A weight-loss program adapted to the menstrual cycle increases weight loss in healthy, overweight, premenopausal women: a 6-mo randomized controlled trial[1]

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ABSTRACT

Background: Hormonal fluctuations during the menstrual cycle influence energy intake and expenditure as well as eating preferences and behavior.

Objective: We examined the effect in healthy, overweight, premenopausal women of a diet and exercise weight-loss program that was designed to target and moderate the effects of the menstrual cycle compared with the effect of simple energy restriction.

Design: A total of 60 healthy, overweight, premenopausal women were included in a 6-mo weight-loss program in which each subject consumed a diet of 1600 kcal/d. Subjects were randomly assigned to either a combined diet and exercise program that was tailored to metabolic changes of the menstrual cycle (Menstralean) or to undergo simple energy restriction (control).

Results: Thirty-one women (19 Menstralean and 12 control women) completed the study [mean ± SD body mass index (in kg/m^2): 32.0 ± 5.2]. Both groups lost weight during the study. In an intention-to-treat analysis, the Menstralean group did not achieve a clinically significant weight loss compared with that of the control group (P = 0.61). In per-protocol analyses, a more-pronounced weight loss of 4.3 ± 1.4 kg (P = 0.002) was shown in adherent Menstralean subjects than in the control group.

Conclusion: A differentiated diet and exercise program that is tailored to counteract food cravings and metabolic changes throughout the menstrual cycle may increase weight loss above that achieved with a traditional diet and exercise program in women who can comply with the program. This trial was registered at clinicaltrials.gov as NCT01622114. *Am J Clin Nutr* 2016;104:15–20.

Keywords: menstrual cycle, obesity, weight loss, hormonal fluctuations, energy expenditure, satiation, energy restriction

INTRODUCTION

Women's weight is influenced by the menstrual cycle, in which changes in hormonal amounts and interactions between hormones modulate fertility. Hormones control the menstrual cycle and effect changes in energy intake, expenditure, and storage while preparing the body for the possibility of pregnancy every month (1–3). Reproduction is a primary biological function, and these hormones may be such strong mediators of eating behavior that they could influence the outcome of a weight-loss regimen (3–9). Therefore, it may be relevant to take the menstrual cycle into consideration as a factor in the physiology of the energy balance in premenopausal women.

The menstrual cycle can be divided into 3 phases as follows: menstruation or the early follicular phase (days 1–4), the late follicular phase that lasts until ovulation (days 5–15), and the luteal phase (days 16–28) (6). Studies have shown that, in the luteal phase of the menstrual cycle, women's energy intakes and energy expenditures are increased, and women experience more frequent cravings for foods, particularly for foods that are high in carbohydrate and fat, than during the follicular phase (5, 7, 10). A trend toward reduced carbohydrate use and increased fat oxidation in the luteal phase has also been reported together with a prolonged time to exhaustion when exercising at submaximal intensities (1). Therefore, the underlying physiology related to each phase of the menstrual cycle may be worth considering as an element in strategies to optimize weight loss. The aim of the current trial was to examine the impact of a diet and exercise weight-loss program that was adapted to the menstrual cycle in healthy, overweight, premenopausal women.

METHODS

Subjects

Sixty overweight-obese women were recruited to the study through advertisements and by word of mouth. Inclusion criteria were as follows: age between 18–40 y, BMI (in kg/m^2) from 25 to 30, and having a regular menstrual cycle ≥6 mo before screening (28 ± 5 d) with a maximum of 4 d of within-subject variation in the cycle duration (11). Exclusion criteria were as follows: any severe health problem (e.g., a history of cancer, HIV or AIDS, diabetes, cardiovascular disease, or untreated

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hypothyroidism), the use of hormonal contraceptives, any hindrance to participating in cardiovascular exercise and strength training, an actual or planned pregnancy, or lactation.

Subjects were prescreened by telephone, and eligible participants were invited to attend a screening visit at the study site. Subjects gave written informed consent before inclusion in this study. The study was approved by the Ethical Committee of the Capital Region of Denmark and was registered at clinicaltrials.gov as NCT01622114. The study was performed at Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark.

