Physical activity and weight loss are independent predictors of improved insulin sensitivity following energy restriction

Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Physical Activity and Weight Loss are Independent Predictors of Improved Insulin Sensitivity Following Energy Restriction

Stefan G. J. A. Camps, Sanne P. M. Verhoef, and Klaas R. Westerterp

Objective: The role of physical activity and the joint effect with sleep duration on insulin sensitivity (IS) during energy restriction followed by weight maintenance were determined.
Methods: One hundred and two subjects (28 males) (mean ± SD age: 40 ± 9 years; BMI: 31.9 ± 3.0 kg/m^2) followed a very-low-energy diet for 8 weeks, followed by a 44-week period of weight maintenance. Body composition (three-compartment model based on body weight, total body water, and body volume), physical activity (accelerometry), sleep (questionnaire, Epworth Sleepiness Scale), and fasting plasma insulin and glucose concentrations were assessed before the diet and at 8, 20, and 52 weeks after the start.
Results: Compared to baseline, IS was improved significantly after 8 weeks ($P < 0.001$) and was higher after 20 weeks ($P < 0.001$) and 52 weeks ($P < 0.05$). After 8, 20, and 52 weeks, 23% ($P < 0.01$), 19% ($P < 0.05$), and 13% ($P < 0.05$), respectively, of the variance in IS improvement was explained by weight loss percentage and change in physical activity counts.
Conclusions: Maintaining daily physical activity during energy restriction is as important as weight loss itself in the improvement of IS; there was no additional effect of change in sleep duration. During weight maintenance, improved IS is maintained better if physical activity returns to baseline or higher.

Obesity (2016) **24**, 291–296. doi:10.1002/oby.21325

Introduction

The increasing prevalence of obesity and its association with an impaired insulin homeostasis are major health problems in our modern world (1,2); both are linked closely to the development of noncommunicable diseases as type 2 diabetes and cardiovascular diseases (3). Overweight and obesity are characterized by the accumulation of excessive fat mass and more free fatty acids in the blood which can lead to an impaired glucose metabolism and a reduced insulin sensitivity (4). Independent from adiposity, physical inactivity, or increased length of time without movement, merely a reduction in body movement and not in activity induced energy expenditure is associated with a reduced clearance of free fatty acids and ingested glucose and less glucose-stimulated insulin secretion, increasing the risk for type 2 diabetes (5,6). Short and long sleep duration are associated with an increased risk for insulin insensitivity (7-9), and although several mechanisms have been proposed, the relationship with physical activity might be pivotal as short and long sleep duration decrease daytime physical activity (9-11).

Losing weight and increasing physical activity independently have a beneficial effect on the glucose metabolism and insulin sensitivity (12,13). However, the addition of aerobic or resistance exercise training to a diet does not enhance the reductions in plasma insulin and glucose levels induced by weight loss (14-16). On the other hand, increasing physical activity in subjects with overweight or obesity improves insulin sensitivity in the absence of weight loss (17,18). The ambiguous results can be explained by the fact that energy restriction leads to a decrease in physical activity (19,20) and that additional exercise training to an energy restricted diet will often be compensated by a reduction of nontraining physical activity (21).

While physical activity and sleep have been studied separately in relation to insulin sensitivity, little is known about the interaction of sleep and physical activity with insulin sensitivity. Recently, Zuo et al. showed that mainly occupational physical activity was negatively associated with insulin resistance and that there was a synergistic effect of low physical activity and short sleep duration on insulin sensitivity (22).

The primary aim of this study was to determine the role of physical activity on insulin sensitivity during energy restriction followed by weight maintenance and secondly the joint effect of sleep duration and physical activity. It was hypothesized that maintaining body movement during energy restriction increases insulin sensitivity and moreover that there is a synergistic effect of physical activity and

Department of Human Biology, Nutrition and Toxicology Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands.
Correspondence: Stefan G. J. A. Camps (sg.camps@maastrichtuniversity.nl).

