Is the Association Between Dietary Fat Intake and Insulin Resistance Modified by Physical Activity?

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The rising prevalence of type 2 diabetes, a condition associated with insulin resistance, is commonly attributed to changes in dietary patterns and physical activity levels in susceptible populations. However, few studies have described the independent effects of dietary intake and physical activity on the degree of insulin sensitivity within populations or examined the possibility of interactions between dietary factors and physical activity. This study was undertaken to describe the relationship between the quantity and pattern of dietary fat intake on fasting insulin levels (a marker of insulin sensitivity) and to investigate whether the association was modified by physical activity. A cross-sectional study of 815 nondiabetic men and women (30 to 71 years) recruited from a population-based sampling frame was undertaken. Diet was characterized using a semiquantitative food frequency questionnaire. Physical activity level (PAL), the ratio of total energy expenditure to basal metabolic rate, was estimated using individually calibrated heart rate monitoring, a method previously shown to be an objective and valid method for assessing total energy expenditure. In a linear regression model adjusted for total energy intake, total fat intake bordered on a significant association with fasting insulin (b = 0.000081; *P* = .058), and the polyunsaturated to saturated fat ratio (P:S ratio) of the diet was negatively associated with fasting insulin concentration (b = -0.37, *P* < .001). A negative association was observed between the PAL and fasting insulin (b = -0.12 , *P* = .025). The association of the P:S ratio and PAL with fasting insulin remained significant when adjusted for each other and for total fat, total energy intake, body mass index (BMI), waist-to-hip ratio (WHR), age, sex, family history of diabetes, smoking status, and alcohol intake (P:S ratio, b = -0.24, *P* = .003; PAL, b = -0.13; *P* = .007). The association with total fat intake was no longer significant in this multivariate model (b = 6.7×10^{-6}; *P* = .858). There was no evidence for an interaction between total dietary fat intake and PAL (b = -0.000048; *P* = .243) or between the P:S ratio and PAL (b = -0.013; *P* = .949). These data demonstrate an independent association between the P:S ratio of the diet, the overall level of physical activity, and the fasting insulin concentration, a marker of insulin sensitivity. There was no evidence that the association between dietary fat intake and insulin resistance was modified by physical activity. The findings provide further support for efforts to promote increases in overall physical activity and modifications in the pattern of dietary fat intake in the whole population.

RESISTANCE TO insulin-stimulated glucose uptake is a strong predictor of the development of type 2 diabetes[1] and may be the common etiologic factor linking the individual components of the cluster of metabolic and hemodynamic abnormalities usually termed the metabolic or insulin resistance syndrome.[2] Each component of this syndrome increases the risk of cardiovascular disease, but in combination, they greatly increase the risk.[3] Although ecologic studies suggest that diet and physical activity have an important role in determining insulin resistance,[4,5] the precise nature of these relationships is uncertain.

Overall, fat intake is positively associated with increased insulin resistance in most,[6,7] but not all,[8] cross-sectional studies. In a prospective cohort study, Marshall et al[9] described a positive association between fasting insulin and high total fat intake.

Considerable evidence exists from both animal and human studies that the composition of the dietary fat[10-12] may be as important as the total intake. In most of these studies, saturated fat tends to have a negative effect on insulin resistance, polyunsaturated fat, particularly n-3 polyunsaturated fat, a beneficial effect, and the effect of monounsaturated fat appears to depend on its source.[9,13,14] When the major sources of monounsaturated fat are meat and dairy products, its effect may be deleterious, but when derived from vegetable sources, it may be neutral or possibly beneficial. Dietary fat ratios can be used to describe the pattern of fat intake. To our knowledge, only 2 previous studies have reported dietary fat ratios, and in those studies, no association was found between the risk of non–insulin-dependent diabetes and the polyunsaturated to saturated fat ratio (P:S ratio).[15,16]

