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ORIGINAL ARTICLE

Sleep and Metabolic Health

Effects of acute sleep loss on leptin, ghrelin, and adiponectin in adults with healthy weight and obesity: A laboratory study

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Abstract

Objective: This study investigated whether blood concentrations of leptin, ghrelin, and adiponectin are affected by acute total sleep deprivation in a sex- and weight-specific manner.

Methods: A total of 44 participants (mean age 24.9 years; 20 women; 19 with obesity) participated in a crossover design, including one night of sleep deprivation and one night of sleep in the laboratory. After each night, fasting blood was collected.

Results: After sleep deprivation, fasting levels of leptin were lower (mean [SE], vs. sleep: 17.3 [2.6] vs. 18.6 [2.8] ng/mL), whereas those of ghrelin and adiponectin were higher (839.4 [77.5] vs. 741.4 [63.2] pg/mL and 7.5 [0.6] vs. 6.8 [0.6] µg/mL, respectively; all $p < 0.05$). The changes in leptin and adiponectin following sleep loss were more pronounced among women. Furthermore, the ghrelin increase was stronger among those with obesity after sleep loss. Finally, the sleep loss-induced increase in adiponectin was more marked among normal-weight participants.

Conclusions: Acute sleep deprivation reduces blood concentrations of the satiety hormone leptin. With increased blood concentrations of ghrelin and adiponectin, such endocrine changes may facilitate weight gain if persisting over extended periods of sleep loss. The observed sex- and weight-specific differences in leptin, ghrelin, and adiponectin call for further investigation.

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INTRODUCTION

A lack of sleep may be a risk factor for weight gain. For example, acute sleep deprivation elicits more robust brain reward responses to food cues [1–4], stimulates food purchases [5], and increases daily food intake [6]. In addition, according to experimental studies, lower serum levels of the satiety-promoting hormone leptin and higher blood concentrations of the endocrine hunger signal ghrelin may account for the hyperphagic effects of acute sleep deprivation [7–10]. Leptin is an adipocyte-derived hormone that activates satiety networks within the brain [11]. Ghrelin, as opposed to leptin, is mainly produced by the stomach and it acts as a hunger hormone, signaling fuel status to the central nervous system [12]. However, some studies have found no alterations or higher leptin and lower ghrelin blood levels following experimental sleep deprivation [13–18].

Data from animal studies suggest that adiponectin, a hormone secreted by the white adipose tissue [19], possesses the properties of a starvation hormone. For example, fasting increases serum and cerebrospinal fluid levels of adiponectin in mice, whereas reduced levels of this adipokine are found after refeeding [20]. It has further been shown to increase food intake [20]. Beyond its role in central nervous system regulation of food intake, adiponectin fulfills numerous metabolic functions, for example, improving insulin sensitivity and reducing inflammation [19]. This adipokine may also play a role in lipid accumulation in adipocytes. For example, lentiviral overexpression of adiponectin in 3 T3-L1 cells (cells differentiating into an adipocyte-like phenotype) enhances glucose uptake, lipid storage, and adipogenesis [21]. Elevated blood levels of adiponectin could therefore represent an endocrine mechanism underlying increased food intake [22] and buildup of body fat deposits following acute total sleep deprivation [23]. However, no clear pattern has emerged regarding the effects of partial or total acute sleep loss on serum levels of adiponectin [15, 24, 25].

An often-neglected factor that may affect the metabolic response to sleep loss is a person's biological sex [18, 26, 27]. For example, a study including 179 adults using accelerometry and eating questionnaires found that, in men only, higher sleep fragmentation index, longer sleep onset latency, and lower sleep efficiency were associated with a greater tendency toward hunger [28]. This result contrasts with findings of a separate study showing that insufficient sleep increased food intake and led to weight gain in women only [29]. Therefore, more studies are needed to investigate how acute sleep loss affects appetite-regulatory pathways in men and women.

Experimental and epidemiological work suggests that chronic sleep loss drives the development of obesity [1–6, 30]. However, evidence is scarce on whether hormones regulating appetite and body composition are differently affected by acute sleep deprivation in people suffering from obesity compared with those with normal weight. To our knowledge, only one study has demonstrated that people with obesity undergoing 14 days of moderate caloric restriction exhibited increased 24-hour blood ghrelin concentrations when concomitantly undergoing sleep restriction [31].

