Fat Consumption and HbA_{1c} Levels

The EPIC-Norfolk Study

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OBJECTIVE — To describe the relationship between total dietary fat and the pattern of fat intake and HbA_{1c}.

RESEARCH DESIGN AND METHODS — In this cross-sectional study, 2,759 men and 3,464 women (40–78 years of age) without a previous diagnosis of type 2 diabetes were recruited from a population-based sampling frame. Diet was assessed using a self-reported semiquantitative food frequency questionnaire.

RESULTS — The HbA_{1c} level was negatively associated with the polyunsaturated fat–to–saturated fat ratio (P:S ratio) of the diet ($\beta = -0.0338$ HbA_{1c}% per SD change in P:S ratio; $P < 0.001$) and positively associated with the total level of fat intake ($\beta = 0.0620$ HbA_{1c}% per SD change in total fat intake; $P < 0.001$), adjusted for age and total energy intake. The associations remained significant when adjusted for each other and for total energy, protein, age, sex, family history of diabetes, BMI, waist-to-hip ratio, physical activity, and smoking (for P:S ratio, $\beta = -0.0200$ HbA_{1c}% per SD change in P:S ratio, $P = 0.013$; for total fat, $\beta = 0.420$% HbA_{1c}% per SD change in total fat intake, $P < 0.001$). The benefits from a high P:S ratio were attributed to a lower saturated fat intake.

CONCLUSIONS — These findings demonstrate independent associations between HbA_{1c} concentration across the normal range of HbA_{1c} and both total fat intake and the pattern of dietary fat intake. They provide further support to efforts promoting modifications in the intake of dietary fat.

Diabetes Care 24:1911–1916, 2001

Dietary fat has long been considered a potentially important modifiable risk factor for diabetes. The evidence for an adverse effect of high total fat and high saturated fat intake on blood glucose levels in nondiabetic populations is quite consistent, whereas the evidence for an effect of polyunsaturated fat intake is less clear (1). Positive associations have been found between the risk of type 2 diabetes or hyperglycemia and total fat intake in both prospective (2,3) and cross-sectional (4,5) studies. Positive associations have also been found with saturated (3,6,7) and animal (8) fat and meat (9) intake. A positive association was reported between polyunsaturated fat intake and hyperglycemia in the Hoorn Study (10), although a reduced risk of type 2 diabetes was associated with increased vegetable fat intake (11) and polyunsaturated fat intake (12) in the U.S. Nurses' Health Study. Eating fish, which is high in n-3 polyunsaturated fat, has a beneficial effect on glycemia (13,14). In a number of other studies, there were no reported associations with dietary fat intake (15–19).

Dietary fat may have an effect on glycemia through obesity. High fat intake may be related to obesity (20–22), which is in turn associated with insulin resistance (23). However, there is evidence of an effect of dietary fat independent of obesity. A number of potential mechanisms have been proposed that may link dietary fat intake and glycemia. The dietary fatty acid profile has been shown to affect the fatty acid profile of skeletal muscle lipids (22), with the proportion of saturated fat in muscle phospholipids positively associated with insulin resistance (24). Impaired glucose utilization may also result from a high-fat diet, which increases the availability of free fatty acids through the Randle glucose fatty acid cycle (25). Studies investigating the mechanisms involved in the insulin resistance and glycemia resulting from high-fat diets suggest that the composition of dietary fat may be particularly important (22).

A review of intervention trials for ischemic heart disease that manipulated dietary fat intake (26) concluded that it may be more important, and also more feasible, to change the polyunsaturated fat–to–saturated fat ratio (P:S ratio) and increase polyunsaturated fat intake, particularly n-3 fats, than decrease total fat and saturated fat intake. Few studies have investigated the pattern of dietary fat intake represented by dietary fat ratios in the context of hyperglycemia and diabetes. To our knowledge, two studies have reported on dietary fat ratios, and they found no association between the risk of diabetes and the P:S ratio (11,19).