It has been suggested that the effect of fat intake on insulin resistance may be modified by the level of physical activity. In a previous study, Mayer et al[17] demonstrated that the positive association between fasting insulin concentrations and total fat intake in female twins was significantly smaller among active compared with sedentary women. Such an interaction may be biologically plausible as sustained aerobic exercise, such as running or walking, increases fat oxidation in muscle[18] and progressively increases the oxidation of fat relative to carbohydrate.[19] However, detecting such interactions is hindered by the precision with which we can quantify physical activity, a complex multidimensional exposure that is difficult to assess in population studies.[20] Previous cross-sectional studies have demonstrated a negative association between physical activity and insulin resistance, but the assessment of activity has been by self-report questionnaire.[9,21-23] These methods are highly subjective, depending on accurate recall of time spent on various activities and usually concentrate on participation in sports and exercise.[24] They are thus generally unable to distinguish between the effects of vigorous physical activity and overall energy expenditure. The ability to make this distinction is

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important if epidemiology is to inform preventive efforts. Overall energy expenditure can be increased with more frequent activities of lower intensity and may, therefore, be a more realistic target for intervention than an increase in participation in vigorous activities.

The problems associated with questionnaire-based methods highlight the need for alternative methods of measuring physical activity, which are objective and reflect total energy expenditure. Heart rate monitoring has recently been developed as a tool for the objective assessment of total energy expenditure in epidemiologic studies[25] and was used in this study. It has previously been shown to be feasible in epidemiologic studies[26] and to be valid by comparison to the gold standard techniques of doubly-labelled water and whole body calorimetry.[27]

The gold standard measure of insulin resistance is obtained using the hyperinsulinemic-euglycemic clamp. However, the method is too complex for large epidemiologic studies, which instead use data from the oral glucose tolerance test to derive estimates of insulin resistance. Two validation studies[28,29] have reported that in individuals with normoglycemia or impaired glucose tolerance, 2 simple indices of insulin resistance, fasting insulin and homeostasis model assessment (HOMA-R), are moderately correlated (|r| ranging from 0.47 to 0.59) with insulin resistance measured by hyperinsulinemic-euglycemic clamp. In a third study,[30] fasting insulin was ranked more highly than HOMA-R as a method for estimating insulin resistance, based on their statistical criteria of strong and consistent association with insulin resistance assessed using the glucose clamp.

The purpose of this study was to investigate the cross-sectional association between fasting insulin concentrations, a measure of insulin resistance, and the quantity and composition of dietary fat and the objectively measured physical activity level (PAL), in a Caucasian population of men and women aged 30 to 71 years. With a view to possibly targeting future recommendations for particular subgroups of the population, the interaction between dietary fat intake and physical activity was also investigated.

SUBJECTS AND METHODS

Study Population

The Ely Study was established in 1990 as a population-based longitudinal cohort study of the etiology and pathogenesis of type 2 diabetes and related metabolic disorders. Details of the study design have been reported elsewhere.[25,31,32] To summarize, a random sample of 1,122 individuals was recruited between 1990 to 1992 from a population-based sampling frame consisting of all adults then aged 40 to 65 years (birth cohorts, 1925 to 1950) who were residing in Ely, Cambridgeshire in 1990 (74% response rate). Between 1994 to 1996, a follow-up study was undertaken of the 1,071 individuals who did not have diabetes by World Health Organization (WHO) criteria at baseline. Twenty individuals had died and of those remaining, 937 attended for follow-up (89% restudy rate). In 1994, a cohort of 167 younger volunteers (birth cohorts, 1955 to 1965) recruited from the sample population were added to the study (51% response rate). The study methods were identical for both groups of volunteers. A subgroup of 815 individuals from the combined cohort with complete biochemical, dietary, and physical activity data was used in this analysis.

Data Collection

All participants underwent a standardized medical examination after an overnight fast. Anthropometric measurements (height, weight, waist, and hip circumferences) were taken with participants dressed in light clothing and without shoes. An oral glucose tolerance test was undertaken in nondiabetic subjects, and fasting insulin concentrations were measured on plasma samples using a specific insulin assay.[33] Family history of diabetes, smoking status, and alcohol intake were assessed by questionnaire. Participants were categorized as either 'having never smoked' or as being an 'ex-smoker' or 'current smoker' (of cigarettes only).

