Prevalence of Overweight and Obesity in Bipolar Patients

Jane L. Elmslie, N.Z.R.D., Ph.D.;
J. Trevor Silverstone, D.M., F.R.C.P., F.R.A.N.Z.C.P.;
Jim I. Mann, D.M., Ph.D., F.R.A.C.P., F.A.C.N.;
Shelia M. Williams, B.Sc. (Hons); and Sarah E. Romans, M.D., F.R.A.N.Z.C.P.

Background: Patients who receive pharmacologic treatment for bipolar illness frequently gain weight. This study evaluated the prevalence of overweight and obesity in an unselected group of bipolar patients and matched reference subjects.

Method: The prevalence of overweight, obesity, and central adiposity was evaluated in 89 euthymic bipolar (DSM-IV) patients and 445 reference subjects, matched for age and sex, using a cross-sectional study design.

Results: Female patients were more often overweight and obese than female reference subjects ($\chi^2 = 9.18$, df = 2, p = .01). The frequency of overweight was similar in male patients and male reference subjects, but male patients were more likely to be obese. Patients were more centrally obese than the general population in women ($\chi^2 = 32.21$, df = 1, p = <.001) and in men ($\chi^2 = 8.81$, df = 1, p = .003). Patients treated with antipsychotic drugs were more obese than patients not receiving these drugs ($\chi^2 = 4.7$, df = 1, p = .03).

Conclusion: Body fat is more centrally distributed in pharmacologically treated bipolar patients than in matched population controls. Obesity is more prevalent in patients than in the general population. Obesity prevalence is clearly related to the administration of antipsychotic drugs.

(J Clin Psychiatry 2000;61:179–184)

Received April 27, 1999; accepted Aug. 26, 1999. From the Department of Human Nutrition (Drs. Elmslie and Mann), Department of Psychological Medicine (Drs. Silverstone and Romans), and the Department of Preventive and Social Medicine (Ms. Williams), University of Otago, Dunedin, New Zealand.

Supported by grants from the Otago Medical Research Foundation, the Health Research Council of New Zealand, and the Neige Todhunter Bequest of the New Zealand Dietetic Association. We thank all the participants in the study and the psychiatrists of the Department of Psychological Medicine who referred them.

Reprint requests to: Jane L. Elmslie, Department of Human Nutrition, University of Otago, P.O. Box 56, Dunedin, New Zealand (e-mail: jane.elmslie@xtra.co.nz).

In the general population, obesity, particularly abdominal obesity, is associated with increased risk of ischemic heart disease, type 2 diabetes mellitus, gall bladder disease, osteoarthritis, and some cancers.[1] Weight gain is a common adverse effect of pharmacologic treatment for bipolar illness,[2] so patients who become overweight as a side effect of treatment may share this risk. In addition, weight gain may cause patients to discontinue treatment with consequent reductions in treatment efficacy and social functioning.[3,4] There have been no controlled studies of obesity prevalence in euthymic bipolar patients. However, uncontrolled studies in schizophrenic patients receiving antipsychotics have reported a wide range of obesity prevalence (32%–67%), with higher rates in women.[5–7] A recent controlled study provided further evidence of this gender difference.[8] In addition, clinically significant central adiposity (obesity in which excess weight is accumulated on the trunk) has been reported in schizophrenic patients receiving antipsychotics.[7] Depending on the definition used, the prevalence of obesity in lithium-treated patients in uncontrolled studies is 12%–19%, 2 to 5 times higher than in the general population.[9,10] Reports concerning obesity prevalence in patients treated with sodium valproate are rare, but 1 study found that 59% of female epileptic patients receiving valproate were obese.[11]

Because appetite and physical activity are affected by episodes of mania and depression, the number of illness episodes and the number of years since the onset of the illness may be important influences on the prevalence of overweight and obesity in bipolar patients.[12] As outlined above, pharmacotherapy may be very important, particularly in patients receiving antipsychotics. Hypothyroidism, which decreases resting energy expenditure (and may therefore affect weight), is a common side effect in bipolar patients receiving lithium.[13]

No controlled data exist regarding the prevalence of overweight and obesity in bipolar patients. Therefore, the aims of our study were to determine, using standardized definitions, the frequencies of overweight, obesity, and central adiposity in community-based, euthymic, bipolar patients and matched healthy population controls and to investigate the relationships between these anthropometric indices and illness duration and severity, thyroid function, and current medication regimen in patients.

