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PAPER

Insulin resistance as a modifier of the relationship between dietary fat intake and weight gain

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OBJECTIVE: To investigate whether insulin resistance modifies the rate of weight gain associated with a high percent of energy intake from dietary fat.
DESIGN: Longitudinal, observational population study.
SUBJECTS: A total of 782 nondiabetic Hispanic and non-Hispanic white free-living adult residents of the San Luis Valley in Colorado.
MEASUREMENTS: Subjects were seen up to three times over a 14-y period. Weight, height, fasting insulin and glucose, diet by 24 h recall, and self-reported physical activity were collected at each visit.
RESULTS: Percentage of energy intake from dietary fat was positively associated with weight gain over time ($P = 0.0103$). High intake of dietary fat was more strongly related to weight gain in women than in men, and in those with lower total energy intake levels. The relationship between weight change and relative macronutrient intake also varied by baseline insulin sensitivity ($P = 0.0025$). Weight gain over time in individuals with relative insulin resistance at baseline, as measured by QUICKI, was the greatest among those who consumed a higher percent of energy from fat.
CONCLUSION: Percentage of total intake from dietary fat predicts weight change independent of total energy intake. Nondiabetic, insulin-resistant individuals are particularly susceptible to the weight gain associated with high levels of dietary fat intake. Further investigation into the relationship between insulin resistance, diet, and weight gain is warranted.
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Keywords: dietary fat; weight change; insulin resistance; QUICKI; macronutrient; mixed models

Introduction

America's 'obesity epidemic' has been well publicized. A national survey of men and women conducted in 1999 and 2000 found that more than 30% of adults in the United States had a body mass index (BMI) of greater than 30 kg/m^2—a figure that characterizes them as obese. The prevalence of overweight, defined as having a BMI of greater than 25 kg/m^2, was 64.5%.[1]

Overweight is associated with both adverse health consequences and increased health care costs. Being overweight or obese is strongly associated with an increased risk of morbidity and mortality. The prevalence of stroke, diabetes, and heart disease increases as BMI increases.[2,3] The association of BMI with adverse health outcomes becomes even stronger in the presence of other risk factors. For example, the incidence attributable to the joint occurrence of smoking and being overweight is greater than the sum of the incidence attributable to each of these risk factors alone.[4]

Yet, while most people know that obesity poses a serious health threat, there are mixed messages around how to lose or maintain weight. In all, 75% of Americans reported some form of weight control practice in the year 2000.[5] However, a review of the scientific literature shows a paucity of long-term studies on weight change and a debate over almost every aspect of dietary advice.

Dietary fat and its role in the obesity epidemic may be the most hotly contested factor in this debate. While a wealth of epidemiological data supports a link between high-fat diets and obesity,[6] only limited evidence targets dietary fat as a cause of significant weight gain.[7] One of the more recent trends in dieting encourages a low-carbohydrate, high-fat and/or high-protein approach. While the physiological rationale behind such diets remains questionable, preliminary studies suggest that many people do lose weight while eating very high-fat diets.[8]

A limited amount of theoretical and clinical data suggest that insulin and insulin resistance play a part in weight

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change, and that this role might be modified by dietary fat intake. While weight gain generally leads to insulin resistance and hyperinsulinemia,[9] the causal relationship between insulin resistance and obesity remains elusive.[10] There is increasing evidence that insulin acts on the central nervous system to limit hunger as body mass increases.[11] In addition, increased insulin resistance may create a metabolic environment that limits fat storage and increases fat oxidation.[12] These mechanisms would be theoretically protective, promoting weight stabilization in a negative feedback manner. In either, or both, of these scenarios, insulin sensitivity might work in an opposite manner to promote weight gain.

Some clinical data suggest that low-carbohydrate diets may be more effective in promoting weight loss in insulin-resistant, but not insulin-sensitive, subjects.[13,14,] However, no published epidemiological studies have explored whether the role of dietary fat intake in predicting weight change depends on an individual's insulin resistance. As the general public becomes increasingly unwilling to accept a generic, and often ineffective, prescription for weight loss, it is crucial to examine individual variation in response to diet in order to determine how dietary advice should be tailored to individual needs.

The purpose of this paper is to use data from a long-term longitudinal observational study to estimate and describe the relation between dietary fat intake and weight gain for adults, and to assess whether this relationship varies according to relative insulin resistance at the initial visit.

