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Metabolic and Behavioral Characteristics of Metabolically Obese but Normal-Weight Women

FLORENCE CONUS, DAVID B. ALLISON, RÉMI RABASA-LHORET, MAXIME ST-ONGE, DAVID H. ST-PIERRE, ANDRÉANNE TREMBLAY-LEBEAU, AND ERIC T. POEHLMAN

Unité Metabolique (F.C., R.R.-L., M.S.-O., D.H.S.-P., A.T.-L.), Département de Nutrition, Faculté de Médecine, Université de Montréal, Montréal, Québec H3T 1A8, Canada; Department of Biostatistics (D.B.A.), Section on Statistical Genetics and Clinical Nutrition Research Center, University of Alabama at Birmingham, Birmingham, Alabama 35294; and Scriptus Medicus (E.T.P.), Montréal, Québec H2L 3R8, Canada

A unique subset of individuals termed metabolically obese but normal weight (MONW) has been identified. These young women are potentially at increased risk for development of the metabolic syndrome despite their young age and normal body mass index. We seek to determine metabolic and behavioral factors that could potentially distinguish MONW women from young women with a normal metabolic profile.

Ninety-six women were classified as MONW (n = 12) or non-MONW (n = 84) based on a cut point of insulin sensitivity (as estimated by the homeostasis model assessment). Potentially distinguishing phenotypes between groups measured included serum lipids, ghrelin, leptin, adiponectin, body composition and body fat distribution, resting and physical activity energy expenditure, peak oxygen uptake, dietary intake, dietary behavior, and family history and lifestyle variables.

Despite a similar body mass index between groups, MONW women showed higher percent body fat, lower fat-free mass, lower physical activity energy expenditure, and lower peak oxygen uptake than non-MONW women. Plasma cholesterol level was higher in MONW women, whereas no differences were noted for other blood lipids, ghrelin, leptin, adiponectin, and resting energy expenditure. MONW women had lower dietary restraint scores than non-MONW women, but no differences were noted in disinhibition, hunger, and dietary intake. Stepwise regression analysis performed on all subjects showed that 33.5% of the unique variance of the homeostasis model assessment was explained with the variables of percentage of body fat (17.1%), level of dietary restraint (10.4%), and age (6%).

Both metabolic and dietary behavioral variables contribute to the deleterious metabolic profile of MONW women. They display lower insulin sensitivity due potentially to a cluster of sedentary behavior patterns that contribute to their higher adiposity. Furthermore, cognitive attitudes toward food (*i.e.* dietary restraint) and concomitant lifestyle behaviors may play a role in regulating insulin sensitivity in MONW women. (*J Clin Endocrinol Metab* 89: 5013–5020, 2004)

OBESITY AND ITS impact on associated comorbidities is a major public health problem in Canada and other industrialized societies (1–3). Despite the recognition of this complex disorder and its impact on the national public health care system, primary and secondary prevention efforts have failed to offset the obesity epidemic (4). It is well recognized that primary prevention efforts directed at mitigating undesirable weight gain and its attendant effects on metabolic syndrome phenotypes are an important public health goal. Thus, the potential identification and eventual treatment of individuals who are susceptible or at risk for the development of the metabolic syndrome should be considered as a step in primary prevention treatment efforts.

A unique subset of individuals termed metabolically obese but normal weight (MONW) has previously been identified (5). These individuals, despite having a normal body mass index (BMI, kg/m^2), display metabolic characteristics that may predispose them to the development of the metabolic syndrome. Despite the clinical recognition of MONW, there exists uncertainty as to the constellation of metabolic, behavioral, and lifestyle phenotypes that characterize these at-risk individuals. Some investigators have suggested, for example, that MONW individuals display several risky phenotypes including reduced insulin sensitivity, greater total fat and central body fat (6–8), and reduced aerobic fitness and physical activity energy expenditure (8, 9) compared with non-MONW individuals. This line of research takes on added importance because MONW individuals are frequently undetected and undiagnosed because of their normal BMI and young age. To address this issue, we attempted to identify the metabolic, behavioral, and lifestyle phenotypes that could distinguish a cohort of MONW *vs.* non-MONW young women.

Abbreviations: BMI, Body mass index; DXA, dual-energy x-ray absorptiometry; HDL, high-density lipoprotein; HOMA, homeostasis model of assessment; LDL, low-density lipoprotein; MONW, metabolically obese but normal weight; RMR, resting metabolic rate; RT3, triaxial accelerometer; $VO_{2\ peak}$, peak oxygen uptake.