Because few studies have investigated the independent association between measures of hyperglycemia and both total dietary fat and the pattern of fat intake, we undertook an analysis of the cross-sectional association between these di-

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Received for publication 31 January 2001 and accepted in revised form 13 July 2001.

Abbreviations: E%, percent total energy intake; EPIC-Norfolk, Norfolk arm of the European Prospective Investigation into Cancer; FFQ, food frequency questionnaire; P:S ratio, polyunsaturated fat–to–saturated fat ratio; WHR, waist-to-hip ratio.

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

etary factors and HbA_{1c}, a measure of hyperglycemia, in a Caucasian population of men and women aged 40–78 years.

RESEARCH DESIGN AND METHODS

— The subjects in this study were participants in the Norfolk arm of the European Prospective Investigation into Cancer (EPIC-Norfolk). EPIC-Norfolk is part of an international multicenter cohort study designed to investigate the relationship between diet and cancer (27). The Norfolk study broadened its scope to include chronic diseases other than cancer as well as lifestyle exposures other than diet. Approval for the study was obtained from the local research ethics committee. Details of the study design have been reported elsewhere (28).

EPIC-Norfolk is a population-based cohort study that recruited volunteers from March 1993 to the end of 1997. General practices in the city of Norwich and surrounding small towns were invited to participate. Initially, all individuals in the age range of 45–74 years in each general practice were invited to take part, although later this was extended to those aged >40 years. Those who consented were invited to attend for a health check. Of the 77,630 individuals invited, 39% consented to take part and 25,633 (33%) attended the health check, which was close to the target recruitment figure of 25,000. In November 1995, midway through recruitment of the cohort, the measurement of HbA_{1c} was introduced. The subcohort selected for this analysis comprised all individuals who had their HbA_{1c} level measured and their data processed by July 1998.

Data collection

Volunteers completed a detailed health and lifestyle questionnaire. It included questions on history of diabetes, family history of diabetes, physical activity, smoking, and diet. Three questions addressed the respondents' personal history of diabetes: they were asked whether a doctor had ever told them that they had diabetes, whether they had modified their diet in the past year because of diabetes, and whether they followed a diabetic diet. A positive response to any of these questions was taken as indicating prevalent diabetes. Family history of diabetes was covered in a question asking whether any of the respondent's immediate family had diabetes. The approximate age at which diabetes was diagnosed in their mother, father, and/or siblings was recorded. Smoking history was derived from two questions: one asked whether they had ever smoked as much as one cigarette a day for as long as 1 year, and the other asked whether they were current smokers. The health and lifestyle questionnaire addressed occupational and nonoccupational physical activity, and a four-point physical activity index was developed that incorporated both components of physical activity.

Habitual diet during the past year was assessed by means of a self-completed semiquantitative food frequency questionnaire (FFQ). The FFQ was based on the questionnaire developed for the U.S. Nurses Health Study (29). The frequency categories remained unchanged, but taking information from the British National Food Survey (30), the lists of foods were modified to reflect the important sources of nutrients in the average British diet. The contribution of different fat types used in food preparation was incorporated into the calculation of fatty acid intake. In a validation study involving 127 women, the correlation between total fat intake estimated by both FFQ and 16-day weighed food records was 0.55 (31), and for saturated and polyunsaturated fat intake, the correlation was 0.56 and 0.37, respectively (S. Bingham, unpublished data).

Standardized health checks were carried out by the research nurses at the EPIC-Norfolk clinic. Anthropometric measurements were taken with participants dressed in light clothing and no shoes. Height was measured to the nearest 0.1 cm using a stadiometer, and weight was measured to the nearest 100 g using Salter scales. BMI was calculated as the weight (kilograms) divided by the height (centimeters) squared. Of those attending the health check, 95% consented to have blood taken. A sample of EDTA-anticoagulated blood was taken for HbA_{1c} measurement. The blood was stored in a refrigerator at 4–7°C until it was transported (within 1 week of sampling) at ambient temperature to be assayed. The HbA_{1c} assays were performed using high-performance liquid chromatography on a Bio-Rad Diamat (Richmond, CA) (32). The coefficient of variation was 3.6% at the lower end of the range (mean 4.9%) and 3.0% at the upper end of the range (9.8%).