Methods

The San Luis Valley Diabetes Study (SLVDS) was designed to study etiologic and prognostic risk factors associated with type II diabetes. In addition to seeing all known diabetic subjects in the two-county study area, a geographically based sample of 1351 persons 20–74 y of age and without a prior history of diabetes was seen for a baseline visit during the period May 1984–August 1988. An oral glucose tolerance test and the 1985 World Health Organization (WHO) criteria for diabetes were used to classify subjects with normal glucose tolerance (NGT) ($n=1027$), impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) ($n=253$), and previously undiagnosed diabetes ($n=71$).[15] Updated 1999 WHO recommendations were used to identify subjects with IFG.[16] Of the 1027 NGT subjects, 245 subjects were subsequently classified as having type II diabetes, IGT, or IFG at follow-up and were therefore excluded. At each visit, those who changed their smoking status or had a pregnancy since their previous visit were thereafter excluded from further analyses ($n=87$ at visit 2, $n=53$ at visit 3). This resulted in a total of 782 subjects at visit 1, 536 subjects (68.5%) at visit 2, and 375 subjects (48.0%) at visit 3. Subjects completed their second and third follow-up visits at averages of 4.9 and 11.2 y, respectively, after their baseline visit.

Data collection and laboratory procedures

The procedures followed were approved and in accordance with the University of Colorado Health Sciences Center human subjects guidelines. All subjects attended the clinic after a minimum 8-h overnight fast and signed informed consent. Fasting blood samples were drawn and then the subject was given 75 g of glucose (Koladex; Orangedex, Custom Laboratories, Baltimore, MD, USA). Blood samples (1 and 2 h) were drawn and interviews and a physical examination were conducted. Glucose was measured using the glucose oxidase method on venous plasma.[17] Total immunoreactive insulin was measured using the double antibody radioimmunoassay (Linco Research Inc., St. Charles, MO, USA).

The Quantitative Insulin Sensitivity Check Index (QUICKI) was used to estimate the insulin resistance based on fasting insulin and glucose levels ($1/(\log \text{fasting insulin} + \log \text{fasting glucose})$). Increases in QUICKI correspond to increasing insulin resistance. This method for estimating the insulin resistance corrects for cases in which hyperglycemia is accompanied by inadequate insulin secretion. In previous studies, QUICKI appeared to better estimate insulin resistance under these conditions than the often used HOMA model.[18,19] QUICKI correlated closely with fasting insulin in our study (correlation $=-0.98$, $P<0.0001$). Since fasting insulin has been commonly used to estimate insulin resistance, results were repeated using log fasting insulin in place of QUICKI. Doing so did not change either the magnitude or the statistical significance of the results, and thus only QUICKI is reported.

The 1980 United States Census self-assessment question on Spanish origin was used to determine ethnicity.[20] BMI was calculated as measured weight in kilograms divided by height in meters squared. The number of grams of alcohol per week was determined using food frequency interview questions about usual type and quantity of alcohol consumed in the last year. Self-reported frequency and duration of vigorous activity in current work and leisure time were assessed, and included any activity considered by the respondent to be strenuous or to cause symptoms such as fatigue, increased heart rate or sweating.

Subjects were administered a 24-h diet recall by bilingual interviewers trained and certified by the Nutrition Coordinating Center at the University of Minnesota. A two-dimensional food-portion visual and three-dimensional aids (eg ruler, cups, bowls, glasses, plates, measuring spoons) were used to estimate the portion sizes. The nutrient analysis was based on version 14 of the Nutrition Coordinating Center's nutrient database released in 1987. Total carbohydrate excluded dietary fiber.[21]

Statistical analysis

Data were analyzed using the PROC MIXED procedure in SAS Version 8.02 (SAS Institute Inc., Cary, NC, USA) to fit a linear mixed model.[22] This model replaces the two-step method for

balanced data, fitting a regression line for weight *vs* time for each subject and then estimating the average rate of weight gain over subjects. Random effects were incorporated to allow each subject to have their own intercept and slope. The major advantage of such a model is that all of the data from the SLVDS can be used without having to balance the design or discard time-varying covariates.[23]

The major outcome of interest is weight change over time. Thus, weight is the dependent variable, with between one and three measures of weight per subject. The linear mixed model used to assess whether percent of energy from fat modifies the rate of weight gain in this population is

$$W_{it} = \alpha_0 + \alpha_1 C_{it}\lambda_{0i} + \beta_0 t + \beta_1 C_{it} t + \lambda_{1i} t + \varepsilon_{it} \qquad (1)$$

W_{it} is the weight in kg of subject i at time t, t is time in years from baseline, C_{it} is percent of energy from fat (%FAT in text) for subject i at time t, and α_0, α_1, β_0, and β_1 are fixed effects parameters describing population average effects. λ_0 and λ_1 are subject-specific adjustments to the intercept and slope and ε_{it} is the random error, with slope and intercept assumed to be bivariate normal and independent of the random error.

