

Dietary Fat Intake as Risk Factor for the Development of Diabetes

Multinational, multicenter study of the Mediterranean Group for the Study of Diabetes (MGSD)

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OBJECTIVE — To investigate the role of dietary factors in the development of type 2 diabetes.

RESEARCH DESIGN AND METHODS — In the context of the Multinational MGSD Nutrition Study, three groups of subjects were studied: 204 subjects with recently diagnosed diabetes (RDM), 42 subjects with undiagnosed diabetes (UDM) (American Diabetes Association criteria—fasting plasma glucose [FPG] ≥ 126 mg/dl), and 55 subjects with impaired fasting glucose (IFG) (FPG ≥ 110 and < 126 mg/dl). Each group was compared with a control group of nondiabetic subjects, matched one by one for center, sex, age, and BMI. Nutritional habits were evaluated by a dietary history method, validated against the 3-day diet diary. In RDM, the questionnaire referred to the nutritional habits before the diagnosis of diabetes. Demographic data were collected, and anthropometrical and biochemical measurements were taken.

RESULTS — Compared with control subjects, RDM more frequently had a family history of diabetes (49.0 vs. 14.2%; $P < 0.001$), exercised less (exercise index 53.5 vs. 64.4; $P < 0.01$), and more frequently had sedentary professions (47.5 vs. 27.4%; $P < 0.001$). Carbohydrates contributed less to their energy intake (53.5 vs. 55.1%; $P < 0.05$), whereas total fat (30.2 \pm 0.5 vs. 27.8 \pm 0.5%; $P < 0.001$) and animal fat (12.2 \pm 0.3 vs. 10.8 \pm 0.3%; $P < 0.01$) contributed more and the plant-to-animal fat ratio was lower (1.5 \pm 0.1 vs. 1.8 \pm 0.1; $P < 0.01$). UDM more frequently had a family history of diabetes (38.1 vs. 19.0%; $P < 0.05$) and sedentary professions (58.5 vs. 34.1%; $P < 0.05$), carbohydrates contributed less to their energy intake (47.6 \pm 1.7 vs. 52.8 \pm 1.4%; $P < 0.05$), total fat (34.7 \pm 1.5 vs. 30.4 \pm 1.2%; $P < 0.05$) and animal fat (14.2 \pm 0.9 vs. 10.6 \pm 0.7%; $P < 0.05$) contributed more, and the plant-to-animal fat ratio was lower (1.6 \pm 0.2 vs. 2.3 \pm 0.4; $P < 0.05$). IFG differed only in the prevalence of family history of diabetes (32.7 vs. 16.4%; $P < 0.05$).

CONCLUSIONS — Our data support the view that increased animal fat intake is associated with the presence of diabetes.

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Abbreviations: 3-DDD, 3-Day Diet Diary; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; RDM, recently diagnosed diabetes; UDM, unknown diabetes.

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

The incidence of type 2 diabetes is increasing rapidly worldwide (1,2). In conjunction with genetic susceptibility, type 2 diabetes is brought on by environmental and behavioral factors, such as sedentary lifestyle and overly rich nutrition with accompanying obesity (2). However, there is still controversy in the literature about the role of the qualitative composition of the diet in the development of glucose intolerance (3,4). In the Zutphen study (5), no association was found between dietary components and the development of diabetes in a 25-year follow-up period. On the other hand, in the Nurses Health Study, an inverse association was found between the development of diabetes and vegetable fat intake (6), but no association with total fat intake (7,8). In the Health Professionals Follow-up Study (9), an inverse association was found between the development of diabetes and the intake of cereal fiber, but not total carbohydrates or fat. In the Iowa Women's Health Study (10), an inverse association was found between the development of diabetes and fiber consumption, but no association with glycemic index or load. Cross-sectional studies have shown that saturated fat was associated with higher fasting plasma glucose (11,12). Intervention studies have shown that high carbohydrate and high mono-unsaturated fat diets improve insulin sensitivity and glucose disposal (13). The large prospective Da Qing Study showed that both dietary and physical activity interventions reduced the incidence of type 2 diabetes in people with impaired glucose tolerance (IGT) (3). Recently, the Finnish Diabetes Prevention Study and the Diabetes Prevention Program (14,15) showed that even modest weight loss, combined with dietary and physical activity modifications, resulted in significant reduction of the incidence of diabetes in subjects with IGT. However, in the above studies, the role of the qualitative composition of the diet was not thoroughly explored.

