Obesity, Dyslipidemia, and Diabetes With Selective Serotonin Reuptake Inhibitors: The Hordaland Health Study

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Objective: This study aimed to examine whether subjects taking selective serotonin reuptake inhibitors (SSRIs) are more likely to have elements of the metabolic syndrome compared with those taking no psychotropic drugs. For comparison, we also studied subjects taking antipsychotic drugs.

Method: We used data from The Hordaland Health Study '97–'99, a general community cross-sectional health survey including 25,315 subjects aged 40 to 49 and 70 to 74 years. For the groups studied, we estimated prevalence and odds ratios (ORs) for obesity, hypercholesterolemia, low high-density lipoprotein cholesterol, hypertriglyceridemia, and diabetes.

Results: We observed an association between use of SSRIs as a group (N = 461) and abdominal obesity (OR = 1.40, 95% CI = 1.08 to 1.81) and hypercholesterolemia (OR = 1.36, 95% CI = 1.07 to 1.73) after adjusting for multiple possible confounders. There was also a trend toward an association between SSRI use and diabetes. In a subgroup analysis of subjects taking SSRIs, the use of paroxetine (N = 187) was markedly associated with both general and abdominal obesity but not with hypercholesterolemia. In contrast, the use of citalopram (N = 142) was not associated with any of the metabolic outcome variables, while the use of any other SSRI (sertraline, fluoxetine, or fluvoxamine) (N = 131) as a mixed subgroup was associated with both abdominal obesity and hypercholesterolemia. We also replicated the previously reported associations between use of antipsychotics and obesity and metabolic disturbances.

Conclusion: We have shown that use of at least some SSRIs is associated with clinical and biochemical elements of the metabolic syndrome. Our data indicate differences in the metabolic side effect profile among various SSRI drugs, although treatment bias might have influenced these results. We suggest that patients taking SSRIs be carefully monitored for obesity and dyslipidemia.

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Tricyclic antidepressants (TCAs) were, for a long time, the cornerstone in the pharmacologic treatment of depression. After the introduction of the selective serotonin reuptake inhibitors (SSRIs) late in the 1980s, treatment with SSRIs has exceeded the use of TCAs and resulted in an increased number of prescriptions for antidepressants.[1–3] TCAs and SSRIs appear to have similar efficacy in the treatment of depression,[4] but the SSRIs have fewer anticholinergic side effects, show less toxicity, and are better tolerated than the TCAs.[5,6]

Nevertheless, there are adverse effects with use of SSRIs. Reports have suggested that long-term treatment may be associated with weight gain, sexual dysfunction, drug interactions, extrapyramidal symptoms, and discontinuation symptoms.[7–9] Since decreased appetite and weight loss are common symptoms of depression, it has been hard to establish whether treatment-associated weight gain is due to the recovery from depression or due to the pharmacologic treatment. In fact, the SSRIs were initially associated with weight loss.[9–11] In contrast, results from a randomized, double-blind trial have suggested that weight gain might be seen during long-term

Table 1. Psychotropic Drug Use According to Category: The Hordaland Health Study '97–'99

Drug Category	N
SSRIs*	
Paroxetine	187
Citalopram	143
Sertraline	77
Fluoxetine	45
Fluvoxamine	10
Antipsychotics†	
Perphenazine	41
Levomepromazine	36
Chlorpromazine	23
Chlorprothixene	23
Prochlorperazine	21
Flupenthixol	14
Zuclopenthixol	13
Clozapine/olanzapine	8
Thioridazine	8
Haloperidol	7
Risperidone	7
Periciazine	4

*Among the 461 subjects taking selective serotonin reuptake inhibitors (SSRIs) only, 1 subject took 2 SSRIs.
†Among the 179 subjects taking antipsychotics only, 22 subjects took 2 antipsychotic drugs, and 2 subjects took 3 antipsychotic drugs.

treatment with paroxetine but not with fluoxetine or sertraline.[12] Another study found no difference between fluoxetine- and placebo-treated subjects regarding weight gain during 1 year of treatment.[10] At present, it is therefore uncertain whether the use of SSRIs is associated with obesity.