Food Frequency Questionnaire

Habitual diet during the past year was assessed by means of a self-completion, semiquantitative food-frequency questionnaire (FFQ). The FFQ developed and validated by the European Prospective Investigation of Cancer (EPIC) was used.[34] This FFQ was based on the questionnaire from the US Nurses' Health Study. The frequency categories remained unchanged, but taking information from the British National Food Survey, the lists of foods were modified to reflect the average British diet. The FFQ was validated on 127 women by comparison with 16-day weighed food records and 7-day diet diaries.[34]

Physical Activity Level

Total energy expenditure was assessed in a subset of 947 participants using heart rate monitoring with individual calibration.[25,26] The oxygen consumption heart rate relationship was assessed at rest, with the subject lying prone and then seated, using an oxygen analyzer. The slope and the intercept of the line relating energy expenditure to heart rate were estimated by asking each subject to cycle on a cycle ergometer at different workloads. Subjects cycled at 50 revolutions/minute, and the workload was progressively increased from 0 W through 37.5 W, 75 W, and 125 W in stages lasting 5 minutes each. At each workload, 3 different readings of heart rate, minute volume, and expired air oxygen concentration were recorded. The 125 W level was only undertaken if the heart rate had not reached 120 beats/minute by the end of the 5 minutes at 75 W. The oxygen concentration in the expired air and minute volume data were used to calculate oxygen consumption after correction for standard temperature and pressure. Energy expenditure (kJ/min) at each time point was calculated as oxygen consumption (mL/min) $\times$ 20.35.[35] Mean resting energy expenditure was taken as the average of the lying and sitting values. Flex heart rate was calculated as the mean of the highest resting pulse rate and the lowest pulse rate upon exercise. The slope and the intercept of the least squares regression line of the exercise points were calculated. $\dot{V}O_{2max}$ was measured from the linear regression as predicted oxygen consumption at the maximal heart rate (220 – age), and results expressed per unit of body weight (kg).

Participants wore a heart rate monitor during the waking hours over a 4-day period following calibration. Heart rate readings were directly downloaded into a computer via a serial interface, and the individual calibration data were used to predict minute energy expenditure for each person. Sleeping energy expenditure was calculated as 95% of basal metabolic rate.[36] The PAL was calculated as the ratio of total energy expenditure to basal metabolic rate[37] and averaged over the 4-day period.

Statistical Analysis

FFQs were excluded if 10 or more lines had not been completed. Individuals with type 2 diabetes were excluded from the analysis because fasting insulin is an appropriate measure of insulin resistance within rather than between glucose tolerance categories.[28] The associations between potential confounding variables, body mass index

Table 1. Characteristics of the Study Population: The Ely Study 1994 to 1996 (N = 815)

