE 1  
Clinical characteristics by birth decade-specific quartiles of height in the FinnDiane Study

	Quartile				<i>P</i>	<i>P</i> adjusted for duration of diabetes
	1st	2nd	3rd	4th		
Number of patients	984	998	990	996	NA	NA
Age (years)	37.5 ± 11.5	38.0 ± 11.6	37.8 ± 11.5	37.8 ± 11.3	0.81	NA
Sex (% men)	51.9	51.3	50.1	51.5	0.87	NA
Blue-collar workers (%)	70.2	66.2	63.1	56.5	<1 × 10 <sup>-5</sup>	<1 × 10 <sup>-5</sup>
Ever smoke (%)	48.0	45.8	48.8	43.5	0.09	0.16
Age at onset of diabetes (years)	11.9 ± 8.2	14.5 ± 8.5	15.9 ± 8.2	16.7 ± 8.1	<1 × 10 <sup>-5</sup>	NA
Duration of diabetes (years)	25.6 ± 12.2	23.4 ± 12.1	22.0 ± 11.7	21.1 ± 11.6	<1 × 10 <sup>-5</sup>	NA
A1C (%)	8.6 ± 1.6	8.5 ± 1.5	8.4 ± 1.5	8.3 ± 1.4	<1 × 10 <sup>-2</sup>	<1 × 10 <sup>-2</sup>
Insulin dose (IU/kg)	0.75 ± 0.28	0.72 ± 0.25	0.70 ± 0.22	0.68 ± 0.23	<1 × 10 <sup>-5</sup>	<1 × 10 <sup>-5</sup>
eGDR (mg · kg <sup>-1</sup> · min <sup>-1</sup> )	5.5 (4.0–8.1)	6.0 (4.3–8.3)	6.2 (4.3–8.5)	6.6 (4.5–8.8)	<1 × 10 <sup>-5</sup>	0.27
Systolic blood pressure (mmHg)	135 ± 20	135 ± 19	134 ± 18	133 ± 18	0.06	0.62
Diastolic blood pressure (mmHg)	79 ± 10	80 ± 10	80 ± 10	80 ± 10	0.56	0.60
Antihypertensive medication (%)	47.9	41.5	36.1	33.4	<1 × 10 <sup>-5</sup>	<1 × 10 <sup>-3</sup>
BMI (kg/m <sup>2</sup> )	25.1 ± 3.6	25.1 ± 3.6	25.0 ± 3.5	24.9 ± 3.4	0.33	0.52
Waist-to-hip ratio	0.87 ± 0.09	0.87 ± 0.09	0.86 ± 0.08	0.87 ± 0.08	0.08	0.49
Total cholesterol (mmol/l)	5.1 ± 1.1	4.9 ± 0.9	5.0 ± 1.2	4.9 ± 1.0	<1 × 10 <sup>-2</sup>	0.08
Triglycerides (mmol/l)	1.11 (0.81–1.62)	1.06 (0.80–1.48)	1.00 (0.75–1.43)	0.98 (0.75–1.37)	<1 × 10 <sup>-5</sup>	<1 × 10 <sup>-5</sup>
Lipid-lowering medication (%)	13.7	11.5	9.4	9.6	<1 × 10 <sup>-2</sup>	0.37
UAER (mg/24 h) ( <i>n</i> = 2,697)	15.0 (6.6–108.5)	12.2 (6.1–51.7)	10.8 (6.0–45.8)	10.6 (5.8–26.8)	<1 × 10 <sup>-5</sup>	<1 × 10 <sup>-2</sup>
eGFR (ml/min per 1.73 m <sup>2</sup> )	86 ± 34	93 ± 48	92 ± 31	97 ± 43	<1 × 10 <sup>-5</sup>	0.02
Microalbuminuria (%)	15.2	14.4	9.4	10.9	<1 × 10 <sup>-3</sup>	<1 × 10 <sup>-2</sup>
Macroalbuminuria (%)	18.3	14.9	13.5	11.3	<1 × 10 <sup>-3</sup>	0.01
End-stage renal disease (%)	10.0	6.2	6.3	5.0	<1 × 10 <sup>-4</sup>	0.03
Diabetic nephropathy (%)	28.3	21.1	19.8	16.3	<1 × 10 <sup>-5</sup>	<1 × 10 <sup>-3</sup>
Laser-treated retinopathy (%)	44.4	38.7	31.3	27.5	<1 × 10 <sup>-5</sup>	<1 × 10 <sup>-5</sup>
Laser-treated retinopathy, normal UAER (%)	18.7	16.2	14.1	11.3	<1 × 10 <sup>-2</sup>	0.10
Cardiovascular disease (%)	12.8	9.3	9.2	8.2	<1 × 10 <sup>-2</sup>	0.93