Statistical analysis

Individuals with diabetes were excluded from the analysis because it was probable that they would have changed their diet after diagnosis or would have altered how they reported it. FFQs were excluded if ≥10 lines had not been completed. For the analysis, the specific fat types were expressed as a percentage of total energy intake (E%), and the pattern of dietary fat intake was summarized by the P:S ratio. The associations between the potential confounding variables of alcohol intake, age, sex, BMI, waist-to-hip ratio (WHR), family history of diabetes, physical activity level, and smoking status and both the exposures and outcome were explored by correlation analysis or analysis of variance. The correlations between the various components of fat and total fat intake were also examined. Linear regression methods were used to investigate the relationship between HbA_{1c} and dietary fat intake in two separate series of models. The first analyzed the relationships between HbA_{1c} and both the P:S ratio and total fat intake, whereas the second investigated the associations between HbA_{1c} and saturated, monounsaturated, and polyunsaturated fat intake. The simplest models included only one dietary fat variable, adjusted for total energy intake and age. The final models included the dietary fat variables adjusted for total energy, protein (E%), alcohol (g/day), age, sex, family history of diabetes, physical activity, smoking status, BMI, and WHR. In the analysis of the P:S ratio, the regression coefficient for the P:S ratio may be interpreted as a change in the pattern of dietary fat at a constant level of total fat intake. The regression coefficient for saturated fat, for example, in the analysis of the three specific fats represents the effect of substituting saturated fat with carbohydrate (33).

RESULTS

— Analysis was undertaken on the 2,759 men and 3,464 women with complete data. A summary of the study population's characteristics is presented in Table 1. The mean age was 58.9 years, and mean BMI was 26.4. Women were significantly younger and had lower BMI, physical activity, smoking levels, and HbA_{1c} than men. A family history of diabetes was reported by 12.6% of the study

Table 1—*Clinical and metabolic characteristics of the study population, EPIC-Norfolk 1995–1997* (n = 6,223)

Characteristic	Men	Women	*P*
n	2759	3464	
Age (years)	59.2 ± 9.2	58.6 ± 9.3	0.013
BMI (kg/m^2)	26.6 ± 3.3	26.2 ± 4.3	<0.001
WHR	0.93 ± 0.056	0.79 ± 0.061	
Positive family history of diabetes	321 (12)	465 (13)	0.038
Physical activity index			
Level 1 (lowest)	1,035 (37)	1,413 (41)	<0.001
Level 2	901 (33)	1,311 (38)	
Level 3	511 (19)	498 (14)	
Level 4	312 (11)	242 (7)	
Smoking history			
Never smoked	933 (34)	1,947 (56)	<0.001
Ex-smoker	1,471 (53)	1,137 (33)	
Current smoker	355 (13)	380 (11)	
HbA_{1c} (%)	5.35 ± 0.704	5.31 ± 0.632	0.007
Total energy intake (kcal)	2,206 ± 619	1,937 ± 548	<0.001
Carbohydrate*	47 ± 6.7	48 ± 6.4	<0.001
Sugars (g/day)	139 ± 54	130 ± 48	<0.001
Starch (g/day)	127 ± 44	111 ± 39	<0.001
Nonstarch polysaccharides (g/day)	18.0 ± 6.4	19.0 ± 6.8	<0.001
Protein*	16 ± 2.8	17 ± 3.1	<0.001
Total fat*†	33 ± 5.8	32 ± 6.0	<0.001
Saturated fat†	12.9 ± 3.4	12.2 ± 3.4	<0.001
Monounsaturated fat*	11.9 ± 2.4	11.1 ± 2.4	<0.001
Polyunsaturated fat*	6.0 ± 1.9	5.9 ± 1.9	0.016
P:S ratio	0.50 ± 0.228	0.52 ± 0.216	0.016

Data are means ± SD or *n* (%). *Percentage of total energy intake; †total fat includes glycerol (not shown) and saturated, monounsaturated, and polyunsaturated fat.

population, with a slightly higher frequency among women. Overall, the study population's diet consisted of 48% carbohydrate, 17% protein, and 33% fat, and the P:S ratio was 0.51. Women tended to consume less fat and more protein, carbohydrate, and fiber than men. The dietary P:S ratio for women was significantly higher. Figure 1 shows that there is a general trend in HbA_{1c} across the quintiles of fat intake and P:S ratio, which appears to be more consistent in women then men.