Since C is a time-varying covariate, its coefficient estimate in the above mixed model represents a weighted average of within-subject effects over time and between-subject (or cross-sectional) effects. Within-subject and between-subject effects may differ, and thus were separated by using a mixed model of the form

$$W_{it} = \alpha_0 + \alpha_1^d(C_{it} - \bar{C}_i) + \alpha_1^m \bar{C}_i + \lambda_{0i} + \beta_1^d(C_{it} - \bar{C}_i)t + \beta_1^m \bar{C}_i t + \lambda_{1i} t + \varepsilon_{it} \qquad (2)$$

The parameter estimate α_1^m for the between-subject main effect of C (referred to as %FAT in the text below) examines whether subjects who on average consume relatively high-fat diets weigh more than those who eat low-fat diets. A statistically significant positive interaction of the between-subject effect for %FAT and time from baseline (β_1^m) would indicate that subjects who generally consume high-fat diets gain more weight over time as compared to their low-fat counterparts. In contrast, the within-subject effect can be thought of as the deviation at each time from the subject's overall average. This main effect (α_1^d) considers whether subjects weigh more than their average weight at visits when they reported higher %FAT than their average %FAT. An interaction of the deviation with time (β_1^d) represents the departure in an individual's weight change as they deviate from their average percent intake of dietary fat. When between- and within-subject effects are equal, model (2) reduces to model (1).

In order to determine whether separate between-subject and within-subject effects are required, we compared α_1^m with α_1^d and β_1^m with β_1^d in model (2). If the mean and deviation coefficients are similar in magnitude and direction, then the interpretation of this model should mirror model (1). If, however, only one of the effects is significant, then a reduced model with the removal of the nonsignificant effect was applied. All models that include interaction terms also include those main effects. Both random effect and fixed effect residuals were checked for normality.

Gender, ethnicity (non-Hispanic White, Hispanic), baseline physical activity (sedentary, moderate, vigorous), baseline BMI, baseline age, and smoking status (never, former, or current) were included in each model as covariates. Total energy intake (kcal/day) was also included in each model as a covariate, in order to separate energy intake from the independent effect of fat as a percentage of energy intake on weight gain. As with %FAT, the time-varying covariate total energy intake was assessed by separating intake into two separate variables—one for the subject-specific mean energy intake over time, and another for deviation from the subject-specific mean. Sex, ethnicity, total energy intake, baseline physical activity, and baseline BMI were also considered as potential modifiers of the association between %FAT and rate of weight change. Finally, baseline insulin resistance was added to the models fitted above in order to assess whether baseline insulin resistance altered the relationship of weight change in response to %FAT.

Estimate statements from the PROC MIXED model were used in order to predict the weight at varying levels of dietary fat intake and to create Figure 1. Weight predictions from each model with statistically significant interactions (baseline insulin resistance, gender, and total energy intake) were graphed against the time from baseline in Figures 2–4.

Results

Baseline characteristics of the 782 subjects included in the analyses, by gender and ethnicity, are shown in Table 1.

