Meta-analysis of resting metabolic rate in formerly obese subjects[1–3]

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ABSTRACT

Background: A low resting metabolic rate (RMR) for a given body size and composition is partly genetically determined and has been suggested to be a risk factor for weight gain. Moreover, a low relative RMR has been reported in some, but not all, studies of formerly obese persons. The inconsistent reports may be due to a lack of statistical power to detect small differences in RMR and improper adjustment for body size and composition.

Objective: We conducted a meta-analysis based on published studies of RMR in formerly obese persons [body mass index (in kg/m^2) ≤27] and matched control subjects who had never been obese.

Design: We performed both an individual subject data meta-analysis and a traditional meta-analysis.

Results: The individual subject data meta-analysis included 124 formerly obese and 121 control subjects. RMR adjusted for differences in fat-free mass and fat mass was 2.9% lower in formerly obese subjects than in control subjects ($P = 0.09$). A low relative RMR (> 1 SD below the mean of the control group) was found in 3.3% of the control subjects and in 15.3% of the formerly obese subjects [difference: 12% (95% CI: 4.7%, 19.3%); $P < 0.003$]. The traditional meta-analysis was based on 12 studies (including 94 formerly obese and 99 control subjects) and included 3 studies not represented in the individual subject data analysis. In this analysis, relative RMR was lower in the formerly obese group than in the control group by 5.1% (95% CI: 1.7%, 8.6%).

Conclusions: Formerly obese subjects had a 3–5% lower mean relative RMR than control subjects; the difference could be explained by a low RMR being more frequent among the formerly obese subjects than among the control subjects. Whether the cause of the low RMR is genetic or acquired, the existence of a low RMR is likely to contribute to the high rate of weight regain in formerly obese persons. *Am J Clin Nutr* 1999;69:1117–22.

KEY WORDS Body composition, fat-free mass, fat mass, formerly obese persons, genes, obesity, resting metabolic rate, weight loss, meta-analysis

INTRODUCTION

The rapidly increasing prevalence of obesity has led to obesity being characterized as an epidemic; according to the World Health Organization, obesity and its complications are the leading health threat globally (1). In the United States, obesity and its major complications (eg, diabetes, ischemic heart disease, stroke, certain cancers, and disability) may account for ≈7% of all health care costs (2). Obesity seems to be caused mainly by a combination of a genetic predisposition and a lifestyle characterized by physical inactivity and excessive intake of energy-dense, high-fat foods (1). Resting metabolic rate (RMR) is the component of energy expenditure that explains the largest proportion of total daily energy needs in individuals, but the contribution of a low RMR to the etiology of obesity is controversial. Several studies have shown that RMR has a strong genetic component (3, 4), and a prospective study in Pima Indians showed that the RMR for a given body composition, ie, RMR adjusted for fat-free mass (FFM) and fat mass (FM), is a predictor of subsequent weight change (5). However, a prospective study in whites did not confirm this finding (6).

It is also well established that energy restriction and weight loss may cause a sustained suppression of the RMR for a given body composition. Whether the origin of the suppression of RMR is genetic or acquired, the suppression of RMR may be important for understanding the high rate of weight regain in obese subjects after weight loss. However, the results of studies comparing formerly obese subjects with control subjects who had never been obese are discordant (7–25). A major shortcoming of most of these studies is a small sample size, mainly 6–12 subjects in each group, which does not allow for detection of differences in RMR < 10–15%. Furthermore, obesity is a heterogeneous condition and the prospective and genetic studies do not suggest that a low RMR is present in the majority of formerly obese subjects. We undertook a meta-analysis to increase the statistical power to detect smaller differences in RMR and to perform exploratory analyses within possible subgroups with low RMRs.