To investigate possible sex- and weight-specific effects of sleep loss, in the present in-laboratory experiment, we measured fasting blood levels of leptin, ghrelin, and adiponectin after one night of sleep and one night of total sleep deprivation (e.g., as occurs in night shift workers and

Study Importance

What is already known?

- Sleep loss has been associated with an increased risk of weight gain and obesity. However, whether acute sleep loss affects hormonal pathways involved in food intake and body composition control differently between men versus women and participants with normal weight versus obesity is not well researched.

What does this study add?

- Acute total sleep deprivation resulted in lower fasting serum concentrations of the satiety hormone leptin and higher plasma levels of hunger-promoting ghrelin. We also found elevated serum adiponectin concentrations following sleep loss. In murine studies, this adipokine has been shown to increase food intake and promote lipid accumulation in adipocytes. Notably, some of these effects may vary by biological sex and weight status.

How might these results change the direction of research?

- The observed sex- and weight-specific differences in leptin, ghrelin, and adiponectin call for further investigation in larger samples.

parents) in a cohort of young adult men and women with either normal weight or obesity. We hypothesized that blood levels of the satiety hormone leptin would drop while those of the hunger-promoting hormone ghrelin would rise in response to sleep loss. However, in light of somewhat controversial findings regarding how sleep loss affects adiponectin [15, 24, 25], we had no a priori hypothesis regarding whether acute sleep loss would increase or decrease blood levels of this adipokine.

METHODS

Participants

The present laboratory study was based on blood samples from 44 participants, mainly university students (mean [SD] age: 24.9 [2.9] years; 20 women). Nineteen participants (nine women) suffered from obesity, that is they had a body mass index (BMI) ≥ 30 kg/m² and an excessive waist circumference (>102 cm for men and >88 cm for women, respectively) [32]. Normal weight ($n = 25$; 11 women) was defined as having BMI <25 and normal waist circumference (<94 cm for men and <88 cm for women, respectively) [32]. All of the included women were on combined

hormonal contraceptives at the time of the study, as hormonal changes naturally occurring across the menstrual cycle can affect appetite regulation, for example [33].

Screening procedures ensured that participants had a good general health status, including that they did not chronically or acutely suffer from somatic or psychiatric diseases. In addition, participants were not shift workers and they did not travel across time zones for at least a month before participation or during the study period.

The experimental procedures were performed following the Declaration of Helsinki and approved by the ethical board of Uppsala, Sweden (DNR2017/560). All participants provided written informed consent before the onset of the study and they were compensated for participation. The ethical board of Uppsala did not classify the study to be a clinical trial. Therefore, no clinical trial was preregistered. The described experiment herein is part of a more extensive study investigating the health consequences of total sleep deprivation [34–36].

Study design and procedure

The present study was based on a randomized crossover design. Participants came to the sleep laboratory for two experimental sessions, including one night when participants stayed awake and one night when they could sleep during an 8-hour window. The testing sessions were counterbalanced across participants and separated by about 1 week. Within 7 days before the first experimental session, participants came to the laboratory for an adaptation night. Women's experimental sessions were scheduled outside their menses.

Participants were continuously supervised in each in-laboratory experimental condition, starting with a standardized dinner at 7:00 p.m. Participants' sleep in the sleep condition was scheduled between 11:00 p.m. and 7:00 a.m. Sleep duration was measured by a SOMNO HD polysomnography recorder (SOMNOmedics GmbH). During the experimental sleep deprivation night, participants watched movies, played board games with the experimenter, or read books under normal indoor light conditions (~500 lux).