When examining the actions of drug treatment, it is also important to keep in mind the possible intrinsic effects of the disorder itself. Indeed, depressive illness has been associated with various metabolic disturbances. Several studies have shown that low cholesterol levels are linked to depression,[13–15] and there are also indications that low serum levels of high-density lipoprotein (HDL) cholesterol may be associated with depression.[16,17] Subjects with obesity are more likely to have experienced depressive mood as compared with normal weight subjects.[18] Moreover, higher rates of depression have been reported in relation to various risk factors for vascular disease, such as diabetes, hypertension, and smoking,[19,20] and depression is reported to increase the risk of diabetes, probably mediated through the effect of abdominal obesity.[21]

We have used data from a large, population-based, cross-sectional health survey in Norway to investigate whether use of SSRIs as a group was associated with obesity, dyslipidemia, or diabetes. Our primary goal was to determine if the prevalence of these metabolic disturbances was increased in subjects using SSRIs, but as a secondary goal we also included a multivariate analysis to explore if there might be a causal relationship. We also examined the effects of some individual SSRI drugs.

In order to assess the validity of the study and to allow for comparisons among drug groups, we also studied participants taking antipsychotic drugs, due to the well-established association between treatment with antipsychotic drugs and metabolic disturbances.

METHOD

Study Population

The Hordaland Health Study '97–'99 (HUSK) was conducted from 1997 to 1999 as a collaboration of the National Health Screening Service in Norway, the University of Bergen, and local health services. All individuals in the Norwegian county of Hordaland who were born from 1953 through 1957 (29,400 subjects) were invited, and a total of 18,581 participated (63%). The study also included 4849 subjects born from 1950 through 1951 and 4338 subjects born from 1925 through 1927, all of whom had participated in an earlier study in 1992 to 1993. Participation rates in these groups were between 73% and 81%, in the end yielding a total of 25,315 participants. Of these, 54.1% were women, and the youngest age group (40–49 years) constituted 87.1% of the study population.

Study measurements included height, weight, waist and hip circumference, and nonfasting analyses of serum total cholesterol, HDL cholesterol, triglycerides, and glucose levels. These data were recorded as continuous variables. A questionnaire (available in Norwegian at: http://www.uib.no/isf/husk/Skjema_oversikt.htm) provided information on various health behaviors, somatic and psychiatric symptoms, and socio-demographic factors. All participants gave informed consent to participate in the HUSK study. The study protocol was approved by the Regional Ethics Committee and by the Norwegian Data Inspectorate.

Assessment of Drug Use

All participants were asked to list all medications and supplements taken on the day before they completed the questionnaire. We classified subjects according to use of an SSRI, an antipsychotic drug, or neither (Table 1). We excluded subjects taking both an SSRI and an antipsychotic drug (N = 39), subjects taking a TCA (N = 229), and subjects taking lithium (N = 61). We did not exclude subjects taking antidepressants other than TCAs and SSRIs, since these drugs constitute a pharmacologically heterogeneous group, and the results were not affected by the exclusion of these subjects. (Data not shown.)

Assessment of Metabolic Disturbances

We categorized the outcome variables as dichotomous categorical variables, with previously defined cutoff levels. We used a cutoff level for general obesity of body mass index (BMI) ≥ 30 kg/m^2. Abdominal obesity was defined as waist circumference > 102 cm (40 in) for men and > 88 cm (35 in) for women, hypercholesterolemia as elevated total cholesterol level ≥ 6.2 mmol/L (240 mg/dL),

low HDL cholesterol level as < 1.03 mmol/L (40 mg/dL) in men and < 1.29 mmol/L (50 mg/dL) in women, and elevated triglycerides level as ≥ 1.7 mmol/L (150 mg/dL). These cutoffs were adopted from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines for dyslipidemia and metabolic syndrome.[22] Diabetes was considered present if the participants self-reported having diabetes in the questionnaire, if they were under treatment with insulin or oral hypoglycemic agents, or if their measured nonfasting blood glucose levels were ≥ 11.1 mmol/L (200 mg/dL).[23]

Description of Covariates

Subjects were divided into 2 groups on the basis of age: (1) those born from 1950 through 1957 and (2) those born from 1925 through 1927. Smoking habits were categorized into never smoker, ex-smoker, and current smoker; consumption of coffee, into 0 cups/day, 1 to 5 cups/day, and > 5 cups/day; and consumption of alcohol, into 0 units/week, 1 to 3 units/week, and > 3 units/week, in which 1 unit equals approximately 12 g pure alcohol. Physical activity was reported in 3 graded categories (< 1 hour exercise/week, 1 to 3 hours exercise/week, > 3 hours exercise/week); and educational level, in 3 categories according to the highest levels of education completed (elementary school or less, high school, college/university).

