Familial influences and obesity-associated metabolic risk factors contribute to the variation in resting energy expenditure: the Kiel Obesity Prevention Study[1–3]

Anja Bosy-Westphal, Andreas Wolf, Frederike Bührens, Britta Hitze, Norbert Czech, Heiner Mönig, Oliver Selberg, Uta Settler, Maria Pfeuffer, Jürgen Schrezenmeir, Michael Krawczak, and Manfred J Müller

ABSTRACT

Background: A low metabolic rate may be inherited and predispose to obesity, whereas a higher metabolic rate in obesity may be acquired by obesity-associated cardiometabolic risk.

Objective: We aimed to explain the interindividual variation in resting energy expenditure (REE) by assessing *1*) the association between REE and body composition, thyroid hormones, and obesity-related cardiometabolic risk factors, and *2*) the familial (genetic and environmental) contribution to REE.

Design: REE and metabolic risk factors (ie, blood pressure and plasma insulin, glucose, and C-reactive protein concentrations) were assessed in 149 two- or three-generation families, including at least one overweight or obese member. Heritability of REE, respiratory quotient (RQ), thyroid hormones [thyrotropin (TSH), free triiodothyronine (FT3) and free thyroxine (FT4)], and body composition (fat-free mass and fat mass) were estimated by using variance components–based quantitative genetic models.

Results: REE adjusted for body composition, sex, and age (REEadj) significantly correlated with systolic and diastolic blood pressure, plasma insulin and glucose concentrations, and the homeostasis model assessment (HOMA) ($r = 0.14–0.31$, $P < 0.05$). Thyroid hormones had a modest influence on REE variance only. Heritability was 0.30 ± 0.07 for REEadj and 0.29 ± 0.08 for REE after additional adjustment for thyroid hormones and metabolic risk. Furthermore, heritability was estimated to be 0.22 ± 0.08 for RQ, 0.37 ± 0.08 for TSH, 0.68 ± 0.06 for FT4, and 0.69 ± 0.05 for FT3 (all significantly larger than zero).

Conclusions: Obesity-related cardiometabolic risk factors contribute to interindividual variation in REE, with hypertension and insulin resistance being associated with a higher REE. REE was moderately heritable, independent of body composition, sex, age, thyroid function, and cardiometabolic risk. *Am J Clin Nutr* 2008;87: 1695–701.

INTRODUCTION

The genetic basis of the main component of daily energy expenditure, namely resting energy expenditure (REE), and substrate utilization [respiratory quotient (RQ)—the relation of carbon dioxide production to oxygen consumption] may also predispose to obesity. Several candidate genes and chromosomal loci have been shown to be associated with metabolic rate and lipid or carbohydrate oxidation (1), but the results of most genetic epidemiologic studies in this field remain contradictory. Correlations in REE and RQ have been shown to be higher in monozygotic than in dizygotic twins (2, 3). On the basis of these findings, ≥40% of the population variance in REE (adjusted for age, sex, body mass, and body composition) was estimated to be genetic. In contrast, the significant familial component of REE (coefficient of heritability of 42%) observed in 80 pairs of mono- and dizygotic twins was entirely accounted for by body weight (4). Similarly, results from overfeeding studies do not support that the inherited susceptibility to obesity is explained by REE (5, 6).

In contrast with twin studies, family studies have consistently suggested that REE is a modestly heritable trait. After adjustment for body size, ≈11% of the observed variance of REE in Pima Indians was due to familial aggregation (7). Path analysis of ≈80 families of the Quebec Family Study has shown that the heritability of REE (adjusted for body composition, sex, and age) is ≈30% and that the heritability of the RQ is ≈20% (8). Segregation analysis of REE provided evidence for a major gene effect independent of body composition (9). In 1064 Nigerian individuals from 153 families, the heritability for REE was also estimated to be 30% after adjustment for sex, age, age^2, fat mass (FM), and fat-free mass (FFM) (10).

The results of family studies therefore suggest a genetic predisposition to obesity that results from a relatively low metabolic

[1] From the Institut für Humanernährung und Lebensmittelkunde, Christian-Albrechts-Universität, Kiel, Germany (AB-W, FB, BH, US, and MJM); the Institut für Medizinische Informatik und Statistik, Universitäts klinikum Schleswig-Holstein, Kiel, Germany (AW and MK); the Klinik für Diagnostische Radiologie, Abt Nuklearmedizin, Universitäts klinikum Schleswig-Holstein, Kiel, Germany (NC); the Klinik für Allgemeine Innere Medizin, Universitäts-klinikum Schleswig-Holstein, Kiel, Germany (HM); the Städtisches Klinikum Braunschweig, Abt Klinische Chemie, Braunschweig, Germany (OS); and the Bundesforschungsanstalt für Ernährung und Lebensmittel, Kiel, Germany (MP and JS).

[2] Supported by a grant from the Bundesministerium für Forschung und Technologie, Netzwerk Molekulare Ernährung, Nahrungsfette und Genvariabilität, Teilprojekt 6.1.2.

[3] Reprints not available. Address correspondence to MJ Müller, Institut für Humanernährung und Lebensmittelkunde, Agrar-und Ernährungswissenschaftliche Fakultät, Christian-Albrechts-Universität zu Kiel, Düsternbrooker Weg 17-19, D-24105 Kiel, Germany. E-mail: mmueller@nutrfoodsc.uni-kiel.de.