In this population, saturated fat intake was highly correlated with monounsaturated fat intake ($r = 0.88$), suggesting common sources for much of their intake. Saturated fat was also correlated with polyunsaturated fat intake ($r = 0.50$), and polyunsaturated fat intake was correlated with monounsaturated fat intake ($r = 0.73$). In addition, total fat intake was highly correlated with saturated fat ($r = 0.93$), monounsaturated fat ($r = 0.98$) and polyunsaturated fat ($r = 0.76$) intakes. Even when adjusted for total energy intake, the correlations between the various subtypes of fat were as high as 0.89. Saturated and monounsaturated fat intakes were highly correlated, and in univariate analysis they showed similar associations with HbA_{1c} ($\beta = 0.00920$, $P < 0.001$; and $\beta = 0.00885$, $P < 0.001$; respectively). In multiple regression analysis, investigating the components of fat simultaneously with total fat intake would have led to unstable estimates of effects because of multicollinearity. Therefore, the P:S ratio was taken as a summary measure representing the pattern of dietary fat intake. The correlation between total fat intake and the P:S ratio ($r = -0.13$), although highly significant, was considerably smaller than with the individual components of dietary fat.

HbA_{1c} was significantly correlated ($P < 0.05$) with all of the potential confounding variables entered into the multiple regression model. Sex, WHR, and physical activity were related to both the P:S ratio and total fat intake, and alcohol intake, age, and smoking were related only to total fat intake. BMI was not significantly correlated with the P:S ratio and total fat intake.

The relationship between the P:S ratio and total dietary fat intake and HbA_{1c} level were investigated using a series of regression models to show how the effect sizes were attenuated by adjusting for confounding. In the simplest models, HbA_{1c} was significantly associated with the P:S ratio ($\beta = -0.155$, $P < 0.001$) and with total fat intake ($\beta = 0.0107$, $P < 0.001$), adjusted for total energy intake and age. In multivariate analysis, adjusting for each other and for total energy intake, protein, alcohol, age, sex, family history of diabetes, physical activity, and smoking, the associations with the P:S ratio ($\beta = -0.0978$, $P = 0.009$) and total fat intake ($\beta = 0.00828$, $P < 0.001$) were attenuated but remained significant. Smoking status attenuated the effect of the P:S ratio. In the full multivariate model, which also included BMI and WHR, HbA_{1c} was significantly associated with BMI ($\beta = 0.0116$, $P < 0.001$) and WHR ($\beta = 0.716$, $P < 0.001$). The association of HbA_{1c} with the P:S ratio ($\beta = -0.0919$, $P = 0.013$) and total fat intake ($\beta = 0.00726$, $P < 0.001$) changed little when BMI and WHR were added. The results (Table 2) suggested that a 1 SD (0.22) increase in the P:S ratio corresponds to a reduction in HbA_{1c} of 0.020%. Similarly, a 1 SD (5.8 E%) reduction in total fat intake corresponds to a reduction in HbA_{1c} of 0.042%. In the fully adjusted analysis, there was evidence of an association between saturated fat intake and HbA_{1c} ($\beta = 0.0143$, $P < 0.001$), but no evidence of an association between polyunsaturated or monounsaturated fat intake and HbA_{1c}.

There was no significant interaction between sex and the P:S ratio, total fat intake, or any of the specific fats ($P \geq 0.20$). Similarly, there was no evidence that the effect of dietary fat differed between those consuming a high-fat diet (fat E% ≥ median) and those consuming a low-fat diet ($P \geq 0.40$).