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Subjects and Methods

Subjects

One hundred four normal-weight young women were recruited to participate in this study. Subjects were recruited by announcements in the University of Montreal area (Montreal, Québec, Canada). Eight subjects had missing blood samples, so statistical analyses were conducted on 96 subjects. The ethnic make-up consisted of 85 European-American women, six Arabian women, three African-American women, one Amerindian woman, and one Asiatic woman. The inclusion criteria for participation were female sex and age 18–35 yr. Exclusion criteria for participation were acute illness, diagnosis of eating disorders, diagnosis

of diabetes, hypertension, or dyslipidemia. Forty-six women (47.9%) in the cohort used oral contraceptives. Five women (5.2%) had amenorrhea. Two women were smokers. They were instructed not to smoke 24 h before testing.

Overview of protocol

The study was approved by the University of Montreal Ethics Committee. After reading and signing the consent form, women participated in a testing sequence as shown in Fig. 1. Each participant was invited to the Unité Métabolique for a comprehensive series of tests. Subjects arrived in the fasting state at 0800 h at the Unité Métabolique. A blood draw was performed for determination of a fasting lipid profile and analyses of insulin, glucose, leptin, adiponectin, and ghrelin. Thereafter, resting metabolic rate and the thermic effect of food were measured. Subjects were served a light lunch, after which body composition and anthropometric measurements were performed. A test for peak oxygen uptake ($VO_{2\ peak}$) was completed in the afternoon, after which dietary, lifestyle, and physical activity questionnaires were administered. Thereafter, the use of an accelerometer to measure physical activity was explained to the subjects, and they left with this device.

Blood samples

Blood samples were collected and measured after an overnight fast (12 h) for plasma concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose and insulin, leptin, adiponectin, and ghrelin. Venous fresh blood samples were collected from the elbow fold in vacuum tubes containing inert gel (Becton Dickinson, Fisher Scientific, Nepean, Ontario, Canada). Plasma was obtained by centrifugation at 1500 rpm for 10 min and analyzed on the day of collection. Analyses were done on the COBAS INTEGRA 400 (Roche Diagnostic, Montreal, Québec, Canada) analyzer for total cholesterol, HDL cholesterol, triglycerides, and glucose combined with specific cassettes containing *in vitro* diagnostic reagent system. Total cholesterol, HDL cholesterol, and triglycerides were used in the following Friedewald formula (10) to estimate LDL cholesterol concentration: LDL cholesterol (mmol/liter) = total cholesterol (mmol/liter) − HDL cholesterol (mmol/liter) − (triglycerides/2.181 [mmol/liter]). Insulin level was determined by electrochemiluminescence "ECLIA" adapted for Elecsys 1010 analyzer, with the Insulin Elecsys (Ref. 12017547) kit (Elecsys Corporation, Lenexa, KS). Homeostasis model assessment (HOMA) was calculated according to the following formula of Matthews *et al.* (11): HOMA = [fasting insulin (μU/ml) × fasting glucose (mmol/liter)]/22.5. Plasma immunoreactive total ghrelin (Phoenix Pharmaceuticals, Belmont, CA), adiponectin, and leptin (Linco Research, St. Charles, MO) levels were measured in duplicate with a commercial RIA procedure using ^{125}I-labeled bioactive human ghrelin, adiponectin, or leptin as a tracer and a rabbit polyclonal antibody raised against full-length peptides.

Resting metabolic rate (RMR)

RMR was measured after a 12-h fast by indirect calorimetry. Concentrations of CO_2 and O_2 were measured using the ventilated hood technique with a SensorMedics Delta Track II (Datex-Ohmeda, Helsinki, Finland). Measurement of gas concentrations were then used to determine 24-h RMR using Weir's equation (12). Subjects were instructed to fast and drink only water for 12 h before testing, consume no alcohol and refrain from smoking for 24 h before testing, refrain from physical activity for 24 h before testing, and keep physical activity to a minimum the morning of the test. Women were tested in the follicular phase of the menstrual cycle. Measurements were performed while subjects were lying in a supine position, without speaking or sleeping and with minimal movement. Measurements were performed during 40 min; the first 10 min were considered as an acclimatization period, and the last 30 min were used for analyses. The temperature of the room was maintained at an average of 22 C. The gas analyzers were calibrated before every measurement for pressure and gas concentrations. The intraclass correlation for RMR, which was determined using test-retest condition in 19 volunteers, was 0.921 in our laboratory.