Data are means ± SD, median (interquartile range), or percentage as appropriate. NA, not applicable.

tion variables, we also omitted total duration of diabetes from the final model (model 9), which did not change the main results (not shown).

**The DCCT.** Of the eligible 1,246 patients, 666 were men and 580 women, and 96.8% were white. At baseline, mean age was 28.7 ± 5.7 years (range 18–39), duration of diabetes 5.8 ± 4.3 years, BMI 23.6 ± 2.8 kg/m<sup>2</sup>, and A1C 8.8 ± 1.5%. Mean height was 178.7 ± 7.1 cm in men and 164.9 ± 6.1 cm in women. Mean age at onset of diabetes was 22.9 ± 7.2 years and <18 years in 25.6% of the patients.

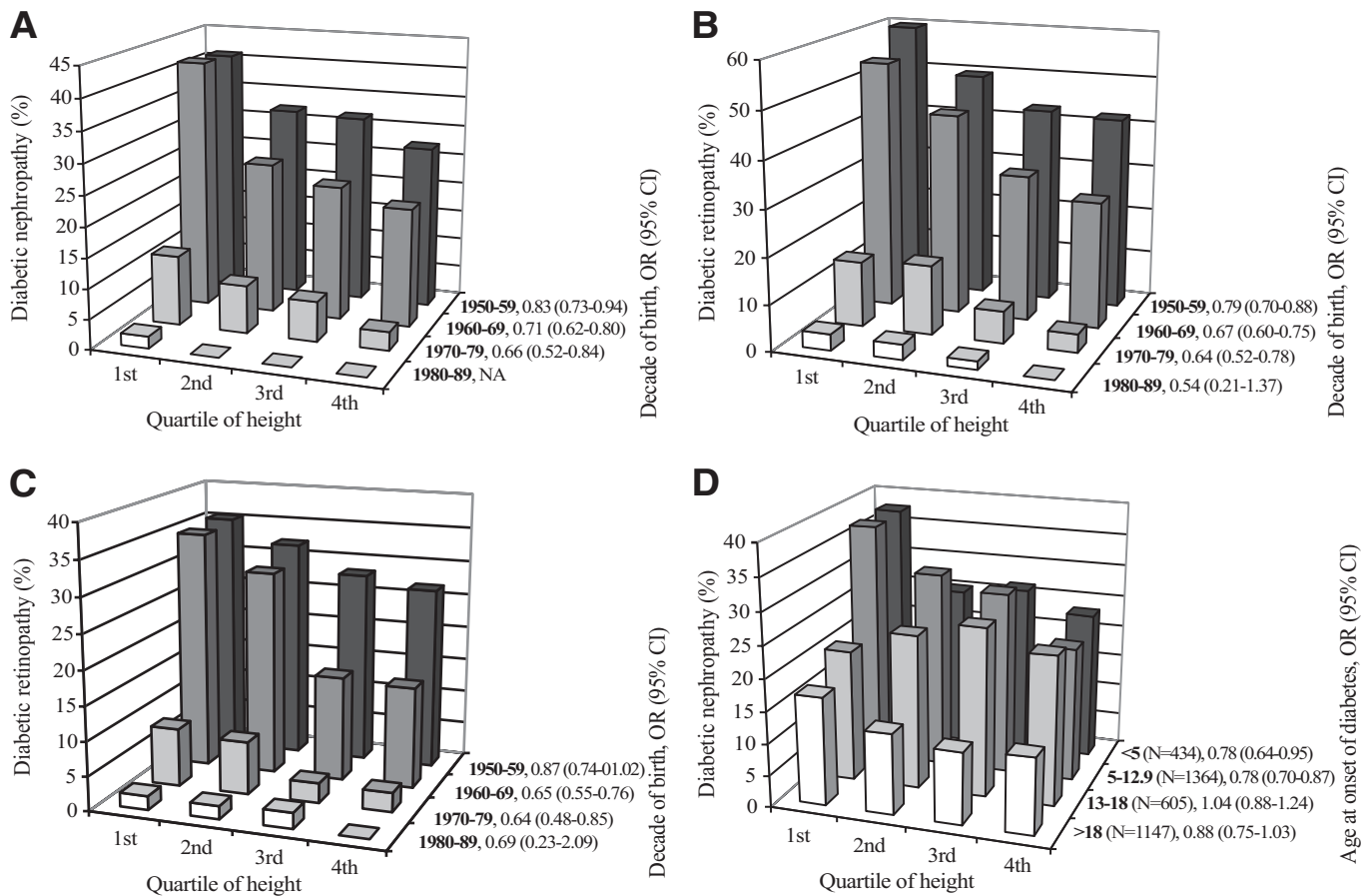
Short stature was associated with lower age at onset of diabetes, longer duration of diabetes, and higher insulin