TABLE 1 Cohort characteristics divided by subgroups

	Subgroups (N = 44)		p value	Normal weight	Obesity	p value
	Men	Women				
Participants, n						
Men/women	24/0	0/20	–	14/11	10/9	–
Normal weight/obesity	14/10	11/9	–	25/0	0/19	–
Age (y)	25.1 ± 2.8	24.7 ± 3.0	0.700	24.9 ± 2.5	25.0 ± 3.4	0.893
BMI (kg/m ²)	27.8 ± 6.7	27.0 ± 6.1	0.690	22.4 ± 1.9	34.1 ± 3.5	<0.001
Waist circumference (cm)	93.5 ± 16.3	87.9 ± 17.7	0.283	78.4 ± 8.3	107.9 ± 8.7	<0.001
MEQ score	53.4 ± 7.7	51.9 ± 9.3	0.591	53.4 ± 9.5	51.9 ± 5.6	0.565

Note: All values shown as mean ± SD unless differently specified. Using independent t tests, no significant differences between the male and female and normal-weight and obesity subgroups were found, except for the expected significant difference in BMI and waist circumference between the normal-weight and obesity subgroup ($p < 0.001$ for both).

Abbreviation: MEQ score, morningness eveningness questionnaire score.

After the overnight fast (i.e., after both sleep and total sleep deprivation), blood was collected at 7:30 a.m. and centrifuged at 1300 relative centrifugal force for 10 minutes at 4 °C. The supernatant was then aliquoted and stored at –80 °C until further analysis. For serum leptin measurements, we used the Human Leptin Quantikine ELISA Kit (DLP00) from Biotechne. Serum adiponectin concentrations were determined by the Human Total Adiponectin/Acrp30 Quantikine ELISA Kit (DRP300; Biotechne). Finally, a commercially available ELISA was used for assaying total ghrelin (EZGRT-89 K; Millipore).

Statistical analysis

All data were analyzed using SPSS Statistics version 28 (IBM Corp.) and shown as mean ± SE, unless otherwise stated. Data were not normally distributed, as assessed by the Kolmogorov–Smirnov test ($p < 0.05$). Therefore, we used the Wilcoxon signed rank test to compare total sleep deprivation and sleep in the entire group and groups stratified by biological sex and weight status. To test for possible sex- and weight-specific effects of acute total sleep deprivation, we determined individual differences in hormonal levels between the wake and sleep conditions for both sexes and weight groups separately. We then used Mann–Whitney *U* tests to compare individual wake–sleep differences between the sex and weight subgroups. A p value < 0.05 was considered significant.

To measure the effect size (r), we divided *Z* statistic derived from the Wilcoxon signed rank test by the square root of the number of observations. The interpretation values for the effect size r are the following: 0.10 to ≤ 0.30 (small effect), $0.30 \leq 0.50$ (moderate effect), and ≥ 0.50 (large effect) [37].

RESULTS

Cohort characteristics and sleep comparisons

BMI and waist circumference were similar for men and women ($p = 0.690$ for BMI [unpaired *t* test]; $p = 0.283$ for waist circumference