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TABLE 1
Previously published studies from which data from formerly obese (FO) and control (C) subjects were used in the individual subject data meta-analysis

Author and reference	Journal	Year	FO/C subjects reported (152/237)	FO/C subjects included (124/121)[1]
Bessard et al (18)	Am J Clin Nutr	1983	5/6	3/6
Dulloo et al (21)	Int J Obes	1986	8/8	7/7
Shah et al (7)	Eur J Clin Nutr	1988	16/16	16/16
Dulloo et al (22)	Am J Clin Nutr	1989	9/9	9/9
Tremblay et al (14)	Int J Obes	1989	9/6	9/6
Bukkens et al (20)	Int J Obes	1991	6/6	6/6
Goldberg et al (17)	Proc Nutr Soc	1991	9/9	8/9
Buemann et al (11)[2]	Am J Clin Nutr	1992	15/7	12/7
Buemann et al (9)[2]	Am J Physiol	1992	8/8	3/3
de Peuter et al (15)	Int J Obes	1992	8/8	6/8
Amatruda et al (16)	J Clin Invest	1993	18/14	18/14
Astrup et al (12)[2]	Am J Physiol	1994	9/9	4/7
Raben et al (13)[2]	Am J Physiol	1994	12/12	12/12
Toubro et al (8)[2]	Clin Sci	1994	9/9	1/1
Larson et al (19)	Am J Clin Nutr	1995	11/110	10/10

[1] Only subjects with a BMI (in kg/m^2) <27 were included.
[2] Five studies from our group were used in this analysis, whereas only one summary paper was included in the traditional meta-analysis (Table 3).

METHODS

We conducted both a meta-analysis based on individual subject data provided by the authors of relevant publications and a traditional meta-analysis based on published results. The studies were identified in a MEDLINE (National Library of Medicine, Bethesda, MD) search covering the period from 1966 to October 1997. The following terms were used: *post* or *reduc** or *former** or *postobese* and *energy expenditure*. A total of 24 potentially relevant publications were identified and 2 additional publications were identified from the reference lists. These 26 publications were reviewed to determine whether they fulfilled the following predetermined inclusion criteria: *1*) The formerly obese subjects had previously had a body mass index (BMI; in kg/m^2) ≥ 30 and had reduced their body weight to a BMI ≤ 27 through nonsurgical weight-reduction regimens. *2*) The control group consisted of persons who had never been obese. *3*) Basal metabolic rate, RMR, or sleeping energy expenditure had been measured by indirect calorimetry by using either a mouthpiece, ventilated hood, or respiratory chamber. An assessment of body composition that allowed calculation of FFM and FM was requested only for the individual subject data meta-analysis.

Inclusion of studies: traditional meta-analysis

Eight of the 26 publications were excluded from the traditional meta-analysis because the formerly obese subjects had mean BMIs >27. The remaining 18 publications fulfilled all criteria for the traditional meta-analysis (7–18, 20–25). Six of the 18 publications were from our department (8–13); one of these papers (10) summarized previously published data and only this study was included because some subject data had been used in more than one publication. Additionally, for the traditional meta-analysis, only one study from the same authors was included if all or some of the subjects had participated twice. Therefore, only 1 (22) of the 2 studies by Dulloo et al (21, 22) was included. Thus, the traditional meta-analysis included 12 studies.

In the traditional meta-analysis, we included the study by Lean and James (23), from which no raw data were available. Moreover, the studies by Shetty et al (24) and Jung et al (25), which lacked assessment of body composition, were included and we estimated mean FFM from body weight on the basis of an equation given in a previous study (26): FFM = 23.67 + 0.37 $\times$ body weight. Because SDs were rarely reported or could rarely be calculated, we performed a rather simple meta-analysis, weighting the study by sample size (27).

Inclusion of studies: individual subject data meta-analysis

For the individual subject data meta-analysis, 7 studies were excluded because they did not meet the inclusion criteria. Additionally, 2 of the publications included in the traditional meta-analysis were excluded because they did not include measurements of body composition (24, 25). Furthermore, for this meta-analysis we preferred to use our 5 original publications (8, 9, 11–13) and not the summary paper. Letters were written to the authors of 11 other publications asking for raw data on body weight, height, FFM, and FM and unadjusted data on basal, sleeping, or resting energy expenditure. All authors or coauthors responded and 10 supplied the requested information (7, 14–22). The authors of one study replied that the individual subject data were no longer available (23). Thus, 15 studies were included in the individual subject data meta-analysis (**Table 1**).