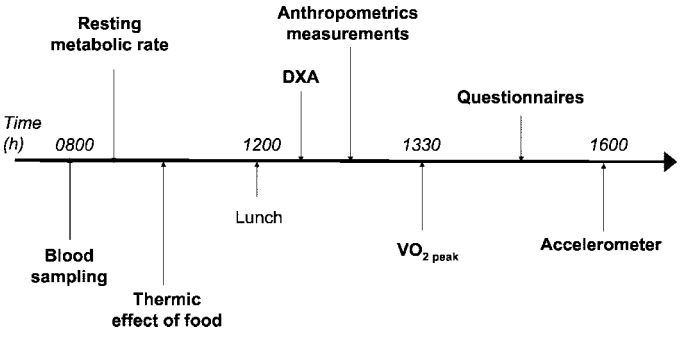

FIG. 1. Overview of testing sequence.

Thermic effect of food

Thermic effect of food was measured during 135 min after ingestion of 10 kcal/kg of body weight (42 kJ/kg) of ENSURE PLUS [Abbott Laboratories, Ville St-Laurent, Québec, Canada; 1.5 kcal/ml (6.3 kJ/ml), 61% carbohydrates, 24% lipids, 15% proteins]. Subjects were allowed to watch movies but were instructed to remain supine with minimal movement. The thermic effect of food was calculated as the difference between the energy expenditure after a meal minus RMR. The gas analyzer was calibrated every 45 min for pressure and gas concentrations. Oral temperature was taken before RMR and during thermic effect of food measurements.

Body composition and anthropometric measurements

Body weight (kg) was measured using an electronic scale (Balance Industrielles Montréal Inc., Montreal, Québec, Canada) to the nearest 20 g, and standing height was measured using a wall stadiometer (Perspective Enterprises, Portage, MI) to the nearest 0.1 cm. Subjects were instructed to take off their shoes before performing these measurements. Both measurements were performed following standard techniques. BMI was calculated as body weight (kg)/height (m^2). Fat-free mass, fat mass, percent total body fat mass, central and peripheral fat mass, bone mass, and bone density were evaluated by dual-energy x-ray absorptiometry (DXA) using a LUNAR, Prodigy system, version 6.10.019 (General Electric Lunar Corporation, Madison, WI). The DXA was calibrated daily using a known calibration standard. In test-retest analyses, the intraclass correlations in 18 subjects were 0.999 for fat mass and 0.998 for fat-free mass. Three circumferences were measured (waist, hip, and thigh). Circumferences were measured with a flexible steel metric tape at the nearest 0.5 cm. Anthropometric measurements were performed according to the standardized guidelines of Norton and Olds (13).

Aerobic capacity ($VO_{2\ peak}$)

Aerobic capacity was assessed on an ergocycle Ergoline 900 (Ergoline, Bitz, Germany), with an Ergocard (Medi Soft, Dinant, Belguim) cardiopulmonary exercise test station. The system was calibrated before every measurement for barometric pressure, relative humidity, and gas concentrations with primary standard gasses. Gas volumes were calibrated using a 2-liter syringe. Aerobic capacity was tested by a progressive test starting at 60 W with an augmentation of 40 W every 3 min. Subjects were asked to maintain a constant speed, and the level of resistance on the wheel was adjusted to preserve a constant power output. O_2 and CO_2 were measured by a direct system using a face mask. $VO_{2\ peak}$ was achieved when the power output could no longer be maintained. Heart rate was monitored during all tests using a POLAR heart rate monitor S610 (Polar Electro Oy, Kempele, Finland). $VO_{2\ peak}$ was defined as the highest 30-sec average of oxygen consumption. A test-retest reliability trial (n = 19) for VO_2 (liter/min) was performed on a sample of young men and women before data collection and yielded an intraclass correlation coefficient of 0.956.

Leisure time physical activity

Energy expenditure in leisure time physical activity was evaluated by the Minnesota Leisure-Time Physical Activity Questionnaire (14). This questionnaire consists of a list of 63 sporting, recreational, yard, and

household activities. The participants were instructed to report whether or not they performed the activity in the last 12 months. The interviewer then asked the volunteer for the period, frequency, and duration of every activity performed. Calculations of energy expenditure were based on the Compendium of Physical Activities Tracking Guide, 2000 (15).

Energy intake

A 24-h dietary recall was used for evaluation of total daily energy intake. The recall was directed by a trained dietician. Portion sizes were evaluated using models of food serving sizes. Energy, protein, lipid, and carbohydrate intake was calculated based on the corrected 2001b Canadian Nutrient File (16). Food quotient was calculated using the following equations: 1) O_2 consumption (liter/d) = (0.966 × protein intake) + (2.019 × fat intake) + (0.829 × carbohydrate intake); 2) CO_2 production (liter/d) = (0.744 × protein intake) + (1.427 × fat intake) + (0.829 × carbohydrate intake), where the intake of protein, fat, and carbohydrate is expressed in grams per day; and 3) food quotient = VCO_2/VO_2 (17).

