Research Article

The Relationship between Stress and Severe Obesity: A Case-Control Study

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What Is It about?

Obesity has a multifactorial etiology. Several etiological factors for obesity have been identified, whereas other factors related to obesity, such as stress, remain poorly understood. Stress has been associated with obesity, chronic diseases, and psychosocial factors. Studies on psychological stress have focused on stress-related psychopathologies. In this study, psychiatric interviews and surveys of coping mechanisms were used to identify stressful events among individuals with obesity. One finding of this study was that stress was more prevalent in a group of severely obese individuals than in a control group. This study provides valuable insight into the relationship between obesity and stress.

Abstract

Background: Several etiological factors for obesity have been identified, whereas other factors related to obesity, such as stress, remain poorly understood. This study used psychiatric methods to examine the relationship between stress and obesity. ***Methods:*** Matched study and control groups were established, and the female and male control subjects were selected separately by random sampling. The control subjects were matched with the case subjects with respect to place of residence, sex, age, date that a pension was granted, and occupation. Psychiatric and psychological methods were assessed using a questionnaire and statistical analyses. ***Results:*** Psychiatric interviews indicated that stress was more prevalent in the study group than in the control group. Separation from parents was nearly significantly more frequently in the study group than in the control group. The questionnaire on coping mechanisms revealed that case subjects tended to resolve their problems in an active manner. ***Conclusions:*** The aim of this case-control study was to examine the relationship between stress

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KARGER

and obesity in individuals receiving a disability pension. We identified stress factors that affect the development of obesity. We believe our study is both necessary and important, as these findings provide valuable insight into the relationship between severe obesity and stress.

Introduction

Several etiological factors of obesity have been identified. Obesity naturally has a multifaceted biological basis that includes genetics, the biological factors related to normal body growth, eating habits, energy expenditures, and adipose tissue function. The development of obesity can be considered from a psychosocial perspective. Until recently, obesity has been a significant public health problem in Finland. Among the Nordic populations, Finns are the second-most obese; however, the number of overweight and obese individuals has recently decreased in every age group. This work examines the connection between stress and obesity.

Stress reflects an individual's response to environmental conditions. Organisms respond to stress via parasympathetic and sympathetic networks. Stress can be categorized into acute and chronic stress. Stress remains poorly understood in obesity.

Chronic stress can act as a risk factor that triggers, exacerbates, or causes weight gain, dyslipoproteinemia, or coronary artery disease [1]. According to Björntorp [2], it is important to examine whether the repeated activation of stress centers is involved in the pathogenesis of abdominal obesity and its comorbidities. One consequence of hormonal imbalance may be "stress eating," which is a poorly defined entity. Researchers have studied the association between adiposity and the magnitude of cardiovascular reactions to acute psychological stress. Blood pressure and heart rate measurements were used to examine the effects of brief stresses [3]. The peripheral hormone ghrelin has an essential role in stress, emotions, and eating process [4]. Ghrelin and leptin concentrations have been associated with interpersonal stress factors associated with weight gain and obesity [5]. Aschbacher et al. [6] indicated that peripheral neuropeptide Y (NPY) plays a major mechanistic role in obesity. Chronic stress is related to metabolic problems during dieting.

Accumulation of fat in visceral adipose tissue around the waist has been regarded as a sign of maladaptation to chronic environmental stress exposure [7]. Stress can drive dysregulation of homeostasis and obesity [8, 9]. "Sickness behavior" refers to a coordinated set of behavioral changes that develop in sick individuals over the course of an infection [10]. Under certain conditions, obesity facilitates the maintenance of homeostasis, likely by increasing the levels of hormones involved in the regulation of energy balance. Under such conditions, obesity is perceived by the physiologist as a necessary biological adaptation rather than a disease [11]. Some researchers believe that passive and active stresses have different influences on a given cardiovascular, immune, or endocrine disease between individuals with obesity and those with normal weight [12]. Newly discovered neural mechanisms related to stress behaviors have been identified. These mechanisms suggest new possibilities to prevent and cure psychopathologies associated with stress. Studies on psychological stress have focused on stress-related psychopathologies [13].