dose per body weight (Table 3). At baseline, stature was not associated with renal status (Table 3). However, none of the patients had nephropathy because baseline nephropathy was an exclusion criterion in the DCCT. At close-out, 8.4% of patients within the lowest quartile of height had developed nephropathy class 4–6 compared with 3.1% in the top three quartiles (*P* < 0.001). In patients diagnosed with diabetes after the age of 18 years, corresponding proportions were 5.4 and 2.5% (*P* = 0.039), respectively. In a Cox regression model for progression to nephropathy class 4–6, patients within the lowest quartile of height had a 2.39-fold higher risk of nephropathy when adjusting for conventional risk factors and the duration of

TABLE 2  
Multivariate associations (logistic regression) of 1st quartile of decade of birth-specific quartile of height with diabetic nephropathy and laser-treated retinopathy in the FinnDiane Study

	Diabetic nephropathy		Laser-treated retinopathy	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Model 1: unadjusted	1.71 (1.44–2.02)	<0.001	1.66 (1.43–1.93)	<0.001
Model 2: model 1 + male sex	1.70 (1.44–2.02)	<0.001	1.66 (1.43–1.93)	<0.001
Model 3: model 2 + duration of diabetes (years)	1.39 (1.16–1.67)	<0.001	1.33 (1.11–1.58)	0.002
Model 4: model 3 + A1C (%)	1.32 (1.10–1.60)	0.004	1.28 (1.07–1.54)	0.008
Model 5: model 4 + systolic blood pressure (mmHg)	1.41 (1.16–1.73)	0.001	1.31 (1.09–1.58)	0.005
Model 6: model 5 + ever smoke	1.36 (1.11–1.67)	0.003	1.31 (1.08–1.58)	0.006
Model 7: model 6 + blue-collar worker	1.35 (1.08–1.68)	0.008	1.28 (1.05–1.57)	0.015
Model 8: model 7 + BMI (kg/m <sup>2</sup> )	1.35 (1.08–1.68)	0.008	1.28 (1.05–1.57)	0.016
Model 9: model 8 + duration of diabetes (years) <18 years	1.12 (0.89–1.41)	0.338	1.12 (0.91–1.38)	0.273





**FIG. 1. A:** Prevalence (%) of diabetic nephropathy (macroalbuminuria, dialysis, or renal transplantation) in Finndiane by quartile of height and decade of birth. ORs (95% CI) for nephropathy per quartile of height are given for each decade of birth. NA, not applicable. **B:** Prevalence (%) of laser-treated retinopathy in Finndiane by quartile of height and decade of birth. ORs (95% CI) for retinopathy per quartile of height are given for each decade of birth. **C:** Prevalence (%) of laser-treated retinopathy in Finndiane by quartile of height and decade of birth. Patients with diabetic nephropathy (macroalbuminuria, dialysis, or renal transplantation) were excluded from the analyses. ORs (95% CI) for retinopathy per quartile of height are given for each decade of birth. **D:** Prevalence (%) of diabetic nephropathy (macroalbuminuria, dialysis, or renal transplantation) in Finndiane by groups of age at onset of diabetes. ORs (95% CI) for nephropathy per quartile of height are given for each decade of birth.

diabetes before the age of 18 years (Table 4). Omitting total duration of diabetes from the final model (model 11) did not change the main results (not shown).

