The Relationship Between Smoking and Microvascular Complications in the EURODIAB IDDM Complications Study

NISHI CHATURVEDI, MRCP
JUDITH M. STEPHENSON, MRCP
JOHN H. FULLER, MRCP

THE EURODIAB IDDM COMPLICATIONS STUDY GROUP

OBJECTIVE — To examine the relationship between smoking and both glycemic control and microvascular complications in patients with insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS — This was a prevalence survey of 3,250 men and women aged 15–60 years with IDDM from 31 diabetes centers in 16 European countries. Participants completed a questionnaire, had retinal photographs taken, and performed a 24-h urine collection. HbA_{1c}, frequency of hypoglycemic and ketoacidotic episodes, urinary albumin excretion rates, and retinopathy were compared by smoking category.

RESULTS — The prevalence of smoking was 35% in men and 29% in women. Current smokers had poorer glycemic control and, among men, were more likely to have had a ketoacidotic episode than were those who never smoked. Ex-smokers had equivalent glycemic control and marginally more hypoglycemic episodes did than those who never smoked. Current smokers had a higher prevalence of microalbuminuria and total retinopathy than did those who never smoked. Ex-smokers had a higher prevalence of macroalbuminuria and proliferative retinopathy than did those who never smoked, but both had a similar prevalence of microalbuminuria. Adjustment for either current or long-term glycemic control could not fully account for these differences.

CONCLUSIONS — Smoking is associated with poorer glycemic control and an increased prevalence of microvascular complications compared with not smoking. Ex-smokers can achieve glycemic control equivalent to and have a prevalence of early complications similar to that of those who never smoked. We suggest that poorer glycemic control can account for some of the increased risk of complications in smokers, and that quitting smoking would be effective in reducing the incidence of complications. Urgent action is required to reduce the high smoking rates in people with IDDM.

From the Department of Epidemiology and Public Health, University College and Middlesex School of Medicine, London, U.K.

Address correspondence and reprint requests to Nishi Chaturvedi, MRCP, Department of Epidemiology and Public Health, University College and Middlesex School of Medicine, 1–19 Torrington Place, London WC1E 6BT, U.K.

Received for publication 14 June 1994 and accepted in revised form 16 February 1995.

AER, albumin excretion rate; CI, confidence interval; IDDM, insulin-dependent diabetes mellitus.

Avoiding microvascular complications, such as nephropathy and retinopathy, is one of the prime therapeutic goals in the management of people with insulin-dependent diabetes mellitus (IDDM) (1). These complications are major contributors to the morbidity and mortality associated with IDDM, but our understanding of factors that initiate or accelerate complications is incomplete, and our ability to intervene is therefore limited. Stringent control of diabetes is one intervention that has been shown to reduce the incidence and progression of complications (2). However, tight control is associated with an increased frequency of hypoglycemic attacks and weight gain and may be difficult, dangerous, and costly to achieve for all patients (2).

Another potentially reversible risk factor associated with high complication rates is cigarette smoking, but the evidence for a relationship between smoking and diabetic control and complications is sparse and conflicting. Some studies report a strong relationship between smoking and microvascular disease (3,4), whereas others show no relationship (5–7). These discrepant findings may be due to methodological limitations of earlier studies, which examined a relatively small number of heterogeneous subjects, did not distinguish between ex-smokers and current smokers, and did not properly adjust for potential confounders (8). Proper adjustment for glycemic control, which may be influenced by smoking (9), when examining the association between smoking and complications has rarely been attempted (10). Furthermore, the relationship between complications and smoking status for those who quit smoking has not often been reported (10,11). This information would be of use to those involved in the difficult task of persuading young people with diabetes to give up smoking (12).

We examined the relationship between smoking and diabetes control and complications in the EURODIAB IDDM

Downloaded from http://diabetesjournals.org/care/article-pdf/18/6/785/443731/18-6-785.pdf by guest on 29 November 2023

complications study, taking into account long-term glycemic control.

RESEARCH DESIGN AND METHODS — Full details of the design and recruitment in the EURODIAB IDDM Complications Study have been published elsewhere (13). In brief, a random sample of 3,250 men and women aged between 15 and 60 years with IDDM were examined in 31 European clinic centers. IDDM was defined as diabetes diagnosed before the age of 36 years and requiring insulin treatment within 1 year of diagnosis. All subjects were required to undergo a health check at their diabetes center. At the center, subjects completed a questionnaire, assisted by their doctor, which included items on smoking status, whether they now smoked and, if not, whether they had ever smoked more than 5 cigarettes/day in the past. Inquiries were also made regarding cigar and pipe smoking. Additional questionnaire items included whether they were initially referred to the clinic for complications (both microvascular and macrovascular) and if so which type of complications, the number of hypoglycemic episodes requiring the help of a third party in the last year, and the number of hospital admissions for ketoacidosis in the last year. Details of medication and demographic variables, including age at completion of education, were also collected.

