

## Adult stature and diabetic complications in patients with type 1 diabetes.

(The FinnDiane Study and the DCCT)

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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 3968 adult patients with type 1 diabetes from the Finnish Diabetic Nephropathy (FinnDiane) Study and 1246 adult patients from the Diabetes Control and Complications Trial (DCCT). In FinnDiane, diabetic nephropathy was defined as urinary albumin excretion  $\geq 300$  mg/24h, dialysis, or renal transplantation. Retinopathy was divided into background and proliferative (laser-treated) retinopathy. In the DCCT, original nephropathy (class 1-6) and retinopathy (ETDRS) classifications were used.

*Results.* In FinnDiane, patients in the lowest quartile of adult height had increased risks of prevalent diabetic nephropathy (odds ratio 1.71, 95% confidence interval 1.44-2.02) and prevalent laser-treated retinopathy (1.66, 1.43-1.93) compared to 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% confidence interval 1.59-4.59), and incident proliferative retinopathy (2.06, 1.15-3.71). In FinnDiane, 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.

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).

In order to prevent or at least 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 gender, 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 which 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 (UAER) in timed urine collections were obtained from the study centers. In addition, one 24h urine collection was completed in which UAER was measured centrally using radioimmunoassay and immunoturbidimetry from 2002. Macroalbuminuria was defined as UAER  $\geq 300$  mg/24h 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/24h 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 (by-pass surgery or angioplasty), stroke, limb amputation, or a peripheral artery procedure.

Renal function (eGFR, estimated glomerular filtration rate) 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 HbA<sub>1c</sub> value was obtained from the study centers.

In this analysis, the criteria for type 1 diabetes were age at diagnosis of diabetes less than 35 years and permanent insulin treatment initiation within one year of diagnosis. Patients below 18 years of age (N=78) were excluded from the analyses due to possible ongoing linear growth. In the FinnDiane database, data on height were available for 3968 adult patients with type 1 diabetes.

**The DCCT:** To replicate the results from the FinnDiane Study, we used publicly available data from the Diabetes Control and Complications Trial (DCCT), available at <http://www.gcrc.umn.edu/gcrc/downloads/dcc.html>. In brief, the DCCT was a randomized intervention study of 1441 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 to 6 as follows: class 1: UAER  $< 40$  mg/24h, class 2: 40-70 mg/24h, class 3: 70-200 mg/24h, class 4: 200-300 mg/24h, class 5:  $> 300$  mg/24h, class 6:  $> 300$  mg/24h plus GFR  $< 70$  ml/min/1.73m<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 to 23 for individual persons, which in turn was based on ETDRS level 10-85 for individual eyes (16). Data on height were complete. Patients less than 18 years of age at study entry (N=195) were excluded due to possible ongoing linear growth, leaving 1246 patients eligible for the analyses.

**Statistical analyses:** SPSS version 15.0.1 software (SPSS Inc., 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 %. Differences between quartiles of height were analyzed by ANOVA for normally distributed continuous variables, otherwise the Kruskal-Wallis test 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 was analyzed by Cox proportional hazard survival regression.

## RESULTS

**The FinnDiane Study:** Data on height were available for 3968 adult patients with type 1 diabetes (2032 men, 1936 women), with a mean age of 37.8 $\pm$ 11.5 years

(range 18.0-77.9 years), duration of diabetes  $23.0 \pm 12.0$  years, BMI  $25.0 \pm 3.5$  kg/m<sup>2</sup>, and HbA<sub>1c</sub>  $8.5 \pm 1.5\%$ . 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 below 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). 56.7% of the patients 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 due to 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 due to stratification for decade of birth, but there were, however, differences in the duration of diabetes across quartiles of height due to 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 Supplement Table 1 (available in the online-only appendix at <http://diabetes.diabetesjournals.org>), 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 genders.

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, HbA<sub>1c</sub>, blood pressure, male gender, 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 (figures 1a-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 (figure 1c).

