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Weight Gain and 10-Year Cardiovascular Risk With Sustained Tobacco Abstinence in Smokers With Serious Mental Illness: A Subgroup Analysis of a Randomized Trial

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ABSTRACT

Objective: People with serious mental illness die earlier than those without mental illness, largely from cardiovascular disease due to high rates of smoking and obesity. The objective of this study was to determine whether the metabolic effects of postcessation weight gain among smokers with serious mental illness attenuated the cardiovascular benefit of tobacco abstinence.

Method: A subgroup analysis was conducted of 65 outpatient smokers with *DSM-IV* diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder from 10 community mental health centers in 6 states who enrolled between March 2008–April 2012 and completed a trial of varenicline for tobacco abstinence. The intervention included a 12-week open-label phase with varenicline followed by a 40-week randomized, placebo-controlled phase in 87 participants who achieved 12-week abstinence. Main outcome measures were smoking status and change from baseline in weight and 10-year Framingham cardiovascular risk score at end of intervention (week 52).

Results: At week 52, 65 participants completed follow-up (33 abstinent; 32 relapsed). At baseline, the 2 groups did not differ in body mass index (mean = 31 kg/m^2), blood pressure, serum glucose, or diagnoses of diabetes (31%) and hypertension (34%). Abstinent participants were older and had a higher mean baseline Framingham risk score (14.2% vs 10.3%, $P = .002$). At week 52, abstinent participants gained more weight than relapsed participants (4.8 vs 1.2 kg, $P = .048$) and, as a result of quitting smoking, had a greater reduction in Framingham risk score (−7.6% vs 0.0%, $P < .001$). There was no effect of study drug assignment on weight or Framingham risk score.

Conclusions: Sustained tobacco abstinence reduced 10-year cardiovascular risk in outpatients with serious mental illness despite significant postcessation weight gain and high prevalence of obesity, diabetes, and hypertension.

Trial Registration: Clinicaltrials.gov identifier: NCT00621777

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Adults with serious mental illness in the United States have a life expectancy that is up to 25 years shorter than those without mental illness, primarily due to cardiovascular disease.[1–5] This mortality gap has been increasing in recent decades because of disproportionately high rates of tobacco use and obesity.[3] Recent estimates indicate that 44%–79% of those with schizophrenia spectrum disorders or bipolar disorder smoke tobacco regularly.[6,7] The rate of obesity among people with serious mental illness is nearly twice the rate among the general population.[8–11] The high prevalence of obesity and cardiometabolic disorders among those with mental illness is attributable to multiple factors, including antipsychotic and antidepressant medication–associated weight gain, disease-specific symptoms, unhealthy lifestyles, and problems with access and adherence to preventive and chronic disease care.[12–21] Moreover, near the time of initial psychiatric diagnosis during young adulthood, people with schizophrenia spectrum disorders have higher rates of hyperlipidemia, hypertension, and prediabetes than their counterparts without serious mental illness.[18,22] Subsequent increases in obesity and smoking following psychiatric diagnosis lead to higher rates of cardiovascular disease and mortality than in age-matched populations without mental illness.[18,19,23–26]

In the general population of smokers, tobacco cessation reduces cardiovascular mortality by approximately 50%,[27] despite a mean postcessation weight gain of 4–5 kg within 1 year of abstinence.[28] Among smokers with serious mental illness, abstinence-associated weight gain has potential to worsen already high rates of obesity, diabetes, and other cardiovascular risk factors and may attenuate the reduction in cardiovascular risk from smoking cessation.[25,29,30] In a cohort study of 3,251 individuals without mental illness, weight gain following smoking cessation did not modify the association of smoking cessation with lower risk of a cardiovascular event.[31] However, the individuals in this cohort were not obese and had low rates of diabetes, hypertension, and hyperlipidemia at baseline.