In 1939, Bruch [14] discussed obesity in childhood resulting from stress inflicted by a child's parents. In addition, Bruch described the phenomenon known as "reactive obesity" in adults. In 1951, obesity was considered a disease of stress [15]. Obesity, chronic diseases, and psychosocial factors have been linked to stress eating [16]. Researchers have found clear connections among stress, obesity, and psychosocial factors [17, 18].

Huh et al. [19] studied when hunger and stress are greatest during the day. These researchers found that high levels of hunger and stress were somewhat associated with afternoon and

Koskia and Naukkarinen: The Relationship between Stress and Severe Obesity:
A Case-Control Study
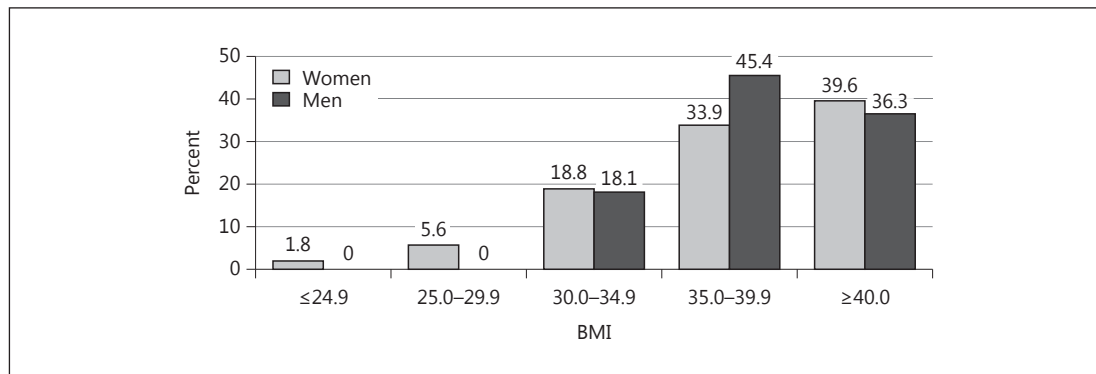
Fig. 1. BMI distribution of the study group.

evening hours. Torres et al. [20] found no associations of cardiovascular or psychological stress with obesity in a group of male subjects. Prentice [21] suggested that eating after stress can worsen health status, particularly in individuals with dysfunctional eating patterns. McInnis et al. [22] explained obesity in terms of cellular disturbances. Maladaptive stress triggers a compensatory mechanism that could explain obesity and overweight.

Several etiological factors of obesity have been identified, but stress remains poorly understood in obesity. The aim of this case-control study was to use psychiatric and psychological methods to examine the relationship between stress and obesity in individuals receiving a disability pension with severe obesity. Using a psychological questionnaire, we examined coping mechanisms employed by individuals in a stressful situation.

Materials and Methods

The Study and Control Groups
The participant sample consisted of all individuals living in southern Finland who were receiving a permanent disability pension primarily due to obesity. One hundred and fifty-two individuals met these criteria. Nineteen individuals had been granted a temporary pension and were excluded from the sample. Additionally, participants who died or stopped receiving a pension were excluded. The study group consisted of 112 individuals (81 women and 31 men). The control subjects were selected from the same region and were receiving a disability pension due to a different primary illness. The controls were matched to the case subjects according to place of residence, sex, age, date that the pension was granted, and occupation. The occupation of the controls was either the same as that of the case subjects or unknown. The controls were selected by random sampling. The male and female controls were selected separately. Three control subjects were selected for each female case subject, and 5 control subjects were selected for each male case subject. For the interview, an attempt was made to include at least 2 control subjects for each female case subject and 3 control subjects for each male case subject. Overall, the study enlisted 510 individuals, of whom 112 were case subjects and 398 were control subjects (Fig. 1). Three letters of invitation to participate in the study were sent to each potential case or control. The letters were discreetly worded and emphasized the confidentiality of the study. Most individuals who did not participate in the study indicated their reasons for refusal in writing. These letters are available upon request.