CONCLUSIONS — In this study, we demonstrated consistent associations between both the pattern and total intake of dietary fat and the level of HbA_{1c} across the normal range of HbA_{1c}. Lower total fat intake as well as higher P:S ratio at a constant level of total fat intake were associ-

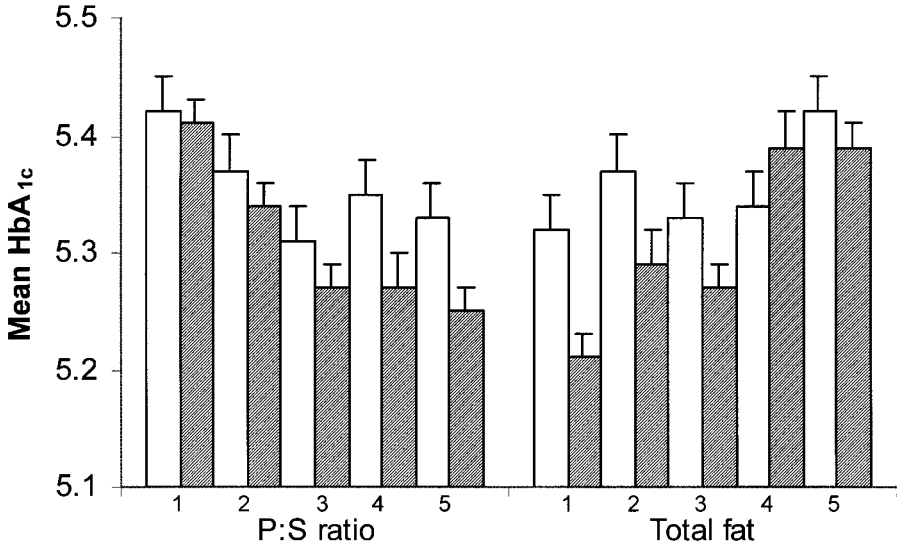

Figure 1—*Observed values of HbA_{1c} by sex-specific quintiles of total fat intake and the P:S ratio. The EPIC-Norfolk Study 1995–1997 (n = 6,223). □, Men; ▨, women.*

ated with lower HbA_{1c}. Saturated fat intake was positively associated with HbA_{1c}, but there was no evidence of an association between monounsaturated or polyunsaturated fat intake and HbA_{1c}, in the multivariate analysis. This suggested that the effect of the P:S ratio was attributable to saturated fat. The results provide further evidence of the adverse effect of high total fat (2–5) and saturated fat (3,4,6,7) intakes on glycemia and the risk of type 2 diabetes, which had been previously observed in some studies. The US Nurses Health Study reported that risk of diabetes was inversely associated with polyunsaturated fat intake, but that no association was found with saturated and total fat intakes (12). The inverse association observed between the P:S ratio and HbA_{1c} in our large population-based study, if confirmed in prospective studies, may provide a realistic target for future intervention.

The KANWU study (34), which investigated the effect on insulin sensitivity of substituting a monounsaturated for a saturated fat diet, reported that the benefits of lowering saturated fat intake were restricted to those in the lower half of total fat intake (<37 E%). We did not observe such an interaction. Total fat intake was lower in our study population, and it may not have been sufficiently high to demonstrate this modification of the effect of saturated fat, if it exists in relation to glycemia.

It is important to consider the possibility that the findings arose through chance, bias, or confounding. Chance was unlikely to be the explanation for the consistent associations between HbA_{1c} and both the P:S ratio and total fat intake observed in this large study. There was little evidence of selection bias. The EPIC-Norfolk study was designed as a population-based cohort study, which would allow comparisons to be made within the cohort, both cross-sectionally and over time. The characteristics of the EPIC-Norfolk cohort are similar to those from nationally representative samples (28). There was no evidence of any difference in age and BMI between the population defined for this analysis and the entire EPIC-Norfolk cohort (35). A definition of diabetes was chosen that would exclude those who may have changed their diet after a diagnosis of diabetes. Of those who reported on the health and lifestyle questionnaire that they had only modified their diet because of diabetes, 72% were also taking diabetic medication(s) or had an HbA_{1c} measurement >7% (35).

