Body Weight, Not Insulin Sensitivity or Secretion, May Predict Spontaneous Weight Changes in Nondiabetic and Prediabetic Subjects

The RISC Study

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OBJECTIVE—Previous studies have found that high insulin sensitivity predicts weight gain; this association has not been confirmed. Our aim was to systematically analyze metabolic predictors of spontaneous weight changes.

RESEARCH DESIGN AND METHODS—In 561 women and 467 men from the Relationship Between Insulin Sensitivity and Cardiovascular Disease (RISC) cohort (mean age 44 years, BMI range 19–44 kg/m², 9% impaired glucose tolerance) followed up for 3 years, we measured insulin sensitivity (by a euglycemic clamp) and β-cell function (by modeling of the C-peptide response to oral glucose and by acute insulin response to intravenous glucose).

RESULTS—Insulin sensitivity was similar in weight gainers (top 20% of the distribution of BMI changes), weight losers (bottom 20%), and weight stable subjects across quartiles of baseline BMI. By multiple logistic or linear regression analyses controlling for center, age, sex, and baseline BMI, neither insulin sensitivity nor any β-cell function parameter showed an independent association with weight gain; this was true in normal glucose tolerance, impaired glucose tolerance, and whether subjects progressed to dysglycemia or not. Baseline BMI was significantly higher in gainers (26.1 ± 4.1 kg/m²) and losers (26.6 ± 3.7 kg/m²) than in weight stable subjects (24.8 ± 3.8 kg/m², P < 0.0001 for both gainers and losers). Baseline waist circumference (or equivalently, BMI or weight) was a positive, independent predictor of both weight gain and weight loss (odds ratio 1.49 [95% CI 1.12–1.97]) in men and (1.67 [1.28–2.12]) in women. In men only, better insulin sensitivity was an additional independent predictor of weight loss.

CONCLUSIONS—Neither insulin sensitivity nor insulin secretion predicts spontaneous weight gain. Individuals who have attained a higher weight are prone to either gaining or losing weight regardless of their glucose tolerance. *Diabetes 60:1938–1945, 2011

The epidemic of obesity and the attendant increased risk of diabetes and cardiovascular disease pose a demand for devising and implementing strategies to combat and/or prevent obesity. Although much work has addressed the metabolic consequences of weight gain, relatively few studies have focused on the metabolic predictors of weight change. Because insulin resistance is, like obesity, a major risk factor for the development of diabetes, it is of special interest to establish the relation of insulin resistance to body weight changes. Several reports have examined the relationship between insulin action and weight gain (Table 1). An early investigation using the euglycemic clamp technique in a small number of obese Pima Indians (1) found that insulin sensitivity, not insulin resistance, predicted spontaneous weight gain. Likewise, in a small clinical study in women (5), clamp-based insulin sensitivity predicted weight regain after initial weight loss. Other studies using a variety of surrogate indices of insulin sensitivity in larger groups of individuals, however, have yielded mixed results, with roughly half of them reporting an association between insulin sensitivity and weight gain and the other half a relation of insulin resistance to subsequent weight gain. With regard to insulin secretion, again, the findings from studies using a host of proxies for β-cell function have been inconclusive (Table 1).

In the present work, we examined the longitudinal data of the Relationship Between Insulin Sensitivity and Cardiovascular Disease (RISC) study, in which a large cohort of nondiabetic subjects underwent a standardized euglycemic-hyperinsulinemic clamp to measure insulin sensitivity and an oral glucose tolerance test (OGTT) and an intravenous glucose tolerance test (IVGTT) to derive measures of β-cell function. Specifically, we asked the question whether weight changes at follow-up, in either direction, could be predicted by baseline insulin sensitivity and/or β-cell function.

RESEARCH DESIGN AND METHODS

RISC is a prospective, observational, cohort study whose rationale and methodology have been published previously (20). In brief, participants were recruited from the local population at 19 centers in 13 countries in Europe according to the following inclusion criteria: either sex, age 30–60 years (stratified by sex and by age according to 10-year age-groups), BMI 17–44 kg/m², and clinically healthy. Initial exclusion criteria were treatment for obesity, hypertension, lipid disorders or diabetes, pregnancy, cardiovascular or chronic lung disease, weight change of ≥5 kg in past month, cancer (in past 5 years), and renal failure. Exclusion criteria after screening were

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Received 18 February 2011 and accepted 21 April 2011.