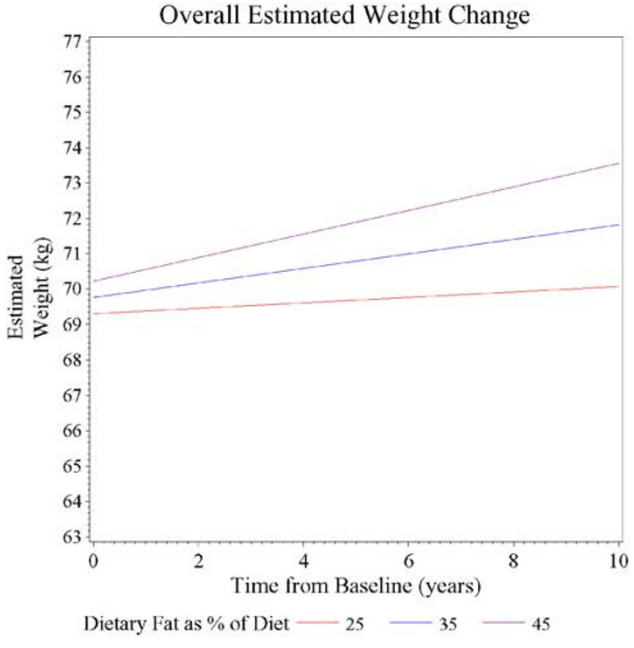

Figure 1

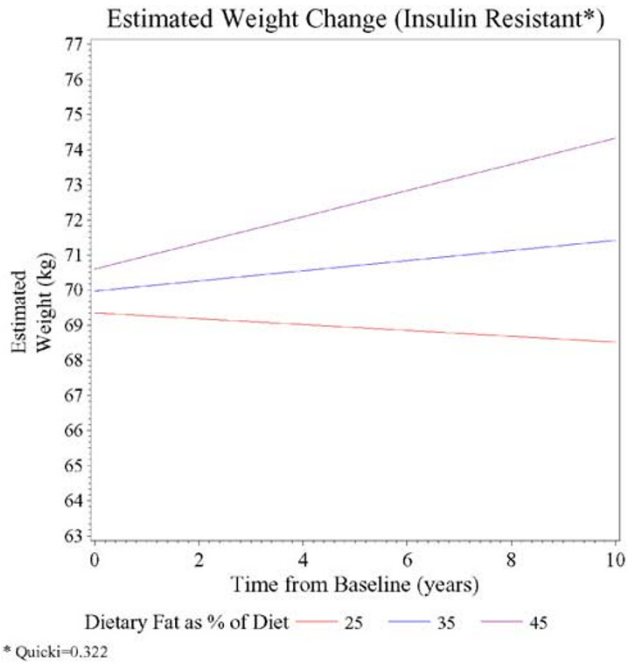

Figure 2

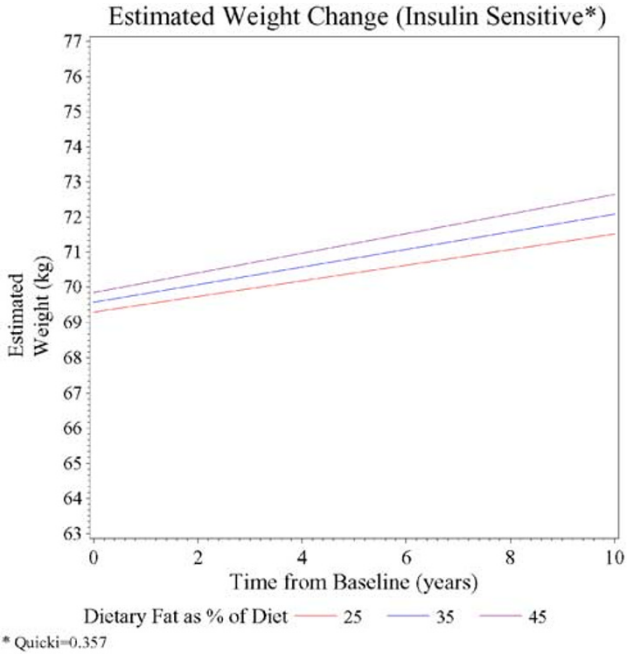

Figure 3

Subjects who completed three visits differed by age at baseline ($P=0.0014$) and energy intake ($P=0.0394$) (data not shown). No trend existed for age by number of visits, while subjects who completed three visits reported higher energy intakes at baseline than those who completed one or two visits only.

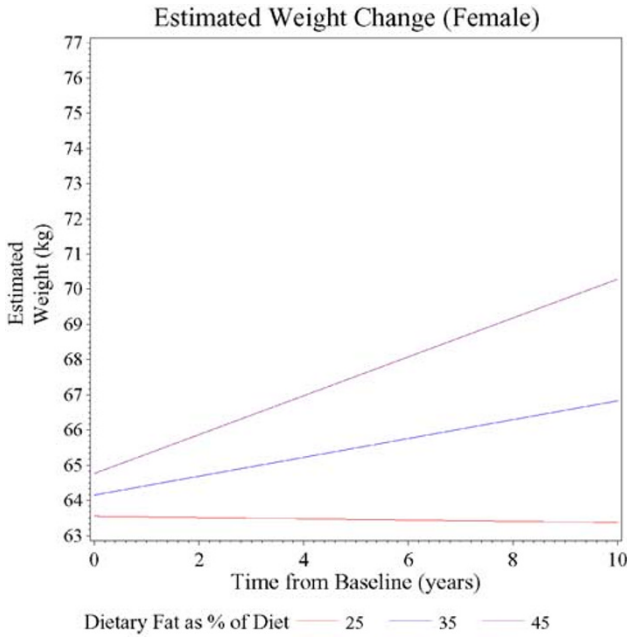

Figure 4

To explore and describe how other variables were related to %FAT and total energy intake, mixed model analyses as described in model (1) were carried out using %FAT and total energy intake separately as the outcome variables in place of weight (Table 2). In those analyses, continuous predictor variables were categorized into equal quartiles in order to identify nonlinear trends. Total intake increased with higher percentage intake of dietary fat ($P=0.0009$) and decreased with older baseline age ($P<0.0001$). Men and non-Hispanic whites reported higher intake levels than women and Hispanics, respectively (both $P<0.0001$). While total intake varied with BMI ($P=0.0104$), the relationship was not linear. Subjects in the highest quartile reported the lowest caloric intake. Such trends were not seen when substituting %FAT as the outcome, where only mean energy intake ($P<0.0001$), smoking status ($P=0.0006$), and age ($P=0.0452$) were associated with the percent of energy from fat.