Study design

With the use of a parallel design, 60 subjects were randomly assigned into one of the following 2 groups: an intervention (Menstralean) or a control group (allocated 1:1).The random assignment was determined by a draw of a note that was marked either "Menstralean" or "Control" from a concealed envelope (**Figure 1**).

All subjects received individual dietetic counseling at weeks 0, 2, 4, 8, 12, 16, 20, and 24. Two registered clinical dietitians gave dietetic counseling to 30 women each. The dietitian gave instructions and advice concerning both the diet and exercise that were appropriate to the respective weight-management programs. Subjects returned to the site for a follow-up visit 2 mo after the end of the dietary intervention (week 32).

Baseline measurements were performed 0–5 d before the initiation of the program of each subject. Women in the Menstralean group commenced their respective programs on the first day of their menstruation; subjects in the control group commenced on a randomly selected and uniformly distributed start date within 28 d.

Weight-loss program

All subjects were instructed in maintaining a diet with a daily energy intake of 1600 kcal during the 6-mo study period.

The Menstralean diet was synchronized to match the menstrual cycle (i.e., a 28-d dietary plan that was separated into 3 phases that corresponded to the following 3 menstrual phases: menstruation (phase 1, days 1–5), the follicular phase (phase 2, days 6–14), and the luteal phase (phase 3, days 15–28). The macronutrient composition of the Menstralean diet was aligned to match each of the 3 phases of the menstrual cycle (**Table 1**). The protein content of the diet was increased to optimize the body's response to increased resistance training in phase 2 and kept at this increased level in phase 3 with an aim to increase satiety, thereby maintaining adherence to a weight-loss diet despite the higher daily energy deficit in this phase. The dietary fat content was increased in phase 3 to accommodate the cravings that are often experienced in this phase. Furthermore, a portion of dark chocolate was allowed to be consumed on days 24–28, thereby increasing the daily caloric limit to 1800 kcal, also with the aim of satisfying cravings.

The control group was instructed to follow a program that was based on the Danish educational, unit-based diet system Kostkalender (The Diet Calendar). The system is built around tables that facilitate a simple calculation of the calorie content of foods and meals, thereby controlling total daily energy intake. This method ensured that there was strict control of energy intake while allowing freedom as to choice of foods. The macronutrient composition of the control diet was persistent throughout the period (Table 1). Compliance with the program was evaluated at dietary sessions at weeks 4 and 8. Compliance $<80\%$ was an exclusion criterion.

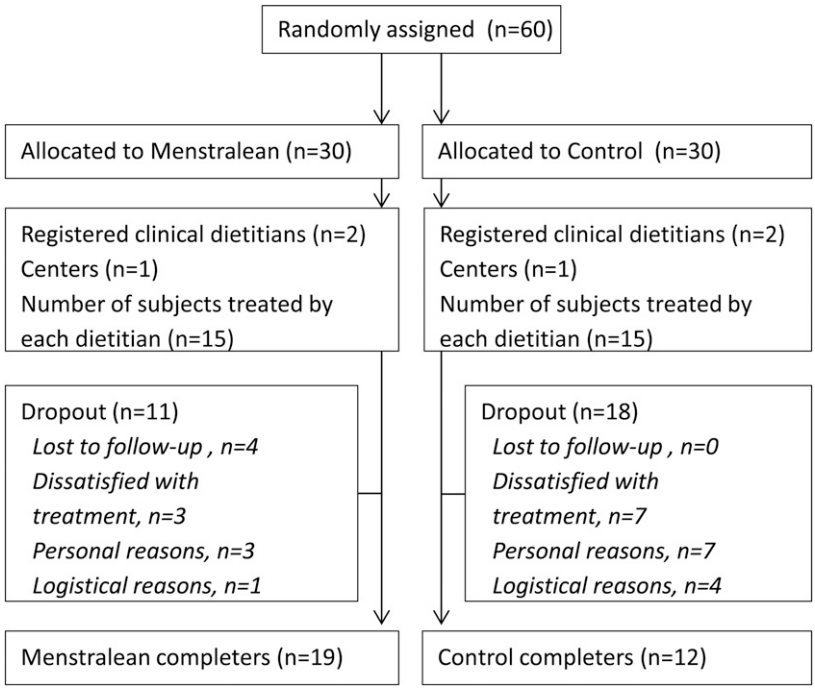

FIGURE 1 Consolidated Standards of Reporting Trials study flowchart.