Funding agencies: The research was funded by Maastricht University.
Disclosure: The authors declared no conflict of interest.
Clinical trial registration: ClinicalTrials.gov identifier NCT01015508
Received: 23 February 2015; **Accepted:** 18 August 2015; **Published online 6 January 2016. doi:10.1002/oby.21325**

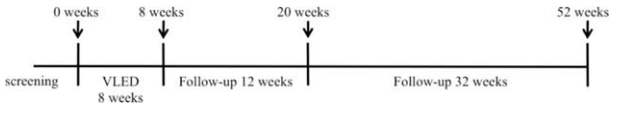

Figure 1 Flow chart of the 52-week program; the measurement points are indicated. VLED: very-low-energy diet.

sleep duration on insulin sensitivity during weight loss and weight maintenance on top of the effect of weight loss itself. Therefore, physical activity, sleep duration, and fasting glucose and insulin were measured before and after a very-low-energy diet (VLED) and during 44 weeks of follow-up.

Subjects and Methods

Subjects

One hundred and two healthy subjects (74 women and 28 men) with a mean age of 40 ± 9 years and with a mean body mass index (BMI) of 31.9 ± 3.0 kg/m^2 were recruited by advertisements in local newspapers and on notice boards at the university. They underwent an initial screening that included measurements of body weight and height and the completion of a questionnaire on general health. All were in good health, not using medication (except for contraception), nonsmokers, and at most moderate alcohol consumers. They were relatively weight stable as defined by a weight change <5 kg for at least 3 months prior to the study. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and procedures were approved by the Ethics Committee of the Maastricht University Medical Centre. Written informed consent was obtained from all participants. This trial was registered at http://www.clinicaltrials.gov as NCT01015508.

Study design

The study covered a full year, starting with a VLED for 8 weeks, followed by a 44-week period of weight maintenance (Figure 1). Subjects came to the university for measurements on four occasions: the day before the start of the diet (baseline), 8 weeks after the start of the diet (end of the diet), 20 weeks after the start of the diet, and 52 weeks after the start of the diet. On each occasion, measurements included body composition, the collection of fasting blood, and sleep questionnaires and were performed from 08.00 in the morning onwards with subjects in a fasted state. Two weeks prior to each measurement day, subjects received an accelerometer to measure physical activity. Subjects were instructed to maintain their newly achieved body weight without specific dietary, physical activity, or sleep instructions.

Diet

The weight loss diet (Modifast; Nutrition et Santé Benelux, Breda, The Netherlands) was followed for a period of 8 weeks. The diet was a protein-enriched formula that provided 2.1 MJ/day (51.9 g of protein, 50.2 g of carbohydrates, and 6.9 g of lipids) and a micronutrient content, which meets the Dutch recommended daily allowance. The VLED was provided to the subjects as sachets with powder. Each sachet represented one meal and three sachets were consumed every day. Besides the provided meal replacements, subjects were allowed to eat vegetables when feeling hungry with the exception of starchy vegetables and legumes, which are relatively high in energy density like potatoes and beans. Subjects were instructed to mix the powder with the amount of water indicated on the packages and were advised to drink water sufficiently throughout the diet period.

Body composition

Height was measured at screening to the nearest 0.1 cm with the use of a wall-mounted stadiometer (model 220; Seca, Hamburg, Germany). Body composition was determined according to Siri's three-compartment model based on body weight, body volume, and total body water (23). Body weight was measured using a calibrated scale (Life Measurement Corporation, Concord, CA). Body volume was measured via air-displacement plethysmography with the BodPod System (Life Measurement Corporation, Concord, CA) (24). The average thoracic gas volume was measured by the BodPod using a standard plethysmographic technique (25). Total body water was determined using deuterium dilution during the preceding night, according to the Maastricht protocol (26). The calculation of total body water from isotope decay involves assumptions on the isotope dilution spaces for ^{2}H, in this case a fixed ratio based on the population mean of the study group as suggested by Speakman et al. (27). BMI was calculated by dividing body weight by height squared (kg/m^2).