	Fasting Insulin (pmol/L)*				
	Quartile 1 (n = 212)	Quartile 2 (n = 210)	Quartile 3 (n = 191)	Quartile 4 (n = 202)	*P* Value
Age (yr)	51.8 (11.2)	54.2 (9.8)	53.5 (11.4)	53.4 (10.5)	.133
BMI (kg/m^2)	24.0 (2.8)	25.4 (3.3)	26.8 (3.6)	29.3 (4.7)	.016
Waist (cm)	79.6 (10.4)	84.2 (10.4)	87.5 (10.9)	96.5 (13.6)	<.001
WHR	0.82 (0.09)	0.85 (0.01)	0.86 (0.10)	0.92 (0.10)	<.001
Family history of diabetes†					
Negative	180 (85)	172 (82)	155 (82)	151 (81)	.070
Positive	32 (15)	38 (18)	36 (18)	51 (19)	
Smoking status†					
Never smoked	117 (55)	110 (52)	107 (56)	99 (49)	.706
Ex-smoker	60 (28)	65 (31)	54 (28)	60 (30)	
Current smoker	35 (17)	35 (17)	30 (16)	44 (21)	
PAL	1.89 (0.45)	1.85 (0.39)	1.81 (0.33)	1.80 (0.34)	.049
Total energy expenditure (kJ)	11,694 (3,410)	11,683 (3,055)	11,754 (2,948)	11,670 (3,391)	.004
Total energy intake (kJ)	8,473 (2,752)	8,406 (2,577)	8,343 (2,691)	8,541 (2,447)	.911
Carbohydrate‡	50 (6.3)	51 (6.1)	50 (6.4)	50 (5.9)	.013
Protein‡	17 (3.4)	17 (3.3)	17 (3.7)	17 (3.5)	.450
Fat‡§	33 (6.4)	32 (5.7)	33 (5.5)	33 (5.8)	.017
Saturated fat‡	11.8 (3.6)	11.6 (3.0)	12.1 (2.9)	12.5 (3.2)	.033
Monounsaturated fat‡	11.2 (2.7)	10.9 (2.4)	11.6 (2.4)	11.7 (2.5)	.005
Polyunsaturated fat‡	6.3 (1.8)	6.0 (1.7)	6.1 (1.8)	6.0 (1.8)	.291
P:S ratio	0.58 (0.24)	0.55 (0.23)	0.54 (0.19)	0.51 (0.20)	.010
Fiber (g/d)	19.0 (7.1)	19.3 (7.1)	18.0 (5.6)	18.1 (6.8)	.120
Alcohol‡	2.9 (4.17)	2.7 (3.54)	2.4 (3.34)	2.8 (3.92)	.532

NOTE. Data are means, with standard deviations in parentheses.

*The median values of the quartiles of fasting insulin were 21, 32, 46 and 78 pmol/L, respectively.

†Data are counts with percentages in parentheses.

‡Percentage of total energy intake.

§Total fat includes glycerol (not shown), saturated, monounsaturated, and polyunsaturated fat.

(BMI), waist, waist-to-hip ratio (WHR), age, sex, family history of diabetes, smoking status and alcohol intake, and the exposures and outcome were investigated by correlation and simple linear regression analysis. Alcohol intake was represented by 5 categories, corresponding to nondrinkers and the 4 quartiles of those who drank alcohol. Multiple linear regression was used to assess the relationship between fasting insulin concentrations and dietary fat intake and PAL, adjusted for BMI, age, sex, family history of diabetes, smoking status and alcohol intake. The analyses were replicated using an alternative measure of insulin resistance, HOMA-R,[38] to confirm whether there was consistency between the 2 estimates of insulin resistance.

In this population, the correlation between saturated fat and monounsaturated fat intake was 0.92, suggesting that the major sources of monounsaturated fat were the same as the sources of saturated fat. The coefficient for the regression of fasting insulin on saturated fat intake adjusted for total energy intake (b = 0.00779, $P = .008$) was very similar to that for the regression on monounsaturated fat intake (b = 0.00775, $P = .036$) suggesting that the effect of monounsaturated fat was similar to that of saturated fat in this population. Other fat types were also highly correlated. The correlation between monounsaturated and polyunsaturated was 0.77, between saturated and polyunsaturated 0.60, and between the fat types and total fat intake, the correlation ranged from 0.80 to 0.98. Including 2 or more of these variables in a multiple regression would lead to unstable estimates of effects and difficulties in interpretation. The correlation between total fat intake and the P:S ratio was considerably smaller ($r = -.162$). Consequently, the P:S ratio was used to represent the pattern of dietary fat intake, and the 2 dietary fat exposures considered in the multivariate analysis were total fat and the P:S ratio. The interactions between total fat intake and PAL, between the P:S ratio and PAL, and between sex and the 3 exposures of interest were investigated. We undertook a subgroup analysis of women to investigate whether menopausal status was an important factor in determining fasting insulin concentrations. Premenopausal was defined as all women less than 50 years and postmenopausal as all women 50 or more years old.[39] The $\log_e$ transformed values of fasting insulin and HOMA-R were used in all analyses because their distributions were highly skewed.