METHOD

Subjects and Controls

All psychiatrists working in the Department of Psychological Medicine at Dunedin Hospital, New Zealand, were requested to ask patients with bipolar disorder under their care if they would be prepared to participate in a study to examine the effects of their medication on body weight. Patients were required to be euthymic at the time of the study and not suffering from any physical illness that could affect body weight. The majority were attending a specialist bipolar clinic. They learned about the study during their scheduled visits to the bipolar clinic or other psychiatry outpatient clinics and were subsequently contacted by one of the authors (J.L.E.) if they were prepared to participate. Eighty-nine participants aged between 18 and 65 years were recruited from 109 eligible patients. Reasons for nonparticipation included refusal to consent (N = 12), postpartum (N = 2), loss of contact with bipolar clinic (N = 4), multiple sclerosis (N = 1), and head injury (N = 1). All participants fulfilled the DSM-IV[14] diagnostic criteria for bipolar disorder.

A reference group (N = 445), matched for sex and within the same 5-year age group, was selected randomly from a national database of subjects (originally recruited from the electoral roll to provide a representative sample of the New Zealand population). They had participated in the Life in New Zealand Survey (LINZ survey),[15] a national health survey designed to assess the overall health of all New Zealanders. Data on anthropometry, blood pressure, blood lipids, low back pain, smoking, alcohol consumption, psychological stress, and chronic physical illnesses such as diabetes, arthritis, asthma, heart disease, and migraine were also available for this sample.

Reference subjects were members of the general public and not recruited from a health care facility.

The study was approved by the Otago ethics committee of the Southern Regional Health Authority. All participants gave written informed consent.

Anthropometric Methods

Anthropometric measurements were performed on 1 occasion, using techniques and equipment employed in the LINZ survey. Height was measured on a stadiometer to the nearest millimeter with subjects standing upright in stocking feet. Subjects were weighed on a hard surface in light indoor clothing. Body weight was measured on electronic scales (model 770; Seca, Vogel and Halke GbmH & Co., Hamburg, Germany) calibrated to ± 0.1 kg. An allowance of 0.5 kg was made for clothing and subtracted from the measured weight. Waist and hip circumferences were measured with a fiberglass tape to the nearest 0.5 cm. Waist measurements were made at the minimum circumference between the rib cage and the iliac crest. Hip measurements were made at the maximum extension of the buttocks while subjects stood in a relaxed manner with feet together. Circumferences were measured over light indoor clothing, with belts and other bulky items removed. Where a waistband prevented a satisfactory waist measurement from being obtained, participants were requested to loosen their clothing to enable a more accurate measurement. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters.[2] Waist:hip ratio was calculated by dividing the waist measurement by the hip measurement. Participants were classed as overweight or obese using the World Health Organization definitions.[16] According to this system, individuals with a BMI ≥ 25 are overweight, while those with a BMI ≥ 30 are obese. Those with waist hip ratios > 0.8 (women) and > 0.9 (men) are considered to be at increased risk of coronary heart disease.[15,17]

Pharmacologic Treatment Regimen

Information about medication regimens was obtained by scrutinizing the relevant sections of patients' hospital case notes for the 12 months preceding the interview for reference to medication types, doses, medication changes, and therapeutic blood levels. Patients who had not been followed in the hospital system for a full year were questioned about their medication use up until the time of referral to the clinic. During the month before the interview, participants were receiving one of the following treatments: antidepressant ± anticonvulsant, antipsychotic ± medication other than lithium, lithium and anticonvulsant, lithium and antidepressant, lithium and antipsychotic, lithium alone, or no medication. Benzodiazepines, hypnosedatives, antihistamines, β-blockers, anticholinergic medication, and medications charted p.r.n. (implying intermittent or sporadic use) or taken for less than 2 weeks were not taken into account. "Time on current medication regimen" relates to the number of months before the interview in which patients' medication regimen remained stable.