Received October 5, 2007.

Accepted for publication January 20, 2008.

rate. One explanation for the discrepant findings in twin studies may be a higher mean age of individuals in the family studies. Age-related comorbidities of obesity may contribute to a higher REE and thus may lead to an overestimation of the familial influences on REE. REE was reported to be associated with several metabolic risk factors, such as blood pressure (11), central or visceral obesity (12–14), plasma insulin concentrations, insulin resistance, or glycemia (15, 16). In addition, REE was 10% higher in subjects with the metabolic syndrome than in healthy adults (17). The thermic effect of thyroid hormones is well known, but the effects of hormonal variations in the euthyroid range remains unclear, and free thyroxine (FT4) may show a closer association with REE than free triiodothyronine (FT3) (18).

The present study set out to *1*) analyze the contribution of obesity-related metabolic risk factors to interindividual variation in REE (adjusted for body composition, sex, and age), and *2*) calculate the familial contribution to REE variance independent of metabolic risk (adjusted for body composition, sex, age, and metabolic risk) and thyroid hormone concentrations.

SUBJECTS AND METHODS

Study population and design

Between July 2003 and April 2006, 149 families were recruited through the Kiel Obesity Prevention Study (KOPS; 19, 20). The main objective of this 3-generation trial was to assess the contribution of genetic factors to obesity and the metabolic syndrome. The study comprised 815 subjects (age range: 4-84 y), including 223 grandparents (mean age: 67.4 ± 7.0 y), 296 parents (43.5 ± 6.4 y), and 296 children (13.0 ± 4.6 y). Participants were recruited through advertisements in local newspapers, through notice-board postings, and by mail contact to families who are continuously followed up in a KOPS subcohort. All participants were white northern Europeans. Inclusion criteria were at least one overweight or obese family member and the study participation of ≥2 grandparents. The study protocol was approved by the ethics committee of the Medical Faculty of the Christian-Albrechts-Universität, Kiel. All subjects provided informed written consent before participation. Parents assented for underage children.

Resting energy expenditure

Indirect calorimetry with a ventilated hood system (Vmax 29n and Vmax software, version 12-1A; SensorMedics, GmbH, Höchberg, Germany) was performed between 0730 and 0900 after an overnight fast in a metabolic ward at constant temperature and humidity. The minimum duration of measurement was 30 min. The first 10 min of each measurement were discarded. Before each measurement, flow calibration was performed with a 3L syringe, and gas analyzers were calibrated by using 2 standard gases (gas 1: 16% O_2, 4% O_2; gas 2: 20% O_2 and 0.75% CO_2). Recalibration of the gas analyzers was undertaken every 5 min during the measurements. Data were collected every 20 s, and the acquired oxygen and carbon dioxide uptake values were converted to REE (kcal/24 h) by using the abbreviated equation of Weir (21). Data from nonphysiologic measurements (RQ > 1.0 or < 0.73) were discarded and excluded from further analyses of REE and RQ (n = 92). The CV for between-day repeated measurements of REE was 5.0% (22).

Anthropometric measurements and body-composition analysis

Body weight was measured to the nearest 0.1 kg on an electronic scale coupled to the BOD-POD Body Composition System (Life Measurement Instruments, Concord, CA). Height was measured on a stadiometer to the nearest 0.5 cm. Waist circumference was measured to the nearest 0.5 cm midway between the lowest rib and the iliac crest while the subject was at minimal respiration. Air-displacement plethysmography was performed by using the BOD-POD device as described in detail elsewhere (23). The BOD-POD software was used to calculate body density as body weight divided by body volume and FM% using Siri's equation (24). Child-specific corrections of air-displacement plethysmography results were used (23). FFM (kg) was calculated accordingly as weight (kg) − FM (kg).

Overweight and obesity were determined by use of corresponding actual German BMI percentiles (>90th and >97th percentiles) for children and adolescents (25) and by World Health Organization criteria for adults (26).

Clinical and metabolic variables

Blood pressure measurements were obtained while the subject was in a seated position with a standard manual sphygmomanometer. Blood samples were taken after the subjects fasted for 8 h overnight and were analyzed following standard procedures. Briefly, plasma glucose was assayed by using a hexokinase enzymatic method. Plasma insulin was measured by radioimmunoassay (RIA), which showed no cross-reactivity with C-peptide and only 14% with proinsulin (Adaltis, Rome, Italy). The homeostasis model assessment (HOMA) was used to calculate insulin resistance (IR) as follows: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 (27). HOMA-IR was not calculated for subjects who had a fasting glucose concentration >7.0 mmol/L or were receiving insulin treatment or oral antidiabetics. Serum concentrations of thyrotropin (TSH), FT3, and FT4 were measured by RIA (DiaSorin, Dietzenbach, Germany); the intra- and interassay CVs were 2.5% and 5.7% (TSH), 4.6% and 6.5% (FT3), and 2.4% and 6.8% (FT4), respectively. The sensitivity limits were 0.02 mIU/mL (TSH), 0.35 pg/mL (FT3), and 1 pg/mL (FT4). RIA test kits from LINCO Research (St Charles, MO) using the doubly-antibody/polyethylene glycol technique were used for determination of plasma leptin and adiponectin. Analytic sensitivity and intra- and interassay CVs were 0.5 ng/mL, 3–8%, and 4–8% for leptin and 1 ng/mL, 2–6%, and 7–9% for adiponectin, respectively. C-reactive protein (CRP) was measured turbidimetrically by using a latex-agglutination test with a sensitivity of 0.1 mg/L and a between-day precision CV < 1.9% (CRP-Dynamik/-Hit917; BIOMED Labordiagnostik GmbH, Oberschleiβheim, Germany). CRP concentrations >5 mg/L were excluded from the analysis. Nonesterified fatty acids (NEFAs) were determined by an enzymatic colorimetric method (Wako NEFA test kit, NEFA C, ACS-ACOD method; Wako Chemicals GmbH, Neuss, Germany). Participants who were taking antihypertensive (14.5%; n = 118), antidiabetic (insulin or oral agents) (2.8%; n = 23), or thyroid hormone (4.8%; n = 39) drugs were excluded from the respective analysis.