At baseline, stature was not associated with retinopathy status, but at close-out, a higher proportion of patients within the lowest quartile of height had developed ETDRS step  $\geq 6$  (minimum of background retinopathy, 21.8 vs. 14.0%,  $P = 0.001$ ) and ETDRS step  $\geq 12$  (minimum of mild proliferative retinopathy, 6.3 vs. 2.9%,  $P = 0.008$ ) compared with the top three quartiles (Table 3). In patients diagnosed with diabetes after the age of 18 years, corresponding proportions were 12.4 versus 10.1% ( $P = 0.360$ ) for ETDRS step  $\geq 6$  and 2.0 versus 1.1% for ETDRS step  $\geq 12$  ( $P = 0.346$ ). In a Cox regression model, stature was not independently associated with development of ETDRS  $\geq 12$  during follow-up (Table 4). For neuropathy (DCCT analytic definition), in contrast to nephropathy and retinopathy, tall stature was associated with higher prevalence (Table 3).

## DISCUSSION

In the Finndiane Study, we show a consistent association between short adult stature and higher prevalence of diabetic nephropathy and retinopathy in men and women with type 1 diabetes. We also show that short stature is

associated with higher prevalence of microalbuminuria. Furthermore, short stature is associated with proliferative retinopathy, even when patients with diabetic nephropathy are excluded, indicating that the association with retinopathy is not solely driven by comorbidity with nephropathy. These cross-sectional data are supported by longitudinal data from the DCCT showing that the incidence of nephropathy and retinopathy are indeed higher in patients with short stature.

A potential association between adult stature and diabetic nephropathy was proposed by Rossing et al. (11), who reported that patients with type 1 diabetes and diabetic nephropathy were shorter than those without nephropathy. However, the finding was confined only to male patients. This observation was later challenged by the EURODIAB Study, which also showed an association between short adult stature and diabetic nephropathy in male patients (12); however, the authors concluded that the association was because of confounding by social class. Before these studies, a small study in 181 patients with type 1 diabetes had suggested that short stature was associated with both nephropathy and retinopathy (17). In subsequent longitudinal studies, stature has (18) and has not (19) been associated with development of micro- and macroalbuminuria in type 1 diabetes. In type 2 diabetes,