Blood pressure was measured twice by a random zero sphygmomanometer (Hawksley, U.K.) with the patient seated and a 5-min interval between measurements. The mean of the two resting blood pressure measurements was used in all analyses. Subjects conducted a 24-h urine collection for the estimation of albumin excretion rates (AERs) after excluding proteinuria due to urinary tract infection. Urinary albumin was measured centrally by an immunoturbidometric method (Sanofi Diagnostics Pasteur, Minneapolis, MN). Microalbuminuria was defined as an AER $\geq$20 μg/min and $<$200 μg/min. Macroalbuminuria was defined as an AER $\geq$200 μg/min. Retinal photographs were taken in all centers, except those in Bucharest, Romania, and Krakow, Poland, and were graded at the Hammersmith Hospital (London, U.K.) against standard photographs. The severity of retinopathy was determined by the grading of the worse eye. In these analyses, two categories of retinopathy were used: any retinopathy and proliferative retinopathy. Blood samples were taken and split; one half were tested locally, and the other half were tested centrally in London for HbA_{1c}. The central HbA_{1c} was analyzed by an enzyme immunoassay (Dako, Ely, U.K.); the reference range was 2.9–4.8%. Results of the last eight local HbA_{1c} tests performed over the previous 2 years were also recorded. The 44 pipe smokers and the 53 cigar smokers were excluded from all analyses, irrespective of their cigarette-smoking status. An additional 20 subjects were excluded because smoking data were either contradictory or missing.

Statistical analysis

Prevalence and medians standardized for age and other variables were calculated by the direct method using the total study population as the standard. Age-standardized median blood pressures were calculated after treated hypertensive subjects were assigned to the upper tail of the blood pressure distribution. This method allows the comparison of blood pressure between groups by taking into account differences in rates of and responses to medication for hypertension (14). AERs were log-transformed before analysis. Continuous variables were analyzed by least-squares regression models. Mean age-adjusted values were calculated as the values predicted in the model when the age and duration variables were held at their mean value. Age and duration were treated as confounders in these analyses, and there was no evidence for an interaction for these variables in the relationship between smoking and microvascular complications. Unadjusted and adjusted odds ratios were calculated using logistic regression. Subjects who had at least one hypoglycemic or ketoacidotic episode in the last year were compared with those who had none. HbA_{1c} measured at the central laboratory was used in all analyses except for those that examined longitudinal glycemic control. For these latter analyses, a correction factor for local HbA_{1c} measurements was estimated by comparing the central HbA_{1c} measurement with that performed locally at the same time. An average of all local HbA_{1c} estimations recorded for each individual was calculated and was then adjusted by this correction factor to obtain a standard estimate that was comparable between centers. Because of missing data, only 2,092 subjects could be used in analyses comparing central HbA_{1c} adjustment with long-term glycemic control. Comparisons between current smokers and those who never smoked and separate comparisons between ex-smokers and those who never smoked were made in all analyses.

RESULTS — In men, current smoking rates varied from 23% in the U.K. and Munich to 53% in Thessaloniki, Greece. Current smoking rates were generally lower in women, ranging from 15% in Cork, Ireland, Lisbon, Portugal, and Northern France to 40% in Budapest, Hungary. The age-standardized prevalence of smoking was 35% (95% confidence interval [CI] 33–37%) in men and 29% (95% CI 27–31%) in women (Table 1). In men, smokers and ex-smokers were more likely to be older than those who never smoked; there was very little difference in age between smoking categories in women. Duration of diabetes was greater in male ex-smokers, but not current smokers, compared with those who never smoked. Male ex-smokers and current smokers were younger when they completed their education compared with those who never smoked; this difference was less marked for women. The proportion of people injecting insulin more than twice a day did not vary by smoking status in either men or women. There was little difference in total dose of

Downloaded from http://diabetesjournals.org/care/article-pdf/18/6/785/443731/18-6-785.pdf by guest on 29 November 2023

