

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 1.48 [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

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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

TABLE 1
Studies relating weight gain to insulin sensitivity/secretion

Reference	N	Men/Women	Age (years)	BMI (kg/m ²)	Follow-up (years)	Method	Result
Swinburn et al. (1991) (1)	192	104/88	18–41	33–35	3.5	Clamp	Insulin resistance is associated with a reduced risk of weight gain.
Valdez et al. (1994) (2)	1,493	634/859	25–64	24–28	8	OGTT	Insulin resistance attenuates further weight gain among the obese.
Schwartz et al. (1995) (3)	97	64/33	25	34–35	3	MTT, OGTT, IVGTT	Relatively reduced insulin release predicts weight gain.
Hoag et al. (1995) (4)	789	382/407	20–74	21–30	4.3	Fasting insulin	Higher initial fasting insulin decreases the risk of subsequent weight gain.
Yost et al. (1995) (5)	10	0/10	36 ± 2	34–36	1.5	Clamp	Change in insulin sensitivity predicts weight regain after an initial weight loss.
Hodge et al. (1996) (6)	3,156	1,486/1,670	25–74	22–26	5	HOMA-IR	In Chinese men, insulin resistance predicts weight gain; in Asian, Indian, and Creole subjects, insulin sensitivity predicts weight gain.
Sigal et al. (1997) (7)	107	48/59	33 ± 10	—	16 ± 4	IVGTT	High AIR predicts weight gain in offspring of two diabetic parents.
Odeleye et al. (1997) (8)	328	147/181	5–9	—	9 ± 2	Fasting insulin	In Pima Indian children, fasting hyperinsulinemia is associated with weight gain.
Folsom et al. (1998) (9)	11,198	4,975/6,223	45–64	21–33	7	Fasting insulin	Hyperinsulinemia predicts weight loss in ARIC but not in CARDIA.
Gould et al. (1999) (10)	767	325/442	40–65	21–30	4.4	OGTT	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) (11)	725	308/417	50–89	21–31	8	HOMA-IR	Insulin resistance is associated with weight loss in the elderly.
Travers et al. (2002) (12)	95	47/48	10–15	—	3	FSIVGTT	Insulin resistance during puberty predicts less subcutaneous fat accumulation.
Mayer-Davis et al. (2003) (13)	1,194	534/660	55	23–37	5	IVGTT	Measures of insulin metabolism appear to have little effect on weight change.
Mosca et al. (2004) (14)	782	349/433	20–74	20–30	14	QUICKI	Insulin resistant individuals are susceptible to weight gain.
Howard et al. (2004) (15)	3,389	0/3,389	62	27	3	HOMA-IR	In postmenopausal women, insulin resistance predicts weight gain.
Silver et al. (2006) (16)	105	64/41	28 ± 9	21–31	26 ± 4	IVGTT	Neither AIR nor insulin sensitivity predicts weight gain.
Pannaciuoli et al. (2007) (17)	253	166/87	18–44	—	7 ± 4	Clamp	In Pima Indians, insulin sensitivity does not predict weight changes in multivariate analysis.
Morrison et al. (2008) (18)	639	0/639	18–19	14–35	10	HOMA-IR	Girls in the top tertiles of HOMA-IR and dietary fat had a greater 10-year increase in BMI.
Adam et al. (2009) (19)	96	67/29	Children	22–32	1	FSIVGTT	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 ≥ 7.0 mmol/L, 2-h plasma glucose (on a standard 75-g OGTT performed in each subject) ≥ 11.0 mmol/L or known diabetes, total serum cholesterol ≥ 7.8 mmol/L, serum triglycerides ≥ 4.6 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 260 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 fitted with a CSA Actigraph (MTI: Manufacturing Technology Inc., Fort Walton Beach, FL) attached to a waist belt for 1 week. The Actigraph is a small (43 g), single-channel recording 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, aliquotted, and stored at -80°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 $240 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ simultaneously with a variable 20% dextrose infusion adjusted every 5–10 min to maintain plasma glucose level within 0.8 mmol/L ($\pm 15\%$) of the target glucose level (4.5–5.5 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 immunofluorometric assay (AutoDELFIA, Insulin kit, Wallac Oy, Turku, Finland) with the following assay characteristics: detection limit $>3 \text{ pmol/L}$, 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 ≥ 7.78 and <11.1 mmol/L), and impaired fasting glycemia (IFG; fasting glucose ≥ 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, $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{\text{FFM}}^{-1}$) as well as the ratio of the M value (21) to the mean plasma insulin concentration measured during the same interval (MI, in units of $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{\text{FFM}}^{-1} \cdot \text{nM}^{-1}$). 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 three blocks: 1) a model for fitting the glucose concentration profile, the purpose of which is to smooth and interpolate 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 \pm 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 χ^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 ρ , and logistic regression was used to predict outcome. Multiple regression analysis was carried out using a forward stepwise model. A *P* value ≤ 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