Statistical analyses

Means ± SDs were used as descriptive statistics. Relations between variables were analyzed by partial correlation taking

age and family identity into account. Plasma concentrations of insulin and CRP, blood pressure, and HOMA-IR were log transformed for correlation analysis. REE was adjusted for the effects of FFM, FM, sex, and age, with covariates retained at $\alpha<0.1$ (REE adj1) in a stepwise multiple linear regression analysis. REE adj1 was further adjusted for metabolic risk factors (blood pressure, fasting plasma glucose, insulin, and HOMA-IR) and thyroid hormones (REE adj2). In this analysis, parameters for the computation of standardized residuals were obtained by applying regression models to 4 sex-by-age groups, with an age cutoff of 18 y. For each thyroid trait, we estimated the effects of sex and age (linear and quadratic). RQ was adjusted for sex-specific effects of NEFA concentrations, age, and the interaction term NEFA × age. Regression coefficients were assessed for statistical significance by using a Wald test, and a P value < 0.05 was considered statistically significant. All analyses were performed by using SPSS 13.0 for WINDOWS (SPSS Inc, Chicago, IL).

After the significant covariates were determined and their effects adjusted for, the familial contribution to the variance in each trait was estimated by using a pedigree-based likelihood approach. Univariate genetic analyses were carried out by using SOLAR (Sequential Oligogenic Linkage Analysis Routines; 23). A total of 149 families, ranging in size from 3 to 10 individuals, were included in the heritability estimation. Heritability (H^2) is defined as the proportion (V_G) of the observed phenotypic variance (V_P) of a particular trait that is attributable to genetic causes, ie, $H^2 = V_G/V_P$. In the case of FFM and FM, mean univariate $H^2 \pm$ SE were calculated from Z-transformed trait values to adjust for age and sex effects.

The variance component method used in the above calculations is based on the fact that relatives share a certain amount of genes identical-by-descent (IBD). The expected genetic variance is then specified as a function of the IBD relation between relatives while the phenotypic variance is estimated from the data. The statistical significance of the estimated heritabilities was assessed by means of a likelihood ratio test comparing the log likelihood including the estimated genetic variance to the log likelihood with the additive genetic variance component constrained to zero.

RESULTS

The descriptive characteristics of the study group, stratified by sex and generation number, are presented in **Table 1**. REE data were available for 388 females and 335 males. The selection criteria used resulted in a high prevalence of overweight (41.3%) and obesity (24.1%) and a mean BMI (in kg/m^2) of 27.7 ± 5.1 in adults. %FM, systolic and diastolic blood pressure, and FPG and CRP concentrations all increased with age, whereas RQ and FT3 tended to decrease. REE was highest in the group of parents. Plasma leptin and adiponectin concentrations were assessed in a subgroup of 347 subjects (218 adults and 129 children and adolescents). Mean plasma concentrations of leptin and adiponectin were 23.4 ± 16.3 and 16.5 ± 9.1 ng/mL in women, 7.5 ± 6.2 and 10.0 ± 5.0 ng/mL in men, 13.4 ± 9.7 and 14.6 ± 5.5 ng/mL in girls, and 6.6 ± 12.0 and 11.8 ± 4.1 ng/mL in boys, respectively.

The major determinants of REE were FFM and age, which accounted for 63% of the trait variance (R^2). Additional effects of FM and sex increased total R^2 to 70% for the full model (**Table 2**). No associations were found between REE and either leptin or adiponectin concentrations, which correlated with FM (R = 0.70, $P < 0.001$ for leptin) and with HOMA-IR for leptin (R =

TABLE 1
Characteristics of the study population, stratified by sex and generation[1]