Eating behavior

Eating behavior was assessed by the self-administrated Three-Factor Eating Questionnaire of Stunkard and Messick (18). This 51-item questionnaire measures three dimensions of human eating behavior. The first factor measures cognitive restrained eating (dietary restraint), which is the perception that one regularly and intentionally eats less than one desires. The second factor represents tendency toward disinhibition: an incidental inability to resist eating cues, inhibition of dietary restraint, and emotional eating. The third factor examines the subjective feeling of general hunger. Every dimension is represented by a score obtained by the sum of points of each item (0 or 1). The Three-Factor Eating Questionnaire has been validated as one accurate measure of cognitive concomitants of eating behavior (18, 19).

Triaxial accelerometer (RT3)

Subjects were asked to wear the RT3 (Stayhealthy, Monrovia, CA) to estimate daily energy expenditure. The RT3 was worn on the right hip of the subject for two weekdays and one weekend day. The RT3 measures acceleration in the anterior-posterior (x), mediolateral (y), and vertical (z) axis and summarizes that information as a vector magnitude. The vector was calculated as the square root of the sum of the squared accelerations for each direction. Activity counts are given for each direction. Thereafter, activity calories per minute were calculated with the following formula: [(activity counts/10) × (body weight × 1.692)]/10,000. The frequency response for the measurement of acceleration was 1 Hz, and data were recorded every minute.

Statistical analyses

Statistical analyses were performed via SPSS for Windows (version 11.0.1; SPSS Inc., Chicago, IL) on an IBM PC compatible computer (IBM, White Plains, NY). Data are presented as means ± SD. Subjects were divided into two groups, MONW and non-MONW. MONW women were categorized by HOMA, which was obtained from the article of Dvorak *et al.* (8) (HOMA > 1.69 for MONW individuals). Levene's test (20) was used to test for equality of variances. Welch's correction was applied if variances were significantly different between groups (21). Unpaired *t* tests were performed to analyze mean differences between two groups. A χ^2 test was performed to analyze differences in reported frequencies of family history of type 2 diabetes, coronary heart disease, dyslipidemia, hypertension, and obesity between MONW and non-MONW women. Pearson correlations were performed to examine the relation between insulin sensitivity and body composition, physical energy expenditure, hormonal levels, and dietary behavior. A linear regression model with stepwise selection determined which variables explained unique variance in HOMA values. Based on exploratory analyses and using biologically plausible hypotheses, independent variables considered in the final model were age, weight, percentage of fat mass, fat-free mass, $VO_{2\ peak}$, physical activity energy expenditure, and dietary restraint. Linear regression models with backward and forward methods were performed to confirm the results of the stepwise method. Analysis of covariance was used to examine differences in groups after RMR was adjusted for fat-free mass and fat mass and after HOMA was adjusted for percentage of fat mass. Homogeneity of slopes and variances was tested and found to be met. $P < 0.05$ was considered statistically significant.

Results

MONW and non-MONW women were classified based on a cut point of HOMA (HOMA > 1.69 for MONW individuals). Based on this criterion, 12 women were classified as MONW, and 84 were classified as non-MONW. Table 1 shows fasting glucose and insulin and insulin sensitivity. By design, MONW women showed a higher HOMA index than non-MONW women ($P < 0.001$), a higher fasting insulin level ($P < 0.001$), and a higher glucose level ($P < 0.043$).

The two smokers and the five women with amenorrhea were in the group of non-MONW women. Women on oral contraceptives were proportionally distributed between the groups; six MONW women (50%) and 40 non-MONW women (47.6%) took oral contraceptives. These proportions were not statistically different ($P = 0.877$).

Subject characteristics

Table 2 shows subject characteristics. Groups were similar with respect to age, body weight, standing height, BMI, birth weight, bone mass, and supine blood pressure. Women classified as MONW, however, had a higher percentage of fat mass ($P < 0.001$), more peripheral fat mass ($P = 0.025$), and less fat-free mass ($P = 0.002$) than non-MONW women. We found no differences between groups for the nine measured skinfold or for the waist, hip, and thigh circumferences (results not shown). Additionally, no statistically significant differences between groups were noted in family history of type 2 diabetes, coronary heart disease, dyslipidemia, hypertension, or obesity.

Blood lipid variables and hormones

Table 3 shows fasting lipids and hormones. Total cholesterol was higher in MONW compared with non-MONW women ($P = 0.023$). No statistically significant differences between groups were found for HDL cholesterol, LDL cholesterol, total cholesterol/HDL cholesterol, fasting triglycerides, ghrelin, leptin, and adiponectin.

