The Distribution of Body Mass Index Among Individuals With and Without Schizophrenia

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Objective: The objective of this study was to estimate and compare the distributions of body mass index (BMI: kg/m^2) among individuals with and without schizophrenia, and, thereby, place the weight gain–inducing effects of antipsychotic drugs into context.

Method: Data sources were (1) the mental health supplement of the 1989 National Health Interview Survey (NHIS; N = 80,130 nonschizophrenic and 150 self-reported schizophrenic individuals), (2) baseline BMI data from a drug trial of the antipsychotic ziprasidone supplied by Pfizer Inc (420 noninstitutionalized individuals with chronic psychotic disorders [DSM-IV schizophrenia or schizoaffective disorder]) and (3) data from the National Health and Nutrition Examination Survey III (NHANES III; N = 17,689 nonschizophrenic individuals) to act as a control group for the ziprasidone trial data.

Results: After age-adjusting BMI in each data set, the NHIS data revealed that men with schizophrenia have mean BMIs similar to those of men without schizophrenia (26.14 vs. 25.63, respectively). In contrast, women with schizophrenia in the NHIS data set had a significantly ($p < .001$) higher mean BMI than did women without schizophrenia (27.36 vs. 24.50, respectively). Moreover, each decile was higher for women with schizophrenia than for women without schizophrenia. Analysis of the ziprasidone and NHANES III data sets revealed that, on average, men with schizophrenia have mean BMIs comparable to those of men without schizophrenia (26.79 vs. 26.52, respectively). In these 2 data sets, women with schizophrenia also had a mean BMI similar to those of women without schizophrenia (27.29 vs. 27.39, respectively).

Conclusion: Although there may be a small subpopulation of schizophrenic individuals who are underweight, individuals with schizophrenia were, on the whole, as obese as or more obese than individuals without schizophrenia, suggesting that weight gain induced by antipsychotic agents is an important concern for many individuals.

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Antipsychotic (neuroleptic) medications are an integral part of the therapeutic program for many individuals with schizophrenia and other psychotic disorders. However, one untoward effect of many antipsychotic drugs is weight gain.[1,2] The extent of weight gain appears to vary from drug to drug and may be due to the drugs' differing degrees of action on the serotonergic,[3] dopaminergic,[4] cholinergic,[3] histaminergic,[5] and other neurotransmitter systems. Not only is weight gain undesirable in its own right (see reference 6), but such a noticeable and undesired side effect may cause some schizophrenic patients to discontinue their medications, predisposing them to relapse.[2]

The aim of this study was to estimate and compare the relative body weight (body mass index [BMI: kg/m^2]) of individuals with and without schizophrenia. We examined large, recent, well-characterized data sets to provide a reasonable proxy for the distribution of BMI at the present time. The result of this comparison might be useful in several respects. Were it found, for example, that most individuals with schizophrenia are lean or underweight, then weight gain associated with antipsychotic medication use might be considered benign or even beneficial. On the other hand, if the distribution of BMI is similar between

those with and without schizophrenia (which would imply that there is a great deal of obesity among schizophrenic individuals), then even modest weight gains associated with antipsychotic drug usage would be of concern, as they would increase the already troublingly high levels of obesity prevalent in the general population.[7,8]

METHOD

Data Sources

Data sources used were the mental health supplement of the 1989 National Health Interview Survey (NHIS), data from a ziprasidone trial (data on file, Pfizer Central Research, Groton, Conn, 1997), and phase III data from the Third National Health and Nutrition Examination Survey (NHANES III). These particular data sets (described below) were chosen because they met the following criteria: (1) raw data were available to us so we could thoroughly examine various aspects of the distribution, including means, standard deviations, and selected quantiles; (2) samples were large, allowing for relatively precise estimation; and (3) sampling properties of the studies were of high quality.

