Behavioral Treatment of Obesity in Patients Taking Antipsychotic Medications

Melissa A. Kalarchian, Ph.D.; Marsha D. Marcus, Ph.D.; Michele D. Levine, Ph.D.; Gretchen L. Haas, Ph.D.; Catherine G. Greeno, Ph.D.; Lisa A. Weissfeld, Ph.D.; and Li Qin, M.S.

Objective: Antipsychotic medications are associated with weight gain and metabolic dysregulation, yet little is known about the management of obesity among individuals with severe and persistent mental illness. Thus we sought to evaluate the potential utility of a behavioral weight control program for this population.

Method: Outpatients receiving psychiatric care at a university medical center who had a body mass index (BMI; weight in kg/[height in m]^2) ≥ 30 and were currently taking antipsychotic medication participated in a 12-week group behavioral weight control program. A medical chart review was conducted for each participant's body weight over the 10 months prior to beginning the program. A multiple baseline design was used to determine the impact of the intervention on BMI through 12-month posttreatment follow-up. We also assessed self-reported eating behavior, physical activity, and health-related quality of life. Data were collected from October 2000 to July 2003.

Results: Among 35 patients who began the program, 29 (83%) completed treatment, with mean (± SD) weight loss of 5.04 (± 7.52) pounds (p = .001) and improvements in eating, activity, and quality of life. At 3-month posttreatment follow-up (N = 27; 77%), total mean weight loss was 7.14 (± 11.47) pounds (p = .003). Results of a longitudinal model based on general estimating equations indicated that, relative to the pretreatment period, BMI decreased significantly during treatment and remained stable through 12-month posttreatment follow-up.

Conclusion: Behavioral weight control is a promising approach to the treatment of obesity among outpatients taking antipsychotic medications, but longer and more robust interventions are needed.

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Received Nov. 1, 2004; accepted Jan. 10, 2005. *From the Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pa. (Drs. Kalarchian, Marcus, Levine, Haas, and Greeno); Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pa. (Dr. Weissfeld and Ms. Qin).*

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Corresponding author and reprints: Melissa A. Kalarchian, Ph.D., Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, 3811 O'Hara Street, Pittsburgh, PA 15213 (e-mail: kalarchianma@msx.upmc.edu).

Both first- and second-generation antipsychotic medications are associated with weight gain.[1] Among the second-generation drugs, clozapine has been associated with the greatest weight gains, and ziprasidone the least.[1,2] Consequently, there has been considerable focus on obesity and metabolic dysregulation among patients taking atypical antipsychotic medications.[3]

Little is known about the management of obesity among individuals with severe and persistent mental illness taking antipsychotic medications. Ball et al.[4] evaluated the effectiveness of the Weight Watchers 1-2-3 Program and supervised exercise sessions for patients with schizophrenia who had olanzapine-related weight gain. Overall, participants in treatment (N = 11) decreased more in body weight and body mass index (BMI; weight in kg/[height in m]^2) than a matched control group (N = 20), but the difference between groups was not significant. However, there was a sex-by-group-by-time interaction such that only men (N = 7) experienced significant weight loss in treatment (about 7 pounds in 10 weeks).

Menza and colleagues[5] evaluated a behavioral weight control program (Healthy Living) for individuals with schizophrenia and schizoaffective disorder in day-treatment programs who reported gaining weight while taking antipsychotic medications. Overweight and obese participants in the yearlong study (N = 31) experienced significant reductions in BMI and other medical risk factors, accompanied by positive changes in nutrition and exercise. Patients

receiving usual care in the same programs (N = 20) gained weight over the course of the study.

In light of the limited information on the impact of weight management in outpatients with severe and persistent mental illness, we sought to evaluate the potential utility of a behavioral weight control program for patients taking antipsychotic medications. We chose to adapt the Stoplight Diet,[6] a program based on sound behavioral principles that has been efficacious in producing weight loss in children and adolescents, as well as their parents.[7,8] We anticipated that this conceptually simple program would be particularly useful in the treatment of individuals with schizophrenia and schizoaffective disorder. We hypothesized that the modest caloric restriction and emphasis on regular physical activity would promote weight loss and improvements in eating behavior, physical activity, and health-related quality of life.