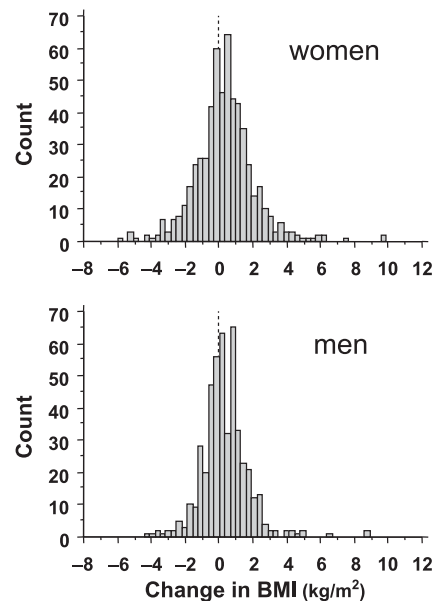


FIG. 1. Frequency distribution plot of BMI changes over 3 years of follow-up in 577 women (top) and 471 men (bottom).

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
<i>n</i>	96	117	281	349	95	110
Age (years)*	44 ± 9	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/m ²)*†	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 _{FFM} ⁻¹ · 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 · min ⁻¹ · kg _{FFM} ⁻¹ · nM ⁻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 (pmol · m ⁻² · min ⁻¹ · mM ⁻¹)*	103 [68]	112 [100]	102 [68]	124 [92]	110 [64]	116 [87]
Rate sensitivity (nmol · m ⁻² · mM ⁻¹)	0.85 [1.1]	0.68 [1.08]	0.85 [1.2]	0.73 [1.31]	0.76 [1.29]	0.93 [1.2]
Potential 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]
AIR _{Cpep} (pmol/L)*	791 [687]	696 [535]	743 [664]	609 [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; AIR_{Cpep}, 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,

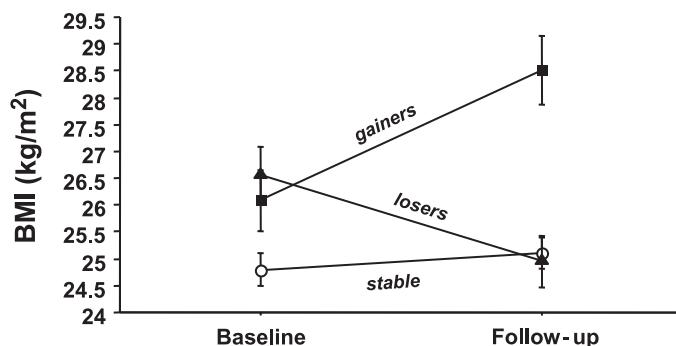


FIG. 2. BMI at baseline and follow-up in subjects in the top (gainers) or bottom (losers) 20% of the distribution of BMI changes and in the remainder of the population (stable). Plots are mean ± SEM.

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 gainers 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 OGTT—had no effect 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,

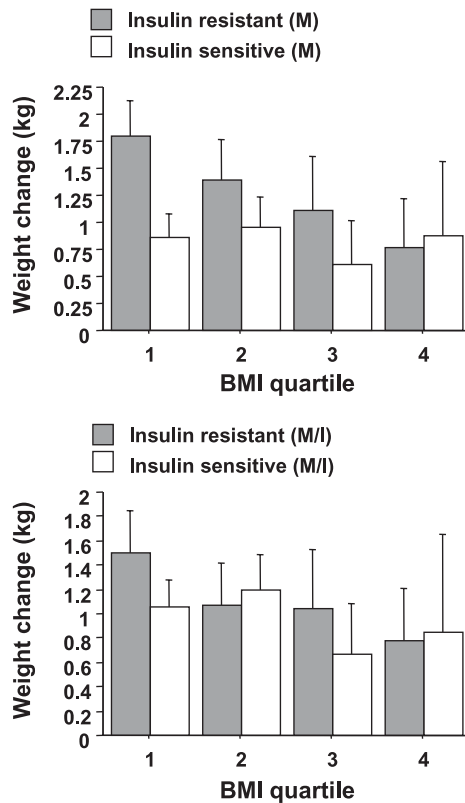


FIG. 3. Weight change (mean ± SEM) according to baseline insulin sensitivity (as the median M value [top] or the M/I value [bottom]) across sex-specific quartiles of baseline BMI. Neither the insulin sensitivity factor nor its interaction with BMI is statistically significant ($P = 0.14$ and $P = 0.60$,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

insulin sensitivity was an additional independent predictor of weight loss in men but not in women (Fig. 4B).