DOI: 10.2337/db11-0217

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| Reference | Studies relating weight gain to insulin sensitivity/secretion |
|-----------|-------------------------------------------------------------|
| Swinburn et al. (1991) | | Insulin resistance is associated with a reduced risk of weight gain. |
| Valdez et al. (1994) | | Insulin resistance attenuates further weight gain among the obese. |
| Schwartz et al. (1995) | | Relatively reduced insulin release predicts weight gain. |
| Hoag et al. (1995) | | Higher initial fasting insulin decreases the risk of subsequent weight gain. |
| Yost et al. (1995) | | Change in insulin sensitivity predicts weight regain after an initial weight loss. |
| Hodge et al. (1996) | | In Chinese men, insulin resistance predicts weight gain; in Asian, Indian, and Creole subjects, insulin sensitivity predicts weight gain. |
| Sigal et al. (1997) | | Measures of insulin metabolism appear to have significant association in predicting weight changes. |
| Odeleye et al. (1997) | | In Pima Indian children, fasting hyperinsulinemia is associated with weight gain. |
| Folsom et al. (1998) | | Hyperinsulinemia predicts weight loss in ARIC but not in CARDIA. |
| Gould et al. (1999) | | In middle-aged women, reduced first-phase insulin release predicts weight gain; fasting hyperinsulinemia predicts a higher waist-to-hip ratio. |
| Wedick et al. (2001) | | Insulin resistance is associated with weight loss in the elderly. |
| Travers et al. (2002) | | Insulin resistance during puberty predicts less subcutaneous fat accumulation. |
| Mayer-Davis et al. (2003) | | Measures of insulin metabolism appear to have significant association in predicting weight changes. |
| Howard et al. (2004) | | In postmenopausal women, insulin resistance predicts weight loss. |
| Silver et al. (2006) | | Neither AIR nor insulin sensitivity predicts weight gain. |
| Pannacciulli et al. (2007) | | In Pima Indians, insulin sensitivity does not predict weight changes in multivariate analysis. |
| Morrison et al. (2008) | | Insulin resistant individuals are susceptible to weight gain. |
| Adam et al. (2009) | | In children, a decrease in insulin sensitivity is associated with a higher fat mass gain. |

MTT, meal tolerance test; FSIVGTT, frequently sampled IVGTT; QUICKI, quantitative insulin sensitivity check index.
arterial blood pressure $\geq 140/90$ mmHg, fasting plasma glucose $\geq 7.0$ mmol/L, 2-h plasma glucose (on a standard 75-g OGTT performed in each subject) $\geq 11.0$ mmol/L or known diabetes, total serum cholesterol $\geq 7.8$ mmol/L, serum triglycerides $\geq 4.0$ mmol/L, and electrocardiogram abnormalities. Baseline examinations began in June 2002, were completed in July 2005, and included 1,538 subjects receiving an OGTT. Of these, 1,308 subjects also received a euglycemic-hyperinsulinemic clamp; their baseline data have been published (21).

All 1,308 subjects of the baseline cohort were recalled 3 years later and 1,048 (80%) participated in the follow-up evaluation. The baseline anthropometric and metabolic characteristics of the 200 subjects who were lost to follow-up were superimposable on those of the subjects who participated (data not shown). The follow-up study included all the baseline measurements (anthropometrics, routine blood chemistry, and OGTT) except for the glucose clamp.

Local ethics committee approval was obtained by each recruiting center. Participants were given detailed written information on the study as well as oral explanation, and they all signed a consent form.

**Lifestyle and medical history.** Information was collected on personal and family medical history of cardiovascular disease, stroke, hypertension, and diabetes in first-degree relatives, as well as information on smoking and alcohol habits and physical activity.

**Physical examination.** Height was measured on a clinic stadiometer; body weight and fat-free mass (FFM) were evaluated by the bioimpedance analysis (Tanita International Division, U.K.), which has been shown to be highly correlated with isotope-derived total body water (22). Waist, hip, and thigh circumferences were measured by tape according to a standardized, written protocol.