TABLE 3  
Clinical characteristics by quartiles of height in the DCCT

	Quartile				Unadjusted <i>P</i>	<i>P</i> adjusted for duration of diabetes
	1st	2nd	3rd	4th		
Number of patients	310	305	326	305	NA	NA
Baseline data						
Age (years)	27.6 ± 5.7	29.0 ± 5.7	29.0 ± 5.6	29.1 ± 5.5	<1 × 10 <sup>-2</sup>	NA
Sex (% men)	53.9	53.4	54.9	51.5	0.86	NA
Race (% white)	94.8	96.4	97.5	98.4	0.07	NA
Hollingshead social class score	26 (15–44)	22 (15–40)	26 (15–43)	22 (15–43)	0.09	0.10
Ever smoke (%)	32.3	23.9	26.4	23.6	0.06	0.03
Age at onset of diabetes (years)	21.1 ± 7.4	23.5 ± 7.1	23.4 ± 7.0	23.6 ± 6.8	<1 × 10 <sup>-3</sup>	NA
Duration of diabetes (years)	6.5 ± 4.4	5.5 ± 4.3	5.7 ± 4.2	5.4 ± 4.1	<1 × 10 <sup>-2</sup>	NA
A1C (%)	8.9 ± 1.6	8.7 ± 1.5	8.7 ± 1.5	8.8 ± 1.5	0.29	0.27
Insulin dose (IU/kg)	0.66 ± 0.22	0.61 ± 0.21	0.62 ± 0.20	0.59 ± 0.20	<1 × 10 <sup>-3</sup>	<1 × 10 <sup>-2</sup>
Total cholesterol (mg/dl)	179 ± 34	180 ± 33	180 ± 34	174 ± 31	0.07	0.07
LDL cholesterol (mg/dl)	112 ± 29	113 ± 29	113 ± 30	107 ± 27	0.03	0.04
Systolic blood pressure (mmHg)	114 ± 12	114 ± 12	115 ± 12	116 ± 11	0.07	0.05
Diastolic blood pressure (mmHg)	72 ± 9	73 ± 9	74 ± 8	73 ± 9	0.14	0.11
BMI (kg/m <sup>2</sup> )	23.8 ± 2.8	23.7 ± 2.8	23.5 ± 2.6	23.5 ± 2.8	0.37	0.42
UAER (mg/24 h)	10.1 (5.8–20.2)	10.1 (5.8–15.8)	10.1 (5.8–15.8)	11.5 (7.2–20.2)	<1 × 10 <sup>-2</sup>	<1 × 10 <sup>-2</sup>
Creatinine clearance (ml/min per 1.73 m <sup>2</sup> )	126 ± 30	124 ± 26	125 ± 27	124 ± 26	0.64	0.68
Nephropathy class 3 (%)	2.3	1.3	1.2	1.0	0.56	0.32
ETDRS retinopathy step ≥6 (%)	7.1	6.6	3.1	4.3	0.07	0.24
Neuropathy, analytic definition (%)	4.8	4.3	9.8	8.9	0.01	<1 × 10 <sup>-2</sup>
Follow-up data (at close-out)						
Nephropathy class 4–6 (%)	8.4	3.0	1.8	4.6	<1 × 10 <sup>-3</sup>	0.048
ETDRS retinopathy step ≥6 (%)	21.8	14.2	14.6	13.2	0.02	0.10
ETDRS retinopathy step ≥12 (%)	6.3	3.3	1.9	3.6	0.03	0.21
Neuropathy, analytic definition (%)	11.1	12.3	15.0	18.2	0.06	<1 × 10 <sup>-2</sup>
Cardiovascular event (%)	8.1	4.9	5.8	7.9	0.31	0.81

Data are means ± SD, median (interquartile range), or percentage as appropriate. NA, not applicable.

stature has also been associated with proteinuria (20), as is also the case for healthy nondiabetic men (21). In contrast, diabetic peripheral neuropathy has been shown to be more common among tall patients (22,23), a finding also seen in the DCCT cohort of the present study. This has been interpreted to be because of a greater axon area exposed to the neurotoxic effects of diabetes.

There is evidence suggesting that adult height is associated with health outcomes, and short stature has not only been associated with metabolic disorders but also with hypertension and CVD. It has, however, been debated whether these associations are simply because of socioeconomic factors because social status and stature are positively correlated (24). The observation of a clear association between short stature and coronary heart disease in the socially homogeneous Physicians Health (25) and Helsinki Businessmen (26) studies would argue against confounding by social class as an alternative explanation for the association. In our analysis, the associations of height with microvascular complications were independent of social class. Although we cannot exclude

residual confounding, these results do make it more likely that the observed association is a manifestation of a true etiological relationship.

It is unlikely that height is a causal factor regarding diabetic nephropathy or retinopathy, but may be a marker of an underlying process that confers increased risk. Short stature could, for example, be secondary to renal osteodystrophy, but this cannot explain the difference in stature seen in the early course of renal disease observed in our study in which patients with microalbuminuria were shorter than those with normal UAER. We cannot rule out common genetic factors, such as IGF-1, that could be associated both with stature and with diabetic complications. The association between short stature and renal disease has previously been hypothesized to reflect a decreased number of nephrons (11,27).

In the FinnDiane Study, short stature was associated with an overall disadvantageous risk factor profile such as glycemic control, insulin sensitivity, and serum lipids. Even in patients with normal UAER, insulin dose and A1C were similarly associated with stature (results not shown).