Clinical Variables

Patients' adherence to pharmacologic treatment was assessed from measurements of serum lithium, carbamazepine, and valproate levels; determined by atomic absorption spectrometry; and evaluated from entries in hospital case notes. Tests of thyroid function were available for 73 patients. Hypothyroidism was defined on the basis of an elevated thyroid-stimulating hormone level. Patients being treated for hypothyroidism at the time of the study were classified as euthyroid. Data from thyroid function tests performed more than a year before the interview were not included. Illness duration and illness severity were established from the bipolar register database in the Department of Psychological Medicine, which contains selected information from patients' clinical case notes, including the age at illness onset and lifetime incidence of manic and depressive episodes.

Statistical Methods

Data were analyzed using SPSS-X for Macintosh version 4.0.1 (SPSS, Inc., Chicago, Ill., 1990). The statistical significance level was set at $\alpha = .05$. Continuous variables were compared using 2-tailed, unpaired Student t tests. Multiple regression analysis was used to adjust for sex, age, socioeconomic status, and smoking and to determine the interaction between sex and illness status in comparisons between patients and reference subjects. Male and female data were also analyzed separately to allow for expected biological variation in size and shape. The relationships between BMI, time on current medication regimen, number of illness episodes, and years since the onset of illness symptoms were examined using multiple regression analysis in patients. Six patients for whom we had incomplete clinical data were omitted from this analysis. To analyze the relationship between the prevalence of obesity and medication regimen, the medication categories were reduced to 2 (taking vs. not taking antipsychotics). Categorical data were compared using the chi-square test or, where the expected values were less than 5, the Fisher exact test.

RESULTS

Participants

The characteristics of the participants are shown in Table 1. There were more male smokers among patients than in the reference group ($\chi^2 = 14.81$, df = 1, $p < .001$) but both groups were similar with regard to socioeconomic status and ethnicity. Female patients were of higher socioeconomic status and smoked more than women in the reference group ($\chi^2 = 6.58$, df = 2, $p = .037$ and $\chi^2 = 11.58$, df = 1, $p < .001$).

Anthropometry

Rates of overweight and obesity in the reference group and the entire LINZ survey were very similar. The interaction between sex and illness status was significant ($R^2 = 13\%$; $p = .02$). The prevalences of overweight and obesity in patients and the reference group are shown in Table 2. Male and female data are presented separately. In women, overweight and obesity (BMI = 25–30 and BMI = 30, respectively) were significantly more frequent among patients ($\chi^2 = 9.18$, df = 2, $p = .01$) than reference subjects. In men, rates of obesity were greater in patients than reference subjects but rates of overweight were not. Mean values for anthropometric measurements are summarized in Table 3. In women, BMI, body weight (kg), and waist:hip ratio were higher in patients. Mean BMI and body weight did not differ significantly in men. Fifty-nine percent of female patients had waist:hip ratios > 0.8 compared with 17% of female reference subjects. This difference was statistically significant ($\chi^2 = 32.21$, df = 1, $p < .001$). In male patients, mean waist:hip ratio was also significantly greater than in male reference subjects. Fifty-eight percent of male patients had waist:hip ratios > 0.9 compared with 35% of male reference subjects ($\chi^2 = 8.81$, df = 1, $p = .003$). Differences between patients and reference subjects remained significant after adjustment for socioeconomic status and smoking.