TABLE 1
Diet and exercise program[1]

	Menstralean group, d			
	Phase I	Phase 2	Phase 3	Control group, d
	1–5	6–14	15–28	1–28
Energy, kcal/d	1600	1600	1600–1800[2]	1600
Carbohydrate, E%	60	50	40	45–50
Protein, E%	20	30	30	15–20
Fat, E%	20	20	30	30
Exercise	Light: 1 time/d	Circuit: 2 d/wk Cardio: 2–3 d/wk	Weight: 2 d/wk Cardio: 2–3 d/wk	Moderate: 30 min/d Vigorous: 2 d/wk

[1]E%, percentage of energy.
[2]Included an optional 200 kcal dark chocolate.

Physical activity

The Menstralean exercise program was also synchronized to the menstrual cycle (Table 1). Subjects were advised to pick one light activity each day from a list of exercises (e.g., walking, yoga, or stretching) when in phase 1. In phase 2, subjects were advised to perform circuit and weight training 2 d each week and to alternate with cardio and interval training 2–3 d/wk. Subjects were advised to alternate weight training with cardiovascular workouts in phase 3 with an aim to optimize the higher energy expenditure during this phase. The control exercise program was performed in accordance with Danish public health guidelines for physical activity, which corresponded to 30 min physical activity/d with high-intensity activity for 20 min ≥2 times/wk.

Measurements

Body weight was measured after subjects had emptied their bladders and were wearing only underwear at each visit and at follow-up, whereas waist circumference was measured at baseline and at weeks 12 and 24. Height was only measured at baseline. Body weight was measured to the nearest 0.1 kg with the use of a calibrated scale (Lindell Tronic 8000; Lindell), height was measured to the nearest 1 cm with the use of a wall-mounted stadiometer, and waist circumference was measured to the nearest 0.5 cm with the use of a nonstretchable measuring tape. Adverse events were registered throughout the project period. Any ongoing adverse events were followed up by telephone until they were resolved or a clinically stable endpoint was reached.

Sample-size calculation

A sample-size calculation showed that 50 subjects were needed to detect a mean ± SD difference of 3.0 ± 5.0 kg with the assumption of a significance level of 5% and 80% power.

Statistical analysis

The primary analysis was for the difference in the change in body weight after 24 wk in all randomly assigned subjects, and missing values were imputed via the means of the last observation carried forward [intention-to-treat (ITT) analysis]. To assess the sensitivity of results to assumptions about patient dropouts, the following 3 additional estimands were considered: *1*) adherence throughout the study period [per-protocol (PP) analysis]; *2*) adherence while in the study (i.e., until dropout or study termination, whichever came first) (available-case analysis); and *3*) if adherence in the study had continued, use of the available-case analysis augmented by multiple imputation (1000 draws) on the basis of the model fitted in scenario *2*) (12). We interpreted these 4 estimands as follows: the current primary (ITT) analysis evaluated the effectiveness of the intervention as if it were applied at a broader population level under the assumption that the achieved weight loss remained under nonadherence (**Figure 2**A). In contrast, the 3 sensitivity analyses evaluated varying degrees of efficacy. The PP analysis showed the efficacy