RESULTS

There were 815 individuals (348 men, 467 women) with complete data. Of the 947 individuals who underwent heart rate monitoring, the FFQs of 79 were incomplete (10 or more lines missing), 24 had diabetes, 21 smoked cigars or pipes, which were not included in the smoking categories used, and 8 had no fasting insulin measure, leaving 815 individuals in the study. A summary of the study population's characteristics is given in Table 1. Between the quartiles of fasting insulin, there were no differences in age, family history of diabetes, smoking status, energy intake, protein, polyunsaturated fat, fiber (nonstarch polysaccharides), and alcohol intake. Individuals in the highest quartile of fasting insulin tended to have higher BMI, waist circumference, WHR, and saturated and monounsaturated fat intake; and lower PAL, total energy expenditure, and P:S ratio.

Table 2 shows the correlation coefficients relating the outcome, exposure, and potential confounding variables. The potential confounders, age, and alcohol intake were not related to

Table 2. Pearson Correlation Coefficients Relating Exposure and Outcome Variables: The Ely Study 1994 to 1996 (N = 815)

	Fasting Insulin*	HOMA-R*	P:S Ratio	Total Fat	Alcohol†	Total Energy	PAL	Age	BMI	Waist
HOMA-R*	0.987‡									
P:S ratio	−0.140‡	0.139‡								
Total fat	0.040	0.041	−0.162‡							
Alcohol†	−0.020	0.002	−0.005	0.063						
Total energy	0.014	0.015	−0.086§	0.910‡	0.115‡					
PAL	−0.078§	−0.081§	−0.064	0.109‖	0.097‖	0.091‖				
Age	0.057	0.074§	0.112‖	−0.098‖	−0.088§	−0.066§	0.037			
BMI	0.512‡	0.515‡	−0.114‖	0.015	−0.077§	−0.023	−0.037	0.042		
Waist	0.501‡	0.520‡	−0.086§	0.094‖	0.112‖	0.059	0.085§	0.133‡	0.763‡	
W:H ratio	0.358‡	0.389‡	−0.025	0.111‖	0.188‡	0.086§	0.135‡	0.185‡	0.389‡	0.827‡

Abbreviations: P:S ratio, polyunsaturated to saturated fat ratio; W:H ratio, waist-to-hip ratio.
*Log_e values used in computations.
†Five categories of intake (median intakes for the categories were 0, 1.0, 4.4, 8.1, 19.4 g/day, respectively).
‡$P \leq .001$.
§$P \leq .05$.
‖$P \leq .01$.

fasting insulin. The P:S ratio was correlated with BMI and waist circumference; total fat intake was correlated with waist circumference and WHR; and PAL was correlated with waist circumference and WHR.

A series of models was used to investigate the relationship between fasting insulin concentration and total fat intake, the P:S ratio, and PAL. When adjusted only for total energy intake, the association between total fat intake and fasting insulin bordered on significance (Table 3, model 1). Fasting insulin concentration was significantly related to the P:S ratio adjusted for total energy intake and to PAL (Table 3, models 2 and 3). In the multivariate model (Table 3, model 4) adjusting for age, sex, family history of diabetes, smoking, and alcohol intake, the association of fasting insulin concentration with the P:S ratio remained (b = -0.405; $P < .001$), and the association with PAL became stronger (b = -0.188; $P < .001$). The association with total fat intake was attenuated and no longer statistically significant. In the full multivariate model (Table 3, model 5), fasting insulin concentration was significantly related to BMI and WHR. All other associations with fasting insulin concentration were attenuated in this model, although the associations between fasting insulin concentration and the P:S ratio (b = -0.241; $P = .003$) and PAL (b = -0.122; $P = .009$) remained highly significant. The interaction between total fat intake and PAL (b = -0.0128; $P = .949$) and between the P:S ratio and PAL (b = -0000480; $P = .243$) did not reach statistical significance at the 5% level and were not included in the final model presented in Table 3 (model 5). The P:S ratio-PAL interaction is illustrated in Fig 1. There was no evidence of an interaction between sex and dietary fat or PAL.