**Physical activity.** Of the 1,048 participants, 711 were recorded accelerometer capable of continuous data collection for up to 22 days. Data are summed over 1-min periods and processed to evaluate energy expenditure during the entire recording period as well as periods of moderate and intense activity (23,24).

**OGTT.** Blood samples were taken before and at 30, 60, 90, and 120 min into the OGTT. Blood samples were separated into plasma and serum, aliquoted, and stored at $-80^\circ$C for glucose, insulin, and C-peptide determination. Samples were transported on dry ice at prearranged intervals to central laboratories.

**Insulin clamp.** On a separate day within 1 week of the OGTT, a euglycemic-hyperinsulinemic clamp was performed in all subjects. Exogenous insulin was infused at a rate of 240 pmol·min$^{-1}$·m$^{-2}$ simultaneously with a variable 20% dextrose infusion adjusted every 5–10 min to maintain plasma glucose level within 0.8 mmol/L (±15%) of the target glucose level (4.5–6.5 mmol/L).

**IVGTT.** In 761 of the 1,048 subjects with follow-up data, the acute insulin response to intravenous glucose (AIR) was measured at the end of the clamp: a glucose bolus (0.3 mg/kg body wt) was injected over 1 min; plasma glucose, insulin, and C-peptide concentrations were measured at 2, 4, 6, and 8 min after the bolus.

**Analytical procedures.** Plasma glucose was measured by the glucose oxidase technique. Serum insulin was measured by a specific time-resolved immuno-fluorometric assay (AutoDELFIA, Insulin kit, Wallac Oy, Turku, Finland) with the following assay characteristics: detection limit $\geq 3$ pmol/L, intra- and interassay variation 1.7 and 3.5%, respectively. The intra- and interassay coefficient of variation was $<5$ and $<10$%, respectively.

**Data analysis.** Fat mass was obtained as the difference between body weight and FFM. Glucose tolerance was categorized into normal glucose tolerance (NGT), fasting plasma glucose $<6.11$ mmol/L and 2-h plasma glucose $<7.78$ mmol/L, impaired glucose tolerance (IGT; fasting glucose $<7.00$ mmol/L, and 2-h glucose $\geq 7.78$ and $\leq 11.1$ mmol/L); and impaired fasting glyceria (IFG; fasting glucose $\geq 6.11$ and $<7.00$ mmol/L).

Insulin sensitivity was calculated as the M value during the final 40 min of the 2-h clamp (normalized to the FFM, pmol·min$^{-1}$·kgFWM$^{-1}$) as well as the ratio of the M value (21) to the mean plasma insulin concentration measured during the same interval (M/I, in units of pmol·min$^{-1}$·kgFWM$^{-1}$·m$^{-1}$). Area under the time-concentration curve was calculated by the trapezium rule. Actigraph readings were summarized as habitual activity (average number of counts per day).

**β-Cell function modeling.** The model used to reconstruct insulin secretion and its control by glucose has been previously described (25,26). In brief, it consists of two sequential blocks: 1) a model for fitting the glucose concentration profile, the purpose of which is to smooth and interpola plasma glucose concentrations; 2) a model describing the dependence of insulin (or C-peptide) secretion on glucose concentration; and 3) a model of C-peptide kinetics—the two-exponential model proposed by Van Cauter et al. (27) to reconstruct insulin secretion rate from C-peptide concentrations in which the model parameters are individually adjusted to the subject’s anthropometric data. Deconvolution of C-peptide concentrations yields fasting insulin secretion rate and total insulin output (over the 2 h of the OGTT). The relationship between insulin release and plasma glucose concentrations is then modeled as the sum of two components. The first component represents the dependence of insulin secretion on absolute glucose concentration at any time point and is characterized by a dose-response function relating the two variables. The characteristic parameter of the dose response is its mean slope in the 5–7 mmol/L glucose range, denoted here as β-cell glucose sensitivity. The dose response is modulated by both glucose-mediated and non–glucose-mediated factors (i.e., nonglucose substrates, gastrointestinal hormones, and neurotransmitters), which are collectively modeled as a potentiation factor. The model parameters are determined from the glucose and C-peptide data under a smoothness constraint on the potentiation factor.