We also classified subjects according to symptoms of depression and anxiety, which had been measured by the Hospital Anxiety and Depression Scale (HADS), a self-administered questionnaire with 7 items for depression (HADS-D subscale) and 7 items for anxiety (HADS-A subscale).[24] Depression was defined as a HADS-D score ≥ 8 and a HADS-A score < 8, anxiety was defined as a HADS-A score ≥ 8 and a HADS-D score < 8, and combined depression and anxiety was defined as both subscale scores ≥ 8.[25] HADS has been found to perform well in assessing depression and anxiety in psychiatric settings as well as in the general population.[25,26]

Statistical Analysis

To investigate how the covariates differed between the groups taking SSRIs and antipsychotic drugs, we compared the distribution of the covariates in each group with their distribution in the group taking no psychotropic drugs, using a χ^2 test. In addition, we compared the group taking antipsychotic drugs with that taking SSRIs. In the group taking no psychotropic drugs, we used logistic regression to study the association between all the covariates and the following outcomes: general obesity, abdominal obesity, and hypercholesterolemia.

We used logistic regression models to estimate odds ratios (ORs) with 95% CIs for the outcomes general obesity, abdominal obesity, lipid disturbances, and diabetes for subjects taking any SSRI and any antipsychotic, using subjects taking no psychotropic drugs as a reference. In a subgroup analysis, we studied the same outcome variables for subjects taking paroxetine, subjects taking citalopram, and a mixed group of subjects taking the remaining SSRIs (sertraline, fluoxetine, or fluvoxamine), with those taking no psychotropic drugs as a reference. The grouping of sertraline, fluoxetine, and fluvoxamine into 1 category was done because of low numbers (< 100) of subjects taking each of these single drugs. One subject who was taking 2 SSRIs was excluded from this subgroup analysis.

We used 2 logistic regression models. In the first multivariate model, we adjusted for age, gender, smoking habits, coffee consumption, alcohol consumption, physical exercise, educational level, psychiatric symptoms, and the use of cholesterol-lowering medications. In a second multivariate model, we also analyzed the associations between SSRI use as a group and lipid disturbances, adding BMI and waist circumference as covariates. We excluded subjects taking cholesterol-lowering medication (N = 746) from analyses in which hypercholesterolemia was the outcome variable. Smoking status, psychiatric symptoms, and coffee and alcohol consumption were coded as dummy variables.

To compare the 3 SSRI groups (paroxetine, citalopram, and mixed), we performed an additional analysis confined to the subjects taking SSRI drugs. In these analyses, we used subjects taking paroxetine as the reference group and performed a global test to assess the differences among the groups. In a post hoc comparison, we compared subjects taking citalopram and the mixed group with those taking paroxetine.

We used Stata software version 8.0 (StataCorp, College Station, Tex.) for the statistical analyses.

As an internal quality control procedure, we performed 2 independent analyses of all major results.

RESULTS

Table 2 shows the unadjusted prevalence rates of the demographic and clinical variables by drug group. The proportion of women was higher among subjects taking SSRIs as compared with the proportion among subjects taking no psychotropic drugs. The covariates included in the multivariate models were all significantly associated with 1 or more of the outcome variables in the group taking no psychotropic drugs (Table 3). We obtained similar results for subjects taking SSRIs and antipsychotic drugs. (Data not shown.)

SSRI Use

A total of 461 subjects (1.8%) reported taking an SSRI without the concomitant use of a TCA, an antipsychotic drug, or lithium. Paroxetine and citalopram were the 2 most frequently used SSRIs (Table 1). The prevalence of

Table 2. Psychotropic Drug Use According to Demographic and Clinical Variables: The Hordaland Health Study '97–'99