TABLE 1. Insulin sensitivity parameters in MONW and non-MONW women

	MONW (n = 12)	Non-MONW (n = 84)	
	Mean ± SD	Mean ± SD	*P*
Glucose (mmol/liter)	4.87 ± 0.28	4.65 ± 0.35	
Insulin (pmol/liter)	70.32 ± 13.75	30.59 ± 12.10	
HOMA	2.19 ± 0.47	0.91 ± 0.38	
HOMA adjusted for % of FM	2.10 ± 0.12	0.93 ± 0.04	<0.001[a]

FM, Fat mass as measured by DXA.

Women were classified as MONW based on a cut point of HOMA (>1.69 for MONW) (8).

Statistics for glucose, insulin, and HOMA are not presented because they are selection criteria for the MONW and non-MONW groups.

[a] Significantly different between MONW and non-MONW women.

TABLE 2. Subject characteristics of MONW and non-MONW women

	MONW (n = 12)	Non-MONW (n = 84)	
	Mean ± SD	Mean ± SD	*P*
Age (yr)	22.5 ± 3.8	23.5 ± 3.7	0.365
Height (m)	1.66 ± 0.07	1.65 ± 0.06	0.603
Weight (kg)	60.19 ± 11.62	59.19 ± 7.84	0.698
Birth weight (kg) (n = 11/63)	3.126 ± 0.417	3.153 ± 0.562	0.887
BMI (kg/m^2)	21.9 ± 3.4	21.8 ± 2.5	0.915
FFM (kg)	37.65 ± 3.19	41.66 ± 4.11	0.002[a]
FM (kg)	20.16 ± 9.42	15.12 ± 5.14	0.095
Central fat mass (kg)	7.85 ± 4.98	5.19 ± 2.27	0.094
Peripheral fat mass (kg)	11.61 ± 4.34	9.38 ± 2.97	0.025[a]
Bone mass (kg)	2.35 ± 0.36	2.40 ± 0.34	0.620
FFM (%)	63.77 ± 7.95	70.89 ± 5.62	<0.001[a]
FM (%)	32.24 ± 8.16	25.04 ± 5.84	<0.001[a]
Bone mass (%)	3.94 ± 0.43	4.07 ± 0.40	0.292
Systolic blood pressure (mm Hg)	108 ± 11	106 ± 10	0.418
Diastolic blood pressure (mm Hg)	67 ± 9	67 ± 10	0.892
Family history of type 2 diabetes (%)	41.7	23.8	0.187

FFM, Fat-free mass; FM, fat mass as measured by DXA.
[a] Significantly different between MONW and non-MONW women.

TABLE 3. Blood lipids parameters in MONW and non-MONW women

	MONW (n = 12)	Non-MONW (n = 84)	
	Mean ± SD	Mean ± SD	*P*
Total cholesterol (mmol/liter)	5.081 ± 1.372	4.394 ± 0.897	0.023[a]
HDL cholesterol (mmol/liter)	1.688 ± 0.429	1.679 ± 0.398	0.939
LDL cholesterol (mmol/liter)	3.003 ± 1.564	2.339 ± 0.752	0.175
Total cholesterol/ HDL cholesterol	3.254 ± 1.623	2.715 ± 0.676	0.279
Triglycerides (mmol/ liter)	0.851 ± 0.347	0.819 ± 0.322	0.748
Leptin (ng/ml) (n = 9/66)	10.76 ± 6.05	8.11 ± 4.68	0.129
Ghrelin (pg/ml) (n = 10/68)	641.80 ± 246.24	777.35 ± 257.440	0.122
Adiponectin (μg/ml) (n = 9/63)	9.18 ± 3.31	10.70 ± 5.54	0.425

[a] Significantly different between MONW and non-MONW women.

Energy expenditure

Table 4 shows the components of daily energy expenditure. We found no differences between groups in RMR (absolute or adjusted rates), fasting respiratory quotient, thermic effect of food, and postprandial respiratory quotient. We did find lower leisure time physical activity levels (measured by questionnaire) in the MONW women compared with non-MONW women ($P < 0.001$) and a lower relative $VO_{2\,peak}$ ($P < 0.001$). No significant difference between groups was observed for daily energy expenditure measured by accelerometer (RT3). Additionally, time spent watching television was greater for MONW women than non-MONW women ($P = 0.029$).