The aim of the present study was to investigate the role of dietary factors in the development of type 2 diabetes in the Mediterranean area. This study is part of the Mediterranean Group for the Study of Diabetes Nutrition Study, which was planned to investigate the dietary habits among Mediterranean countries, in both the general and the diabetic population.

RESEARCH DESIGN AND METHODS

The study protocol has been described in detail (16). In brief, a total of 4,254 subjects, 2,090 nondiabetic and 2,163 with known type 2 diabetes, were recruited in nine centers in six countries. There were three centers in Greece, two in Italy, and one each in Algeria, Bulgaria, Egypt, and Yugoslavia. At least 150 nondiabetic subjects, randomly selected from a defined geographical region, were recruited in each center. Moreover, 204 subjects with type 2 diabetes diagnosed during the 2 months preceding the examination were recruited from the above centers.

Inclusion criteria were age 35–60 years and, for the nondiabetic subjects, a free diet for at least 3 months before the study.

Subjects were studied after an overnight (12-h) fast. A venous blood sample was taken for biochemical measurements. A patient report form was filled in, comprising demographic data, medical and family history, and smoking habits. Anthropometrical measurements comprised height without shoes, weight with light clothing, waist circumference (midway between the rib cage and the iliac crest), hip circumference (maximal circumference between the iliac crest and the thigh region), and blood pressure in the sitting position after 5 min rest (mean of two measurements).

A dietary history method was used for the evaluation of dietary habits (17–19). A dietary questionnaire comprising 78 questions translated into the local languages was filled in by a trained examiner (dietitian or nurse) during a 30- to 45-min session. The questions referred to the daily or weekly consumption of various foodstuffs (milk, meat, fish, etc.) or groups of foodstuffs (fruit, pasta, etc.). The estimation of the amounts consumed was based in all centers on standardized household measures and portion sizes agreed on during the training sessions of the examiners and translated into grams.

The 204 subjects with recently diagnosed diabetes were asked to carefully remember and describe their dietary habits before the diagnosis of the disease and not the diet prescribed after the diagnosis. The questionnaires were centrally analyzed with a specially constructed computer program at the Co-ordinating Center (Diabetes Center, Athens, Greece). The food composition tables used as databases for the analysis were McCance-Widdowson's and Trichopoulou (20,21), to which data for local specialties (bulgur, couscous, etc.) was added, based on information on food composition provided by each participating center.

Before starting the study, the dietary questionnaire was validated against the 3-Day Diet Diary (3-DDD), two weekdays and a holiday, which has been successfully used in the EURODIAB Study (22). In a group of 100 subjects from all centers, the dietary questionnaire compared satisfactorily with the 3-DDD (16).

Exercise was estimated as mild, moderate, and vigorous (hours/week). An arbitrary exercise index was computed according to the following formula: exercise index = (hours of mild exercise/week \times 1) + (hours of moderate exercise/week \times 2) + (hours of vigorous exercise/week \times 3).

Ethics approval for the study was obtained in each country by the appropriate committee.

In the present study, the 204 subjects with recently (<2 months) diagnosed diabetes (RDM) were matched one by one for sex, age, BMI, and center of origin with an equal number of randomly selected nondiabetic subjects. Furthermore, 42 subjects with unknown diabetes (UDM) (fasting plasma glucose [FPG] \geq 126 mg/dl by American Diabetes Association criteria) (23) and 55 subjects with impaired fasting glucose (IFG) (FPG \geq 110 and <126 mg/dl) were matched as above with normal subjects. Thus, 204 subjects with newly diagnosed diabetes, 42 subjects with unknown diabetes, and 55 subjects with IFG were compared with sex-, age-, BMI-, and center-matched nondiabetic subjects.

Statistical analysis

Data are presented as means \pm SE. For continuous variables with normal distribution, Student's *t* test and paired *t* test were used. Continuous variables with skewed distribution were log-trans-

formed before statistical analysis. To avoid multiplicity errors, all *P* values were adjusted for multiple comparisons according to Bonferroni. Categorical variables were evaluated with the χ^2 test, Yate's correction. The relative risk, with 95% CI, was calculated from 2×2 tables. The statistical analysis was performed with the SPSS statistical package, version 10.1 (Chicago, IL).