In a separate set of analyses, we sought to determine whether insulin sensitivity or secretion was associated with weight gain in those individuals whose glucose tolerance deteriorated over the 3 years of follow-up. To this end, we classified as progressors those individuals ($n = 128$) who stepped up along the sequences NGT→IFG, NGT→IGT, NGT→T2DM (type 2 diabetes), IFG→IGT, IFG→T2DM, and IGT→T2DM between baseline and follow-up. In comparison with subjects who were NGT both at baseline and follow-up ($n = 820$), progressors had worse insulin sensitivity ($106 [79]$ vs. $137 [84]$ $\mu\text{mol} \cdot \text{kg}_{\text{FFM}}^{-1} \cdot \text{min}^{-1} \cdot \text{nM}^{-1}$; $P < 0.0001$) and β -cell glucose sensitivity ($95 [51]$ vs. $122 [81]$ $\text{pmol} \cdot \text{m}^{-2} \cdot \text{min}^{-1} \cdot \text{mM}^{-1}$; $P < 0.0001$), but without significant differences between weight gainers or losers and weight stable subjects. Insulin secretion,

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 trending 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 ($\text{BMI} = 35 \text{ kg/m}^2$)

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/m^2)‡	-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 $P \leq 0.05$. †Significant for weight category at $P \leq 0.05$.