Data From the 1989 National Health Interview Survey

The NHIS is an annual survey conducted by the National Center for Health Statistics. Each year, a survey is conducted of a large sample (typically just over 100,000 individuals). The sample is selected through a random, stratified sampling procedure designed to acquire a representative cross-section of the United States civilian, noninstitutionalized population. In addition to a core survey, which collects self-reported height and weight of each individual 18 years of age and older, supplemental surveys are given that vary each year. Self-reported weight has been shown to be highly correlated with measured weight.[9] In 1989, a mental health supplement was included. This supplement ascertained (through self-report) whether respondents had been diagnosed as schizophrenic within the last 12 months. More details about this survey can be obtained from the U.S. Department of Health and Human Services.[10] There were 80,130 individuals without schizophrenia and 150 individuals with schizophrenia with complete data available for analyses.

Baseline Data From an Antipsychotic Drug Trial

Pfizer Central Research in Groton, Conn., supplied baseline data (including measured height and weight) from a clinical trial of ziprasidone. The total sample size was 420 (289 men, 131 women) noninstitutionalized (i.e., residing in the community for at least 3 months) individuals 18 years of age or older with a primary diagnosis of chronic or subchronic DSM-IV schizophrenia or schizoaffective disorder. In some cases, individuals who had less than 80% of the lower weight limit or greater than 160% of the upper weight limit of their ideal weight for gender, height, and frame as established in the 1983 Metropolitan Life Insurance height and weight tables were screened but excluded from the trial[11] (this is addressed in the sensitivity analysis described below). Unfortunately, the percentages of persons excluded from the trial for being either underweight or overweight was not recorded. Moreover, individuals with clinically significant hematologic, renal, cardiovascular, hepatic, gastrointestinal, endocrine (including poorly controlled diabetes with a blood glucose level above 180 mg/dL, but not adequately treated hypothyroidism or hyperthyroidism), pulmonary, dermatologic, oncologic, and neurologic disease; women of childbearing potential not practicing adequate contraception; and those with clinically significant laboratory abnormalities also were excluded from the trial.

Data From the Third National Health and Nutrition Examination Survey

NHANES III is part of an ongoing set of surveys conducted by the National Center for Health Statistics.[12] Like the NHIS, these surveys use random, stratified sampling procedures to recruit large samples. NHANES III data were collected from 1988 through 1991. Raw data were available on a representative sample of the U.S. civilian, noninstitutionalized population. Data on age, sex, and measured height and weight were available for a total of 17,689 individuals (8271 men, 9418 women) without schizophrenia over the age of 18 years. Because NHANES III comprises a large, nationally representative sample of persons without schizophrenia, it is an ideal control group for the baseline data from the ziprasidone trial. That is, it allows us to ask how schizophrenic individuals in the trials compare with the general population.

Data Analysis

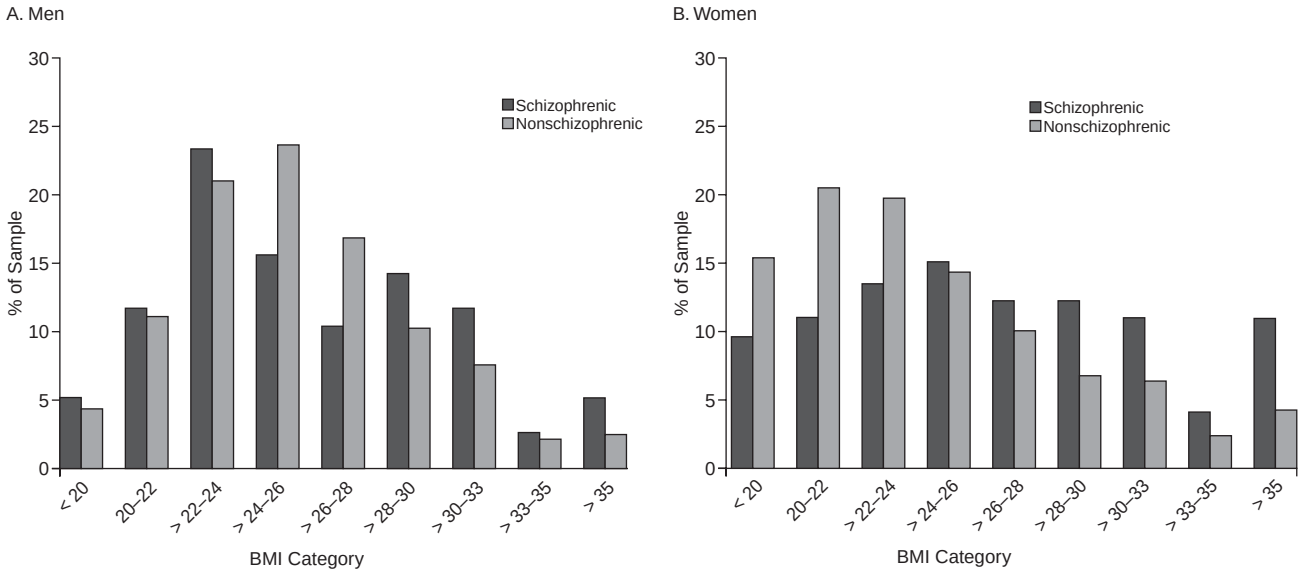
Before the analysis of each data set, BMI was adjusted for age by regressing BMI on age, age^2, and age^3 (to allow for the nonlinear association of age with BMI), using ordinary least squares regression, and saving the residuals (i.e., predicted value – observed value). To improve interpretability, a linear transformation was taken such that the residuals had their original mean and variance. Because exploratory analyses of NHIS data conducted by the current authors suggested that gender might moderate the relationship between BMI and schizophrenia status, all analyses were conducted separately by gender. For each data set, mean age-adjusted BMIs and deciles were computed for both men and women with and without schizophrenia. Tests of significance included 2 sample t tests with the Welch approximation[13] for age-adjusted mean differences in BMI between individuals with and