Most smoking cessation clinical trials exclude people with serious mental illness; thus, knowledge about cardiovascular risk and weight gain associated with sustained tobacco abstinence is limited.[32] To address this gap, we performed a subgroup analysis on 65 smokers with serious mental illness (schizophrenia, schizoaffective, or bipolar disorder) who completed a double-blind, randomized, placebo-controlled trial of varenicline for sustained smoking abstinence over 1 year[33] to evaluate the impact of 1-year tobacco abstinence on weight gain and 10-year Framingham cardiovascular risk score.

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METHODS

This study was approved and monitored by the institutional review boards at Massachusetts General Hospital and the 9 other study sites and by an independent data and safety monitoring board. All participants provided written informed consent, and possible side effects were fully explained. The trial is registered at Clinicaltrials.gov (identifier: NCT00621777).

Participants

Adult outpatient smokers with schizophrenia, schizoaffective, or bipolar disorder (based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria[34]) from 10 community mental health centers in 6 states enrolled in a trial of varenicline treatment for sustained tobacco abstinence between March 2008–April 2012.[33] Eligibility for the study required self-reported smoking of 10 or more cigarettes per day for at least the prior year, confirmed by expired carbon monoxide levels higher than 9 ppm; willingness to take varenicline and set a quit date; and use of a stable dose of antipsychotic (schizophrenia spectrum) or mood-stabilizing (bipolar disorder) medication for at least 30 days prior to enrollment. Participants were required to continue antipsychotic or mood-stabilizing medications throughout the trial at a dose that could be adjusted by the prescribing physician. Exclusion criteria included current suicidal or homicidal ideation, hospitalization for suicidality in the prior 12 months, other active substance use disorder, or major depressive episode in the prior 6 months.

The study design included a 12-week open-label treatment phase with varenicline and cognitive behavioral therapy (CBT) followed by a randomized, placebo-controlled maintenance treatment phase with varenicline (1.0 mg twice a day) or identical placebo added to a tapering schedule of CBT (15 one-hour sessions) over 40 weeks. At 12 weeks, those who reported not smoking for the previous 14 days, confirmed by expired carbon monoxide of less than 9 ppm, were considered to be abstinent and were eligible for the randomized maintenance phase of the study (weeks 12 to 52).

Measures

At baseline, information on demographics, psychiatric diagnoses, medical and smoking history, and concomitant medications was obtained. Each participant completed the Fagerström Test for Nicotine Dependence[35] to assess severity of nicotine dependence. As part of a smoking history questionnaire, participants rated the extent to which smoking reduced their hunger for food ("moderately" = ratings ≥ 4 on a 7-point scale), their recall of increased eating during previous quit attempts (yes/no), their belief about how much quitting smoking would improve their health ("very much" = ratings of ≥ 8 on a 10-point scale), and their concern about the possibility of weight gain if they stopped smoking ("concerned" = ratings of ≥ 8 on a 10-point scale).[36] Height and weight were measured at baseline, and weight was subsequently measured at 14 follow-up visits. Serum was collected at baseline and week 52 for measurement of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and glucose. Although participants were asked to present for serum samples in a fasting state, most had not fasted prior to the visit. A diagnosis of cardiovascular disease was made for participants who endorsed a current or past diagnosis of transient ischemic attacks, cerebral vascular accidents, stroke, angina, myocardial infarction, congestive heart failure, peripheral vascular disease, or coronary artery disease. A diabetes diagnosis was assigned for participants who endorsed a current or past history of diabetes, reported using medication to control hyperglycemia, or had a screening serum glucose level of 200 mg/dL or greater. Hypertension and hyperlipidemia diagnoses were made for participants who endorsed current or past history of high blood pressure or high cholesterol or prescription of current medication to control blood pressure or cholesterol.

A Framingham 10-year General Cardiovascular Disease (CVD) risk score[37] was calculated for each randomized participant at baseline and week 52. The risk score included gender, age, total cholesterol, HDL, and systolic blood pressure, as well as yes/no indicators for treatment of systolic blood pressure, diagnosis of diabetes, and smoking status. All participants were smokers at baseline. Participants were considered to be abstinent at week 52 (end of treatment) if they reported not smoking for the previous 21 days, confirmed by expired carbon monoxide of less than 9 ppm.