Table 1—*Demographic and biochemical variables by smoking category and sex*

	Men			Women		
	Never smoked	Ex-smokers	Current smokers	Never smoked	Ex-smokers	Current smokers
Age-standardized prevalence (%)	43	23	35	57	14	29
Mean age (years)	30	38§	33§	33	35*	32
Mean diabetes duration (years)	13	18§	13	15	16	14
Age at completion of education (years) (age and center adjusted)	20	17†	18‡	18	16*	17
Insulin dose (U/kg) (age and duration adjusted)	0.68	0.63	0.67	0.64	0.63	0.67
Injection frequency >2 times/day (%) (age and center standardized)	48	46	46	53	57	57
HbA_{1c} (%) (age adjusted)	6.3	6.5	6.9§	6.6	6.4	6.9†
HbA_{1c} (%) (age, duration, center, referred with complications, and education adjusted)	5.8	6.0	6.3§	6.6	6.5	7.0§
Median systolic blood pressure (mmHg) (age standardized)	123	124	121	118	117	114*
Mean AER (μg/min) (age adjusted)	17.20	29.35‡	22.69†	14.45	16.86	17.57*
Mean AER (μg/min) (age, blood pressure, duration, HbA_{1c}, education, and center adjusted)	15.85	21.38†	20.42‡	10.86	12.76*	13.68†

For men, n = 1,594; for women, n = 1,539. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, §$P < 0.0001$, current or ex-smokers compared with those who never smoked.

insulin or in median blood pressure by smoking category for both sexes.

HbA_{1c} was significantly higher in current smokers than in those who never smoked (6.9 vs. 6.3% in men, $P < 0.0001$; and 6.9 vs. 6.6% in women, $P < 0.01$). There was, however, no difference in HbA_{1c} when ex-smokers were compared with those who never smoked. In men, ex-smokers were 1.48 times more likely to have had at least one hypoglycemic episode than were those who never smoked ($P < 0.01$), and this increased risk was still present, although not significant, when adjusted for confounders such as age, duration of diabetes, glycemic control, education, and center (Table 2). In contrast, current smokers were more likely to have had at least one ketoacidotic episode compared with those who never smoked, and this increased risk persisted when adjusted for age, duration, and education and was reduced, but still significant, when further adjusted for glycemic control. In women, current and ex-smokers were less likely to have had at least one hypoglycemic episode; there was no consistent relation between smoking status and ketoacidotic episodes.

Ex-smokers were particularly likely to have been referred to the clinic with a complication associated with diabetes (27 vs. 22% in men, $P < 0.001$; and 28 vs. 25% in women, $P < 0.05$) (Table 3). Of those referred for complications,

Table 2—*Risk (odds ratio) of at least one hypoglycemic or one ketoacidotic episode in the year before examination, comparing ex-smokers and current smokers with those that never smoked*

	Men		Women	
Episodes	Current smokers	Ex-smokers	Current smokers	Ex-smokers
n	554	361	447	219
Hypoglycemic	1.13 (0.89–1.44)	1.48 (1.13–1.94)†	0.75 (0.58–0.96)*	0.91 (0.66–1.25)
Hypoglycemic [1]	1.16 (0.90–1.49)	1.25 (0.93–1.68)	0.75 (0.58–0.97)*	0.86 (0.62–1.19)
Hypoglycemic [2]	1.23 (0.95–1.59)	1.29 (0.96–1.74)	0.82 (0.59–1.14)	0.80 (0.61–1.03)
Ketoacidotic	1.99 (1.30–3.06)†	1.13 (0.65–1.94)	1.06 (0.72–1.56)	0.94 (0.56–1.59)
Ketoacidotic [1]	2.06 (1.31–3.24)†	1.40 (0.76–2.59)	1.01 (0.67–1.51)	1.07 (0.63–1.83)
Ketoacidotic [2]	1.76 (1.11–2.80)*	1.28 (0.68–2.39)	0.97 (0.64–1.45)	1.13 (0.66–1.94)

Data are odds ratios (95% CI). Episodes labeled 1 are adjusted for age, duration, education, and center. Episodes labeled 2 are adjusted for age, duration, education, HbA_{1c}, and center. *$P < 0.05$, †$P < 0.01$, current or ex-smokers compared with those who never smoked.

Downloaded from http://diabetesjournals.org/care/article-pdf/18/6/785/443731/18-6-785.pdf by guest on 29 November 2023

Table 3—*Patients referred to center with complications, standardized by age and center*

	Men			Women		
	Never smoked	Ex-smokers	Current smokers	Never smoked	Ex-smokers	Current smokers
n	679	361	554	873	219	447
Any complications (%)	22 (21–23)	27 (26–28)‡	25 (24–26)‡	25 (23–27)	28 (27–29)*	27 (26–28)
Referred with complications						
n	131	102	153	238	65	127
Past history of laser therapy (%)	25 (23–27)	35 (32–38)†	21 (18–24)	26 (23–29)	24 (22–26)	24 (22–26)
Past history of renal disease (%)	12 (10–14)	20 (18–22)*	16 (14–18)	18 (15–21)	9 (8–10)	12 (10–14)*

Data are means (95% CI). *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, current or ex-smokers compared with those who never smoked.

male ex-smokers were also more likely to have a past history of laser therapy and renal disease.