RESULTS— The characteristics of case and control groups are shown in Table 1. Waist-to-hip ratio was lower in RDM and UDM compared with control subjects (0.88 ± 0.01 vs. 0.90 ± 0.01 , $P < 0.05$, and 0.88 ± 0.01 vs. 0.93 ± 0.01 , $P < 0.01$, respectively). Family history of diabetes was more frequent in all case groups (RDM 49.0 vs. 14.2%, $P < 0.001$; UDM 38.1 vs. 19.0%, $P < 0.05$; and IFG 32.7 vs. 16.4%, $P < 0.05$).

The degree of physical activity, judged by the profession and the exercise index, was lower in RDM and UDM compared with control subjects (sedentary profession 47.5 vs. 27.4%, $P < 0.001$, and 58.5 vs. 34.1%, $P < 0.05$; exercise index 53.5 vs. 64.4, $P < 0.01$, and 43.7 vs. 54.4, $P > 0.05$, respectively).

In Table 2, the composition of the diet is compared between the cases and control subjects. The RDM group showed lower carbohydrate intake (313 ± 7 vs. 336 ± 7 g/day; $P = 0.035$) and percent carbohydrate contribution to the energy intake (53.5 ± 0.5 vs. $55.1 \pm 0.6\%$; $P = 0.039$) but higher percent protein contribution (16.3 ± 0.2 vs. $15.8 \pm 0.1\%$; $P = 0.013$). Moreover, total and animal fat contribution to the energy intake was higher (30.2 ± 0.5 vs. $27.8 \pm 0.5\%$, $P = 0.0001$, and 12.2 ± 0.3 vs. $10.8 \pm 0.3\%$, $P = 0.003$, respectively), whereas the plant-to-animal fat ratio was lower (1.5 ± 0.1 vs. 1.8 ± 0.1 ; $P = 0.007$). UDM compared with control subjects showed lower carbohydrate percent contribution (47.6 ± 1.7 vs. $52.8 \pm 1.4\%$; $P = 0.028$), higher animal fat intake (36.0 ± 3.0 vs. 29.0 ± 2.0 g/day; $P = 0.043$), and higher total and animal fat percent contribution to the energy intake (34.7 ± 1.5 vs. $30.4 \pm 30.4 \pm 1.2\%$, $P = 0.036$, and 14.2 ± 0.9 vs. $10.6 \pm 0.7\%$, $P = 0.004$). The diet of IFG subjects did not show any differences compared with that of control subjects.

Fig. 1 depicts the distribution of cases and control subjects among the quartiles

Table 1—Characteristics of subjects with recently diagnosed diabetes, unknown diabetes, impaired fasting glucose, and their control groups

	RDM	Control RDM	UDM	Control UDM	IFG	Control IFG
Sex (M/F)	117/87	117/87	31/11	31/11	36/19	36/19
Age (years)	50.5 ± 0.6	49.5 ± 0.5	47.3 ± 1.5	47.2 ± 1.5	47.6 ± 1.2	47.4 ± 1.2
BMI	27.5 ± 0.2	27.3 ± 0.2	27.9 ± 0.6	27.9 ± 0.6	27.8 ± 0.5	27.7 ± 0.4
Waist-to-hip ratio	0.88 ± 0.01*	0.90 ± 0.01	0.88 ± 0.01†	0.93 ± 0.01	0.90 ± 0.01	0.90 ± 0.01
Waist circumference	91.1 ± 0.6	89.9 ± 0.6	92.9 ± 2.0	94.6 ± 2.0	92.3 ± 1.7	92.1 ± 1.7
Systolic blood pressure	134.5 ± 1.2‡	128.3 ± 1.2	127.9 ± 2.7	127.4 ± 2.9	134.7 ± 2.8*	127.4 ± 2.4
Diastolic blood pressure	83.3 ± 0.7*	81.0 ± 0.7	81.6 ± 1.4	80.9 ± 1.7	85.6 ± 1.7	81.9 ± 1.4
FPG	167.2 ± 6.1‡	83.0 ± 0.9	165.4 ± 9.1‡	80.6 ± 2.0	116.1 ± 0.5‡	85.8 ± 1.7
Cholesterol						
Total	215.1 ± 4.8‡	186.8 ± 4.5	216.2 ± 10.0	195.5 ± 9.8	214.5 ± 8.9	192.2 ± 7.0
HDL	45.6 ± 2.3†	37.5 ± 1.2	41.7 ± 3.0	38.5 ± 2.2	42.1 ± 2.6	36.5 ± 2.2
LDL	132.9 ± 4.0	133.2 ± 4.1	154.9 ± 9.7	144.8 ± 9.4	139.6 ± 7.9	128.9 ± 6.7
Triglycerides	199.7 ± 10.4‡	136.7 ± 9.1	181.0 ± 31.2	162.1 ± 16.8	178.6 ± 16.8	157.9 ± 13.9
Family history of diabetes (%)	49.0‡	14.2	38.1*	19.0	32.7*	16.4
Smoking (%)	19.1	18.6	31.0	26.2	27.3	27.3
Sedentary profession (%)	47.5‡	27.4	58.5*	34.1	50	48.1
Exercise index	53.5 ± 2.2†	64.4 ± 2.8	43.7 ± 5.0	54.4 ± 6.1	41.7 ± 3.5	47.5 ± 5.4