Table 1. Comparison of the Age-Adjusted BMI Distributions of Schizophrenic and Nonschizophrenic Men and Women in the 1989 NHIS Sample[a]

	Men			Women		
BMI	Schizophrenic (N = 77)	Nonschizophrenic (N = 37,337)	p Value	Schizophrenic (N = 73)	Nonschizophrenic (N = 42,793)	p Value
Mean	26.14	25.63	.338[b]	27.36	24.50	< .001[c]
Standard deviation	4.60	4.03	.021[d]	7.30	5.16	< .001[e]
Percentile						
10th	21.26	21.25	.991	19.89	19.30	.686
20th	22.30	22.50	.790	21.16	20.49	.583
30th	23.13	23.40	.696	23.47	21.45	.073
40th	23.96	24.23	.685	24.98	22.38	.016
50th	25.47	25.08	.553	26.10	23.39	.011
60th	26.69	25.98	.286	27.95	24.51	.002
70th	28.44	27.03	.041	29.06	26.00	.007
80th	29.81	28.44	.068	32.14	27.98	6.58×10^{-4}
90th	32.93	30.70	.013	36.00	31.20	.001

[a]The p values for the difference between the groups' percentiles are based on the Bahadur large sample approximation (Cox and Hinkley[15]). Abbreviations: BMI = body mass index, NHIS = National Health Interview Survey.
[b]t = 0.97, df = 76.2. Based on t test with Welch approximation which does not assume homogeneity of variance when comparing the means of 2 distributions.[13]
[c]t = 3.35, df = 72.1. See footnote b for description of t test.
[d]Based on the Levene test for equality of variances.[14] The null hypothesis is that the variance (or standard deviation) of age-adjusted BMI groups is the same; the alternative is that the variances are different.
[e]F = 13.06. See footnote d for description of F test.

Figure 1. Age-Adjusted BMI Distributions Among Schizophrenic and Nonschizophrenic Individuals in the 1989 NHIS Sample



without schizophrenia, the Levene test for the equality of variances,[14] and the Bahadur large sample approximation for the differences between the groups' percentiles.[15] With respect to the ziprasidone versus NHANES III comparison, we first used the data of the entire pool of subjects from both samples and then, in a sensitivity analysis, re-analyzed the data excluding persons from both data sets who did not meet the weight criteria for inclusion in the ziprasidone trial (i.e., < 80% ideal body weight or > 160% ideal body weight as defined by the 1983 Metropolitan Life Insurance height and weight tables[11]).