TABLE 4. Energy expenditure in MONW qnd non-MONW women

	MONW (n = 12)	Non-MONW (n = 84)	
	Mean ± SD	Mean ± SD	*P*
RMR (kJ/24 h)	5216 ± 653	5100 ± 705	0.591
RMR adjusted for FFM and FM (kJ/24 h)	5278 ± 183	5091 ± 63	0.351
Oral temperature (C)	36.4 ± 0.4	36.4 ± 0.3	0.945
Fasting RQ	0.820 ± 0.056	0.822 ± 0.048	0.874
TEF (kJ/24 h)	980 ± 262	1106 ± 302	0.174
Postprandial RQ	0.900 ± 0.039	0.893 ± 0.038	0.541
LTA (kJ/24 h) (n = 11/84)	1335 ± 517	2141 ± 1457	<0.001[a]
RT3 (kJ/24 h) (n = 10/78)	2288 ± 602	2682 ± 950	0.206
VO_2 peak (ml O_2/ kg·min)	30.8 ± 3.9	38.4 ± 6.8	<0.001[a]
Hours of watching TV/ video per wk	9.3 ± 3.8	6.2 ± 4.5	0.029[a]

FFM, Fat-free mass; FM, fat mass; RQ, respiratory quotient; TEF, thermic effect of food; LTA, leisure time physical activity.
[a] Significantly different between MONW and non-MONW women.

TABLE 5. Energy intake in MONW and non-MONW women

	MONW (n = 11)	Non-MONW (n = 83)	
	Mean ± SD	Mean ± SD	*P*
Energy (kcal/24 h)	10,105 ± 2,675	9,911 ± 2,986	0.838
Protein (g/24 h)	113.5 ± 62.9	103.8 ± 42.2	0.502
Lipids (g/24 h)	80.1 ± 23.0	78.7 ± 36.8	0.865
Carbohydrates (g/24 h)	312.4 ± 95.7	321.2 ± 105.2	0.792
Energy from proteins (%)	22 ± 8	21 ± 6	0.710
Energy from lipids (%)	33 ± 9	32 ± 10	0.771
Energy from carbohydrates (%)	51 ± 9	53 10	0.403
FQ	0.864 ± 0.024	0.869 ± 0.028	0.540

FQ, Food quotient.

TABLE 6. Dietary behavior in MONW and non-MONW women as measured by the Three-Factor Eating Questionnaire

	MONW (n = 12)	Non-MONW (n = 84)	
	Mean ± SD	Mean ± SD	*P*
Dietary restraint	6.5 ± 3.9	9.0 ± 3.9	0.038[a]
Disinhibition	5.3 ± 3.4	5.5 ± 3.1	0.844
Hunger	4.4 ± 3.2	5.7 ± 3.1	0.178

[a] Significantly different between MONW and non-MONW women.

Energy intake and dietary behavior

Table 5 shows energy, protein, lipid, and carbohydrate intake, their respective contribution to total energy intake, and food quotient. No difference was found for dietary intake variables between MONW and non-MONW women. Table 6 contains the results of the Three-Factor Eating Questionnaire. The MONW group had a lower level of dietary restraint ($P = 0.038$). However, no significant differences were found for the factors of disinhibition and hunger.

Simple correlations

Pearson correlations were examined between insulin sensitivity (HOMA) and selected variables. Figure 2 shows the correlation between HOMA and percent body fat (r = 0.422, $P < 0.001$). The correlations between HOMA and other factors were as follows: maximal aerobic capacity, r = −0.358 ($P < 0.001$); fasting leptin, r = 0.326 ($P = 0.004$); fasting ghrelin, r = −0.312 ($P = 0.005$); hours of watching television/videos, r = 0.309 ($P = 0.003$); RMR, r = 0.298 ($P = 0.003$); dietary restraint, r = −0.258 ($P = 0.011$); and leisure time physical activity energy expenditure, r = −0.217 ($P = 0.035$).

Multivariate analysis

We performed stepwise regression analysis to examine the independent predictors of HOMA. Table 7 illustrates the summary of the model. Results shows that the variables of percentage of fat mass, dietary restraint, and age were independent predictors of HOMA, collectively explaining 33.5% of the variance ($P = 0.005$). Results derived from backward and forward methods confirmed the results obtained with the stepwise method. Because percentage of fat mass was the first variable to be selected in the model, we then examined whether differences in HOMA persisted between groups after statistical adjustment for this variable. When HOMA was adjusted for percentage of fat mass, the difference between MONW women and non-MONW women remained significant ($P < 0.001$).

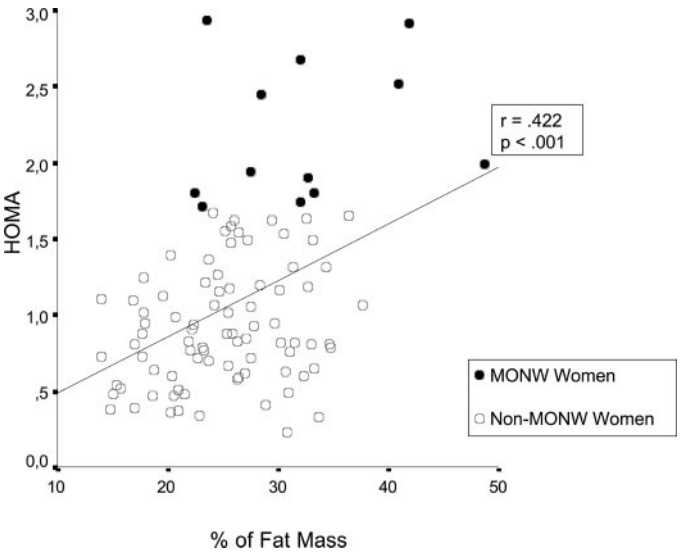

FIG. 2. Relationship between HOMA and percentage of fat mass in MONW women and non-MONW women.