Data are means ± SE. *P < 0.05; †P < 0.01; ‡P < 0.001.

of animal fat intake. RDM and UDM cases cluster in the upper quartiles and control subjects in the lower quartiles of the distribution (Fig. 1A and B), and this difference is statistically significant. IFG cases and control subjects do not show different distribution among quartiles of animal fat intake (Fig. 1C). The relative risk for having diabetes is 1.8 for RDM and 3.1 for UDM in the two upper quartiles of animal fat intake compared with the two lower quartiles (P < 0.01 for both).

CONCLUSIONS— The incidence of type 2 diabetes depends on the interplay

between genetic and environmental factors. A positive family history strongly predisposes to the development of type 2 diabetes (24). This is confirmed in the present study, not only for those with newly diagnosed and undiagnosed type 2 diabetes but also for subjects with IFG.

Lack of exercise is associated with an increased risk of diabetes, even after adjustment for BMI (25). Intervention studies suggest that prevention of obesity and increase of exercise can reduce the risk of progression of IGT to type 2 diabetes (3,14,15), but data for subjects with normal glucose tolerance is lacking. Less

physical activity characterizes both RDM and UDM in this study, as judged by sedentary profession and the exercise index. Although the evaluation of exercise was done by indirect methodology, our findings are in line with the current literature.

A relationship between energy intake and the incidence of diabetes has been documented, mainly through the development of obesity, which is considered the most potent environmental factor (26–28). However, the relation of diabetes incidence with the qualitative composition of the diet is less than certain and the data in the literature are controversial.

Table 2—Comparison of the energy and nutrient intake between subjects with recently diagnosed diabetes, unknown diabetes, impaired fasting glucose, and their control groups

	RDM	Control RDM	UDM	Control UDM	IFG	Control IFG
Energy intake (kcal/day)	2,354 ± 48	2,449 ± 50	2,317 ± 106	2,447 ± 143	2,536 ± 116	2,641 ± 130
Carbohydrates (g/day)	313 ± 7*	336 ± 7	278 ± 16	323 ± 20	324 ± 16	327 ± 17
Fat (g/day)	79 ± 2	76 ± 2	89 ± 5	83 ± 6	87 ± 6	95 ± 6
Animal fat (g/day)	32 ± 1	29 ± 1	36 ± 3†	29 ± 2	31 ± 2	36 ± 3
Plant fat (g/day)	45 ± 1	45 ± 2	51 ± 4	52 ± 5	54 ± 4	56 ± 4
Proteins (g/day)	93 ± 2	95 ± 2	92 ± 4	92 ± 4	93 ± 4	100 ± 5
Fibers (g/day)	29.3 ± 0.6	28.3 ± 0.6	25.7 ± 1.4	26.9 ± 1.5	26.8 ± 1.5	28.5 ± 1.6
Carbohydrates (% of total energy)	53.5 ± 0.5‡	55.1 ± 0.6	47.6 ± 1.7§	52.8 ± 1.4	51.2 ± 1.2	49.6 ± 1.2
Proteins (% of total energy)	16.3 ± 0.2	15.8 ± 0.1	16.3 ± 0.6	15.2 ± 0.4	15.0 ± 0.4	15.4 ± 0.4
Fat (% of total energy)	30.2 ± 0.5¶	27.8 ± 0.5	34.7 ± 1.5#	30.4 ± 1.2	30.6 ± 1.1	32.1 ± 1.2
Animal fat (% of total energy)	12.2 ± 0.3**	10.8 ± 0.3	14.2 ± 0.9††	10.6 ± 0.7	10.9 ± 0.6	12.5 ± 0.7
Plant fat (% of total energy)	16.7 ± 0.3	16.2 ± 0.4	19.5 ± 1.1	18.9 ± 1.1	18.9 ± 1.0	18.6 ± 1.1
Plant/animal fat	1.5 ± 0.1‡‡	1.8 ± 0.1	1.6 ± 0.2	2.3 ± 0.4	2.2 ± 0.3	1.9 ± 0.3