Variable	Subjects Taking No Psychotropic Drugs	Subjects Taking SSRIs	Subjects Taking Antipsychotics
Sex, N (%)		p < .01*	p < .01†
Men	11,436 (46.3)	113 (24.5)	72 (40.2)
Women	13,239 (53.6)	348 (75.5)	107 (59.8)
Age, N (%)		NS	p < .01*†
70–74 y	3160 (12.8)	57 (12.4)	53 (29.6)
40–49 y	21,515 (87.2)	404 (87.6)	126 (70.4)
Smoking status, N (%)		p < .01*	p < .01*
Never smoker	9274 (38.3)	154 (33.8)	70 (39.3)
Ex-smoker	6994 (28.9)	96 (21.1)	28 (15.7)
Current smoker	7954 (32.8)	205 (45.1)	80 (44.9)
Coffee consumption, N (%)		NS	NS
0 cups/d	2591 (10.7)	57 (12.7)	13 (7.5)
0–5 cups/d	15,514 (64.2)	278 (62.1)	112 (64.4)
> 5 cups/d	6051 (25.0)	113 (25.2)	49 (28.2)
Alcohol consumption, N (%)‡		p < .01*	p < .01*
0 units/wk	6660 (27.0)	184 (40.0)	88 (49.2)
0–3 units/wk	10,080 (40.9)	139 (30.2)	43 (24.0)
> 3 units/wk	7935 (32.2)	138 (29.9)	48 (26.8)
Physical exercise last year, N (%)		p < .01*	p < .01*
< 1 h/wk	13,791 (58.8)	290 (67.0)	128 (77.6)
1–3 h/wk	6487 (27.6)	90 (20.8)	29 (17.6)
> 3 h/wk	3187 (13.6)	53 (12.2)	8 (4.8)
Educational level, N (%)		p < .01*	p < .01*†
Elementary school	5127 (21.3)	145 (32.2)	77 (45.0)
High school	10,867 (45.1)	177 (39.2)	65 (38.0)
University/college	8126 (33.7)	129 (28.6)	29 (17.0)
Psychiatric symptoms, N (%)		p < .01*	p < .01*†
None	16,837 (80.1)	156 (39.6)	80 (55.2)
Depression	751 (3.6)	21 (5.3)	11 (7.6)
Anxiety	2302 (11.0)	99 (25.1)	26 (17.9)
Comorbid depression and anxiety	1128 (5.4)	118 (29.9)	28 (19.3)
Use of cholesterol-lowering drugs, N (%)		NS	NS
Yes	703 (2.8)	21 (4.6)	9 (5.0)
No	23,972 (97.2)	440 (95.4)	170 (95.0)

*Compared with subjects taking no psychotropic drugs, using a χ^2 test.
†Compared with subjects taking SSRIs, using a χ^2 test.
‡One unit ≈ 12 g pure alcohol.
Abbreviations: NS = nonsignificant, SSRI = selective serotonin reuptake inhibitor.

abdominal obesity was 24.8% in subjects taking SSRIs compared with 15.8% in those taking no psychotropic drugs (Table 4). The prevalence of general obesity (15.7% vs. 11.2% in nonusers) and hypercholesterolemia (32.6% vs. 27.9% in nonusers) was also elevated in the group of subjects taking SSRIs. A total of 7.2% of subjects taking SSRIs had both general obesity and hypercholesterolemia, while 11.4% had both abdominal obesity and hypercholesterolemia.

In the first multivariate model, we found that the associations between the use of SSRIs and general obesity, abdominal obesity, and hypercholesterolemia were significant (Table 4). There was also a trend in the data toward an association between SSRI use and diabetes, although the number of diabetic subjects was notably low.

When separately analyzing the 2 age groups of younger and older subjects, we found that, for subjects aged 40 to 49 years, the associations were strengthened between SSRI use and general obesity (OR = 1.50, 95% CI = 1.10 to 2.06, p = .011), abdominal obesity (OR = 1.61, 95% CI = 1.23 to 2.11, p < .001), and hypercholesterolemia (OR = 1.45, 95% CI = 1.13 to 1.87, p = .004). For subjects aged 70 to 74 years, there was only a weak, nonsignificant trend toward higher prevalence of general obesity, abdominal obesity, and hypercholesterolemia in the subjects taking SSRIs, while we found no significant associations between SSRI use and metabolic disturbances after adjusting for potential confounding factors. The gender-stratified results did not differ from the results obtained in the main model. (Data not shown.)

We also analyzed the associations between SSRI use and lipid disturbances in a second multivariate model adding BMI and waist circumference as covariates. The association between SSRI use and hypercholesterolemia was minimally altered by this approach (OR = 1.29, 95% CI = 1.01 to 1.62, p = .041), while the association with hypertriglyceridemia and low HDL cholesterol remained insignificant.