METHOD

Design

The study employed a multiple baseline design. Specifically, we conducted a medical chart review for each participant's body weight over the 10-month period prior to starting the treatment group. We documented weights for 3 months (range, 2–4 months), 6 months (range, 5–7 months), and 9 months (range, 8–10 months) prior to the start of treatment. This extended baseline allowed us to evaluate whether the initiation of treatment was associated with a change in BMI trajectory.

The treatment program consisted of 12 weekly behavioral group sessions, followed by 2 biweekly booster sessions and 2 monthly booster sessions, for a total of 16 sessions over 6 months. Research assessments were conducted at pretreatment, posttreatment (after session 12), and 3-, 6-, and 12-month posttreatment follow-up. The study protocol was approved by the University of Pittsburgh Institutional Review Board.

Participants

Outpatients receiving care at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, with a BMI of 30 or greater and currently taking antipsychotic medication were eligible for the study. All participants were diagnosed with schizophrenia or related psychoses. Patients were recruited from a medication clinic or referred by their doctor or mental health provider. Individuals who were mentally retarded, were participating in another weight control program, or had evidence of severe global cognitive deficits (Folstein Mini-Mental State Examination[9] score < 25) were excluded.

Sixty-one patients attended study information sessions. After the principal investigator explained the study, 45 individuals signed written informed consent. Nine patients dropped out of the study prior to attending the first treatment session, most of whom reported that they had enrolled in the study to collect the payment for completing the baseline assessment, but had not intended to participate in the intervention. One additional patient was excluded from the study because she was unsteady on her feet and could not be weighed on our portable digital scale. Thus, the final sample included 35 individuals who consented and began treatment. Most patients (25; 71.4%) were taking clozapine, and the rest were taking other antipsychotic medications.

Treatment

Treatment consisted of 12 weekly group sessions, followed by 2 biweekly booster sessions, then 2 monthly booster sessions. Sessions lasted 60 minutes and consisted of a weight check, individualized review of self-monitoring records, and a group presentation of the behavioral weight control program. A doctoral-level clinical psychologist and a registered dietitian conducted the intervention groups. Each session ended with a group walk led by a study research assistant. All participants obtained medical clearance from their physician to participate in the research study intervention.

An eating plan was developed for use with this study based on the Stoplight Diet.[6] Food is classified according to the colors of a stoplight: Green (Go! Include as many as you can.), Yellow (Caution! Eat in limited amounts.), and Red (Stop! Think before you eat.). Table 1 shows examples of Red, Yellow, and Green foods. Participants were instructed to increase their intake of fruits and vegetables (Green and Yellow foods), while decreasing the number of foods high in fat and sugar (Red foods). Participants also were directed to decrease sedentary activities, especially time spent watching television. Participants were provided with pedometers and instructed to gradually increase their walking toward a goal of 10,000 steps per day. Psychoeducation focused on the role of eating and activity in weight management, and the importance of medication compliance.

Standard behavioral techniques were used to help participants implement and maintain the recommended changes in eating and activity. Participants self-monitored food type, amount, and "color" (Red, Yellow, or Green), as well as pedometer steps and body weight. Self-monitoring records were reviewed at each treatment session in order to identify eating and activity patterns. Individual feedback was provided with goals for behavior change. Participants were awarded points for behavior change that could be exchanged for gift certificates to local stores. Additional behavioral strategies included the use of stimulus control techniques to minimize cues for eating and increase cues for activity, social assertiveness training for situations involving eating and exercise, and relapse prevention strategies to promote long-term maintenance of behavior change.