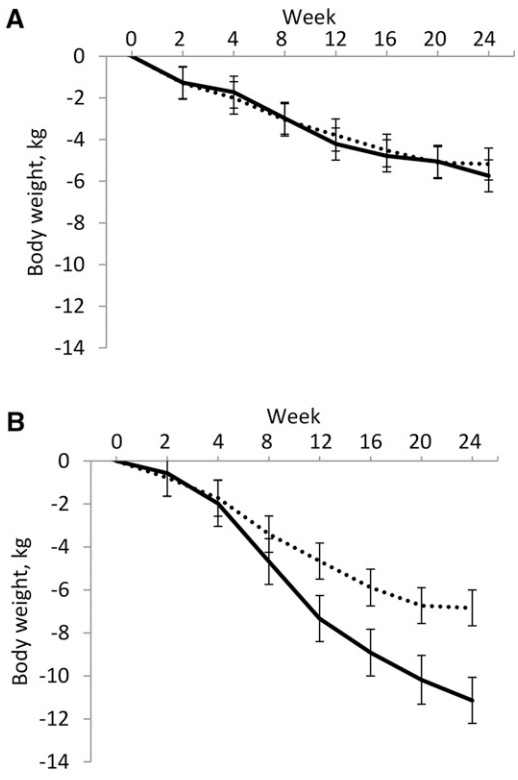

FIGURE 2 Mean ± SE changes from baseline in the Menstralean group (solid line) and the control group (dotted line). (A) Body weights of all patients who were randomly assigned (Menstralean group: $n = 30$; control group: $n = 30$) (intention-to-treat analysis). (B) Body weights of all patients who adhered throughout the study period (Menstralean group: $n = 19$; control group: $n = 12$) (per-protocol analysis).

in the subpopulation that adhered to the treatment until the very end of the study (Figure 2B). The available-case analysis without imputation described the efficacy in the subpopulation that adhered as long as they were comfortable with the treatment and, hence, possibly responded better to the intervention than did the PP population. Consequently, the longer this subpopulation remained in the study, the stronger the effect could be (**Figure 3**A). Finally, the available-case analysis with imputation prolonged the effects observed until dropout but without allowing any additional subsequent effect modification (Figure 3B).

For all 4 estimands, linear mixed models were fitted. These models contained intervention-time interactions (both treated as categorical variables) as well as adjustment for age and baseline body weight and BMI as fixed effects next to subjects as random effects. In addition, the serial correlation of repeated measurements within subjects was captured through a spatial Gaussian correlation structure. Model checking was based on a visual inspection of residual and quantile-quantile plots. The difference in the change in waist circumference after 24 wk was evaluated with the use of an available-case analysis via a similar linear mixed model except that the serial correlation was not modeled. Differences in dropouts were evaluated with the use of a chi-square test. Statistical analyses were carried out with the statistical environment R (R Foundation for Statistical Computing) (13), in particular with the use of the extension packages lme4, nlme, lsmeans, and multcomp. $P < 0.05$ was considered significant. Results are shown as means ± SEs.

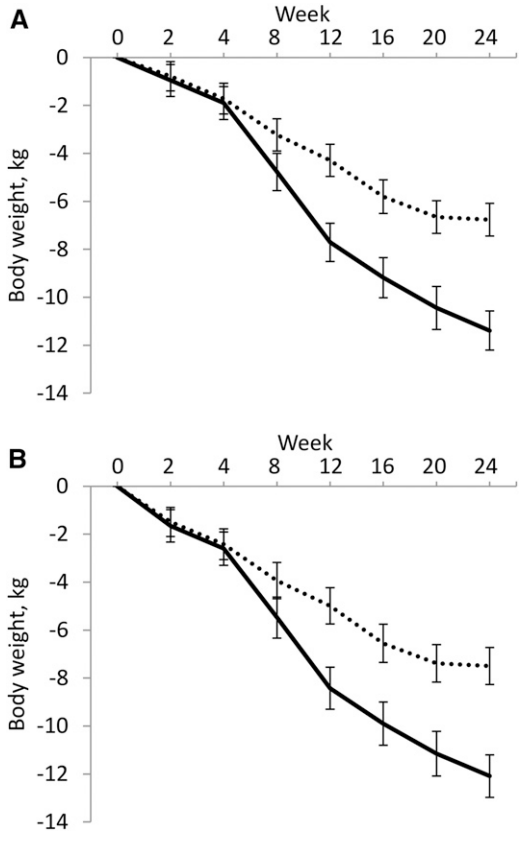

FIGURE 3 Mean ± SE changes from baseline in the Menstralean group (solid line) and the control group (dotted line). (A) Body weight by available-case analyses without multiple imputation. (B) Body weight by available-case analyses with multiple imputation. Menstralean group: $n = 30$; control group, $n = 30$.