Data are means ± SE. All P values were adjusted for multiple comparisons according to Bonferroni. *P = 0.035; †P = 0.043; ‡P = 0.039; §P = 0.028; ||P = 0.013; ¶P = 0.0001; #P = 0.036; **P = 0.003; ††P = 0.004; ‡‡P = 0.007.

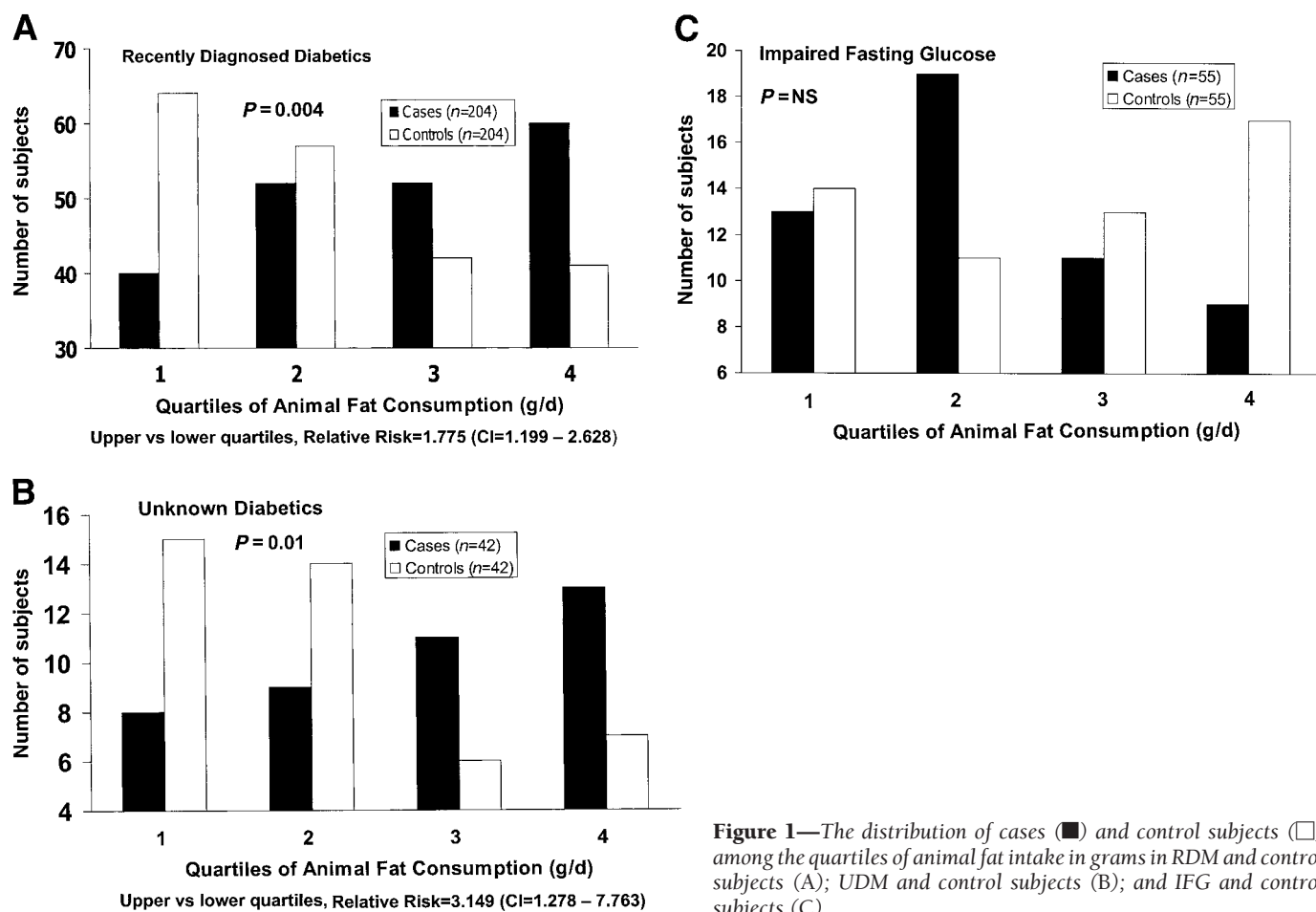


Figure 1—The distribution of cases (■) and control subjects (□) among the quartiles of animal fat intake in grams in RDM and control subjects (A); UDM and control subjects (B); and IFG and control subjects (C).