Table 1. Examples of Foods Classified as Red, Yellow, and Green in a Study of Behavioral Treatment of Obesity in Patients Taking Antipsychotic Medications[a]

Type of Food	Red	Yellow	Green
Fruits	Peaches canned with sugar	Orange juice	Bananas
	Cranberry sauce		Apples
Vegetables	French fries	Yams	Carrots
	Baked beans	Pinto beans	Broccoli
Dairy	Chocolate milk	Skim milk	NA
	Regular yogurt	Nonfat yogurt	
Protein	Chicken nuggets	Steamed fish	NA
	Bacon	Hard-boiled eggs	
Grains	Sweetened cereal	Unsweetened oatmeal	NA
	Prepackaged rice mix	Air-popped popcorn	
	Bread stuffing	Hamburger buns	
Combination foods	Egg rolls	Chicken noodle soup	NA
	Pizza	Chili	
Fats and sweets	Candy bars	Vanilla wafers	Fat-free salad dressing
	Butter	Pudding	Butter spray
Beverages	Regular soda	Low-calorie cocoa	Diet soda
	Coffee with creamer	Apple juice	Unsweetened tea

[a]Food classifications are adapted from the Stoplight Diet. For more information, see Epstein and Squires.[6]
Abbreviation: NA = not applicable.

Assessments

Height was measured once at the start of the study. Body weight was measured in street clothes without shoes on a portable digital scale at each assessment. Research assistants read self-report questionnaires to participants individually at each assessment to ensure completion and comprehension. Subjects were paid a total of $150 for completing all 5 assessments. Assessments were conducted between October 2000 and July 2003.

Self-report questionnaires included the following: the Eating Behavior Inventory (EBI),[10] a self-report measure of 26 specific behavioral strategies conducive to weight loss with acceptable internal consistency and satisfactory test-retest reliability; the Paffenbarger (Harvard Alumni Activity Survey),[11] a brief recall interview used to assess physical activity, including walking, in the last week; and the Medical Outcomes Study (MOS) Short-Form Health Survey (SF-36),[12] a 36-item self-report questionnaire used to evaluate health-related quality of life. The MOS includes scales to assess physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health perceptions. It has well-established reliability and validity, and has been shown to be appropriate in diverse populations, including mental health samples.[13]

Analytic Plan

Descriptive statistics were used to summarize demographic characteristics of study participants. t Tests (for continuous variables) and χ^2 analyses (for categorical variables) were utilized to detect differences between those who lost weight and gained weight during treatment, as well as to compare those who dropped out to those who completed treatment.

To determine whether treatment was associated with improvements in body weight, eating, activity, and health-related quality of life, we used paired t tests to examine changes pretreatment to posttreatment. Linear regression models, controlling for baseline BMI, were used to probe whether changes in these factors were related to decreases in BMI during treatment. Each model was fit with change in BMI (pretreatment BMI–posttreatment BMI) as the outcome variable. Each model then included baseline BMI and the change in the covariate of interest from pretreatment to posttreatment as predictor variables.

To test the hypothesis that the intervention would have a positive impact on BMI trajectory, we fit a longitudinal model using generalized estimating equations. We included terms for time (each time point from the medical chart review, weekly weights in treatment, booster sessions, and follow-up assessments), period (pretreatment, treatment, boosters, and posttreatment), and interaction of time with period. Because patients taking clozapine, the majority of the sample, did not differ in BMI trajectory from those taking other medications, we grouped all patients together for all analyses.

To evaluate potential factors related to BMI change during treatment, further models were fit using generalized estimating equations. For these analyses, time was limited to the weekly treatment sessions (first treatment session attended—last treatment session attended), and baseline BMI was included as a covariate. Selected other covariates (medication [clozapine or other], number of years taking antipsychotic medications, sex, age, race) were then included in each model, one at a time. To assess changes over time, each model included an interaction term of time with each covariate. All generalized estimating equation models were fit using an exchangeable

variance structure, and terms were retained or dropped based on the statistical significance of each term.

RESULTS

Sample Characteristics

Participants were 65.7% (23/35) white and 54.3% (19/35) male. Mean (± SD) age was 42.0 (± 10.3) years, and participants reported having taken antipsychotic medication for 17.1 (± 10.4) years. Mean BMI at study entry was 36.5 (± 5.2). Most participants had pursued some education beyond high school (22/30; 73.3%). Specifically, 7 patients completed college, 15 reported some college or associate's degree, 7 reported completing high school or general equivalency diploma, and 1 patient reported some high school. Education information was not collected for the first 5 study participants.