	Grandmothers (n = 126)	Mothers (n = 135)	Daughters (n = 127)	Grandfathers (n = 69)	Fathers (n = 123)	Sons (n = 143)
Age (y)	66.7 ± 7.2[2]	42.2 ± 5.8	12.4 ± 4.1	68.8 ± 6.7	45.7 ± 6.6	13.6 ± 5.1
Height (m)	1.62 ± 0.06	1.67 ± 0.07	1.54 ± 0.17	1.74 ± 0.06	1.81 ± 0.07	1.62 ± 0.18
Weight (kg)	74.83 ± 14.64	74.28 ± 15.89	50.68 ± 19.76	83.04 ± 10.44	90.70 ± 15.09	58.87 ± 23.48
BMI (kg/m^2)	28.6 ± 5.6	26.7 ± 5.6	20.6 ± 5.3	27.4 ± 3.4	27.6 ± 4.2	21.42 ± 5.43
FFM (kg)	42.63 ± 6.08	46.91 ± 6.35	35.35 ± 11.40	58.37 ± 5.96	65.75 ± 8.64	45.40 ± 16.87
FM (%)	42.32 ± 6.31	35.58 ± 8.28	28.28 ± 9.37	29.54 ± 5.44	26.76 ± 7.19	21.52 ± 10.48
Prevalence						
Overweight (%)	40.5	32.6	20.5	58.0	48.0	20.3
Obesity (%)	31.7	23.0	29.9	17.4	23.6	25.2
TSH (mU/L)	1.39 ± 1.17	1.78 ± 1.33	2.38 ± 1.17	1.58 ± 0.90	1.43 ± 0.86	2.33 ± 1.10
FT4 (pg/mL)	16.66 ± 3.35	16.20 ± 2.97	15.48 ± 2.51	16.11 ± 3.19	16.45 ± 2.70	16.14 ± 3.08
FT3 (pg/mL)	3.53 ± 0.97	3.88 ± 1.15	4.65 ± 1.26	3.67 ± 0.96	4.09 ± 0.92	4.90 ± 1.30
Systolic BP (mm Hg)	143.4 ± 24.3	121.1 ± 14.0	109.0 ± 11.3	144.4 ± 21.4	129.1 ± 16.7	112.0 ± 10.5
Diastolic BP (mm Hg)	85.4 ± 9.1	78.8 ± 9.2	71.2 ± 8.7	85.5 ± 10.4	82.7 ± 8.8	72.2 ± 7.9
FPG (mmol/L)	5.69 ± 1.40	5.10 ± 0.87	4.83 ± 0.52	5.90 ± 1.42	5.50 ± 1.08	4.95 ± 0.43
Insulin (mU/L)	15.04 ± 10.63	11.50 ± 8.92	12.90 ± 9.25	14.78 ± 9.49	12.91 ± 9.34	11.45 ± 5.70
HOMA-IR (mU/L × mmol/L)	3.46 ± 2.11	2.56 ± 2.21	2.62 ± 1.29	3.20 ± 1.90	2.84 ± 1.48	2.53 ± 1.29
CRP (mg/L)	1.94 ± 1.28	1.41 ± 1.11	0.72 ± 0.81	1.56 ± 1.02	1.23 ± 1.06	0.64 ± 0.77
NEFA (mmol/L)	0.50 ± 0.20	0.42 ± 0.23	0.41 ± 0.21	0.45 ± 0.19	0.30 ± 0.15	0.38 ± 0.22
REE (mJ/d)	6.12 ± 1.12	6.36 ± 1.10	5.93 ± 1.10	7.17 ± 1.21	8.43 ± 1.52	7.18 ± 1.72
RQ	0.84 ± 0.07	0.85 ± 0.07	0.86 ± 0.07	0.85 ± 0.07	0.86 ± 0.07	0.87 ± 0.07

[1] FFM, fat-free mass; FM, fat mass; TSH, thyrotropin; FT4, free thyroxine; FT3, free triiodothyronine; BP, blood pressure; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; NEFA, nonessential fatty acid; REE, resting energy expenditure; RQ, respiratory quotient.

[2] $\bar{x} \pm$ SD (all such values).

TABLE 2
Regression analysis of resting energy expenditure (REE, in MJ/d), used to adjust REE for potential covariates (REEadj1)

Covariates	Regression coefficient β[1] (n = 717)	Coefficient of determination (R^2)[2]
Fat-free mass (kg)	0.0716 (<0.001)	0.58 (1.03)
Age (y)	−0.0221 (<0.001)	0.63 (0.97)
Fat mass (kg)	0.0424 (<0.001)	0.67 (0.91)
Sex[3]	0.641 (<0.001)	0.70 (0.88)
Regression intercept	2.98 (<0.001)	

[1] P values in parentheses.
[2] SEE in parentheses.
[3] Female = 0, male = 1.

0.42, $P < 0.001$) and for adiponectin ($R = -0.14$, $P < 0.05$). The correlation between REE, adjusted for body composition, age, and sex (REEadj1) and waist circumference and metabolic risk factors was analyzed across 4 sex-by-age groups to identify covariates for further adjustment of REEadj1 (= REEadj2; **Table 3**). REEadj1 was positively correlated with systolic blood pressure in adults of both sexes, whereas diastolic blood pressure was a significant determinant of REEadj1 in males only. In men, REEadj1 was also significantly correlated with $_{log}$insulin concentrations, $_{log}$HOMA-IR, and waist circumference. In addition, both groups of children showed a positive association between REEadj1 and FPG concentration that was not observed among adults. Thyroid hormones were not significantly correlated with REEadj1 in any sex-by-age group, with the exception of TSH ($R = -0.34$, $P < 0.001$) and FT4 ($R = -0.20$, $P < 0.05$) in boys. Possible covariates affecting the variance of REEadj1 were analyzed in 4 sex-by-age groups, and the results are shown in **Table 4**. Together with the interaction term age × FT4, systolic blood pressure in women and diastolic blood pressure in men were independent predictors of REE adjusted for body composition, sex, and age in adults. In underage subjects, FPG concentrations together with age × FT4 in females, and TSH concentrations in males were the main independent predictors of REEadj1. Seventy percent of the interindividual variance in REE was explained by body composition, sex, and age (Table 2). Metabolic risk factors and thyroid hormone concentrations explained between 9% and 20% (Table 4) of the residual variance in REE (= REEadj1). Thus the total variance in REE that could be explained by body composition, age, sex, thyroid hormones, and metabolic risk factors was calculated to be 70% plus 9–20% of the 30% variance unexplained by body composition, age, and sex, which resulted in a total of 73–76%.