KARGER

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). According to WHO guidelines, the weight categories were defined as follows: overweight, BMI 25–29; obese, BMI 30–34; severely obese, BMI 35–40; and morbidly obese, BMI >40.

The Sickness Insurance Act and the National Pensions Act provide insurance against disability for all residents of Finland. The National Pensions Scheme offers basic pension insurance that covers all Finnish citizens. Age, professional skills, and other factors are also important considerations when evaluating claims of disability. Individual differences in working capacity should be recognized, accounting for the age of the applicant.

The study protocol was approved by the ethics committees of Hesperia/Aurora Hospital (Community Psychiatric Hospital in Helsinki) and Lapinlahti Hospital (Psychiatric Clinic of Helsinki University)/Psychiatric Center of Helsinki University. An informed consent form was signed by each patient, and the ethical principles of the Declaration of Helsinki were followed throughout the study.

Methods

A psychiatric interview form was used in this study. One of the authors interviewed all of the participants. Additionally, ICD 9–10 and DSM III disease classifications were used. DSM III recommends the use of a multiaxial system of evaluation to ensure that valuable information for planning treatment and for predicting individual outcomes is recorded using 5 axes. The first 3 of these axes constitute an official diagnostic evaluation. Axis IV, Severity of Psychosocial Stressors, and axis V, Highest Level of Adaptive Functioning in the Past Year, are used in special clinical or research settings. The Global Assessment Scale (GAS) was used to measure social, occupational, and psychological functioning. In addition, the standard occupational classifications of the Social Insurance Institution (1982) were used.

The questionnaire used in this study examined coping mechanisms. This assessment was originally developed by Saari [23] and was modified by Keltikangas-Järvinen, who changed the wording and added one alternative to the questionnaire (alternative 9). The form has 10 alternative questions describing various behavioral possibilities in stressful and problematic situations. The respondent ranks the alternatives on a scale of 1–10 according to how well they describe him or her. Alternative 1 best describes the personality of the respondent. Alternative 2 represents the second-best description, alternative 3 the third-best, and so on. When the respondent considers an alternative to be completely unsuitable, they can draw a line through this alternative. According to Saari's definition [23], alternatives 4, 7, 8, and 10 represent active methods of problem-solving, whereas alternatives 5, 6, and 9 are examples of giving up on trying to solve a problem.

Statistical Methods

The statistical methods used in this study included χ^2 tests, t tests, a conditional logistic linear model, and calculation of means, Pearson correlation coefficients, and percent distributions. The data distributions are presented graphically. Because the study and control groups were matched, differences between these groups were analyzed by calculating numbers, percentages, and means, and then performing paired t tests. Variables displaying statistically significant differences between groups were further analyzed using a linear logistic model. The results that remained significant after the logistic linear regression analysis were further assessed to determine the risk ratios and the upper and lower confidence limits. The statistical analyses were performed on a computer using Statistical Package for the Social Sciences software (SPSS for Windows 18/Windows; Chicago, IL, USA). The conditional logistic analyses were performed using the Generalized Linear Interactive Modeling (GLIM) program [24]. GLIM analysis is straightforward provided that the data are arranged in a convenient individual-by-individual format, which typically corresponds to the method of compilation. A

Koskia and Naukkarinen: The Relationship between Stress and Severe Obesity:
A Case-Control Study

