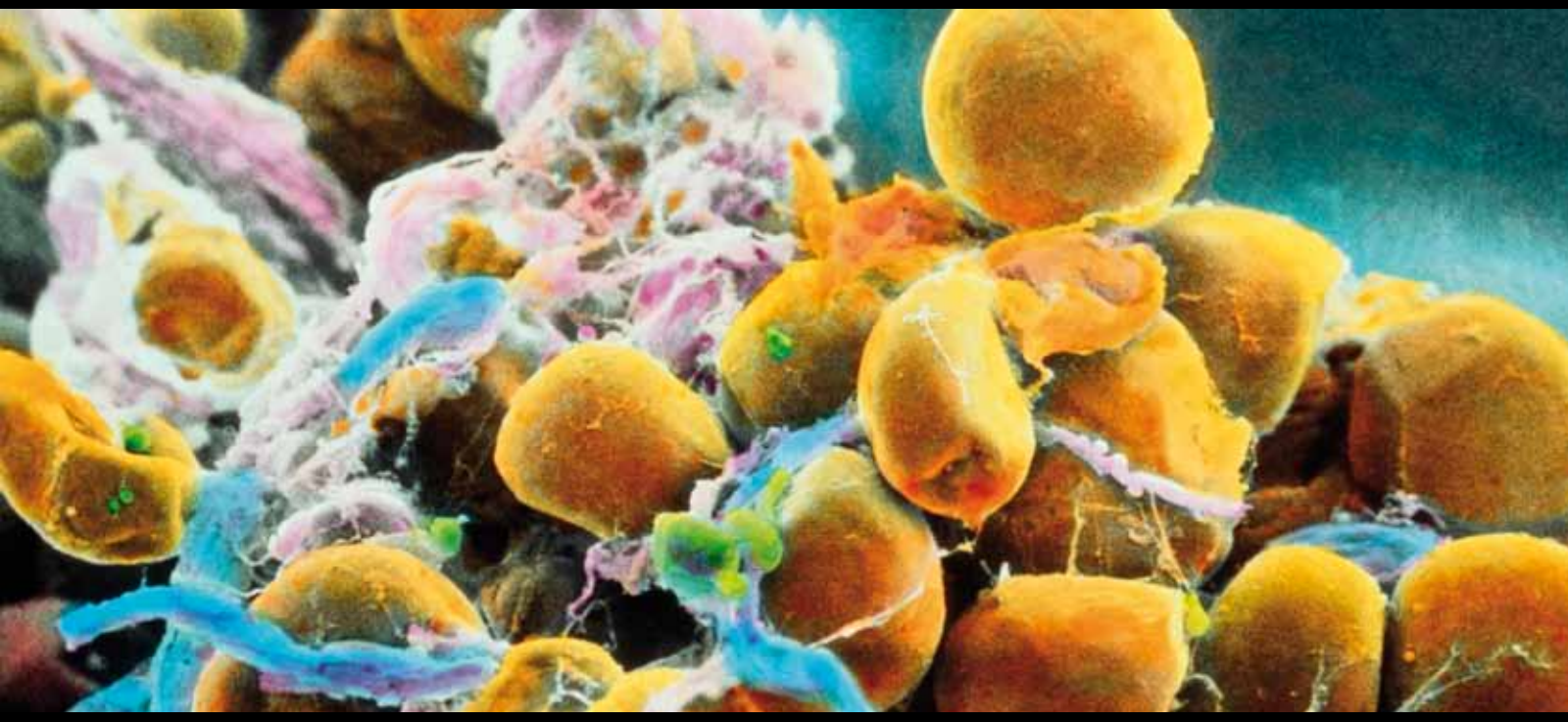
Journal of Obesity

Depression, Obesity, Eating Behavior, and Physical Activity

Guest Editors: Kristin L. Schneider, Austin S. Baldwin, Devin M. Mann, and Norbert Schmitz



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Editorial Board

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Editorial

Depression, Obesity, Eating Behavior, and Physical Activity

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1. Introduction to Special Issue

My coeditors and I are delighted to share this special issue of the Journal of Obesity focused on understanding the comorbidity between obesity and depression. Depression is highly comorbid with obesity [1–3] and may impede weight loss treatment [4–9]. Just as a successful reduction in the obesity epidemic must entail a multilevel approach to obesity, the papers contained in this special issue represent a diverse examination of the depression and obesity comorbidity. Papers include an examination of individual and environmental factors relevant to depression and obesity, child and adult samples, animal models, and laboratory and epidemiological studies. A brief overview of the papers follows.

Obesity in childhood is highly predictive of adult obesity [10, 11]. Thus, there has been an increasing focus on the prevention of obesity in children to address the epidemic. Research suggests that in utero factors can contribute to childhood obesity (e.g., [12–14]). Expanding on this work, K. G. Ingstrup and colleagues explored whether symptoms of maternal distress during pregnancy predict childhood obesity at age 7 in a large prospective cohort study in Denmark. Parents are one source of influence discussed in the review article by S. Russell-Mayhew and colleagues regarding mental health issues in childhood obesity. They raise important questions about the challenges overweight and obese children face that can contribute to poorer health outcomes.

In adults, the positive association observed between depression and obesity is relatively robust, though the relationship between suicidal ideation and obesity, particularly in women, is less clear. G. Zhao and colleagues used NHANES data to examine the relationship between suicide and obesity, waist-hip ratio, and waist circumference. Though depression may not necessarily hinder weight loss treatment [15, 16], the increased suicidal ideation observed in obese women suggests that depression symptoms should not be ignored during weight loss treatment.

The fact that negative moods can both prompt and result from binge eating episodes, and that binge eating is associated with obesity, suggests that a conversation about depression and obesity would be remiss if it did not include binge eating. R. F. Petersen and colleagues examined the relationship between binge eating disorder, depression, anxiety, and caloric intake in overweight and obese adult women to elucidate how negative mood states impact food intake in the context of binge eating disorder. The work of J. W. Jahng and colleagues provides additional insight into why negative moods may result in binge eating by exploring the dopaminergic activity of rats during fasting and refeeding cycles. These papers nicely set the stage for the study by C. Cifani and colleagues who explored a potential treatment agent for binge eating, *Hypericum perforatum*, more commonly known as St. John's Wort, in rats.

Lastly, as physical activity may serve as a protective factor for obesity and depression, it is important to understand the barriers and facilitators to engagement in physical activity.

W. Yang and colleagues explore some of the individual and environmental variables that are associated with engagement in leisure time physical activity. These factors may serve as important treatment targets for interventions that seek to increase physical activity as a potentially parsimonious treatment for comorbid obesity and depression.

Although the articles in this special issue address a range of topics relevant to the depression and obesity comorbidity, there is clearly much more work to be done to reduce the comorbidity. We hope that this special issue stimulates ideas for future research and facilitates interventions for prevention and treatment.

Kristin L. Schneider
Austin S. Baldwin
Devin M. Mann
Norbert Schmitz

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Research Article

Effect of *Hypericum perforatum* Extract in an Experimental Model of Binge Eating in Female Rats

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Purpose. The present study evaluated the effect of *Hypericum perforatum* dry extract in an experimental model of binge eating (BE). *Methods*. BE for highly palatable food (HPF) was evoked in female rats by three 8-day cycles of food restriction/re-feeding and acute stress on the test day (day 25). Stress was induced by preventing access to HPF for 15 min, while rats were able to see and smell it. *Hypericum perforatum* dry extract was given by gavage. *Results*. Only rats exposed to both food restrictions and stress exhibited BE. The doses of 250 and 500 mg/kg of *Hypericum perforatum* extract significantly reduced the BE episode, while 125 mg/kg was ineffective. The same doses did not affect HPF intake in the absence of BE. The dose of 250 mg/kg did not significantly modify stress-induced increase in serum corticosterone levels, suggesting that the effect on BE is not due to suppression of the stress response The combined administration of 125 mg/kg of *Hypericum perforatum* together with Salidroside, active principle of *Rhodiola rosea*, produced a synergic effect on BE. *Conclusions*. The present results indicate for the first time that *Hypericum perforatum* extracts may have therapeutic properties in bingeing-related eating disorders.

1. Introduction

Episodes of binge eating (BE) in humans are characterized by compulsive, nonhomeostatic consumption of an unusually large quantity of highly palatable food (HPF) in a short period of time. Even though not hungry, subjects eat more rapidly than normal until feeling uncomfortably full. These episodes are accompanied by subjective sense of loss of control over eating and are associated with feeling of distress, disgust, depression, being guilty about overeating, and eating alone because of embarrassment [1].

BE represents a central feature of bulimia nervosa, in which episodes of BE are followed by behaviours aimed at avoiding weight gain, such as self-induced vomiting. Intense and persistent BE episodes represent a typical phenomenon occurring also in subjects suffering from binge eating disorder (BED) [2] that is probably the most prevalent eating disorder [3]. It is characterized by repeated episodes of BE in the absence of compensatory behaviours to avoid weight gain. The DMS-IV-TR [1] indicates among diagnostic criteria for BED that BE episodes should occur at least 2 days per week for six months. The BED is associated with significant medical and psychiatric comorbidity [4–6]. It is estimated that BE afflicts approximately 5% of the US adult population at some time in their life [7], and it contributes to aggravate obesity and associated pathologies [3, 8–10].

A large body of evidence suggests that dieting, stress and negative affective states represent possible triggers of BE in patients suffering from BED or bulimia nervosa [11, 12]. Indeed, dieting periods are a common finding in the history of binge eaters, although hunger per se appears to be not enough to induce BE in the absence of stress and negative affective states [13, 14]. Considerable evidence suggests that BE may be caused by a unique interaction between dieting and stress; thus, environmental stress and a history of cyclic food restrictions may be responsible for its precipitation and maintenance [15–17]. Accordingly, recurring food restrictions are consistently

the strongest predictor of overeating in response to stress [11].

Despite a growing recognition of the consequences of bulimia nervosa and of BED on public health, satisfactory treatments are not available at present [18]. Medications that have been suggested to reduce BE in clinical studies, like topiramate [19, 20] or sibutramine [21, 22] are associated with a variety of adverse side effects, which represent a serious problem during chronic treatment [23–25]; in particular, sibutramine has been recently withdrawn from the European market. Fluoxetine has been approved by the FDA for bulimia nervosa, but evidence for its efficacy is reported inconclusive [26]. Apparently, treatment of BED and bulimia nervosa cannot simply rely on pharmacological agents aimed at reducing food intake in general, like serotonergic drugs. Innovative treatments for bulimia nervosa and BED, devoid of severe side effects, are strongly needed.

BE episodes appear to be characterized by uncontrollable urge to obtain and consume food, which is similar to that exhibited by addicted individuals towards drug of abuse. Evidence is accumulating that excessive intake of certain foods under specified conditions produces behaviours and changes in the brain that resemble an addiction-like state [27–31]. Neural systems that motivate and reinforce drug abuse have been proposed to underlie also behaviours associated with compulsive food seeking and food intake [32–36]. In this regard, it is interesting to note that several drugs that influence alcohol addiction have been reported to reduce BE in experimental models (such as naloxone [37], naltrexone, and baclofen [38, 39] and topiramate [40]) as well as in clinical studies [41–43].

Previous studies have shown that acute administration of *Hypericum perforatum* extract attenuates alcohol intake in genetically selected alcohol-preferring rats by influencing the motivational properties of ethanol [44–50].

Extracts of *Hypericum perforatum*, the common plant usually called St. John's wort, are known to exert antidepressant effects in humans [51–55] and antidepressant-like actions in laboratory animals in different experimental models [56–61].

Hypericum perforatum contains a variety of biologically active compounds, including the naphthodianthrones hypericin and pseudohypericin, and the phloroglucinol derivatives hyperforin, adhyperforin, and several flavonoids [51, 62, 63]. A further reason of interest in the effect of *Hypericum perforatum* on BE is raised by the finding that it has been reported to exhibit antistress properties. In this regard, several papers have shown that some of its active principles bind to CRF-1 receptors and exhibit antagonist activity at these receptors [64–67]. Moreover, *Hypericum perforatum* extracts have been shown to reduce the hypothalamic-pituitary-adrenal (HPA) axis activation following chronic treatment [68], to reduce restraint stress-induced increases in plasma ACTH and corticosterone levels following acute administration [69], and to counteract the negative effects of corticosterone on hippocampal cell proliferation [70]. Since stress is a key determinant of BE, a reduction of the response to stress might represent an effective mechanism for suppression of BE. Therefore, we thought it of interest to evaluate whether *Hypericum perforatum* extracts attenuate BE evoked in female rats by combining stress and food restrictions [40].

Moreover, the effect of *Hypericum perforatum* on BE was also evaluated in combination with salidroside, active principle of the dry extract of *Rhodiola rosea* (family Crassulaceae) [71, 72].

Rhodiola rosea roots contain a variety of biologically active compounds, including organic acids, flavonoids, tannins, and phenolic compounds. Phenylpropane and phenylethane phenolic glycosides, such as salidroside, rosavin, syringing, and triandrin are considered the most important active principles [71].

Recently our group reported that *Rhodiola rosea* extract and salidroside suppress BE, interfering with stress mechanisms [73].

In the present study, it was evaluated whether the combined administration of *Hypericum perforatum* and salidroside might offer advantages over their separate administration.

2. Material and Methods

A preclinical model has been recently developed by our group to investigate the neuro- and psychobiology of BE and to identify innovative pharmacological treatments [40]. This model is derived with modifications from the original model developed by Hagan et al. [74]. It uses female rats in relation to the higher prevalence of binge-type eating disorders in women than in men [1, 3] and combines three 8-day cycles of food restriction/refeeding and acute stress (on the 25th day) to evoke BE for HPF in Sprague-Dawley rats.

2.1. Animals. Female Sprague-Dawley rats (Charles River, Calco, Como, Italy) were used. Their body weight was 225–250 g at the beginning of the experiments. Rats were acclimated to individual cages under a 12 h light/dark cycle (lights on at 08:00 a.m.) with ad libitum chow and water for 2 weeks prior to the experiments. They were kept in a room at constant temperature (20–22°C) and humidity (45–55%). Rats were kept in individual cages with metallic walls; the floor and the front wall were made of metallic grid. The dimensions of the cage floor were 30 cm × 30 cm; the cage was 30 cm high. A front door (30 cm × 20 cm) made of metallic grid was present in the anterior wall of the cage to get access to the inside of the cage; the remaining part of the front wall was equipped with a drinking burette.

2.2. Diet. Animals were offered standard rat food pellets (4RF18, Mucedola, Settimo Milanese, Italy (2.6 kcal/g). The HPF was a paste in texture, prepared by mixing Nutella (Ferrero, Alba, Torino, Italy) chocolate cream (5.33 kcal/g; 56%, 31%, and 7% from carbohydrate, fat, and protein, resp.), grounded food pellets (4RF18, Mucedola, Settimo Milanese, Italy), and water in the following weight/weight percent ratio: 52% Nutella, 33% food pellets, and 15% water. The HPF diet had a caloric content of 3.63 kcal/g. HPF was offered in a coffee cup; the handle of the cup was inserted into

the metallic grid of the anterior wall of the cage and fixed to the wall. Standard pellets were offered inside a metallic grid container that was hung on the anterior wall of the cage; it was removed from the cage to measure its weight in order to determine food pellet intake.

2.3. The Stressful Procedure. For 15 min, the coffee cup containing HPF was placed inside a metallic grid container that was hanged up on the anterior wall of the cage. In these conditions, the animal was able to see the cup in which it received HPF on day 5, 6, 13, and 14 of the first two cycles, was able to see the HPF itself, and to smell its odour. In this 15 min period, the rat engaged in repeated movements of the forepaws, head, and trunk aimed at obtaining the HPF, but it was not able to reach it. This procedure was adopted to generate a mild stressful condition that causes a significant increase in serum corticosterone levels [41]. Rats underwent the stressful procedure between 10.00 and 12.00 h. After 15 min, the cup was placed inside the cage of rats of the stress groups, so that HPF became accessible to them.

2.4. Drug Treatment. Hypericum perforatum dry extract, containing 0.1% hypericin and 3.8% hyperforin, was a generous gift of Indena, Milano, Italy. It was dissolved in 2% ethanol and water and administered by gavage (2 ml/kg) at doses of 125–500 mg/kg [75] 1 h before access to HPF. Salidroside, an active principle of *Rhodiola rosea* extract, was purchased from Chengdu Biopurify Phytochemicals Ltd. (Chengdu, Sichuan, China). It was dissolved in 2% ethanol and water and administered by gavage (2 ml/kg) 1 h before access to HPF at the dose of 312 μg/kg. Control rats received vehicle administration by gavage (2 ml/kg). In experiment 4, the volume of administration was 1 ml/kg for both compounds.

2.5. Experimental Procedure

Experiment 1. Effect of Repeated Food Restrictions and Acute Stress of HPF Intake in Female Rats. Forty female rats were used. They were divided in 4 groups of 10 animals, matched for body weight and daily food intake: (1) the nonrestricted and not exposed to stress group (NR + NS), (2) the restricted and not exposed to stress group (R + NS), (3) the non-restricted and exposed to stress group (NR + S), and (4) the restricted and exposed to stress group (R + S).

Rats were subjected to 3 consecutive 8-day cycles followed by the final test on day 25. Each 8-day cycle was as follows: (a) the control group (NR + NS) had chow ad libitum for 4 days, on days 5-6, it received chow ad libitum + HPF for 2 h (from 10:00 a.m., i.e., 2 h after the beginning of the light phase of the cycle); on days 7-8, it had chow ad libitum; on day 25, it was not exposed to stress; (b) the second group (R + NS) had chow restricted to 66% of the usual intake for 4 days, was offered chow ad libitum and HPF for 2 h on days 5-6 and only chow on days 7-8; on day 25, it was not exposed to stress; (c) the third group had chow and HPF as controls (NR + NS), but on the test day (day 25), it was exposed to stress (NR + S); (d) the fourth group (R + S) had food available like group R + NS and on day 25, it was exposed to stress.

The 8-day cycle was repeated three times, but in the third cycle, the animals did not have access to HPF on day 21 and 22.

It has been recently reported by our group that in the estrous phase of the ovarian cycle, female rats do not exhibit BE in the adopted model [76], while in all the other three phase of the ovarian cycle they exhibit BE without significant differences in intensity. Therefore, immediately after the test on day 25, vaginal smears were collected and analysed under microscope to assess the ovarian phase, and data from rats in the estrous phase were not included in the statistical analysis. Vaginal smears were analysed by an experienced experimenter blind to treatment conditions.

Food intake was expressed as mean kcal/kg ingested ± S.E.M.; it was measured for 2 h, since previous experiments showed no differences among groups after this period. HPF intake was measured at 15, 30, 60, and 120 min after access to it. Food pellet intake was measured only at 2 h, in relation to the findings of previous studies showing that the food pellet intake was very small and to avoid disturbance to the animals during the test.

Experiment 2. Effect of Hypericum perforatum Extract on BE Evoked by Cycles of Food Restriction and Exposure to Acute Stress. Eighty female rats were used. They were divided in 2 groups of 40 animals, matched for body weight and daily food intake: (1) the nonrestricted and not exposed to stress group (NR + NS) and (2) the restricted and exposed to stress group (R + S). Only these two groups were used since Experiment 1 confirmed that BE is not expressed in the R + NS and NR + S groups. Rats were subjected to 3 consecutive 8-day cycles followed by the final test on day 25, as reported in Experiment 1.

Each group of 40 rats was divided in 4 subgroups of 10 rats, treated, respectively, with vehicle or with *Hypericum perforatum* dry extract (125, 250, or 500 mg/kg) given by gavage 1 h before access to HPF. Food intake was expressed as mean kcal/kg ingested ± S.E.M. HPF intake was measured at 15, 30, 60, and 120 min after access to it. Food pellet intake was measured only at 2 h.

Experiment 3. Effect of Hypericum perforatum Dry Extract Given in Combination with Salidroside on BE in Female Rats. Additional eighty female rats received the same procedures of the NR + NS and R + S rats in the Experiments 1 and 2. On the test day (day 25), NR + NS and R + S rats were treated by gavage as follows (10 rats per group): (a) vehicle + vehicle, (b) vehicle + Salidroside 312 μg/kg, and (c) *Hypericum perforatum* extract 125 mg/kg + vehicle, *Hypericum perforatum* extract 125 mg/kg + Salidroside 312 μg/kg. Food intake was expressed as mean kcal/kg ingested ± S.E.M. HPF intake was measured at 15, 30, 60, and 120 min after access to it. Food pellet intake was measured only at 2 h.

Experiment 4. Effect of Hypericum perforatum Extract and Salidroside on Serum Corticosterone Levels Following Cycles of Food Restriction and Exposure to Acute Stress

Experiment 4*a.* To assess if the doses of *Hypericum perforatum extract* (250 and 500 mg/kg) that reduced BE have an effect on the increased corticosterone levels in the R + S group, additional fifty-four Sprague-Dawley rats were used. They were divided in two groups (NR + NS and R + S) of 27 animals, were subjected to three cycles of 8 days with the same procedure described under Experiment 1. At the end of the third cycle (on day 25) in each group, 9 animals received vehicle, 9 animals received *Hypericum perforatum* dry extract, 250 mg/kg, and other 9 rats received *Hypericum perforatum* dry extract, 500 mg/kg. The R + S group received drug administration 45 min before exposure to the stressful procedure and was sacrificed at the end of the 15 min period of stress. The NR + NS group was administered vehicle or *Hypericum perforatum* dry extract, 250 or 500 mg/kg and then sacrificed 60 min later.

Experiment 4*b.* Additionally forty-five Sprague-Dawley rats, divided in two groups: NR + NS ($n = 9$) and R + S ($n = 36$), were subjected to three cycles of 8 days with the same procedure described under Experiment 1. At the end of the third cycle (on day 25), 9 NR + NS rats received vehicle + vehicle, R + S rats were divided in four groups of 9 animals that received: vehicle + vehicle, vehicle + Salidroside 312 μg/kg, *Hypericum perforatum* dry extract (125 mg/kg) + vehicle, and *Hypericum perforatum* dry extract (125 mg/kg) and salidroside 312 μg/kg. The R + S group received drug administration 45 min before exposure to the stressful procedure and was sacrificed at the end of the 15 min period of stress. The NR + NS group was administered vehicle and then sacrificed 60 min later.

Blood samples were collected from the rat trunk after decapitation. To improve serum separation from whole blood, samples were allowed to clot at room temperature before centrifugation (1000 ×g for 10 min). Serum was transferred into clean tubes and stored at −20°C until the assay. Taking into account the circadian rhythm of corticosterone, all sacrifices were carried out between 12.00 and 2.00 p.m., that is, during the diurnal period when its concentrations are relatively constant [77, 78]. Assessment of serum corticosterone level was done by means of enzyme immunoassay (EIA) using a commercially available kit (Arbor Assays, Ann Arbor, MI, USA), which utilizes microplate reader set at 450 nm. Serum samples were diluted 1 : 100 in appropriate assay buffers in order to be within the calibration curve range and assayed in duplicate. The detection limit of the assay was 16.9 pg/mL; intra- and interassay coefficients of variations were, respectively, 5.1 and 7.9%.

2.6. Statistical Analysis. Results are expressed as means ± S.E.M. Data were analyzed by two-ways analysis of variance (ANOVA) with between-subject comparisons for experimental groups or drug treatments and within-subject comparison for time of observation when appropriate (Systat 13.0). Post hoc comparison was carried out by the Bonferroni test. Statistical significance was set at $P < 0.05$.

3. Results

Experiment 1. Effect of Repeated Food Restrictions and Acute Stress of HPF Intake in Female Rats. Thirty female rats (of the 40 used in the experiment) proved not to be in the estrous phase at the moment in which the experiment was carried out. Only data from these animals (6–8 per group) were subjected to statistical analysis.

As shown in Figure 1, body weight of rats was reduced during the 4 days of food restriction, but immediately afterwards the animals increased their food intake and rapidly recovered their body weight to control levels by the end of each cycle. On the test day, body weight of the 4 groups of animals, as well as their food intake in the previous 24 h, was not significantly different.

The ANOVA revealed a highly significant difference in 2 h HPF intake in the 4 groups of rats ($F(3, 26) = 19.32$; $P < 0.001$). As shown in Figure 2 and in Table 1, HPF intake in the R + S group was markedly higher than that of the control (NR + NS) group. HPF intake of R + S rats was very pronounced in the first 15 min of access to it; these animals never engaged in competing behaviours, but continuously remained over the cup containing HPF and focused their attention on the intake. Cumulative HPF intake in the R + S group was significantly higher than in controls up to 120 min after access to it. HPF intake of the NR + S group was not significantly different from that of controls (NR + NS), indicating that stress was not enough to induce BE. Moreover, also HPF intake of the R + NS group was not significantly different from that of controls (NR + NS), indicating that cycles of food restriction are not enough to induce BE.

The intake of standard food pellet was very small (about 3–5% of the overall calories intake in the 2 h test), and it was affected neither by food restriction, nor by stress, and nor by the combination of both. In the 2 h test, rats of the R + S group ate 176.2 kcal/kg of HPF and only 6.5 kcal/rat of food pellets.