Table 3. The Associations Between Covariates and General Obesity, Abdominal Obesity, and Hypercholesterolemia in Subjects Taking No Psychotropic Drugs: The Hordaland Health Study '97–'99

	Odds Ratio (95% CI)*		
Covariate	General Obesity†	Abdominal Obesity‡	Hypercholesterolemia§
Sex			
Male	1	1	1
Female	0.79 (0.72 to 0.87)	1.43 (1.31 to 1.56)	0.68 (0.63 to 0.73)
Age group			
70–74 y	1	1	1
40–49 y	1.08 (0.93 to 1.25)	0.60 (0.53 to 0.67)	0.25 (0.23 to 0.28)
Smoking status			
Never smoker	1	1	1
Ex-smoker	0.99 (0.90 to 1.09)	1.08 (0.99 to 1.17)	1.04 (0.97 to 1.11)
Current smoker	0.70 (0.63 to 0.77)	0.75 (0.69 to 0.82)	1.13 (1.06 to 1.21)
Coffee consumption			
0 cups/d	1	1	1
1–5 cups/d	0.75 (0.65 to 0.86)	0.80 (0.73 to 0.88)	1.24 (1.10 to 1.39)
> 5 cups/d	0.82 (0.70 to 0.97)	0.85 (0.73 to 0.98)	1.38 (1.21 to 1.58)
Alcohol consumption‖			
0 units/wk	1	1	1
1–3 units/wk	0.76 (0.68 to 0.85)	0.80 (0.73 to 0.88)	1.03 (0.95 to 1.12)
> 3 units/wk	0.78 (0.69 to 0.89)	0.91 (0.82 to 1.02)	1.16 (1.06 to 1.27)
Physical exercise¶	0.76 (0.71 to 0.82)	0.72 (0.67 to 0.76)	0.88 (0.84 to 0.93)
Education#	0.74 (0.69 to 0.79)	0.82 (0.77 to 0.86)	0.84 (0.80 to 0.88)
Psychiatric symptoms			
No symptoms	1	1	1
Depression	1.49 (1.21 to 1.84)	1.31 (1.07 to 1.60)	1.01 (0.85 to 1.21)
Anxiety	0.90 (0.76 to 1.05)	1.04 (0.91 to 1.18)	0.92 (0.82 to 1.02)
Comorbid depression and anxiety	1.27 (1.06 to 1.54)	1.21 (1.02 to 1.43)	0.92 (0.79 to 1.07)
Use of cholesterol-lowering drugs			
No	1	1	NA
Yes	1.27 (0.98 to 1.63)	1.42 (1.15 to 1.76)	NA

*The covariates in the model include age, gender, smoking habits, coffee consumption, alcohol consumption, physical exercise, educational level, anxiety, depression, and use of cholesterol-lowering medications.
†Body mass index ≥ 30 kg/m^2.
‡Waist circumference > 102 cm for men and > 88 cm for women.
§Total cholesterol ≥ 6.2 mmol/L.
‖One unit ≈ 12 g pure alcohol.
¶Odds ratios per increasing level. The levels were < 1 hour of exercise/wk, 1–3 hours of exercise/wk, and > 3 hours of exercise/wk.
#Odds ratios per increasing level. The levels were elementary school or less, high school, and college/university.
Abbreviation: NA = not applicable.

Table 4. Associations Between Psychotropic Drug Use and Obesity, Dyslipidemia, and Diabetes: Hordaland Health Study '97–'99

		Subjects Taking SSRIs				Subjects Taking Antipsychotics			
				Multivariate Model‡				Multivariate Model‡	
Variable	Subjects Taking No Psychotropic Drugs, N (%)*	N (%)*	p Value†	Odds Ratio (95% CI)	p Value	N (%)*	p Value†	Odds Ratio (95% CI)	p Value
General obesity§	2760 (11.2)	72 (15.7)	.003	1.38 (1.03 to 1.87)	.034	44 (24.6)	< .001	2.30 (1.54 to 3.46)	< .001
Abdominal obesity‖	3888 (15.8)	114 (24.8)	< .001	1.40 (1.08 to 1.81)	.011	74 (42.0)	< .001	3.36 (2.34 to 4.81)	< .001
Hypercholesterolemia¶	6870 (27.9)	150 (32.6)	.025	1.36 (1.07 to 1.73)	.012	69 (38.8)	.001	1.50 (1.03 to 2.17)	.034
Low HDL cholesterol#	9674 (39.3)	194 (42.2)	.205	0.98 (0.79 to 1.22)	.855	96 (53.6)	< .001	1.53 (1.08 to 2.18)	.018
Hypertriglyceridemia**	9296 (37.7)	169 (36.7)	.666	1.13 (0.89 to 1.42)	.308	85 (47.5)	.007	1.57 (1.09 to 2.26)	.015
Diabetes††	439 (1.8)	13 (2.8)	.098	1.43 (0.73 to 2.80)	.293	16 (9.1)	< .001	3.23 (1.61 to 6.46)	.001