Table 1. Basic characteristics of the study participants

	Study group	Control group	p (χ^2 test)
Subject status, n	112	262	
No answer (male/female), n	5 (1/4)	22 (8/14)	
Dropped out (male/female), n	37 (9/28)	61 (18/43)	
Consented (male/female), n	75 (22/53)	179 (67/112)	
Age at psychiatric examination (years), %			
20–24	–	0.6	
25–29	1.4	0.6	
30–34	–	0.6	
35–39			
40–44	–	1.2	
45–49	4.3	2.9	
50–54	14.5	9.4	
55–59	31.9	27.1	
60–64	43.5	48.8	
65–69	4.3	8.8	
BMI, %			
≤24.9	1.3	34.3	
25.0–29.9	4.0	47.3	
30.0–34.9	18.7	14.2	
35.0–39.9	37.3	3.6	
≥40.0	38.7	0.6	
Marital status, %			0.0894
Unmarried	10.7	15.7	
Married	62.7	59.6	
Widowed	14.7	13.5	
Divorced	6.7	10.7	
Common-law marriage	5.3	0.6	
Education level, %			0.2457
Primary school	89.3	90.4	
Lower secondary school	6.7	2.2	
High school	–	2.2	
Other	4	3.9	
Occupational category, n			
Male	22	66	0.901
Female	53	112	0.5930
Technical, scientific, sociological, and artistic work, %			
Male	0	0	
Female	0	4.5	
Total	0	2.2	
Accounting and clerical work, %			
Male	4.5	1.5	
Female	5.7	2.7	
Total	5.1	2.1	
Commercial work, %			
Male	4.5	4.5	
Female	17.0	10.7	
Total	10.8	7.6	
Agricultural, forestry, and fishing, %			
Male	0	3.0	
Female	7.5	7.1	
Total	3.7	5.1	
Transport and communication work, %			
Male	27.3	24.2	
Female	7.5	4.5	
Total	17.4	14.3	

Table 1 (continued)

	Study group	Control group	p (χ^2 test)
Industrial work, %			
Male	50.1	48.6	
Female	17.0	21.4	
Total	33.5	35.0	
Service work, %			
Male	13.6	18.2	
Female	45.3	49.1	
Total	29.5	33.7	
Total, %			
Male	100	100	
Female	100	100	
Total	100	100	
Social classification, %	According to Bruun's social classification		0.050 (male) 0.936 (female)
First social class	4.2	2.3	
Second social class	12.5	17.7	
Third social class	50.0	57.7	
Fourth social class	33.3	22.3	

major advantage of this technique is that it is easy to use and has inherent flexibility; thus, all of the data for individual study participants should be analyzed using this program whenever possible. The observations in each set were based on 1 case that was matched to 0–5 controls. Therefore, because these observations could be considered as counts, the error distribution can be considered to follow a Poisson distribution, and the link function can be considered as a logarithmic function. Thus, the model is a special form of log-linear model. The linear predictor in the systematic part of the model for each observation is a (linear) function of the observed exposure variables for each individual plus a constant (set) term, which may vary from matched set to matched set. In the literature concerning the analysis of case-control data, this model is termed a "conditional logistic regression" (a description of data analysis that may be misleading to those familiar with generalized linear model terminology). These groups were used for the statistical analysis. The group of case subjects would have remained small using this method; however, missing controls were replaced by the next-best matched control. The matched-control approach may have resulted in the exclusion of subject data from the statistical analysis because no control may have been available for certain case subjects. For several case subjects, multiple specific variables were lacking, which further reduced the number of observations available for comparisons [25]. A difference between groups was considered highly statistically significant when the probability (p) of error in rejecting the null hypothesis was <0.001 (***). A difference was statistically significant when $p < 0.01$ (**) and nearly statistically significant when $p < 0.05$ (*).

Refusal to Participate

The mean age of the participating men and women was 59 and 61 years, respectively. Thirty-one individuals had a primary school education, and 34 individuals had no vocational education of any type. Table 1 shows that the individuals who refused to participate (28 women and 9 men) had the same education level, age, and sex distributions as the participating individuals.