Experiment 2. Effect of Hypericum perforatum Extract on BE Evoked by Cycles of Food Restriction and Exposure to Acute Stress. Fifty-seven female rats (of the 80 used in the experiment) proved not to be in the estrous phase at the moment in which the experiment was carried out. Only data from these animals (6–8 per group) were subjected to statistical analysis. As shown in Figure 3, following vehicle administration, HPF intake in the R + S group was markedly higher than that of the NR + NS group. The ANOVA revealed a highly significant difference in 2 h HPF intake in the 2 groups of rats following vehicle administration ($F(1, 12) = 16.88$; $P < 0.01$).

As shown in Figure 3, in the NR + NS group, the ANOVA revealed a nonsignificant treatment effect ($F(3, 25) = 2.82$; $P = 0.059$). Following the highest dose of 500 mg/kg of *Hypericum perforatum* extract, a marked trend to the

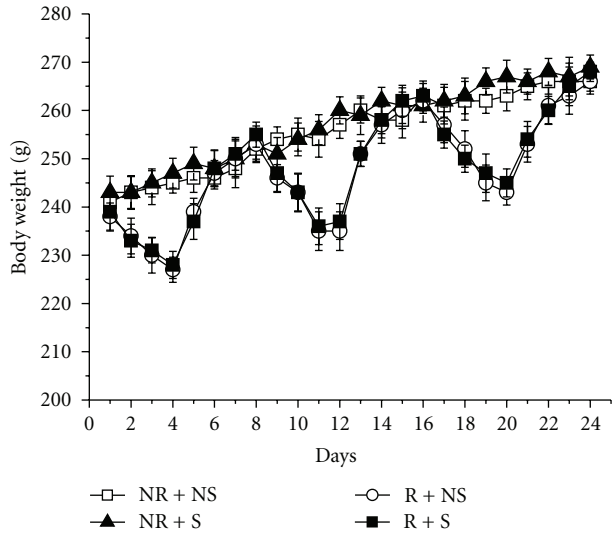

Figure 1: Body weight of female rats during the three 8-day cycles of food restriction/refeeding. Values are means ± S.E.M.

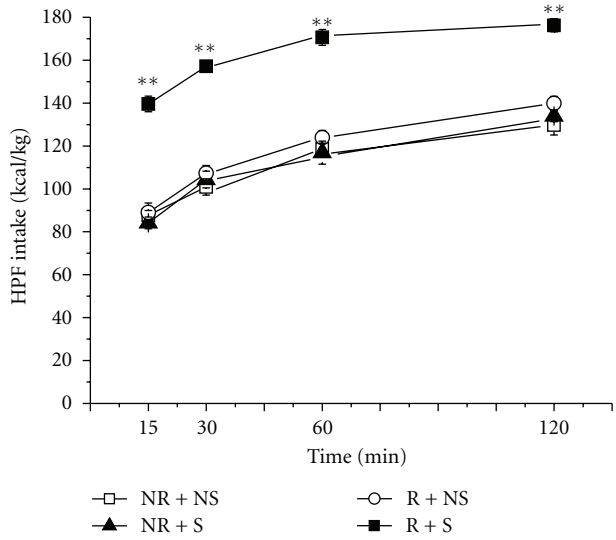

Figure 2: HPF intake (kcal/kg) on the test day in female rats exposed to either cycles of food restriction or stress or the combination of both. Data are means ± S.E.M. Statistical difference from controls (NR + NS): $^{**}P < 0.01$.

Table 1: HPF intake in grams on the test day in female rats exposed to either cycles of food restriction or stress or the combination of both. Data are means ± S.E.M. Statistical difference from controls (NR + NS): $^{**}P < 0.01$.

Group	15 min	30 min	60 min	120 min
NR + NS	6.6 ± 0.2	7.6 ± 0.3	9.0 ± 0.3	9.8 ± 0.3
NR + S	6.2 ± 0.1	7.7 ± 0.6	8.6 ± 0.6	9.8 ± 0.4
R + NS	7.6 ± 0.6	8.1 ± 0.6	9.4 ± 0.8	10.6 + 1.2
R + S	10.5 ± 0.4**	11.9 ± 0.4**	12.9 ± 0.4**	13.3 + 0.5**

reduction of HPF intake was observed, but the difference was not statistically significant.

The *Hypericum perforatum* extract significantly reduced HPF intake in the R + S group ($F(3, 24) = 7.41$; $P < 0.001$). The effect was statistically significant only at 15 min following administration of 250 mg/kg and up to 60 min following administration of 500 mg/kg; the dose of 125 mg/kg did not significantly reduce BE.

Experiment 3. Effect of Hypericum perforatum Dry Extract Given in Combination with Salidroside on BE in Female Rats. Sixty female rats (of the 80 used in the experiment) were not in the estrous phase (6–9 per group). Following vehicle administration, a highly significant difference in 2 h HPF intake in the 2 groups of rats following vehicle administration was observed (data of NR + NS group were not shown).

The ANOVA revealed a highly significant treatment effect only in R + S group ($F(3, 28) = 5{,}98$; $P < 0.01$).

As shown in Figure 4, *Hypericum perforatum* extract (125 mg/kg) did not significantly modify HPF intake. Salidroside (312 μg/kg) reduced HPF intake; the combination of *Hypericum perforatum* extract (125 mg/kg) and Salidroside (312 μg/kg) increased the reduction of HPF in comparison to that observed after Salidroside alone. Following Salidroside (312 μg/kg) treatment, the difference from vehicle-treated rats was statistically significant only at 15 min ($P < 0.05$); with *Hypericum perforatum* extract (125 mg/kg) and Salidroside (312 μg/kg), the effect was statistically significant up to 60 min ($P < 0.05$).

Thus, when the dose of 125 mg/kg of *Hypericum perforatum* extract (i.e., per se inactive) was administered together with Salidroside 312 μg/kg, the antibinge effect proved to be more intense, longer lasting, and reached the level of $P < 0.01$ as statistical significance in comparison to the effect observed following Salidroside 312 μg/kg alone ($P < 0.05$).

Experiment 4. Effect of Hypericum perforatum Extract and Salidroside on Serum Corticosterone Levels Following Cycles of Food Restriction and Exposure to Acute Stress

Experiment 4a. Forty-two female rats (of the 54 used in the experiment) were not in the estrous phase at the moment in which the experiment was carried out (6–8 per group).

Two-way ANOVA showed significant group effect ($F(1, 36) = 20.7$, $P < 0.01$). As reported in Figure 5, exposure to HPF without access to it significantly increased corticosterone levels in the serum samples obtained from R + S rats, in comparison to those from NR + NS rats (Bonferroni post hoc test, $P < 0.05$).

On the other hand, the ANOVA revealed neither a drug treatment effect ($F(2, 36) = 3.3$, $P > 0.05$), nor a group-drug treatment interaction ($F(2, 36) = 0.1$, $P > 0.05$) on serum corticosterone levels. The administration by gavage of *Hypericum perforatum* extract at either dose used (250 or 500 mg/kg) failed to reduce the increase in serum corticosterone levels in the R + S group. Post hoc tests showed that serum corticosterone levels in R + S rats, treated with the 2 doses of *Hypericum perforatum* extracts, were comparable to those of R + S rats treated with vehicle ($P > 0.05$), but

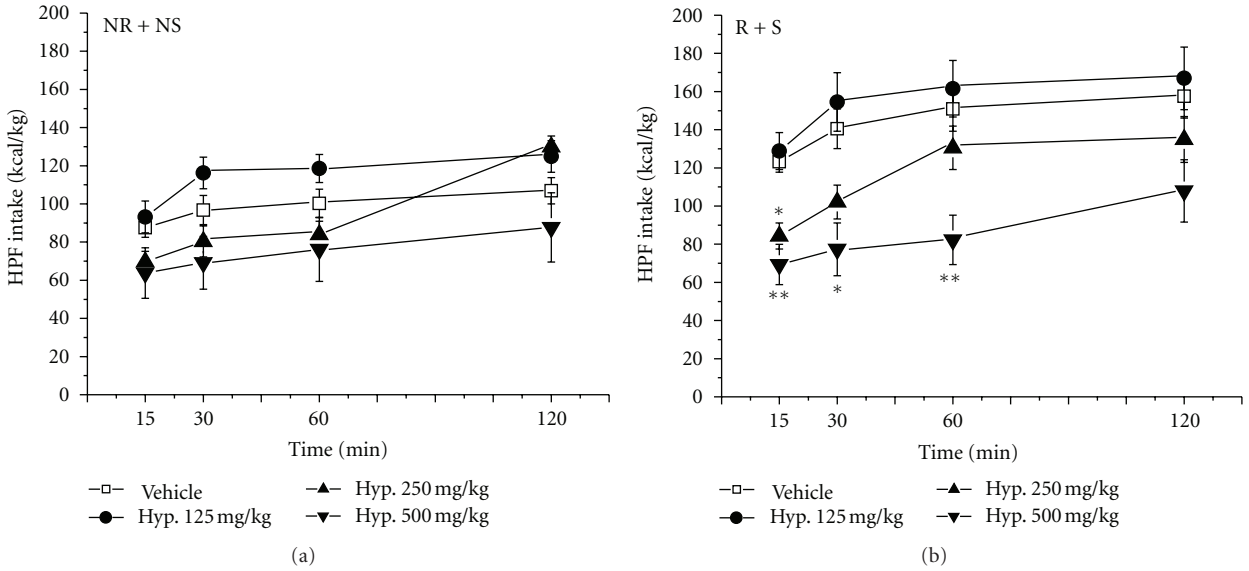

Figure 3: Effect of intragastric administration of different doses of *Hypericum perforatum* extract or vehicle on HPF intake on the test day in R + S and NR + NS rats. Data are means ± S.E.M. Statistical difference from vehicle-treated rats: $^{*}P < 0.05$; $^{**}P < 0.01$.

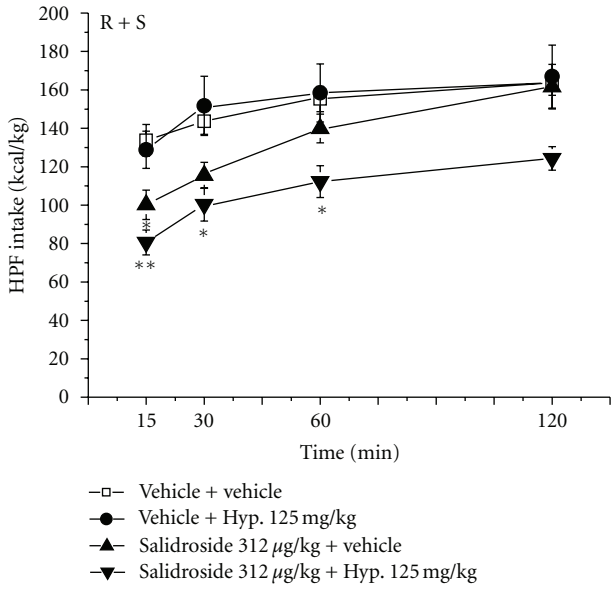

Figure 4: Effect of the combined administration of *Hypericum perforatum* extract, 125 mg/kg, and Salidroside 312 μg/kg on HPF intake on the test day in R + S rats. Data are means ± S.E.M. Statistical difference from vehicle + vehicle-treated rats: $^{*}P < 0.05$, $^{**}P < 0.01$.

were statistically different from those of NR + NS rats, either treated or not treated with *Hypericum perforatum*.

Experiment 4b. Thirty-six female rats (of the 45 used in the experiment) were not in the estrous phase at the moment in which the experiment was carried out (6–9 per group).

Two-way ANOVA showed significant group effect ($F(1, 34) = 93.4$, $P < 0.01$). As reported in Figure 6, exposure to HPF without access to it significantly increased corticosterone levels in the serum samples obtained from R + S rats, in comparison to those from NR + NS rats (Bonferroni post hoc test, $P < 0.01$).

On the other hand, the ANOVA revealed no drug treatment effect in R + S group ($F(3, 23) = 1.64$, $P > 0.05$) on serum corticosterone levels.

4. Discussion

The present study confirms that stress or repeated food restrictions, given separately, are not enough to induce BE, but the combination of both determinants is required. Previous work by Cifani et al. [40] has shown that the experimental model of BE adopted in the present study possesses, in addition to face and construct validity, also predictive validity, since both topiramate and sibutramine abolish BE.

The administration by gavage of a dry extract of *Hypericum perforatum*, 250 mg/kg, significantly reduced the increase in HPF intake in the R + S group (subjected to both stress and repeated food restrictions), and the dose of 500 mg/kg completely reduced it. On the other hand, 125 mg/kg did not significantly influence HPF intake in the R + S group. While suppressing the increase in HPF intake in the R + S group, the three doses tested of *Hypericum perforatum* extract did not significantly reduce HPF in the control group (NR + NS) even if a clear trend of reduction was shown by the highest tested dose (500 mg/kg).

The mechanisms accounting for this selective effect on BE remain to be elucidated. As mentioned in the Introduction, *Hypericum perforatum* extracts have been reported to influence stress mechanisms. Several papers have shown that some of its active principles bind to CRF-1 receptors and

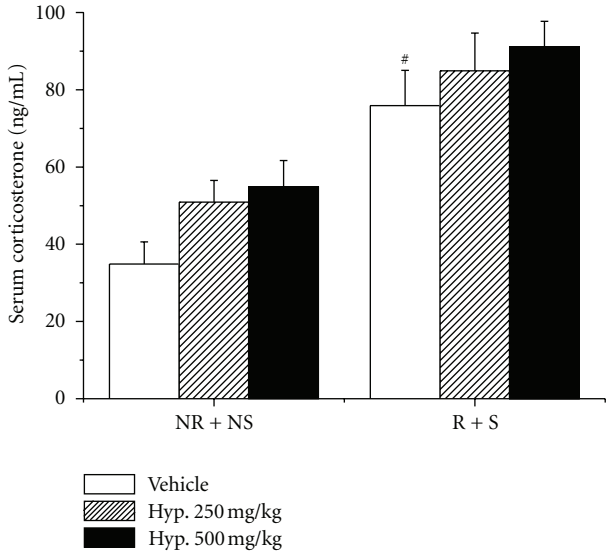

Figure 5: Effect of *Hypericum perforatum* extract (250 or 500 mg/kg) or its vehicle on serum corticosterone levels in R + S rats and in NR + NS rats. Data are means ± S.E.M (n = 6–8 rats per group). Statistical difference vehicle R + S rats versus vehicle NR + NS: $^{\#}P < 0.05$; statistical difference from vehicle-treated rats in each group was never statistically significant.

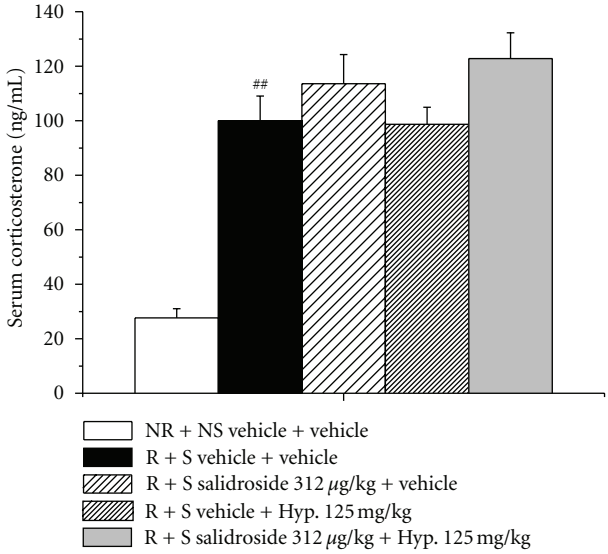

Figure 6: Effect of the combined administration of *Hypericum perforatum* extract, 125 mg/kg, and Salidroside 312 μg/kg on serum corticosterone levels in R + S rats. Data are means ± S.E.M (n = 6–8 rats per group). Statistical difference vehicle R + S rats versus vehicle NR + NS: $^{\#\#}P < 0.01$; statistical difference from vehicle-treated rats in R + S group was never statistically significant.

exhibit antagonist activity at these receptors [64–67]. Moreover, *Hypericum perforatum* extracts have been reported to reduce HPA axis activation following chronic treatment [68] and to reduce restraint stress-induced increases in plasma ACTH and corticosterone levels following acute administration [69]. Corticosterone has been proposed to have motivational properties and to influence drug-seeking behaviour in rats [79–82], suggesting that it may have a role in the control of compulsive behaviour, like that exhibited in episodes of BE. However, a recent study of our group has shown that peripheral administration of corticosterone is not able to induce BE in rats exposed to repeated cycles of food restrictions; moreover, metyrapone, a glucocorticoid synthesis inhibitor, does not affect BE [83]. On the other hand, the same study has shown that a CRF-1 receptor antagonist completely blocks BE in the experimental model adopted [83]. Taken together, these findings suggest that CRF controls BE through CRF-1 receptors mainly in extrahypothalamic brain areas, rather than in the hypothalamic structures controlling the HPA axis. The results of Experiment 3 indicate that in our experimental conditions *Hypericum perforatum* does not influence HPA axis activation; however, it cannot be excluded that it abolishes BE by blocking central CRF-1 receptors in extrahypothalamic brain area.

On the other hand, the inhibition of the BE may be achieved also by suppressing addictive-like behaviours, in particular those related to the binge/intoxication stages of addiction [84]. In this regard, it is interesting to note that *Hypericum perforatum* has been reported to suppress voluntary alcohol intake, ethanol self-administration and the alcohol-deprivation effect in genetically selected alcohol-preferring rats [44–50, 75], including the Marchigian Sardinian alcohol-preferring rats that represent an interesting experimental model of alcohol abuse [85]. Therefore, *Hypericum perforatum* may influence motivation and compulsive behaviours towards HPF in BE episodes, as it does towards alcohol.

Among the active principles identified in *Hypericum perforatum* extracts, apparently pseudohypericin is the most potent CRF-1 receptor antagonist [68], but also hypericin exhibited high binding affinity for human CRF-1 receptors [65]. Other *Hypericum perforatum* constituents with high affinity for the CRF-1 receptor are also bisanthraquinone glycosides [64] and flavonoids [68]. Hyperforin and hyperforin derivatives do not bind with high affinity at CRF1 receptors and are not involved in the control of HPA axis function [86]. On the other hand, hyperforin has been proposed to be the main active principle responsible for the effect of *Hypericum perforatum* in the control of alcohol abuse [75]. The extract used in the present study had a very low hypericin content (0.1%) and a rather high hyperforin content (3.8%). These data favour the hypothesis that hyperforin may have a major role in the suppressive effect of *Hypericum perforatum* on BE; accordingly, the mechanism of action may be more likely related to suppression of addictive-like behaviours than to interference with stress mechanisms.

It is interesting to note that *Hypericum perforatum* was able to increase the effect of Salidroside, that in our previous study, showed to be the active principle of *Rhodiola rosea* extracts responsible for the selective effect in reducing BE [73].

Recently, the effect of Salidroside on expression and secretion of neuropeptide Y (NPY) in neuroglia cells has been demonstrated [87]. Since it is well documented that NPY reduces consummatory ingestive behaviour by about

40% [88, 89], it has been suggested [87] that the effect of Salidroside on BE is mediated by NPY.

In conclusion, the present findings suggest that *Hypericum perforatum* extracts and Salidroside may be useful for treatment of bingeing-related eating disorders.

Conflict of Interests

The authors have no conflict of interests to declare.

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Research Article

Increased Mesohippocampal Dopaminergic Activity and Improved Depression-Like Behaviors in Maternally Separated Rats Following Repeated Fasting/Refeeding Cycles

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We have previously reported that rats that experienced 3 h of daily maternal separation during the first 2 weeks of birth (MS) showed binge-like eating behaviors with increased activity of the hypothalamic-pituitary-adrenal axis when they were subjected to fasting/refeeding cycles repeatedly. In this study, we have examined the psychoemotional behaviors of MS rats on the fasting/refeeding cycles, together with their brain dopamine levels. Fasting/refeeding cycles normalized the ambulatory activity of MS rats, which was decreased by MS experience. Depression-like behaviors, but not anxiety, by MS experience were improved after fasting/refeeding cycles. Fasting/refeeding cycles did not significantly affect the behavioral scores of nonhandled (NH) control rats. Fasting/refeeding cycles increased dopamine levels not only in the hippocampus but also in the midbrain dopaminergic neurons in MS rats, but not in NH controls. Results demonstrate that fasting/refeeding cycles increase the mesohippocampal dopaminergic activity and improve depression-like behaviors in rats that experienced MS. Together with our previous paper, it is suggested that increased dopamine neurotransmission in the hippocampus may be implicated in the underlying mechanisms by which the fasting/refeeding cycles induce binge-like eating and improve depression-like behaviors in MS rats.

1. Introduction

Neonatal maternal separation is considered as an animal model of stressful experience early in life. A number of studies have demonstrated that neonatal maternal separation may lead to permanent alterations in the characteristics of the hypothalamic-pituitary-adrenal (HPA) axis responding to stress [1–3] and the development of depression- [4, 5] and anxiety-like behaviors [6, 7] later in life. We have previously demonstrated that rats experienced 3 h of daily maternal separation during the first 2 weeks of birth (MS) exhibit depression- and anxiety-like behaviors [8, 9] with altered response of the HPA axis to stress challenges later in life [10, 11]. Dysfunction of the HPA axis is implicated in the pathogenesis of eating disorders [12–14], and symptoms of anxiety and depression are associated with the pathophysiology of eating disorders [15, see for review], especially with binge-like eating disorders [16, 17]. Our MS rats showed binge-like eating behavior when they were challenged with repeated fasting/refeeding cycles during adolescent period, and their binge-like eating behavior appeared to be related with increased activity of the HPA axis [11].

The dopaminergic system has been of particular interest, as dopamine in the nucleus accumbens (NAc) has been shown to be associated with motivation, reward, and hedonia [18]. Our MS rats showed anhedonia, a symptom of depression, with decreased dopaminergic activity in the NAc responding to acute stress [19, 20]. It has been suggested that serotonergic transmission regulates dopamine release within the NAc [21], and malregulation of dopaminergic activity in the NAc by serotonin may be involved in a depressive phenotype [22]. Although serotonin contents

in the NAc of our MS rats did not significantly differ from nonhandled (NH) control rats, not only serotonin contents in the hippocampus and the raphe but also gene expression of serotonin reuptake transporter in the raphe nucleus were decreased in our MS rats [8, 20]. Serotonergic dysfunction is implicated in a variety of psychiatric disorders, including major depression [23, 24] and anxiety [25], and serotonin neurotransmission in the hippocampus is believed to be involved in the regulation of the HPA axis activity throughout life. Thus, it is likely that decreased serotonin neurotransmission in the hippocampus may be implicated in the pathophysiology of depression- and/or anxiety-like behaviors [8, 9], likely in relation with dysfunctions of the HPA axis activities [10, 11] in our MS rats.

The hippocampus as well as the NAc receives dopaminergic fibers from the ventral mesencephalon [26–28], and dopamine modulates the hippocampal plasticity [29–31]. The hippocampal dysfunction is associated with symptoms of depression [32, 33]. The hippocampus is known to be involved in the feedback regulation of the HPA axis activity, and dysfunction of the HPA axis is implicated in the pathophysiology of anxiety [34], depression [35], and eating disorders [12, 14]. Together with our previous reports demonstrating that our MS rats show anxiety- and depression-like behaviors [8, 9] and binge-like eating behavior with increased HPA axis activity when they are subjected to repeated fasting/refeeding cycles [11], it was hypothesized that the fasting/refeeding cycles may alter dopamine neurotransmission in the hippocampus of our MS rats, perhaps leading to an alteration in anxiety- and/or depression-like behaviors. In this study, we have examined the changes in the brain dopamine contents and the psychoemotional behaviors following repeated fasting/refeeding cycles in MS and NH rats.

2. Materials and Methods

2.1. Animals. Sprague-Dawley rats were purchased (Samtako Bio, Osan, Korea) and cared in a specific-pathogen-free barrier area with constant control of temperature (22 ± 1°C), humidity (55%), and a 12/12 hr light/dark cycle (lights on at 07:00 AM). Standard laboratory food (Purina Rodent Chow, Purina Co., Seoul, Korea) and membrane filtered purified water were available *ad libitum*. Animals were cared according to the Guideline for Animal Experiments, 2000, edited by the Korean Academy of Medical Sciences, which is consistent with the NIH guidelines for the Care and Use of Laboratory Animals, revised 1996. All animal experiments were approved by the Committee for the Care and Use of Laboratory Animals at Seoul National University.

2.2. Experimental Protocol. Nulliparous females and proven breeder males were used for breeding in the laboratory of the animal facility, and the pups were reared in a controlled manner to minimize and standardize unwanted environmental stimulation from *in utero* life. Twelve hours after confirming delivery (PND 1), pups were culled to 5 males and 5 females per litter. Each litter was assigned either for the maternal separation (MS) group or for the nonhandled (NH) group. MS was performed as we previously described [8–11]. In brief, MS pups were removed from their dam and home cage and placed closely together in a new cage bedded with woodchips (Aspen Shaving, Animal JS Bedding, Cheongyang, Korea) for 180 min and then returned to their home cage and dam. MS was performed at room temperature, that is, no additional treatment to keep the pups warm during the separation period, other than placing them closely together, was offered and pup-cooling during MS was expected. MS was performed during 9:00 h–12:00 h daily from PND 1 through 14, and then the pups were left with their dam undisturbed until weaning on PND 22. The NH group remained undisturbed until weaning except for routine cage cleaning. For cage cleaning, all rats were moved to a clean cage twice a week. Female pups were excluded from the study, because our previous studies supporting the rationale to plan the present study had been performed with male offspring [11]. On the weaning day, 4 male pups were randomly selected from each litter and placed 2 pups together in each cage. Two pups in one cage were subjected together to repeated fasting/refeeding cycles, that is, a 24-h fasting followed by a 24-h refeeding repeatedly (RFR) from PND 28, and the rest 2 littermates in another cage remained with free access to chow as the fed control (FC) group. The RFR groups (NH/RFR or MS/RFR) were deprived from food, but not water, for 24 h every other day from 09:00 AM, otherwise had *ad libitum* access to chow and water during refeeding days. The FC groups (NH/FC or MS/FC) received free access to chow and water for the whole experimental period.