RQ was not dependent on body composition or body size, but was significantly associated with age ($R = -0.15$, $P < 0.001$) and NEFA concentration ($R = -0.18$, $P < 0.001$). RQ showed no relation with measures of glucose metabolism or insulin resistance (FPG, $_{log}$insulin concentrations, and $_{log}$HOMA-IR). Because no difference in covariate association was observed between underage subjects and adults, the adjustment of RQ was carried out for the whole group of males and females. Stepwise multiple regression analysis identified the interaction term age × NEFA concentration as the only significant predictor of RQ, explaining 2–6% of the interindividual variation in RQ. As revealed by the significant age × NEFA interactions, RQ concentrations significantly decreased with increasing age at high NEFA (NEFA > 0.5 mmol/L; $R = -0.27$, $P = 0.001$) concentrations but not at low NEFA concentrations (NEFA ≤ 0.5 mmol/L; $R = 0.07$, $P = 0.172$).

Of the thyroid hormone traits, TSH was adjusted for age and age^2, FT4 was adjusted for age, and FT3 was adjusted for age and sex. FT4 and FT4adj were inversely associated with $_{log}$HOMA-IR or $_{log}$insulin concentrations in adults ($R = -0.15$ and -0.21; $P < 0.01$), whereas in children and adolescents there was a weak and positive correlation between FT3adj and $_{log}$HOMA-IR or $_{log}$insulin concentrations ($R = 0.13$ and 0.13, $P < 0.05$).

Univariate residual heritabilities for REE, after adjustment for body composition, age, and sex (REEadj1) and metabolic risk factors and thyroid hormone concentrations (REEadj2), are shown in **Table 5**. The heritabilities of RQ and the physiologic determinants of REE are also given. REEadj1 showed a modest heritability of 30% that was only slightly lower after additional adjustment for thyroid hormone concentrations and metabolic risk factors. The heritability of RQ was even lower, amounting to only 17% and 22% for RQ and RQadj, respectively. In contrast, the heritability of FT3 and FT4 was high and reached 68–69% for the age- and sex-adjusted traits.

DISCUSSION

Association between REE or RQ and obesity-related metabolic risk factors

There were significant associations of REE with systolic and diastolic blood pressure, FPG, insulin concentrations, and

TABLE 3
Age- and relatedness-corrected correlation coefficients between resting energy expenditure, adjusted for body composition, age and sex (REEadj1), waist circumference, and metabolic risk factors[1]

	Women	Underage females[2]	Men	Underage males[2]
Waist circumference	0.01 (254)	0.06 (122)	0.20 (0.006, 186)	0.14 (139)
logBP, systolic	0.14 (0.027, 248)	0.16 (0.079, 121)	0.19 (0.008, 186)	0.08 (136)
logBP, diastolic	0.09 (248)	0.08 (121)	0.25 (0.001, 186)	0.19 (0.028, 136)
FPG	0.12 (0.051, 251)	0.22 (0.020, 111)	0.07 (182)	0.31 (<0.001, 130)
logInsulin	0.09 (243)	0.06 (104)	0.25 (0.001; 179)	0.09 (127)
logHOMA-IR	0.06 (233)	0.10 (100)	0.21 (0.007, 165)	0.14 (126)
logCRP	0.12 (0.087, 192)	−0.11 (73)	0.10 (142)	0.03 (105)

[1] P values are provided with n values in parentheses. BP, blood pressure; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; CRP, C-reactive protein.
[2] Underage was defined as <18 y.

TABLE 4
Covariate effects on the phenotype of resting energy expenditure, adjusted for fat-free mass (FFM), fat mass (FM), sex, and age (REEadj1)[1]

Covariates	Women (n = 225)	Underage females[2] (n = 89)	Men (n = 178)	Underage males[2] (n = 108)
logBP, systolic[3]	1.925 (0.039)	NS	NS	NS
logBP, diastolic[3]	NS	NS	5.826 (<0.001)	NS
FT4[3]	NS	NS	NS	NS
Age × FT4[3]	−0.0005 (0.008)	−0.0028 (0.005)	−0.0006 (0.018)	NS
FT3	NS	NS	NS	NS
Age × FT3	NS	NS	NS	NS
TSH[3]	NS	NS	NS	−0.260 (<0.001)
Age × TSH	NS	NS	NS	NS
logHOMA-IR	NS	NS	NS	NS
FPG[3]	NS	0.271 (0.033)	NS	0.560 (0.006)
logInsulin	NS	NS	NS	NS
Regression intercept	2.31	6.13	−3.84	4.85
Coefficient of determination, R^2 [4]	0.10 (0.78)	0.13 (0.66)	0.09 (1.01)	0.20 (0.78)

[1] The results were used to derive REEadj2 for both sexes. BP, blood pressure; FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyrotropin; HOMA-IR, homeostasis model assessment of insulin resistance; FPG, fasting plasma glucose.
[2] Underage was defined as <18 y.
[3] P values are provided with n values in parentheses.
[4] SEE in parentheses.