The major issue affecting the inferences that can be drawn from this study is confounding, not only with other lifestyle factors that are linked to dietary behavior but also with other components of the diet itself. The observed association is independent of obesity, as measured by BMI and WHR. Whether obesity is a true confounder or not depends on whether it is part of the causal pathway between dietary fat and HbA_{1c}. Although many previous studies have shown that dietary fat intake is associated with obesity (22), as in the US Nurses Health Study (12), there was no evidence of this in our study. Consequently, obesity is unlikely to be acting as a confounder in this population. If it is on the causal pathway, then adjustment for obesity constitutes over-adjustment. We considered smoking to be a potential confounder because previous studies have shown it to be a risk factor for diabetes (36,37), and an earlier analysis of this dataset showed a significant association with HbA_{1c} (38). In the multivariate analysis, the addition of physical activity made little difference to the main effects of the P:S ratio and total fat. Although this may indicate that there was only minor confounding of these factors with physical activity, it could also be a reflection on the relative imprecision of the assessment of physical activity, leaving the possibility of residual confounding.

Table 2—*Multiple regression models predicting HbA_{1c} with the P:S ratio, total fat intake, and fat types, EPIC-Norfolk 1995–1997 (n = 6,223)**

	Without adjustment for BMI and WHR		With adjustment for BMI and WHR	
Independent variables	β	*P*	β	*P*
Analysis of P:S ratio and total fat				
P:S ratio	−0.0217	0.010	−0.0200	0.013
Total fat (E%)	0.0453	<0.001	0.0420	<0.001
Analysis of specific dietary fat types				
Saturated fat (E%)	0.0462	<0.001	0.0476	<0.001
Monounsaturated fat (E%)	0.0153	0.281	0.0107	0.451
Polyunsaturated fat (E%)	0.00467	0.643	0.00534	0.595

Data are regression coefficients per standard deviation change in the independent variable. *Adjusted for total energy intake, protein (E%), alcohol (g/day), age, sex, family history of diabetes, physical activity, and smoking status.

Confounding by other dietary factors is possible if dietary constituents are associated with each other and with HbA_{1c}. We have previously shown that fruit and green leafy vegetable consumption and vitamin C intake are negatively associated with HbA_{1c} (35). In our multivariate analysis, we adjusted for the caloric and noncaloric effects of carbohydrate. However, measurement error may lead to incomplete adjustment and the presence of residual confounding.

Measurement error may affect the association between exposure and outcome. Usual diet was assessed by an FFQ that was shown to have a correlation of 0.55 with 16-day weighed food records for estimated total fat intake (31), and it had correlations of 0.56 and 0.37 with saturated fat and polyunsaturated fat intake, respectively (S. Bingham, unpublished data). A study (39) comparing levels of fatty acid intake measured by an FFQ similar to the one used in EPIC-Norfolk (by diet records and by subcutaneous fat aspirate) indicated that for the P:S ratio, the FFQ and the diet records gave similar estimates, because the correlation was ~0.40 between the fat aspirate and FFQ measures and the fat aspirate and diet record measures. Any measurement error will tend to attenuate the observed association with HbA_{1c}.

Our study showed that, independently, a 1 SD increase in the mean P:S ratio (to 0.73) was associated with an estimated 0.020% decrease in HbA_{1c} levels, and that a 1 SD decrease in total fat intake was associated with a 0.042% decrease in HbA_{1c} levels. A recent study of the EPIC-Norfolk cohort reported that in men, HbA_{1c} is a continuous risk factor for all-cause mortality (40). In that analysis, a reduction in HbA_{1c} of 0.1% throughout the whole population corresponded to a fall in excess mortality of 5%. In this study, we have demonstrated an association between lower HbA_{1c} and both a low total fat intake and a high dietary P:S ratio. If confirmed in prospective studies, these findings suggest that relatively small modifications in the quantity and pattern of dietary fat intake could bring about changes in HbA_{1c}, which may have far-reaching benefits.

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