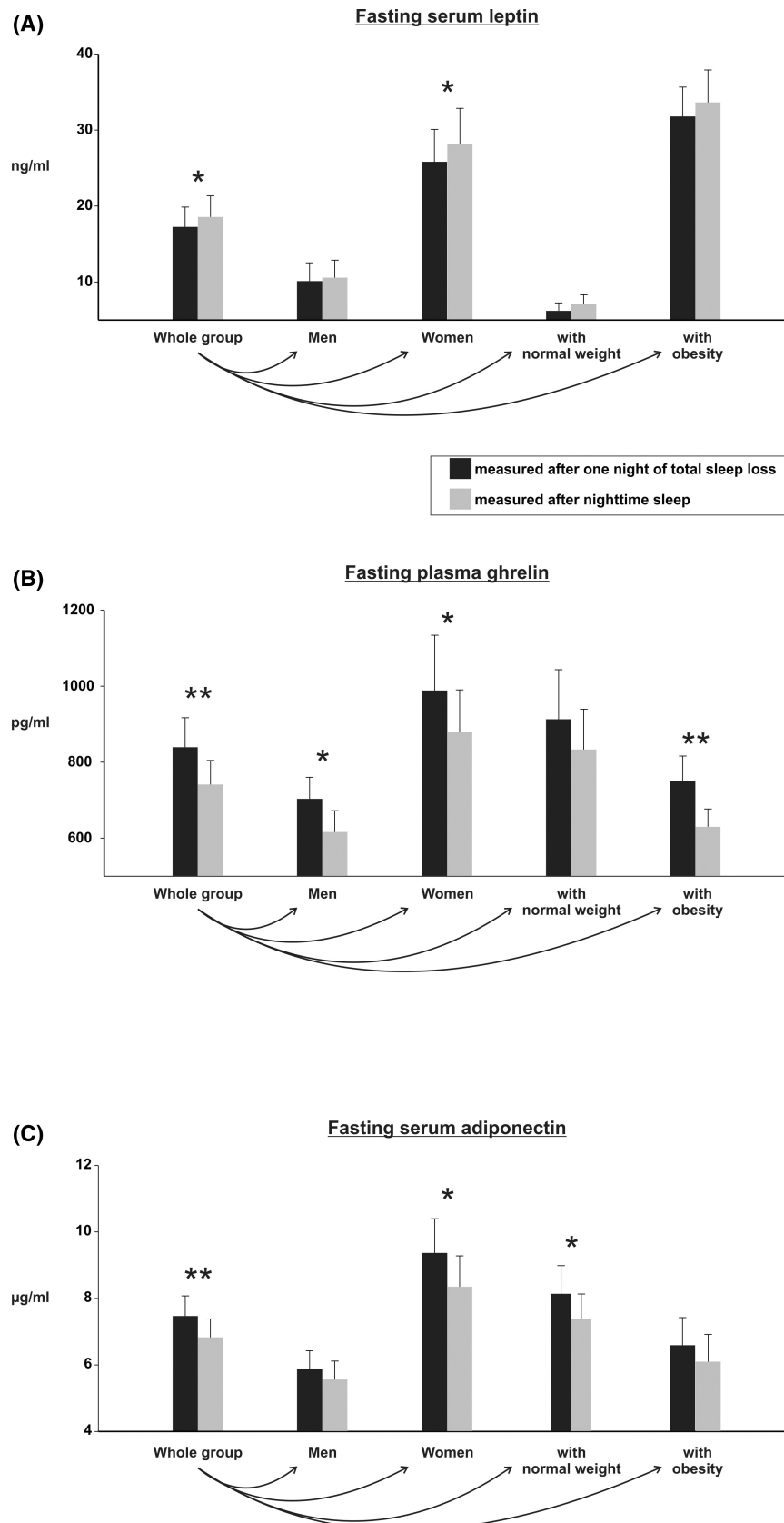


FIGURE 1 Effects of acute total sleep deprivation on fasting blood levels of (A) leptin, (B) ghrelin, and (C) adiponectin. Whole group, $N = 44$; male subgroup, $n = 24$; female subgroup, $n = 20$; subgroup with normal weight, $n = 25$; subgroup with obesity, $n = 19$. * $p < 0.05$ (Wilcoxon signed rank test); ** $p < 0.01$ (Wilcoxon signed rank test)

[unpaired *t* test]; Table 1); however, both measures strongly differed between the weight groups ($p < 0.001$ for BMI [unpaired *t* test]; $p < 0.001$ for waist circumference [unpaired *t* test]; Table 1). No differences in age and chronotype, assessed by [38], were found between men and women and those with normal weight and obesity, respectively (Table 1).

Total sleep duration did not differ between sex and weight groups (total sleep duration: men vs. women, 7.3 ± 0.5 vs. 7.2 ± 0.6 hours, $p = 0.725$ [unpaired *t* test]; those with normal weight vs. those with obesity: 7.4 ± 0.5 vs. 7.0 ± 0.6 hours, $p = 0.086$ [unpaired *t* test]).

Leptin

After total sleep deprivation, serum concentrations of leptin were about 7% lower than levels measured after sleep (17.3 ± 2.6 vs. 18.6 ± 2.8 ng/mL, $p = 0.037$ [Wilcoxon signed rank test], $r = 0.22$; Figure 1A). A sex-stratified analysis revealed that, following total sleep deprivation, serum leptin was significantly lower in women (sleep loss vs. sleep: 25.8 ± 4.3 vs. 28.1 ± 4.7 ng/mL, $p = 0.030$ [Wilcoxon signed rank test], $r = 0.34$; Figure 1A) but not in men (sleep loss vs. sleep: 10.1 ± 2.4 vs. 10.6 ± 2.3 ng/mL, $p = 0.458$ [Wilcoxon signed rank test], $r = 0.11$; Figure 1A); however, individual wake-sleep differences in serum leptin did not reach significance between men and women (-0.5 ± 0.7 vs. -2.3 ± 0.9 ng/mL, $p = 0.138$ [Mann-Whitney *U* test]).