HOMA-IR (Table 3). Our results agree with those of previous studies, showing a higher REE in type 2 diabetes (3, 7, 15, 28). Similarly, hyperglycemia and glycemic intolerance were associated with an increase in REE (16, 29, 30). REE was also positively correlated with fasting insulin concentrations in nondiabetic schizophrenia patients (31) and with insulin resistance (insulin clamp method) in both diabetic and nondiabetic patients with liver cirrhosis (32). Contradictory results were reported by De Luis et al (33), who found no association between REE and systolic blood pressure or insulin resistance in 87 obese nondiabetic patients. REE was also not found to differ between mildly hyperglycemic and diabetic obese patients (34). It is tempting to speculate that the discrepant results are explained by the possibility that the effects of insulin resistance on REE are dependent on whether insulin resistance is primarily caused by a genetic disposition or is mainly caused by obesity and a sedentary lifestyle associated with a minor genetic contribution. The former idea is supported by the finding of a lower REE (35) and an impaired mitochondrial function (36, 37) in nondiabetic relatives of patients with type 2 diabetes. A genetic predisposition to type 2 diabetes may also confer a higher risk for low REE (hypometabolism) and thus weight gain. However, longitudinal studies are needed to prove this hypothesis and to prospectively investigate the impact of low REE in relatives of patients with type 2 diabetes.

In contrast, acquired insulin resistance as a consequence of obesity may lead to a higher REE by increasing protein turnover, futile cycling, gluconeogenesis, and the activity of the sympathetic nervous system (for a review *see* 38). This agrees with the idea that an increased REE at an impaired glucose tolerance is a metabolic consequence of obesity that is directed against further weight gain (6, 39).

However, the relation between acquired insulin resistance in obesity and REE may be time-dependent. Mitochondrial degeneration has been shown to occur in obesity, independent of type 2 diabetes (40). In that study, smaller mitochondria were associated with lower insulin sensitivity. Thus, a lower REE may result from mitochondrial dysfunction induced by oxidative stress from the chronic overload of metabolic pathways, a mechanism that may also be involved in the lower REE at the acquired insulin resistance of aging (41).

Both fasting plasma insulin and free fatty acids are regarded as determinants of fat and glucose oxidation (42, 43). However, there were inverse correlations between RQ and NEFA concentrations or age only. This finding indicates an increase in fat oxidation with increasing body fat, lipolysis, or fat intake.

TABLE 5
Univariate heritabilities (H^2) of resting energy expenditure (REE), respiratory quotient (RQ), thyroid hormones, and body composition[1]

	H^2	P	n
REEadj1 (MJ/d)	0.30 ± 0.07[2]	< 0.0001	655
REEadj2 (MJ/d)	0.29 ± 0.08	0.0001	594
RQ	0.17 ± 0.07	0.0065	613
RQadj	0.22 ± 0.08	0.0018	552
TSH	0.27 ± 0.08	0.0003	679
TSH adj	0.37 ± 0.08	< 0.0001	679
FT3	0.62 ± 0.06	< 0.0001	681
FT3 adj	0.69 ± 0.05	< 0.0001	681
FT4	0.66 ± 0.06	< 0.0001	681
FT4 adj	0.68 ± 0.06	< 0.0001	681
FFM (kg)	0.33 ± 0.06	< 0.0001	737
FM (kg)	0.53 ± 0.06	< 0.0001	737

[1] The familial contribution to the variance in each trait was estimated by using a pedigree-based likelihood approach. Univariate genetic analyses were carried out by using SOLAR software (23). TSH, thyrotropin; FT3, free triiodothyronine; FT4, free thyroxine; FFM, fat-free mass; FM, fat mass.
[2] $\bar{x}$ ± SD (all such values).

Heritability of REE and RQ

We estimated the heritability of REE to be ≈30% (Table 5). The familial (genetic and environmental) contribution to REE was only slightly lower after adjustment for blood pressure and

FPG concentrations and was therefore independent of obesity-associated metabolic risk factors.

The impact of inherited reduction in metabolic rate on weight gain and, thus, obesity has been questioned by a number of publications but was confirmed by other authors (for a review *see* 44). One possible explanation of discrepant results is that a considerable weight gain over time results only from a small daily surplus of calories. Because of methodologic limitations, the origin of a few calories of positive energy balance cannot be sufficiently detected by current measurement methods of energy intake (eg, dietary records) or of energy expenditure (eg, 24-h heart rate monitoring). Genetic research offers yet another perspective to the subject. Thus far, all monogenetic causes of obesity have been found to be associated with increased appetite and food intake but with nearly unchanged energy expenditure. These findings render energy expenditure unimportant but favor excess energy intake as the main cause of weight gain. However, the heritability of REE, the main component of daily energy expenditure, was ≈30% in our studies and other family studies (10, 8). This implies that the interaction between genes and the environment (eg, adherence to a healthy lifestyle or addiction to an obese environment) determines the phenotype. The finding of a similarly specific metabolic rate in obese and lean subjects (45–47) at first sight contradicts the idea that a low REE is a main cause of obesity. One reason for the undetected association between low REE and obesity may be that obesity-related metabolic risk factors mask the lower metabolic rate that initially contributed to weight gain.