Twenty-nine of 35 participants (82.9%) completed weekly treatment, with a mean of 10.6 (± 1.7) sessions attended. Mean weight loss during treatment was 5.04 (± 7.5) pounds (paired $t = -3.61$, $p = .001$). Twenty patients lost weight during treatment (range, 1.4–24.8 pounds), and 9 individuals gained weight (range, 0.2–9.4 pounds). No differences were identified between patients who lost weight as compared to those who gained weight during the 12 weekly sessions. Body weight continued to decline during the period of booster sessions, with a mean weight loss of 7.14 (± 11.47) pounds among 27 participants (77.1%) completing the 3-month posttreatment assessment (paired $t = -3.23$, $p = .003$), corresponding to a loss of 3.2% of initial body weight.

We compared individuals who completed weekly treatment to those who dropped out with respect to demographic factors. Eighty percent (20/25) of those who completed treatment had pursued some education beyond high school as compared to 40% of dropouts (2/5), a marginally significant result ($\chi^2 = 3.4$, $p = .065$). No other differences were identified between dropouts and completers.

Impact of Treatment on BMI Trajectory

With respect to BMI trajectory, the final model retained a term for time, 3 terms for period (treatment, boosters, and posttreatment, with pretreatment as the reference), and an interaction term between time and treatment period. Findings from the model indicated that relative to the pretreatment period, BMI decreased during the weekly treatment period ($\beta_{time*period} = -0.04408$, $p = .003$), and remained stable throughout the posttreatment periods (Figure 1). Estimates derived from a similar model for body weight indicate that 9 months prior to the start of treatment, mean body weight was 235.74 pounds; 6 months prior, it was 235.84; and 3 months prior, it was 235.94. During treatment, estimated mean body weight dropped from 236.99 at the start to 232.22 at the end of the 12-week intervention. At 3-, 6-, and 12-month posttreatment follow-up, mean body weights were 230.55, 231.45, and 231.65 pounds, respectively.

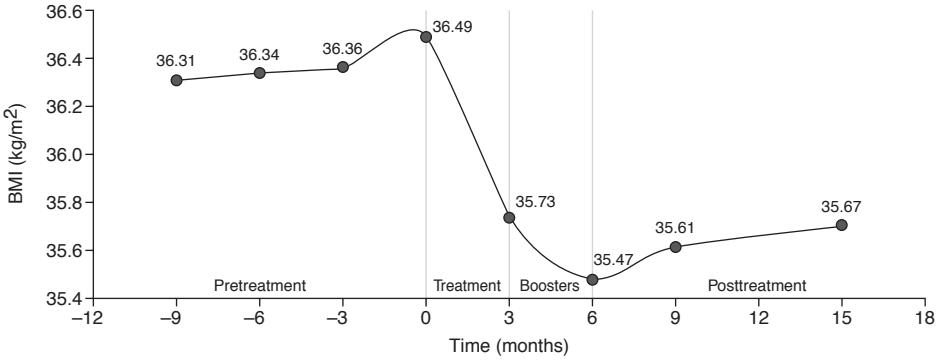
After controlling for initial BMI, age ($\beta = -0.023$, $p = .006$) and number of years taking antipsychotic medications ($\beta = -0.022$, $p = .028$) were associated with BMI during weekly treatment, indicating that older patients and those who had been taking medication for a greater number of years were significantly more obese. The interaction of time with age ($\beta = -0.0028$, $p = .058$) and time with number of years taking antipsychotics ($\beta = -0.0035$, $p = .052$) approached significance, indicating a trend for older patients and those who had taken antipsychotics for a greater number of years to exhibit a more favorable BMI trajectory during treatment. None of the remaining covariates (medication, education, sex, and race), or the interactions of these factors with time, were significant.