NH/RFR and MS/RFR rats ($n = 10$ per each group, total 20 rats from 10 different litters) were subjected to the behavioral sessions from PND 54 at the end of the 13th refeeding session, and they remained on the repeated fasting/refeeding cycles during the whole experimental period. Age-matching free fed control pups in each NH and MS group (NH/FC and MS/FC, $n = 7$-8 per each group, total 15 rats from 8 different litters) were processed in parallel.

2.3. Ambulatory Activity. NH/RFR and MS/RFR rats and their age-matching free fed control rats (NH/FC and MS/FC) were subjected to the ambulatory test on PND 54. On each trial, the rat was placed in the center of the activity chamber (43.2 cm in length, 42.2 cm in width, and 30.5 cm in height, MED Associates, VT, USA), a transparent acryl chamber equipped with two horizontal planes of 16 infrared photocell-detector pairs placed in x, y dimension, spaced 2.5 cm apart, and its ambulatory activity was monitored by the computerized system for 60 min. Light condition of the test room was maintained in the same intensity with animal rooms under day-light condition. Ambulatory activity was measured as the total counts of beam interruptions in the horizontal sensor during each consecutive 5-min session. The activity chamber was cleaned with 70% ethanol after each use to eliminate any olfactory cues of the previously tested rat.

2.4. Elevated Plus Maze. Two days after the ambulatory activity test (at the end of the 14th refeeding session), rats

were subjected to the behavioral assessment in an elevated plus maze, a plus-shaped acryl maze with two opposite open arms (50 cm in length and 10 cm in width) and two opposite closed arms (50 cm in length, 10 cm in width, and 31 cm in height), extending out from a central platform (10 cm × 10 cm). The whole apparatus was elevated 50 cm above the floor. The test procedure was followed as previously described [7]. Each rat was placed in the center of the maze facing one of the open arms and then allowed to explore the open or closed arms of the maze for 5 min. The time spent in the different arms was recorded, respectively. Four paws had to be inside the entrance line to each arm, which signaled the start of the time spent in the specific arm, and then the end time was recorded when all four paws were outside the line again. The maze was cleaned with 70% ethanol after each test to prevent influences of the previously tested rat.

After the end session of maze test, rats were allowed to rest in their home cages for a week to minimize any effects of previous stress and then subjected to the forced swim test.

2.5. Forced Swim Test. Rats were subjected to the forced swim test at the end of the 18th refeeding session, according to the method previously described [36]. Each rat was allowed to swim in a glass cylinder (54 cm in height and 24 cm in diameter) filled with water in 40 cm of depth (23–25°C) for 5 min, and the test sessions were recorded by a video camera from the side of the cylinder. Duration of rat's immobility in the water was scored from videotapes by a trained observer who was blinded to the experimental conditions. Immobility was defined as the state in which rats were judged to be making only the movements necessary to keep their head above the surface.

Rats were placed in the test room at least 2 h prior to each test to minimize unwanted stress effects, and all behavioral assessments were performed between 9:00 AM and 12:00 PM of the day to avoid the influences of circadian variances. Behavioral scoring was done with the observer blind of the treatment of the rats.

2.6. High-Performance Liquid Chromatography. A week after the end session of behavioral tests (PND 70), satiated rats were rapidly decapitated after brief anesthesia in a carbon dioxide chamber. Tissue samples of the dorsal hippocampus, the nucleus accumbens, and the midbrain covering the ventral tegmental area and substantia nigra were rapidly dissected on ice immediately after decapitation, frozen in liquid nitrogen, and stored at −80°C until used. Tissue contents of dopamine and its metabolite dihydroxyphenylacetic acid (DOPAC) were measured by high-performance liquid chromatography (Waters Instrument, Model 700, Milford, MA, USA), which consisted of a 600 E solvent delivery system equipped with a 2487 UV Detector set at 254 nm and a 717 Autosampler. The mobile phase, comprising of 88% distilled water, 2% acetonitrile, and 10% ammonium acetate buffer (0.1 M, pH 5.0), was pumped at a rate of 1 mL/min. The column used is a Atlantis dC18 (150 × 4.6 mm, 5 μm particle size, Waters, Milford, MA, USA).

2.7. Statistical Analysis. Data were analyzed by one- and two-way (maternal separation X feeding condition) analysis of variance (ANOVA) and preplanned comparisons between groups performed by *post hoc* Fisher's Protected Least Significant Difference (PLSD) test, using StatView software (Abacus, Berkeley, CA). Significance was set at $P < 0.05$, and all values were presented as means ± SE.

3. Results

3.1. Behavioral Assessments. Rats were subjected to the ambulatory activity test on PND 54 (Figure 1). Two-way ANOVA of the activity counts revealed main effects of maternal separation ($F(1,18) = 4.875$, $P = 0.0405$, total counts), feeding condition ($F(1,18) = 4.602$, $P = 0.0458$, initial 10 min; $F(1,18) = 13.833$, $P = 0.0016$, total counts), and an interaction between maternal separation and feeding condition ($F(1,18) = 7.451$, $P = 0.0138$, initial 10 min). Main effects of feeding condition ($F(1,18) = 6.109$, $P = 0.0237$, initial 10 min; $F(1,18) = 15.653$, $P = 0.0009$, total counts) and an interaction between maternal separation and feeding condition ($F(1,18) = 9.841$, $P = 0.0057$, initial 10 min) were found in the distance travelled. Not only the ambulatory counts but also the distance travelled in the activity chamber during the initial 10 min was decreased in MS/FC rats compared with NH/FC controls, and the total ambulatory counts and travel distance during 60 min of the test session were also decreased in MS/FC rats compared with NH/FC controls (Figure 1). Repeated fasting/refeeding cycles significantly increased the ambulatory activities of MS rats (MS/FC versus MS/RFR) both in the activity counts and the distance travelled, but not of NH rats. These results reveal that repeated fasting/refeeding cycles do not affect the ambulatory activities in NH rats, but normalize them in MS rats which were decreased by MS experience.

In order to assess anxiety-like behaviors, rats were subjected to the elevated plus maze test after the 14th refeeding session (Figure 2). Analysis of the % arm entry (percent entries into the closed or open arms out of total arm entries) with 2-way ANOVA revealed main effects of MS ($F(1,27) = 4.604$, $P = 0.0410$ for closed arms, $F(1,27) = 4.604$, $P = 0.0411$ for open arms), no effect of feeding condition, and no interaction between MS and feeding condition. MS/FC rats visited the closed arms more, and the open arms less, than NH/FC rats. Repeated fasting/refeeding cycles did not affect the arm entry of MS rats.

In order to assess depression-like behaviors, rats were subjected to forced swim test after the 18th refeeding session (Figure 3). Two-way ANOVA revealed an interaction between MS and feeding condition ($F(1,26) = 4.291$, $P = 0.0484$). Immobility duration of MS/FC rats was longer than NH/FC rats and shortened after repeated fasting/refeeding cycles. Repeated fasting/refeeding cycles did not alter the immobility duration of NH rats.

3.2. Dopamine Contents in the Brain Regions. After the 21st refeeding session (PND 70), tissue contents of dopamine and its metabolite DOPAC in the hippocampus, the midbrain

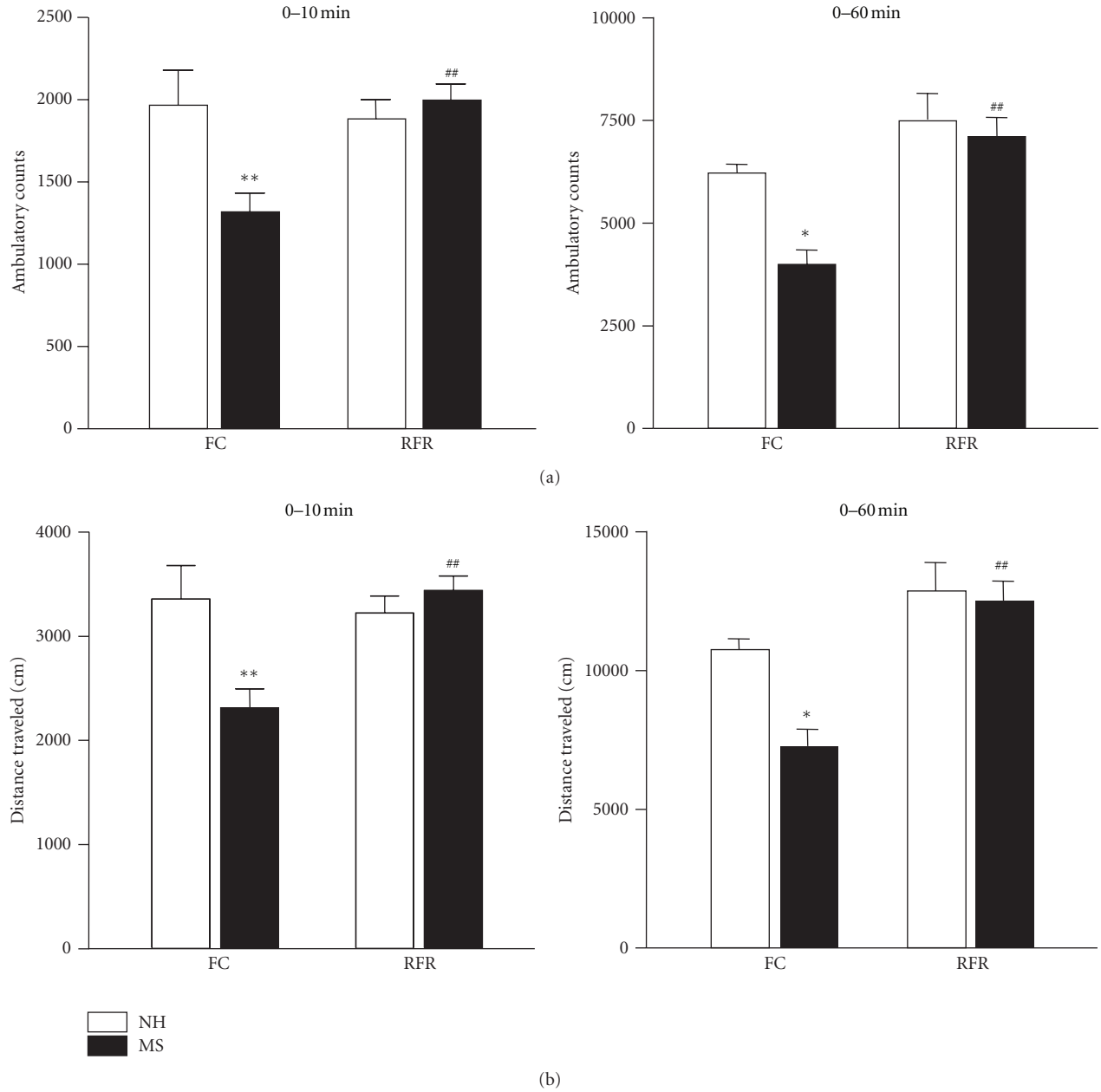

Figure 1: Ambulatory counts (a) and travel distance (b) of NH and MS rats, which were recorded consecutively at every 5 min during 60 min of test period. NH/RFR and MS/RFR rats and their age-matching free fed control rats (NH/FC and MS/FC) were subjected to the ambulatory test on PND 54 at the end of the 13th refeeding session. $^{*}P < 0.05$, $^{**}P < 0.01$ versus NH/FC, $^{\#\#}P < 0.01$ versus MS/FC, NH: nonhandled, MS: maternal separation, FC: free fed control, RFR: repeated fasting/refeeding, min: minutes. Data are presented as means ± S.E.

covering substantia nigra and ventral tegmental area, and the nucleus accumbens were analyzed (Figure 4). Analysis of dopamine contents with 2-way ANOVA revealed interactions between MS and feeding condition in the hippocampus ($F(1,11) = 5.344$, $P = 0.0412$) and the midbrain dopaminergic neurons ($F(1,11) = 6.093$, $P = 0.0312$). Dopamine and DOPAC levels in the brain regions of MS/FC rats did not significantly differ from NH/FC rats. Dopamine and DOPAC levels in the hippocampus of MS rats were markedly increased by repeated fasting/refeeding cycles, but not in NH rats (Figure 4(a)). Repeated fasting/refeeding cycles significantly increased dopamine level in the midbrain of MS rats, where most of dopaminergic neurons in the brain are located (Figure 4(b)). Dopamine and DOPAC levels in the nucleus accumbens of MS rats were not significantly changed by repeated fasting/refeeding cycles (Figure 4(c)). Repeated fasting/refeeding cycles did not affect the tissue contents of dopamine and DOPAC in all three brain regions of NH rats.

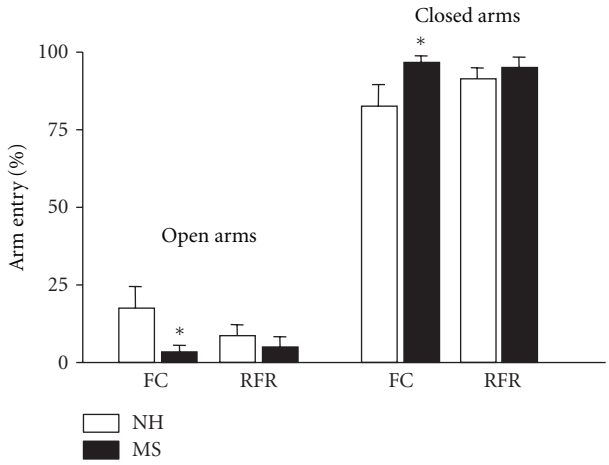

Figure 2: Percent arm entries during elevated plus maze test. The test was performed 2 days after the ambulatory test, at the end of the 14th refeeding session. $^{*}P < 0.05$ versus NH/FC, NH: nonhandled, MS: maternal separation, FC: free fed control, RFR: repeated fasting/refeeding. Data are presented as means ± S.E.

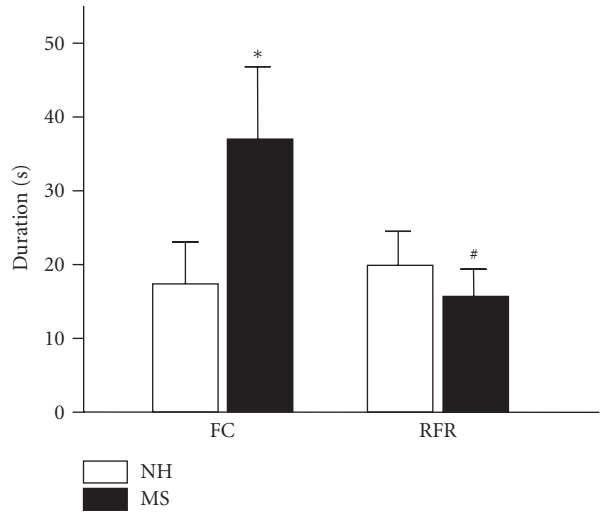

Figure 3: Immobility durations of rats during forced swim test. Rats were subjected to forced swim test at the end of the 18th refeeding session. $^{*}P < 0.05$ versus NH/FC, $^{\#}P < 0.05$ versus MS/FC, NH: nonhandled, MS: maternal separation, FC: free fed control, RFR: repeated fasting/refeeding, sec: seconds. Data are presented as means ± S.E.

4. Discussion

In this study, we have demonstrated that repeated fasting/refeeding cycles increase dopamine levels not only in the midbrain dopaminergic neurons but also in the hippocampus of MS rats and these increases are not observed in NH rats, suggesting an increased activity of the mesohippocampal dopaminergic pathway in MS rats, but not in NH, by repeated fasting/refeeding cycles. The increased DOPAC levels by repeated fasting/refeeding cycles in the hippocampus of MS rats further supported an increased dopaminergic activity in their mesohippocampal pathway, since released dopamine is converted to DOPAC after reuptake by the nerve terminal. We have previously reported that repeated fasting/refeeding cycles promote sustained hyperphagia in our MS rat model, in relation with increased activity of the HPA axis [11]. Hippocampus is known to be involved in the regulation of the HPA axis activity. Thus, it is suggested that increased dopamine neurotransmission in the mesohippocampal pathway may be implicated in the increased HPA axis activity by repeated fasting/refeeding cycles in our MS rat model.

Previous studies have reported that dopamine modulates the hippocampal plasticity with both synapse-specific and activity-dependent mechanisms [29–31]. Human studies have suggested that the hippocampal malfunction is associated with symptoms of depression [32, 37, 38]. Optimal function of the hippocampal formation is critical for the regulation of the HPA axis and stress response, dysregulation of which is observed in almost half of all depressed patients [39, 40]. In this study, MS rats showed depression-like behaviors with increased immobility during swim test, in accordance with our previous report [8]. Interestingly, repeated fasting/refeeding cycles appeared to improve the depression-like behaviors of MS rats, that is, immobility duration was reduced in the MS rats that subjected to repeated fasting/refeeding cycles, compared to their free fed control group. Contrarily, repeated fasting/refeeding cycles did not alter the behavioral scores measuring depression-like behaviors in NH rats. Taken together, it is concluded that increased dopamine neurotransmission in the hippocampus is likely involved in the regulatory mechanisms underlying the improved depression-like behaviors of MS rats by repeated fasting/refeeding cycles.

Disruption of dopaminergic function within the nucleus accumbens (NAc) caused anhedonia, a core symptom of major depressive disorder, in rodents [41], and dopamine neurotransmission in the NAc responding to food was blunted by chronic mild stress, an animal model of depression [42]. Our previous studies have suggested that blunted mesolimbic dopaminergic activity responding to acute stress is associated with depression-like behaviors including anhedonia (decreased pleasure-seeking behavior) in our MS rat model [8, 19, 20]. In this study, repeated fasting/refeeding cycles did not significantly increase dopamine levels in the reward center NAc not only in NH rats but also in MS rats, suggesting that the improved depression-like behaviors in MS rats by repeated fasting/refeeding cycles may not comprise an improvement of hedonic behavior. Thus, the present result does not seem to support the idea that repeated fasting/refeeding cycles may increase the hedonic value of food consumed in MS rats, which may contribute to a sustained hyperphagia at refeeding days during the cycles as observed in our previous report [11]. However, this is not yet sure because either a hedonic behavior *per se* or dopamine release responding to food consumption was not measured in this study.

Negative emotions appear to be associated with eating behaviors. Eating has been viewed as a strategy to improve negative mood [43] and to mask stress [44]. Obese binge eaters experience an increased tendency to binge in response

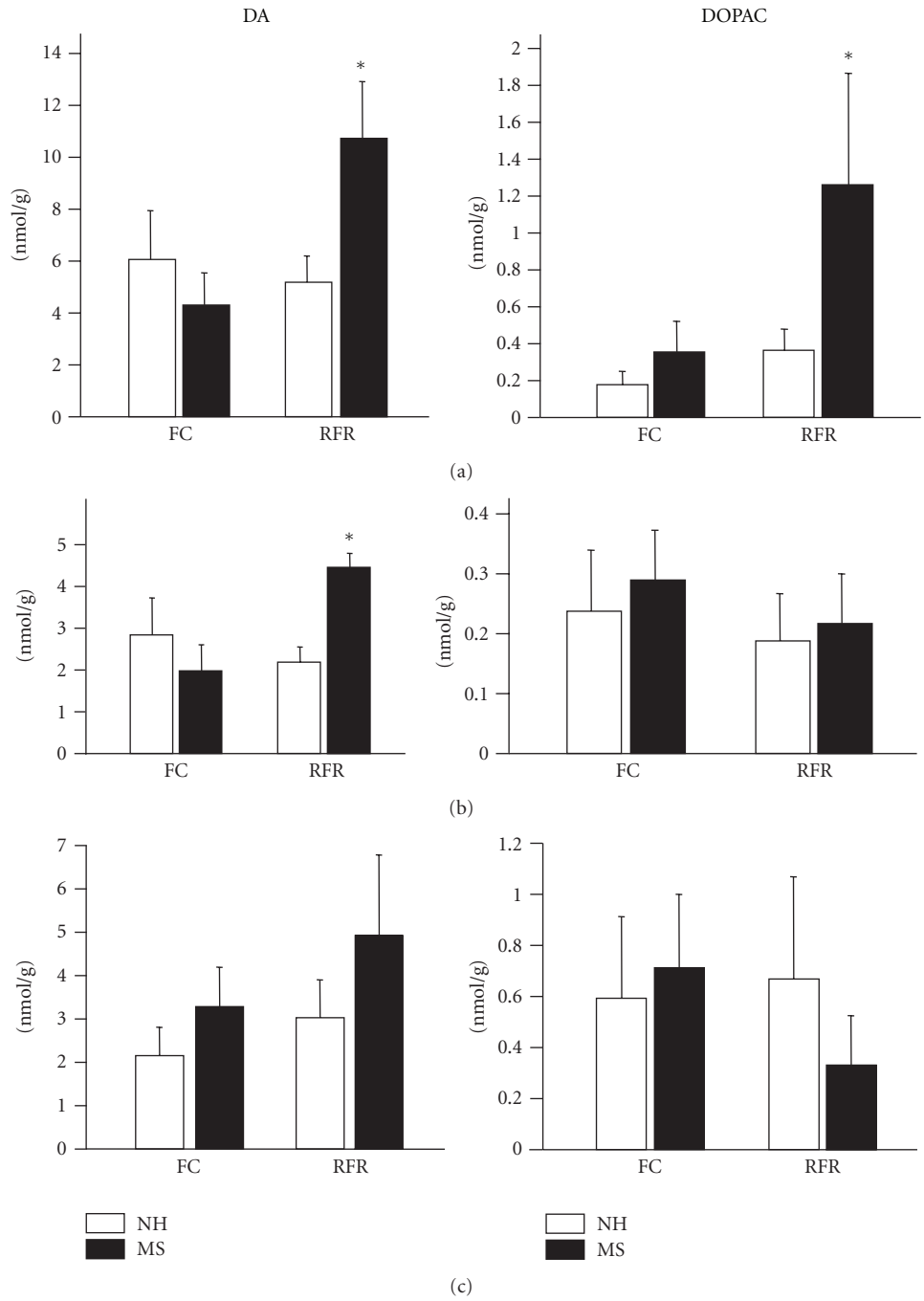

Figure 4: Tissue contents of dopamine (DA) and dihydroxyphenylacetic acid (DOPAC) in the hippocampus (a), the ventral tegmental area and substantia nigra (b), and the nucleus accumbens (c). After the 21st refeeding session (PND 70), rats were rapidly decapitated, and the tissue contents of DA and DOPAC were analyzed by high-performance liquid chromatography. $^*P < 0.05$ versus MS/FC, NH: nonhandled, MS: maternal separation, FC: free fed control, RFR: repeated fasting/refeeding. Data are presented as means ± S.E.

to negative mood [45, 46]. Also, it was reported that even healthy, normal-weight persons regulate negative emotions by eating [47–49]. In a rat model of neonatal maternal separation, consumption of high fat diet reduced anxiety- and depression-like symptoms [50, 51], suggesting that negative emotions developed by early life stressful experience can be improved by eating. This is further supported by the present results demonstrating that depression-like behaviors, though not anxiety, of MS rats were improved during repeated fasting/refeeding cycles, and that the behavioral scores of NH rats were not changed by fasting/refeeding cycles. It should be noticed that rats were subjected to the behavioral assessments when satiated with refeeding, and MS rats showed binge-like eating on each refeeding day

[11]. Thus, it is plausible that the improved depression-like behaviors in MS rats subjected to fasting/refeeding cycles might be a consequence of binge-like eating during refeeding days which possibly occurred to cope with the metabolic stress challenges during fasting/refeeding cycles. Indeed, the depression-like behavioral scores of MS rats on the cycles when measured on fasting day were still higher than NH controls (data not shown).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors that regulate development, maintenance, and morphological plasticity of neuronal systems. It has been reported that BDNF promotes the survival and differentiation of cultured dopaminergic neurons [52, 53], enhances dopamine turnover in the brain [54], and elevates activity-dependent release of dopamine [55], suggesting that BDNF plays a crucial role in regulating dopaminergic tone. Previous studies have reported that BDNF expression is reduced [51] or increased [56] in the hippocampus of MS rats that subjected to a similar separation protocol used in this study, and consumption of high fat diet normalized the hippocampal BDNF expression in MS rats [51]. Also, increased hippocampal BDNF was shown to modulate depression-like behaviors induced by acute stress [57] or chronic unpredictable stress [58]. Furthermore, chronic antidepressant treatment in rats reduced depression-like behaviors and increased hippocampal BDNF mRNA [59]. Taken together, it is speculated that BDNF may play a role in the regulation of the mesohippocampal dopaminergic activity by repeated fasting/refeeding cycles in our MS rats. Studies on the regulatory mechanisms underlying the increased mesohippocampal dopaminergic activity by fasting/refeeding cycles are currently under our consideration.