As seen in Figure 1, there was a significant association between %FAT and estimated weight change ($P=0.0103$) after adjusting for potential confounding variables (Table 3, Model 2). As detailed in the Methods section, %FAT was separated into mean intake across visits and deviations from the mean in order to examine between-subject and within-subject effects. While the interaction of %FAT and time from baseline (between-subject effect) proved significant ($P=0.0178$), there were no statistically significant within-subject effects ($P=0.8686$) (Table 3, Model 1). Therefore, a

Table 1 Baseline characteristics of subjects

	Male		*Female*	
Baseline variable	*NHW (n = 213)*	*Hispanic (n = 136)*	*NHW (n = 267)*	*Hispanic (n = 166)*
BMI	25.7 ± 3.28	24.7 ± 3.78	24.3 ± 4.4	25.0 ± 4.64
Age (y)	52.6 ± 11.8	51.8 ± 13.2	51.2 ± 12.3	48.9 ± 13.6
Insulin sensitivity (QUICKI)	0.339 ± 0.03	0.340 ± 0.03	0.348 ± 0.03	0.336 ± .03
Percent of energy from fat (%)	38.9 ± 8.70	37.8 ± 9.76	38.2 ± 8.89	37.2 ± 8.89
Total energy intake (kcal/day)	2565 ± 1028	2068 ± 972	1713 ± 816	1386 ± 645
Mostly sedentary	36 (16.9%)	33 (24.3%)	71 (26.6%)	72 (43.4%)
Moderate activity	87 (40.9%)	43 (31.6%)	97 (36.3%)	37 (22.3%)
Vigorous activity	90 (42.2%)	60 (44.1%)	99 (37.1%)	57 (34.3%)

Continuous variables expressed as means ± standard deviation. Category variables expressed as number and percent of total.

reduced model using only mean %FAT was used for subsequent analyses.

The association between %FAT and estimated weight change is stronger in persons who are more insulin resistant at the initial visit, in women than in men, and in those with relatively lower overall caloric intakes. The three-way interaction of baseline insulin resistance with mean %FAT and time was highly significant ($P = 0.0025$) (Table 3, Model 3). These results are presented graphically in Figures 2 and 3, with baseline insulin resistance, as measured by QUICKI, estimated at the 25 and 75% quartiles (0.322 and 0.357, respectively). The association between %FAT and weight gain becomes stronger as insulin resistance increases. In other words, high fat intake was more strongly associated with weight gain among subjects with relatively high insulin resistance.

Weight change associated with mean %FAT varied by both gender ($P = 0.0017$) (Table 3, Model 4) and average total energy intake ($P = 0.0020$) (Table 3, Model 5). As shown in Figures 4 and 5, the relationship between weight gain and mean %FAT was stronger in females than in males, with higher fat intake predictive of weight gain only in females (females, $P = 0.0002$; males, $P = 0.7635$). Figures 6 and 7 display the association between the average energy intake, weight change, and %FAT. (Intake is estimated at the 25 and 75% quartiles—1299 and 2281 calories/day, respectively). With increasing energy intake, the magnitude of the association between weight change and %FAT decreased. Baseline insulin sensitivity was added to both of these models, but not found to be statistically significant in a four-way interaction with gender ($P = 0.9437$) or mean energy intake ($P = 0.2852$).

Discussion

The present study was conducted to examine the relationship between percent of energy derived from dietary fat and weight gain, and to further explore whether baseline insulin resistance modifies this relationship. A number of conclusions can be drawn from this study. First, the percent of total energy intake from dietary fat predicts weight change. Second, while diets high in dietary fat also tend to be high in total calories, weight change is associated with dietary fat intake even after adjusting for total energy intake. Third, insulin resistance appears to modify this effect; greater weight gain is associated with high levels of dietary fat intake in the most insulin-resistant individuals. Fourth, the effect of macronutrient composition of the diet on weight change varies by gender.

On average, subjects in this study gained an estimated 0.23 kg/y, translating into an approximate 2.5 kg (5.6 pound) weight gain for subjects over 11 y. The relatively modest weight change among most subjects supports the 'set point' theory, which argues that the body fights to maintain weight by self-adjusting energy metabolism.[24] This premise acknowledges that complex homeostatic mechanisms keep the difference between energy intake (calories consumed) and energy expenditure (resting metabolic rate, physical activity, and the thermic effect of food) close to zero.[25] However, set point theory does not explain the trend towards higher rates of obesity in the US, nor the fact that some subjects in the SLVDS cohort managed to gain or lose significant amounts of weight over time. A modification of the set point theory, termed the 'settling zone' theory, proposes that environmental and cognitive stimuli can influence where a person falls within a range of weights around their set point.[26] This hypothesis recognizes that eating behavior often depends more on the amount and variety of the food available than on the physiological measures of energy need.