In all studies the formerly obese and control subjects were sex matched, and hence sex was not taken into account in the meta-analysis. In studies in which energy expenditure was measured during intake of diets of various macronutrient compositions, the composition with the lowest carbohydrate content was selected because previous reports suggested that formerly obese subjects may increase their energy expenditure in response to a carbohydrate content supplying $>55\%$ of total energy (12, 23). To achieve measurements with the lowest variability, a sleeping metabolic rate was preferred over a basal metabolic rate, which was preferred over RMR. Nine studies (146 subjects) had used respiratory chambers (7, 9, 11, 12, 17–19, 21, 22), whereas a ventilated hood or mask or mouthpiece was used in the remaining 6 studies (99 subjects). If more than one measurement had been carried out, the last measurement was used. In the individual subject data meta-analysis only subjects with a BMI ≤ 27 were included; when subjects had participated in more than one study or when the subject's data were used in more than 1 publication, only one data set was included.

TABLE 2
Results of the individual subject data meta-analysis of resting metabolic rate (RMR) in formerly obese and control subjects[1]

	Control subjects (n = 121)	Formerly obese subjects (n = 124)	Group difference (95% CI)	P
RMR (kJ/d)	6200 ± 1005[2]	6123 ± 912	76 (−165, 318)	0.54
Body weight (kg)	62.9 ± 8.9	66.5 ± 9.1	−3.6 (−5.9, −1.3)	0.002
Fat-free mass (kg)	47.1 ± 7.2	48.4 ± 7.5	−1.3 (−3.1, 0.5)	0.16
Fat mass (kg)	15.8 ± 5.0	18.1 ± 4.6	−2.2 (−3.5, −1.1)	0.0003
Fat mass (%)	24.8 ± 6.3	27.3 ± 5.6	−2.5 (−4.0, −0.9)	0.003
adjRMR$_{FFM+FM}$ (kJ/d)	6252 ± 915	6072 ± 743	180 (−29, 390)	0.09
adjRMR$_{FFM+FM+study}$ (kJ/d)	6252 ± 890	6073 ± 753	178 (−28, 386)	0.08

[1] adjRMR$_{FFM+FM}$, RMR adjusted for differences in fat-free mass and fat mass; adjRMR$_{FFM+FM+study}$, RMR adjusted for FFM, FM, and study.
[2] $\bar{x}$ ± SD.

Unadjusted values of RMR were compared between formerly obese and control subjects and subsequently adjusted for differences in FFM and FM by using the linear regression described by Ravussin and Bogardus (28). The adjusted values were compared by two-sample t tests, after the distribution was controlled for normality. A low RMR was defined as a value >1 SD below the mean of the control group, and a high RMR as a value >1 SD above the mean of the control group. The proportions of subjects in each group that fell within a single category (low RMR or high RMR) were compared separately by using Fisher's exact test.

RESULTS

As a result of the inclusion criteria, with the requirements of only one data set per subject and a BMI ≤27, the selection of formerly obese and control subjects for the individual subject data meta-analysis produced 2 groups with 124 and 121 subjects, respectively (Table 1). The mean body weight of the formerly obese subjects was slightly higher than that of the control group (**Table 2**), which could be accounted for mainly by a 2-kg significantly higher body FM in the formerly obese group. RMR was 6200 (95% CI: 6051, 6348) kJ/d in the formerly obese group and 6123 (95% CI: 5977, 6270) kJ/d in the control group (NS). When RMR was properly adjusted for differences in FFM and FM, the formerly obese group had a 2.9% lower value than the control group (P = 0.09). There was no heterogeneity (P = 0.15). When RMR was expressed per kg FFM, the formerly obese subjects had a 4.1% (95% CI: 0.2%, 8.1%) lower RMR than did the control subjects (P = 0.04). Whether the adjustment was performed by linear regression or by analysis of covariance with FFM, FM, and "study" as covariates did not essentially change the outcome [2.9% (95% CI: −0.5%, 6.4%); group effect: P = 0.08, analysis of covariance].