Table 1. Characteristics of Patients and the Reference Group

Variable	Female Patients (N = 41)	Female Reference Group (N = 205)	Male Patients (N = 48)	Male Reference Group (N = 240)
Age range, y	18–64	19–62	19–65	18–64
Age, y, mean (SD)	40 (11)	40 (11)	39 (12)	40 (12)
SES classification[a,b]				
SES 1, N (%)	22 (54)	58 (28)	9 (19)	67 (28)
SES 2, N (%)	7 (17)	55 (27)	11 (23)	53 (22)
SES 3, N (%)	11 (27)	58 (28)	26 (54)	110 (46)
Smoker, N (%)[b]	21 (51)	48 (23)	23 (48)	49 (20)
Maori, N (%)	3 (7)	10 (5)	3 (6)	13 (5)

[a]Socioeconomic status classification (SES) is the same as that used in the Life in New Zealand Survey, with 1 representing the highest and 3 the lowest.
[b]Values for socioeconomic status and smoking are based on 40 female patients, 171 female reference subjects, 46 male patients, and 230 male reference subjects because data from the remainder contained missing responses for one or another of these variables.

Table 2. Prevalence of Overweight and Obesity in Bipolar Patients and the Reference Group[a]

	Women		Men	
Variable	Patients (N = 41)	Reference Group (N = 205)	Patients (N = 48)	Reference Group (N = 240)
Age, y, mean (SD)	40 (11)	40 (11)	39 (12)	40 (12)
Healthy weight, N (%)[b]	15 (37)	127 (62)	25 (52)	113 (47)
Overweight, N (%)[c]	18 (44)	51 (25)	14 (29)	103 (43)
Obese, N (%)[d]	8 (20)	27 (13)	9 (19)	24 (10)

[a]Variables have been weighted to reflect the age structure of the New Zealand population. Body mass index (BMI) = kg/m^2.
[b]Healthy weight: BMI = 20–24.99.
[c]Overweight: BMI = 25–29.99.
[d]Obese: BMI ≥ 30.

Pharmacologic Treatment

The most frequently prescribed medication regimen was lithium alone (N = 23, 26%), followed by lithium and an antipsychotic (N = 17, 19%), with smaller numbers of patients being treated with other regimens (Table 4). The mean serum lithium level was 0.65 ± 0.15 mmol/L. Nine of 30 patients (30%) receiving antipsychotic medication were obese compared with 6 of 47 patients (13%) treated with other drug combinations and 1 of 12 patients (8%) not receiving medication. This difference was statistically significant ($\chi^2 = 4.7$, df = 1, $p = .03$). The rate of obesity in patients receiving lithium alone was 1.5 times greater than in the general New Zealand population and slightly higher than rates observed in patients receiving other treatments, except those receiving antipsychotics. Thirty-three percent of patients (N = 29) had been on a stable

Table 3. Comparison of Anthropometric Measurements: Patients (N = 89) vs. Reference Subjects (N = 445)[a]

	Women						Men					
	Patients (N = 41)		Reference Group (N = 205)		Mean Difference	Adjusted Mean Difference[b]	Patients (N = 48)		Reference Group (N = 240)		Mean Difference	Adjusted Mean Difference[b]
Measurement	Mean	SD	Mean	SD	(95% CI)	(95% CI)	Mean	SD	Mean	SD	(95% CI)	(95% CI)
BMI	26.7	5.3	24.9	5.0	1.8 (0.1 to 3.5)	1.7 (0.02 to 3.4)	26.2	3.9	26.0	4.6	0.2 (–1.2 to 1.6)	–0.08 (–1.3 to 1.1)
Weight (kg)	73.3	15.7	65.9	13.1	7.4 (2.8 to 11.9)	7.2 (2.6 to 11.8)	80.8	14.5	80.3	12.9	0.4 (–3.7 to 4.5)	–0.36 (–4.6 to 3.9)
WHR	0.82	0.06	0.75	0.07	0.07 (0.05 to 0.10)	0.07 (0.05 to 0.09)	0.91	0.07	0.88	0.07	0.04 (0.01 to 0.06)	0.02 (0.01 to 0.05)

[a]Abbreviations: CI = confidence interval, WHR = waist:hip ratio (waist measurement:hip measurement).
[b]Adjusted differences are based on 40 female patients, 46 male patients, 171 female reference subjects, and 230 male reference subjects because data from the remainder contained missing responses for 1 or more confounding variables (socioeconomic status, smoking).