In conclusion, fasting/refeeding cycles may increase the mesohippocampal dopaminergic activity and improve depression-like behaviors in rats with MS experience. Together with our previous report demonstrating that MS rats exhibit a binge-like eating behavior during fasting/refeeding cycles [11], it is suggested that increased dopamine neurotransmission in the hippocampus may be implicated in the underlying mechanisms by which the fasting/refeeding cycles induced binge-like eating and improved depression-like behaviors in MS rats. Underlying mechanisms by which fasting/refeeding cycles increase the mesohippocampal dopaminergic activity should be further studied.

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Review Article

Mental Health, Wellness, and Childhood Overweight/Obesity

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Childhood obesity is a growing concern, and while progress has been made to understand the association between multiple biological factors (i.e., genetics, nutrition, exercise etc.), little is known about the relationship between mental health and childhood obesity. In this paper, we offer a review of current evidence about the association between mental health and childhood obesity. A systematic literature search of peer-reviewed, English-language studies published between January 2000 and January 2011 was undertaken and resulted in 759 unique records, of which 345 full-text articles were retrieved and 131 articles were included. A theoretical model is proposed to organize the paper and reflect the current state of the literature and includes psychological factors (i.e., depression and anxiety, self-esteem, body dissatisfaction, eating disordered symptoms, and emotional problems); psychosocial mediating variables (i.e., weight-based teasing and concern about weight and shape), and wellness factors (i.e., quality of life and resiliency/protective factors). We conclude with a number of recommendations to support the creation of solutions to the rise in childhood obesity rates that do not further marginalize overweight and obese children and youth and that can potentially improve the well-being of all children and youth regardless of their weight status.

1. Introduction

Obesity, a state of excess body fat, is commonly assessed using the body mass index (BMI), a ratio of weight (kg) to height (m^2), and a BMI of over 30 kg/m^2 is considered obese [1]. In children, the BMI is plotted on growth charts for interpretation relative to a healthy reference population and percentiles are then used to define obese (>95th percentile) and overweight (>85 percentile) [2]. The prevalence of obesity and overweight among children has shown dramatic increases over the past 25 years [3]. While recent analyses suggest that rising childhood obesity rates may be leveling off [4], more than 1/3 of children under the age of 11 in Canada are either overweight or obese [5–7]. Most efforts to "reverse the epidemic of obesity" [8, page 717] have focused on nutrition or food intake and physical activity levels with the measure of success being decreased weight or BMI. To date, the rate of efficacy of this prevention approach is 21% [9] suggesting the need to search for additional ways to intervene. One area that has yet to receive meaningful examination is how mental health may influence or be influenced by efforts at preventing obesity. The purpose of the present paper is to provide an overview of research linking mental health indices to obesity and to challenge the current notion that prevention should focus solely on nutrition, weight, and physical activity.

2. Literature Review Criteria

A systematic literature search of peer-reviewed, English-language studies published between January 2000 and January 2011 was undertaken on computerized psychological, social science, medical, and education databases including Psychology and Behavioral Sciences Collection, PsycINFO, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Educational Resources Information Centre (ERIC), Cochrane Database of Systematic Reviews (DSR), and Cochrane Central Register of Controlled Trials

(CCTR). Keyword combinations are listed in Table 1. Research on the physical health consequences of overweight or obesity was excluded; as were research articles that took up issues of measurement of overweight/obesity. Because this paper focused specifically on mental health and wellness in relation to the prevention of childhood obesity, some of the contextual (i.e., media, family), economic (i.e., food and diet industries), environmental (i.e., poverty), biological (i.e., metabolism), behavioural (i.e., sleep), and cultural (i.e., ethnicity) correlates of obesity are not reviewed.

In total, 759 unique records were obtained from the searches, 345 full-text articles were retrieved, and 131 articles were included in the document.

3. Overview

Obesity is not a psychological disorder, but some researchers and clinicians argue that it should be considered a mental or behavioural issue [10]. As it currently stands, obesity remains a medical condition, and, perhaps for this reason, research has focused neither on understanding the psychological impact of living with obesity nor the influence of mental health on the development of obesity. Although mental health professionals have been involved in the treatment and/or prevention of obesity, it is implicitly assumed that weight loss or the prevention of weight gain, respectively, will solve the psychological/emotional issues than may accompany excess weight which may not be the case. It should be noted that the treatment of pediatric obesity may vary with age particularly as approaches to childhood obesity migrate to a more integrated shared-responsibility model of service delivery [11]. The focus of this paper is on psychosocial constructs as they relate to influencing the prevention of childhood obesity and as such experiences from clinical settings or evidence of successful family-based treatment approaches are beyond the scope of this paper.

Some psychosocial factors have been identified and studied; however, research usually examines each construct independently with little consideration for the relationship between excess weight and a broad range of psychosocial constructs concurrently [12]. Research has not yet uncovered a clear model to elucidate these relationships. It is unclear to what extent psychosocial issues coexist in overweight/obese children or whether the strength or nature of the association changes with increasing weight [12]. A recent review by Wardle and Cooke [13] included 53 studies examining the relationship between obesity and psychosocial factors distinguishing clinical and community samples. Evidence for a causal or predictive relationship between obesity and mental health is inconclusive at best. The direction of the relationship between mental health and obesity certainly remains unclear as most of the studies are cross-sectional (e.g., [13, 14]). Of the limited longitudinal data available, some studies find evidence that mental distress predicts overweight or weight gain (e.g., [15, 16]), others find no associations between weight status and mental health (e.g., [17, 18]), and one found that behavioural issues predicted becoming overweight [19]. Despite these associations, it is clear that not all overweight/obese children experience psychosocial issues. In fact, some research suggests that concern about weight and shape (not actual weight) [20–22] and/or being the victim of weight-based teasing [23] may in fact account for any individual differences in psychosocial outcomes [12].

Despite the inconsistencies and uncertainties arising from the current evidence base, there appears to be some consensus that obesity is a potential risk factor with regard to children's and adolescents' psychological and emotional well-being and that vigilance for potential difficulties is a responsible approach to take [23, page 193].

4. Proposed Model

Given the lack of a clear model that elucidates the relationship between mental health and overweight/obesity, we propose a theoretical model (see Figure 1) (This figure was expanded and adapted from figures shown by Rebecca Puhl at the Canadian Obesity Network 1st Canadian Summit on Weight Bias and Discrimination). Main concepts in this model include psychological factors, mediating variables, and wellness factors. Most research has not examined these psychosocial factors in one study, and this paper aims to look at these factors together.

5. Psychological Factors

5.1. Depression and Anxiety. A recent review concluded that the majority of studies find a prospective relationship between eating disturbances and depression [24]. However, this relationship is not unidirectional; depression may be both a cause and a consequence of obesity [25]. Additionally, in a clinical sample of obese adolescents, a higher lifetime prevalence of anxiety disorders was reported compared to nonobese controls [26], although some studies demonstrate no significant relationship between increased BMI and increased anxiety symptoms [27]. Thus, the relationship between obesity and anxiety may not be unidirectional and is certainly not conclusive.

5.2. Self-Esteem. Research findings comparing overweight/obese children with normal-weight children in regards to self-esteem have been mixed [28]. Some studies find that obese children have lower self-esteem [29] while others do not [21, 30]. There is some consensus in the literature that the global approach to self-esteem measurement with children who are overweight/obese is misleading as the physical and social domains of self-esteem seem to be where these children are most vulnerable [31].

5.3. Body Dissatisfaction. Research has consistently found that body satisfaction is higher in males than females at all ages [32]. Gender differences may reflect the Westernized cultural ideals of beauty in that thinness is the only culturally defined ideal for females, while males are encouraged to be both lean *and muscular.* Thus, there is a linear relationship between body dissatisfaction and increasing BMI for girls; while for boys a U-shaped relationship suggests that boys

Table 1: Search terms used.

Population	Intervention	Outcome	Type of study
Child Preschool Adolescent Pediatrics Young people High school	Health policy Health promotion Health education	(a) Overweight Obesity Body weight Body mass index Body image (b) Mental health Depression Anxiety Psychological (c) Wellness Adaptation Resilience Quality of life Lifestyle (d) Social stigma Prejudice Teasing Bullying Peer victimization	Excluding: editorials comments

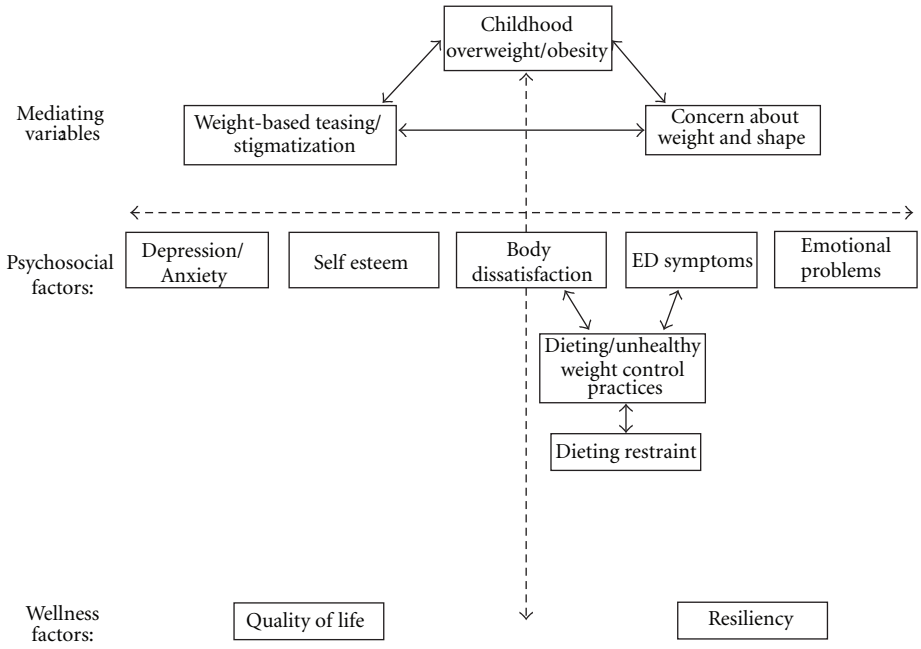

Figure 1: Proposed model.

with BMIs at the low and high extremes experience high levels of body dissatisfaction [33, 34].

5.3.1. Dieting/Unhealthy Weight Control Practices. A less well-known public health issue that elevates risk for obesity is the evidence of increased frequencies of *unhealthy dieting behaviours* among young people. Restrictive dieting is linked to both disordered eating/eating disorders and weight gain/obesity [35, 36]. *Unhealthy* weight control behaviours were reported by 57% of girls and 33% of boys, and *extremely*

unhealthy behaviours were reported by 12% girls and 5% of boys among 4,476 adolescents in public schools in Minnesota [37].

5.3.2. Dietary Restraint. Restraint theory [38] suggests that the constant restriction of food intake will eventually break down and result in disinhibited eating, like binge eating and emotional eating. This pattern can lead to decreased sensitivity of the body's natural hunger and satiety cues and an overreliance of contextual cues for eating [39]. Dietary restraint is associated with obesity (cross-sectional data; [40]) and predictive of future weight gain in youth [35, 41].

5.4. Eating Disorder Symptoms. Traits associated with eating disorders appear to be common in adolescent obese populations, particularly for girls [42]. A number of studies have shown higher prevalence of eating-related pathology (i.e., binge eating episodes, drive for thinness, impulse regulation) in obese children/youth [43, 44].

5.5. Emotional Problems. In one of the few studies to investigate the psychological impact of being overweight/obese in children, Cornette [45] reviewed 10 published studies over a 10-year period (1995–2005) with sample sizes greater than 50 and concluded that all participants reported some level of psychosocial impact as a result of their weight status. Being younger, female, and with an increased perceived lack of control over eating seemed to heighten the psychosocial consequences.

6. Mediating Variables

Two mediating factors emerged for understanding how overweight/obesity impacts psychosocial health and wellness and vice versa: (a) weight-based stigmatization and teasing and (b) weight and shape concerns.

6.1. Weight-Based Stigmatization and Teasing. Weight-based stigmatization is defined as "negative weight-related attitudes and beliefs that are manifested through stereotypes, bias, rejection, and prejudice toward children and adolescents because they are overweight or obese" [45, page 558]. Given the increase in the rate of childhood overweight/obesity, some people [46] have hypothesized simply by virtue of exposure that stigmatization or bias would have decreased. On the contrary, negative views of obese children are even higher than 40 years ago [10, 47]. The visible nature of obesity (i.e., it is not something that you can hide) as well as the assumption that obesity can be controlled (i.e., eat less and move more) is important determinants of weight bias. Obesity is considered to be one of the "most stigmatizing and least socially acceptable conditions in childhood" [30, page 1818]. The effects of this weight bias can be seen even years later. "Childhood obesity is related to fewer years of education, lower family income, higher poverty rates, and lower marriage rates in later young adulthood" [48]. Puhl and Latner [49] completed a comprehensive literature review on childhood weight-based stigmatization and found that children demonstrate weight bias by associating obesity with a number of undesirable traits and preferring to associate with nonobese peers. Children with more negative attitudes towards weight more likely rate an obese peer negatively and tease and bully children who appear overweight, with few cultural differences [49].

Experiences of weight-based teasing have been hypothesized as a mediating variable in the development and maintenance of overweight and obesity [50]. Not only do overweight/obese children have increased risk of experiencing significant victimization, but peer victimization has been linked to negative psychosocial and health outcomes [51] as well. "Peer victimization refers to the experience of overt (e.g., pushing, hitting, kicking) or relational (e.g., gossiping, teasing, ignoring, excluding) forms of aggression as perpetuated by an individual or group of peers" [52, page 721]. In one sample, 50% of obese boys and 58% of obese girls report experiencing significant problems with peers [46]. Obese children are almost twice as likely to be the victim of peer victimization, with girls more often reporting relational issues and boys reporting overt issues as both the victim and the perpetrator [10, 52, 53]. Being teased about weight is predictive of binge eating among adolescents [54] and is cross-sectionally associated with higher levels of disordered eating [55]. In addition to triggering body dissatisfaction and disordered eating, weight-based teasing has been linked to suicide attempts [23], implicated as a predictor of depressive symptoms [50], positively associated with anxiety, loneliness, social isolation, and parent reports of internalizing and externalizing behaviour problems [56] and experiences of shame [57] and negatively associated with physical activity [56].

6.2. Concern about Weight and Shape. A number of recent studies indicate that *perceived* overweight or *concern about weight*, rather than *actual* weight status, is predictive of the psychosocial/emotional fall-out of overweight/obesity [58]. Erickson et al. [59] were the first researchers to examine weight status and concern about weight and shape in relation to psychological outcomes. They found that, in a sample of 8-year-old girls, those with high weight and shape concern experienced more depressive symptoms than those with low levels of weight concern, *regardless of weight status*. Since then a number of other researchers have investigated the role of weight and shape concerns. In a sample of 7- to 13-year-old boys and girls, Allen et al. [20] found that (a) overweight children were more concerned about weight and shape than were healthy weight children and (b) regardless of weight status, children with high weight and shape concern reported lower levels of self-esteem and higher levels of body dissatisfaction and depression than children with low weight and shape concern. More recently, Jansen et al. [21] explored the idea that "feeling fat" may be more important than "being fat" in terms of the psychological well-being of 12 and 13 year olds. In a representative German sample of over 17000 children and youth, obese children who considered their body weight "just right" perceived a higher quality of life than normal weight children who considered themselves "far too fat" [60]. Cumulatively, these results suggest that weight

and shape concern rather than weight itself can account for differences in the psychological consequences of childhood overweight/obesity.

6.3. Summary. Existing studies can be used to speculate about relationships and links between factors. For example, teasing about weight in childhood may be related to emotional suffering, but at this point the direction of the relationship remains untested empirically. So while there is a level of confidence in the psychosocial factors, mediating variables and wellness factors presented in the model, the relationships between these variables are not clearly articulated through an examination of the literature. Further research through causal modeling or path analyses will help elucidate the relationships between the variables taken up in this paper.

7. Obesity Impact on Wellness/Wellness Impact on Obesity

In relation to obesity, much is known about healthy lifestyle (i.e., nutrition and physical activity), but little is known about well-being [13]. In fact, many of the recommendations for the treatment of child and adolescent overweight and obesity focus on physical outcomes like BMI and body composition with disregard for their impact on psychological or social well-being.

7.1. Quality of Life. Given that the psychosocial health of obese and overweight children and youth has been studied from a largely psychopathological perspective, measures often report on specific issues (i.e., depression and behavioural concerns). However, this approach fails to recognize or capture the limitations of well-being that may not meet specific diagnostic criteria. Emerging literature on quality of life (QOL) is beginning to fill this gap. "Quality of life can be defined as a multidimensional construct that reflects one's self-perceptions of enjoyment and satisfaction with life" [61, page 407]. Overweight children have reported lower QOL than non-overweight peers [51]. Studies suggest that the lower QOL for overweight children is related to physical functioning and psychosocial domains [62, 63], still obese children when compared to healthy-weight children are up to five times more likely to report lower global health-related QOL scores and in one study could not be distinguished in terms of scores from children with cancer receiving chemotherapy [31]. Some studies even indicated that differential QOL perceptions for children vary in the degree to which children are overweight [61]. Clinical samples show a stronger and more consistent association between overweight and lower QOL than population-based samples [64].

8. Resilience

Young people who show resilience have been found to have access to protective factors in three broad areas: (a) within themselves, (b) in their families, and (c) within the communities in which they live [65]. Resilience is defined as "the process of coping with adversity, change, or opportunity in a manner that results in the identification, fortification, and enrichment of resilient qualities or protective factors" [66, page 308]; it is a complex phenomenon that focuses on protective factors that contribute to positive outcomes despite the presence of risk [67, 68]. Certainly in the context of our obesogenic and fat-phobic culture, obese and overweight children that are able to thrive and excel in spite of their current context would help us understand the concept of resiliency. Unfortunately, these questions have not been taken up in the literature to date. More research is needed to determine the reasons for resilience in children that are overweight or obese [69].

While traditional methods to enhance the health and well-being of young people have utilized a problem-focused paradigm, a focus on QOL and resilience provides opportunity to view childhood obesity and overweight through a lens of positive mental health and development. "In the absence of consensus about the causal pathways leading to the obesity epidemic, it is hard to devise a public health response that can affect its course" [70, page 40]. Public health can support the creation of solutions that do not further marginalize overweight and obese children and youth [69] and that can potentially improve the lives of all children and youth regardless of weight status.

9. Stop the Focus on Weight

Healthy lifestyle behaviours are important for the whole population regardless of weight status; weight is not a behaviour and therefore should not be an object of behaviour modification [71]. The discourse engendered by a focus on weight could increase psychological discontent for children/youth who struggle with body issues or eating problems by encouraging unhealthy self-monitoring [72] or unhealthy weight control practices. QOL shows potential as an outcome measure to quantify the impact of overweight/obesity on overall functioning and as a tool for planning appropriate interventions and protocols [51] that considers the "whole" child, as well as the health and wellness of all children, regardless of weight status. Rather than viewing overweight/obesity as a medical issue, reducing the incidence of overweight/obesity must be seen as a public health matter that is the shared responsibility of public, government, and corporate entities [73]. The focus on weight is a well-traveled but ineffective and unproductive path mired in excess focus on personal responsibility. A shift to weight-neutral outcomes has shown evidence of success in randomized control trials (see Bacon and Aphramor [74] for a review). Significant improvements in physiological measures, health behaviours, and psychosocial outcomes (like self-esteem and body image) have been found to result from approaches that focus on weight-neutral rather than weight-loss goals [74].

10. Intervene with Weight Bias

Weight bias is prevalent and being stigmatized triggers a maladaptive cycle of poor mental and physical health, which

compromise uptake of the health behaviours necessary for the prevention of obesity and overweight. Recommendations to include weight bias awareness in the field of obesity, particularly obesity prevention efforts, have been largely ignored [75]. Health promotion experts have a unique opportunity to build psychosocial resilience among individuals and communities in an effort to reduce or prevent weight-related disorders. Individual factors are often the focus in childhood obesity literature, so refocusing on healthy relationships (e.g., healthy communication, problem-solving) shifts the focus one step outside the sole responsibility of the person who may literally and figuratively carry extra weight. In many ways, obesity is a social justice issue [76] and focusing on the relationship and contextual factors offers opportunities for intervention outside of the individual. Without consideration of weight-related issues as socially constructed and maintained, intervention efforts will likely fall short because it seeks to foster change from within the system rather than transforming the system that created the problems in the first place [77].

11. Promote Healthy Body Image

It is possible that the very public health strategies designed to combat the obesity epidemic may in fact engender the type of dialogue and environment that contribute to its development. Overweight children are even more concerned about weight than their normal-weight counterparts and even normal-weight children with high weight and shape concern report higher body dissatisfaction and depressive symptoms [20]. "It is critical that the possible iatrogenic impacts of health promotion messages are considered so that interventions do not trigger body image problems among target populations" [78, page 190]. A focus on early identification and prevention of weight and shape concern could reduce negative psychological outcomes for children of all weight statuses [20].

12. Target Adult Role Models

A number of recent documents suggest that a public health response to childhood obesity should include intervention across multiple sectors [78, 79]. Parents and teachers are important role models for influencing children's attitudes and behaviours towards their bodies. Unfortunately, parental antifat bias [80] and focus on the importance of physical appearance [81] contribute to increased weight-bias attitudes in children. Similarly, teachers, attitudes towards weight, particularly towards obesity, may have harmful effects on children's emerging body image [54]. Common school-based practices such as discussing "healthy" weights without consideration of diversity, weighing students, displaying children's weights, discussing "healthy" eating [82], and reading literature with negative weight-bias and thin-ideal messages [83] have the often unrecognized potential for contributing to body dissatisfaction, weight bias, disordered eating, harmful peer comparisons regarding body size, and weight-related teasing. Thus, shifting focus from weight and shape to models of health, wellness, and resilience is critical to enhance the well-being of children and adolescents, regardless of weight status [84].

13. Expand the Focus of Research

Perhaps instead of comparative studies that examine obese versus nonobese populations, researchers should seek an understanding of what factors put some obese people at risk or, even better, what protective factors explain why some overweight/obese people are psychologically healthy in an obesogenic environment [85]. There is an absence of any systematic research on psychosocially and physically healthy overweight/obese individuals [69], in part because the idea that overweight or obesity may be that a rational, freely chosen, or rewarding personal attribute is just not considered [86] and the assumption continues that overweight/obese people are by definition unhealthy. The focus on resiliency and wellness in research on childhood obesity is in its infancy. In one of the only studies to approach childhood obesity from an asset model, Fenton et al. [78] found positive associations between healthy body image in adolescence and three variables, (a) ease of communication with parents, (b) teacher interested in students as people, and (c) feeling intelligent, and two demographic indicators (a) perceived family affluence and (b) household composition (presence of father figure in home). Indeed identifying the mechanisms that protect psychological well-being as well as targeting potential mediators to assess importance and relationships between mechanisms [13] is an important call to action for the research community.

14. Conclusion

"Systematic action and shared responsibility are necessary foundations on which to develop effective policies that support optimal child health and well-being" [87, page 199]. The emergence of social ecological models for understanding obesity is useful for considering the range of influences that contribute to obesity [88]. This paper focused primarily on one facet of influence, namely, mental health and wellness, which is arguably one of the most neglected areas of study in our understanding of childhood overweight/obesity. However, it must be noted that the complexity is not adequately accounted for in this paper. Nonetheless, intervening for the psychosocial emotional health of overweight/obese children should be a focus in and of itself and not just an "add-on" measure to a primary outcome that is targeting weight reduction or the cessation of weight gain. Public health policy in the area of childhood obesity needs to encourage healthy body image, advocate that healthy behaviours come in every shape and size, and consider weight bias and weight and shape concerns as fundamental. In terms of mental health and wellness, this type of shift in paradigm could benefit all children and youth potentially for generations to come.

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Research Article

Binge Eating Disorder Mediates Links between Symptoms of Depression, Anxiety, and Caloric Intake in Overweight and Obese Women

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Despite considerable comorbidity between mood disorders, binge eating disorder (BED), and obesity, the underlying mechanisms remain unresolved. Therefore, the purpose of this study was to examine models by which internalizing behaviors of depression and anxiety influence food intake in overweight/obese women. Thirty-two women (15 BED, 17 controls) participated in a laboratory eating-episode and completed questionnaires assessing symptoms of anxiety and depression. Path analysis was used to test mediation and moderation models to determine the mechanisms by which internalizing symptoms influenced kilocalorie (kcal) intake. The BED group endorsed significantly more symptoms of depression (10.1 versus 4.8, $P = 0.005$) and anxiety (8.5 versus 2.7, $P = 0.003$). Linear regression indicated that BED diagnosis and internalizing symptoms accounted for 30% of the variance in kcal intake. Results from path analysis suggested that BED mediates the influence of internalizing symptoms on total kcal intake (empirical $P < 0.001$). The associations between internalizing symptoms and food intake are best described as operating indirectly through a BED diagnosis. This suggests that symptoms of depression and anxiety influence whether one engages in binge eating, which influences kcal intake. Greater understanding of the mechanisms underlying the associations between mood, binge eating, and food intake will facilitate the development of more effective prevention and treatment strategies for both BED and obesity.