Physical activity monitoring

Physical activity was monitored in 2-week intervals based on measuring body movement using the previously validated Tracmor$_D$ triaxial accelerometer (DirectLife, Philips Consumer Lifestyle) (28). The device is small and lightweight and was carried at an elastic belt around the waist. Subjects were instructed to wear the accelerometer during waking hours, except during showering and water activities. A diary was used to report periods in which the subject was not wearing the accelerometer during the day to check for missing data and wearing time. The accelerometer output was processed to determine body movement by force and duration, and not energy expenditure, by measuring physical activity counts. Total physical activity counts were calculated over the 2-week monitoring period, and the sum of counts was divided by the number of monitoring days to determine the average physical activity counts per day (28). Average physical activity counts per day are then a measure for daily physical activity. Days during which data were missing or subjects carried the accelerometer for <10 h were excluded and the average was calculated on the remaining data, considering daily physical activity an ergodic process. Subjects with less than 7 days would have been excluded; however, all subjects met these criteria and none were excluded.

Sleep

Questionnaires were used to assess sleep duration and daytime sleepiness. For sleep duration the questions were: "How many hours do you usually sleep per night during weekdays?" and "How many hours do you usually sleep during weekend days?" A total weekly sleep score was calculated as follows: [(hours sleep weekdays $\times$ 5) + (hours sleep weekend days $\times$ 2)/7] (10). Subjects with between 7 and 9 h of sleep (average sleepers) were included to exclude very short and very long sleepers (29). Daytime sleepiness was assessed through the Epworth Sleepiness Scale (ESS). Subjects rated the

likelihood of falling asleep in eight specific situations on a 0-3 scale, with 0 meaning no chance at all to fall asleep and 3 meaning a high chance of falling asleep. The total score can range from 0 to 24, with a score of 10 or higher suggesting excessive daytime sleepiness (30).

Biochemical analysis

Blood was collected into EDTA-containing tubes and centrifuged (1000×*g*, 10 min, 4°C), and the plasma was immediately frozen in liquid nitrogen and stored at −80°C until analysis. Plasma glucose concentration was analyzed enzymatically on a Cobas Mira automated spectrophotometer (Roche Diagnostica). Plasma insulin was measured with a double-antibody radioimmunoassay (Insulin RIA 100, Kabi-Pharmacia, Uppsala, Sweden). Insulin sensitivity was assessed by the homeostasis model assessment index for insulin resistance ($HOMA_{IR}$), calculated as [plasma glucose (mmol/l) times plasma insulin (mU/l)] divided by 22.5 (31).

Calculations and statistical analysis

One-way repeated measures ANOVA with Bonferroni's adjustment for multiple comparisons were used to compare the results across 0, 8, 20, and 52 weeks. Linear and multiple hierarchical regression analysis have been performed independently for each time point to determine relations and interactions between dependant and independent variables. Multiple hierarchical regression analysis is performed to evaluate the contributions of variables above and beyond previously entered predictors, as means of statistical control, and for examining incremental validity. The order of variable entry into the analysis was baseline $HOMA_{IR}$, gender, age, weight loss%, counts change, and hours sleep change (the last two have been interchanged but this did not influence results), based on the results described in the introduction. Independent variables indicating change over time represent the delta compared to baseline. R^2 values are given as a measure of the correlation of the total model while standardized beta values are given as a measure of how strongly each predictor variable influences the dependent variable. The signs (plus or minus) indicate the direction of the relationship between the variables. Collinearity diagnostics as part of the multiple regression procedure were performed to check for problems with multicollinearity between the independent variables. Tolerance values were not below 0.8 and variance inflation factor (VIF) values were not higher than 1.2, indicating there was no problem of collinearity. Age and gender were used as covariates in all tests. The data were analyzed using SPSS 20.0 (SPSS, Chicago, IL). All data are presented as means ± standard deviations (SDs).