Age at onset of diabetes was associated with adult stature (table 1). Therefore, in figure 1d we divided the patients based on age at onset of diabetes. 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, while 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 towards a higher prevalence of nephropathy in patients with short stature:  $17.0$  vs.  $11.9\%$  in 1<sup>st</sup> quartile vs. 2<sup>nd</sup>-4<sup>th</sup> 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 not longer associated with

nephropathy or retinopathy. Due to possible collinearity between the diabetes duration 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 1246 patients, 666 were men and 580 women, and 96.8% were Caucasian. At baseline, mean age was  $28.7 \pm 5.7$  years (range 18-39 years), duration of diabetes  $5.8 \pm 4.3$  years, BMI  $23.6 \pm 2.8$  kg/m<sup>2</sup>, and HbA<sub>1c</sub>  $8.8 \pm 1.5\%$ . Mean height was  $178.7 \pm 7.1$  cm in men and  $164.9 \pm 6.1$  cm in women. Mean age at onset of diabetes was  $22.9 \pm 7.2$  years, and below 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 since 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 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% vs. 10.1% ( $P = 0.360$ ) for ETDRS step  $\geq 6$  and 2.0% vs. 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. Short stature is furthermore associated with proliferative retinopathy even when patients with diabetic nephropathy are excluded, indicating that the association with retinopathy is not solely driven by co-morbidity 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*, who reported that patients with type 1 diabetes and diabetic nephropathy were shorter than those without nephropathy (11). 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 due to confounding by social class. Prior to 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, stature has also been associated with proteinuria (20), as is also the case for healthy non-diabetic 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 due to 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 cardiovascular disease. It has, however, been debated whether these associations are simply due to 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 Studies (26) 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 *per se* 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 also 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 HbA<sub>1c</sub> were similarly associated with stature (results not shown). 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, since 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 *per se*, 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 as a consequence 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. before age 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 among 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. Overall we postulate that two main mechanisms are in play: one through childhood exposure to diabetes, and secondly a common soil hypothesis i.e. 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 which 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 causation 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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**Figure Legend:**

**Figure 1a.** Prevalence (%) of diabetic nephropathy (macroalbuminuria, dialysis or renal transplantation) in FinnDiane by quartile of height and decade of birth. Odds ratios (95% CI) for nephropathy per quartile of height are given for each decade of birth. NA: Not applicable.

**Figure 1b.** Prevalence (%) of laser-treated retinopathy in FinnDiane by quartile of height and decade of birth. Odds ratios (95% CI) for retinopathy per quartile of height are given for each decade of birth.

**Figure 1c.** 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. Odds ratios (95% CI) for retinopathy per quartile of height are given for each decade of birth.

**Figure 1d.** Prevalence (%) of diabetic nephropathy (macroalbuminuria, dialysis or renal transplantation) in FinnDiane by groups of age at onset of diabetes. Odds ratios (95% CI) for nephropathy per quartile of height are given for each decade of birth.

## REFERENCES.

1. Tuomilehto J, Borch-Johnsen K, Molarius A, Forsén T, Rastenyte D, Sarti C, Reunanen A: Incidence of cardiovascular disease in type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. *Diabetologia*. 41:784-790, 1998
2. Borch-Johnsen K, Andersen PK, Deckert T: The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia*. 28:590-596, 1985
3. Forsén T, Eriksson J, Qiao Q, Tervahauta M, Nissinen A, Tuomilehto J: Short stature and coronary heart disease: A 35-year follow-up of the Finnish cohorts of the seven countries study. *J Intern Med*. 248:326-332, 2000
4. Langenberg C, Hardy R, Kuh D, Wadsworth ME: Influence of height, leg and trunk length on pulse pressure, systolic and diastolic blood pressure. *J Hypertens*. 21:537-543, 2003
5. Brown DC, Byrne CD, Clark PM, Cox BD, Day NE, Hales CN, Shackleton JR, Wang TW, Williams DR: Height and glucose tolerance in adult subjects. *Diabetologia*. 34:531-533, 1991
6. Asao K, Kao WH, Baptiste-Roberts K, Bandeen-Roche K, Erlinger TP, Brancati FL: Short stature and the risk of adiposity, insulin resistance, and type 2 diabetes in middle age: The third national health and nutrition examination survey (NHANES III), 1988-1994. *Diabetes Care*. 29:1632-1637, 2006
7. Jacobson JD, Cousins L: A population-based study of maternal and perinatal outcome in patients with gestational diabetes. *American Journal of Obstetrics & Gynecology*. 161:981-986, 1989
8. Basso O, Wilcox AJ, Weinberg CR, Baird DD, Olsen J: Height and risk of severe pre-eclampsia. A study within the Danish National Birth Cohort. *Int J Epidemiol*. 33:858-863, 2004
9. Barker DJ: The fetal and infant origins of disease. *Eur J Clin Invest*. 25:457-463, 1995
10. Gordin D, Hiilesmaa V, Fagerudd J, Rönnback M, Forsblom C, Kaaja R, Teramo K, Groop PH: Pre-eclampsia but not pregnancy-induced hypertension is a risk factor for diabetic nephropathy in type 1 diabetic women. *Diabetologia*. 50:516-522, 2007
11. Rossing P, Tarnow L, Nielsen FS, Boelskifte S, Brenner BM, Parving HH: Short stature and diabetic nephropathy. *BMJ*. 310:296-297, 1995
12. Chaturvedi N, Fuller J, Stephenson J: Short stature and diabetic nephropathy. *BMJ*. 310:1199, 1995
13. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41, 1976
14. Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, Wadén J, Rönnback M, Rosengård-Bärlund M, Björkesten CG, Taskinen MR, Groop PH, FinnDiane Study G: Metabolic syndrome in type 1 diabetes: Association with diabetic nephropathy and glycemic control (the FinnDiane study). *Diabetes Care*. 28:2019-2024, 2005
15. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 14:977-986, 1993
16. The Diabetes Control and Complications Trial Research Group: The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial. *Arch Ophthalmol*. 113:36-51, 1995