1. Introduction

Although there is considerable comorbidity between obesity, eating disorders, and other major psychiatric disorders, the mechanisms underlying these associations have yet to be resolved. Binge eating disorder (BED), often associated with elevated body weight and mood disorders, is under consideration for inclusion in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V). BED is defined by the DSM-IV as a provisional eating disorder diagnosis characterized by recurrent episodes of binge eating without weight control compensatory behavior and includes (1) "eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most people would eat during a similar period of time and under similar circumstances" and (2) "a sense of lack of control over eating during the episode." In addition, individuals with BED must experience distress about their binge eating and endorse three of the following symptoms: eating more rapidly than normal, eating until uncomfortably full, eating large amounts when not hungry, eating alone because of embarrassment, and feeling disgusted, depressed, or guilty about overeating [1].

Although obesity is not a requirement for a BED diagnosis, research indicates that approximately 70% of those

meeting criteria for BED are obese [2]. While the prevalence of BED in community samples ranges from 2–5%, approximately 30% of obese individuals seeking weight control treatment meet criteria for BED [3, 4]. The recurrent overeating that characterizes BED, along with the absence of compensatory behaviors exhibited by those with bulimia nervosa (BN), is most likely responsible for the high frequency of obesity in this group. Laboratory studies have demonstrated that obese BED individuals consume significantly more kilocalories (kcal) during an overeating episode than obese individuals without a BED diagnosis [5–13].

Psychiatric disorders, including depression and anxiety, have been associated with obesity and BED. The lifetime prevalence of major depressive disorder (MDD) and anxiety disorders in the United States is estimated at 17% and 29%, respectively [14]. However, within obese populations, reported lifetime prevalence rates are increased to 32.8% for depression and 30.5% for anxiety [15]. Additionally, Strine et al. found adults with a current or lifetime diagnosis of depression or anxiety were significantly more likely to engage in unhealthy behaviors such as physical inactivity and to be obese [15]. Furthermore, research shows that obese individuals with comorbid BED have even greater rates of depression and anxiety than obese individuals without BED [2, 16–19]. For example, Grilo et al. report, in a study of 404 BED patients, that lifetime history estimates were elevated to 52% for mood and 37.1% for anxiety disorders [17].

Despite general acknowledgment of the associations between bodyweight, BED, and comorbid psychiatric disorders, the mechanisms underlying these relationships remain largely unknown. Previously, we have reported that overweight/obese women with BED consume significantly greater kcal intake during a laboratory eating episode than weight-matched women without BED (2305 versus 1462 kcal) [13]. To extend this work, we assessed symptoms of depression and anxiety in this sample and sought to examine how internalizing behaviors and BED may be associated with kcal intake during the laboratory eating episode. Based on the literature, we hypothesized that participants meeting BED criteria would endorse significantly more symptoms of depression and anxiety than weight-matched non-BED controls. However, the impact of a BED diagnosis and symptoms of depression and anxiety on kcal intake was less clear as there are several potential mechanisms responsible for the association. It is possible that increased kcal intake is the result of BED symptomatology. For instance, those with BED may use binge eating to alleviate or escape symptoms of depression and anxiety. Additionally, in converse, it is possible that BED symptomatology such as distress regarding lack of control overeating specifically elevates internalizing symptoms. For example, depression may increase food intake through increased appetite, a clinical feature of atypical depression subtype. Furthermore, it is possible that having both a BED diagnosis and elevated symptoms of depression and anxiety synergistically influence food intake in a nonadditive manner.

A common statistical approach to examining relationships between variables is path analysis, in which alternative models can be applied to evaluate theoretical relationships and determine directionality of effects. We assessed three alternative models, depicted in Figure 1, to determine the mechanism of association that best fit our data. Path analysis was employed to evaluate three potential models: (1) the symptoms of depression and anxiety increase susceptibility to BED, which in turn influences caloric intake (Figure 1(a)), (2) a BED diagnosis influences symptoms of depression and anxiety, which subsequently influences caloric intake (Figure 1(b)) and (3) a BED diagnosis and symptoms of depression and anxiety function interdependently in relation to energy intake (Figure 1(c)).

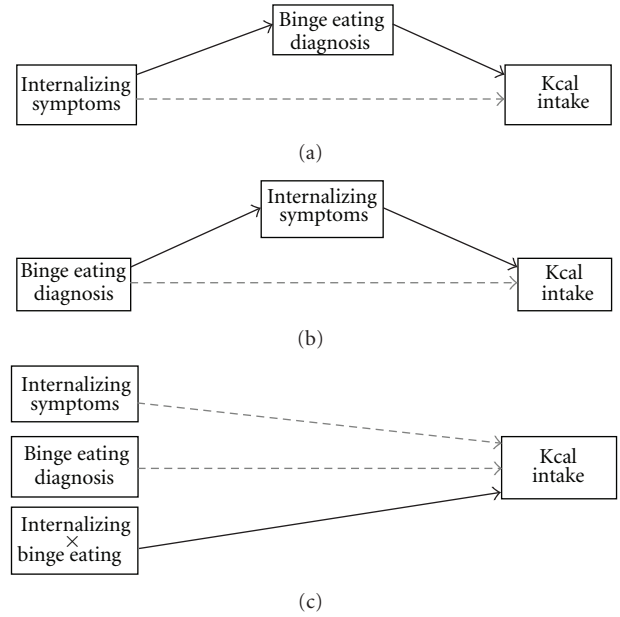

Figure 1: Theoretical models examined: (a) binge eating disorder mediates the associations between internalizing symptoms and kilocalorie intake, (b) internalizing symptoms mediate the association between binge eating disorder and kilocalorie intake, and (c) binge eating disorder interacts with internalizing symptoms in the prediction of kilocalorie intake. Note: internalizing: symptoms of depression and anxiety.

2. Methods

2.1. Participants. Participants were recruited by newspaper and online advertisements inviting women at least 50 pounds overweight and between the ages of 18 and 45 to participate in a paid research study. Thirty-two women, including 15 meeting DSM-IV criteria for BED and 17 overweight/obese controls with no history of any binge eating or eating disorder behaviors, participated in the study. These women were recruited as part of a larger study examining food intake and energy expenditure measured via the doubly labeled water method [13, 20].

2.2. Group Assignment. Potential participants were interviewed with the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P) [21], and

the Eating Disorder Examination (EDE), Version 12.0D [22] to determine study eligibility and group assignment. Additionally, a medical history, physical exam, and battery of laboratory tests were completed to detect unstable medical conditions, such as diabetes and impaired thyroid function, which would influence eligibility. Participants were excluded from the study if they had any unstable medical or psychiatric conditions, met DSM-IV criteria for substance abuse or dependency within 6 months of participation, or were currently dieting or participating in a weight-loss program. Those with any history of BN or compensatory behaviors were also excluded. Non-BED controls were free of any current or past eating disorder symptoms. The protocol was reviewed and approved by the Institutional Review Board at the University of Minnesota, and all participants took part in the informed consent process and signed a consent form. Participants were paid $300 upon completion of the entire study protocol.

2.3. Laboratory Binge Eating Episode. This study utilized a protocol our group has previously reported [12, 13, 23]. In brief, participants were interviewed by a research dietician regarding their general eating patterns and foods on which they typically snacked or overate. They indicated which items from a standardized list of snack foods appealed to them and could suggest extra foods or recipes. Based on the information gathered during the interview, a tray of binge foods was created for each participant incorporating their personalized snacking preferences. Each participant received 6 to 10 different kinds of food on their snack tray. Food items were presented in excessive quantities (two to three times what they endorsed eating during a binge) to ensure that binge size was not limited by quantity of food.

Participants were admitted to the General Clinical Research Center (GCRC) for an overnight stay to participate in several study activities. They were instructed not to consume any food or caloric beverages between 12 and 5 PM. At approximately 5:30 PM, they were presented with a multiple-item array of foods, including their personalized binge tray and a standard hospital dinner and were instructed to "Let yourself go and eat as much as you like." They were left alone in a private room to eat for as long as they liked and signaled the nursing staff when they were finished. The GCRC metabolic kitchen staff measured pre- and postprandial quantities of food. Caloric and macronutrient intake for the laboratory eating episodes were calculated using Nutritionist IV [24].

2.4. Self-Report Measures of Depression and Anxiety. During the initial evaluation, participants completed the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) which are widely used self-report questionnaires consisting of items addressing how one has been feeling in the last week and measure the severity of depression and anxiety symptoms [25, 26]. The scales have high internal consistency coefficients (i.e., BDI upwards of 0.80), and validity with other clinical assessments [27, 28]. Scores on these indices range from 0 to 63 and correspond to normal (0–9 BDI, 0–7 BAI), mild (10–18 BDI, 8–15 BAI), moderate (19–29 BDI, 16–25 BAI), and severe (30–63 BDI, 26–63 BAI) depression and anxiety.

2.5. Analytic Strategy and Model Validation. A set of three, theoretically driven path models (see Figure 1) were tested using Mplus version 5.0 [29]. As MacKinnon and colleagues [30] have suggested, the traditional *causal steps approach* [31, 32] may lack the statistical power to detect some meaningful indirect effects. The mediation analyses presented here utilized the *product of coefficients* strategy [30, 33] to evaluate the extent to which a predictor influences an outcome through some intermediary variable (Figures 1(a) and 1(b)). In doing so, the *indirect effect* is derived by taking a ratio of the product of the path coefficients from (1) the independent variable to the mediator and (2) the mediator to the dependent variable over the normal-theory standard error for that product (i.e., $(\beta 1 * \beta 2)/\mathrm{SE}_{(\beta 1 * \beta 2)}$), the results of which are evaluated with respect to the Z-distribution. Moderation (Figure 1(c)) was assessed via the partial path coefficient for a product term (i.e., $\beta/\mathrm{SE}_{\beta}$) in the presence of its individual components and evaluated with respect to a t-distribution.

To protect against potential bias introduced by the small size of our sample, evidence of significance was assessed via permutation testing [34]. From the originally observed data, ten thousand novel datasets were generated via the random reordering of individuals' values on BED and kcal intake. This procedure was performed in R version 2.9.1 [35]. Each of the permuted datasets can thus be reanalyzed within Mplus version 5.0 [29], with respect to the three alternative models depicted in Figure 1, and the test statistics from each iteration can be used to generate null distributions for each of the effects being scrutinized. Criteria for significance (i.e., empiric P values) can be calculated using the formula $(p + 1)/(n + 1)$, where p is the number of null tests that are more significant than the test conducted with the original data and n is the total number of permutations (i.e., 10,000) on which the analyses are rerun. As a result, we are able to assess whether each of the hypothesized models would achieve significance in a much larger sample (i.e., 320,000), given the characteristics of our observed sample.

3. Results

3.1. Descriptive Statistics. Of the thirty-two women participants, 27 were European-American, 3 were African-American (9.4%), and 2 were Asian-American (6.3%). Means and standard deviations for total energy intake, depression and anxiety scores, and potential covariates (i.e., age and BMI) are presented by BED diagnosis on the diagonal in Table 1. ANOVA indicated that there were significant group differences in depression scores (10.1 versus 4.8, $F(1, 30) = 9.308$, $P = 0.005$) and anxiety scores (8.5 versus 2.7, $F(1, 30) = 10.830$, $P = 0.003$) with BED participants having significantly higher mean scores than controls across these indices. No intergroup differences were found regarding BMI ($F(1, 30) = 3.203$, $P = 0.784$), or age ($F(1, 30) = 10.737$, $P = 0.674$). Table 2 reports

the prevalence of lifetime clinical depression and anxiety diagnoses by group. The BED group had significantly greater prevalence of mild depression (60 versus 17.6%, $\chi^2 = 6.10$, $P = 0.014$), mild/moderate anxiety (33.3 versus 5.9%, $\chi^2 = 3.94$, $P = 0.047$), and anxiety disorders (46.7 versus 11.8%, $\chi^2 = 4.80$, $P = 0.028$). A detailed examination of food intake and energy expenditure in these participants is reported in additional manuscripts from our group [13, 20].

Pearson's correlation coefficients for bivariate associations between study variables are presented in the off-diagonal cells in Table 1. Within each cell, associations are presented separately for participants diagnosed with BED (top), weight-matched controls (middle), and across the entire sample (bottom). Significant positive correlations were found between kcal intake and depression, kcal intake and anxiety, and depression and anxiety within the full sample. When assessed within groups, no significant correlations were found except between depression and anxiety scales in the control group. Since neither BED nor internalizing symptoms were associated with age or BMI, these latter variables were not included in the path models described below.

3.2. Model Fitting. Separate path models were run to test (a) the intermediary role of BED in associations between depression and anxiety symptoms and caloric intake, (b) the intermediary role of depression and anxiety symptoms in associations between BED and caloric intake, and (c) the interactive influences of BED and symptoms of depression and anxiety on caloric intake. In each case, the theoretical model accounted for a significant amount (~30%) of the variance in energy intake. However, examination of the three alternative theoretical models revealed important mechanistic differences in the relationship between BED and symptoms of depression and anxiety as they serve to jointly influence energy intake. Results of the models (Table 3) depicted in Figures 1(a) and 1(b) suggest that, while kcal intake is significantly influenced by both depression and anxiety symptoms ($\beta_{\text{total, depression}} = 0.409$, $P = 0.006$; $\beta_{\text{total, anxiety}} = 0.399$, $P = 0.003$) and binge eating status ($\beta_{\text{total, BED}} = -0.508$, $P \leq 0.001$), the effects attributed to symptoms of depression and anxiety operate, in large part, through the influences they have on BED ($\beta_{\text{indirect, depression via BED}} = 0.197$, $P = 0.052$; $\beta_{\text{indirect, anxiety via BED}} = 0.212$, $P = 0.046$). Note that the sign of the effects reflect coding of 1 for BED and 2 for controls in all analyses. That is, roughly half of the influence of depression (~48%) and anxiety (~53%) on caloric intake is mediated through BED. In contrast, the influence of BED status on caloric intake appears not to be mediated by symptoms of depression or anxiety ($\beta_{\text{indirect, BED via depression}} = -0.103$, $P = 0.282$; $\beta_{\text{indirect, BED via anxiety}} = -0.096$, $P = 0.329$); rather, those direct effects remained strong ($\beta_{\text{direct, BED with depression}} = -0.404$, $P = 0.027$; $\beta_{\text{direct, BED with anxiety}} = -0.411$, $P = 0.014$). Results of the model depicted in Figure 1(c) indicate that BED and symptoms of depression and anxiety do not interdependently influence caloric intake, that is, neither the model including depression nor the model including anxiety yielded significant partial path coefficients for an interaction between BED and the corresponding depression or anxiety symptoms ($\beta_{\text{BED}x\text{depression}} = -0.279$, $P = 0.598$; $\beta_{\text{BED}x\text{anxiety}} = -0.268$, $P = 0.609$) after taking into account their combined main effects, in each case accounting for less than 1% of the total variance.

As described above, post hoc analyses were conducted with 10,000 permuted datasets to determine whether the results observed with respect to the first theoretical model (i.e., BED mediating the association between symptoms of depression and anxiety and caloric intake) were simply due to chance and/or an artifact of the modest size of the present sample. The null distributions generated from these analyses suggested that the indirect effects of both depression and anxiety through BED were highly significant; as far fewer than 5% of the tests exceeded the P values observed in the original data. In fact, of the 10,000 randomly generated datasets, only seven yielded indirect effects of depression through BED that were more significant than the effect observed in the original data ($P = 0.0008$), with only thirty-eight indirect effects of anxiety on BED exceeding the observed level of significance ($P = 0.0009$).

4. Discussion

The purpose of this study was to examine models by which internalizing symptoms of depression and anxiety influence food intake in overweight/obese women. Our results indicate that BED women endorse significantly more symptoms of depression and anxiety. Additionally, linear regression indicated that BED diagnosis and internalizing symptoms accounted for 30% of the variance in kcal intake. Furthermore, results from path analysis imply that BED mediates the influence of internalizing symptoms on total kcal-intake, which suggests the associations between internalizing symptoms and food intake are best described as operating indirectly through a BED diagnosis.

The present study found that overweight/obese women with BED endorsed more symptoms of depression and anxiety than non-BED weight-matched controls. Mean scores for the BDI and the BAI indicated mild depression and anxiety in the BED group but normal levels in the control group. Other studies have found elevated depression and anxiety scores in BED individuals [5, 9, 18, 19, 36, 37]. For example, in a study by Fandiño et al., depression and anxiety scores were significantly greater in the BED group than those in the obese control group as assessed by the Symptom Checklist 90 and the BDI [37]. The lifetime prevalence of MDD in the BED and control groups was 46.7% and 29.4%, respectively. These rates are similar to previous reports in BED [2, 16–19] and non-BED obese groups [15]. Lifetime prevalence of anxiety disorders was similar to rates of depression in the BED group (46.7%) but was much lower in the control group (11.8%). It is possible that the lower rates of anxiety disorders in the control group were due to the inclusion of overweight women or was an artifact of the limited sample size.

Laboratory studies have demonstrated that those with BED have greater total food intake than obese controls

Table 1: Group means and intercorrelations for study variables.

	1	2	3	4	5
(1) Age	30.1 (6.7) 31.3 (8.5)				
(2) Body mass index (kg/m^2)	−0.17 −0.14 −0.15	34.3 (5.5) 34.9 (7.2)			
(3) Depression symptoms	−0.09 0.06 −0.04	−0.33 0.34 0.04	**10.1** (**4.8**) **4.8** (**5.0**)		
(4) Anxiety symptoms	−0.05 0.35 0.04	−0.29 0.24 −0.08	0.34 0.66** 0.57***	**8.5** (**6.5**) **2.7** (**3.1**)	
(5) Kilocalorie intake	−0.10 −0.26 −0.19	−0.06 0.54* 0.02	0.28 0.15 0.41*	0.27 0.00 0.40*	**2305.1 (834.0)** **1461.8 (641.9)**

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Notes: off-diagonal cells depict Pearson's correlation coefficients for participants diagnosed with binge eating disorder (top; $n = 15$), controls (middle; $n = 17$), and the overall sample (bottom; $n = 32$); values on the diagonal reflect means and standard deviations for cases (top) and controls (bottom), with boldface type indicating group differences ($P < 0.01$) as assessed via F-statistic with 1, 30 degrees of freedom.

Table 2: Lifetime clinical depression and anxiety diagnoses by group.

Diagnosis	BED n (%)	Control n (%)	Chi-square	P value
BDI-mild	9 (60%)	3 (17.6%)	6.10	**0.014**
BAI-mild/moderate	5 (33.3%)	1 (5.9%)	3.94	**0.047**
MDD	7 (46.7%)	5 (29.4%)	1.01	0.314
Dep NOS	1 (6.7%)	0 (0%)	1.17	0.279
GAD	1 (6.7%)	0 (0%)	1.17	0.279
Social phobia	4 (26.7%)	1 (5.9%)	2.61	0.106
Specific phobia	2 (13.3%)	0 (0%)	2.42	0.120
Panic disorder	1 (6.7%)	0 (0%)	1.17	0.279
PTSD	1 (6.7%)	0 (0%)	1.17	0.279
Anx NOS	0 (0%)	2 (11.8%)	1.88	0.170
Any Dep Dx	8 (53.3%)	5 (29.4%)	1.89	0.169
Any Anx Dx	7 (46.7%)	2 (11.8%)	4.80	**0.028**
Any Dep/Anx Dx	10 (66.7%)	6 (35.3%)	3.14	0.077

Note: BED: binge eating disorder, Chi-square: Pearson's Chi-square 1 degree of freedom test, BDI-mild: mild depression as assessed by the Beck Depression Inventory which corresponds to scores 10–18, BAI-mild/moderate: mild to moderate anxiety as assessed by the Beck Anxiety Inventory which corresponds to scores 8–25, MDD: major depressive disorder, Dep NOS: depressive disorder not otherwise specified, PTSD: posttraumatic stress disorder, Anx NOS: anxiety disorder not otherwise specified, any Dep Dx: any DSM-IV depressive disorder diagnosis, any Anx Dx: any DSM-IV anxiety disorder diagnosis, any Dep/Anx Dx: any DSM-IV depressive or anxiety disorder diagnosis, dysthymic disorder, and obsessive compulsive disorder were omitted from table because no participants met criteria for these disorders.

Table 3: Standardized effects coefficients, standard errors, and corresponding P values for mediation models.

Predictor	Mediator	Total effect			Direct effect			Indirect (mediated) effect			
		β	SE	P value[a]	β	SE	P value[a]	β	SE	P value[a]	Empirical P value[b]
Model 1											
Depression	BED	0.409	0.150	0.006	0.212	0.183	0.247	0.197	0.101	0.052	0.0008
Anxiety	BED	0.399	0.136	0.003	0.187	0.181	0.301	0.212	0.106	0.046	0.0009
Model 2											
BED	Depression	−0.508	0.136	<0.001	−0.404	0.182	0.027	−0.103	0.096	0.282	—
BED	Anxiety	−0.508	0.136	<0.001	−0.411	0.168	0.014	−0.096	0.099	0.329	—

[a] Corresponding to the two-tailed test statistics for models run with sample data.

[b] Corresponding to the two-tailed test statistics for a series of analyses with 10,000 permuted datasets.

Note: BED: binge eating disorder, signs of effects reflect coding of BED status as 1 and control as 2 in all analyses.

when instructed to overeat [5–13]. Two such studies have reported on both food intake and depression symptoms [5, 9]. In a sample of 10 obese BED women and 9 obese controls, Yanovski et al. found that the BED group consumed significantly more kcals (2962 versus 2017) and had significantly greater depression scores as measured by the BDI (18.9 versus 5.4) than controls. Additionally, they observed significant positive correlations between kcal intake and BDI score ($r^2 = 0.41$) and between binge meal energy intake and BDI ($r^2 = 0.28$). Geliebter and colleagues compared consumption of a liquid test-meal for 30 obese BED individuals (18 women) and 55 obese controls (43 women). The BED group consumed significantly more grams (1,032 versus 737) of the liquid test meal and endorsed significantly higher depression scores assessed by the Zung Depression Scale. However, a significant correlation between test meal intake and depression score was not found. The discrepancy could be due to several study design differences, including proportion of BED and control participants, inclusion of men, and type of food intake (solid versus liquid meal).

Furthermore, results from linear regression indicated that BED diagnosis and symptoms of depression and anxiety accounted for a significant amount (~30%) of the variance in caloric intake. However, examination of the three alternative models revealed important mechanistic differences in the relationship between BED, symptoms of depression, and anxiety and subsequent energy intake. The model that best fit our data indicated that BED mediated the influence of depression and anxiety symptoms on total kcal intake (Figure 1(a)). Specifically, our results suggest that the associations found between symptoms of depression and anxiety and food intake are best described as operating indirectly through a BED diagnosis, that is, symptoms of depression and anxiety influence whether one engages in pathological binge eating, which, in turn, influences caloric intake. Our findings did not support model b (BED predicted symptoms of depression and anxiety which, in turn, influence kcal intake), or model c (a significant interaction between symptoms of depression and anxiety and BED as being predictive of kcal intake).

These results highlight the importance of mood in relation to a BED diagnosis and subsequent caloric intake. Other research has also implicated mood in BED. Telch et al. interviewed 60 obese women with BED regarding their definition of binge eating, and 33% reported it as eating to regulate negative affect [38]. With the advent of the ecological momentary assessment procedures (EMA), prospective data on precursors to binge eating in the natural environment have been collected [39–43]. A study by Stein et al. found in 33 obese women with BED that negative mood was significantly greater at prebinge times than at nonbinge times and that participants attributed binge eating to mood more frequently than hunger or violation of extreme dietary restraint (abstinence violation) [41]. Additionally, a study by Hilbert and Tuschen-Caffier found that mood preceding a binge eating episode was more negative than mood prior to regular eating or at random assessments in a sample of 20 obese women with BED [42]. Furthermore, in a meta-analysis of 36 EMA studies of BED and BN, negative affect was significantly greater preceding binge eating relative to average affect and affect before regular eating [43]. A growing body of literature implicates negative affect as a precursor to binge eating in BED.

The implications of the present study are potentially relevant to the clinical treatment of BED and obesity. Research has indicated that mood and eating disorder diagnoses affect weight loss, and other treatment efforts. For example, Pagoto et al. reported that both BED and depression were associated with less weight loss and depression was associated with study attrition [44]. Furthermore, in BED treatment, depression symptoms have been associated with both attrition from cognitive-behavioral therapy and severity of eating disorder psychopathology [45]. The current results suggest that targeting mood may be useful in the treatment of BED and accentuate the importance of considering mood and BED status in weight management.

Among the major strengths of this study were utilizing path analysis to test relationships between BED, symptoms of depression and anxiety, and kcal intake as well as using permutation procedures for model validation and statistical support. EMA studies have consistently demonstrated negative affect as a precursor to binge eating [43] in BED. However, these studies have relied on self-report of food intake. Research indicates that obese and BED populations tend to underreport their food intake [13, 20, 46–51]. Therefore, a further strength of this work was the inclusion of laboratory-measured food intake to avoid inaccuracies often associated with self-report of dietary intake. Potential limitations include limited sample size and age range, exclusion of male participants, and use of self-report questionnaires to measure symptoms of depression and anxiety. Future research is warranted to confirm our findings and should seek to compare energy intake and depression and anxiety in both women and men. Greater understanding of the mechanisms underlying the associations of depression and anxiety symptoms, binge eating, and caloric intake will facilitate the development of more effective prevention and treatment strategies for both BED and obesity.