Analyses

All continuous outcomes, with the exception of change in Framingham risk score, were analyzed in hierarchical mixed models, in which week 52 abstinence was modeled as a between-subject effect and time as a categorical within-subject effect. The hierarchical mixed models were adjusted for site and psychiatric medication type (ie, mood stabilizers, first-generation antipsychotics, second-generation antipsychotics excluding clozapine, and clozapine) as static between-subject covariates and used antedependent covariance structures to model time covariances. Values were log-transformed when necessary to meet assumptions of normality and homogeneity of variance. Framingham risk scores were calculated only at baseline and week 52, and therefore changes in this measure were analyzed without time effects. Categorical outcomes were modeled in analogous hierarchical mixed models for

Clinical Points

- High rates of smoking and obesity among people with serious mental illness are responsible for early mortality, largely due to cardiovascular disease; the extent of weight gain after smoking cessation and its impact on cardiovascular risk is unknown.
- This study demonstrates that sustained tobacco abstinence resulted in substantial weight gain but a large reduction in the Framingham cardiovascular risk score.
- These results highlight the need for making treatment of tobacco use and obesity a priority for all clinicians caring for patients with serious mental illness.

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binomial outcomes and with autoregressive covariance structures for time effects. We conducted a sensitivity analysis to assess the influence of parameters other than smoking on the Framingham risk score at the end of the study by calculating a second risk score assuming all study participants were "never" smokers. Significance was reported at a 2-sided $\alpha = .05$, and means are presented as raw mean ± SD values unless otherwise noted. All analyses were performed in SAS 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

Two hundred three participants enrolled in the 12-week open-label phase of the study. Eighty-seven participants (43%) achieved 14-day point-prevalence smoking abstinence at week 12 and were enrolled in the 40-week double-blind, placebo-controlled maintenance phase (40 received varenicline, and 47 received placebo). Sixty-five participants (75%) completed a week 52 visit and contributed endpoint data for smoking, weight, and physiologic measurements; 22 participants did not complete the study. Of the 65 participants who completed the study, 33 (24 in the varenicline group; 9 in the placebo group) remained abstinent through week 52 ("abstinent group"), and 32 relapsed ("relapsed group").

Participants in the abstinent group were older than those who relapsed, had higher baseline rates of hyperlipidemia, and were more likely to have been assigned to varenicline than participants in the relapsed group (73% vs 28%, $P < .001$) (Table 1). Otherwise, there were no significant between-group differences in demographics, smoking characteristics, concerns about smoking-related weight gain or health risks, or baseline cardiometabolic diagnoses. Overall, 34% of participants had hypertension, 31% had diabetes, 55% had hyperlipidemia, and 13% had cardiovascular disease. Most participants (88%) had a diagnosis of schizophrenia or schizoaffective disorder, and 85% were taking a second-generation antipsychotic medication.

Participants in both groups were similarly obese at baseline, with mean body mass indices (BMIs) of 31.4 kg/m^2 in the abstinent and 31.2 kg/m^2 in the relapsed group (Table 2) (group effect: $F_{1,298} = 0.19$, $P = .66$). Those in the abstinent group had higher median baseline Framingham risk scores (14.2% vs 10.3%, group effect: $F_{1,50} = 10.48$, $P = .002$) and higher serum glucose levels at baseline (98 vs 89 mg/dL, group effect: $F_{1,228} = 7.34$, $P = .007$) than those in the relapsed group, but there were no significant between-group differences in blood pressure, triglycerides, or other lipid measurements. Those who did not complete the 40-week randomized phase of the trial (n = 22) did not differ in baseline characteristics from participants who completed the study (N = 65); 32% of those who did not complete the study had been assigned to varenicline and 68% to placebo (data not shown).