Table 4. Relationships Between Pharmacologic Treatment Regimen, Obesity, and Thyroid Function

Variable	Anticonvulsant ± Antidepressant	Antipsychotic ± Medications Other Than Lithium	Lithium and Anticonvulsant	Lithium and Antidepressant	Lithium and Antipsychotic	Lithium Alone	No Medication
N	7	13	8	9	17	23	12
Gender							
Men	3	11	4	5	5	13	7
Women	4	2	4	4	12	10	5
Obese	1	4	1	0	5	4	1
Hypothyroid	1	1	1	2	3	1	0

medication regimen for < 6 months, while 67% (N = 60) and 48% (N = 43) had been on a stable regimen for ≥ 6 months and ≥ 12 months, respectively. Complete records of pharmacologic treatment during the year prior to the study were available for all except 6 patients.

Clinical Variables

The mean ± SD duration of illness was 16 ± 9 years. The mean ± SD number of manic and depressive episodes was 3 ± 2 and 4 ± 3, respectively. After controlling for age, sex, and medication regimen, statistically significant relationships were not found between BMI and length of time on current medication regimen or years since the onset of illness symptoms ($R^2 = 4\%$ and $R^2 = 3\%$). Similarly, no significant association was found between BMI and lifetime incidence of manic and depressive episodes ($R^2 = 1\%$). Poor medication adherence was significantly more common among obese patients ($\chi^2 = 10.34$, df = 1, p = .001). Nine of 73 patients (12%) showed evidence of hypothyroidism (see Table 4). Thyroid function status was not significantly associated with age (over or under 40 years) or medication regimen, but hypothyroidism was significantly more common in men who were overweight or obese (p = .003).

DISCUSSION

Main Findings

This study is the first to compare the frequency of overweight and obesity in a group of unselected, community-based, euthymic bipolar patients and matched reference subjects. We found prevalences of overweight and obesity among female patients that were respectively 1.8 and 1.5 times greater than in reference subjects, the excess fat being centrally distributed (59% of patients had a waist:hip ratio > 0.8 compared with only 17% of reference subjects). Obesity, but not overweight, was more common among male patients than reference subjects and waist:hip ratios were also significantly higher (58% of male patients had a waist:hip ratio > 0.9 compared with 35% of male reference subjects).

Comparison With Uncontrolled Studies

In uncontrolled studies,[9,10] the reported frequency of obesity in patients treated with lithium is between 2 and 5 times that in the general population,[9,10] which is greater than what we have found. Similarly, among those treated with antipsychotics, a 2- to 4-fold increase in obesity has been reported.[5,6] While our controlled data suggest lower prevalence rates for obesity overall than those reported previously, it seems clear that female bipolar patients are much more likely to be overweight than other New Zealand women. Our finding is in agreement with previous studies which have found that female patients treated with lithium experience larger weight gains than men and that overweight and obesity are more frequent in women treated with antipsychotics.[2,5–8] The reason for this gender difference is unclear and requires further investigation. We found that both male and female bipolar patients were more centrally obese than the general population. A higher prevalence of central adiposity has been found previously in hospitalized female schizophrenic patients.[7] In

keeping with previous findings in nonbipolar patients,[5–8] antipsychotic drugs were associated with a significantly higher prevalence of obesity (2.5 times greater than the general population) in our sample.[5–8] Lithium monotherapy was also associated with increased prevalence of obesity (1.5 times greater than the general population), although this was not statistically significant. No association was found between BMI, lifetime incidence of manic and depressive episodes, duration of illness, or length of time on current medication regimen. However, as previous studies have shown,[3] obese patients were more likely to experience difficulties with medication adherence. Although it would have been desirable to explore the relationship between the medication dose and BMI, the diversity of prescribing patterns precluded this.