Discussion

Although there has long been the clinical recognition of MONW individuals, a rudimentary understanding of the etiology of this disorder only started to emerge in the 1980s (5). These at-risk individuals, despite having a normal BMI and a young age, display metabolic characteristics that may contribute to the development of the metabolic syndrome (6). To add to this body of literature, we attempted to provide new information on metabolic, lifestyle, and behavioral factors that characterize the profile of young MONW women. We found that a higher level of relative body fatness, a cluster of sedentary physical activity behaviors, and a lower level of dietary restraint were factors implicated in the deleterious metabolic profile of this unique at-risk population.

Body composition

MONW women, despite having a normal BMI, showed distinct differences in body composition compared with non-MONW young women. We found that MONW women demonstrated a higher relative fat mass, a lower fat-free mass, and a tendency for greater central fat mass. All of these body composition factors could be related to reduced insulin sensitivity. Moreover, in multiple regression analysis, percentage of body fat was the strongest single predictor of lower insulin sensitivity (as estimated by HOMA). Although, previous studies have postulated an inverse relationship between adiposity and insulin sensitivity (22–25), we were surprised that this relationship was evident even within a young, nonobese population with a relatively low to normal BMI. Our data on normal-weight women confirm those found by Dvorak *et al.* (8) and Tai *et al.* (26). These results support the hypothesis of Ruderman *et al.* (6), who suggested that MONW individuals are mildly obese when compared with individuals of similar weight and height. Collectively, the relative level of body fatness (but not BMI) may be an important first step to screen and identify MONW women in the general population.

A logical question is why are MONW women mildly obese? To understand factors implicated in the regulation of body composition between MONW women and non-MONW women, we carefully measured several aspects of daily energy expenditure including RMR, thermic effect of food, and substrate oxidation. We initially hypothesized that MONW women would show a lower RMR, a lower thermic effect of a meal, and a reduced reliance on lipid oxidation, as evidenced by a higher fasting and postprandial respiratory quotient than non-MONW women. These phenotypes have been shown to predict fat gain (27–29). This hypothesis, however, was not supported in our study because no dif-

TABLE 7. Stepwise regression analysis regarding independent predictors of insulin sensitivity estimated by HOMA (n = 94) in MONW and non-MONW women

Dependent variable	Step	Independent variable	Relationship (+/−)	Partial r^2	Total r^2 cumulative	*P*
HOMA	1	% of fat mass	+	0.171	0.171	<0.001
	2	Dietary restraint	−	0.104	0.275	<0.001
	3	Age	−	0.060	0.335	0.005

Equation: HOMA = 1.319 + (0.04002 × % of fat mass) − (0.04643 × dietary restraint) − (0.03792 × age).

ferences were found between the two groups for these variables.

A more plausible explanation for differences in body fatness may be related to the clustering of sedentary behaviors in MONW women. We assessed several variables of physical activity, including leisure time physical activity energy expenditure, a direct determination of $VO_{2\ peak}$, daily physical activity energy expenditure (using an accelerometer), and the number of hours spent watching television. We noted that MONW women were less aerobically fit, expended less calories in their physical activity periods, and spent a greater portion of their time watching television. These types of biological attributes and behaviors likely contribute to the positive energy balance that leads to greater adiposity and higher total cholesterol among MONW women. A logical next step, in terms of treatment, would be to examine the effects of mild caloric restriction and/or exercise programs to improve the metabolic profile of MONW women.