One limitation of our study was that our heritability estimates do not allow differentiation between shared environmental (household) effects and genotype × environment interactions. Such effects can mimic additive genetic effects and, if existent, would thus be included in our estimates of H^2.

The heritability estimate for RQ was 0.17 and increased by 5% after adjustment for variance arising from age and NEFA concentrations (Table 5). Our data thus confirm data from the Quebec Family Study, which showed the heritability of RQ to be ≈20% (8). In our study, the highest heritability estimates were obtained for thyroid hormones (Table 5). Considering the associations between FT4 and HOMA-IR in adults and between FT3 and HOMA-IR in children and adolescents and a heritability estimate of 0.39 ± 0.12 for HOMA-IR that was previously published from the KOPS Family Study (20), there might be a small contribution of shared familial (genetic and environmental) variance between these 2 traits.

In conclusion, obesity-related cardiometabolic risk factors contribute to interindividual variation in REE, with hypertension and insulin resistance being associated with a higher REE. Our findings provide further evidence that REE and RQ are moderately heritable, independent of body composition, sex, age, thyroid function, and cardiometabolic risk.

The authors' responsibilities were as follows—AB-W and MJM: study design; AB-W, FB, and BH: data collection; AB-W, HM, NC, US, MP, JS, AW, and OS: data analysis; AB-W, MK, and MJM: discussion of data; AB-W, AW, and MK: statistics; and AB-W and MJM: writing of the manuscript. There are no conflicts of interest.

REFERENCES

1. Raikinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: the 2005 update. Obesity 2006;14:529–644.
2. Bouchard C, Trembley A, Nadeau A, et al. Genetic effect in resting and exercise metabolic rates. Metabolism 1989;38:364–70.
3. Fontvieille AM, Lillioja S, Ferraro RT, Ravussin E. Twenty four hour energy expenditure in Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1992;354:753–9.
4. Hewitt JK, Stunkard AJ, Carroll D, Sims J, Turner JR. A twin study approach towards understanding genetic contributions to body size and metabolic rate. Acta Genet Med Gemellol 1991;40:133–7.
5. Deriaz O, Fournier G, Tremblay A, Despres JP, Bouchard C. Lean body mass composition and resting energy expenditure before and after long-term overfeeding. Am J Clin Nutr 1992;56:840–7.
6. Trembley A. Is the insulin resistance syndrome the price to be paid to achieve body weight stability? Int J Obes Relat Metab Disord 2005;29: 1295–8.
7. Bogardus C, Lillioja S, Ravussin E, et al. Familial dependence of the resting metabolic rate. N Engl J Med 1986;315:96–100.
8. Bouchard C, Deriaz O, Perusse L, Tremblay A. Genetics of energy expenditure in humans. In: Bouchard C, ed. The genetics of obesity. Boca Raton, FL: CRC Press, 1994:135–46.
9. Rice T, Trembley A, Deriaz O, Perusse L, Rao DC, Bouchard C. Genetic Pleiotropy for resting metabolic rate with fat-free mass and fat mass: The Quebec Family Study. Obes Res 1996;4:125–31.
10. Wu X, Luke A, Cooper RS, et al. A genome scan among Nigerians linking resting energy expenditure to chromosome 16. Obes Res 2004; 12:577–81.
11. Luke A, Adeyemo A, Kramer H, Forrester T, Cooper RS. Association between blood pressure and resting energy expenditure independent of body size. Hypertension 2004;43:555–60.
12. Armellini F, Zamboni M, Mino A, Bissoli L, Micciolo R, Bosello O. Postabsorptive resting metabolic rate and thermic effect of food in relation to body composition and adipose tissue distribution. Metabolism 2000;49:6–10.
13. Dionne I, Desperes J-P, Bouchard C, Trembley A. Gender differences in the effect of body composition on energy metabolism. Int J Obes Relat Metab Disord 1999;23:312–9.
14. Lührmann PM, Herbert BM, Neuhäuser-Berthold M. Effects of fat mass and body fat distribution on resting metabolic rate in the elderly. Metabolism 2001;50:972–5.
15. Weyer C, Snitker S, Rising R, Bogardus C, Ravussin E. Determinants of energy expenditure and fuel utilization in man: effects of body composition, age, sex ethnicity and glucose tolerance in 916 subjects. Int J Obes Relat Metab Disord 1999B;23:715–22.
16. Gougeon R, Lamarche M, Yale JF, Venuta T. The prediction of resting energy expenditure in type 2 diabetes mellitus is improved by factoring for glycemia. Int J Obes Relat Metab Disord 2002;26:1547–52.
17. Jacobsen P, Rankinen T, Trembley A, Perusse L, Chagnon YC, Bouchard C. Resting metabolic rate and respiratory quotient: results from a genome-wide scan in the Quebec Family Study. Am J Clin Nutr 2006; 84:1527–33.
18. Johnstone AM, Murison SD, Duncan JS, Rance KA, Speakman JR. Factors influencing variation in basal metabolic rate include fat-free mass, fat mass, age, and circulating thyroxine but not sex, circulating leptin, or triiodothyronine. Am J Clin Nutr 2005;82:941–8.
19. Danielzik S, Czerwinski-Mast M, Langnäse K, Dilba B, Müller MJ. Parental overweight, socioeconomic status and high birth weight are the major determinants of overweight and obesity in 5–7-y-old children: baseline data of the Kiel Obesity Prevention Study (KOPS). Int J Obes Relat Metab Disord 2004;28:1494–502.
20. Bosy-Westphal A, Onur S, Geisler C, et al. Common familial influences on clustering of metabolic syndrome traits with central obesity and insulin resistance: the Kiel Obesity Prevention Study. Int J Obes Relat Metab Disord 2007;31(5):784–90.
21. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949;109:1–9.
22. Bader N, Bosy-Westphal A, Dilba B, Müller MJ. Intra- and interindividual variability of resting energy expenditure in healthy male subjects—biological and methodological variability of resting energy expenditure. Br J Nutr 2005;94:843–9.
23. Bosy-Westphal A, Danielzik S, Becker C, et al. There is need for optimal body composition data analysis using air-displacement plethysmography in children and adolescents. J Nutr 2005;135:2257–62. (Published erratum appears in J Nutr 2006;136:711.)
24. Siri WE. Body composition from fluid spaces and density: analysis of methods. In: Brozek J, Henschel A, eds. Techniques for measuring body