There are several possible explanations as to why the effect of bipolar illness or its treatment on obesity is less striking in this than in previous studies. Most earlier investigations involved hospitalized patients among whom other etiologic factors for obesity may apply.[5–7] For example, hospitalized patients are less likely than community-based individuals to have regular physical activity, and they are also more likely to have particularly severe forms of the illness, whereas we studied a totally unselected, diagnostically homogeneous group of patients more representative of the disease in the community. The response rate was high, and the frequencies of overweight and obesity among nonresponders obtained from entries in hospital case notes were similar to those of the participants, confirming the representative nature of the sample. The carefully selected reference group enabled us to take into account the possible confounding effects of smoking and socioeconomic status, 2 important determinants of obesity at the population level.[18,19] In addition, the reference group's anthropometric measurements did not differ appreciably from those reported for the entire LINZ survey and are therefore likely to reflect closely those in the New Zealand population as a whole.

Risk Associated With Body Fat Distribution

Although the extent of the problem of overweight and obesity in bipolar patients may not be as great as suggested by the earlier uncontrolled studies, the increase in central adiposity in comparison with the reference population is of considerable clinical relevance. It has been clearly established that excess body fat of this distribution is associated with the "metabolic syndrome"[20] as well as an increased risk of type 2 diabetes mellitus and ischemic heart disease. Increased rates of impaired glucose tolerance and diabetes have been reported in patients receiving antipsychotic and antidepressant drugs, and a similar risk is almost certain to apply to the patient group we have studied.[21,22] It is therefore of considerable importance to identify whether specific lifestyle factors (lack of physical activity, individual dietary factors) are implicated in the etiology of central adiposity in bipolar patients so that appropriate treatment strategies may be developed.

Thyroid Function

Drugs used to treat bipolar affective disorder, particularly lithium, have been shown to influence thyroid function.[23–25] In view of the role of thyroid hormones in the regulation of basal metabolic rate, an association between obesity and hypothyroidism might be expected in pharmacologically treated bipolar patients. The lack of this association among female patients supports the observation of Vestergaard et al.[2] that weight gain in lithium-treated patients occurs independent of thyroid function. However, the significant association in men is surprising, and the reasons for it are unclear. Because thyroid function data were unavailable for 16 patients, the reliability of this association is uncertain. This interpretation is supported by the high frequency of clinical obesity in those treated with antipsychotics, compounds not usually associated with disturbances in thyroid function. This suggests that factors other than thyroid function are more important determinants of obesity in bipolar patients.

Limitations

The unequal numbers and unequal distributions of men and women in each medication regimen limited our ability to examine the associations between medication regimen and obesity prevalence. In addition, because of the diversity in prescribing patterns, we were unable to examine the associations between medication regimen and dosage and measures of body fatness and body fat distribution. The third important limitation relates to the thyroid function data, which were not available for all patients. Clearly, it would have been desirable to test thyroid function in all study participants. However, we were mindful that a requirement for extra blood tests might discourage participation and therefore elected to use only available clinical data.

CONCLUSIONS

We have shown that overweight (BMI 25–29.99) is significantly more prevalent in nonhospitalized female bipolar patients and there is a similar trend for rates of obesity. Among men, we found a tendency toward higher rates of obesity in patients, but rates of overweight do not show a comparable trend. Both male and female patients tend to be more centrally obese than reference subjects, placing them at increased risk of cardiovascular disease and diabetes. The prevalence of obesity among our patients is clearly related to the administration of antipsychotic drugs, but less so to lithium or anticonvulsants. It is unlikely that the illness itself is a cause of overweight or obesity, since only 1 of the 11 patients who were receiving no medication was obese. These results suggest that the

prevalence of overweight and obesity in bipolar patients is influenced more by pharmacologic treatment and gender than the illness itself or mediating factors such as socioeconomic status and smoking.

Future Research

In the future, strategies should be developed to limit weight gain in bipolar patients, especially women and those patients who require antipsychotic medication. The reasons for the differing frequencies of overweight and obesity in men and women and factors associated with insulin resistance should also be investigated.

Drug name: carbamazepine (Tegretol and others).