An empirical index of β-cell function during the OGTT was calculated as the insulinogenic index—the ratio of incremental insulin to incremental glucose concentrations at 30 min into the OGTT (28). AIR was calculated as the mean insulin increment between 2 and 8 min after glucose injection; this response was also expressed as the mean C-peptide increment during the same time interval (3).

**Statistical analysis.** Data are reported as mean ± SD; variables with skewed distribution are summarized as median and interquartile range and were logarithmically transformed for use in parametric statistical testing. Group values were compared by the Mann-Whitney U test, the Kruskal-Wallis test for continuous variables, or the $\chi^2$ test for nominal variables; paired values were compared by the Wilcoxon test. ANCOVA was used to adjust group comparisons for potential confounders (center, sex, age, and BMI). Simple associations were tested by Spearman $\rho$, and logistic regression was used to predict outcome. Multiple regression analysis was carried out using a forward stepwise model. A $P$ value $\leq 0.05$ was considered statistically significant.

**RESULTS**

The distribution of the BMI changes between baseline and follow-up (Fig. 1) shows that in the whole cohort, both men and women gained weight over 3 years (0.9 [4.6] and 0.9 [4.6] kg, respectively; $P < 0.0001$ vs. zero). On the basis of attained changes of body weight at follow-up, subjects were classified as weight gainers if the change in sex-specific BMI was in the top quintile of the distribution of BMI changes or as weight losers if the corresponding change was in the bottom quintile of the distribution; otherwise, subjects were considered to be weight stable.

The anthropometric and baseline metabolic variables for these three groups are given in Table 2. In both gainers and

![FIG. 1. Frequency distribution plot of BMI changes over 3 years of follow-up in 577 women (top) and 471 men (bottom).](image-url)
TABLE 2
Anthropometric and baseline metabolic characteristics by weight change at follow-up

|                         | Weight loser | Weight stable | Weight gainer |
|-------------------------|--------------|---------------|--------------|
|                         | Men | Women | Men | Women | Men | Women |
| n                       | 96  | 117  | 281 | 349  | 95  | 110  |
| Age (years)*            | 44 ± 6 | 46 ± 8 | 44 ± 9 | 45 ± 8 | 43 ± 8 | 44 ± 8 |
| Weight (kg)**†          | 85 ± 11 | 71 ± 12 | 82 ± 12 | 65 ± 11 | 85 ± 14 | 70 ± 13 |
| BMI (kg/m²)**†          | 26.8 ± 3.1 | 26.3 ± 4.3 | 25.7 ± 3.2 | 24.1 ± 3.9 | 26.7 ± 3.8 | 25.5 ± 4.3 |
| Fat mass (%)**†         | 23 ± 6 | 35 ± 7 | 21 ± 6 | 31 ± 7 | 23 ± 7 | 34 ± 7 |
| Waist (cm)**†           | 95 ± 9 | 85 ± 11 | 92 ± 10 | 80 ± 11 | 96 ± 11 | 84 ± 11 |
| NGT/IFG/IGT (%)         | 8/0/0 | 9/0/2 | 24/1/1 | 29/0/3 | 8/0/0 | 9/0/1 |
| Fasting glucose (mmol/L)* | 5.23 ± 0.53 | 4.93 ± 0.6 | 5.21 ± 0.49 | 4.98 ± 0.51 | 5.12 ± 0.48 | 4.94 ± 0.70 |
| 2-h glucose (mmol/L)*   | 5.18 ± 0.60 | 4.84 ± 0.58 | 5.13 ± 1.19 | 4.94 ± 0.75 | 5.12 ± 0.48 | 4.94 ± 0.70 |
| M (μmol · kg⁻¹FFM · min⁻¹)* | 48 [23] | 55 [29] | 49 [24] | 60 [25] | 44 [23] | 53 [20] |
| Steady-state plasma insulin (pmol/L)* | 407 [124] | 397 [104] | 397 [129] | 393 [114] | 409 [111] | 390 [110] |
| M/I (μmol · m⁻² · kg⁻¹FFM · min⁻¹)* | 110 [70] | 137 [92] | 116 [68] | 154 [83] | 103 [72] | 138 [60] |
| Fasting insulin SR (pmol · m⁻² · min⁻¹)* | 69 [33] | 71 [38] | 73 [41] | 64 [34] | 74 [44] | 73 [36] |
| Total insulin output (nmol · m⁻²)† | 38 [18] | 41 [15] | 39 [17] | 39 [17] | 39 [21] | 40 [15] |
| Glucose sensitivity   (μmol · m⁻² · min⁻¹ · nM⁻¹)* | 103 [68] | 112 [100] | 102 [68] | 124 [92] | 110 [64] | 116 [87] |
| Rate sensitivity (μmol · m⁻² · mM⁻¹)‡       | 0.65 [1.1] | 0.68 [1.08] | 0.85 [1.2] | 0.73 [1.31] | 0.76 [1.29] | 0.93 [1.2] |
| Potentiation ratio       | 1.59 [1.18] | 1.71 [1.29] | 1.75 [1.21] | 1.76 [1.35] | 1.72 [1.15] | 1.46 [1.18] |
| AIR (pmol/L)**†         | 127 [192] | 86 [165] | 89 [208] | 93 [157] | 128 [169] | 104 [155] |
| AIRCpep (pmol/L)*       | 791 [687] | 696 [535] | 743 [664] | 690 [603] | 838 [535] | 677 [536] |
| Insulinogenic index (pmol/mmol) | 75 [77] | 78 [80] | 73 [62] | 74 [77] | 75 [61] | 80 [61] |