Male ex-smokers were more likely to have proliferative retinopathy and more likely to have macroalbuminuria at examination than were those who never smoked (Table 4). Current smokers were more likely to have microalbuminuria than were those who never smoked in both sexes.

The confounding effect of glycemic control on mean AERs and the risk of having albuminuria or retinopathy in comparison with those who never smoked were examined in Table 5. Each of these values was adjusted first by the central measurement of HbA_{1c} and then by the mean of the eight previous measurements of HbA_{1c} performed locally, with the latter providing a long-term assessment of glycemic control. Adjustment for local long-term control attenuated the relationship between smoking and complications compared with the central measurement, but the association remained statistically significant. Further adjustment for other confounders, such as blood pressure, education, center, and lipids and lipoproteins (data not shown for latter adjustment), made no significant difference to the relationship between smoking and microvascular complications.

The odds ratios for any retinopathy in men were further adjusted for AER. For ex-smokers, the risk of any retinopathy compared with the risk for those who never smoked changed from 1.82 ($P = 0.02$) to 1.75 ($P = 0.03$). The odds ratio for current smokers changed from 1.71 ($P = 0.009$) to 1.63 ($P = 0.03$).

CONCLUSIONS — Current smoking rates are alarmingly high in this European IDDM population, despite repeated demonstrations of the increased risk of morbidity and mortality in people with IDDM and the marked exaggeration of these effects in people who smoke (15,16).

This is the largest study to examine the relationship between smoking and diabetes control and complications in both men and women. We show that current smokers had marginally poorer glycemic control (0.6% in men and 0.3% in women) compared with those who never smoked, while ex-smokers had equivalent levels of control (10,17). In men, ex-smokers were more likely to have experienced at least one hypoglycemic episode in the last year, while current smokers were more likely to have experienced at least one ketoacidotic episode, compared with those who never smoked. Much of this association, at least for hypoglycemic episodes, could be accounted for by differences in glycemic control.

Table 4—*Prevalence of complications at examination standardized by age, duration, HbA_{1c}, and center*

	Men			Women		
	Never smoked	Ex-smokers	Current smokers	Never smoked	Ex-smokers	Current smokers
n	679	361	554	873	219	447
All retinopathy (%)	40 (38–42)	56 (54–58)§	46 (44–48)†	44 (42–46)	43 (41–45)	43 (41–45)
Proliferative retinopathy (%)	8 (7–9)	15 (13–17)§	6 (5–7)	12 (11–13)	10 (9–11)	9 (7–11)*
Microalbuminuria (%)	21 (19–23)	23 (22–24)	28 (26–30)‡	18 (16–20)	21 (20–22)	23 (21–25)*
Macroalbuminuria (%)	6 (5–7)	16 (15–17)§	9 (8–10)*	9 (8–10)	8 (7–9)	8 (7–9)

Data are means (95% CI). *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, §$P < 0.0001$, current or ex-smokers compared with those who never smoked.

Downloaded from http://diabetesjournals.org/care/article-pdf/18/6/785/443731/18-6-785.pdf by guest on 29 November 2023

Table 5—*Mean AERs and risks (odds ratios) of albuminuria and retinopathy by smoking status, comparing adjustment by centrally measured HbA_{1c} and mean of eight HbA_{1c} tests performed locally*

	Men			Women		
	Never smoked	Ex-smokers	Current smokers	Never smoked	Ex-smokers	Current smokers
n	476	239	346	565	147	319
AER						
Age and centrally measured HbA_{1c} adjusted	17.10	28.84‡	20.84*	15.09	20.32*	17.94*
Age and local HbA_{1c} adjusted	17.38	28.58‡	20.37	14.69	20.46*	17.91*
Risk of any retinopathy [1]	1.00	1.82*	1.71†	1.00	1.05	1.00
Risk of any retinopathy [2]	1.00	1.75*	1.62*	1.00	1.09	1.04
Risk of albuminuria [1]	1.00	1.51*	1.65†	1.00	1.52	1.48*
Risk of albuminuria [2]	1.00	1.48	1.60†	1.00	1.62*	1.53*

Risks labeled 1 are adjusted for age, duration, systolic blood pressure, education, center, and central HbA_{1c}; risks labeled 2 are adjusted for age, duration, systolic blood pressure, education, center, and local HbA_{1c}. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, current or ex-smokers compared with those who never smoked.