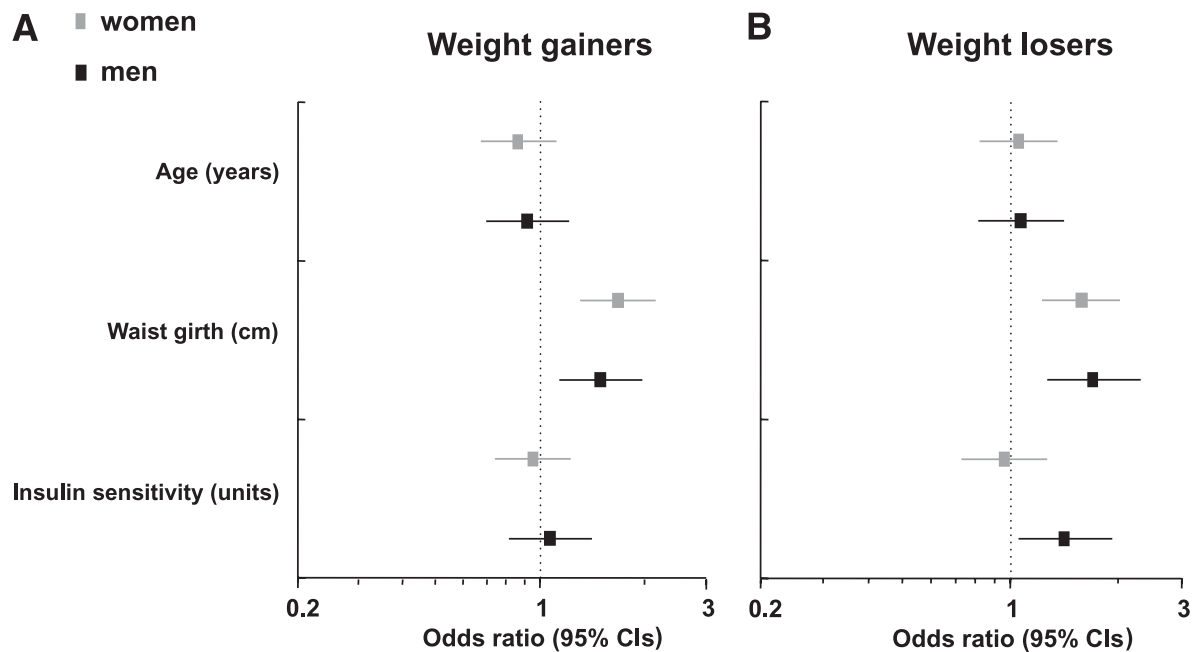


FIG. 4. A: Multiple logistic regression for the odds of being a weight gainer according to baseline age, waist girth, and insulin sensitivity (as the *M/I*). Odds ratios (ORs) and 95% CIs are calculated for 1 SD of the predictor variable. For each 10-cm increase in waist circumference, the OR is 1.48 (95% CI 1.12–1.97) in men and 1.67 (1.28–2.12) in women. When using *M* instead of *M/I*, the OR is 1.01 (0.76–1.36) for men and 0.89 (0.68–1.17) for women. **B:** Multiple logistic regression for the odds of being a weight loser according to baseline age, waist girth, and insulin sensitivity (as the *M/I*). ORs and 95% CIs are calculated for 1 SD of the predictor variable.

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.

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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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REFERENCES

1. Swinburn BA, Nyomba BL, Saad MF, et al. Insulin resistance associated with lower rates of weight gain in Pima Indians. *J Clin Invest* 1991;88:168–173
2. Valdez R, Mitchell BD, Haffner SM, et al. Predictors of weight change in a bi-ethnic population. The San Antonio Heart Study. *Int J Obes Relat Metab Disord* 1994;18:85–91
3. Schwartz MW, Boyko EJ, Kahn SE, Ravussin E, Bogardus C. Reduced insulin secretion: an independent predictor of body weight gain. *J Clin Endocrinol Metab* 1995;80:1571–1576
4. Hoag S, Marshall JA, Jones RH, Hamman RF. High fasting insulin levels associated with lower rates of weight gain in persons with normal glucose tolerance: the San Luis Valley Diabetes Study. *Int J Obes Relat Metab Disord* 1995;19:175–180
5. Yost TJ, Jensen DR, Eckel RH. Weight regain following sustained weight reduction is predicted by relative insulin sensitivity. *Obes Res* 1995;3:583–587
6. Hodge AM, Dowse GK, Alberti KG, Tuomilehto J, Gareeboo H, Zimmet PZ; Mauritius Non-communicable Disease Study Group. Relationship of insulin resistance to weight gain in nondiabetic Asian Indian, Creole, and Chinese Mauritians. *Metabolism* 1996;45:627–633
7. Sigal RJ, El-Hashimy M, Martin BC, Soeldner JS, Krolewski AS, Warram JH. Acute postchallenge hyperinsulinemia predicts weight gain: a prospective study. *Diabetes* 1997;46:1025–1029
8. Odeleye OE, de Courten M, Pettitt DJ, Ravussin E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes* 1997;46:1341–1345
9. Folsom AR, Vitelli LL, Lewis CE, Schreiner PJ, Watson RL, Wagenknecht LE. Is fasting insulin concentration inversely associated with rate of weight gain? Contrasting findings from the CARDIA and ARIC study cohorts. *Int J Obes Relat Metab Disord* 1998;22:48–54
10. Gould AJ, Williams DE, Byrne CD, Hales CN, Wareham NJ. Prospective cohort study of the relationship of markers of insulin resistance and secretion with weight gain and changes in regional adiposity. *Int J Obes Relat Metab Disord* 1999;23:1256–1261
11. Wedick NM, Mayer-Davis EJ, Wingard DL, Addy CL, Barrett-Connor E. Insulin resistance precedes weight loss in adults without diabetes: the Rancho Bernardo Study. *Am J Epidemiol* 2001;153:1199–1205
12. Travers SH, Jeffers BW, Eckel RH. Insulin resistance during puberty and future fat accumulation. *J Clin Endocrinol Metab* 2002;87:3814–3818
13. Mayer-Davis EJ, Kirkner GJ, Karter AJ, Zaccaro DJ. Metabolic predictors of 5-year change in weight and waist circumference in a triethnic population: the insulin resistance atherosclerosis study. *Am J Epidemiol* 2003;157:592–601
14. Mosca CL, Marshall JA, Grunwald GK, Cornier MA, Baxter J. Insulin resistance as a modifier of the relationship between dietary fat intake and weight gain. *Int J Obes Relat Metab Disord* 2004;28:803–812
15. Howard BV, Adams-Campbell L, Allen C, et al. Insulin resistance and weight gain in postmenopausal women of diverse ethnic groups. *Int J Obes Relat Metab Disord* 2004;28:1039–1047
16. Silver RJ, Mehta S, Soeldner JS, Martin BC, Warram JH, Goldfine AB. Acute insulin secretion as a predictor of weight gain in healthy humans. *Obesity (Silver Spring)* 2006;14:67–72
17. Pannaciuoli N, Ortega E, Koska J, Salbe AD, Bunt JC, Krakoff J. Glucose response to an oral glucose tolerance test predicts weight change in nondiabetic subjects. *Obesity (Silver Spring)* 2007;15:632–639
18. Morrison JA, Glueck CJ, Horn PS, Schreiber GB, Wang P. Pre-teen insulin resistance predicts weight gain, impaired fasting glucose, and type 2 diabetes at age 18–19 y: a 10-y prospective study of black and white girls. *Am J Clin Nutr* 2008;88:778–788