Data are mean ± SD and median [interquartile range] unless otherwise indicated. SR, secretion rate; AIRCpep, acute insulin response as the C-peptide response. *Significant for sex at $P \leq 0.05$ or less. †Significant for weight category at $P \leq 0.05$ or less.

losers, baseline BMI was significantly higher than in weight stable subjects (Fig. 2). On the clamp, insulin sensitivity was better in women than men across weight categories. After controlling for sex only, insulin sensitivity was significantly lower in subjects whose weight changed in either direction as compared with the weight stable group when using the M value; this difference, however, was no longer significant when using the M/I value, that is, normalizing the M value for the steady-state plasma insulin concentration during the clamp (which did not differ across weight change categories). Of the β-cell function parameters, fasting insulin secretion and AIR were significantly different across groups (Table 2).

To further test whether insulin sensitivity was related to weight change, we grouped subjects according to their baseline insulin sensitivity (below or above the median) and tested whether the corresponding weight changes, used as a continuous variable, were different. As shown in Fig. 3, insulin sensitivity was not significantly associated with weight change across quartiles of baseline BMI (when using either the M value or the M/I index of insulin sensitivity) or in those participants ($n = 15$) who had developed type 2 diabetes at follow-up.

The gain in weight (or BMI or waist circumference) at follow-up in gains was larger than the corresponding loss in the losers (Table 3). In a logistic regression model adjusting for center and age, baseline waist circumference, but not insulin sensitivity, was a significant predictor of a subject being a gainer (with the weight stable subjects as the reference group). This result held true for men and women (Fig. 4A) and was not altered when using quartiles of baseline waist instead of the continuous variable or when using baseline body weight, BMI, or the waist-to-hip ratio instead of waist circumference as the predictor. Moreover, the result was not affected by including any other metabolic variable (physical activity, fasting insulin, fasting insulin secretion, total insulin output, glucose sensitivity, or AIR) in the model. Also, replacing M/I with M (or quartiles thereof) did not change the outcome. In a multiple regression model, the change in body weight (or BMI) at follow-up, used as a continuous variable, was significantly dependent on baseline waist but not on insulin sensitivity.

In these adjusted models, baseline glucose tolerance— as category (i.e., IGT or NGT) or as mean glucose concentration during the OGGT—had no affect on subsequent weight change.