RESULTS

A total of 60 women with mean ± SD BMI of 32.0 ± 5.2 were included in the study (30 women/group). Baseline characteristics between groups are shown in **Table 2**. Thirty-one participants completed the 24-wk intervention. The dropout rate was 38% (11 of 30 subjects) in the Menstralean group compared with 61% (18 of 30 subjects) in the control group ($P = 0.07$). Reasons for dropout are presented in Figure 1. None of the women were excluded because of noncompliance.

The primary analysis (ITT) showed a nonclinically significant greater weight loss of 0.6 ± 1.1 kg in the Menstralean group than in the control group ($P = 0.61$) (Figure 2A). The PP analysis showed a more-pronounced weight loss of 4.3 ± 1.4 kg ($P = 0.002$) in the Menstralean group than in the control group, which corresponded to weight reductions from baseline of 11.1 ± 1.1 and 6.8 ± 0.8 kg, respectively (percentage reductions: 14.3% ± 1.4% and 8.3% ± 1.0%, respectively) (Figure 2B). Similar differences in weight loss were shown for the available case analyses without and with multiple imputation [4.63 ± 1.07 kg ($P < 0.0001$) and 4.59 ± 1.12 kg ($P < 0.0001$), respectively] (Figure 3). Waist circumference was reduced more in the Menstralean group (2.8 ± 1.6 cm) than in the control group ($P = 0.08$) (**Figure 4**). No adverse events were registered during the study.

DISCUSSION

The Menstralean weight-loss program was designed to accommodate changes in dietary preferences and energy expenditure during the menstrual cycle. The 3 analyses of efficacy all indicated that the Menstralean group achieved an additional weight loss of ∼5 kg than was achieved with the traditional weight-loss program (Figures 2B and 3). However, the dropout rate was relatively high at 38% (11 of 30 subjects) in the Menstralean group compared with 61% (18 of 30 subjects) in the control group. We were not surprised that the dropout rate was very high in the control group because it has been well established that disappointment by being allocated to a control group and achieving only a modest weight reduction result in a higher attrition in control groups in weight-loss studies. The insignificant weight loss seen in the ITT analysis (Figure 2A) clearly showed that the success was entirely driven by the 62% of the women who managed to complete the program. In short, we showed a clear biological effect of the intervention under

TABLE 2
Baseline characteristics of all randomly assigned participants[1]

	Control group ($n = 30$)	Menstralean group ($n = 30$)
Age, y	29.5 ± 7.1	32.4 ± 7.0
Body weight, kg	87.0 ± 11.2	91.6 ± 17.3
Height, cm	167.3 ± 5.1	167.1 ± 6.7
BMI, kg/m^2	31.2 ± 4.3	32.8 ± 5.9
Waist circumference, cm	95.0 ± 13.4	97.2 ± 11.5

[1]All values are mean ± SDs.

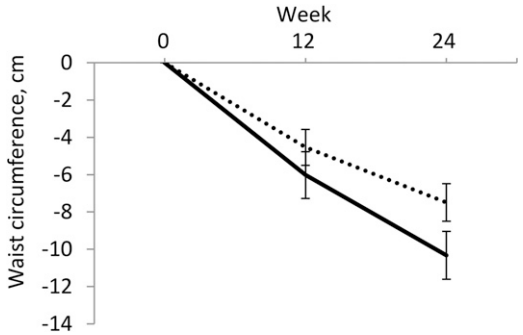

FIGURE 4 Mean ± SE waist circumferences for all patients in the Menstralean group (solid line) and the control group (dotted line) until dropout or study termination (available-case analysis). Waist circumference was measured from n = total subjects (Menstralean group/control group) at the 3 time points as follows: week 0, n = 58 (28/30); week 12, n = 34 (21/13); and week 24, n = 31 (19/12).

varying degrees of adherence, whereas the effectiveness in general clinical practice may be much more limited.

In healthy, premenopausal women who are not taking hormonal contraceptives, both energy intake and food preferences have been shown to change because of hormonal fluctuations during the menstrual cycle (3, 5–7, 10, 14). The highest preference for sweetness is shown in the luteal phase, and in this phase, ad libitum energy intake has been shown to be significantly higher (≤165 kcal more than in the follicular phase) (5, 6). Traditional weight-loss programs have generally specified energy intake and the level of physical activity often as a repeating weekly schedule. The Menstralean program met the natural increase in energy intake and changes in preferences by allowing an increased dietary fat content and an extra 200 kcal/d (as dark chocolate) in the luteal phase.