RMR adjusted for body composition and study in the 124 formerly obese subjects and the 121 control subjects was normally distributed (**Figure 1**). A low RMR adjusted for body composition was found in 4 control subjects (3.3%) and 19 formerly obese subjects (15.3%). This difference of 12% (95% CI: 4.7%, 19.3%) was highly significant (P < 0.003). In the upper end of the distribution, no significant difference was found between the 2 groups (formerly obese, 8.1%; control subjects, 12.4%; z = 0.911, P = 0.36). Exclusion of the 3 studies in which low-fat, high-carbohydrate diets were used did not change any of the conclusions, and no effect of diet composition on RMR could be found when the study variable was taken into account.

The traditional meta-analysis included 12 studies (125 formerly obese and 119 control subjects) (**Table 3**). In an unweighted analysis, relative RMR was 4.2% (95% CI: 0.6%, 7.8%) lower in the formerly obese group than in the control group. When the studies were weighted by sample size, the result was essentially unchanged [5.1% (95% CI: 1.7%, 8.6%)].

DISCUSSION

The present meta-analysis is the first compilation of a large sample of data on RMR in formerly obese subjects and never-obese control subjects. The analysis showed that, after differences

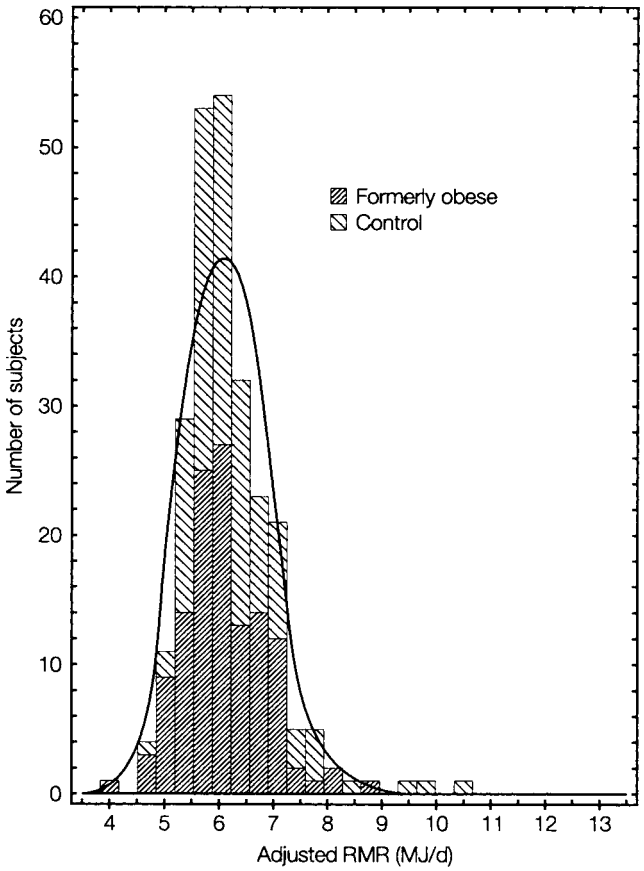

FIGURE 1. Distribution of resting metabolic rate (RMR), adjusted for fat-free mass and fat mass, in 124 formerly obese and 121 matched control subjects.

TABLE 3
Studies included in and results of the traditional meta-analysis of resting metabolic rate (RMR) in formerly obese (FO) and control (C) subjects from 12 studies[1]