When stratifying the analysis for weight status, we found that serum leptin was lower among participants with normal weight and obesity (sleep loss vs. sleep: with normal weight, 6.2 ± 1.0 vs. 7.1 ± 1.2 ng/mL, $r = 0.26$; with obesity, 31.8 ± 3.9 vs. 33.6 ± 4.3 ng/mL, $r = 0.22$; Figure 1A); however, the differences in leptin did not reach significance between the sleep conditions ($p \geq 0.069$). Likewise, individual wake-sleep differences in serum leptin did not differ between the weight subgroups (those with normal weight vs. those with obesity: -0.9 ± 0.4 vs. -1.9 ± 1.2 ng/mL, $p = 0.337$ [Mann-Whitney *U* test]).

Ghrelin

We found about 100 pg/mL higher plasma ghrelin levels following acute total sleep deprivation (vs. sleep, 839.4 ± 77.5 vs. 741.4 ± 63.2 pg/mL, $p = 0.003$ [Wilcoxon signed rank test], $r = 0.32$; Figure 1B). The significant difference in plasma ghrelin between the sleep and total sleep deprivation conditions was confirmed in both sexes and those with obesity (men: 703.6 ± 56.6 vs. 616.2 ± 56.1 pg/mL, $p = 0.024$ [Wilcoxon signed rank test], $r = 0.34$; women: 988.8 ± 145.3 vs. 879.1 ± 111.2 pg/mL, $p = 0.049$ [Wilcoxon signed rank test], $r = 0.31$; with normal weight: 913.0 ± 130.4 vs. 833.5 ± 106.0 pg/mL, $p = 0.095$ [Wilcoxon signed rank test], $r = 0.25$; and those with obesity: 750.4 ± 65.8 vs. 629.9 ± 47.1 pg/mL, $p = 0.007$ [Wilcoxon signed rank test], $r = 0.44$; Figure 1B). When comparing individual wake-sleep

differences in plasma ghrelin between the sex and weight subgroups, no significance was found (men vs. women: 87.4 ± 51.9 vs. 109.7 ± 52.5 pg/mL, $p = 0.762$ [Mann-Whitney *U* test]; those with normal weight vs. those with obesity: 79.5 ± 58.5 vs. 120.4 ± 39.9 pg/mL, $p = 0.471$ [Mann-Whitney *U* test]).

Adiponectin

Serum adiponectin was about 10% higher after total sleep deprivation than sleep (7.5 ± 0.6 vs. 6.8 ± 0.6 μ g/mL, $p = 0.003$ [Wilcoxon signed rank test], $r = 0.31$; Figure 1C). These sleep deprivation effects were also found among women and those with normal weight (men: 5.9 ± 0.5 vs. 5.6 ± 0.6 μ g/mL, $p = 0.056$ [Wilcoxon signed rank test], $r = 0.28$; women: 9.4 ± 1.0 vs. 8.4 ± 0.9 μ g/mL, $p = 0.025$ [Wilcoxon signed rank test], $r = 0.35$; with normal weight: 8.1 ± 0.8 vs. 7.4 ± 0.7 μ g/mL, $p = 0.040$ [Wilcoxon signed rank test], $r = 0.29$; and those with obesity: 6.6 ± 0.8 vs. 6.1 ± 0.8 μ g/mL, $p = 0.053$ [Wilcoxon signed rank test], $r = 0.31$; Figure 1C). Individual wake-sleep differences in serum adiponectin between the sex and weight subgroups did not reach significance (men vs. women: 0.3 ± 0.2 vs. 1.0 ± 0.5 μ g/mL, $p = 0.164$ [Mann-Whitney *U* test]; those with normal weight vs. those with obesity: 0.8 ± 0.3 vs. 0.5 ± 0.3 μ g/mL, $p = 0.951$ [Mann-Whitney *U* test]).