17. Penfold J, Chase HP, Marshall G, Walravens CF, Walravens PA, Garg SK: Final adult height and its relationship to blood glucose control and microvascular complications in IDDM. *Diabetic Med.* 12:129-133, 1995
18. Hovind P, Tarnow L, Rossing P, Jensen BR, Graae M, Torp I, Binder C, Parving HH: Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: Inception cohort study. *BMJ.* 328:1105, 2004
19. Rossing P, Hougaard P, Parving HH: Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients: A 10-year prospective observational study. *Diabetes Care.* 25:859-864, 2002
20. Fava S, Azzopardi J, Watkins PJ, Hattersley AT: Adult height and proteinuria in type 2 diabetes. *Nephrology Dialysis Transplantation.* 16:525-528, 2001
21. Gould MM, Mohamed-Ali V, Goubet SA, Yudkin JS, Haines AP: Microalbuminuria: Associations with height and sex in non-diabetic subjects. *BMJ.* 306:240-242, 1993
22. Sosenko JM, Gadia MT, Fournier AM, O'Connell MT, Aguiar MC, Skyler JS: Body stature as a risk factor for diabetic sensory neuropathy. *Am J Med.* 80:1031-1034, 1986
23. Cheng YJ, Gregg EW, Kahn HS, Williams DE, De Rekeneire N, Narayan KM: Peripheral insensate neuropathy - a tall problem for US adults? *Am J Epidemiol.* 164:873-880, 2006
24. Walker M, Shaper AG, Wannamethee G: Height and social class in middle-aged british men. *Journal of Epidemiology & Community Health.* 42:299-303, 1988
25. Hebert PR, Rich-Edwards JW, Manson JE, Ridker PM, Cook NR, O'Connor GT, Buring JE, Hennekens CH: Height and incidence of cardiovascular disease in male physicians. *Circulation.* 88:1437-1443, 1993
26. Strandberg TE: Inverse relation between height and cardiovascular mortality in men during 30-year follow-up. *Am J Cardiol.* 80:349-350, 1997
27. Brenner BM, Chertow GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *American Journal of Kidney Diseases.* 23:171-175, 1994
28. Groop PH, Forsblom C, Thomas MC: Mechanisms of disease: Pathway-selective insulin resistance and microvascular complications of diabetes. *Nature Clinical Practice Endocrinology & Metabolism.* 1:100-110, 2005
29. Fagerudd J, Forsblom C, Pettersson-Fernholm K, Saraheimo M, Wadén J, Rönnback M, Rosengård-Bärlund M, Björkesten CG, Thorn L, Wessman M, Groop PH, FinnDiane Study Group: Low birth weight does not increase the risk of nephropathy in Finnish type 1 diabetic patients. *Nephrology Dialysis Transplantation.* 21:2159-2165, 2006
30. Rossing P, Tarnow L, Nielsen FS, Hansen BV, Brenner BM, Parving HH: Low birth weight. A risk factor for development of diabetic nephropathy? *Diabetes.* 44:1405-1407, 1995
31. Nelson RG, Morgenstern H, Bennett PH: Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. *American Journal of Epidemiology.* 148: 650-656, 1998
32. Writing Team for the DCCT/EDIC Group: Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: The epidemiology of diabetes interventions and complications (EDIC) study. *JAMA.* 290:2159-2167, 2003