Since weight change results from an imbalance between energy intake and expenditure, a likely explanation for the increasing rates of overweight and obesity is an excess of calories consumed. Fat contains 37.6 kJ/g (or roughly 9 kcal/g), while carbohydrates and protein each only contain 16.7 kJ/g (4 kcal/g).[27] For this reason, high-fat foods are often energy dense; smaller portions of a high-fat food result in a relatively large energy intake. Foods high in fat also tend to be high in palatability. Thus, if we eat in volume and for pleasure, rather than simply for energy, we should take in more calories if we eat high-fat, rather than low-fat, foods.

Table 2 Predictors of total caloric intake and % of caloric intake from dietary fat

Effect	*Category*	*Mean intake (kcal)*[b]	P-*value*	*Mean fat (% of kcal)*[a]	P-*value*
Gender	Male	2219		36.6	
	Female	1521		37.1	
	(M/F)		<0.0001		0.3654
Ethnicity	NHW	2041		36.7	
	Hispanic	1699		36.9	
	(W/NHW)		<0.0001		0.6212
Baseline physical activity	Sedentary	1820		36.9	
	Moderate	1907		36.5	
	Vigorous	1883		37.1	
	(Overall)		0.3446		0.5676
Baseline smoking status	Never	1908		35.9	
	Former	1864		38.2	
	Current	1839		36.3	
	(Overall)		0.4299		0.0006
Baseline insulin resistance[b]	Most IS (>0.357)	1815		36.8	
	IS (0.339–0.357)	1864		37.0	
	IR (0.322–0.339)	1927		36.7	
	Most IR (<0.322)	1874		36.7	
	(Overall)		0.4391		0.9497
Baseline body mass index	Low (BMI<22)	1838		36.7	
	Normal (22–25)	1931		36.4	
	Overweight (25–27)	1959		37.5	
	Obese (>27)	1753		36.7	
	(Overall)		0.0104		0.4711
Baseline age (y)	Youngest (<41.5)	1992		36.8	
	Middle (41.5–51.9)	1974		37.4	
	Older (51.9–61.1)	1897		37.4	
	Oldest (>61.1)	1617		35.7	
	(Overall)		<0.0001		0.0452
Percent of energy from fat[c]	Least (<32.1%)	1719		N/A	
	Low (32.1–36.7%)	1908		N/A	
	High (36.7–41.1%)	1865		N/A	
	Highest (>41.1%)	1987		N/A	
	(Overall)		0.0009		
Calories/day[c]	Least (<1299)	N/A		34.7	
	Low (1299–1750)	N/A		37.0	
	High (1750–2280)	N/A		37.3	
	Highest (>2280)	N/A		38.2	
	(Overall)				<0.0001

[a]Least-squares means, adjusted for all covariates as shown. [b]Measured by QUICKI. [c]Mean across visits.

Previous studies support this hypothesis. In a meta-analysis of *ad libitum* low-fat diets, the energy intakes of those given low fat diets averaged 71–84% of the energy intake of the control group.[28] Researchers have also shown that people tend to eat a constant weight of food, regardless of total energy or macronutrient composition, and that the presence of highly palatable foods is positively correlated with energy intake.[29]

As expected, the percentage of intake from dietary fat was highly correlated with total intake in this cohort. However, after adjusting for total energy intake, dietary fat still predicted weight change over time. Subjects who derived a higher proportion of their energy from fat generally gained more weight than those who reported eating low-fat diets, despite similar total energy intake. This relationship was even stronger when baseline insulin resistance was added to the model. As shown in Figure 2, the positive association between dietary fat intake and weight gain magnifies as insulin resistance increases.

As previously discussed, weight gain must be the result of positive energy balance, so how can these observations