When the same set of analyses (logistic and multiple regression) were performed to compare weight losers with weight stable subjects, we found that a higher waist circumference was a significant independent predictor of weight loss in both women and men. In the logistic model,

**FIG. 2.** BMI at baseline and follow-up in subjects in the top (gainers) or bottom (losers) 20% of the distribution of BMI changes and in the remainder of the population (stable). Plots are mean ± SEM.
basal and total, was higher in progressors than NGT stable subjects, again, without significant differences between weight gainers or losers and weight stable individuals. Finally, by restricting the analysis to the progressors group, there were no differences in insulin sensitivity, β-cell glucose sensitivity, AIR, or insulin secretion (fasting and total) between weight gainers or losers and weight stable subjects.

**DISCUSSION**

The RISC cohort is composed of relatively young, essentially healthy women and men of European descent. During 3 years of observation, the average weight of the cohort increased spontaneously at a rate of 0.3 kg per year (or 0.4% of initial body weight per year). Upon classifying individuals into weight gainers or losers based on a purely statistical criterion (the upper and lower sex-specific quintile of the distribution of BMI changes), weight stable subjects were the 281 men whose weight changed between −2.9 and 5.4 kg and the 349 women whose weight changed between −3.1 and 5.4 kg over 3 years. This is a rather liberal definition of weight stability, which accounts not only for body size (height and sex) but also for the upward trend of weight gain of the entire cohort. More accurately, per our definition, weight stable subjects were those whose overall adiposity did not change much beyond the normal age-related trend.

The first finding in this cohort is that baseline insulin sensitivity, measured by the clamp technique, was not associated with subsequent weight gain or loss. This held true also when comparing more insulin resistant with more insulin sensitive subjects in different BMI strata, thereby ruling out the possibility of missing an interaction between baseline insulin sensitivity and adiposity on subsequent weight changes. Furthermore, when accounting for potential confounders—center, age, and baseline adiposity (as indexed by waist girth, total body weight, or BMI)—in a multivariate logistic model, the level of insulin sensitivity was not a significant predictor of weight gain in either men or women (Fig. 4A).

The two previous studies that used the clamp to measure insulin sensitivity (1,5) arrived at the conclusion that better insulin sensitivity predicts weight gain or, conversely, that insulin resistance protects against weight gain (1). The reasons for the discrepancy are multiple. The study by Yost et al. (5) in 10 obese women actually found an association between gain in insulin sensitivity in subjects attaining a stable weight loss and amount of weight regained 1.5 years later; thus, these results do not speak for insulin sensitivity being a general predictor of weight gain. The study by Swinburn et al. (1) was carried out in 192 young (age ~25 years), very obese (BMI = 35 kg/m²).

**FIG. 3.** Weight change (mean ± SEM) according to baseline insulin sensitivity (as the median M value [top] or the M/I value [bottom]) across sex-specific quartiles of baseline BMI. Neither the insulin sensitivity factor nor its interaction with BMI is statistically significant (P = 0.14 and P = 0.60, respectively, for M and M/I).

**TABLE 3**

Baseline clinical and metabolic phenotype according to subsequent changes in glucose tolerance

| Weight loser | Weight stable | Weight gainer |
|--------------|---------------|---------------|
| **Men** | **Women** | **Men** | **Women** | **Men** | **Women** |
| Body weight (kg)‡ | −3.4 [3.0] | −4.6 [3.5] | 0.9 [2.4] | 0.9 [2.8] | 5.8 [3.1] | 6.3 [3.3] |
| BMI (kg/m²)‡ | −1.1 [0.84] | −1.65 [1.17] | 0.29 [0.86] | 0.35 [0.99] | 1.86 [0.86] | 2.32 [1.33] |
| Waist (cm)† | −3 ± 5 | −4 ± 7 | 1 ± 3 | 1 ± 6 | 5 ± 6 | 6 ± 6 |