Dietary restraint

To our knowledge, this is the first study to examine eating behavior in MONW women. We specifically used the Three-Factor Eating Questionnaire to determine levels of dietary restraint, disinhibition, and hunger. Although the two groups showed similar energy intake, we found that MONW volunteers showed less dietary restraint (6.5 ± 3.9 *vs.* 9.0 ± 3.9, $P = 0.038$) than non-MONW women. No differences, however, were noted in measures of disinhibition and hunger. This finding suggests that MONW women are less consciously preoccupied with consciously restraining their food intake. Moreover, dietary restraint (control of food intake by thought and will power) was an independent predictor of insulin sensitivity in multiple regression analysis, explaining 10.4% of the variability of insulin sensitivity. The relationship between dietary restraint and plasma insulin response has been considered in the literature but not within the context of the MONW model. For example, Teff and Engelman (30), in accordance with our data, showed a positive correlation between dietary restraint and level of cephalic phase insulin release. Other studies have shown a link between dietary restraint and physiological variables. For example, Tepper (31) showed a greater cephalic phase salivary response in restrained eaters compared with unrestrained eaters. In addition, Anderson *et al.* (32) and McLean *et al.* (33) showed a higher level of salivary and urinary cortisol in restrained subjects. However, Pirke *et al.* (34) showed a lower fasting insulin level during the night in restrained subjects compared with unrestrained subjects. Although the mechanism cannot be elucidated, our results extend those of others by reporting a relationship between dietary restraint and insulin sensitivity in MONW women.

Hormones

Several hormonal factors, particularly ghrelin and leptin, have recently been reported to be involved in the regulation of energy homeostasis and body fatness. Ghrelin and leptin may act as messengers between gastrointestinal tract and adipose tissues (from which they are respectively derived) and the central nervous system (35–38). Ghrelin and leptin levels are reported to be involved in the control of appetite and insulin sensitivity, and their dysregulation may be associated with the development of obesity-related disturbances (39–45). In this investigation, we examined the hypothesis that differences in blood concentrations of both hormones could explain, at least in part, the differences in the metabolic profile of MONW and non-MONW women. We initially hypothesized that MONW subjects would have lower ghrelin and higher leptin levels than non-MONW women. Contrary to our hypothesis, ghrelin and leptin levels were not different between MONW and non-MONW women. These results suggest that the magnitude of difference in insulin sensitivity may be too subtle to differentiate leptin and ghrelin concentrations between MONW and non-MONW women. Subsequently, it is unlikely that ghrelin or leptin could be used as a biomarker of the MONW women. We also examined adiponectin in MONW and non-MONW young women because adiponectin has been shown to be inversely correlated with the HOMA index (46–50). We hypothesized that adiponectin would be lower in MONW individuals (51), but our results did not support this hypothesis; which is concordant with the findings of Silha *et al.* (42). However, it is premature to discard hypotheses regarding hormonal parameters and MONW profile. Our results may be due to the lower number of subjects in the MONW group. Based on statistical power calculation, we would need 17 MONW women to obtain significant results at a $P < 0.05$ and $\beta = 0.80$.

We also considered family history and birth weight in an attempt to better understand the MONW profile. Ruderman *et al.* (6) considered these two variables as identifying factors for MONW individuals. However, in our study, none of these variables were found to be statistically different between the two groups. It should be noted that family history of diabetes remained almost 2-fold higher in the MONW group *vs.* the non-MONW group. This is not to say that these variables may not be important in the MONW profile; larger sample sizes may be needed to fully understand their contribution and potential influence.

It is known that the development of insulin resistance occurs on a physiological continuum. Thus, a potential criticism of our findings is the use of a cut point for HOMA to initially define the MONW group. First, it should be appreciated, however, that HOMA has been found to be an acceptable proxy of insulin sensitivity when compared with the gold standard of the euglycemic-hyperinsulinemic clamp (11, 52–56). Second, our selection of the 1.69 value is based on previous work in which the clamp was used with MONW individuals (8). Third, a recent study on diabetic but normal-weight individuals lends support to the use of the 1.69 value as a discriminating factor for MONW women (56). Last, we also examined the use of the quantitative insulin sensitivity check index as an alternative approach to estimated insulin sensitivity. The prediction of the quantitative insulin sensitivity check index in multiple regression analysis yielded similar results to those found in HOMA. These similar results are potentially due to the high correlation between the two indices in our sample ($n = 96$, $r = -0.907$, $P < 0.001$).

Summary

Both metabolic and dietary behavioral variables are independently associated with the deleterious metabolic profile of MONW women. In particular, MONW women display lower insulin sensitivity potentially due to a cluster of sedentary behavior patterns that contribute to higher levels of adiposity. Furthermore, dietary restraint may play a role in regulating insulin sensitivity in MONW women. Moreover, these results extend previous works by identifying the role of dietary restraint as a distinguishing phenotype in MONW women. These phenotypes may be useful in the eventual identification of MONW women with a goal of preventing the development of the metabolic syndrome in young women.

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Address all correspondence and requests for reprints to: Florence Conus, Unité Metabolique, Département de Nutrition, Faculté de Médecine, 2405 Chemin de la Côte Ste-Catherine, Université de Montréal, Montréal, Québec H3T 1A8, Canada. E-mail: Florence.conus@umontreal.ca.

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