Results

Body composition

After the 8 weeks of VLED, weight loss was on average 9.4 ± 4.2 kg ($P < 0.001$) consisting of 7.6 ± 3.3 kg of fat mass (FM) and 1.8 ± 2.2 kg of fat free mass (FFM). After 20 and 52 weeks, there was a significant average weight loss compared to baseline, 8.4 ± 4.9 kg ($P < 0.001$) and 5.9 ± 4.9 kg ($P < 0.001$), respectively. Weight loss after 52 weeks was significantly less compared to 8 and 20 weeks ($P < 0.05$). After 20 weeks, this was 7.7 ± 4.6 kg of FM and 0.7 ± 2.0 kg of FFM and after 52 weeks 5.6 ± 5.2 kg of FM and 0.3 ± 2.0 kg of FFM. As a percentage of the starting weight, subjects lost on average 10.2 ± 4.1% ($P < 0.001$). After 20 weeks, weight loss was 9.1 ± 5.0% ($P < 0.001$) and weight loss was still 6.2 ± 6.1% after 52 weeks compared to baseline ($P < 0.001$). FM decreased from 41.8 ± 6.3% to 37.3 ± 7.5% ($P < 0.001$). After 20 and 52 weeks, FM was significantly lower as compared to baseline, 36.8 ± 7.6% ($P < 0.001$) and 38.3 ± 6.5% ($P < 0.001$), respectively. The data showed a large inter-individual variation in weight loss, indicating a difference in the success of weight loss and of maintaining the lost weight. In addition, the variation in weight loss and weight maintenance was not explained by different levels of physical activity or sleep duration at baseline or at 8, 20, or 52 weeks or by a better maintenance of the amount of physical activity during the diet and follow-up.

Glucose/insulin homeostasis

Fasting glucose concentration at baseline was on average 4.9 ± 0.4 mmol/l and did not change after 8, 20, and 52 weeks with values of 4.8 ± 0.4, 4.9 ± 0.4, and 5.0 ± 0.4 mmol/l, respectively.

Fasting insulin concentration decreased from 17.0 ± 6.7 mU/l at baseline to 11.7 ± 4.9 mU/l after 8 weeks of VLED ($P < 0.001$). After 20 weeks, fasting insulin concentration did not change compared to 8 weeks with an average value of 11.9 ± 4.7 mU/l and was still significantly lower compared to baseline ($P < 0.001$). After 52 weeks, fasting insulin concentration did not change significantly compared to 8 weeks with an average value of 13.7 ± 7.2 mU/l and was still significantly lower compared to baseline ($P < 0.05$).

$HOMA_{IR}$ decreased from 3.7 ± 1.6 at baseline to 2.5 ± 1.2 after 8 weeks of VLED ($P < 0.001$). After 20 weeks, $HOMA_{IR}$ did not change significantly compared to 8 weeks with an average value of 2.6 ± 1.1 and was still significantly lower compared to baseline ($P < 0.001$). After 52 weeks, $HOMA_{IR}$ was still significantly lower compared to baseline with an average value of 3.0 ± 1.7 ($P < 0.01$); however, the value was higher compared to 8 weeks ($P < 0.01$).

Physical activity

Physical activity was on average 1.63 ± 0.36 Mcounts/day at baseline and decreased to 1.56 ± 0.45 Mcounts/day ($P < 0.05$) after 8 weeks of energy restriction. After 20 weeks, physical activity increased significantly to 1.65 ± 0.43 Mcounts/day compared to 8 weeks ($P < 0.01$). There was no significant difference between baseline and 20 weeks. After 52 weeks, physical activity increased significantly to 1.66 ± 0.52 Mcounts/day compared to 8 weeks ($P < 0.01$). There was no significant difference between baseline and 52 weeks.

Sleep duration

Average sleep duration at baseline was on average 8.1 ± 0.6 h/day and increased significantly to 8.4 ± 0.7 h/day after weight loss ($P < 0.05$). After 20 and 52 weeks, average sleep duration was 8.3 and 8.2 h/day, respectively; this was not significantly different from baseline or 8 weeks. Moreover, after 8 weeks, there was a significant negative correlation between change in body weight and the change in average hours sleep ($R^2 = 0.04$, $P < 0.05$).