Author and reference	Number of subjects (FO/C)	Value used for RMR	FFM		RMR		RMR/FFM		Difference: FO compared with C[2]
			C	FO	C	FO	C	FO	
			kg		*MJ/d*		*MJ·d^{-1}·kg^{-1}*		*%*
Jung et al, 1981 (25)	4/6	BMR	40.5[3]	46.1	4.704	4.944	0.1161	0.1072	−7.7
Shetty et al, 1981 (24)	5/5	RMR	43.3[3]	47.2	5.329	5.665	0.1231	0.1200	−2.5
Bessard et al, 1983 (18)	5/6	SMR	41.8	49.1	5.183	6.147	0.1240	0.1252	1.0
Shah et al, 1988 (7)	16/16	SMR	45.6	43.5	4.761	4.219	0.1044	0.0970	−7.1
Lean et al, 1988 (23)[4]	7/6	SMR	41.9	45.6	5.080	5.167	0.1212	0.1133	−6.5
Dulloo et al, 1989 (22)[5]	9/9	RMR	45.8	49.5	6.304	6.243	0.1376	0.1261	−8.4
Tremblay et al, 1989 (14)	9/6	RMR	60.3	60.5	6.591	7.418	0.1095	0.1230	12.3
Goldberg et al, 1991 (17)	9/9	BMR	42.4	44.5	5.815	5.867	0.1370	0.1329	−3.7
Bukkens et al, 1991 (20)	6/6	SMR	42.6	43.6	5.549	5.172	0.1310	0.1200	−8.4
de Peuter et al, 1992 (15)	8/8	RMR	44.5	47.7	5.758	5.985	0.1306	0.1245	−4.7
Amatruda et al, 1993 (16)	18/14	RMR	45.5[6]	46.8	5.611	5.516	0.1233	0.1177	−4.5
Astrup et al, 1996 (10)[7]	28/28	RMR	46.7	46.4	6.402	5.849	0.1371	0.1261	−8.0

[1] FFM, fat-free mass; BMR, basal metabolic rate; SMR, sleeping metabolic rate.
[2] In the total meta-analysis (n = 125 FO and 119 C subjects), the difference was −5.1% (95% CI: −8.6, −1.7; P = 0.008).
[3] Estimated.
[4] Raw data were not available; therefore, this study was included only in this analysis.
[5] Because of overlapping of subjects, only 1 of the 2 studies by Dulloo et al was included in this analysis.
[6] Determined by ^{40}K counting.
[7] Five studies from our group were included in the individual subject data meta-analysis (Table 1). For this meta-analysis, however, we included a single summary paper to reduce the error of the estimate.

in body size and composition were taken into account, formerly obese subjects had a 3–5% lower RMR than never-obese control subjects. In addition, a larger proportion of the formerly obese subjects had a low RMR (15.3% compared with 3.3%; $P < 0.003$), and this subgroup of formerly obese subjects could entirely account for the slightly lower mean RMR in the formerly obese group. The traditional meta-analysis and the individual subject data meta-analysis produced coherent conclusions, although the significance of the group difference was dependent on the method of adjustment for differences in body size and composition.

Most of the studies included in the 2 analyses were the same, but some differences in the strategy were planned to make the 2 approaches complementary. In some instances, measurements from some of the same formerly obese and control subjects were reported in 2 or 3 publications. Data from one publication only were included in the traditional meta-analysis, whereas one individual data set only was included in the individual subject data meta-analysis. The individual subject data meta-analysis also excluded individuals with a BMI ≥27 from studies that were included because the mean BMI of the subjects was <27. By contrast, 2 studies reported no data on body composition and could be included in the traditional meta-analysis only (24, 25), for which we estimated FFM. However, the exclusion of these 2 studies did not change the outcome of the analysis. Furthermore, we failed to collect individual data from one of the eligible studies (23), which was thus included only in the traditional meta-analysis. In these studies, relative RMR was lower in the formerly obese group than in the control subjects by 7.7% (24), 2.5% (25), and 6.5% (23), respectively. If these studies had been included in the individual subject data meta-analysis, it is likely that the outcome of the 2 meta-analyses would have been even more consistent.

Our findings may explain why the separate studies had conflicting results. No studies found a higher RMR in formerly obese subjects than in control subjects, but several studies found no significant difference in RMR between formerly obese and control subjects. These studies included ≤18 subjects in each group (Table 1), however, and therefore did not include enough subjects to detect a group difference of 3–5% or to identify a subgroup with a lower RMR. Other studies with only 6–12 subjects per group reported a significantly lower RMR in the formerly obese group, which may have been attributable to chance or to a few formerly obese subjects with a low RMR. Lack of proper adjustment for differences in body composition between formerly obese and control subjects is also a problem; eg, the previously reported 15% lower RMR of the formerly obese subjects compared with the control subjects in the study by Shah et al (7) was reduced to 7% after adjustment for differences in FFM and FM (Table 3).