Table 3 Linear mixed models testing correlates of weight change

Factor	*Model 1*		*Model 2*		*Model 3*		*Model 4*		*Model 5*	
	B	P-*value*	*B*	P-*value*	*B*	P-*value*	*B*	P-*value*	*B*	P-*value*
Intercept	−6.853	0.0003	−7.075	0.0002	−13.686	0.2463	−7.522	0.0004	−10.111	0.0002
Time (from baseline)	−0.213	0.2555	−0.243	0.1847	−8.133	0.0006	−0.729	0.0034	−1.574	0.0006
Gender (male-female)	11.263	0.0258	11.263	<0.0001	11.200	<0.0001	12.331	<0.0001	11.174	<0.0001
Ethnicity (NHW-hispanic)	6.298	<0.0001	6.322	<0.0001	6.393	<0.0001	6.322	<0.0001	6.310	<0.0001
Smoking status (nonformer)	−0.154	0.6991	−0.100	0.7982	−0.152	0.6996	−0.149	0.7048	−0.130	0.7410
Smoking status (noncurrent)	−0.906	0.0582	−0.851	0.0732	−0.965	0.0444	−0.904	0.0567	−0.853	0.0729
Activity level (sedentary–vigorous)	−0.382	0.4536	−0.381	0.4532	−0.350	0.4940	−0.386	0.4472	−0.355	0.4844
Activity level (sedentary–moderate)	−0.236	0.6111	−0.213	0.6458	−0.125	0.7891	−0.221	0.6338	−0.173	0.7099
Baseline age (y)	−0.076	<0.0001	−0.074	<0.0001	−0.075	<0.0001	−0.074	<0.0001	−0.075	<0.0001
Baseline BMI	2.765	<0.0001	2.765	<0.0001	2.719	<0.0001	2.764	<0.0001	2.763	<0.0001
Average intake (MEANCAL) (1000 kcal/day)	0.999	0.0006	1.008	0.0005	1.019	0.0005	1.002	0.0005	2.890	0.0160
Average fat % (%Fat)	0.046	0.1052	0.046	0.1027	0.384	0.2323	0.061	0.1100	0.129	0.0307
Time*%Fat	0.012	0.0178	0.013	0.0103	0.208	0.0012	0.028	<0.0001	0.047	0.0002
Deviation from average intake	0.272	0.1108								
Deviation from %FAT	0.002	0.9200								
Time*Deviation from %FAT	−0.001	0.8686								
Baseline insulin resistance (QUICKI)					23.083	0.5032				
%FAT*Insulin resistance					−0.997	0.2905				
Time*Insulin resistance					23.227	0.0009				
Time*%Fat*Insulin resistance					−0.576	0.0025				
%FAT*Gender							−0.032	0.5707		
Time*Gender							0.954	0.0087		
Time*%FAT*Gender							−0.031	0.0017		
MEANCAL*%Fat									−0.050	0.1076
Time*MEANCAL									0.750	0.0012
Time*MEANCAL*%Fat									−0.020	0.0020

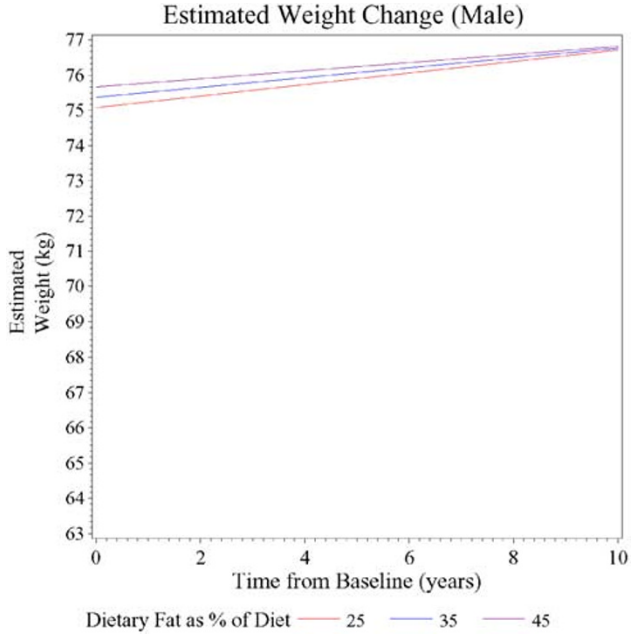

Figure 5

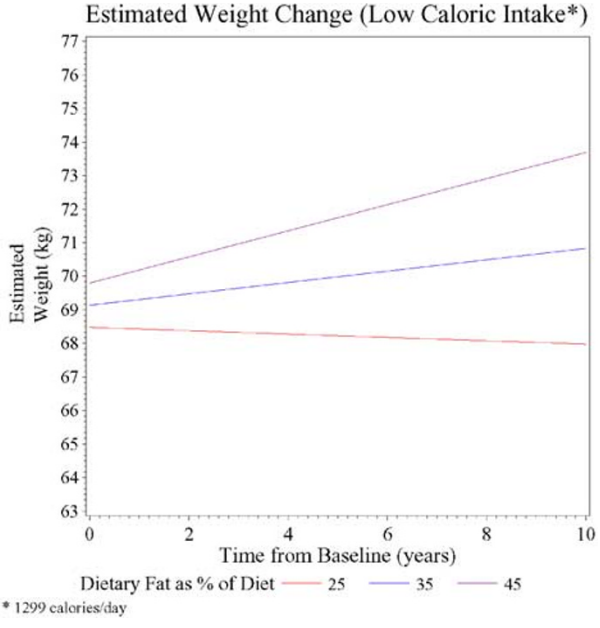

Figure 6

be explained? As suggested by Flatt,[30] increased fat intake may influence substrate oxidation, promoting fuel storage. Another potential explanation is that higher fat intake may result in reduced post-prandial insulin excursions due to the smaller carbohydrate load. This effect may be even more important in insulin-resistant individuals. As there is