Interaction

Regression analysis revealed that baseline $HOMA_{IR}$ explained almost 40% ($P < 0.001$) of the variance in the decrease in $HOMA_{IR}$

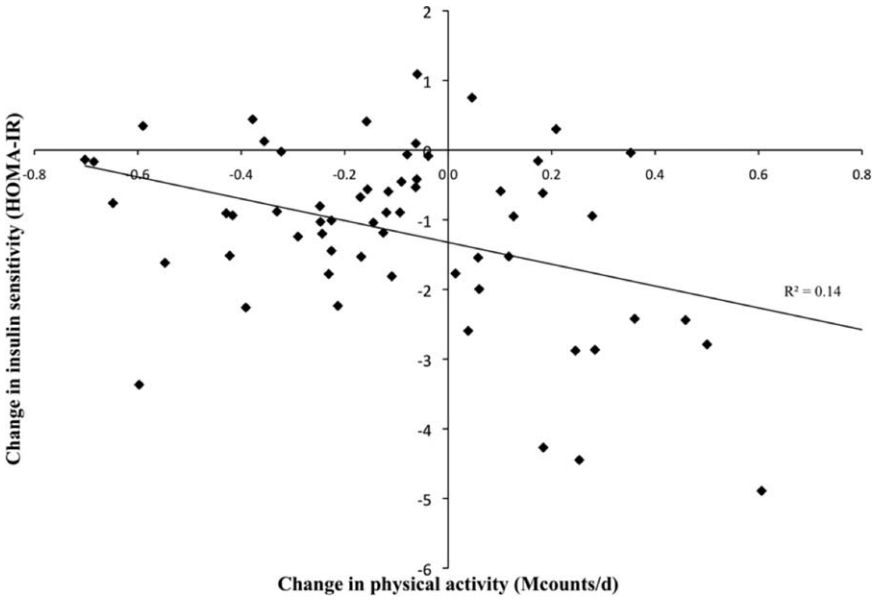

Figure 2 Correlation of the change in insulin sensitivity ($HOMA_{IR}$) against the change in physical activity (Mcounts/day) after 8 weeks of VLED ($R^2 = 0.14$, $P < 0.01$) (actual data points). $HOMA_{IR}$: homeostasis model assessment index for insulin resistance; VLED: very-low-energy diet.

after weight loss. Furthermore, after 20 and 52 weeks, 49% ($P < 0.001$) and 23% ($P < 0.01$), respectively, of the variance in the change in $HOMA_{IR}$ was explained by the baseline value of $HOMA_{IR}$.

Besides baseline $HOMA_{IR}$, the regression model combining age, gender, change in body weight, change in sleep duration and change in physical activity counts explained an additional 23% ($P < 0.01$) of the variance in the change in $HOMA_{IR}$ after 8 weeks of VLED. The independent contributions of change in body weight ($R^2 = -0.08$, $P < 0.01$) and the change in physical activity counts ($R^2 = 0.14$. $P < 0.01$) were statistically significant (Figure 2) (actual data points).

After 20 weeks, the regression model explained an additional 19% ($P < 0.05$) of the variance in the change of $HOMA_{IR}$ besides baseline $HOMA_{IR}$, with significant independent contributions of change in body weight ($R^2 = 0.07$, $P < 0.05$) and the change in physical activity counts ($R^2 = 0.09$, $P < 0.05$).

After 52 weeks, the regression model explained an additional 13% ($P < 0.05$) of the variance in the change of $HOMA_{IR}$ on top of the explained variance by baseline $HOMA_{IR}$; with a significant independent contribution of change in body weight ($R^2 = 0.08$, $P = 0.05$). There was a trend for a significant contribution of change in physical activity counts ($R^2 = 0.05$, $P = 0.10$) (Table 1). The decrease in explained variation after 52 weeks is due to the increased variance and increased influences from variables that were not controlled for during follow-up.

Discussion

Measurements of physical activity, sleep duration, and fasting glucose and insulin before and after a VLED and during 44 weeks (week 52) of follow-up showed that the improvement in insulin sensitivity is mostly dependent on the amount of weight loss and daily physical activity and not on sleep duration. During the weight loss phase, to improve insulin sensitivity, maintaining daily physical activity is as important as weight loss itself.