RESULTS

Results From the NHIS

Table 1 lists the mean, standard deviation, and deciles of the age-adjusted BMI distribution for each of the 2 subsamples by gender. The fourth and seventh columns of Table 1 also report the significance of the differences between these data for the samples of persons with and without schizophrenia. On average, men with schizophrenia had BMIs very similar to those of men without schizophrenia. Moreover, there were small differences in the up-

Table 2. Comparison of the Age-Adjusted BMI Distributions of all Schizophrenic and Nonschizophrenic Men and Women in the Ziprasidone and NHANES III Samples[a]

	Men			Women		
BMI	Ziprasidone (N = 289)	NHANES III (N = 8271)	p Value	Ziprasidone (N = 131)	NHANES III (N = 9418)	p Value
Mean	26.79	26.52	.346[b]	27.29	27.39	.882[c]
Standard deviation	5.05	4.90	.242[d]	7.17	6.54	.001[e]
Percentile						
10th	20.78	21.12	.492	18.76	20.27	.152
20th	22.23	22.64	.440	20.76	21.97	.170
30th	23.77	23.86	.814	22.01	23.44	.079
40th	25.10	24.85	.496	22.99	24.86	.017
50th	26.61	25.89	.047	26.06	26.28	.776
60th	27.71	26.99	.050	28.82	27.84	.210
70th	28.50	28.28	.565	31.91	29.71	.007
80th	30.09	29.89	.629	34.88	32.13	.002
90th	33.67	32.42	.012	36.66	35.93	.489

[a]The p values for the difference between the groups' percentiles are based on the Bahadur large sample approximation (Cox and Hinkley[15]). Abbreviation: NHANES III = National Health and Nutrition Examination Survey III.
[b]t = .953, df = 8558. Based on t test with the Welch approximation which does not assume homogeneity of variance when comparing the means of 2 distributions.[13]
[c]t = .149, df = 133.02. See footnote b for description of t test.
[d]F = 1.37. Based on the Levene test for equality of variances.[14] The null hypothesis is that the variance (or standard deviation) of age-adjusted BMI groups is the same; the alternative is that the variances are different.
[e]F = 10.37. See footnote d for description of F test.

per 3 deciles, which suggest that the most overweight third of men with schizophrenia were slightly more overweight than the most overweight third of men without schizophrenia. Complementary graphic representation of the data, along 9 BMI categories, is shown in Figure 1A. In contrast, women with schizophrenia had a statistically ($p < .001$) and clinically significantly higher mean BMI than women without schizophrenia. Moreover, each decile was higher for the women with schizophrenia than women without schizophrenia. This suggests that women with schizophrenia are overrepresented among the obese and underrepresented among the very thin/underweight (see Figure 1B). Finally, results for both men and women indicate that either there is no subgroup of noninstitutionalized schizophrenic persons that are unusually thin (beyond what would be expected in any population) or that the subgroup is very small (i.e., much less than 10% of noninstitutionalized schizophrenic persons sampled).

Results From the Ziprasidone/NHANES III Data

Table 2 lists the mean, standard deviation, and deciles of age-adjusted BMI distribution for the baseline ziprasidone trial data compared with the NHANES III data. On average, men with and without schizophrenia had virtually identical BMIs. As Table 2 shows, most deciles were similar, but the first through third were marginally lower among men with schizophrenia and the fourth through ninth were somewhat higher. By the same token, women with chronic schizophrenia also displayed BMIs similar to those of women without schizophrenia. Most deciles were similar; however, the first through fifth were marginally lower for women with schizophrenia, and the sixth through ninth were somewhat higher. Figure 2 shows the proportions of persons with and without schizophrenia falling into 9 BMI classifications. Essentially the same pattern emerged in the sensitivity analysis when the subjects with nonqualifying BMIs (N = 1448; 7.9% of the total sample) were excluded from the analysis (Table 3).