Conflict of Interests

The authors declare no conflict of interest.

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Research Article

Associations between Overall and Abdominal Obesity and Suicidal Ideation among US Adult Women

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Obesity is associated with increased risks for mental disorders. This study examined associations of obesity indicators including body mass index (BMI), waist circumference, and waist-height ratio with suicidal ideation among U.S. women. We analyzed data from 3,732 nonpregnant women aged ≥20 years who participated in the 2005–2008 National Health and Nutrition Examination Survey. We used anthropometric measures of weight, height, and waist circumference to calculate BMI and waist-height ratio. Suicidal ideation was assessed using the Item 9 of the Patient Health Questionnaire-9. Odds ratios with 95% conference intervals were estimated using logistic regression analyses after controlling for potential confounders. The age-adjusted prevalence of suicidal ideation was 3.0%; the prevalence increased linearly across quartiles of BMI, waist circumference, and waist-height ratio (P for linear trend <0.01 for all). The positive associations of waist circumference and waist-height ratio with suicidal ideation remained significant ($P < 0.05$) after adjustment for sociodemographics, lifestyle-related behavioral factors, and having either chronic conditions or current depression. However, these associations were attenuated after both chronic conditions and depression were entered into the models. Thus, the previously reported association between obesity and suicidal ideation appears to be confounded by coexistence of chronic conditions and current depression among women of the United States.

1. Introduction

The rising tide of obesity continues to be a major concern of public health in the USA and worldwide. The prevalence of obesity, defined usually by a body mass index (BMI) of ≥30 kg/m^2, has increased substantially from 13.3% during 1960–1962 to 33.8% during 2007-2008 among US adults [1–3] with noticeable differences between men and women (32% versus 36% in 2007-2008) [1]. In addition to its substantial impact on physical health (i.e., obesity-related chronic conditions), obesity is also associated with increased risks of psychiatric or mental disorders such as depression, anxiety, mania, panic attacks, and social phobia in both men and women [4–8].

With regard to suicidal behaviors and suicide mortality, a vast majority of previous studies including large, prospective cohort studies have shown that among men, BMI is inversely associated with suicidal ideation, suicide attempt, or suicide death and thus provides protection from suicide mortality [4, 9–13]. Although the mechanism underlying the inverse relationship remains unknown, evidence suggests that low levels of blood cholesterol and markers of insulin sensitivity in lean men may interfere with circulating tryptophan metabolism and brain serotonin production, thereby increasing the risk for suicide attempts and suicide death [14–17]. Among women, a longitudinal follow-up study using the National Health Interview Survey Linked Mortality data reported that for a 5 kg/m^2 increase in BMI, the relative risk of suicide death decreased by 24% after controlling for sociodemographics, region of residence, number of chronic conditions, number of psychiatric conditions, activity limitation, and self-rated health [10]. However, the National Longitudinal

Alcohol Epidemiologic Survey study showed that a 10 kg/m^2 increase in BMI was associated with 22% increased likelihood for past-year suicidal ideation among adult US women after controlling for sociodemographics, lifetime disease history, and substance use [18]. Another study conducted on Canadian women also reported that obesity was associated with increased likelihoods of lifetime and past-year suicidal ideation and suicide attempts when controlling for age, education, psychiatric disorders and comorbidity, and physical illness burden assessed as Charlson Comorbidity Index [6]. Thus, the associations between BMI and suicidal behaviours or suicide death among women remain uncertain. Moreover, in the previous studies, only BMI as an indicator of overall obesity was evaluated; the association between abdominal obesity and suicidal behaviors is largely unknown. To further shed light on these issues, the present study, by using a large nationally representative sample, aimed to (1) examine the prevalence of suicidal ideation among US adult women across quartiles of BMI, a measure of overall obesity, and across quartiles of waist circumference and waist-height ratio (WHR), measures of abdominal obesity, and (2) examine the associations of BMI, waist circumference, and WHR with suicidal ideation while controlling for multiple potential confounders including sociodemographic characteristics, lifestyle-related behavioral risk factors, obesity-related chronic physical conditions, and current depression status, most of which have been included as covariates in the previous studies [6, 10, 18]. We hypothesized that a positive association may exist between abdominal obesity and suicidal ideation as well as between overall obesity and suicidal ideation independent of behavioral risk factors, obesity-related chronic physical conditions, and current depression status among US women.

2. Subjects and Methods

We analyzed data from the National Health and Nutrition Examination Survey (NHANES) 2005–2008, a nationally representative sample obtained using a multistage stratified sampling design from the noninstitutionalized civilian US population. Survey participants were initially interviewed at home and were then invited to a mobile examination center, where they received various examinations and provided blood samples for laboratory tests. Details about the NHANES survey design and operation have been described elsewhere [19]. All procedures involving human subjects were reviewed and approved by the Research Ethics Review Board of the National Center for Health Statistics at the Centers for Disease Control and Prevention. Written informed consent was obtained from all participants.

We examined interview data from women aged ≥20 years who attended the mobile examination center. Anthropometric measurements were performed by trained health technicians. Weight was measured in pounds on a Toledo digital scale with participants only wearing underwear, disposable paper gowns, and foam slippers. Standing height was measured with a stadiometer to the nearest 0.1 cm. BMI was calculated from measured weight (kg) and height (m). Waist circumference was measured at a point immediately above the iliac crest on the midaxillary line at minimal respiration to the nearest 0.1 cm. Waist-height ratio (WHR) was calculated from measured waist circumference (cm) and height (cm). The quartiles of BMI, waist circumference, and WHR were created based on their distributions among women aged ≥20 years after taking into account the sampling weights.

Suicidal ideation was assessed using the 9th item of the Patient Health Questionnaire-9 (PHQ-9) [20, 21], which has been used widely to assess suicidal ideation in psychiatric research [22–26]. Specifically, participants were asked about how often over the previous two weeks they had been bothered by thoughts of being better off dead or of hurting themself in some way. Their response options were categorized as (1) not at all, (2) several days, (3) more than half the days, and (4) nearly every day. Participants with an affirmative response to the options (2) to (4) were defined as having suicidal ideation.

Sociodemographic variables in the analyses included age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other race), educational status (<high school diploma, high school graduate, and >high school diploma), marital status (married or living with a partner, divorced/widowed/separated, and never married), and family poverty-income ratio (calculated as a ratio of family income to poverty threshold and categorized as <1.0, 1.0–<3.0, ≥3.0). Health-related behavioral risk factors included smoking, physical activity, and alcohol use, which were assessed based on participants' self-reports. For smoking, participants were asked if they had smoked at least 100 cigarettes in their entire life and if they were smoking cigarettes now. Participants were then categorized as current smokers (those who had smoked at least 100 cigarettes during their lifetime and were still smoking), former smokers (those who had smoked at least 100 cigarettes during their lifetime but stopped), and never smoked (those who had smoked less than 100 cigarettes during their lifetime). Physical activity was assessed by asking participants whether, over the past 30 days, (1) they had engaged in specific moderate or vigorous leisure-time activities, (2) they had walked or bicycled as part of getting to and from work, or school, or to do errands (transportation activities), and (3) they had done any tasks in or around their home or yard for at least 10 minutes that required moderate or greater physical effort (household activities). If a confirmative answer of "yes" was recorded, participants were then asked about how many times and the average duration each time they engaged in the activities over the past 30 days. Based on the Metabolic equivalent task (MET) score for specific activities, we calculated the average daily metabolic equivalent-hour index (MET-hr/day) that summed transportation, household, and leisure-time physical activity and participants were then dichotomized as physically active (MET-hr/day >0) and inactive (MET-hr/day $=0$). Alcohol consumption was assessed by asking respondents how many days per week or per month they had had at least 1 drink (equivalent to a 12-ounce beer, a 5-ounce glass of wine, or a drink with 1 shot of liquor) of any alcoholic beverages during the past 30 days and how many drinks they had on average on the days when they drank. We calculated the average number of daily

drinks, and participants were then dichotomized as having excessive drinking (>1 drink/day) and not (≤1 drink/day).

Chronic conditions included hypertension, diabetes, coronary artery disease (i.e., coronary heart disease, angina pectoris, or heart attack), congestive heart failure, stroke, arthritis, asthma, chronic bronchitis, emphysema, thyroid problem, liver disease, renal disease or renal failure, sleep disorders, disability, and cancer. Most of the conditions were assessed by asking participants whether they had ever been told by a healthcare professional that they had these conditions or whether they still had asthma, chronic bronchitis, thyroid problem, or liver disease at the time when the survey was conducted. Mean systolic and diastolic blood pressures were calculated as the average of the last two readings of systolic or diastolic blood pressure for participants who had three measurements, as the last reading for participants who had two measurements, and as the only reading for participants who had one measurement. Participants who were on antihypertension medications or had systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg were defined as having hypertension [27]. Disability status was assessed by asking participants whether (1) they were limited in any way in any activities including limitations from working and walking or experiencing confusion/memory problems because of physical, mental, or emotional problems and (2) they were required to use special equipments such as a cane, a wheelchair, a special bed, or a special telephone because of any health problem. Participants with an affirmative response to either question were defined as having a disability. The number of the above chronic conditions was summed and participants were defined as having none of the conditions, 1-2 conditions, or ≥3 conditions.

Current depressive symptoms were assessed using the items 1 to 8 of the PHQ-9, which has been shown to provide a valid measure of depressive symptoms and severity in the general population [28]. Briefly, participants were asked about symptoms of depression they experienced in the past 2 weeks, which included little interest or pleasure in doing things; feeling down, depressed, or hopeless; trouble falling asleep, staying asleep, or sleeping too much; feeling tired or having little energy; a poor appetite or eaten too much; feeling bad as a failure or letting self or family down; trouble concentrating on things such as reading the newspaper or watching TV; and moving or speaking too slowly, or moving around a lot more than usual because of being so fidgety or restless. A total depression score was calculated as described elsewhere [7, 28, 29]; participants with a score of ≥10 were defined as having current depression. The scoring of ≥10 has a sensitivity and specificity of 88% for major depression [21].

3. Statistical Analysis

The prevalence of suicidal ideation was estimated and age-standardized to the 2000 female population in the USA The regression coefficient (β), odds ratio (OR), and 95% confidence interval (CI) for having suicidal ideation were estimated by conducting logistic regressions using each obesity indicator (BMI, waist circumference, and WHR) as a predictor while controlling for covariates including sociodemographic characteristics, lifestyle-related behaviors, chronic conditions, and current depression. A body of evidence has shown that obesity is associated with a variety of risky lifestyle behaviors (such as physical inactivity and alcohol use) and health outcomes (such as obesity-related chronic physical conditions and mental disorders) [7, 8, 30–37]. On the other hand, the sociodemographic factors, risky lifestyle behaviors, stressful life events including severe chronic or terminal illness, and psychiatric and psychological factors are important risk factors related to suicidal ideation or suicidal behaviors [38–41]. Therefore, we included these variables as study covariates in our analyses; similar covariates have also been used in the previous studies.

Trends in the prevalence of suicidal ideation were tested using orthogonal contrasts, and the trends in the ORs were tested using the median values for the quartiles of BMI, waist circumference and WHR in logistic regression models. SUDAAN (Software for the Statistical Analysis of Correlated Data, Release 9.0, Research Triangle Institute, Research Triangle Park, NC) was used to account for the complex sampling design.

4. Results

Among 5,399 female participants aged ≥20 years, exclusions included pregnant women ($n = 382$) and women with missing values for suicidal ideation ($n = 537$), BMI ($n = 94$), waist circumference ($n = 307$), or WHR ($n = 310$). After further excluding those who had missing values for study covariates, 3,732 nonpregnant women (median age: 46 years) remained in our analyses. Approximately 73.7% were non-Hispanic white, 10.8% non-Hispanic black, 6.7% Hispanic, and 8.8% other racial/ethnic participants. About 59.3% attained an educational level of greater than a high school diploma, 61.8% were married or living with partners, and 52.2% had a poverty-income ratio of ≥3.0. The percentages of women with unhealthy lifestyle behaviors were 20.6% for current smoking, 19.5% for physical inactivity, and 6.8% for excessive alcohol drinking. In addition, 39.8% reported having 1-2 chronic conditions, 23.1% reported having ≥3 of chronic conditions, and 8.2% reported having current depression.

Overall, the unadjusted and age-adjusted prevalence of suicidal ideation was 3.1% (95% CI: 2.5–3.8%) and 3.0% (95% CI: 2.4–3.8%), respectively (Table 1). The prevalence of suicidal ideation was the lowest in non-Hispanic white women or in women who had an educational level of >high school diploma, who were married or living with partners, or who had a poverty-income ratio of ≥3.0 among their respective categories (Bonferroni corrected $P < 0.05$ for all). However, the prevalence was significantly higher in women with poor health behaviors ($P < 0.05$ for all), chronic conditions ($P < 0.01$), or current depression ($P < 0.01$) compared to their counterparts (Table 1).

The means of the obesity indicators were 28.5 kg/m^2 for BMI, 94.4 cm for waist circumference, and 0.58 for WHR among study participants. The age-adjusted prevalence of suicidal ideation increased linearly with increasing quartiles of BMI, waist circumference, and WHR (P for linear

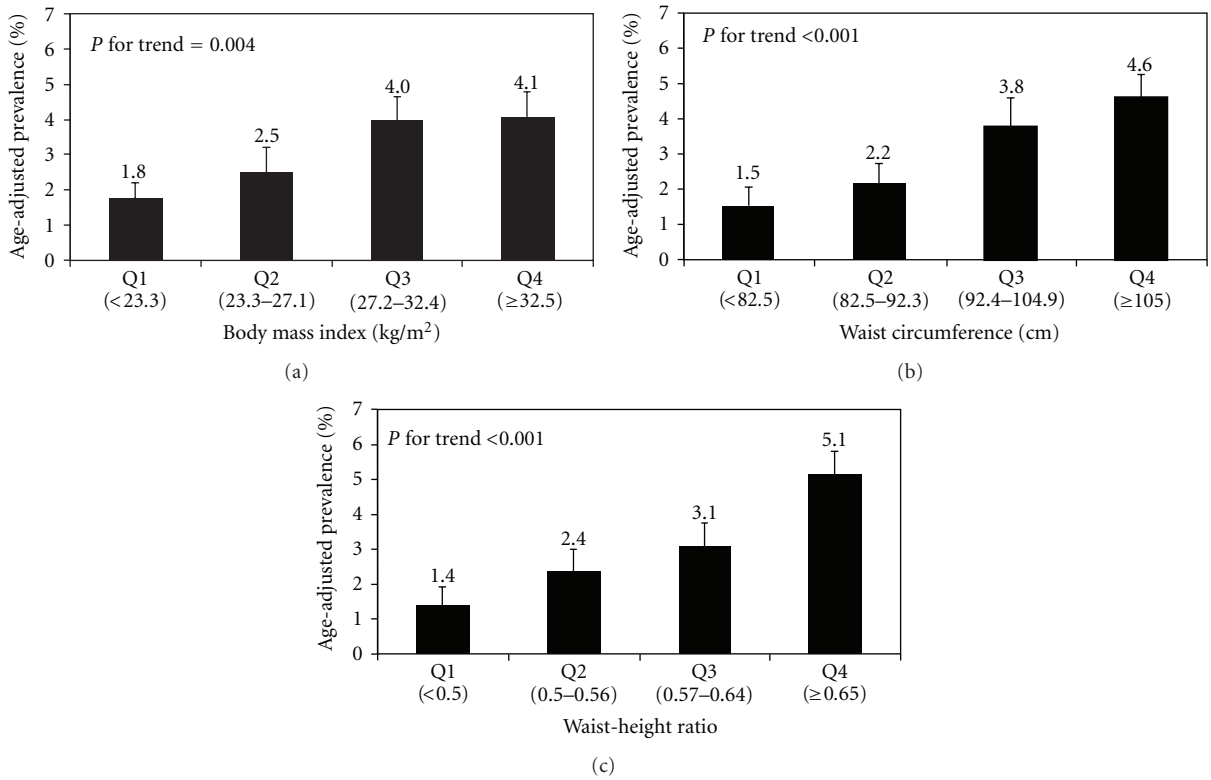

Figure 1: Age-adjusted prevalence (with standard error) of having suicidal ideation among US adult women by quartiles of body mass index, waist circumference, and waist-height ratio, NHANES 2005–2008.

trend < 0.01 for all) (Figure 1). Similarly, the unadjusted ORs for suicidal ideation also increased linearly across quartiles of BMI, waist circumference, and WHR ($P < 0.01$ for all, Model 1, Table 2). Adjustment for sociodemographic variables and lifestyle-related behavioral factors had little effects on these ORs (Model 2). After further adjustment for either chronic conditions (Model 3) or current depression (Model 4), the positive associations of waist circumference and WHR with suicidal ideation were attenuated but remained statistically significant ($P < 0.05$). However, when adjusting simultaneously for both chronic conditions and current depression (Model 5), the strength of the associations was reduced substantially. The association of BMI with suicidal ideation was attenuated after further adjustment for either chronic conditions or current depression or both (Models 3–5). These similar patterns persisted when continuous BMI, waist circumference, and WHR were entered in the models (Table 3).

5. Discussion

To our knowledge, our study is the first to examine the associations between anthropometric indicators for obesity and suicidal ideation among women in a large, population-based, nationally representative sample. Although our study demonstrated a significantly increasing trend in the prevalence of suicidal ideation with increasing levels of the three indicators for obesity, the associations between obesity and suicidal ideation seem to be confounded by having chronic conditions or current depression, either individually (for the association between BMI and suicidal ideation) or jointly (for the associations between waist circumference and WHR and suicidal ideation).

Suicide is one of the leading mental health problems in the world with enormous consequence [42, 43]. From 1990–1992 to 2001–2003, the prevalence of suicidal ideation, plans, or attempts did not vary much in the US population despite a dramatic increase in treatment [44]. In 2007, suicide accounted for more than 34,000 deaths and was the 11th leading cause of death in the United States [42]. Regarding suicidal ideation, results of previous studies showed that the lifetime prevalence of suicidal ideation was 15.6% in the adult US population [40]. A recent study showed that about 3.7% of US adults (3.5% of men and 3.9% of women) reported having suicidal thoughts in the past year [45]. Our study further revealed that about 3.0% of US women reported having suicidal ideation in the past 2 weeks.

Multiple risk factors for suicidal ideation or suicidal behaviors have been reported including sociodemographic factors (such as younger age, being female, less educated, and not being married), DSM-IV disorders (such as anxiety disorders, mood disorders, impulse-control disorders, depression, and substance abuse), chronic physical conditions (such as disability, chronic physical pain, terminal illness, and life-threatening diseases), some medications, and firearm ownership [24, 26, 39–41, 46–48]. Previous studies exploring the relationships between BMI and risk of suicide mortality

Table 1: Prevalence estimates of suicidal ideation among US women aged ≥20 years by selected characteristics, NHANES 2005–2008.

	n	%*	95% CI
Total			
Unadjusted	3,732	3.1	2.5–3.8
Age-adjusted	3,732	3.0	2.4–3.8
Demographic characteristic			
Age (yr)			
20–39	1,195	2.5	1.6–3.8
40–59	1,283	3.8	2.8–5.3
≥60	1,254	2.6	1.7–4.1
Race/ethnicity			
Non-Hispanic white	1,866	2.2[a]	1.4–3.4
Non-Hispanic black	787	3.7[ab]	2.3–5.8
Mexican American	664	5.8[b]	3.7–8.9
Other	415	6.1[b]	3.8–9.6
Education			
<high school diploma	971	6.5[a]	4.7–9.1
High school graduate	893	3.3[ab]	2.0–5.5
>high school diploma	1,868	2.0[b]	1.3–3.0
Marital status			
Married/living with partner	2,072	2.3[a]	1.6–3.1
Divorced/widowed/separated	1,115	5.0[b]	3.3–7.6
Never married	545	4.1[ab]	2.6–6.6
Poverty-income ratio			
<1.0	706	7.6[a]	5.6–10.4
1.0–2.9	1,572	4.7[a]	3.6–6.0
≥3.0	1,454	1.0[b]	0.6–1.7
Lifestyle-related behavioral factor			
Smoking			
Current smoking	729	5.5[a]	4.0–7.5
Former smoking	736	1.4[b]	0.8–2.4
Never	2267	2.6[b]	2.0–3.4
Excessive drinking			
Yes	206	5.9[a]	3.8–8.9
No	3,526	2.8[b]	2.2–3.4
Physical activity			
Yes	2,758	2.6[a]	2.0–3.4
No	974	5.0[b]	3.6–6.9
Comorbidity			
Number of chronic conditions			
0	1,259	1.0[a]	0.6–1.6
1-2	1,457	2.7[b]	2.0–3.6
≥3	1,016	8.8[c]	5.7–13.2
Current depression			
Yes	357	20.3[a]	15.8–25.7
No	3,375	1.4[b]	1.0–2.1

[*] Values labeled with different superscripts within a categorical variable were statistically significant from each other, Bonferroni corrected $P < 0.05$.

Table 2: Odds ratios with 95% confidence intervals for suicidal ideation among US women aged ≥20 years by quartiles of BMI, waist circumference, and waist-height ratio, NHANES 2005–2008 (n = 3,732).

		Model 1			Model 2			Model 3			Model 4			Model 5		
	n	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Body mass index (kg/m^2)																
Q1 (<23.3)	773	1.00			1.00			1.00			1.00			1.00		
Q2 (23.3–27.1)	896	1.51	0.68	3.36	1.58	0.75	3.31	1.52	0.70	3.28	1.48	0.65	3.39	1.45	0.63	3.34
Q3 (27.2–32.4)	1,062	2.19	1.28	3.72	2.19	1.35	3.54	1.82	1.09	3.06	1.76	1.07	2.90	1.66	1.00	2.75
Q4 (≥32.5)	1,001	2.55	1.32	4.92	2.78	1.50	5.15	1.93	1.00	3.75	2.04	0.95	4.35	1.73	0.81	3.72
P-trend		*0.002*			*<0.001*			*0.067*			*0.065*			*0.188*		
Waist circumference (cm)																
Q1 (<82.5)	770	1.00			1.00			1.00			1.00			1.00		
Q2 (82.5–92.3)	896	1.48	0.67	3.28	1.44	0.64	3.26	1.42	0.63	3.23	1.26	0.55	2.91	1.30	0.56	3.01
Q3 (92.4–104.9)	1,044	2.35	1.10	5.00	2.12	0.96	4.68	1.81	0.78	4.22	1.65	0.69	3.92	1.57	0.65	3.82
Q4 (≥105.0)	1,022	3.15	1.63	6.10	3.13	1.60	6.11	2.19	1.02	4.72	2.16	0.98	4.80	1.89	0.83	4.29
P-trend		*<0.001*			*<0.001*			*0.035*			*0.027*			*0.102*		
Waist-height ratio																
Q1 (<0.50)	610	1.00			1.00			1.00			1.00			1.00		
Q2 (0.50–0.56)	882	1.78	0.82	3.88	1.75	0.78	3.90	1.62	0.70	3.75	1.44	0.64	3.26	1.39	0.60	3.21
Q3 (0.57–0.64)	1,092	2.13	0.91	4.99	1.97	0.80	4.84	1.72	0.66	4.46	1.42	0.52	3.91	1.36	0.48	3.84
Q4 (≥0.65)	1,148	4.03	1.90	8.55	3.48	1.59	7.59	2.39	0.98	5.85	2.38	1.02	5.58	2.05	0.82	5.11
P-trend		*<0.001*			*<0.001*			*0.049*			*0.033*			*0.106*		

* Model 1: unadjusted; Model 2, adjusted for demographic characteristics (age, race, education, marital status, poverty-income ratio) and lifestyle-related behaviors (current smoking, excessive drinking, and physical activity); Model 3: further adjusted for the number of chronic conditions (including diabetes, hypertension, congestive heart failure, coronary artery disease, stroke, arthritis, asthma, chronic bronchitis, emphysema, liver disease, thyroid disease, renal diseases, sleep disorders, cancer, and disability); Model 4: further adjusted for current depression; Model 5: further adjusted for both the number of chronic conditions and current depression.

or suicidal behaviors among women have yielded mixed results [6, 10, 18]. This may have resulted from different study settings with different outcomes assessed (the risk of suicide death versus lifetime or past-year suicidal ideation or suicidal attempts) and different covariates adjusted for. The present study provides further evidence that a high BMI level was associated with an increased likelihood for suicidal ideation among US adult women independent of sociodemographic variables and lifestyle risk factors; however, this positive association no longer existed after taking into consideration the chronic conditions or current depression status as demonstrated in the present study. Importantly, our results also showed that both chronic conditions and current depression were significantly associated with suicidal ideation. Thus, the previously reported association between BMI and suicidal ideation may have been confounded by existence of obesity-related chronic conditions or depression, which deserves further investigation.