In the subgroup analysis of women, we found that there was no evidence of a difference between pre- and postmenopausal women (b = 0.0376; $P = .618$; 4% difference in fasting insulin). Nor was there evidence of an interaction between

Table 3. Multiple Regression Models Predicting Fasting Insulin With P:S Ratio and PAL as Explanatory Variables: The Ely Study 1994 to 1996 (N = 815)

Independent Variable	Model 1*	Model 2	Model 3*	Model 4*	Model 5*
Total fat (g/d)	0.0000812 (0.058)	—	—	0.0000398 (0.361)	8.08×10^{-6} (0.828)
P:S ratio	—	−0.370 (<0.001)	—	−0.405 (<0.001)	−0.241 (0.003)
PAL	—		−0.119 (0.05)	−0.188 (0.001)	−0.122 (0.009)
BMI (kg/m^2)	—	—	—	—	0.0534 (<0.001)
WHR				—	1.84 (<0.001)
Age (yr)	—	—	—	0.00486 (0.013)	0.000709 (0.680)
Sex†	—	—	—	−0.169 (<0.001)	0.182 (<0.001)
Family history of diabetes‡	—	—	—	0.137 (0.007)	0.0700 (0.106)
Smoking: Overall	—	—	—	(0.174)	(0.121)
Ex-smoker§				−0.00388 (0.936)	−0.612 (0.139)
Current smoker§				0.0985 (0.079)	0.0375 (0.435)
Alcohol intake: Overall	—	—	—	(0.310)	(0.680)
Category 1‖				−0.0186 (0.774)	0.0116 (0.833)
Category 2‖				−0.104 (0.107)	−0.0127 (0.816)
Category 3‖				−0.109 (0.100)	−0.031 (0.582)
Category 4‖				−0.0396 (0.565)	0.0449 (0.445)

NOTE. Data are regression coefficients, with *P* values in parentheses.
*Adjusted for total energy intake; †relative to men; ‡relative to individuals with no family history of diabetes; §relative to individuals who have never smoked; ‖relative to individuals who do not drink alcohol (median intakes for the categories were 0, 1.0, 4.4, 8.1, 19.4 g/d, respectively).

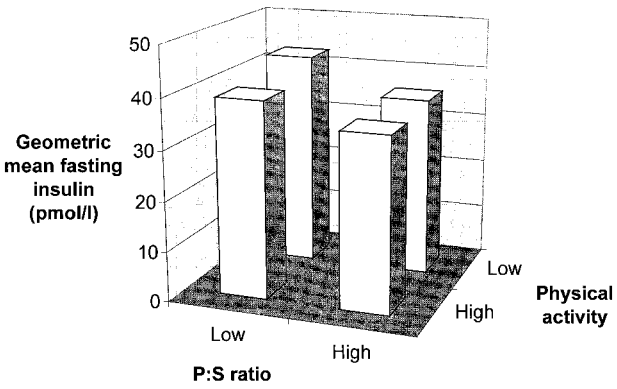

Fig 1. Predicted values of fasting insulin: The Ely Study 1994 to 1996 (N = 815). The figure shows predicted values from the model with fasting insulin (log_e) regressed on P:S ratio, PAL, total fat, total energy intake, BMI, WHR, age, sex, family history of diabetes, smoking status, and alcohol intake and the interaction between the P:S ratio and PAL. This is equivalent to model 5 (Table 3), but with the interaction term added in. The interaction term coefficient was -0.0140 ($P = .945$).

menopausal status and the dietary fat variables or PAL ($P > .2$) in analyses adjusted for total energy intake, BMI, WHR, age, sex, family history of diabetes, smoking status, and alcohol intake.