*The total numbers vary slightly between the outcome variables due to missing values.
†p Value comparing the prevalence of the outcome variables in subjects taking drugs in this class versus those taking no psychotropic drugs, using a χ^2 test.
‡Adjusted for age, gender, smoking habits, coffee consumption, alcohol consumption, physical exercise, educational level, anxiety, depression, and use of cholesterol-lowering medications for all outcomes except for hypercholesterolemia, in which subjects using cholesterol-lowering medications were excluded.
§Body mass index ≥ 30 kg/m^2.
‖Waist circumference > 102 cm for men and > 88 cm for women.
¶Total cholesterol ≥ 6.2 mmol/L.
#High-density lipoprotein (HDL) cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women.
**Triglycerides ≥ 1.7 mmol/L.
††Diabetes was considered to be present if the subjects self-reported having diabetes in the questionnaire, if they were on treatment with insulin or oral hypoglycemic agents, or if their measured nonfasting blood glucose levels were ≥ 11.1 mmol/L.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 5. Associations Between Use of Various SSRIs and Obesity, Dyslipidemia, and Diabetes: Hordaland Health Study '97–'99

	Multivariate Model*	
Outcome measure	Odds Ratio (95% CI)	p Value
Paroxetine (N = 187)		
General obesity†	1.80 (1.17 to 2.77)	.007
Abdominal obesity‡	1.69 (1.16 to 2.48)	.007
Hypercholesterolemia§	1.20 (0.82 to 1.77)	.339
Low HDL cholesterol‖	1.08 (0.77 to 1.52)	.653
Hypertriglyceridemia¶	1.37 (0.96 to 1.94)	.083
Diabetes**	2.36 (1.00 to 5.60)	.051
Citalopram (N = 142)		
General obesity†	0.80 (0.42 to 1.50)	.486
Abdominal obesity‡	0.73 (0.42 to 1.26)	.255
Hypercholesterolemia§	1.27 (0.82 to 1.96)	.278
Low HDL cholesterol‖	0.92 (0.62 to 1.37)	.694
Hypertriglyceridemia¶	0.77 (0.50 to 1.20)	.245
Diabetes**	1.12 (0.34 to 3.71)	.853
Sertraline, fluoxetine, and fluvoxamine (N = 131)		
General obesity†	1.55 (0.91 to 2.63)	.104
Abdominal obesity‡	1.81 (1.15 to 2.84)	.010
Hypercholesterolemia§	1.65 (1.08 to 2.51)	.020
Low HDL cholesterol‖	0.92 (0.62 to 1.37)	.674
Hypertriglyceridemia¶	1.24 (0.82 to 1.88)	.304
Diabetes**	0.82 (0.42 to 1.60)	.568

*Adjusted for age, gender, smoking habits, coffee consumption, alcohol consumption, physical exercise, educational level, anxiety, depression, and use of cholesterol-lowering medications for all outcomes except for hypercholesterolemia, in which subjects taking cholesterol-lowering medications were excluded.
†Body mass index ≥ 30 kg/m^2.
‡Waist circumference > 102 cm for men and > 88 cm for women.
§Total cholesterol ≥ 6.2 mmol/L.
‖High-density lipoprotein (HDL) cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women.
¶Triglycerides ≥ 1.7 mmol/L.
**Diabetes was considered present if the subjects self-reported having diabetes in the questionnaire, if they were on treatment with insulin or oral hypoglycemic agents, or if their measured nonfasting blood glucose levels were ≥ 11.1 mmol/L.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Use of Various SSRIs

Differences among the various SSRIs may exist with respect to the presence of treatment-related metabolic disturbances. We therefore performed separate subgroup analyses of the outcome variables for the paroxetine group (N = 187), citalopram group (N = 142), and mixed group (sertraline, fluoxetine, or fluvoxamine, N = 131). The prevalence of general obesity was 19.3% with paroxetine use, 11.3% with citalopram use, and 15.4% in the mixed group, as compared with 11.2% in the reference group. The same pattern was found for abdominal obesity, in which the prevalence was 28.9% in the paroxetine group, 16.9% in the citalopram group, 27.1% in the mixed group, and 15.8% in the reference group. Hypercholesterolemia was equally common in the paroxetine group (33.7%) and in the mixed group (33.6%), whereas the prevalence was lower in the citalopram group (29.8%) and in the reference group (27.9%). The prevalence of diabetes was 3.8% in the paroxetine group, 2.1% in the citalopram group, 2.3% in the mixed group, and 1.8% in the reference group.