**Table 1.** Clinical characteristics by birth decade-specific quartiles of height in the FinnDiane Study. Values are mean±SD, median (interquartile range), or % as appropriate. eGDR: Estimated glucose disposal rate. UAER: Urinary albumin excretion rate. eGFR: Estimated glomerular filtration rate. NA: Not applicable.

	1st	2nd	3rd	4th	P value	P value adjusted for duration of diabetes
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
Gender (% men)	51.9	51.3	50.1	51.5	0.87	NA
Blue collar workers (%)	70.2	66.2	63.1	56.5	<1 x 10 <sup>-5</sup>	<1 x 10 <sup>-5</sup>
Ever smokers (%)	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 x 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 x 10 <sup>-5</sup>	NA
HbA <sub>1c</sub> (%)	8.6±1.6	8.5±1.5	8.4±1.5	8.3±1.4	<1 x 10 <sup>-2</sup>	<1 x 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 x 10 <sup>-5</sup>	<1 x 10 <sup>-5</sup>
eGDR (mg/kg/min)	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 x 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 x 10 <sup>-5</sup>	<1 x 10 <sup>-3</sup>
Body mass index (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 x 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 x 10 <sup>-5</sup>	<1 x 10 <sup>-5</sup>
Lipid-lowering medication (%)	13.7	11.5	9.4	9.6	<1 x 10 <sup>-2</sup>	0.37
UAER (mg/24h), N=2697	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 x 10 <sup>-5</sup>	<1 x 10 <sup>-2</sup>
eGFR (ml/min/1.73m <sup>2</sup> )	86±34	93±48	92±31	97±43	<1 x 10 <sup>-5</sup>	0.02
Microalbuminuria (%)	15.2	14.4	9.4	10.9	<1 x 10 <sup>-3</sup>	<1 x 10 <sup>-2</sup>
Macroalbuminuria (%)	18.3	14.9	13.5	11.3	<1 x 10 <sup>-3</sup>	0.01
End-stage renal disease (%)	10.0	6.2	6.3	5.0	<1 x 10 <sup>-4</sup>	0.03
Diabetic nephropathy (%)	28.3	21.1	19.8	16.3	<1 x 10 <sup>-5</sup>	<1 x 10 <sup>-3</sup>
Laser-treated retinopathy (%)	44.4	38.7	31.3	27.5	<1 x 10 <sup>-5</sup>	<1 x 10 <sup>-5</sup>
Laser-treated retinop., normal UAER (%)	18.7	16.2	14.1	11.3	<1 x 10 <sup>-2</sup>	0.10
Cardiovascular disease (%)	12.8	9.3	9.2	8.2	<1 x 10 <sup>-2</sup>	0.93

**Table 2.** Multivariate associations (logistic regression) of 1<sup>st</sup> quartile of decade of birth-specific quartile of height with diabetic nephropathy and laser-treated retinopathy in the FinnDiane Study. OR: Odds ratio.

	<b>Diabetic nephropathy</b>		<b>Laser-treated retinopathy</b>	
	<b>OR (95% CI)</b>	<b>P value</b>	<b>OR (95% CI)</b>	<b>P value</b>
Model 1: Unadjusted	1.71 (1.44-2.02)	<0.001	1.66 (1.43-1.93)	<0.001
Model 2: Model 1 + male gender	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 + HbA <sub>1c</sub> (%)	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 smoker	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 + body mass index (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) before age 18 years	1.12 (0.89-1.41)	0.338	1.12 (0.91-1.38)	0.273