Table 1. Baseline Characteristics by Smoking Status Achieved at Week 52

Characteristic	Total (N = 65)	Relapsed at Week 52 (n = 32)	Abstinent at Week 52 (n = 33)
Demographics			
Age, mean (SD), y	49.1 (10.0)	46.4 (10.4)	51.8 (9.0)*
Female, n (%)	24 (37)	14 (44)	10 (30)
Race, n (%)			
White	48 (74)	23 (72)	25 (76)
Black	12 (19)	6 (19)	6 (18)
Other	5 (8)	3 (9)	2 (6)
Hispanic ethnicity, n (%)	2 (3)	1 (3)	1 (3)
Less than high school education, n (%)[a]	14 (22)	6 (19)	8 (24)
On disability, n (%)	36 (55)	17 (53)	19 (58)
Smoking characteristics			
Expired carbon monoxide, median [IQR], ppm[a,b]	16 [10, 24]	16 [10, 24]	15 [10, 24]
Cigarettes per day, median [IQR][b]	20 [14, 20]	20 [15, 23]	16 [12, 20]
FTND score, mean (SD)[c]	5.9 (2.0)	5.9 (2.0)	6.0 (1.9)
Smoking moderately reduces hunger, n (%)	36 (55)	17 (53)	19 (58)
Increased eating when not smoking, n (%)[a]	42 (67)	19 (59)	23 (74)
Thinks quitting will improve health very much, n (%)	54 (83)	26 (81)	28 (85)
Concerned about gaining weight with quitting, n (%)	26 (40)	13 (41)	13 (39)
Cardiometabolic diagnoses			
Hypertension, n (%)[a]	22 (34)	8 (25)	14 (44)
Diabetes, n (%)[a]	20 (31)	10 (31)	10 (31)
Hyperlipidemia, n (%)[a]	35 (55)	13 (41)	22 (69)*
Cardiovascular disease, n (%)[a]	8 (13)	5 (16)	3 (10)
Psychiatric diagnoses			
Schizophrenia or schizoaffective disorder, n (%)	57 (88)	27 (84)	30 (91)
Bipolar disorder, n (%)	8 (12)	5 (16)	3 (9)
Psychiatric medications			
First-generation antipsychotic, n (%)	8 (12)	4 (13)	4 (12)
Second-generation antipsychotic, n (%)	55 (85)	27 (84)	28 (85)
Assigned to study drug (varenicline), n (%)	33 (51)	9 (28)	24 (73)**

[a]Data for education and expired carbon monoxide available for 63 subjects (31 relapsed, 33 abstinent); data for increased eating available for 63 subjects (32 relapsed, 32 abstinent); data for cardiovascular disease available for 62 subjects (31 relapsed, 31 abstinent); data for hypertension, diabetes, and hyperlipidemia diagnoses available for 64 subjects (32 relapsed, 32 abstinent).
[b]Log-transformed for comparison of relapsed and abstinent groups.
[c]Total score 0–10; higher score indicates higher nicotine dependence.[35]
*$P < .05$ for comparison of relapsed and abstinent groups.
**$P < .001$ for comparison of relapsed and abstinent groups.
Abbreviations: FTND = Fagerström Test for Nicotine Dependence, IQR = interquartile range.

Effect of Sustained Abstinence on Weight

The mean change in weight at the end of the 12-week open phase did not differ between the abstinent and relapsed groups (2.8 ± 3.8 vs 2.2 ± 4.3 kg, group effect at week 12: $F_{1,235} = 0.00$, $P = .97$). At week 52, mean weight gain was greater in the abstinent group than in the relapsed group (4.8 ± 6.6 kg vs 1.2 ± 6.5 kg, group effect at week 52: $F_{1,235} = 3.94$, $P = .048$) (Figure 1A). There was no effect of study drug assignment during the relapse prevention phase (varenicline or placebo) on change in weight over time (treatment effect: $F_{1,55} = 1.33$, $P = .25$; treatment-by-time interaction: $F_{1,55} = 1.15$, $P = .29$) (Figure 1B). At week 52,

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Table 2. Cardiometabolic Risk Factors Over 1 Year for Subjects Who Were Abstinent or Who Relapsed to Smoking at Week 52