TABLE 4

Cox regression models for 1st quartile of height and progression to diabetic nephropathy class 4–6 (of nephropathy class 1–6) and ETDRS retinopathy level  $\geq 12$  (of ETDRS scale 1–23) in the DCCT

	Nephropathy		Retinopathy	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Model 1: unadjusted	2.70 (1.59–4.59)	<0.001	2.06 (1.15–3.71)	0.016
Model 2: model 1 + male sex	2.70 (1.59–4.59)	<0.001	2.07 (1.15–3.72)	0.015
Model 3: model 2 + duration of diabetes (years)	2.44 (1.43–4.15)	0.001	1.84 (1.02–3.30)	0.043
Model 4: model 3 + A1C (%)	2.18 (1.28–3.71)	0.004	1.51 (0.83–2.74)	0.177
Model 5: model 4 + systolic blood pressure (mmHg)	2.20 (1.29–3.75)	0.004	1.51 (0.83–2.75)	0.176
Model 6: model 5 + ever smoke	2.17 (1.27–3.71)	0.004	1.50 (0.82–2.73)	0.187
Model 7: model 6 + Hollingshead social class score	2.38 (1.36–4.16)	0.003	1.38 (0.74–2.56)	0.306
Model 8: model 7 + BMI (kg/m <sup>2</sup> )	2.40 (1.37–4.21)	0.002	1.34 (0.72–2.49)	0.363
Model 9: model 8 + nonwhite	2.35 (1.34–4.13)	0.003	1.49 (0.80–2.77)	0.213
Model 10: model 9 + intensive treatment group	2.21 (1.26–3.90)	0.006	1.08 (0.57–2.05)	0.804
Model 11: model 10 + duration of diabetes (years) <18 years	2.39 (1.34–4.25)	0.003	1.13 (0.59–2.17)	0.707

Similarly in the DCCT, insulin dose per body weight was also higher in short patients despite no differences in obesity. These consistent associations between short stature and features of insulin resistance are noteworthy, because insulin resistance, and especially pathway-specific insulin resistance, has been implicated in the pathogenesis of diabetic microvascular complications (28). Impaired growth and development in utero and during early childhood may lead to metabolic diseases in adulthood, and these frequently include features of insulin resistance (6), thereby providing a possible link between growth, final stature, and diabetic complications. Birth weight, however, was not previously associated with diabetic nephropathy in the FinnDiane Study (29), in contrast to other studies (30,31), even though an association between birth weight and adult height was seen (29).

Childhood growth may also be impaired by inadequately controlled diabetes, and in the present study, earlier age at onset of diabetes was associated with shorter adult height. This may indicate that exposure to diabetes in childhood may translate into both shorter adult height and increased risk of future complications, possibly because of “metabolic memory” (32). Some support for this was seen in the FinnDiane Study, where duration of exposure to diabetes during the years of linear growth (i.e., <18 years) appeared to account for much of the association between shorter height and microvascular complications. Conversely, in both FinnDiane and DCCT, similar associations or trends with shorter adult height were also seen, even in patients with onset of diabetes older than 18 years, indicating that childhood exposure to diabetes is not the only explanation. The proportions of patients that developed diabetes before the age of 18 years were different between the FinnDiane (67.4%) and DCCT studies (25.6%), and these cohorts consequently differed in their power to detect associations within each age-at-onset subgroup. We postulate that two main mechanisms are in play: one through childhood exposure to diabetes and secondly a common soil hypothesis, that is, that the same factors lead to both shorter adult height and increased risk of diabetic complications.

This study has some limitations. We do not have data on childhood growth and pubertal development that could have provided insights into the interaction between growth and complications from type 1 diabetes. The cross-sectional nature of the data in FinnDiane is a theoretical limitation, although the likelihood of reverse cau-

sation is low. In addition, the data from DCCT suggest that the direction of causality is such that height precedes the diabetic complications. The associations between stature and diabetic complications could still be confounded by factors we have not considered or by imperfect measurement of those confounders that have been included in our analysis.

In conclusion, this study indicates that short adult stature is associated with higher prevalence and incidence of microvascular complications in patients with type 1 diabetes. Understanding the mechanisms underlying these associations could identify novel preventative strategies.

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