19. Adam TC, Toledo-Corral C, Lane CJ, et al. Insulin sensitivity as an independent predictor of fat mass gain in Hispanic adolescents. *Diabetes Care* 2009;32:2114–2115
20. Hills SA, Balkau B, Coppack SW, et al.; EGIR-RISC Study Group. The EGIR-RISC STUDY (The European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease risk): I. Methodology and objectives. *Diabetologia* 2004;47:566–570
21. Ferrannini E, Balkau B, Coppack SW, et al.; RISC Investigators. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. *J Clin Endocrinol Metab* 2007;92:2885–2892
22. Strain GW, Wang J, Gagner M, Pomp A, Inabnet WB, Heymsfield SB. Bioimpedance for severe obesity: comparing research methods for total body water and resting energy expenditure. *Obesity (Silver Spring)* 2008;16:1953–1956
23. Brage S, Brage N, Franks PW, et al. Branched equation modeling of simultaneous accelerometry and heart rate monitoring improves estimate of directly measured physical activity energy expenditure. *J Appl Physiol* 2004;96:343–351
24. Balkau B, Mhamdi L, Oppert JM, et al.; EGIR-RISC Study Group. Physical activity and insulin sensitivity: the RISC study. *Diabetes* 2008;57:2613–2618
25. Mari A, Tura A, Gastaldelli A, Ferrannini E. Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation. *Diabetes* 2002;51 (Suppl. 1):S221–S226
26. Mari A, Schmitz O, Gastaldelli A, Oestergaard T, Nyholm B, Ferrannini E. Meal and oral glucose tests for assessment of β -cell function: modeling analysis in normal subjects. *Am J Physiol Endocrinol Metab* 2002;283:E1159–E1166
27. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes* 1992;41:368–377
28. Mari A, Ferrannini E. Beta-cell function assessment from modelling of oral tests: an effective approach. *Diabetes Obes Metab* 2008;10(Suppl. 4):77–87
29. Colditz GA, Willett WC, Stampfer MJ, London SJ, Segal MR, Speizer FE. Patterns of weight change and their relation to diet in a cohort of healthy women. *Am J Clin Nutr* 1990;51:1100–1105
30. Rissanen AM, Heliövaara M, Knekt P, Reunanen A, Aromaa A. Determinants of weight gain and overweight in adult Finns. *Eur J Clin Nutr* 1991;45:419–430
31. Ravussin E, Gautier JF. Metabolic predictors of weight gain. *Int J Obes Relat Metab Disord* 1999;23(Suppl. 1):37–41
32. Fine JT, Colditz GA, Coakley EH, et al. A prospective study of weight change and health-related quality of life in women. *JAMA* 1999;282:2136–2142
33. Sherwood NE, Jeffery RW, French SA, Hannan PJ, Murray DM. Predictors of weight gain in the Pound of Prevention study. *Int J Obes Relat Metab Disord* 2000;24:395–403
34. Rosenbaum M, Leibel RL, Hirsch J. Obesity. *N Engl J Med* 1997;337:396–407
35. Hall KD. Mechanisms of metabolic fuel selection: modeling human metabolism and body-weight change. *IEEE Eng Med Biol Mag* 2010;29:36–41
36. Kataja-Tuomola M, Sundell J, Männistö S, et al. Short-term weight change and fluctuation as risk factors for type 2 diabetes in Finnish male smokers. *Eur J Epidemiol* 2010;25:333–339
37. Field AE, Manson JE, Taylor CB, Willett WC, Colditz GA. Association of weight change, weight control practices, and weight cycling among women in the Nurses' Health Study II. *Int J Obes Relat Metab Disord* 2004;28:1134–1142
38. Schmitz KH, Jacobs DR Jr, Leon AS, Schreiner PJ, Sternfeld B. Physical activity and body weight: associations over ten years in the CARDIA study. *Coronary Artery Risk Development in Young Adults*. *Int J Obes Relat Metab Disord* 2000;24:1475–1487