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Results

Basic Characteristics of the Study Participants

Table 1 presents participants' basic characteristics. The mean weights of the case subjects (n = 75) and the control subjects were 106.2 kg (SD = 18) and 72.3 kg (SD = 14.3), respectively. Among the case subjects, 91% (68 subjects) had received a secondary somatic diagnosis from the Social Insurance Institution. In particular, the most common type of secondary diagnosis was "diseases of the musculoskeletal system and connective tissue," which had been diagnosed in 38% of the case subjects. Among the control subjects, a disease pertaining to the cardiovascular organs was the primary diagnosis (20% of all control subjects). All of the control subjects had been diagnosed with a primary illness other than obesity.

Results of the Research

During the psychiatric interview, the participants were asked about the point in their life when obesity began to develop. The most significant time point was marriage, which a χ^2 test revealed was statistically significant (p = 0.0027), followed by family problems, which a χ^2 test indicated was not statistically significant (p = 0.053). In addition, becoming pregnant, giving birth, and having an abortion were associated with weight gain. Table 2 presents these results.

Few participants in both groups had divorced parents (1–2%). Additionally, illegitimacy was rare in both groups (7–5%). However, 23% of the participants in the study group and 9% of the controls had been separated from their parents for another reason. In the study group, the number of individuals receiving a disability pension primarily because of obesity was higher than it was among the individuals in the control group. This difference was nearly statistically significant according to the paired t test (p = 0.022) and the logistic linear model (risk ratio = 2.9; confidence limits: 1.6–5.1).

Differences in axes IV and V of the DSM III were found between the case subjects and the control subjects. Regarding axis IV, over two-thirds of the participants were diagnosed with some level of stress, but a higher proportion of participants in the study group were assigned to level 4 (the second-highest stress level). The mean stress levels for the study and control groups were calculated according to the DSM III axis IV. The mean stress level for the study group (25 people) was 4.44, with a standard deviation of 0.5831. The mean stress level for the control group (42 people) was 4.119, with a standard deviation of 1.1519. There were no differences between groups based on data analysis using the conditional logistic linear model.

In the study group, 70 participants were diagnosed with an axis V disorder (Highest Level of Adaptive Functioning in the Past Year). The mean level of functioning in the study group was 4.386, with a standard deviation of 0.9215. In the control group (154 people), the mean value was 3.9805, with a standard deviation of 0.8891 (p = 0.002). This difference was statistically significant: functioning was better in the study group than in the control group.

The overall functioning of the groups was assessed using the GAS. The study group (75 people) had a mean GAS score of 4.6, with a standard deviation of 0.6779. The control group (175 people) had a mean GAS score of 4.8343, with a standard deviation of 0.7588 (p = 0.022). This difference was nearly statistically significant.

The rankings regarding active coping mechanisms are expressed as means. For alternatives 4 ("I pour out my worries and tell my friends about what has happened") and 10 ("I start everything from the beginning with more energy than before"), the differences were the opposite of what was expected. For alternative 4, the mean rankings by the case and control subjects were 5.6 and 4.8, respectively. For alternative 10, the mean rankings by the case and control subjects were 5.3 and 4.4, respectively. There were no differences in rankings between the groups for alternative 7 ("I ask others for advice") or 8 ("I try to figure

Table 2. The point in life when obesity began

Time point	Study group (n = 75)	Control group (n = 253)	p (χ² test)
Getting married, n			0.0027
Yes	13	9	
No	56	159	
Pregnancy, n			0.345
Yes	11	9	
No	39	94	
A severe or long-term illness, n			0.130
Yes	8	11	
No	61	157	
Loss of a near person (death, divorce, etc.), n			0.493
Yes	3	3	
No	61	165	
Family problems, n			0.053
Yes	7	5	
No	62	161	
Problems in personal relationships, n			0.650
Yes	1	0	
No	68	166	
Occupational problems (stress, unemployment, etc.), n			0.128
Yes	6	5	
No	63	161	
Type of work, or changes in working conditions, n			0.7416
Yes	2	8	
No	68	158	
Difficulties associated with economic challenges, n			1.000
Yes	0	1	
No	69	164	
Extramarital sexual relations, n			1.000
Yes	0	1	
No	69	164	
Having an abortion, n			0.132
Yes	2	1	
No	48	99	
Giving birth, n			0.277
Yes	10	5	
No	40	95	
Changes in life situations, n			0.503
Yes	1	7	
No	68	159	
Other situations, n			
Yes	16	16	
No	53	150	