Changes in Eating, Activity, and Health-Related Quality of Life

Participants increased their mean (± SD) total EBI score by 13.42% (± 15.44) during weekly treatment, representing a significant increase in behaviors associated with behavioral weight management (paired $t = -4.66$, $p = .0001$). Examination of the individual questionnaire items indicated that 5 of 26 eating behaviors improved significantly. The most strongly adopted behaviors were recording the type and quantity of food eaten (paired $t = -7.34$, $p < .0001$) and keeping a weight graph (paired $t = -4.60$, $p < .0001$). Other behaviors that increased were eating foods that one believes will aid one in losing weight (paired $t = -2.22$, $p = .036$), keeping 1 or 2 raw vegetables available for snacks (paired $t = -2.50$, $p = .02$), and storing food in containers where it is not readily visible or in a closed container (paired $t = -2.07$, $p = .05$). Improvements in 2 eating behaviors were significantly associated with reductions in BMI during treatment after controlling for BMI at study entry: keeping 1 or 2 raw vegetables available for snacks ($\beta = -0.3775$, $p = .045$) and carefully watching the quantity of food eaten ($\beta = -0.3424$, $p = .003$). Participants' self-reports of mean number of city blocks walked per day went from 9.71 (± 10.13) at pretreatment to 16.75 (± 20.19) at posttreatment, although the increase was not significant (paired $t = -1.60$, $p = .124$) and not associated with change in BMI during weekly treatment ($\beta = -0.0138$, $p = .256$).

With respect to health-related quality of life during weekly treatment, 3 of 8 subscales of the SF-36 improved significantly: physical functioning (paired $t = -3.55$, $p = .002$), general health (paired $t = -2.07$, $p = .049$), and pain (paired $t = -2.56$, $p = .017$). Patients also reported marginally significant increases in energy (paired $t = -1.97$, $p = .06$) and social functioning (paired $t = -1.77$, $p = .09$). Role limitations due to emotional problems, role limitations due to physical health, and emotional well-being did not change over the course of treatment. Only increase

Figure 1. BMI Trajectory for GEE Analysis of Participants in Behavioral Treatment Program for Patients Taking Antipsychotic Medications



Abbreviations: BMI = body mass index, GEE = generalized estimating equation.

in energy (β = –0.0353, p = .01) was significantly associated with BMI decrease during weekly treatment.

DISCUSSION

The association between antipsychotic medication and weight gain is well established, yet little is known about the management of obesity among patients taking antipsychotic medications. Although behavioral approaches have proven effective in producing weight loss in the general adult population of 1 to 2 pounds per week for up to 6 months,[14] patients with severe and persistent mental illness are routinely excluded from controlled weight management treatment trials. This investigation is among the first preliminary studies to document that behavioral weight control is a feasible and promising approach to the treatment of obesity in this population. Results indicate that participants in a behavioral weight control program adapted for outpatients taking antipsychotic medications experienced significant reductions in body weight and BMI, accompanied by improvements in eating, activity, and health-related quality of life.

Relative to patients' BMI trajectory prior to treatment, participants' BMI decreased significantly during weekly treatment and remained stable at follow-up. However, small increases in BMI were documented during the pretreatment and posttreatment intervals (see Figure 1), and it is not unlikely that over time these trends would lead to significant increases in BMI. That is, patients' BMI may have been on a modest upward trajectory prior to starting the behavioral treatment program, and may have resumed this trajectory after contact with the treatment program ended. However, the observation that BMI continued to decrease after the end of weekly treatment during the period of booster sessions, corresponding to a maximum weight loss of 7.14 pounds and 3.2% of initial body weight at 3 months posttreatment, suggests that lengthening the duration of contact with the program could serve to enhance weight loss and maintenance.

Although there is growing consensus that a sustained decrease of 7% to 10% of initial body weight is a reasonable goal associated with modest health benefits, current clinical guidelines caution that a standard approach to weight loss might work differently in diverse patient populations.[14] Findings from the present study are similar to a quasi-experimental study with yearlong follow-up[5] in which 87% of severely mentally ill patients completed the intensive 12-week portion of a behavioral weight loss program, with weight loss of 6.6 pounds and improvements in health parameters such as hemoglobin A_{1c} and blood pressure. Both the current study and the Menza et al. study[5] achieved somewhat more promising results than a small study of patients taking olanzapine,[4] in which only men lost a significant amount of weight. Collectively, these studies do suggest that behavioral weight control can have positive effects not only on weight, but also on medical, behavioral, and psychological parameters.