These results confirm the improvement of insulin sensitivity as a result of energy restriction (12) and indicate that maintaining physical activity or a smaller decrease in physical activity during weight loss is beneficial for the glucose metabolism on top of the weight loss solely which is in line with prior studies showing that physical

TABLE 1 Multiple regression results of a model combining gender, age, weight loss percentage, physical activity counts change, and hours sleep change to predict changes in insulin resistance after 8, 20, and 52 weeks

	Beta; 8 weeks	Beta; 20 weeks	Beta; 52 weeks
Gender	0.016	−0.26	−0.072
Age	0.032	0.160	0.019
Weight loss (%)	0.283*	0.262*	0.273*
Counts change	−0.376**	−0.298*	−0.217
Hours sleep change	−0.094	0.066	−0.042
Baseline $HOMA_{IR}$	−0.631***	−0.699***	−0.480**
Total R^2 value	0.63***	0.68***	0.36**

Standardized beta values are shown for each individual parameter and for the total model at 8, 20, and 52 weeks. In the bottom row, the total R^2 value for the model combining all parameters are shown for 8, 20, and 52 weeks. Significance is indicated with $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.
$HOMA_{IR}$: homeostasis model assessment index for insulin resistance.

activity improves insulin sensitivity (13). On average, the results show a decrease in physical activity during energy restriction, which is also seen in previous studies (19,20). However, this study now points out that avoiding or minimizing the decrease in physical activity during energy restriction has a beneficial effect on insulin sensitivity improvement during weight loss. Furthermore, after 20 weeks, subjects who show a return to baseline physical activity or higher maintain more improved insulin sensitivity compared to subjects who retain a lower daily physical activity. These results seem contradictory to studies that show no effect of additional aerobic or resistance training to a diet on insulin sensitivity (14-16). However, previous studies have shown that energy restriction leads to a decrease in physical activity (19,20) and that additional exercise during a diet will be compensated by a reduction of nontraining physical activity (21). Since extra training will often be compensated, it seems of great importance to track daily physical activity patterns, which can be measured using portable accelerometers (32) to avoid more sedentariness during weight loss.

During 44 weeks of follow-up after the VLED, insulin sensitivity improvement was maintained; $HOMA_{IR}$ decreased from a baseline of 3.7 ± 1.6 to 3.0 ± 1.7 after 44 weeks of follow-up ($P < 0.01$). The improvement was a function of weight loss and physical activity; however, the contribution decreased over time. In addition to their influence in, a large part of the variance in improvement of insulin sensitivity at 8, 20, and 52 weeks was explained by insulin sensitivity at baseline, which showed that a greater improvement was reached in subjects with a lower initial insulin sensitivity (Table 1). The results during follow-up are in line with higher insulin sensitivity during weight loss maintenance (33,34) and with more physical activity (13). The sustained improved insulin sensitivity after 44 weeks despite the partial weight regain is in accordance with previous results (35-37).

Sleep duration was increased after 8 weeks of energy restriction as observed before (38). Sleeping longer was significantly related to a higher percentage weight loss. This could mean that people sleeping longer lose more weight, or that people losing more weight sleep longer. However, during 44 weeks of follow-up, sleep duration returned to baseline values while weight loss was maintained. This would indicate that the negative energy balance caused the increased sleep duration and not the other way around. Increasing sleep duration could be a way to reduce energy expenditure.

A limitation of this study is that diet and physical activity were not standardized during the 44-week follow-up. On the other hand, due to the absence of advice on diet and physical activity, this study reflects achievements in free-living conditions. Additionally, physical activity was measured objectively with accelerometers. Future research could focus on the influence of the amount of high, medium, and low physical activity to gain more insight in what is beneficial for insulin sensitivity during weight loss, besides daily physical activity. Another limitation is the use of self-reported sleep durations, although previous studies have shown a good agreement between self-reported and measured sleep duration (39,40). The authors notice that $HOMA_{IR}$ may not be the best measure for insulin sensitivity; still, it is a very useful approach in a longitudinal approach. The observed interindividual variation in the results allowed changes in insulin sensitivity to be correlated to a wide range from successful to unsuccessful weight maintenance. At the same time, the observed variation in the change of physical activity and sleep duration allowed us to correlate these variables over a wide range with insulin sensitivity. One of the major advantages with regard to other studies was the longitudinal approach in which an 8-week VLED was followed by a 44-week follow-up, to investigate the interaction between physical activity, sleep duration and insulin sensitivity during weight loss and weight maintenance.