out why this happened to me"). The mean total rankings of all alternatives representing active coping mechanisms were 22.8 for the case subjects and 21.5 for the control subjects ($p = 0.306$). For alternatives 6 ("I try to think about other things") and 9 ("I drop everything, I don't want to do anything else about it"), the differences between the groups were minimal. Members of both groups rarely chose alternative 5 ("I go out to have a good time"). The mean total rankings of all alternatives representing giving up on problem-solving were 6.6 for the case subjects and 8.7 for the control subjects. This difference was statistically significant

Koskia and Naukkarinen: The Relationship between Stress and Severe Obesity:
A Case-Control Study

Table 3. Coping mechanisms

	Study group (n = 73)		Control group (n = 173)		Total (n = 246)	
	mean	SD	mean	SD	mean	SD
Statement 1	3.22	4.21	2.87	4.01	2.98	4.06
Statement 2	3.90	4.27	4.47	4.32	4.30	4.31
Statement 3	1.30	3.05	1.74	3.23	1.61	3.18
Statement 4	5.75	3.98	4.99	4.13	5.22	4.09
Statement 5	0.67	2.21	1.01	2.67	0.91	2.54
Statement 6	4.66	3.87	4.97	3.95	4.87	3.92
Statement 7	5.38	3.99	5.35	3.78	5.36	3.83
Statement 8	6.66	3.39	6.90	3.29	6.83	3.32
Statement 9	1.14	2.64	1.45	2.85	1.35	2.78
Statement 10	5.30	3.61	4.52	3.74	4.75	3.71

Statements: 1, I lose my temper. I am angry. I behave aggressively; 2, I get depressed. I blame myself; 3, I sulk. I am angry with others; 4, I pour out my worries and tell my friends about what has happened; 5, I go out to have a good time; 6, I try to think about other things; 7, I ask others for advice; 8, I try to figure out why this happened to me; 9, I drop everything; I don't want to do anything else about it; 10, I start everything from the beginning with more energy than before.

(p = 0.037). Among the alternatives that reflected giving up, only alternative 6 ("I try to think about other things") was an applicable response to stressful situations in both groups. Table 3 shows these data.

The relationship between tolerance to stress and obesity (as indicated by BMI at the time of the study) was measured using Pearson correlation coefficients. Among females, the Pearson correlation coefficients for stress statement 2 and stress statement 5 were –0.149 (p = 0.030) and –0.1095 (p = 0.085), respectively. Among males, the Pearson correlation coefficient for stress statement 6 was –0.1806 (p = 0.048), which was nearly statistically significant. The Pearson correlation coefficient for stress statement 9 was –0.148 (p = 0.087). The Pearson correlation coefficient for stress statement 10 was 0.1637 (p = 0.07). Based on these results, no clear relationship between obesity and stress was identified.

Discussion

Statement of Principal Findings

The basic characteristics were similar between the study and control groups because the two groups were matched. In this study, more stress factors were identified in the study group than in the control group. "Getting married" was a statistically significantly stressful life event. Additionally, the prevalence of "family problems" was more common in the study group. Separation from parents was more frequent among the participants in the study group than among those in the control group, and this difference was nearly statistically significant. Regarding DSM III axis IV, more stress factors were diagnosed in the study group. The GAS scores were higher in the control group than in the study group. According to the results for coping mechanisms, the participants in the study group solved their problems more actively than the participants in the control group.