Clinical guidelines emphasize considering patient characteristics in obesity treatment programs by adapting the setting and staffing for the program, considering how the obesity treatment program integrates into other aspects of patient health care and self-care, and expecting and allowing for program modifications based on patient responses and preferences.[13] Our primary recruitment site was a medication clinic for patients with severe and persistent mental illness. Behavioral treatment groups were held at the same location and scheduled to coordinate with the days and times when patients taking clozapine report for mandatory blood work. We worked with a nutritionist and the participants in the initial treatment group to simplify the eating plan. Modifications to treatment format included streamlined self-monitoring forms and a point system to reinforce changes in eating, physical activity, and body weight. Furthermore, when working with

patients to implement lifestyle changes, we focused on issues of particular relevance to this patient population, such as transportation, budget, and housing situation. These adaptations to a standard behavioral weight control program were designed to address the needs of patients with severe and persistent mental illness and stand in contrast to the study that did not make significant population-specific modifications to the Weight Watchers program for patients with olanzapine-related weight gain.[4]

Participants in the present study were compliant with the intervention as evidenced by good retention and attendance, as well as self-reported increases in targeted behaviors such as self-monitoring, healthy eating, and walking. The patient sample was distinctive in 2 ways that may have enhanced compliance. First, the majority of study participants were taking clozapine (71%). As most participants had taken clozapine for many years, they entered the study having already demonstrated compliance with mandatory blood work. Second, most (73%) reported having pursued some education beyond high school. As we found that patients with more education tended to be less likely to drop out of the study, the relatively high education level of participants may have enhanced overall participation in the program.

After controlling for initial BMI, older patients and those who had been taking antipsychotic medications for a greater number of years tended to have greater BMIs and experience larger BMI reductions in treatment relative to younger patients and those who had been taking medications for fewer years. Additional factors such as type of medication, dosage, regimen changes, psychiatric symptomatology, severity of illness, weight concerns, living arrangement, smoking, race, or sex may relate to weight control. Further research is needed to pinpoint sources of variability in outcome and to tailor the psychoeducational, dietary, and behavioral components of the intervention to the unique needs of particular subgroups of patients.

Study limitations include its uncontrolled design, limited range of psychiatric and medical outcomes assessed, and inclusion of patients following different medication regimens. However, findings do support the need for controlled, prospective trials to document the effects of behavioral weight control on multiple outcomes such as insulin sensitivity, lipid profile, and blood pressure in addition to psychosocial functioning and health-related quality of life, relative to standard care. In light of the modest weight losses achieved in studies reported thus far, research efforts should also focus on the development of longer and more robust interventions, and on the prevention of weight gain among newly diagnosed patients.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), ziprasidone (Geodon).

REFERENCES

1. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
2. Taylor DM, McAskill R. Atypical antipsychotics and weight gain: a systematic review. Acta Psychiatr Scand 2000;101:416–432
3. Nasrallah HA, Newcomer JW. Atypical antipsychotics and metabolic dysregulation: evaluating the risk/benefit equation and improving the standard of care. J Clin Psychopharmacol 2004;24(5 suppl 1):S7–S14
4. Ball MP, Coons VB, Buchanan RW. A program for treating olanzapine-related weight gain. Psychiatr Serv 2001;52:967–969
5. Menza M, Vreeland B, Minsky S, et al. Managing atypical antipsychotic-associated weight gain: 12 month data on a multimodal weight control program. J Clin Psychiatry 2004;65:471–477
6. Epstein LH, Squires S. The Stoplight Diet for Children: An Eight-Week Program for Parents and Children. Boston, Mass: Little, Brown and Co; 1988
7. Epstein LH, Valoski A, Kalarchian MA, et al. Do children lose and maintain weight easier than adults: a comparison of child and parent weight changes from six months to ten years. Obes Res 1995;3:411–417
8. Epstein LH, Valoski A, Wing RR, et al. Ten-year follow-up of behavioral family-based treatment for obese children. JAMA 1990;264:2519–2523
9. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
10. O'Neil PM, Currey HS, Hirsch AA, et al. Development and validation of the Eating Behavior Inventory. J Behav Assess 1979;1:123–132
11. Paffenbarger RS Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol 1978;108:161–175
12. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36), 1: conceptual framework and item selection. Med Care 1992;30:473–483
13. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36), 2: psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31: 247–263
14. National Heart, Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. National Institutes of Health publication 98-4083. Washington, DC: National Heart, Lung, and Blood Institute; 1998