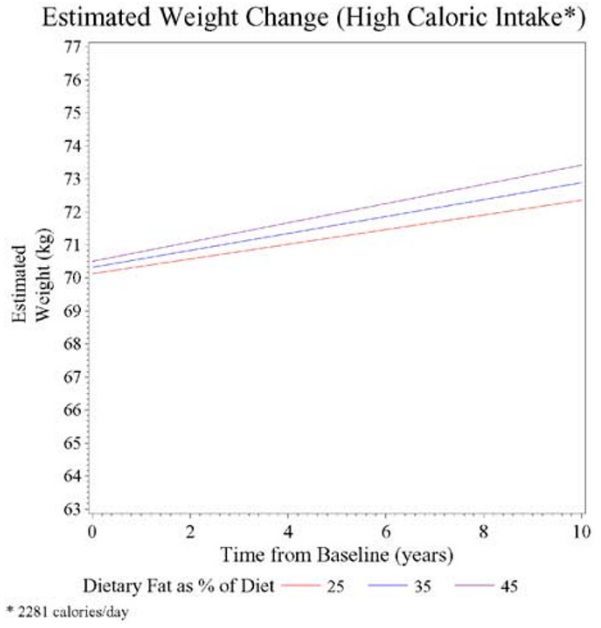

Figure 7

increasing evidence that insulin acts on the central nervous system to inhibit hunger,[31] the reduced insulin excursions may promote greater intake in those on a high-fat diet compared to individuals on a high-carbohydrate diet. It is possible that high fat intake could lead to under-reporting or underestimation of total energy intake, so those who consumed a high-fat diet were in fact consuming more total calories. Finally, it is also possible that individuals consuming higher fat diets were more likely to overestimate their activity level.

The relationship of dietary fat and weight change varied according to gender and total intake. While it is known that the effects of energy restriction, diet composition, and exercise on weight change differs between men and women,[32] the theoretical basis for such differences remain unclear. It is more obvious that the effect of dietary fat intake on weight gain might vary by whether an individual is in a hypocaloric or hypercaloric state.

Many longitudinal studies, including the SLVDS, have shown that fasting insulin, a marker of insulin resistance, is positively associated with weight gain.[33–35] In contrast, it has also been argued that insulin resistance may protect against weight gain.[36,37] This inverse relationship was found in two studies; one involved a multi-ethnic population of Mauritians, and the other a relatively young and lean cohort.[38,39]

With such strong relationships between insulin resistance and both diet and weight, it seems surprising that the only previously published studies that specifically examine insulin resistance as a modifier of the relationship between diet and weight change are clinical studies in which subjects were obese and on a low-energy diet.[12] These studies suggest that such individuals lose more weight on high-fat diets than on traditional high-carbohydrate diets. While we did not directly assess the energy balance, the current data from the San Luis Valley do not support the conclusion that high-fat diets lead to weight loss or retard weight gain. In fact, insulin-resistant subjects who reported high dietary fat intake gained the most weight. This suggests that insulin-resistant subjects should pay particular attention to their relative percentage of energy intake from fat, consistent with findings from randomized controlled trials to prevent type II diabetes.[40]

A potential limitation of this study is the use of self-reported dietary intake and physical activity. Subjects, especially those who are overweight, have been found to under-report their energy intake.[41] Overweight subjects may also selectively under-report certain macronutrients.[42,43] Accuracy in reporting dietary fat intake has been reported to vary[44] by baseline BMI, age, smoking status, gender, and education level.[45] However, a highly significant association between the percent of energy intake from fat and weight gain remained after adjustment for factors where differential under-reporting may have occurred. In addition, self-reported dietary fat as a percent of energy intake did not vary by BMI.

It was unexpected to find that physical activity was not associated with weight change in these data. Clear evidence of the role of physical activity in weight maintenance exists in the literature. In multiple studies, individuals who exercise gain less weight over time both after a planned weight loss and without any prior attempts at weight change.[46–49] Exercise may also allow adaptation to a high-fat diet, thereby specifically modifying the proposed relationship between dietary fat and weight gain.[50] Our activity measure was limited to three categories in analysis (sedentary, moderate, and vigorous) and thus may not have adequately captured true activity levels. In addition, the length of the interval between visits could be a problem if physical activity levels were changing over the follow-up period.

In conclusion, it appears that the habitual intake of a diet high in dietary fat does predict weight gain over time, especially in individuals with insulin resistance. Persons with insulin resistance are also at an increased risk of developing type II diabetes—one of the most debilitating diseases associated with obesity. Experts recommend weight loss to these individuals as a method of reducing this risk. The findings presented here suggest that tailored dietary advice to those characterized as insulin resistant should include messages to reduce dietary fat intake.

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