The strength of the present study is that we were able to simultaneously assess the relationships between abdominal obesity as measured by waist circumference and WHR and suicidal ideation. Abdominal obesity has been shown to be associated with impaired health, impaired quality of life, and psychiatric disorders [5, 8, 49, 50]. However, results of a previous study showed that waist-hip ratio was not a predictor of suicide mortality among 46,755 male participants in the Health Professionals Follow-up Study [12]. Results of the present study demonstrated that both waist circumference and waist-height ratio were positively associated with suicidal ideation among US adult women irrespective of having either chronic conditions or current depression; however, as shown for BMI, these associations appeared to be confounded jointly by chronic conditions and current deperssion.

Studies have shown that both physical conditions and mental disorders are associated with higher risks for suicidal ideation or suicidal behaviors [40, 51–56]. Our findings that the associations between obesity indicators (i.e., BMI, waist circumference, and waist-height ratio) and suicidal ideation diminished in the present study after controlling for either chronic conditions or current depression or both suggest that impaired physical health or mental disorders may have individually (for overall obese women) or jointly (for abdominally obese women) contributed to an increased risk for suicidal ideation among obese population.

Our study has several limitations. First, suicidal ideation was assessed based on self-report of a single item on the PHQ-9 and thus subject to recall bias. Second, although we have included a number of physical chronic conditions in our analyses, the severity of each individual chronic condition was unknown, so we were unable to weigh differently the impact of a specific chronic condition on the association between obesity indictors and suicidal ideation. Third, we

Table 3: Regression coefficients (β) with standard errors (SEs) for suicidal ideation among US women aged ≥20 years by continuous BMI, waist circumference, and waist-height ratio*, NHANES 2005–2008.

	β	SE	P for linear trend
Body mass index (kg/m^2)			
Model 1	0.043	0.011	*<0.001*
Model 2	0.048	0.010	*<0.001*
Model 3	0.029	0.012	*0.020*
Model 4	0.031	0.015	*0.047*
Model 5	0.022	0.016	*0.166*
Waist circumference (cm)			
Model 1	0.023	0.004	*<0.001*
Model 2	0.024	0.004	*<0.001*
Model 3	0.015	0.005	*0.010*
Model 4	0.015	0.006	*0.025*
Model 5	0.011	0.007	*0.117*
Waist-height ratio			
Model 1	4.419	0.808	*<0.001*
Model 2	4.128	0.779	*<0.001*
Model 3	2.630	0.934	*0.008*
Model 4	2.762	1.076	*0.015*
Model 5	2.102	1.034	*0.073*

* Model 1: unadjusted; Model 2, adjusted for demographic characteristics (age, race, education, marital status, poverty-income ratio) and lifestyle-related behaviors (current smoking, excessive drinking, and physical activity); Model 3: further adjusted for the number of chronic conditions (including diabetes, hypertension, congestive heart failure, coronary artery disease, stroke, arthritis, asthma, chronic bronchitis, emphysema, liver disease, thyroid disease, renal diseases, sleep disorders, cancer, and disability); Model 4: further adjusted for current depression; Model 5: further adjusted for both the number of chronic conditions and current depression.

assessed the potential role of current depression in confounding the relationship of obesity with suicidal ideation in the present study; however, we were unable to evaluate the possible effects of other psychiatric disorders, antipsychotic medication use, emotional functioning, social support, and family history of suicidal behaviors on the association due to lack of data. Finally, potentially protective factors including life satisfaction, social support, and coping were not assessed either.

In conclusion, our results from this large, population-based study suggest that depression and chronic physical conditions may explain much of the association between obesity and suicidal ideation among US adult women. Although the exact mechanisms mediating the association between obesity and suicidal ideation remain to be elucidated, results from the present study may have important implications for preventing suicidal ideation. Our findings suggest that combined intervention programs targeting obesity management and the prevention/treatment of obesity-related physical chronic conditions and depression may help to reduce the prevalence of suicidal ideation and ultimately reduce risk of suicide mortality. Currently, obesity among US adults is a major public health concern after decade of increase in its prevalence [2, 57, 58]. Thus, efforts on screening and assessing obesity-related physical and mental disorders may provide useful information for preventing suicidal behaviors in this population.

Conflict of Interests

The authors declare that they have no conflict of interests.

Disclaimer

The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Research Article

Maternal Distress during Pregnancy and Offspring Childhood Overweight

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Background. Maternal distress during pregnancy increases the intrauterine level of glucocorticoids, which may have long-term health consequences for the child. *Objective*. To examine if distress as a combined measure of anxiety, depression, and stress of the mother during pregnancy was associated with offspring childhood overweight at age 7. *Methods*. We performed a cohort study using prospective data from 37,764 women and child dyads from the Danish National Birth Cohort (1996–2002). At a telephone interview at approximately 30 weeks gestation, the women reported whether they felt anxious, depressed, or stressed. The 95 percentile for body mass index in an international reference defined childhood overweight at any given age. Logistic regression was used for the analyses. *Results*. The prevalence of overweight children at 7 years of age was 9.9%. Prenatal exposure to maternal distress during pregnancy was not associated with childhood overweight at 7 years of age (adjusted OR 1.06 (95% CI 0.96; 1.18)). In analyses stratified on sex, a small tendency of overweight was seen in boys (OR 1.15 (0.99; 1.33)), but not in girls (OR 0.98 (0.85; 1.13)). *Conclusions*. Maternal distress during pregnancy appeared to have limited, if any, influence on the risk of overweight in offspring at 7 years of age.

1. Introduction

Childhood overweight is a substantial problem among children. In 2003, the prevalence of overweight among Danish children aged 6–8 years was 15% and 21% among boys and girls, respectively [1]. Ideally, the prevention of childhood overweight and obesity should begin as early as possible, which may even be before birth [2]. Changes to the intrauterine environment, caused by stress or malnutrition of the mother during pregnancy, may modify fetal metabolism by influencing regulatory hormonal pathways. Such disturbances may persist after fetal life and affect the growth and health of the child [2].

Psychosocial factors such as maternal distress during pregnancy, physiological or psychological, increase the release of glucocorticoids (cortisol) [3]. Cortisol may be passed on from the mother to the child through the placenta [4] and potentially affect the developmental processes of the child. Expecting mothers who reported higher levels of stress or who worried about their pregnancy were found to have higher levels of salivary cortisol measured in the evening [5]. Measures of maternal stress during pregnancy have been associated with later health of the child including the risk of offspring pediatric disease [6], cerebral palsy [7], astma (in boys only) [8], and type 1 diabetes, [9] but not with epilepsy [10] or autism [11]. Also maternal bereavement due to loss of a relative, either while pregnant or one year before conception, has also been linked to childhood overweight [12] but it is not known if this association is present at lower maternal stress levels. We investigated whether children of mothers, who felt anxious, depressed, stressed, or worried while pregnant, had a higher risk of overweight at 7 years of age. Since different hormonal changes during pregnancy may potentially trigger different expressions in boys and girls [13], we also took into account the sex of the child.

2. Methods

2.1. Study Population. The study was based on the Danish National Birth Cohort (DNBC), which was established from 1996 to 2002 where 100,419 pregnancies were enrolled from a total of 92,276 mainly Scandinavian women. A description of the enrolment and design has previously been published [14].

Computerised telephone interviews at approximately gestational weeks 16 and 30 and when the child was 6 and 18 months old were used to obtain information about prenatal exposures, maternal health, use of medicine, lifestyle, and the health and development of the child [14]. The questionnaires to the women contained a specific protocol for the interviewer to follow to generate uniformity across the different interviewers. A 7-year follow up was completed in spring 2011 and consisted of a web-based or posted questionnaire about the health, lifestyle, and development of the child including weight and height. The parents received the questionnaire in the month of the child's 7th birthday.

For the present study, mothers and their offsprings were included if they had participated in the 7-year follow up (n = 53,838). We excluded children with missing data on height, weight, or date of height and weight measurement and children with more than 30 days between measurement of height and weight (n = 4,592). We also excluded twins and triplets (n = 828), and for mothers who participated with more than one child in the cohort, all other children than the firstborn within the study period were excluded (n = 4,814). Children born before gestational week 37 (n = 1,723), children born to mothers with diabetes (n = 427), and children whose mothers had not participated in the early and late pregnancy interview (n = 3,690) were also excluded. The final study population consisted of 37,764 mother-child dyads. All participants provided informed written consent and the study was approved by all of the scientific ethics committees in Denmark and by the Danish National Data Protection Agency.

2.2. Maternal Distress. The mothers' report of feeling anxious, depressed, or stressed during pregnancy was considered the main exposure. It was based on nine questions (Table 1) from the second pregnancy interview in approximately gestational week 30 (interquartile range 29–33). Their answer related to the entire pregnancy experienced at that point in time. The six questions about anxiety and depression originated from the validated Symptoms Checklist-92 (SCL-92) [15, 16] and had originally five answer categories but only three were used for the women in the DNBC. For each woman, a likert score was generated by summing the scores for each of the three questions for anxiety and depression ("not at all" = 0, "a little" = 1, and "a lot" = 2). The reliability of the questions was assessed using Cronbach alpha coefficients. For anxiety and depression the coefficients were 0.56 and 0.53 respectively. The three questions about stress originated from the validated General Health Questionnaire 60 (GHQ60) [17] with an original four answer categories where 0 = "better than normal," 1 = "same as normal," 2 = "worse than normal," and 3 = "much worse than normal."

Table 1: Questions about anxiety, depression, and stress during pregnancy*. "Have you. . .."

Questions	Covering	Items taken from
felt frightened and anxious for any reason?	Anxiety	SCL-92
felt nervous or at unease?	Anxiety	SCL-92
felt tense and exhausted?	Anxiety	SCL-92
felt that the future looked hopeless?	Depression	SCL-92
felt sad or blue?	Depression	SCL-92
felt that everything was a big effort?	Depression	SCL-92
felt under a constant pressure?	Stress	GHQ-60
been more touchy and quick-tempered than usually?	Stress	GHQ-60
felt that the demands on you were too big?	Stress	GHQ-60

GHQ-60; General Health Questionnaire 60, SCL-92; Symptoms Checklist 92 (26–28).
*From the second interview at approximately gestational week 30.

It was therefore decided to generate a stress score as follows 1 = "not at all," 2 = "a little," and 3 = "a lot," which had a Cronbach alpha of 0.42. A combined measure of distress was generated as a combined added score for all nine questions and had a Cronbach alpha of 0.74. For all four variables, the women were divided into two groups according to the cut-off value closest to the 80th percentile thus women exceeding this cutoff will be referred to as feeling anxious, depressed or stressed. However, for anxiety, only 11.7% of the mothers belonged to the high exposure category, because a large group of women had a sum score of 2, which prevented us from using the 80th percentile to define the high exposure category. Therefore, being anxious was a less inclusive measurement than measures of depression and stress.

Maternal worrying was based on two questions: worrying about the birth or worrying about the unborn child. They were asked both in the early and late pregnancy interview and the mother was categorized as worried, only if she answered yes at both points in time. *Support from surroundings* regarded the mothers contact to family members by phone or in person with "every day" or "several times a week" categorized as often.

Socioeconomic status was based on the education and job situation of both the mother and the father and defined as the highest level within the couple. It was categorized in three groups: leaders and parents with higher education was categorized as "high," parents with intermediate length of education as "intermediate," and unemployed or uneducated parents as "low."

2.3. Childhood Overweight. For each child, the body mass index (BMI) (kg/m^2) was calculated using the weight and height of the child, which were either measured by the parents, the general practitioner, or the school nurse. It was up to the parents to choose which earlier measured weight and height they would record in the questionnaire

and therefore some chose measures taken by the general practitioner at the 5-year health examination. The age span of the children was 5–8 years with 80% being 7 years old. Childhood overweight, was defined by using the sex and age-specific BMI references proposed by Cole et al. [18], where the 95 percentiles at any given age were used as the cut-off point for overweight [18]. We grouped the children in intervals of 6 months. For 7 years of age the cut-off points for overweight were 17.92 kg/km^2 and 17.75 kg/km^2 for boys and girls, respectively.

2.4. Covariates. Additional factors associated with childhood overweight were chosen a-priori based on the available literature. Information about parity, maternal prepregnancy BMI, smoking and recreational exercise during pregnancy came from the early pregnancy interview. Information about gestational weight gain and duration of breastfeeding came from the interview 6 months postpartum. These and other variables were categorized according to Table 2.

2.5. Statistical Methods. Firstly, we examined maternal characteristics according to maternal distress and childhood overweight by using the Chi-square test. Next, we used multiple logistic regression models to estimate odds ratios for the association between maternal distress and other psycho-social factors and overweight of the children at 7 years of age. In the first adjusted model, we controlled for; age, parity, prepregnancy BMI, smoking during pregnancy, and socioeconomic status. In a second adjusted analysis, we also controlled for breastfeeding, gestational weight gain and recreational exercise of the mother. For one of the distress variables (anxiety), we found a significant difference in overweight between boys and girls. We therefore added an interaction term to the model so that the results could also be shown separately for boys and girls. Results are presented with 95% confidence intervals and P values below 0.05 were considered statistically significant. All analyses were carried out using the statistical computer programme STATA (Version 10 Stata Corp, 4905 Lakeway Drive, College Station, TX 77845, USA).

3. Results

Distress during pregnancy was reported in 12.3% of the mothers with 11.7% of them feeling anxious, 17.9% depressed, and 20.6% stressed. Mothers who were less than 25 years old, singles, smokers, or gained more than 20 kg during pregnancy were more likely to feel anxious or depressed. Mothers who had given birth before more often reported feeling depressed and stressed than primiparous mothers. Also, mothers in the lowest social group more often felt depressed.

The mean BMI of the children in the study population was mean 15.7 (SD 1.7), and the prevalence of overweight children was 9.9%, 8.7% in boys and 11.5% in girls. Mothers who were overweight or obese before pregnancy or had a large gestational weight gain more often had overweight children. Also, mothers of overweight children were slightly younger, more often multiparous, smokers, or of medium or low socioeconomic status. Further, they were less likely to exercise during pregnancy and they breastfed their children for at shorter period.

3.1. Pregnancy Distress in Relation to Childhood Overweight. In the adjusted analyses, we found no association between maternal distress during pregnancy and the risk of overweight in the child (OR 1.06 (0.96; 1.18)) (Table 3). In boys, a modest increased risk of overweight was indicated (OR 1.15 (0.99; 1.33)) but not in girls (OR 0.98 (0.85; 1.13)). The same pattern was observed when analysing feelings of anxiety, depression, or stress separately. Adding adjustment for breastfeeding, gestational weight gain and recreational exercise of the mother to the model only let to minor changes in the estimates (results not shown).

A modest increased risk of childhood overweight was seen in children of mothers who worried during pregnancy about the birth or the health of the child (OR 1.10 (1.00; 1.22)) and estimates were similar in boys and girls. Lack of social support seemed to be slightly protective against childhood overweight (OR 0.93 (0.82; 1.04)) whereas children of mothers of low or medium socioeconomic status had an increased risk of overweight. Only in the analysis of anxiety did we find that the sex of the child seemed to modify the association with childhood overweight ($P = 0.05$).

4. Discussion

In this population of women, we did not find maternal distress during pregnancy to be clearly associated with childhood overweight in the offspring at 7 years of age. Neither did separate measures for maternal feelings of anxiety, depression, and stress support any association.

It was a biologically plausible hypothesis that maternal distress during pregnancy may cause childhood obesity due to alterations of the metabolism of the child (2–5). Studies investigating the associations between prenatal distress and childhood overweight are, however, scarce. In a recent study by Li et al. [12], maternal bereavement, due to loss of a child or husband, was associated with childhood overweight, and most strongly for losses happening before conception than during pregnancy. Losing a child or husband causes severe distress and sadness in a pregnant mother, whereas the levels of distress measured in our study were more commonly experienced feelings of anxiety, depression, and stress and not caused by an identified specific event. Moreover, the exposure contrast in our cohort may be relatively low due to the healthy nature of the women who were of higher socioeconomic status and had better outcomes than the general pregnant population in Denmark [19]. Thus, the relatively mild measurement of distress (emotional stress) compared to a more severe type of bereavement may play a role for the contrast of the exposure in this study. On the other hand, in the study by Li et al. [12], the association between bereavement and offspring overweight did not show up until the children were around 10 years of age. So, our finding of little association between distress during

Table 2: Maternal distress during pregnancy covering anxiety, depression, and stress, and childhood overweight according to maternal characteristics.

			Maternal mental health				
	Total		Maternal distress	Feeling anxious	Feeling depressed	Feeling stressed	Childhood overweight
	n	%	%	%	%	%	%
Total population	37,764	100.0	12.3	11.7	17.9	20.6	9.9
Maternal age							
<25	4,337	11.5	15.6	14.5	15.5	13.5	10.5
25–28	15,919	42.2	38.4	39.8	38.3	38.7	9.7
39–34	13,012	34.5	33.3	33.6	33.2	34.8	9.8
≥35	4,496	11.9	12.7	12.1	13.0	13.0	10.1
Marital status							
Married/partner	36,164	98.2	96.5	96.7	96.3	97.1	9.7
Single	645	1.8	3.5	3.3	3.7	2.9	14.1
Missing	955						
Parity							
Primiparous	18,817	49.8	43.3	51.4	43.6	40.0	9.1
Multiparous	18,947	50.2	56.7	48.6	56.4	60.0	10.7
Prepregnancy BMI							
Underweight <18,5	1,523	4.1	4.5	4.2	4.5	4.5	3.7
Normal weight 18,5–24,9	26,182	70.5	68.1	69.1	67.2	69.5	7.5
Overweight 25–29,9	6,924	18.6	20.2	19.4	20.9	19.1	15.3
Obese ≥ 30	2,539	6.8	7.2	7.3	7.4	6.9	22.0
Missing	596						
Gestational weight gain							
<10 kg	3,637	12.0	12.5	12.1	12.8	12.0	12.4
10–15 kg	13,837	45.6	44.4	42.3	41.6	45.6	8.2
16–19 kg	6,472	21.3	19.4	19.8	19.5	21.3	9.0
≥20 kg	6,422	21.2	26.7	25.8	26.0	21.2	12.1
Missing	7,396						
Smoking in pregnancy							
None	32,413	85.9	76.8	78.5	78.4	79.9	9.0
0–10 cigarettes/day	4,208	11.1	17.4	16.5	16.5	15.4	14.6
>10 cigarettes/day	1,103	3.0	5.8	5.0	5.1	4.7	19.3
Missing	40						
Socioeconomic status							
Higher	26,191	69.6	61.7	65.4	61.3	66.9	8.4
Middle	10,302	27.4	32.5	30.2	32.9	28.7	12.9
Lower	1,150	3.1	5.8	4.4	5.8	4.4	15.7
Missing	121						
Breastfeeding							
None or <14 weeks	8,629	28.2	37.4	32.8	33.4	30.1	12.4
14–21 weeks	13,089	42.7	37.8	39.4	39.1	40.2	8.6
≥22 weeks	8,908	29.1	27.8	27.8	27.5	29.7	8.7
Missing	7,138						
Sex—child							
Boy	19,343	51.2	51.3	50.2	51.3	51.3	8.7
Girl	18,421	48.8	48.7	49.8	48.7	48.7	11.1

Table 2: Continued.

	Total		Maternal mental health				
			Maternal distress	Feeling anxious	Feeling depressed	Feeling stressed	Childhood overweight
	n	%	%	%	%	%	%
Exercise—mother							
0 min/week	22,315	60.7	66.2	63.4	66.1	64.6	10.36
1–120 min/week	7,965	21.7	18.4	20.1	18.8	19.7	8.98
120–240 min/week	4,413	12.0	10.2	10.9	10.2	10.4	9.13
240–420 min/week	1,579	4.3	3.8	4.0	3.6	3.8	8.04
>420 min/week	521	1.4	1.4	1.6	1.3	1.5	11.52
Missing	971						

Table 3: Maternal distress during pregnancy and risk of childhood overweight at age 7.

	All children			Boys			Girls		
		Crude OR	Adjusted[1]		Crude OR	Adjusted[1]	Crude risk	Crude OR	Adjusted[1]
	Overweight %	95% (CI)	95% (CI)	Overweight %	95% (CI)	95% (CI)	Overweight %	95% (CI)	95% (CI)
Maternal distress									
A little	9.63	Ref.	Ref.	8.4	Ref.	Ref.	11.1	Ref.	Ref.
A lot	11.27	1.19	1.06 (0.96; 1.18)	10.7	1.30	1.15 (0.99; 1.33)	11.8	1.08	0.98 (0.85; 1.13)
Feeling anxious									
A little	9.73	Ref.	Ref.	8.5	Ref.	Ref.	11.1	Ref.	Ref.
A lot	10.91	1.14	1.06 (0.95; 1.17)	10.7	1.29	1.15 (0.99; 1.34)	11.2	1.00	0.97 (0.84; 1.12)
Feeling depressed									
A little	9.61	Ref.	Ref.	8.4	Ref.	Ref.	10.9	Ref.	Ref.
A lot	11.09	1.17	1.02 (0.94; 1.12)	10.2	1.24	1.07 (0.93; 1.21)	12.0	1.11	0.99 (0.87; 1.12)
Feeling stressed									
A little	9.65	Ref.	Ref.	8.4	Ref.	Ref.	11.0	Ref.	Ref.
A lot	10.74	1.13	1.05 (0.97; 1.14)	9.9	1.20	1.11 (0.98; 1.25)	11.6	1.06	1.00 (0.89; 1.12)
Being worried									
A little	9.59	Ref.	Ref.	8.4	Ref.	Ref.	10.8	Ref.	Ref.
A lot	11.55	1.23	1.10 (1.00; 1.22)	10.3	1.25	1.10 (0.96; 1.27)	12.8	1.21	1.11 (0.97; 1.26)
Lack of social support									
No	9.98	Ref.	Ref.	8.8	Ref.	Ref.	11.2	Ref.	Ref.
Yes	8.60	0.85	0.93 (0.82; 1.04)	7.6	0.85	0.92 (0.78; 1.09)	9.6	0.85	0.94 (0.80; 1.10)
Socioeconomic status									
High	8.41	Ref.	Ref.	7.4	Ref.	Ref.	9.5	Ref.	Ref.
Intermediate	12.92	1.61	1.31 (1.21; 1.42)	11.6	1.59	1.28 (1.14; 1.44)	14.3	1.59	1.33 (1.20; 1.48)
Low	15.65	2.02	1.49 (1.25; 1.80)	12.8	1.84	1.29 (0.98; 1.69)	18.5	2.16	1.66 (1.32; 2.09)

[1]Adjusted for age, parity, prepregnancy BMI, smoking during pregnancy and socioeconomic status.

pregnancy and overweight of the children at 7 years of age is to some extent in agreement with this study.

Gender-specific effects may exist as hormonal changes during pregnancy due to maternal distress may lead to different expressions in boys and girls and result in different disease profiles [13]. Our study indicated a minor gender difference in the association between maternal distress and childhood overweight as boys had a modest increased risk and girls did not. However, this finding was not statistically significant and needs to be replicated in other data sources.

Children of mothers who tended to worry during pregnancy had a slightly increased risk of overweight. Possibly, the same mechanisms as with maternal distress are at play or it may be that these mothers are more protective of their children. However, a previous study in the same cohort of feelings of distress, covering anxiety, depression, and stress during the first 6-month postpartum did also not find an increased risk of childhood overweight [20]. Although parenting strategies may differ depending on levels of distress, it does not seem to be of clinical importance. Our results also indicate that children of women with lack of social support had a small decreased risk for overweight.

This study has several strengths and limitations that need to be addressed. The availability of the DNBC with its prospective design and detailed data collection presented a unique opportunity to study the associations between maternal distress during pregnancy and childhood overweight. Due to the large size of the cohort, the statistical precision was high so it should be possible to detect true relevant associations.

Our information on maternal distress relied on self-reported data. This may cause misclassification of the exposure, but since the mothers had no knowledge of the later weight status of their child at the time of the pregnancy interview this is not likely to cause serious bias and if so, would most likely underestimate the effect. The classification of distress is important as stressor-specific pathways may differ between the different types of stress [21]. Tegethoff et al. previously studied different types of stress in the same cohort and found emotional stress and life stress, associated with different types of diseases in the offspring [6]. We analyzed both combined and separate measures of maternal distress, which is measured like Tegethoff et al.'s measurement of emotional stress and found no association with overweight in the offspring. Neither did we find life stress to be associated with childhood overweight in separate analyses.

Childhood overweight of the child was based on self-reported information from the parents on weight and height of the child, who was measured either by the parents, the general practitioner or the school nurse. We expect some measurement error, but unrelated to the level of maternal distress during pregnancy and therefore it should not cause any serious misclassification bias, but only attenuate the associations under study. This was also supported by a validation study in 1200 children participating in the 7-year follow up, which found no systematic errors.

To reach the final study population, we excluded approximately 40% of the women who initially participated in the pregnancy interviews because they did not participate in the 7-year follow up. A recent study found that participants in the 7-year follow up were more often of high socioeconomic status and healthier [22]. We also confirmed this finding in sub analyses of our data and moreover found mothers who reported to be anxious, depressed, or stressed during pregnancy to be less likely to participate in the follow up. This selection may bias our results if it was also associated with childhood overweight. We have no data to investigate this, but believe this problem is minor as for similar exposure-outcome associations, based on participation in the 7-year follow up, such bias appeared to be small [22].