REFERENCES

1. Pi-Sunyer FX. Health implications of obesity. Am J Clin Nutr 1991;53: 1595S–1603S
2. Vestergaard P, Poulstrup M, Schou M. Prospective studies in a lithium cohort, 3: tremor, weight gain, diarrhea, psychological complaints. Acta Psychiatr Scand 1988;78:434–441
3. Gitlin MJ, Cochran SD, Jamison KR. Maintenance lithium treatment: side effects and compliance. J Clin Psychiatry 1989;50:127–131
4. Jamison KR, Akiskal HS. Medication compliance in patients with bipolar disorder. Psychiatr Clin North Am 1983;6:175–192
5. Gopalaswamy AK, Morgan R. Too many chronically mentally disabled patients are too fat. Acta Psychiatr Scand 1985;72:254–258
6. Silverstone T, Smith G, Goodall E. Prevalence of obesity in patients receiving depot antipsychotics. Br J Psychiatry 1988;153:214–217
7. Stedman T, Welham J. The distribution of adipose tissue in female patients receiving psychotropic drugs. Br J Psychiatry 1993;162:249–250
8. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999;60:215–220
9. Muller-Oerlinghausen B, Passoth PM, Poser W, et al. Impaired glucose tolerance in long-term lithium-treated patients. Int Pharmacopsychiatry 1979;14:350–362
10. Chen Y, Silverstone T. Lithium and weight gain. Int Clin Psychopharmacol 1990;5:217–225
11. Isojarvi JI, Laatikainen TJ, Knip M, et al. Obesity and endocrine disorders in women taking valproate for epilepsy. Ann Neurol 1996;39:579–584
12. Cassidy W, Flanagan N, Spellman M, et al. Clinical observations in manic-depressive disease: a quantitative study of one hundred manic-depressive patients and fifty medically sick controls. JAMA 1957;164:1535–1546
13. Salata R, Klein I. Effects of lithium on the endocrine system: a review. J Lab Clin Med 1987;110:130–136
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
15. Mann J, Nye T, Wilson B, et al. Life in New Zealand Commission Report: Health. Wellington, New Zealand: Hillary Commission for Recreation and Sport; 1991
16. James P. Obesity: a preventable disease. Report From the International Obesity Task Force (IOTF). Geneva, Switzerland: World Health Organization; 1996
17. Kannel WB, Cupples LA, Ramaswami R, et al. Regional obesity and risk of cardiovascular disease: the Framingham Study. J Clin Epidemiol 1991; 44:183–190
18. Klesges RC, Klesges LM, Meyers AW. Relationship of smoking status, energy balance, and body weight: analysis of the Second National Health and Nutrition Examination Survey. J Consult Clinical Psychol 1991;59: 899–905
19. Stunkard AJ. Socioeconomic status and obesity. Ciba Foundation Symposium 1996;201:174–182; discussion 182–193
20. Sattar N, Tan CE, Han TS, et al. Associations of indices of adiposity with atherogenic lipoprotein subfractions. Int J Obesity Relat Metab Disord 1998;22:432–439
21. Muller-Oerlinghausen B, Passoth PM, Poser W, et al. Effect of long-term treatment with neuroleptics or lithium salts on carbohydrate metabolism. Arzneimittelforschung 1978;28:1522–1524
22. Paykel ES, Mueller PS, De La Vergne PM. Amitriptyline weight gain and carbohydrate craving. Br J Psychiatry 1973;123:501–507
23. Bentsen K, Gram L, Veje A. Serum thyroid hormones and blood folic acid during monotherapy with carbamazepine or valproate. Acta Neurol Scand 1983;67:235–241
24. Invitti C, Danesi L, Dubini A, et al. Neuroendocrine effects of chronic administration of sodium valproate in epileptic patients. Acta Endocrinol (Copenh) 1988;118:381–388
25. Bocchetta A, Bernardi F, Burrai C, et al. The course of thyroid abnormalities during lithium treatment: a two-year follow-up study. Acta Psychiatr Scand 1992;86:38–41