Strengths and Weaknesses of the Study

This is the first study of individuals receiving a permanent disability pension due to obesity. One strength of this study is the nonselective sampling of individuals with severe obesity. The subjects were interviewed individually by the author, which may have improved the reliability of the results. Because the control group was carefully selected by matching each case subject with a control subject according to place of residence, age, sex, occupation, and date that the pension was granted, disability represented a unifying factor between the two groups, which strengthens the reliability of the conclusions. This approach provided access to data from a greater number of people with severe obesity. The controls were selected by random sampling of data from the Social Insurance Institution of Finland. This study covers a representative sample of the Finnish population. Five control subjects per case subject were selected to ensure a reliable analysis because the group of men was small. The difference in age between groups was not examined given the research setting. In this study, the control group and the study group were chosen such that food access was similar between groups. We did not attempt to explain stress in cell levels or in a special illness group. Differences in social class between the study and control groups were matched due to the research setting. Physical activity and smoking were not evaluated in our study. BMI distribution was determined according to the WHO classification. The researcher who performed the interviews did not become aware of the BMI of the individuals until the statistical analysis.

Strengths and Weaknesses in Relation to Other Studies

Recently, researchers have found a connection between child abuse and obesity [26]. Shankardass et al. [27] identified a connection between parental stress and obesity. We found many reasons for the development of obesity similar to those reported by Bruch [14].

Phillips et al. [28] studied weight during pregnancy and the postpartum period. Weight gain was detected extremely early in pregnancy. Liu and Umberson [29] found that children who experience more stress subsequently experience more stress as adults. Women have higher BMI than men. Udo et al. [30] observed a stronger connection between weight and stress among females than among males.

The case subjects in this study suffered from external stress more often than the control subjects, a finding that is in agreement with previous results [31–33]. Acute stress causes central obesity [34], and chronic stress causes obesity [35]. George et al. [36] researched eating behavior and reported the same findings as Pervanidou and Chrousos [35]. Low tolerance to stress, eating habits, and food addiction are critical drivers of obesity development [37]. The authors of this study (on stress and severe obesity) have the same opinion.

A study in Canada produced identical results to our study, i.e., obesity and comorbid psychological problems are risk factors for unemployment [38]. Czegledi [39] highlighted psychological factors associated with lifestyle. Having a focused coping strategy was associated with the relationship between emotional eating and individual behaviors.

This study (stress and severe obesity) did not examine associations between stress and BMI or gender differences, as explored in the study by Barry and Petry [40]. Rolls et al. [41] found differences in the factors related to obesity between genders. Women have more stress and are more dissatisfied about their weight. Our study did not examine gender differences. Additionally, the effect of sociocultural factors on eating habits was minimized in this study.

Possible Mechanisms and Implications for Clinicians or Policy Makers

According to Sinha and Jastreboff, stress is related to obesity. The neurobiology of stress is associated with hunger and energy. Those mechanisms should be the focus of further research [42]. Help should be provided to obese individuals who suffer from stress [43]. The authors of this study agree with Christaki et al. [44] that new methods are needed to care for

obese women who have problems with stress. We must seriously consider the role of psycho-physiological factors in stress [45]. Preventive measures must be implemented in the workplace [46]. According to McGrath [47], obesity is an epidemiologic illness associated with many medical complications (e.g., diabetes). The authors of the current report believe that doctors' limited knowledge regarding mind/body connections is a reason for the increasing prevalence of obesity. Susceptibility to obesity and differences between the effects of different stress factors must be considered [48]. O'Brien et al. [49] emphasized that the psychological mechanisms of obesity are not fully understood.

To our knowledge, this study is the first to examine individuals receiving a permanent disability pension due to obesity. This article is focused on stress and severe obesity using psychiatric and psychologic methods. This study is both necessary and important, and these findings provide valuable insight into the relationship between severe obesity and stress. We believe that severe obesity is a serious problem at the individual level.

Ethics Statement

This research was ethically conducted in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors declare no conflicts of interest.

Author Contributions

M.K. designed the study, performed the experiments, analyzed the data, and wrote the manuscript. H.N. reviewed the manuscript.

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