In conclusion, the study shows that the improvement in insulin sensitivity is mostly dependent on the amount of weight loss and the quantity of daily physical activity and not on sleep duration. During the weight loss phase, to improve insulin sensitivity, maintaining daily physical activity is as important as weight loss itself. Furthermore, during weight maintenance, improved insulin sensitivity is maintained better if physical activity returns to baseline or higher.

References

1. Catenacci VA, Hill JO, Wyatt HR. The obesity epidemic. *Clin Chest Med* 2009;30:415-444, vii.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2009;87:4-14.
3. Lorenzo C, Wagenknecht LE, D'Agostino RB, Jr., Rewers MJ, Karter AJ, Haffner SM. Insulin resistance, beta-cell dysfunction, and conversion to type 2 diabetes in a multiethnic population: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2010;33:67-72.
4. Strasser B. Physical activity in obesity and metabolic syndrome. *Ann N Y Acad Sci* 2013;1281:141-159.
5. Ford ES, Li C, Zhao G, Pearson WS, Tsai J, Churilla JR. Sedentary behavior, physical activity, and concentrations of insulin among US adults. *Metabolism* 2010;59:1268-1275.
6. Thorp AA, Healy GN, Owen N, et al. Deleterious associations of sitting time and television viewing time with cardiometabolic risk biomarkers: Australian Diabetes, Obesity and Lifestyle (AusDiab) study 2004-2005. *Diabetes Care* 2010;33:327-334.
7. Chaput JP, Despres JP, Bouchard C, Astrup A, Tremblay A. Sleep duration as a risk factor for the development of type 2 diabetes or impaired glucose tolerance: analyses of the Quebec Family Study. *Sleep Med* 2009;10:919-924.
8. Patel SR. Reduced sleep as an obesity risk factor. *Obes Rev* 2009;10 Suppl2:61-68.
9. Tuomilehto H, Peltonen M, Partinen M, et al. Sleep duration, lifestyle intervention, and incidence of type 2 diabetes in impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabetes Care* 2009;32:1965-1971.
10. Garaulet M, Ortega FB, Ruiz JR, et al. Short sleep duration is associated with increased obesity markers in European adolescents: effect of physical activity and dietary habits. The HELENA study. *Int J Obes (Lond)* 2011;35:1308-1317.
11. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med* 2005;165:863-867.
12. Olefsky J, Reaven GM, Farquhar JW. Effects of weight reduction on obesity. Studies of lipid and carbohydrate metabolism in normal and hyperlipoproteinemic subjects. *J Clin Invest* 1974;53:64-76.
13. Lin CY, Chen PC, Kuo HK, Lin LY, Lin JW, Hwang JJ. Effects of obesity, physical activity, and cardiorespiratory fitness on blood pressure, inflammation, and insulin resistance in the National Health and Nutrition Survey 1999-2002. *Nutr. Metab Cardiovasc Dis* 2009;20:713-719.
14. Snel M, Gastaldelli A, Ouwens DM, et al. Effects of adding exercise to a 16-week very low-calorie diet in obese, insulin-dependent type 2 diabetes mellitus patients. *J Clin Endocrinol Metab* 2012;97:2512-2520.
15. Janssen I, Fortier A, Hudson R, Ross R. Effects of an energy-restrictive diet with or without exercise on abdominal fat, intermuscular fat, and metabolic risk factors in obese women. *Diabetes Care* 2002;25:431-438.
16. Trussardi Fayh AP, Lopes AL, Fernandes PR, Reischak-Oliveira A, Friedman R. Impact of weight loss with or without exercise on abdominal fat and insulin resistance in obese individuals: a randomised clinical trial. *Br J Nutr* 2013;110:486-492.
17. LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. *J Appl Physiol (1985)* 2005;99:1205-1213.
18. Laaksonen DE, Lindstrom J, Lakka TA, et al. Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. *Diabetes* 2005;54:158-165.
19. Camps SG, Verhoef SP, Westerterp KR. Weight loss induced reduction in physical activity recovers during weight maintenance. *Am J Clin Nutr* 2013;98:917-923.
20. Redman LM, Heilbronn LK, Martin CK, et al. Metabolic and behavioral compensations in response to caloric restriction: implications for the maintenance of weight loss. *PLoS One* 2009;4:e4377.