Risk Factor	Week 52 Smoking Status	Baseline (N = 65; all smoking)	Week 12 (N = 65; all abstinent)	Week 52 (N = 65; 32 relapsed, 33 abstinent)	Time, *P* Value	Time × Smoking Status, *P* Value
Weight, mean (SD), kg	Relapsed	91.9 (23.4)	92.3 (24.0)	93.4 (24.4)	.05	.01
	Abstinent	95.4 (16.7)	97.7 (17.7)	100.2 (15.6)	< .001	
Weight gain > 5 kg, %	Relapsed	…	25	32	.12	.05
	Abstinent	…	23	58	.001	
Body mass index, mean (SD), kg/m^2	Relapsed	31.2 (7.2)	32.0 (7.7)	31.6 (7.5)	.05	.01
	Abstinent	31.4 (5.4)	32.3 (5.6)	33.0 (5.0)	< .001	
Systolic blood pressure, mean (SD), mm Hg	Relapsed	121 (19)	126 (18)	124 (18)	.48	.69
	Abstinent	121 (15)	128 (14)	128 (14)	.96	
Diastolic blood pressure, mean (SD), mm Hg	Relapsed	79 (14)	83 (14)	84 (13)	.26	.65
	Abstinent	80 (10)	83 (9)	83 (7)	.72	
Total cholesterol, mean (SD), mg/dL	Relapsed	185 (35)	…	173 (37)	.16	.17
	Abstinent	188 (31)	…	187 (44)	.87	
LDL cholesterol, mean (SD), mg/dL	Relapsed	107 (32)	…	95 (34)	.05	.80
	Abstinent	110 (26)	…	101 (38)	.09	
HDL cholesterol, mean (SD), mg/dL	Relapsed	47 (15)	…	46 (14)	.36	.76
	Abstinent	43 (11)	…	44 (10)	.61	
Triglycerides, median [IQR], mg/dL	Relapsed	143 [86, 251]	…	143 [112, 243]	.30	.74
	Abstinent	186 [126, 268]	…	235 [164, 301]	.13	
Serum glucose, median [IQR], mg/dL	Relapsed	89 [79, 104]	95 [87, 110]	95 [85, 118]	.05	.24
	Abstinent	98 [89, 119]	97 [87, 130]	115 [99, 145]	.004	
Framingham General CVD Risk Score, median [IQR], %	Relapsed	10.3 [5.7, 18.1]	…	9.3 [6.9, 13.6]	1.00	< .001
	Abstinent	14.2 [9.1, 26.6]	…	9.3 [6.6, 14.3]	< .001	
Framingham General CVD Risk Score if nonsmoker, median [IQR], %	Relapsed	5.5 [3.0, 9.8]	…	5.3 [3.9, 7.6]	.96	.50
	Abstinent	7.7 [5.0, 14.8]	…	9.3 [6.6, 14.3]	.36	
Weeks abstinent from smoking, mean (SD)	Relapsed	0	5.6 (2.8)	14.2 (10.6)	< .001	< .001
	Abstinent	0	6.6 (2.1)	41.0 (10.2)	< .001	

Abbreviations: CVD = cardiovascular disease, HDL = high-density lipoprotein, IQR = interquartile range, LDL = low-density lipoprotein.
Symbol: … = not applicable.

mean BMI increased more in the abstinent group than in the relapsed group (group-by-time interaction: $F_{5,298} = 3.05$, $P = .01$), and the proportion of patients who gained more than 5 kg compared to baseline increased from week 12 to week 52 in the abstinent group (23% to 58%, time effect within group: $F_{4,235} = 4.95$, $P < .001$) but not in the relapsed group (25% to 32%, time effect within group: $F_{4,235} = 1.85$, $P = .12$) (Table 2).