Current smokers had a higher prevalence of microalbuminuria compared with those who never smoked. In contrast, male ex-smokers had a higher prevalence of macroalbuminuria, but a similar prevalence of microalbuminuria, compared with those who never smoked. We show that a past history of renal disease is more common in ex-smokers than in current smokers and those who never smoked, and we hypothesize that efforts to cease smoking are intensified when macroalbuminuria is present. One explanation for the similar prevalence of microalbuminuria in ex-smokers and those who never smoked in our study could be that the effects of smoking on microvascular complications may not persist once smoking is discontinued. The observation that the rate of progression to albuminuria is reduced in those who stop smoking further supports our hypothesis (10,18).

Our findings may help to clarify the confusion regarding the relationship between smoking and renal disease, with some studies showing no relationship (6,7) and others a relationship with either microalbuminuria (10,19,20) or nephropathy (4,21). At least part of that confusion may be due to the categorization in other studies of current and ex-smokers as one smoking group. Similarly, previous studies have concluded that there is no association between smoking and retinopathy (5,6,8,22,23), while others suggest there is a relationship either in both sexes (3) or in women only (4). We show that in men the prevalence of any retinopathy is greater in current and ex-smokers compared with those who never smoked, but the prevalence of proliferative retinopathy is only greater in ex-smokers. We also show that a past history of laser therapy is more common in ex-smokers. This supports and extends our hypothesis of the association between smoking and renal disease, with ex-smokers having more severe disease and current smokers having a greater prevalence of early complications compared with those who never smoked. The retinopathy findings are not simply explained by the association of smoking with microalbuminuria because adjustment for AER attenuated, but did not abolish, the smoking-retinopathy relationship.

Despite large numbers, these relationships were either weaker or absent in women; HbA_{1c} was not as different between current smokers and those who never smoked as it was in men. The 0.3% difference in HbA_{1c} is not clinically significant, and this might account for the general lack of association between smoking status and either hypoglycemic episodes or microvascular complications. The lower rates of proliferative retinopathy in current smokers compared with those who never smoked may be of interest, but the difference is relatively modest in this study.

We demonstrate that the relationship between smoking status and microvascular complications is attenuated after adjustment for HbA_{1c}. One measurement of HbA_{1c} may bear little relation to long-term glycemic control, especially if those patients with complications are assisted in improving control. We adjusted for HbA_{1c} measured on approximately eight occasions over the previous 2 years and showed that there is further attenuation of the relationship between smoking and complications. Only one other study has adjusted for long-term measures of HbA_{1c}, and it confirms our finding of a persistent relationship between smoking and renal complications, but was unable to show a persistent relationship between smoking and retinopathy (10). We asked respondents to classify their own smoking habits and did not validate these self-reports. It is likely that the prevalence of current smoking is underreported (24,25). In this study, current smokers could have misclassified themselves as either ex-smokers or those who never

Downloaded from http://diabetesjournals.org/care/article-pdf/18/6/785/443731/18-6-785.pdf by guest on 29 November 2023

smoked. This would mean that the relationships we observed when we compared current smokers with those who never smoked are probably a slight underestimate of the true relationship, while the relationship we observed between ex-smokers and those who never smoked may be exaggerated. Similarly, we have no information on the amount smoked or the exact date of quitting for ex-smokers; despite these limitations, we have shown clear differences in the relationship between smoking status and diabetes control and complications. Although this is a clinic-based study, the majority of people with IDDM in these European centers would be under the care of the diabetes clinic. There may still be potential for selection bias in this study population, in that people who smoke may be more or less likely to be referred than those who do not, and similarly, people who attend clinics may have a higher or lower prevalence of complications than those who do not. However, it is unlikely that the relationship between smoking and complications would differ between those referred and those not referred. Similarly, it is unlikely that the relationship between smoking and complications differs substantially between those who responded and those who did not in this study; among nonresponders, current smokers would have to have more than a quarter the risk of any retinopathy of those who never smoked to nullify the 1.71 times increased risk of retinopathy observed for current male smokers who did respond.

These data are cross-sectional and cannot provide substantial evidence to support the hypothesis of a causal relationship. Nevertheless, our explanation is the most plausible interpretation of our data, and it is matched by findings from prospective studies (18,26). It is unlikely that selective mortality of smokers would substantially affect people at the younger end of our age distribution, and in any case, because heavier smokers are more likely to suffer from this effect than lighter smokers, we may have underestimated the true relationship between smoking and microvascular complications.

Several mechanisms have been proposed to explain why smokers with diabetes have an increased risk of microvascular complications compared with those who never smoked. We and others show that smokers have poorer metabolic control compared with those who never smoked (9,10,17), and we suggest that much of the effect of smoking on microvascular disease acts through its effect on glycemic control. Other suggestions to explain the effects of smoking on diabetes-related complications independent of control include the effects of smoking on platelet aggregation (27) and tissue hypoxia (28) and its stimulatory effects on insulin antagonists, such as cortisol and adrenaline. Smoking has been related to insulin resistance, hyperinsulinemia, and a higher glucose response to insulin infusion, and this may account for the poorer glycemic control observed in people with IDDM who smoke (29,30).