5. Conclusion

The etiology of childhood overweight is still poorly understood. In conclusion, this study in a generally healthy population of Scandinavian women did not provide evidence to the hypothesis that prenatal maternal distress causes childhood overweight. Further studies with more exact measures of psychosocial distress, continuous measures of distress, and in populations with higher stress levels are needed to perhaps find a threshold as to when more commonly experienced distress in the mother during pregnancy may cause childhood overweight and obesity.

Abbreviations

BMI: Body mass index
OR: Odds ratio
WHO: World Health Organization.

Conflict of Interests

The authors declare no conflict of interests.

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Research Article

Evaluation of Personal and Built Environment Attributes to Physical Activity: A Multilevel Analysis on Multiple Population-Based Data Sources

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Background. Studies have documented that built environment factors potentially promote or impede leisure time physical activity (LTPA). This study explored the relationship between multiple built environment factors and individual characteristics on LTPA. *Methods*. Multiple data sources were utilized including individual level data for health behaviors and health status from the Nevada Behavioral Risk Factor Surveillance System (BRFSS) and community level data from different data sources including indicators for recreation facilities, safety, air quality, commute time, urbanization, population density, and land mix level. Mixed model logistic regression and geographic information system (GIS) spatial analysis were conducted. *Results*. Among 6,311 respondents, 24.4% reported no LTPA engagement during the past 30 days. No engagement in LTPA was significantly associated with (1) individual factors: older age, less education, lower income, being obesity, and low life satisfaction and (2) community factors: more commute time, higher crime rate, urban residence, higher population density, but not for density and distance to recreation facilities, air quality, and land mix. *Conclusions*. Multiple data systems including complex population survey and spatial analysis are valuable tools on health and built environment studies.

1. Background

It is stated that 24.1% of adult Americans were reported to be conducting no leisure time physical activities (LTPA) during the past month [1], and the US national prevalence of adult overweight and obesity (body mass index >25 kg/m^2) is at 68.0% (95% CI, 66.3%–69.8%) [2]. Research indicates that even a small increase in daily physical activity may prevent weight gain [3] and could limit the health complications associated with obesity, such as high blood pressure, type 2 diabetes, high cholesterol levels, and asthma [4].

Many factors have been attributed to inhibiting or promoting LTPA: environment, the built environment, public policy, and an individual's health status. Studies have documented that built environmental factors impede physical activity (PA) including limited connectivity of street layout, unsafe living areas (i.e., high violent crime rates, high property crime rates) [5, 6], air pollution [7–9], poor urban design and land use mix [10–12], a high commuting time by car [13], and the lack of recreation facilities (i.e., parks, gyms, community centers, and swimming pools) [9, 14–16]. Studies indicate that health factors that negatively influence physical activity comprise obesity, hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease (COPD), asthma, and health-related quality of life [17, 18]. However, studies on LTPA involving individual level behaviors, health status, and other community level built environment factors based on statewide population-based complex sampling survey are lacking.

This study explores the relationship between LTPA and the built environment as well as other health indicators using both individual and community level data from multiple statewide population-based databases, which provides opportunities to reflect the real-world interactions between individual health behaviors and their built environment.

2. Methods

2.1. Subjects. The study sample included adults who participated in the Nevada BRFSS telephone interviews from January 2006 through December 2007 ($n = 7,373$). The BRFSS is a state-based telephone health survey that obtains information regarding an individual's health status, health risk behaviors, preventive health practices, and use/access to health care [19]. Standard US Center for Chronic Disease Prevention and Health Promotion (CDC) BRFSS sampling protocol was used.

Inclusion criteria for subject participation were as follows: (1) 18 years or older, (2) able to speak English, (3) phone was not a cellular phone number, (4) answered the physical activity question, (5) resided in a private residence within the State of Nevada, and (6) home was within a zip code with more than 30 BRFSS subjects. Oral consent was obtained prior to initiating the telephone interview. The Office of Human Subjects Research Protection, University of Nevada, Reno approved the study.

2.2. Study Variables. Data obtained from the 2006 and 2007 Nevada BRFSS included general individual demographics, chronic disease status, and life satisfaction. In addition, the subject's response to the binary dependent variable "During the past month, did you participate in any physical activities?" was also obtained. Each subject's residential geographic area was based upon their zip code and a "buffer zone" which refers to a geocoded spherical area in which the subject's home is the centroid.

Data regarding air quality, population density, commute time, distance to recreational facilities, property crime, and violent crime were obtained from multiple data sources based on zip codes. Datasets used were from the US Census Bureau, the US Environmental Protection Agency (EPA), the Environmental Systems Research Institute (ESRI), the Federal Highway Administration, and the Federal Bureau of Investigation or local law enforcement agencies.

The zip code-based independent variables were defined as follows.

(1) Air quality is based upon pollutant concentrations of ground-level ozone, particulate matter, carbon monoxide, sulfur dioxide, and nitrogen dioxide with good, fair, poor classifications set by the EPA.

(2) The 2000 US Census Bureau definitions of urbanization were used. Urban area refers to central city of ≥50,000 persons and population density 1,000 persons per square mile. Urban cluster (sometimes referred to as suburban) has population of 2,500 to <50,000 persons inside a principal city or >2,500 persons outside urbanized areas and may contain adjoining territory with 500 to 1,000 persons per square mile. Rural area is all territory located outside urbanized areas and urban clusters (US Census Bureau, created April 30, 2002 and revised December 3, 2009).

(3) Population density is the midyear-estimated population of people divided by the land area (square mile).

(4) Commute time is the average minutes the residents in an area (zip-code) are required to conduct a one way commute to work by car.

(5) Property crime rates is the number of offenses of burglary, larceny theft, motor vehicle theft, and arson per 100,000 population.

(6) Violent crime was based upon four offenses: murder and no negligent manslaughter, forcible rape, robbery, and aggravated assault. The violent crime rate is reported per 100,000 population.

(7) Land mix level was calculated based on the ratio of numbers of stories divided by 100,000 population.

For those variables without specific classifications, they were divided to three groups based on <33.3 percentile, 33.3–66.7 percentile, and >66.6 percentile, then renamed as low, medium, or high. For the variables only available for the county level, the zip codes within that county were categorized within the same category (low, medium, or high).

Individual-based independent variables were defined as follows.

(1) Overweight is a body mass index (BMI) between 25.0 and 29.9 kg/meter^2, and obese is a BMI ≥ 30 kg/meter^2.

(2) Demographic factors and health conditions such as age, sex, race, and diabetes.

(3) Distance to a recreational facility was presence of one or more recreational facilities within a 0.5 mile, 1 mile, or 3 miles radius from subjects' residence using ArcInfo version 9.2. The three groups are mutually exclusive, for example, if they answered yes to residing within 0.5 mile then they are excluded from the 1 or 3 mile groups. Recreational facilities include parks, golf courses, and fitness centers.

(4) Recreational facility density was the number of recreational facilities within a 0.5 mile, 1 mile (number >0.5 miles to 1 mile), or 3 miles (number >1 mile to 3 miles) radius from subjects' residence using ArcInfo version 9.2.

2.3. Statistical Analysis. The analyses were weighted for the probability of survey sample selections: a telephone number, the number of adults in a household, and the number of telephones in a household. A final poststratification adjustment was made for nonresponses and households without telephones.

Since the data involves individual and community level variables, the multilevel mixed modeling logistic regression was conducted. The use of aggregate community level data, alone, to make inference about individual-level relationships can introduce bias due to heterogeneity in exposure variable of interest and other covariates within groups. Multilevel modeling takes into account the hierarchical structure of the data. The model used LTPA as the dependent variable and other risk factors including demographics, health status, and built environment factors (e.g., community crime rate, air

Table 1: Characteristics of study participants ($n = 6311$).

Factors	Categories	Study sample frequency	Study sample percentage
Sex	Male	2761	43.8
	Female	3550	56.3
Age	Age 18 to 34 years	1066	16.9
	Age 35 to 54 years	2344	37.3
	Age 55 or older years	2881	45.8
Education level	Didnot graduate or graduated from high school	2320	36.8
	Attended college or technical school	2075	33.0
	Graduated from college or technical school	1903	30.2
Marital status	Single	2702	42.9
	Married or a member of an unmarried couple	3595	57.1
Race	White/non-Hispanic	4689	74.9
	Black/non-Hispanic	145	2.3
	Hispanic	677	10.8
	Other	749	12.0
Annual household income	Income less than $25,000	1226	22.0
	Income between $25,000 and $50,000	1572	28.2
	Income more than $50,000	2785	49.9
Employment status	Out of work	2685	42.7
	Employed or self-employed	3611	57.4
Engaged in leisure time physical activity within the past 30 days	Yes	4758	75.4%
	No	1553	24.4%

quality, population density, and commute time) as independent variables. After individually evaluating the relationships between LTPA, health status, and built environment factors, demographic data were added as control factors to obtain the final model. Demographic factors entered were age, gender, race/ethnicity, education, income, employment, and marital status. The "buffer zone" categories were then added to the model.

ArcInfo version 9.2 was used for the decoding and buffer zone analysis. Statistical software SAS version 9.1 was utilized for both descriptive and multilevel mixed model logistic regressions analyses.

3. Results

Among 6,311 study participants, 56.3% were female, and 45.8% aged 55 years or older (Table 1). A total of 75.6% participants reported engaging in LTPA during the past 30 days. Compared to others, male (77.34%), age 18–34 years old (77.01%), White/non-Hispanic (78.67%), higher income (82.91%), and higher educated (84.46%) groups have higher prevalence of engaging in LTPA (Table 2).

The adjusted odds ratios in Table 3 were derived from the multilevel mixed model logistic regressions as outlined in the statistical method section, which were adjusted for sex, age, race, marital status, annual household income, education level, and employment status. Among demographic factors, significantly associated with LTPA, are younger age (age 18–34 versus age >55 AOR 1.84; age 35–54 versus age >55 AOR 1.27), higher education (graduated college versus less than college AOR 1.80; graduated college versus some college AOR 1.36), and higher income (high income versus low income AOR 1.92; high income versus middle income AOR 1.52). sex, race, and marital and employment status did not significantly differ.

Self-reported overall good health, life satisfaction, and health insurance are significantly related to engaging in LTPA (AOR 2.37, 1.95, and 1.32, resp.). In addition, subjects who are neither overweight nor obese (AOR 1.57) or overweight (AOR 1.41) have significantly higher odds of engaging in LTPA than subjects who are obese. Respondents with or without diabetes or asthma showed no significant LTPA difference.

Among built environment community level indicators, factors significantly associated with LTPA included less commute time (AOR 1.28), lower violent crime (AOR 1.43), lower property crime (AOR 1.58), living in rural (versus urban) (AOR 1.29), and living in less population dense

Table 2: Weighted prevalence of potential factors related to conducting physical activity.

	Factors	Categories	Frequency	Weighted percentage	95% CI* for weighted percentage	
Individual level	Sex ($n = 4796$)	Male	2151	77.34	74.95	79.73
		Female	2645	72.53	70.22	74.83
	Age ($n = 4782$)	Age 18 to 34 years	858	77.01	73.24	80.78
		Age 35 to 54 years	1839	76.83	74.33	79.33
		Age 55 or older years	2085	70.9	68.53	73.27
	Race ($n = 4752$)	White/non-Hispanic	3657	78.67	76.95	80.39
		Black/non-Hispanic	101	71.59	62.53	80.66
		Hispanic	455	65.45	60.32	70.59
		Other	539	70.4	65.26	75.54
	Marital status ($n = 4784$)	Single	1932	71.8	68.93	74.68
		Married or a member of an unmarried couple	2852	76.77	74.74	78.8
	Annual household income ($n = 4279$)	Income less than 35,000	751	61.13	56.63	65.62
		Income between 35,000 and 50,000	1162	72.87	69.49	76.25
		Income more than 50,000	2366	82.91	80.8	85.01
	Education level ($n = 4787$)	Didnot graduate or graduated from high school	1562	66.21	63.17	69.25
		Attended college or technical school	1596	77.37	74.63	80.11
		Graduated from college or technical school	1629	84.46	82.07	86.85
	Employment status ($n = 4784$)	Out of work	1898	69.64	66.95	72.33
		Employed or self-employed	2886	78.12	76	80.23
	General overall health ($n = 4788$)	Fair or poor	580	54.31	49.74	58.88
		Excellent/very good/good	4208	79.11	77.35	80.87
	Life satisfaction ($n = 4663$)	Satisfied	4465	76.13	74.41	77.86
		Dissatisfied	198	53.23	45.53	60.93
	Diabetes status ($n = 4792$)	No prediabetes or boarder line diabetes	4417	75.88	74.14	77.62
		Yes	375	63.79	58.35	69.22
	Body mass index ($n = 4663$)	Neither overweight nor obese	1800	78.58	75.94	81.23
		Overweight	1822	77.05	74.39	79.71
		Obese	1041	67.81	64.17	71.44
	Asthma status ($n = 5112$)	Current	372	69.21	63.21	75.21
		Former	206	78	69.62	86.38
		Never	4159	75.24	73.46	77.03

Table 2: Continued.

	Factors	Categories	Frequency	Weighted percentage	95% CI* for weighted percentage	
Community level	Violent crime rate ($n = 4796$)	Low crime	1638	77.07	74.39	79.75
		Middle crime	1960	79.77	77.78	81.76
		High crime	1198	72.48	69.89	75.07
	Property crime rate ($n = 4796$)	Low crime	725	79.15	75.76	82.54
		Middle crime	2843	76.88	74.7	79.07
		High crime	1228	72.81	70.14	75.47
	Air quality ($n = 4796$)	Good	758	74.36	70.81	77.91
		Fair	154	65.95	58.32	73.59
		Poor	3884	75.13	73.34	76.91
	Commute time ($n = 4556$)	Less commute time	1605	77.34	74.78	79.89
		Middle commute time	1409	73.86	70.93	76.8
		More commute time	1542	74.68	71.98	77.39
	Population Density (per Sq mile) ($n = 4796$)	Low density	1572	77.18	74.73	79.63
		Middle density	1657	79.28	76.50	82.06
		High density	1567	71.91	69.36	74.45
	Urbanized ($n = 4796$)	Rural	2779	79.09	77.06	81.11
		Suburban	735	73.84	70.09	77.58
		Urban	1282	72.18	69.27	75.08
	Land mix level ($n = 4796$)	Low land mix level	1542	74.39	71.61	77.17
		Middle land mix level	1681	76.37	73.63	79.11
		High land mix level	1573	74.22	71.23	77.21

Of the 7,373 eligible study participants, 6,311 answered the questions regarding demographics and physical activity and included in the analysis.
*CI = confidence interval.

areas (AOR 1.31). Factors not significantly associated with LTPA were residential distance to a park, recreation facility (Table 4), air quality, or land mix.

4. Discussion

This statewide study indicated that all health indicators, except diabetes and asthma status, and the majority of built environment factors (commute time, community safety, population density, and rural residence) were significantly associated to LTPA after controlling for sex, age, race, marital status, annual household income, education level, and employment status. However, the likelihood of engaging in LTPA was not significant related to density and distance to a recreation facility, air quality, and land mix.

Therefore, potential factors that could encourage LTPA are reporting good health status or life satisfaction, not being obese, high community safety, and residing in less urbanized areas. These findings emphasize the need to include personal-level factors when examining the interaction between individuals and their environment. Furthermore, access to recreation facilities may not directly be a driving force for participation in LTPA. This study's results align with some, but not all, previous findings.

4.1. Health-Related Quality of Life. Those who reported overall good health and life satisfaction were twofold as likely to engage in LTPA compared to those who reported poor health and not being satisfied with their life (AOR 1.95; CI: 1.51, 2.52). This is consistent with the 2001 BRFSS national data. Brown et al. revealed men exhibited 0.54 (95% CI 0.48, 0.62) and women 0.64 (95% CI 0.58, 0.71) odds of reporting impaired mental health between those conducting moderate or vigorous physical activity levels to inactive respondents after adjusting for age, race, education, smoking status, and BMI [20].

It remains debatable whether those in good health and satisfied with life are more vibrant and interested in

Table 3: Adjusted odds ratio for factors related to conducting leisure time physical activity.

	Factors	Categories	Adjusted odds ratio (AOR)*	95% Confidence intervals		*P* value
Individual level	Sex	Male versus female	1.09	0.94	1.26	0.261
	Age	Age 18 to 34 versus age >55 years	1.84**	1.45	2.32	<0.0001
		Age 35 to 54 versus age >55 years	1.27**	1.06	1.51	0.0083
	Race	White/non-Hispanic versus other	1.22	0.99	1.51	0.064
		Black/non-Hispanic versus other	0.87	0.55	1.39	0.555
		Hispanic versus other	0.99	0.74	1.32	0.925
	Marital	Married or a member of an unmarried couple versus single	1.00	0.86	1.17	0.992
	Education	Graduated college versus less than college	1.80**	1.48	2.19	<0.0001
		Graduated college versus some college	1.36**	1.13	1.66	0.0017
	Income	High income versus low income	1.92**	1.55	2.39	<.0001
		High income versus middle income	1.52**	1.27	1.83	<0.0001
	Employee	Employed or self-employed versus out of work	0.99	0.84	1.17	0.931
	General health	Good versus poor	2.37**	1.98	2.83	<0.0001
	Diabetes	No diabetes versus have diabetes	1.21	0.96	1.52	0.114
	BMI	Neither overweight nor obese versus obese	1.57**	1.31	1.88	<0.0001
		Overweight versus obese	1.41**	1.18	1.67	0.0001
	Life satisfaction	Satisfied versus not satisfied	1.95**	1.51	2.52	<0.0001
	Asthma	Never has asthma versus yes, current asthma	1.05	0.82	1.34	0.683
		Never has asthma versus former asthma	0.89	0.62	1.29	0.547
	Health plan	Has insurance versus no insurance	1.32**	1.08	1.62	0.007
Community level	Air quality	Good versus poor	1.13	0.88	1.45	0.353
		Fair versus poor	0.87	0.57	1.34	0.518
	Commute time	Less commute time versus more commute time	1.28**	1.03	1.59	0.029
		Middle commute time versus more commute time	1.13	0.91	1.41	0.266
	Violent	Low crime versus high crime	1.43**	1.16	1.75	0.0008
		Middle crime versus high crime	1.58**	1.27	1.97	0.0001
	Property	Low crime versus high crime	1.25	0.97	1.60	0.082
		Middle crime versus high crime	1.44**	1.18	1.76	0.0006
	Urbanized	Rural versus urban	1.29**	1.04	1.60	0.022
		Suburban versus urban	1.04	0.78	1.40	0.789
	Population density	Less population density versus more population density	1.31**	1.06	1.63	0.015
		Middle population density versus more population density	1.39**	1.10	1.76	0.007
	Land mix level	Low land mix level versus high land mix level	0.91	0.73	1.15	0.444
		Middle land mix level versus high land mix level	1.02	0.81	1.30	0.839

*Community level odds ratios were adjusted for sex, age, race, marital status, annual household income, education level, and employee status.
**Significant <0.05 *P* value level.

Table 4: Relationship between distance to recreation facilities and leisure physical activity.

Categories	Adjusted odds ratio (AOR)*	95% confidence intervals		*P* value
Within 0.5 mile buffer zone distance**	1.16	0.75	1.80	0.51
Within 1 mile buffer zone distance	1.05	0.75	1.48	0.77
Within 3 mile buffer zone distance	1.20	0.83	1.72	0.34

*Odds ratios were adjusted for sex, age, race, marital status, annual household income, education level, and employee status.
**Buffer zone is ageocoded spherical area in which the subject's home is the centroid.

conducting physical activity than those in poor health or unsatisfied with life. Studies observed that PA reduced the prevalence of impaired mental health status, and others found that initiating a physical activity program significantly improved subjects' psychological well being [20].

4.2. Safety. Neighborhood safety is a salient concern, a frequently reported LTPA impediment by subjects [5, 6, 21]; however, findings are consistently using less objective crime-related measures [5, 6]. Studies, similar to this study, found individuals living in more crime-prone areas engaged in less LTPA than those living in low-crime neighborhoods [6, 22]. Reviewing published studies, Foster and Giles-Corti surmised, for the most part, respondents' emotional perception of safety, specifically "fear" of crime, elicits a strong constraint on PA behavior (generally walking), yet the built environment cannot be ignored [5].

4.3. Urbanization/Population Density/Land Mix. This study investigated three geographic constructs: urbanization, population density, and land mix regarding an individual's transport choice. The study findings disclosed that those residing in rural or low-populated density areas in Nevada were more likely to be more active than urban or higher population density area residents (AOR 1.29; CI 1.04 1.60 and AOR 1.23; CI 1.07, 1.42, resp.), which contradict the bulk of the literature, including the National Health Interview Survey [10, 12, 23–25]. This questions the belief that rural residents' LTPA is inhibited by isolation, distance, cost of transportation, lack of PA facilities, and insufficient infrastructure [12, 26, 27]. Furthermore, the current findings oppose earlier studies where higher density neighborhoods have higher levels of LTPA [7, 12, 28, 29].

The CDC found a dose response; PA decreases by degree of rurality [27] not observed in this study. There was no significant difference between suburban and urban residents (Table 3). Many reasons have been set forth for the lack of the observed dose response. One aspect is the variance in geographic classification. Rural living includes overlapping elements of population density and land mix. As aforementioned, Nevada is composed of two major metropolitan areas with adjacent suburbs and vast expanses between small cities/townships; therefore, rural classification may capture characteristics of living in proximity to facilities and social support. In addition, population density delineated areas are unrelated to categorical township (population of people divided by the land area). Others have postulated that a threshold exists for population density. Increasing density levels will reduce vehicle motor transport, but only above a certain threshold level [10]. Furthermore, no single definition is used compounding the variance in observed results. Researchers acknowledge this weakness in measuring the relationship between built environment and PA [28, 30].

Land mix attempts to capture convenience, a balanced mix of destinations (i.e., stores, service, and work) in walkable or biking distance from their residence [31]. Studies found residents do not take advantage of opportunities of running errands on bicycle or foot [32]. The Federal Highway Administration national transportation data found that although the destinations are in walking or biking distance, more than 90% of all trips take place by automobile [7]. Air pollution and the weather modify an individual's travel choice and outdoor activity [8, 9, 33]. The frequency warnings to limit outdoor exposure during the fire session in Nevada may account for the lack of significant association between land mix and LTPA found in this study (AOR 0.91–1.02; P value >0.05).

4.4. Density and Distance to Recreation Facilities. Over the years, the number of studies evaluating convenient recreation facilities and physical activity has grown exponentially. It is now recognized that access to recreational opportunities may not independently influence sedentary behavior [14, 34, 35]. More in-depth exploration uncovers the complexity components of the relationship [28, 35].

Several systematic literature reviews [5, 28, 35–37] found a "reasonably" positive relationship for access, availability, and convenience of recreational facilities to physical activity. Yet, ambiguity exists regarding the direction (positive, negative, null, or mixed correlates) [5, 14, 16, 28, 35–39]. Within multiple literature reviews, only half of the studies exhibited a significant positive association with higher PA intensity influencing density and distance study outcomes [14, 16, 37]. The current study provides further documentation that an individual's likelihood of conducing LTPA is not significantly interrelated to the density or distance to physical activity facilities at the 0.5, 1.0, and 3.0 miles buffer zones from their residents (Table 4).

A major limitation in this study arises from the design of the BRFSS survey. It is a cross-sectional, self-report survey and subject to recall and reporting bias. Sedentary adults tend to inaccurately report their physical activity intensity [40]. In addition, the BRFSS excludes persons residing in households without telephones and those households that rely solely on cell phones. However, in order to overcome these limitations, especially addressing nonresponse and

exclusion biases, the data analysis process included weighting procedures to equalize the probabilities among the census population distributions.

Another BRFSS sampling bias may have been introduced because about 15% of BRFSS subjects had insufficient data for geographical coding. An accurate physical address was required to establish subjects' residence within a zip code and to create a "buffer zone." Without this pertinent information geographical coding was not possible.

Additionally, GIS and other databases used were purchased or obtained by various agencies and industries. Some of the data may not represent current information. Furthermore, merging these various databases required developing new constructs.

The generalizability of the findings from this study may be limited by the characteristics of Nevada geographic and demographics. As indicated previously, Nevada has two major cities and a vast expanse between rural towns and has distinct fire sessions that may limit outdoor activities based on air quality. However, the multiple data systems and GIS spatial analysis procedure may be an effective means for other states to determine associations between physical activity and built environment and individuals characteristics.

This study has several strengths. GIS data was obtained for the whole state providing uniquely diverse categories for built environment factors. Statewide BRFSS was used providing a rich database for a specific subject's demographic and health status which enables accessing risk factors of outdoor or nonoutdoor physical activity at both individual level and community level.

5. Conclusion

This study found that incorporating multiple data systems and GIS spatial analysis was a valuable tool in analyzing a complex population survey. In addition, physiological and psychological factors that affect overall health and life satisfaction should not be overlooked. Reporting good health and life satisfaction were the two most "powerful" correlates to engaging in LTPA with adjusted odds ratios 2.37 and 1.95, respectively. Future studies are needed to determine if good health and life satisfaction promote physical activity or if physical activity promotes good health and life satisfaction. The present results suggest policy makers should consider strategies, physiological and/or environmental, to enhance life satisfaction. As well as approaches to reduce violence, property crime rates, and commute time, focusing special attention on Nevada residents who are low-income, older, and living in urban or more population dense areas.

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