DISCUSSION

We demonstrate in a cohort of young adults with either normal weight or obesity that acute total sleep deprivation is linked to lower serum levels of the adipokine leptin and higher blood levels of ghrelin. Leptin acts as a satiety-promoting signal, whereas ghrelin stimulates food intake [11, 12]. Whether this shift from a satiety- toward a hunger-promoting hormone facilitates weight gain, as seen after a more prolonged period of sleep loss [29], is unclear. We also found that serum adiponectin levels were elevated following total sleep deprivation. This peptide is secreted by adipocytes and is often termed a “good” adipokine owing to its anti-inflammatory, antiatherogenic, antidiabetic, and cardioprotective effects [19]. However, animal data suggest that adiponectin increases food intake and that it may promote lipid accumulation in adipocytes [20, 21]. Whether the observed rise in adiponectin following acute total sleep deprivation could explain increased food intake and buildup of body fat under chronic conditions of sleep loss [39, 40] is unclear.

Sex-specific analyses indicated that the drop in serum leptin was larger in women after total sleep deprivation; however, no significant interaction between biological sex and experimental condition was found. Furthermore, we found that the increase in blood levels of adiponectin was slightly more pronounced among women. In contrast, no differences were observed in the effects of sleep loss on plasma ghrelin. Our findings contrast with some previous results. For example, no sex differences in serum leptin were

found when studying the impact of repeated partial sleep loss on daytime serum leptin profiles in normal-weight men ($n = 14$) and women ($n = 13$) with multiethnic backgrounds [25]. In contrast, women exhibited lower blood levels of the satiety-promoting incretin glucagon-like peptide 1 [25]. Notwithstanding these discrepancies, both studies suggest that sleep loss may affect hormones involved in regulating energy balance differently in men and women.

Chronic sleep loss has been associated with an increased risk of gaining weight and developing obesity [1–6, 30]. Although no significant interaction between weight status and experimental condition was detected, we observed that the rise in plasma ghrelin after sleep loss was more distinct among those with obesity. In contrast, the sleep loss-induced increase of serum adiponectin appeared to be larger in participants with normal weight. Our results could suggest, if others confirm, that acute total sleep deprivation affects hormones involved in appetite and body composition control differently between people with obesity and those with normal weight; however, the underlying mechanisms are still unclear.

Several limitations apply to our study. First, blood was only measured once in the morning after sleep and total sleep deprivation. Therefore, we cannot rule out that the observed endocrine effects of acute total sleep deprivation were restricted to the morning. Consequently, sex- and weight status-specific effects of acute total sleep deprivation on the herein measured hormones may have emerged or disappeared if blood had been collected at other times of the day. It must also be noted that the observed effects sizes of acute total sleep deprivation on the measured hormones ranged from small to moderate. Another limitation of our study is that we did not measure food intake. Therefore, it remains unclear whether the observed hormonal changes due to acute sleep loss would lead to excessive food intake. The latter is particularly relevant as previous studies have shown that insufficient sleep over 5 consecutive days results in weight gain of about 1 kg despite changes in satiety hormones such as ghrelin and leptin [29]. With these limitations in mind, our findings must be replicated in more extensive studies, also employing other sleep deprivation protocols (e.g., partial sleep loss or sleep fragmentation), both inside and outside the laboratory environment.

In conclusion, our study suggests that acute total sleep deprivation shifts the endocrine balance from the satiety hormone leptin toward the hunger-promoting hormone ghrelin. In addition, increased adiponectin following acute total sleep loss could explain increased food intake and lipid accumulation in adipocytes, as previously observed after one night of sleep loss [22, 23]. The observed sex- and weight-specific differences in leptin, ghrelin, and adiponectin call for further investigation in larger samples. ○

AUTHOR CONTRIBUTIONS

Christian Benedict, Maria Ilemosoglou, Joachim Engström, and Lieve T. van Egmond conceived and designed the project. Maria Ilemosoglou, Joachim Engström, Elisa M.S. Meth, Jasmin Annica Keller, and Lieve T. van Egmond performed the majority of the experiments. Heike Vogel ran the hormonal assays. All wrote the manuscript.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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