Model 5 (Table 3) predicted that an increase in the P:S ratio of 1 corresponded to a 27% reduction in fasting insulin, and an increase in PAL of 1 corresponded to a decrease in fasting insulin of 13%. It predicted that a nonobese male with low P:S ratio and low PAL would have a fasting insulin concentration of 44.2 pmol/L (95% confidence interval [CI]: 41.3, 47.3), while a female with similar characteristics would have a fasting insulin concentration of 36.2 pmol/L (95% CI: 33.8, 38.9). Being obese increased fasting insulin concentrations by approximately 22 pmol/L, while having a diet with a high P:S ratio reduced fasting insulin by approximately 5 pmol/L and having a high PAL reduced fasting insulin by approximately 4 pmol/L. For the purposes of prediction, low P:S ratio or PAL was defined as the median value of the lowest tertile of the P:S ratio or PAL, while high P:S ratio or PAL was defined as the median value of the top tertile of the P:S ratio or PAL. Nonobese was taken as the median values of BMI and WHR of individuals with BMI less than 30 kg/m^2 and WHR less than the sex-specific medians, and obese the median values of those with BMI $\geq$ 30 kg/m^2 and WHR greater than the sex-specific means.

Fasting insulin was highly correlated with HOMA-R ($r = .987$; $P \leq .001$). Results of the regression analysis of HOMA-R on dietary fat variables and PAL, adjusted for potential confounders, gave very similar results to the analysis of fasting insulin. In the equivalent analysis to model 5 (Table 3), the regression coefficients for total fat intake, the P:S ratio, and PAL were 7.57×10^{-6} ($P = .849$), -0.257 ($P = .003$), and -0.150 ($P = .002$), respectively. Because the 2 analyses corresponded closely, the results for HOMA-R are not fully presented.

DISCUSSION

In this study, we have demonstrated significant negative associations between 2 potentially modifiable lifestyle factors and insulin resistance. If these cross-sectional observations are confirmed in longitudinal analyses, they may form the basis for the design of preventive interventions.

As with all epidemiologic analyses, it is important to consider the possibility of chance, bias, and confounding. Chance is unlikely to be the explanation for the consistent associations, which were found in this moderately large study. There was little evidence of selection bias. At baseline, the study population did not differ significantly from the general population with respect to socioeconomic and anthropometric characteristics. A high percentage (89%) of volunteers was re-examined at follow-up, although there was a nonsignificant tendency for younger men, overweight women, and smokers to be under-represented. Consequently, selection bias is unlikely to have affected the results, but the associations with fasting insulin may have been weakened by the loss to follow-up of some individuals who may have been at higher risk of being insulin-resistant.

PAL was measured objectively, reducing the possibility of recall bias. Total fat intake and the P:S ratio were assessed by FFQ rather than an objective biomarker, which may introduce the potential for bias. A study in a sample of American men comparing fatty acid intake assessed by subcutaneous fat aspirate, 2-week diet records, and an amended version of the FFQ used in the US Nurses' Health Study[40] suggested that estimates of fat intake from the FFQ were as valid as those from the diet records. Their results showed weak correlations for saturated and monounsaturated fat and moderate correlations for polyunsaturated fat and the P:S ratio, indicating that the P:S ratio may represent the pattern of dietary fat adequately.

Of the potential confounders, only BMI, WHR, and sex were significantly related to fasting insulin in the multiple regression model. Age and family history of diabetes, known risk factors for increased insulin resistance,[41,42] were not significantly associated with fasting insulin in this study. The effect of age may have been lost as a result of including only those who had undertaken heart rate monitoring. Those not included were significantly older (mean, 59.5 years) than those included (mean, 53.8 years). Fasting insulin concentration did not differ between those included and those excluded (b = 0.0948; $P = .0683$). However, the effects of both age and family history were attenuated by adjustment for BMI and WHR, suggesting that at least part of the effect was mediated through obesity. Fasting insulin concentration was significantly associated with BMI and WHR, which attenuated the association of fasting insulin with all other independent variables. In other studies, the associations of fasting insulin with dietary fat intake[6,17] and with physical activity[43,44] were similarly attenuated by measures of obesity. When nondiabetic individuals gain weight, insulin resistance increases by 30% to 40% when they become more than 35% to 40% over ideal weight.[45] Conversely, weight loss, even modest weight loss, usually produces a reduction in insulin resistance.[46] A lifestyle that reduces the likelihood of weight gain should reduce the risk of insulin resistance.