Smokers may have an attitude about disease that is less compliant and careful than those who have never smoked, resulting in poorer glycemic control and an increased risk of complications. Factors such as diet, exercise, and attitudes about a healthy lifestyle may also vary by smoking status and may also affect the risk of diabetes complications. We show that the frequency of insulin injections did not differ in current smokers and those who never smoked, suggesting that at least in this respect smokers are no less compliant than those who never smoked. Smokers without diabetes also have higher HbA_{1c} levels compared with those who never smoked (31), so that the effect of smoking on HbA_{1c} may be a biochemical effect (29) rather than one due to poor compliance. In one of the few studies designed to test this hypothesis, psychological attitudes of smoking and nonsmoking people with diabetes were shown not to differ (9).

In conclusion, we show that the prevalence of smoking in people with IDDM in Europe is high and that it is associated with an increased prevalence of microvascular complications, at least partly mediated through poorer glycemic control. Ex-smokers can achieve good glycemic control, and there is a suggestion from our data that the prevalence of new complications is similar to that of those who have never smoked. These findings provide clear scientific evidence to support health care workers in their difficult task of persuading smokers with diabetes to quit smoking (12). We propose that efforts to reduce the rate of complications in people with IDDM should not underestimate the value of encouraging smoking cessation as an efficient and cheap intervention to be considered along with more expensive and potentially hazardous attempts to tighten glycemic control.

Acknowledgments— The study was part of the EURODIAB Concerted Action Programme, which is financially supported by the Commission of the European Communities. Additional financial support from ICI UK, Fidia, Bayer, Miles-Ames, Novo Nordisk, and Pfizer is gratefully acknowledged.

The participation of all of the patients in the study is gratefully acknowledged.

APPENDIX— EURODIAB investigators are as follows: B. Karamanos, C. Tountas, A. Kofinis, K. Petrou, and N. Katsilambros (Hippokration Hospital, Athens, Greece); R. Giorgino, M. Cignarelli, M.L. De Cicco, and I. Ramunni (Istituto di Clinica Medica, Endocrinologia e Malattie Metaboliche, Universita di Bari, Bari, Italy); C. Ionescu-Tirgoviste, C.M. Iosif, D. Pitei, and S. Buligescu (Clinic of Diabetes, Nutrition & Metabolic Diseases, Bucharest, Romania); G. Tamas, Z. Kerenyi, A.M. Ahmed, J. Toth, and P. Kempler (Tetenyi Teaching Hospital and Semmelweis University, Budapest, Hungary); Se. Muntoni, M. Songini, M. Stabilini, M. Fossarello, S. Pintus, and Sä. Muntoni (Ospedale San Michele, Cagliari, Italy); J.B. Ferriss, C.C. Cronin, A.E. Whyte, and P.E. Cleary (Cork Regional

Downloaded from http://diabetesjournals.org/care/article-pdf/18/6/785/443731/18-6-785.pdf by guest on 29 November 2023