Meta-analyses may also suffer from publication bias, in which positive studies showing a lower RMR in formerly obese subjects are favored because negative studies remain unpublished. We find this possibility less likely, however. Of the retrieved studies, 13 reported no significant difference between formerly obese and control subjects and only 4 reported a significantly lower RMR in formerly obese subjects (7–9, 11).

Most obese subjects fail to lose enough weight during nonsurgical treatment programs to normalize their body weight; thus, the formerly obese subjects included in the present meta-analysis may not be representative of all obese persons. Some studies suggest that obese subjects characterized by a high energy expenditure, a high fat oxidation rate, and high sympathetic activity tone are more successful at losing weight than those with corresponding low levels (29), whereas other studies found no significant difference in energy expenditure between obese patients who were successful or unsuccessful at losing weight (16). Other studies suggest that formerly obese persons who are successful at losing

weight are characterized by compliance with a low-fat, high-carbohydrate diet and regular physical activity (30). One would therefore expect that a larger proportion of the treatment-resistant obese subjects would have a low RMR in a weight-normalized state. Prospective studies are required to elucidate this hypothesis.

This meta-analysis gives no indication of the cause of the higher proportion of formerly obese subjects compared with control subjects who had a lower RMR for a given body size and composition. Two distinctly different possibilities should be considered. *1*) The low RMR is secondary to the former obese state, a product of the weight loss, or due to a negative energy balance during the measurement. *2*) The low RMR preceded the obese state and constituted a predisposing factor for weight gain and obesity in the preobese state.

First, it cannot be ruled out that being obese for some time induces by a yet unknown mechanism a sustained suppression of the RMR in some persons. Second, it is possible that weight loss produces an irreversible depression in the metabolic rate, but there is little if any evidence to support this (31). Nutritionally insufficient diets may cause excessive loss of lean body mass, but there is no indication that the formerly obese subjects in our analysis had a lower FFM than the control subjects (Table 2). Third, it is well established that energy restriction, beyond the effect on FFM and FM, suppresses the RMR (32). Several studies have shown that a reduction in energy intake below energy requirements for weight maintenance suppresses the RMR (32, 33). We carefully reviewed the descriptions of the cause of the formerly obese subjects' weight loss, antecedent body weight change, and energy balance at the time of the RMR measurement. Although not all studies provided sufficient details, most indicated that great care was taken to include only subjects who were weight stable. However, in studies in obese subjects in which changes in RMR were examined before, during, and after weight loss in response to energy restriction, the appropriate adjustment of RMR clearly showed that within the same individual, there is an adaptive reduction in RMR (34, 35). Part of this reduction may be a normal physiologic phenomenon induced by energy restriction and weight loss (33). A low relative RMR could also be a phenotype preceding the obese state and a trait that predisposes to weight gain and obesity. Rice et al (36) analyzed RMR in the Québec Family Study. After adjustment for the effect of FFM and FM, a major genetic effect was unambiguous and compelling. These authors suggested that the distribution of adjusted RMR was composed of 3 genotypes: a homozygous dominant genotype producing a subgroup with a low RMR, a heterozygous genotype producing values around and above mean values, and a homozygous recessive genotype giving rise to a small subgroup with high adjusted RMR values. In the present analysis, we found slightly more subjects with a high RMR in the control group than in the formerly obese group (12.4% compared with 8.1%), but the difference was not significant.

If a low RMR is a genetically determined trait, several recently discovered genes should be considered. Mutations and polymorphisms in the genes coding for the β_3-adrenergic receptor and uncoupling proteins may have some influence on RMR for a given body size and composition (37). The combination of some of these genotypes has been suggested to be associated with a high risk of weight gain in adult life (38). So, it is possible that the uncoupling protein and β_3-adrenergic receptor genes are determinants of RMR and are permissive factors promoting weight gain in susceptible individuals as a result of other possible additive genetic, environmental, and behavioral factors.

In conclusion, our meta-analyses showed that formerly obese persons had a 3–5% lower mean relative RMR than control subjects, and the difference could be explained by a low RMR being more frequent among the formerly obese subjects than among the control subjects. This finding may be due to a genetic effect or to an adaptive response to weight loss not associated with body composition that may increase the susceptibility of formerly obese persons to weight regain.

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