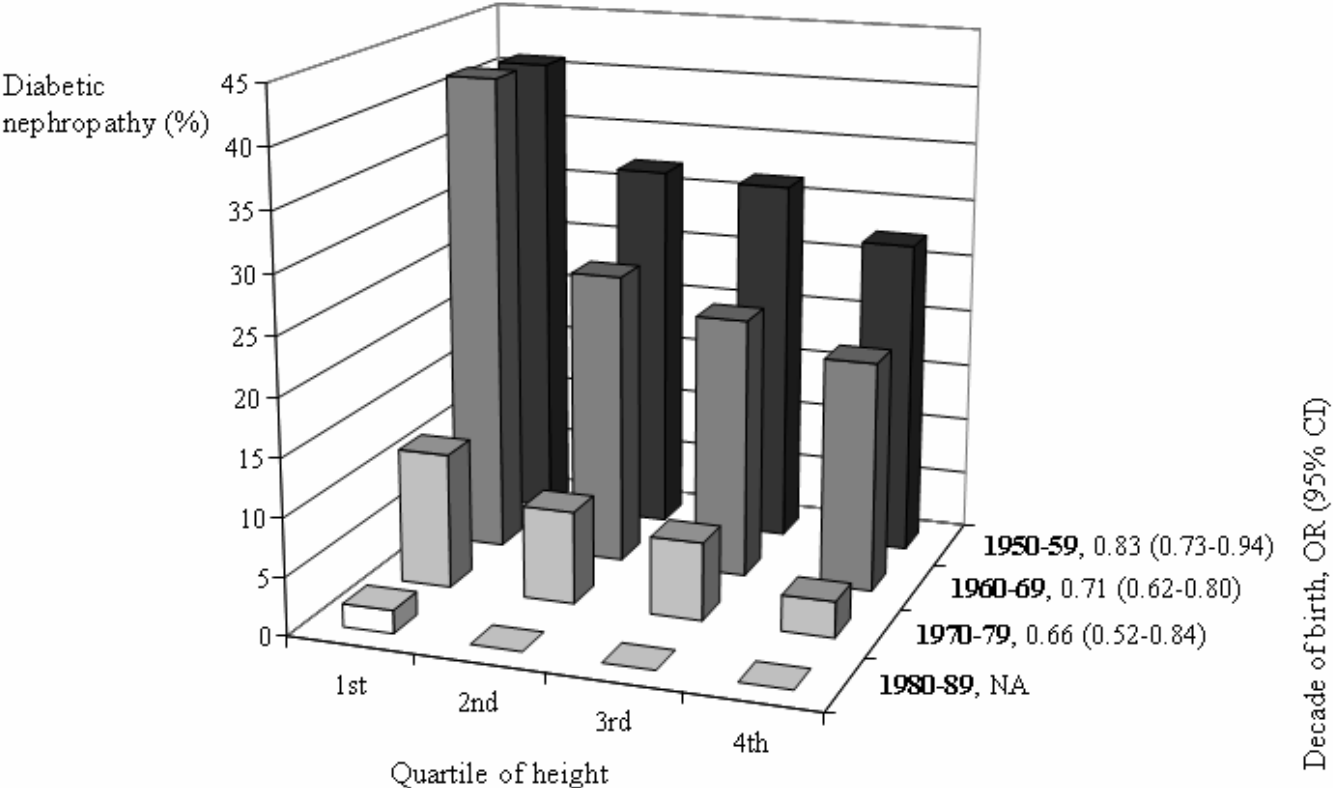
**Table 3.** Clinical characteristics by quartiles of height in the DCCT. Values are mean±SD, median (interquartile range), or % as appropriate. UAER: Urinary albumin excretion rate. GFR: Glomerular filtration rate. NA: Not applicable.

	1st	2nd	3rd	4th	Unadjusted P value	P value adjusted for duration of diabetes
Number of patients	310	305	326	305	NA	NA
<b>Baseline data</b>						
Age (years)	27.6±5.7	29.0±5.7	29.0±5.6	29.1±5.5	<1 x 10 <sup>-2</sup>	NA
Gender (% men)	53.9	53.4	54.9	51.5	0.86	NA
Race (% Caucasian)	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 smokers (%)	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 x 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 x 10 <sup>-2</sup>	NA
HbA <sub>1c</sub> (%)	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 x 10 <sup>-3</sup>	<1 x 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
Body mass index (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/24h)	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 x 10 <sup>-2</sup>	<1 x 10 <sup>-2</sup>
Creatinine clearance (ml/min/1.73m <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 x 10 <sup>-2</sup>
<b>Follow-up data (at close-out)</b>						
Nephropathy class 4-6 (%)	8.4	3.0	1.8	4.6	<1 x 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 x 10 <sup>-2</sup>
Cardiovascular event (%)	8.1	4.9	5.8	7.9	0.31	0.81

**Table 4.** Cox regression models for 1<sup>st</sup> 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. HR: Hazard ratio.