Hospital, Cork, Ireland); M. Toeller, A. Klischan, T. Forst, and F.A. Gries (Diabetes Forschungsinstitut), and W. Wagener (Medizinische Klinik E., Universitat Dusseldorf, Dusseldorf, Germany); R. Rottiers and H. Priem (University Hospital of Ghent, Ghent, Belgium); P. Ebeling, M. Sinisalo, and V.A. Koivisto (University Hospital of Helsinki, Helsinki, Finland); B. Idzior-Walus, B. Solnica, L. Szopinska-Ciba, and K. Solnica (University School of Medicine, Krakow, Poland); H.M.J. Krans, H.H.P.J. Lemkes, J.J. Jansen, and J. Brachter (University Hospital of Leiden, Leiden, The Netherlands); J. Nunes-Correa and J. Boavida (Portuguese Diabetic Association, Lisbon, Portugal); G. Michel and R. Wirion (Centre Hospitalier, Luxembourg); A.J.M. Boulton, H. Ashe, D.J.S. Fernando (Manchester Royal Infirmary, Manchester, U.K.); G. Pozza, G. Slaviero, G. Comi, B. Fattor, and F. Bandello (Ospedale San Raffaele, Milan, Italy); H.U. Janka, A. Nuber, and H. Mehnert (City Hospital Schwabing, Munich, Germany); D. Ben Soussan, M.-C. Fallas, P. Fallas (Centre Hospitalier de Valenciennes, Valenciennes, France); E. Jepson and S. McHardy-Young (Central Middlesex Hospital, Middlesex, U.K.), and J.H. Fuller, D.J. Betteridge, and M. Milne (University College Hospital, NW London, U.K.); G. Crepaldi and R. Nosadini (Instituto di Medicina Interna, Padua, Italy); G. Cathelineau, B. Villatte Cathelineau, M. Jellal, N. Grodner, and P. Gervais Feiss (Hospital Saint-Louis, Paris, France); F. Santeusanio, G. Rosi, M.R.M. Ventura, C. Cagini, and C. Marino (Instituto di Patologia Medica, Policlinico, Perugia, Italy); R. Navalesi, G. Penno, R. Miccoli, M. Nannipieri, and S. Manfredi (Instituto di Clinica Medica II, Pisa, Italy); G. Ghirlanda, P. Cotroneo, A. Manto, C. Teodonio, and A. Minnella (Universita Cattolica del Sacro Cuore, Rome, Italy); J.D. Ward, S. Tesfaye, C. Mody, and C. Rudd (Royal Hallamshire Hospital, Sheffield, U.K.); G.M. Molinatti, F. Vitelli, M. Porta, G.F. Pagano, P. Cavallo Perin, P. Estivi, R. Sivieri, Q. Carta, and G. Petraroli (Clinica Medica B, Patologia Medica, Ospedale Molinette, and Ospedale "Agnelli," Turin, Italy); N. Papazoglou, G. Manes, G. Triantaphyllou, A. Ioannides, G. Skazagar, and I. Kontogiannis (General Hospital of Thessaloniki, Thessaloniki, Greece); M. Muggeo, V. Cacciatori, F. Bellavere, P. Galante, and M.L. Gemma (Cattedra di Malatties del Metabolismo, Verona, Italy); K. Irsigler, H. Abrahamian, C. Gurdet, B. Hornlein, and C. Willinger (Hospital Vienna Lainz, Vienna, Austria); S. Walford, E.V. Wardle, and S. Hughes (New Cross Hospital, Wolverhampton, U.K.); G. Roglic, Z. Resman, Z. Metelko, and Z. Skrabalo (Vuk Vrhovac Institute for Diabetes, Zagreb, Croatia).

Steering Committee members were: J.H. Fuller (London); H. Keen, Chairman (London); H.M.J. Krans (Leiden); R. Navelesi (Pisa); A.-K. Sjolie (Aarhus); J. Stephenson (London); M. Toeller (Dusseldorf); G.-C. Viberti (London); and J. Ward (Sheffield).

Coordinating center was: J.H. Fuller, J. Stephenson, M. Milne, and T. Partridge at University College and Middlesex School of Medicine, London, U.K.

Central laboratories were: G. John, The Royal London Hospital; and G.-C. Viberti, M. Mattock, A. Collins, and R. Sharp Guy's Hospital, London, U.K.

Retinopathy coordination was: A.-K. Sjolie, Aarhus University Hospital, Aarhus, Denmark.

Retinopathy grading center was: E. Kohner, S. Aldington, and S. Cockley, Hammersmith Hospital, London, U.K.

References

1. Krans HMJ, Porta M, Keen H: *Diabetes Care and Research in Europe: the St. Vincent Declaration Action Programme*. Copenhagen, World Health Organization, 1991
2. 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* 329:977–986, 1993
3. Paetkau ME, Boyd TAS, Winship B, Grace M: Cigarette smoking and diabetic retinopathy. *Diabetes* 26:46–49, 1977
4. Muhlhauser I, Sawicki P, Berger M: Cigarette-smoking as a risk factor for macroproteinuria and proliferative retinopathy in type I (insulin-dependent) diabetes. *Diabetologia* 29:500–502, 1986
5. Moss SE, Klein R, Klein BEK: Association of cigarette smoking with diabetic retinopathy. *Diabetes Care* 14:119–126, 1991
6. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Ellis D, LaPorte RE, Kuller LH, Wolfson SK, Drash AL: Factors associated with avoidance of severe complications after 25 years of IDDM: Pittsburgh Epidemiology of Diabetes Complications Study 1. *Diabetes Care* 13:741–747, 1990
7. West KM, Ahuja MMS, Bennett PH, Grab B, Grabauskas V, Mateo de Acosta O, Fuller JH, Jarrett RJ, Keen H, Kosaka K, Krolewski AS, Miki E, Schliack V, Teuscher A: Interrelationships of microangiopathy, plasma glucose and other risk factors in 3583 diabetic patients: a multinational study. *Diabetologia* 22:412–420, 1982
8. West KM, Erdreich LS, Stober JA: Absence of a relationship between smoking and diabetic microangiopathy. *Diabetes Care* 3:250–252, 1980
9. Lundman BM, Asplund K, Norberg A: Smoking and metabolic control in patients with insulin-dependent diabetes mellitus. *J Intern Med* 227:101–106, 1990
10. Chase HP, Garg SK, Marshall G, Berg CL, Harris S, Jackson WE, Hamman RE: Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA* 265:614–617, 1991
11. Klein R, Klein BEK, Davis MD: Is cigarette smoking associated with diabetic retinopathy? *Am J Epidemiol* 118:228–238, 1983
12. Ardron M, MacFarlane IA, Robinson C, van Heyingen C, Calverley PMA: Anti-smoking advice for young diabetic smokers: is it a waste of breath? *Diabetic Med* 5:667–670, 1988
13. The EURODIAB IDDM Complications Study Group: Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. *Diabetologia* 37:278–285, 1994