composition. Washington, DC: National Academy of Sciences, 1961: 223–44.
25. Kromeyer-Hauschild K, Wabitsch M, Kunze D, et al. Perzentile für den Body-Mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher. (Percentiles for body mass index in children and adolescents from German samples.) Stichproben Monatsschr Kinderheilkd 2001;149:807–18.
26. WHO. Obesity: preventing and managing the global epidemic. World Health Organ Tech Rep Ser 2000;894.
27. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
28. Bitz C, Toubro S, Larsen TM, et al. Increased 24h-energy expenditure in type 2 diabetes. Diabetes Care 2004;27:2416–21.
29. Huang KC, Kormas N, Steinbeck K, Loughnan G, Caterson ID. Resting metabolic rate in severely obese diabetic and non-diabetic subjects. Obes Res 2004;12:840–5.
30. Martin K, Rust PF, Wallace P, Gravey WT. Estimation of resting energy expenditure considering effects of race and diabetes status. Diabetes Care 2004;27:1405–11.
31. Fan X, Anderson EJ, Copeland PM, et al. Higher fasting serum insulin is associated with increased resting energy expenditure in nondiabetic schizophrenia patients. Biol Psychiatry 2006;60:1372–7.
32. Perseghin G, Mazzaferro V, Benedini S, et al. Resting energy expenditure in diabetic and nondiabetic patients with liver cirrhosis: relation with insulin sensitivity and effect of liver transplantation and immunosuppressive therapy. Am J Clin Nutr 2002;76:541–8.
33. De Luis DA, Aller R, Izaola O, Gonzalez Sagrado M, Conde R. Resting energy expenditure, cardiovascular risk factors and insulin resistance in obese patients. Ann Nutr Metab 2005;49:381–5.
34. Ryan M, Salle A, Guilloteau G, Genaitay M, Livingstone MB, Ritz P. Resting energy expenditure is not increased in mildly hyperglycaemic patients. Br J Nutr 2006;96:945–8.
35. De Pergola G, Pannacciulli N, Minenna A, Martina RA, Cannito F, Giorgino R. Fuel metabolism in adult individuals with a wide range of body mass index: effect of a family history of type 2 diabetes. Diabetes Nutr Metab 2003;16:41–7.
36. Patti ME, Butte AJ, Crunkhorn S, et al. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. Proc Natl Acad Sci U S A 2003;8: 8466–71.
37. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type II diabetes. N Engl J Med 2004;350:664–71.
38. Weyer C, Bogardus C, Pratley RE. Metabolic factors contributing to increased resting metabolic rate and decreased insulin-induced thermogenesis during the development of type 2 diabetes. Diabetes 1999A;48: 1607–14.
39. Pannacciulli N, Bunt JC, Ortega E, et al. Lower total fasting plasma adiponectin concentrations are associated with higher metabolic rates. J Clin Endocrinol Metab 2006;91:1600–3.
40. Kelley DE, He J, Menshikova EV, Ritov V. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes 2002;51:2944–50.
41. Petersen KF, Befroy D, Dufour S, et al. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science 2003;300:1140–2.
42. Astrup A, Buemann B, Christensen NJ, et al. The contribution of body composition, substrates, and hormones to the variability in energy expenditure and substrate utilization in premenopausal women. J Clin Endocrinol Metab 1992;74:279–86.
43. Toubro S, Soerensen TI, Hindsberger C, Christensen NL, Astrup A. Twenty-four-hour respiratory quotient: the role of diet and familial resemblance. J Clin Endocrinol Metab 1998;83(8):2758–64.
44. Astrup A, Gotzsche PC, van de Werken K, et al. Meta-analysis of resting metabolic rate in formerly obese subjects. Am J Clin Nutr 1999;69: 1117–22.
45. Prentice AM, Black AE, Coward WA, et al. High levels of energy expenditure in obese women. BMJ 1986;292:983–7.
46. Das SK, Saltzman E, McCrory MA, et al. Energy expenditure is very high in extremely obese women. J Nutr 2004;134(6):1412–6.
47. Müller MJ, Bosy-Westphal A, Klaus S, et al. World Health Organization equations have shortcomings for predicting resting energy expenditure in persons from a modern, affluent population: generation of a new reference standard from a retrospective analysis of a German database of resting energy expenditure. Am J Clin Nutr 2004;80:1379–90.