Using the first multivariate logistic regression analysis, the use of paroxetine was strongly associated with general and abdominal obesity and was borderline significantly associated with diabetes. In contrast, the use of citalopram was not associated with any of the metabolic outcome variables (Table 5). The subjects in the group taking the remaining SSRIs (mixed group) were more likely to have abdominal obesity and hypercholesterolemia than the reference group, but the numbers of subjects taking each of these drugs were too low to allow for further drug-specific analysis.

To facilitate comparison among the SSRI groups, we repeated this analysis confined to subjects taking the SSRIs, with those taking paroxetine as the reference. In the global test, the differences among the 3 SSRI groups were only significant for abdominal obesity (p = .02). Post hoc comparisons showed that the citalopram group had a lower prevalence than the paroxetine group for both abdominal obesity (OR = 0.38, 95% CI = 0.19 to 0.77, p = .007) and general obesity (OR = 0.42, 95% CI = 0.19 to 0.94, p = .035). The difference between the paroxetine and mixed group was not significant.

Antipsychotic Use

One hundred seventy-nine subjects (0.7%) reported the use of at least 1 antipsychotic drug without concomitant use of an SSRI, a TCA, or lithium. Only 8 subjects (4.4% of those taking antipsychotics only) were taking clozapine or olanzapine, which are known to be particularly prone to cause weight gain and dyslipidemia.[27] General obesity, abdominal obesity, the lipid disturbances, and diabetes all had an increased prevalence among those taking antipsychotics, and these outcomes were significantly associated with the use of antipsychotic drugs in the multivariate models as well (Table 4). These results were not affected by subsequent exclusion of subjects taking clozapine or olanzapine. (Data not shown.)

DISCUSSION

In this large, population-based study, we found that subjects taking SSRIs as a group had a significantly increased prevalence of general obesity, abdominal obesity, and hypercholesterolemia, compared with those taking no SSRIs, TCAs, lithium, or antipsychotic drugs. The associations with general and abdominal obesity and hypercholesterolemia were significant after adjustment for age, gender, and several covariates. Since the individual SSRIs might display differences in their side effect profile, we also performed a subgroup analysis of the various SSRIs. Interestingly, paroxetine was strongly associated with general and abdominal obesity but

not significantly associated with hypercholesterolemia, whereas citalopram was associated with neither obesity nor hypercholesterolemia. In the mixed group of subjects taking sertraline, fluoxetine, or fluvoxamine, SSRI treatment was significantly associated with abdominal obesity (although to a lesser degree than for paroxetine) and with hypercholesterolemia. As expected, antipsychotic drug use had a far stronger association with most of the metabolic outcome measures than did SSRI use.

To the best of our knowledge, this study is the first to demonstrate that the use of some SSRIs is associated with both obesity and hypercholesterolemia in a general population. There have been a few clinical studies investigating the effect of long-term treatment with SSRIs on weight alone, and our finding of an association between paroxetine use and obesity is in line with the data of Fava et al.[12] reporting weight gain after 26 to 32 weeks of paroxetine treatment. In the Fava et al. study, there was no statistically significant weight gain for subjects taking fluoxetine or sertraline. We found no association between the use of citalopram and metabolic disturbances, which is in line with the results of Mackle and Kocsis.[28] We also replicated the association of antipsychotic drug treatment with metabolic disturbances, which has previously been shown in several clinical trials and in population-based studies. (For a review, see reference 29.) This replication supports the notion that our study population and methods were adequate for studying drug-associated metabolic disturbances.