Prospective epidemiological studies have shown an association between various dietary factors and the development of type 2 diabetes. In most studies, dietary habits are evaluated by self-administered dietary questionnaires, type 2 diabetes diagnosis is self-reported, and the relation of dietary factors with the incidence of type 2 diabetes is investigated, not after stratification, but after multiple statistical adjustments for various confounding factors, which may lead to inaccuracies (8,29–31).

In the present case-control study, subjects with recently diagnosed type 2 diabetes and subjects from the general population with unknown type 2 diabetes or IFG were compared with control nondiabetic subjects, matched one by one for age, sex, ethnicity, and BMI. This is an advantage that renders the results perfectly comparable between cases and control subjects.

Furthermore, the dietary questionnaires were not self-administered, as in most similar studies, but were answered under the help and guidance of a trained

person, making the evaluation much more accurate. The dietary history method used was considered reliable: it is a generally accepted method (17) and has been validated against a frequently used method, the 3-DDD, in a representative group of subjects from all centers. Both methods reflect recent dietary habits and cannot detect possible secular changes of the diet. In the RDM group, there was great effort to focus on the dietary habits before the diagnosis of diabetes. Of course some bias cannot be excluded; nevertheless the findings in RDM totally agree with those in UDM, where the diagnosis of diabetes was not known to either the subject or the examiner, a fact that excludes any bias related to the presence of diabetes.

The role of dietary fat in the risk for type 2 diabetes development remains uncertain. In a recent prospective study comprising 42,500 male participants, total and saturated fat intake were associated with a higher risk of type 2 diabetes, but these associations disappeared after

adjustment for BMI (30). In subjects with IGT, fat consumption predicts the incidence of diabetes (32). A high intake of vegetable fat was inversely associated with the risk of type 2 diabetes, in both the Nurses Health Study and the Iowa Women's Study (6,29).

Animal fat intake was found to be associated with insulin resistance (33), but in most studies concerning the general population, the association between saturated fat and diabetes is either absent or very weak (29,34,35)

In the present study, fat intake was strongly associated with both recently diagnosed type 2 diabetes and undiagnosed type 2 diabetes. The association in this last group is important, since neither the examiner nor the subject knew the diagnosis of type 2 diabetes at the time of evaluation and thus the data are representative of the real dietary habits of the subjects. The presence of type 2 diabetes is especially associated with animal fat intake. In both RDM and UDM, distribution of diabetes along the quartiles of animal

fat intake shows the same trends—namely, cases accumulate to the higher quartiles of animal fat intake, whereas control subjects show exactly the opposite. Moreover, the relative risk of diabetes in the upper two quartiles in comparison to the lower is significantly higher, ranging from 1.8 for RDM to 3.1 for UDM. Thus our data provide evidence for an association between animal fat intake and the presence of diabetes.

The mechanisms underlying the association of fat intake with type 2 diabetes are far from clear. The effect may be mediated through changes in insulin sensitivity. An intervention study in healthy volunteers has shown that when total fat contribution to the energy intake is less than 37%, as is the case in the present study, saturated fat is inversely related to insulin sensitivity (36).

The close association of animal fat intake with recently diagnosed type 2 diabetes, but also with unknown type 2 diabetes, in the present study could be explained by changes in insulin sensitivity, through the mechanisms suggested in the literature.

The findings concerning animal fat intake presented above refer to subjects with recently diagnosed and unknown diabetes, but not those with IFG. Unfortunately, we could not study subjects with IGT by the World Health Organization criteria, which represents another stage in the development of glucose intolerance, and evaluate possible associations with dietary factors.

In summary, we have presented data showing that both subjects with recently diagnosed diabetes and subjects with undiagnosed fasting hyperglycemia in the diabetic range, compared with perfectly matched control subjects, have higher intake of fat and especially animal fat. Our data support the view that increased animal fat in the diet may contribute to increased incidence of diabetes.

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