DISCUSSION

The NHIS data suggested that noninstitutionalized women with schizophrenia were, on average, more likely to be overweight than women without schizophrenia. Moreover, each decile of the BMI distribution for women with schizophrenia was higher than the corresponding decile for women without schizophrenia. This suggests that, on average, noninstitutionalized women with schizophrenia are more overweight than women without schizophrenia and that there is no evidence of a subpopulation of unusually thin or undernourished individuals with schizophrenia beyond that which would be expected in the general population. In contrast, among the men, there was little difference (if any) in BMI between those with and without schizophrenia and also no evidence of an unusual frequency of underweight. The reasons for the gender difference observed with respect to the NHIS data are unclear. We can speculate, however, that differences in hormone levels might partially account for the differences observed. That is, sex hormones (e.g., prolactin) may moderate the effect of antipsychotic agents on body weight.[16]

The results from the comparison of the ziprasidone and NHANES III data sets showed no difference in age-adjusted BMI between women with schizophrenia and women in the general population. However, these analyses were consistent with the NHIS in that women with schizophrenia were no thinner than women without

Figure 2. Age-Adjusted BMI Distributions Among Schizophrenic and Nonschizophrenic Individuals in the Ziprasidone and NHANES III Samples

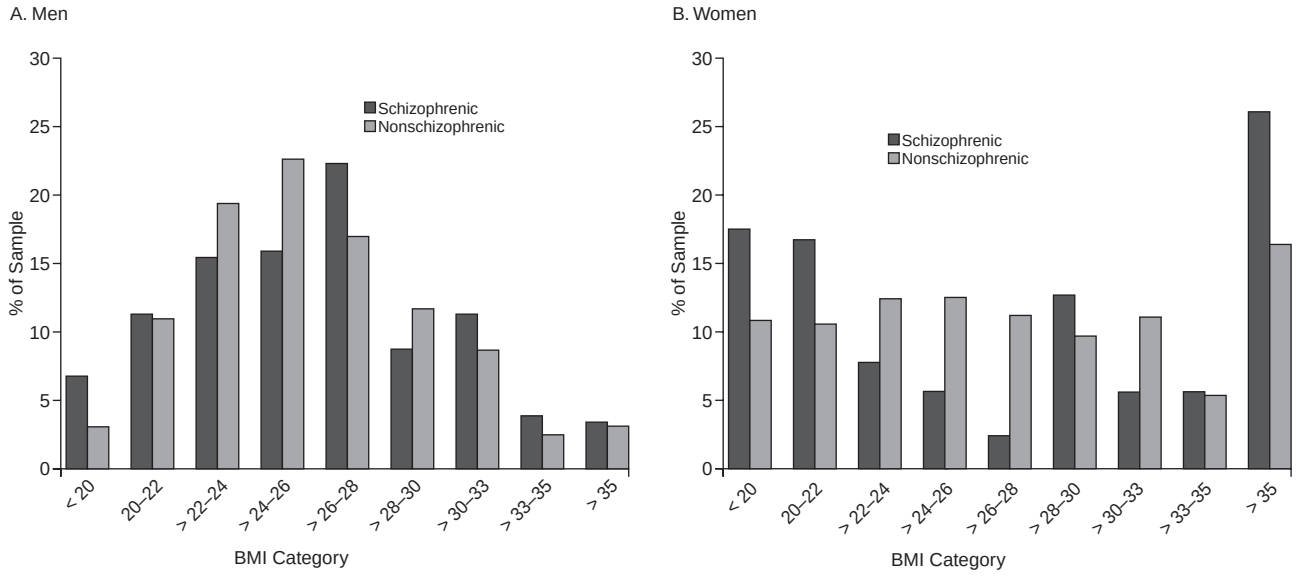


Table 3. Comparison of the Age-Adjusted BMI Distributions of Schizophrenic and Nonschizophrenic Men and Women in the Ziprasidone and NHANES III Samples Excluding Nonqualifying BMIs[a]

	Men			Women		
BMI	Ziprasidone (N = 281)	NHANES III (N = 7693)	p Value	Ziprasidone (N = 126)	NHANES III (N = 8561)	p Value
Mean	26.72	26.52	.519[b]	27.60	27.39	.757[c]
Standard deviation	5.25	4.89	.051[d]	7.68	6.54	.000[e]
Percentile						
10th	20.30	21.01	.192	18.11	20.08	.096
20th	21.85	22.58	.108	20.50	21.83	.176
30th	23.52	23.70	.668	21.44	23.35	.035
40th	24.85	24.73	.766	23.00	24.72	.049
50th	26.57	25.77	.048	27.44	26.23	.160
60th	27.73	26.95	.053	28.93	27.85	.216
70th	28.61	28.32	.489	32.98	29.79	.000
80th	30.44	30.01	.344	35.46	32.45	.002
90th	33.98	32.81	.032	37.62	36.38	.292