	<b>Nephropathy</b>		<b>Retinopathy</b>	
	<b>HR (95% CI)</b>	<b>P value</b>	<b>HR (95% CI)</b>	<b>P value</b>
Model 1: Unadjusted	2.70 (1.59-4.59)	<0.001	2.06 (1.15-3.71)	0.016
Model 2: Model 1 + male gender	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 + HbA <sub>1c</sub> (%)	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 smoker	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 + body mass index (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 + non-Caucasian	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) before age 18 years	2.39 (1.34-4.25)	0.003	1.13 (0.59-2.17)	0.707

Figure 1a.



**Figure 1b.**

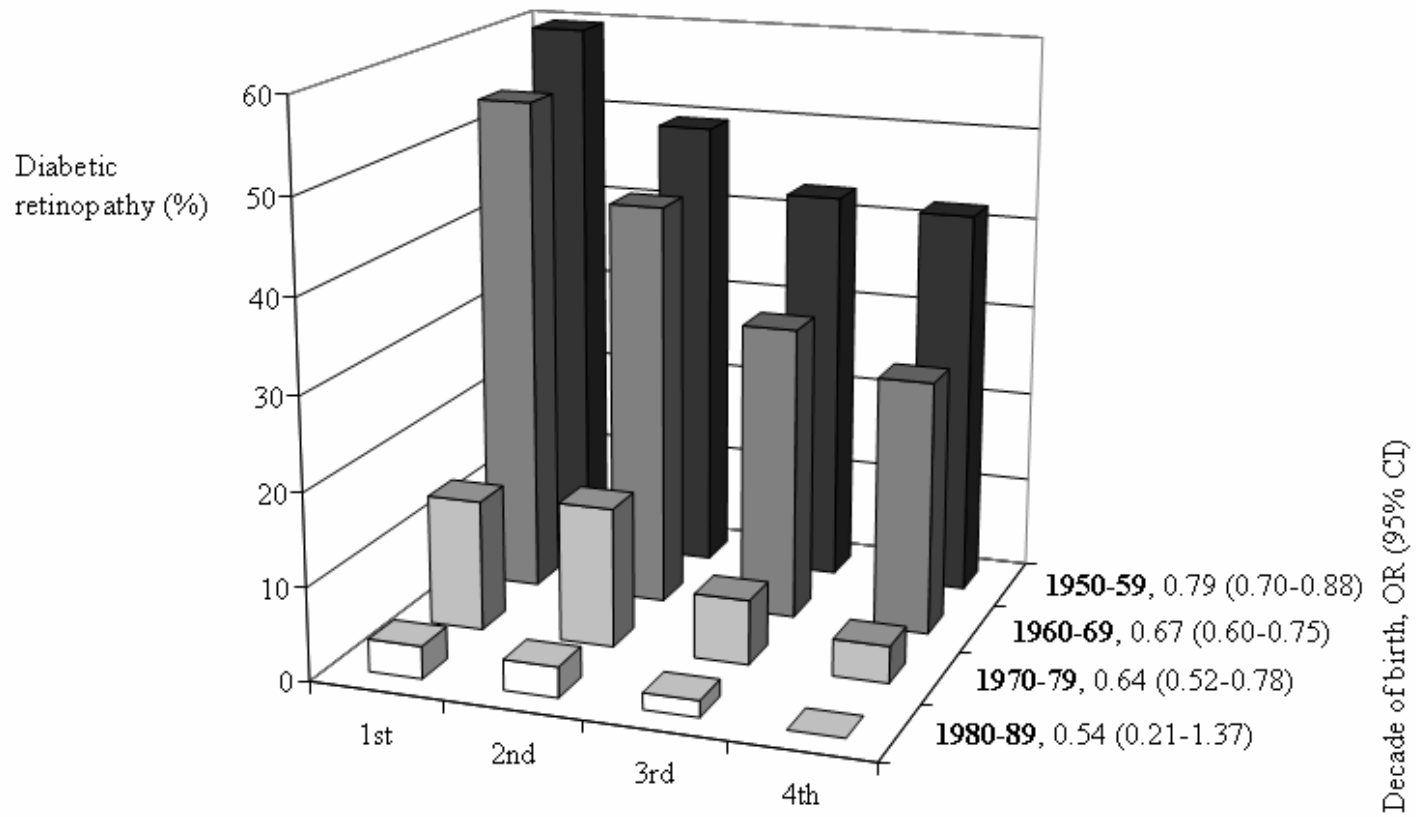
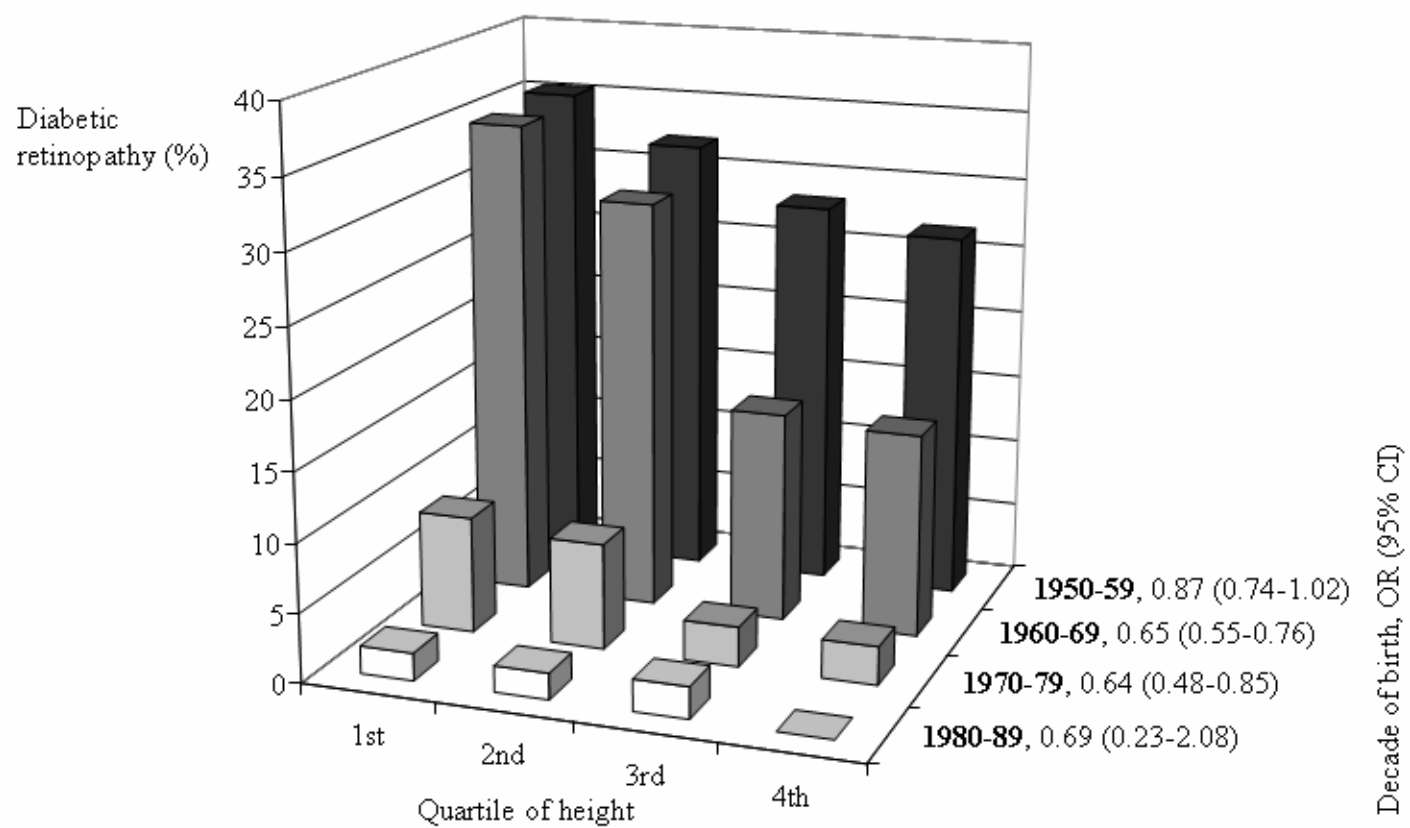


Figure 1c.



**Figure 1d.**