A high-fat diet is associated with obesity[47-50] and with insulin resistance.[10-12,51] Saturated fat is consistently associated

with increased insulin resistance.[9,13,14] The evidence for polyunsaturated fat is not as strong, although consumption of fish, which is rich in polyunsaturated fat,[52] or vegetable fat,[15] has been shown to reduce the risk of type 2 diabetes. Fasting insulin concentration was negatively associated with the P:S ratio in this study, which is consistent with previous findings that the effect of dietary saturated fat is generally detrimental and polyunsaturated fat beneficial on insulin resistance.[9,13,14]

In this study, overall energy expenditure, represented by PAL, was negatively associated with fasting insulin. This important observation suggests that increasing overall energy expenditure by any form of activity, not only through sport and exercise, may reduce insulin resistance, a finding of potential public health importance. Other studies have found that increased physical activity is associated with reduced insulin resistance.[9,21-23,43,44,53,54] However, in these studies, physical activity was assessed with methods that are subjective and more closely associated with fitness than energy expenditure.

Measurement error may affect the associations between exposures and outcome, usually attenuating the true relationships when the error is unrelated to outcome status. Repeated heart rate monitoring permitted the measurement error to be estimated together with the reliability coefficient.[26] Taking this reliability coefficient (0.50) and applying a univariate correction to the observed regression coefficient for the regression of fasting insulin on PAL, suggested that the true regression coefficient was closer to −0.244 than the observed -0.122 (true regression coefficient = observed regression coefficient/reliability coefficient). This translates into a 28% reduction in fasting insulin compared with the observed 13% reduction. The effect size of the P:S ratio would also be attenuated through measurement error, but this study did not include repeated measurement of P:S ratio, and therefore the degree of attenuation cannot be estimated. Although the observed effects of the P:S ratio and of PAL on fasting insulin concentrations were of similar magnitude, it is difficult to rank the true effects of the P:S ratio and PAL on insulin resistance without knowing the error in the measurement of the P:S ratio.

In the UK, the prevalence of obesity doubled between 1980 and 1990, while UK national statistics show trends over the past 50 years of decreasing physical activity, estimated by energy intake, and increases in the P:S ratio and in the proportion of fat in the diet.[55] This ecologic evidence suggests that currently physical activity may be a more important determinant of obesity, and hence possibly also of insulin resistance, than dietary fat intake. The hypothesis is consistent with the report from a prospective Finnish study[56] that low physical activity levels were more important than any dietary factors in determining weight gain. Studies at the individual level, which seek to evaluate the relative importance of dietary factors and physical activity on insulin sensitivity, would need to use objective measures of exposure with known bivariate error structure.

In conclusion, the study provided further evidence of the close relationship between fasting insulin concentration and obesity. Adjusted for potential confounding factors, there was no evidence of an association between fasting insulin and total fat intake. Independently of obesity, the composition of dietary fat and PAL were associated with fasting insulin concentrations. Clearly, both of these factors could also affect insulin resistance through an effect on obesity. Therefore, adjustment for BMI and WHR might constitute overadjustment, as in this instance, obesity would be a mediating rather than a confounding factor. The consistent association with the P:S ratio is important because it may be more feasible to manipulate the composition of dietary fat than it is to alter total dietary fat intake. Similarly, increasing overall energy expenditure within a population may be more achievable than increasing the participation in vigorous physical activity. Figure 1, which illustrates the interaction between the P:S ratio and PAL, shows that the effects of the P:S ratio and PAL were additive, and that there was no evidence that physical activity modified the association between fasting insulin concentration and dietary fat intake. The lack of interaction between the P:S ratio and PAL suggests that increasing the P:S ratio of dietary fat would benefit the population as a whole, rather than specific subgroups only.

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