Diets that are high in protein have been proven to be more satiating and have been shown to aid weight loss and weight-loss maintenance (15–17). High-protein meals increase satiety and fullness and reduce hunger and energy intake in subsequent meals and in the next 24 h (15, 18, 19). The protein content of the Menstralean diet was higher than that recommended by both Danish and US public health authorities (20, 21). In the follicular and luteal phases (phases 2 and 3), the Menstralean diet included 30% of energy from protein. It is reasonable to assume that the higher protein content in the Menstralean diet aided the overall adherence to energy restriction through a higher satiating effect as well as by preserving levels of energy expenditure despite the dieting regimen (17, 22). To assess if the Menstralean diet had an additional effect on weight loss than does a constant high-protein diet, we could have included a third arm in the study in which the proportion of protein was increased but nonchanging through the menstrual phases. The combination of a higher protein content, especially in the luteal phase, combined with meeting the more frequent and intense cravings for sweet foods by allowing dark chocolate may have increased adherence to the diet and, thus, caused the additional weight loss in the Menstralean group.

Limitations of the current study include a high dropout rate, which was highest in the control group. Control subjects reported the main reasons for dropout as "being dissatisfied with treatment" and "personal." Subjects were eager to try a new weight-loss program and may have been less motivated when they were randomly assigned to the control program because this program resembled other programs that many had tried before with little or no success. In the Menstralean group, the dropout rate was lower, although it was still quite high for a 6-mo trial, and suggested that the program may have been difficult to follow. It is challenging to practice 3 alternating dietary and exercise regimens throughout each menstrual cycle in normal daily life.

Another limitation of the study is the open-label design, which is unavoidable in dietary intervention trials because they cannot be conducted in a blinded fashion. This design might have created a bias that affected the weight loss ratio. However, the weight loss of 7 kg over 6 mo in the control group was actually better than that generally shown with energy restriction and exercise programs.

Subjects in the current study, and in the majority of previous investigations on food and energy intakes during the menstrual cycle, did not use hormonal contraceptives (3, 5–7, 10, 14). More than 30% of the childbearing women in developed countries use oral contraception. The evidence of the effect of oral contraceptives on food intake has been contradictory.

The 3 phases of the Menstralean diet were designed to match the mean length of the phases in the menstrual circle. A new confirmatory study might benefit from the inclusion of a higher personalized adaptation to the hormonal flux and menstrual cycle by taking into consideration the high variation in the cycle length between women. Such a study would have the potential to accommodate dietary preferences and physical exercise capabilities and, thereby, improve adherence, reduce the dropout rate, and even further increase weight loss. In addition, in a confirmatory study, the registration of a care provider (i.e., clinical dietitian) would allow for adjustment for any potential difference within groups that was caused by differences in skills to enhance the women's adherence to the program.

In conclusion, to the best of our knowledge, this is the first report of a study that has examined the impact of a differentiated diet and exercise weight-loss program that was synchronized with the menstrual cycle in a group of healthy, overweight, premenopausal women. Our data provide suggestive evidence that synchronizing dietary composition and exercise with the menstrual cycle can have an additive effect to a traditional diet and exercise program.

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The authors' responsibilities were as follows—NRWG: prepared the manuscript; NRWG, CR, and AA interpreted the results; CR: conducted all of the statistical work; SDP: provided the daily management of the study; SDP, TML, JOH, and AA: designed the study; and all authors: critically reviewed the final manuscript before endorsing it. Sierra Research Group had no influence on the design, implementation, analysis, interpretation, or dissemination of the study. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. Dye L, Blundell J. Menstrual cycle and appetite control: implications for weight regulation. Hum Reprod 1997;12:1142–51.
2. Ovesen P, Vahl N, Fisker S, Veldhuis JD, Christiansen JS, Jørgensen JOL. Increased pulsatile, but not basal, growth hormone secretion rates and plasma insulin-like growth factor I levels during the periovulatory interval in normal women. J Clin Endocrinol Metab 1998;83:1662–7.