The large sample size and the use of a general population make chance findings unlikely as an explanation for the results and contribute to the strength of the study. We had access to data on a large number of demographic and lifestyle factors as well as accurate information on drug use. Furthermore, the study design allowed us to examine 2 separate age groups, and we chose to include the older subjects in the analysis because antidepressants are frequently used in this age group, and biologically, our a priori hypothesis was that a drug-mediated effect on weight and lipid parameters should not be dependent on age. We found that the associations between the use of SSRIs as a group and obesity and dyslipidemia were absent in the elderly subjects. Disease-related loss of lean muscle or fat mass in elderly subjects may, however, lead to underestimation of drug effects and explain the absence of an association.[30]

Interestingly, we noticed that the association between use of SSRIs as a group and hypercholesterolemia was comparable in size to the similar association between use of antipsychotics as a group and hypercholesterolemia. In contrast, the use of antipsychotics had a stronger association with obesity, low HDL cholesterol, hypertriglyceridemia, and diabetes. This finding raises the possibility that these drugs can cause hypercholesterolemia by different mechanisms, separately from an effect mediated through weight gain, although disease-related processes may also be involved. Such a direct effect of drugs on cholesterol levels has previously been demonstrated for β-blockers, protease inhibitors, tamoxifen, and isotretinoin, among others.[31–34] Moreover, the association between SSRI use and hypercholesterolemia was minimally affected by the additional adjustment for general obesity and abdominal obesity in a multivariate analysis. With respect to possible molecular mechanisms for psychotropic drug-induced metabolic side effects, we have recently demonstrated that several antipsychotics, TCAs, and, to a lesser degree, SSRIs induce transcriptional activation of cholesterol and fatty acid biosynthesis in cultured cells.[35–37] This lipogenic effect could represent a common mechanism for explaining in part the lipid disturbances observed.

Study Limitations

The cross-sectional design of the present study limits causal inference. Thus, the psychiatric disorders or related lifestyle factors, rather than the psychotropic drugs per se, could possibly account for the obesity and dyslipidemia. Depression has indeed been associated with serum lipid disturbances, but mostly with lower serum cholesterol levels,[13–15] which is in contrast to our present findings. Also, we found that the associations remained significant after adjusting for multiple possible risk factors for obesity and lipid disturbances. These findings support the hypothesis that the use of some SSRI drugs per se, rather than the underlying psychiatric disorders, is causally associated with the observed metabolic effects.

Another limitation is that the measured lipid levels were nonfasting, due to practical issues in the study implementation. Thus, the data analysis of triglyceride levels must be interpreted with caution.

We also lacked information on the duration of the use of drugs, which may have led to inclusion of subjects who had recently commenced treatment with the drug of interest. Such a potential bias would most probably contribute to an underestimation of the true associations, since we assume that the metabolic disturbances would take some time to develop. This limitation is, however, of particular concern for the interpretation of the SSRI subgroup analysis. Paroxetine was introduced in Norway in 1993 as the second SSRI available and was the first to come into widespread use. Citalopram was introduced 2 years later, in 1995, and the HUSK survey was performed from 1997 to 1999. Thus, it is possible that subjects taking paroxetine on average had been treated for a longer period of time than the subjects taking citalopram.

Even if we cannot establish a causal relationship, we have demonstrated that subjects taking some of the SSRIs have a higher prevalence of obesity and hypercholesterolemia as compared with subjects not taking SSRIs, TCAs,

antipsychotic drugs, or lithium. According to the ATP III guidelines, every subject with elevated low-density lipoprotein or total cholesterol levels should at least be treated with lifestyle changes.[22] In total, we observed such elevated lipid levels in more than 30% of the subjects taking SSRIs or antipsychotic drugs. Lifestyle changes can be hard to implement in psychiatric patients, and the subjects are likely to have additional risk factors for cardiovascular disease, such as obesity and smoking.[38] On this background, monitoring for weight gain and dyslipidemia should be considered for patients taking SSRIs, and if such adverse effects appear, pharmacologic intervention may become necessary.

CONCLUSION

We have demonstrated that persons taking at least some SSRIs are more likely to be obese and to have hypercholesterolemia than those not taking these drugs. Still, larger and longer controlled randomized clinical trials are needed to explore a possible causal relationship between the use of individual SSRIs and obesity and lipid disturbances. In particular, the potential differences among various SSRI drugs should be investigated. At present, more attention should be drawn to the cardiovascular risk profile of SSRIs in general, and our data imply that those taking SSRIs should be carefully monitored for metabolic side effects.

Drug names: citalopram (Celexa and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), isotretinoin (Claravis, Amnesteem, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), prochlorperazine (Compazine, Compro, and others), risperidone (Risperdal and others), sertraline (Zoloft and others), tamoxifen (Soltamox, Nolvadex, and others).

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