Downloaded from http://diabetesjournals.org/care/article-pdf/18/6/785/443731/18-6-785.pdf by guest on 29 November 2023

14. White IR, Chaturvedi N, McKeigue PM: Median analysis of blood pressure for a sample including treated hypertensives. *Stat Med* 13:1635–1641, 1994
15. Moy CS, LaPorte RE, Dorman JS, Songer TJ, Orchard TJ, Kuller LH, Becker DJ, Drash AL: Insulin-dependent diabetes mellitus mortality: the risk of cigarette smoking. *Circulation* 82:37–43, 1990
16. Gay EC, Cruickshanks KJ, Cai Y, Kostraba JN, Gale SM, Hamman RF, Baron A: Smokers with IDDM experience excess morbidity. *Diabetes Care* 15:947–952, 1992
17. Bott U, Jorgens V, Grusser M, Bender R, Muhlhauser I, Berger M: Predictors of glycemic control in type I diabetic patients after participation in an intensified treatment and teaching programme. *Diabetic Med* 11:362–371, 1994
18. Sawicki PT, Bender R, Didjurgeit U, Heinemann L, Muhlhauser I, Berger M: Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 17: 126–131, 1994
19. Gatling W, Mullee MA, Knight C, Hill RD: Microalbuminuria in diabetes: relationships between urinary albumin excretion and diabetes related variables. *Diabetic Med* 5:348–351, 1988
20. Microalbuminuria Collaborative Study Group United Kingdom: Risk factors for development of microalbuminuria in insulin-dependent diabetic patients: a cohort study. *Br Med J* 306:1235–1239, 1993
21. Norden G, Nyberg G: Smoking and diabetic nephropathy. *Acta Med Scand* 215: 257–261, 1984
22. Rand LI, Krolewski AS, Aiello LM, Warram JH, Baker RS, Maki T: Multiple factors in the prediction of risk of proliferative diabetic retinopathy. *N Engl J Med* 313:1433–1438, 1985
23. Christiansen JS: Cigarette smoking and prevalence of microangiopathy in juvenile-onset insulin-dependent diabetes mellitus. *Diabetes Care* 1:146–149, 1978
24. Britten N: Validity of claims to lifelong non-smoking at age 36 in a longitudinal study. *Int J Epidemiol* 17:525–529, 1988
25. Masson EA, MacFarlane IA, Priestley CJ, Wallymahmed ME, Flavell HJ: Failure to prevent nicotine addiction in young people with diabetes. *Arch Dis Child* 67:100–102, 1992
26. Watts GF, Harris R, Shaw KM: The determinants of early nephropathy in insulin-dependent diabetes mellitus: a prospective study based on the urinary excretion of albumin. *Q J Med* 79:365–378, 1991
27. Mustard JF, Murphy EA: Effect of smoking on blood coagulation and platelet survival in man. *Br Med J* 1:846–849, 1963
28. Sagone AL, Lawrence T, Balcerzak SP: Effect of smoking on tissue oxygen supply. *Blood* 41:845–851, 1973
29. Facchini FS, Hollenbeck CB, Jeppesen J, Chen Y-DI, Reaven GM: Insulin resistance and cigarette smoking. *Lancet* 339: 1128–1130, 1992
30. Helve E, Yki-Järvinen H, Koivisto VA: Smoking and insulin sensitivity in type I diabetic patients. *Metabolism* 35:874–877, 1986
31. Modan M, Meytes D, Rozeman P, Benyosef S, Sehayek E, Benyosef N, Lusky A, Halkin H: Significance of high HbA_1 levels in normal glucose tolerance. *Diabetes Care* 11:422–428, 1988

Downloaded from http://diabetesjournals.org/care/article-pdf/18/6/785/443731/18-6-785.pdf by guest on 29 November 2023