21. Wu T, Gao X, Chen M, van Dam R. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. *Obes Rev* 2009;10:313-323.
22. Zuo H, Shi Z, Yuan B, et al. Interaction between physical activity and sleep duration in relation to insulin resistance among non-diabetic Chinese adults. *BMC Public Health* 2012;12:247.
23. Siri WE. Body composition from fluid spaces and density: analysis of methods. *Nutrition* 1993;9:480-491 (discussion, 92).
24. Ginde SR, Geliebter A, Rubiano F, et al. Air displacement plethysmography: validation in overweight and obese subjects. *Obes Res* 2005;13:1232-1237.
25. McCrory MA, Mole PA, Gomez TD, Dewey KG, Bernauer EM. Body composition by air-displacement plethysmography by using predicted and measured thoracic gas volumes. *J Appl Physiol (1985)* 1998;84:1475-1479.
26. Westerterp KR, Wouters L, van Marken Lichtenbelt WD. The Maastricht protocol for the measurement of body composition and energy expenditure with labeled water. *Obes Res* 1995;3Suppl1:49-57.
27. Speakman JR, Nair KS, Goran MI. Revised equations for calculating CO_2 production from doubly labeled water in humans. *Am J Physiol* 1993;264:E912-E917.
28. Bonomi AG, Plasqui G, Goris AH, Westerterp KR. Estimation of free-living energy expenditure using a novel activity monitor designed to minimize obtrusiveness. *Obesity (Silver Spring)* 2010;18:1845-1851.
29. Chaput JP, Despres JP, Bouchard C, Tremblay A. The association between sleep duration and weight gain in adults: a 6-year prospective study from the Quebec Family Study. *Sleep* 2008;31:517-523.
30. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-545.
31. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004;27:1487-1495.
32. Bonomi AG, Plasqui G, Goris AH, Westerterp KR. Improving assessment of daily energy expenditure by identifying types of physical activity with a single accelerometer. *J Appl Physiol* 2009;107:655-661.
33. McLaughlin T, Schweitzer P, Carter S, et al. Persistence of improvement in insulin sensitivity following a dietary weight loss programme. *Diabetes Obes Metab* 2008; 10:1186-1194.
34. Capel F, Klimcakova E, Viguerie N, et al. Macrophages and adipocytes in human obesity: adipose tissue gene expression and insulin sensitivity during calorie restriction and weight stabilization. *Diabetes* 2009;58:1558-1567.
35. Lien LF, Haqq AM, Arlotto M, et al. The STEDMAN project: biophysical, biochemical and metabolic effects of a behavioral weight loss intervention during weight loss, maintenance, and regain. *Omics* 2009;13:21-35.
36. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348:2082-2090.
37. Flechtner-Mors M, Ditschuneit HH, Johnson TD, Suchard MA, Adler G. Metabolic and weight loss effects of long-term dietary intervention in obese patients: four-year results. *Obes Res* 2000;8:399-402.
38. Verhoef SP, Camps SG, Gonnissen HK, Westerterp KR, Westerterp-Plantenga MS. Concomitant changes in sleep duration and body weight and body composition during weight loss and 3-mo weight maintenance. *Am J Clin Nutr* 2013;98:25-31.
39. Hauri PJ, Wisbey J. Wrist actigraphy in insomnia. *Sleep* 1992;15:293-301.
40. Lockley SW, Skene DJ, Arendt J. Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. *J Sleep Res* 1999;8:175-183.