3. Davidsen L, Vistisen B, Astrup A. Impact of the menstrual cycle on determinants of energy balance: a putative role in weight loss attempts. Int J Obes (Lond) 2007;31:1777–85.
4. Buffenstein R, Poppitt SD, McDevitt RM, Prentice AM. Food intake and the menstrual cycle: a retrospective analysis, with implications for appetite research. Physiol Behav 1995;58:1067–77.
5. Lissner L, Stevens J, Levitsky D, Rasmussen K, Strupp B. Variation in energy intake during the menstrual cycle: implications for food-intake research. Am J Clin Nutr 1988;48:956–62.
6. Johnson WG, Corrigan SA, Lemmon CR, Bergeron KB, Crusco AH. Energy regulation over the menstrual cycle. Physiol Behav 1994;56: 523–7.
7. Pliner P, Fleming AS. Food intake, body weight, and sweetness preferences over the menstrual cycle in humans. Physiol Behav 1983;30: 663–6.
8. Mannucci E, Ognibene A, Becorpi A, Cremasco F, Pellegrini S, Ottanelli S, Rizzello SM, Massi G, Messeri G, Rotella CM. Relationship between leptin and oestrogens in healthy women. Eur J Endocrinol 1998; 139:198–201.
9. Hormes JM, Timko CA. All cravings are not created equal. Correlates of menstrual versus non-cyclic chocolate craving. Appetite 2011;57: 1–5.
10. Dalvit SP. The effect of the menstrual cycle on patterns of food intake. Am J Clin Nutr 1981;34:1811–5.
11. Chiazze L Jr., Brayer FT, Macisco JJ Jr., Parker MP, Duffy BJ. The length and variability of the human menstrual cycle. JAMA 1968;203: 377–80.
12. The International Council for Harmonisation. E9(R1): Addendum to statistical principles for clinical trials on choosing appropriate estimands and defining sensitivity analyses in clinical trials. Geneva, Switzerland: ICH Secretariat; 2014.
13. R Core Team. R: A language and environment for statistical computing. 2014. R Foundation for Statistical Computing, Vienna, Austria.
14. Wright P, Crow RA. Menstrual cycle: effect on sweetness preferences in women. Horm Behav 1973;4:387–91.
15. Westerterp-Plantenga MS, Lejeune M, Nijs I, Van Ooijen M, Kovacs E. High protein intake sustains weight maintenance after body weight loss in humans. Int J Obes Relat Metab Disord 2004;28:57–64.
16. Larsen TM, Dalskov S-M, van Baak M, Jebb SA, Papadaki A, Pfeiffer AF, Martinez JA, Handjieva-Darlenska T, Kunešová M, Pihlsgård M. Diets with high or low protein content and glycemic index for weight-loss maintenance. N Engl J Med 2010;363:2102–13.
17. Leidy HJ, Clifton PM, Astrup A, Wycherley TP, Westerterp-Plantenga MS, Luscombe-Marsh ND, Woods SC, Mattes RD. The role of protein in weight loss and maintenance. Am J Clin Nutr 2015;101(Suppl): 1320S–9S.
18. Harper A, James A, Flint A, Astrup A. Increased satiety after intake of a chocolate milk drink compared with a carbonated beverage, but no difference in subsequent ad libitum lunch intake. Br J Nutr 2007;97: 579–83.
19. Ratliff J, Leite JO, de Ogburn R, Puglisi MJ, VanHeest J, Fernandez ML. Consuming eggs for breakfast influences plasma glucose and ghrelin, while reducing energy intake during the next 24 hours in adult men. Nutr Res 2010;30:96–103.
20. Nordic Council of Ministers. Nordic nutrition recommendations 2012: integrating nutrition and physical activity. 2014. Copenhagen, Denmark
21. US Department of Health and Human Services and U.S. Department of Agriculture. Dietary Guidelines for Americans, 2005. 6th ed. Washington (DC): US Government Printing Office; 2005.
22. Halton TL, Hu FB. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. J Am Coll Nutr 2004;23:373–85.