[a]The p values for the difference between the groups' percentiles are based on the Bahadur large sample approximation (Cox and Hinkley[15]).
[b]t = 644, df = 7972. Based on t test with the Welch approximation which does not assume homogeneity of variance when comparing the means of 2 distributions.[13]
[c]t = .311, df = 127.6. See footnote b for description of t test.
[d]Based on the Levene test for equality of variances.[14] The null hypothesis is that the variance (or standard deviation) of age-adjusted BMI groups is the same; the alternative is that the variances are different.
[e]F = 17.05. See footnote d for description of F test.

schizophrenia. As with the NHIS results, among men, there were no notable differences in age-adjusted BMI between individuals with and without schizophrenia. The reasons why we observed a significant difference in age-adjusted BMI among women in the NHIS but not the ziprasidone/NHANES III comparison are unclear. One possible explanation is that height and weight data in the NHIS were self-reported and not obtained by measurement as they were in the ziprasidone/NHANES III data sets. In addition, restrictions on the enrollment of women of childbearing potential, as well as the exclusion of individuals with significant cardiovascular disease or uncontrolled hypertension and those being treated with other psychotropic agents (including those sometimes associated with weight gain, such as tricyclic antidepressants, lithium, and valproic acid), may have introduced a relative bias favoring the inclusion of patients with lower body weight in the ziprasidone data set.

It is important to point out that, regardless of which sex and data set are considered, overall, the BMI distributions

of individuals with schizophrenia were generally consistent with the BMI distributions of modern, developed societies. That is, the mean BMIs were rather high, and a substantial proportion of the population appeared to be obese.

A related limitation is that in no case did we have a sample of individuals with schizophrenia that was at once large, nationally representative, and in which height and weight were measured rather than self-reported. This may limit the generalizability somewhat. We did have, however, one sample that was large and based on measured heights and weights (the ziprasidone trial) and another that was nationally representative (the NHIS subjects). However, certain groups of schizophrenic individuals (e.g., the homeless) were not represented in our data sets, thereby limiting the generalizability of our findings relative to such groups. By the same token, the incidence of self-reported schizophrenia in the NHIS subjects (0.2%) was lower than expected, suggesting that some underreporting may have influenced our findings somewhat. The shortcoming inherent in self-report surveys is one of the reasons that we used additional data sets to address the research question. The ziprasidone trial had strict inclusion criteria with respect to the diagnosis of schizophrenia, as well as measured height and weight. The NHANES III included measured height and weight. The overall consistency between the 2 sets of analyses suggests that problems associated with self-report data did not invalidate the results derived from the NHIS.

Moreover, although the exclusion criteria for the ziprasidone study included being treated with other psychotropic medications sometimes associated with weight gain, we have no way of determining the duration of prior treatment. By the same token, current medication or treatment duration of the schizophrenic persons from the NHIS was not investigated. Again, despite these limitations, there was an overall similarity in the results obtained between the 2 sets of analyses.

In sum, these data suggest that the distribution of BMI among individuals with schizophrenia is characterized by being too high for the most part rather than too low. Although there are clearly some individuals with schizophrenia from the measured ziprasidone data set who have a degree of underweight that may be unhealthy, as with the rest of the population, they are the exception. That is, average weight to overweight is the rule. This suggests that the weight gain observed with many antipsychotic agents[1] is potentially both a clinical and a public health concern.

An important clinical implication of these findings is that the often substantial weight gain associated with the otherwise remarkably beneficial antipsychotic medications in common use is not to be dismissed. We find little support for the proposition that many individuals with schizophrenia are too thin, and thus weight gain is a desirable side effect of neuroleptic treatment. Rather, our findings, coupled with the well-documented adverse health effects of weight gain and obesity, suggest that the weight gain associated with the use of currently available neuroleptics is not merely a clinical concern for the individual patient, but a broader public health concern as well. This fact underscores the need for antipsychotic medications with little propensity to cause weight gain.

Drug name: valproic acid (Depakene and others).

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