Data are median [interquartile range] and mean ± SD. ‡Significant for their interaction at P ≤ 0.05. †Significant for weight category at P ≤ 0.05.
Pima Indians. Of note is that a subsequent study in an expanded group of adult Pima Indians reported that the M value on the clamp was no longer a predictor of weight gain when controlling for baseline body weight (17). Also peculiar is the finding in this ethnic group that children with fasting hyperinsulinemia—a proxy for insulin resistance—have been reported to be at enhanced risk of subsequent weight gain (8). On the other hand, although no other study has used the gold standard method in a large population sample, studies using surrogate indices of insulin sensitivity (from fasting insulin to homeostasis model assessment of insulin resistance [HOMA-IR] to IVGTT-based indices) have yielded contradictory results (Table 1). In some cases, the association between insulin sensitivity and weight gain was not adjusted for confounders such as sex, age, or baseline weight. The current study included a much larger cohort of men and women, with BMIs ranging from lean to very obese, and our analyses accounted for the main determinants of insulin sensitivity, namely, sex, age, and BMI. In addition, we used both categorical grouping (weight gainers or stable weight) and the longitudinal changes in body weight as a continuous variable, and we explored possible interactions among potential predictors. It therefore seems possible to conclude that in people of European ancestry, insulin sensitivity per se has little bearing on future weight changes.

We also systematically sought associations between weight gain and β-cell function by calculating fasting insulin secretion, insulinogenic index and total insulin output, model-derived β-cell glucose sensitivity, and the AIR load. Together, these parameters explore both the absolute insulin secretory response and the sensitivity of the secretory machinery to glucose stimulation. Some of these parameters (e.g., fasting insulin secretion and AIR) were, if anything, higher in gainers than stable weight subjects, as expected from their higher baseline BMI. When accounting for the latter (as well as insulin sensitivity), however, none of the insulin secretion indices were found to be an independent predictor of weight gain.

It has been reported that insulin hyposecretion predicts and precedes weight gain in subjects at high risk for diabetes, such as Pima Indians (3), and in whom the subsequent hyperinsulinemia may be an adaptive response of the central nervous system conferring resistance to further weight gain. Although we did not reproduce this finding in the whole cohort, we tested the hypothesis in the subgroup of individuals whose glucose tolerance deteriorated at follow-up (progressors). Baseline insulin sensitivity and glucose sensitivity were impaired and absolute insulin secretion was increased in these subjects as compared with those who remained glucose tolerant over time. However, there were no differences in any of the β-cell function parameters between those who gained weight and those who did not. Finally, neither insulin sensitivity nor insulin secretion predicted weight changes in subjects with IGT at baseline or among progressors.

The most consistent and powerful predictor of weight gain was the initial body mass (whether indexed as weight, BMI, or waist circumference), which resisted all statistical adjustments in both the logistic and continuous analyses. This finding has not emerged clearly even from large epidemiological studies and has not been emphasized (29–33). Apparently unreported is the parallel result: that a higher initial body weight also predicted spontaneous weight loss and that again, neither insulin sensitivity nor insulin secretion added to the prediction. Taken together, these findings suggest that subjects who gain weight may derive from the same pool of individuals in the general population who strive to lose weight after weight gain. In other words,
persons with dysregulation of body weight maintenance are generally heavier than people with a healthy weight control and may be captured in a phase of weight accretion (weight gainers) or weight loss (weight losers) when observed at some time point in follow-up (34,35). Serial longitudinal observations may reveal, at least in some of them, a pattern of alternate phases of weight gain and loss, with an overall upward trajectory (36,37).

Of note is that in male, but not female, weight losers, a better insulin sensitivity was also independently associated with more weight loss at follow-up (Fig. 4B). Although in the whole dataset insulin sensitivity showed a modest, positive association ($\rho = 0.14$, $P < 0.0001$) with the level of physical activity (as assessed by the Actigraph), the finding in male weight losers could not be explained by a higher level of physical activity (38). Specific studies are needed to further explore the role of insulin sensitivity in spontaneous, as opposed to diet-induced (5), weight loss.

A limitation of the current study is the relatively short follow-up. Nevertheless, our conclusions are likely to be generalizable not only because of the sample size and quality of the measurements but also because the starting cohort was composed of relatively lean subjects at an appropriate age to study factors related to weight gain.

ACKNOWLEDGMENTS

The RISC Study was supported by EU Grant QLG1-CT-2001-01252.

No potential conflicts of interest relevant to this article were reported.

E.R. researched data and literature and wrote the manuscript. E.M., A.N., B.B., G.M., P.P., and T.K. carried out the studies and revised the manuscript. A.M. performed the mathematical modeling. E.F. conceived the design, carried out the studies and data analysis, and revised the manuscript.

APPENDIX

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