Effect of Sustained Abstinence on Cardiovascular Risk

Serum glucose level increased compared to baseline in both the abstinent (increase of 17 mg/dL, pairwise comparison $t_{228} = 3.21$, $P = .002$) and the relapsed groups (increase of 6 mg/dL, pairwise comparison $t_{228} = 2.86$, $P = .005$) by week 52. There were no group differences in changes (ie, group-by-time interactions) in serum glucose, blood pressure, or serum lipids (Table 2). Those in the abstinent group had a greater decrease in the Framingham risk score than those in the relapsed group (−7.6% ± 7.9% vs 0.0% ± 5.6%, $F_{1,50} = 15.49$, $P < .001$). Figure 2 shows the change in Framingham risk score for the 65 participants by their baseline Framingham risk scores, comparing abstinent versus relapsed groups (Figure 2A) and varenicline versus placebo groups (Figure 2B). On the basis of simple linear regressions of change in risk scores by baseline risk score, the Framingham risk scores decreased significantly for abstinent participants ($P < .001$) but not for relapsed participants ($P = .70$) (Figure 2A). The reduction from baseline to week 52 in Framingham risk scores was significant for participants in both the varenicline ($P < .001$) and the placebo ($P < .001$) groups (Figure 2B).

Participants were followed for an additional 12 weeks after completing the 52-week treatment phase. An analysis of the change in weight during the 12-week posttreatment follow-up phase was performed on participants who completed visits at both weeks 52 and 64. Seven participants were not included in this analysis; 6 participants who had been abstinent at week 52 subsequently relapsed and did not follow up at week 64, and 1 participant who had relapsed at week 52 became abstinent at week 64. Of the 58 participants included in this analysis, those who were abstinent at week 52 but had relapsed to smoking at week 64 (n = 10) lost weight (−2.8 ± 4.3 kg), but those who did not change smoking status from week 52 to week 64 had no significant change in weight (group effect $F_{2,49} = 5.19$, $P = .009$).

We performed a sensitivity analysis to assess the influence of nonsmoking risk factors on the Framingham risk score by assessing change in Framingham risk scores assuming that all participants (N = 65) were "never" smokers. In this analysis, there was no between-group difference in the change in the Framingham risk score from baseline to week 52 (time-by–smoking status effect, Table 2).

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Figure 1. Change in Weight Over 52 Weeks by Smoking Status and Study Drug Assignment

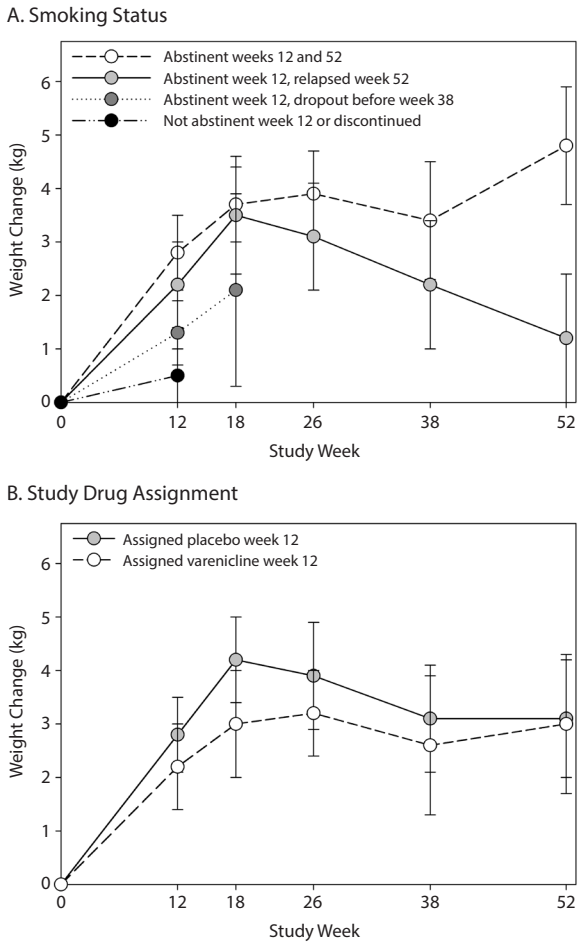
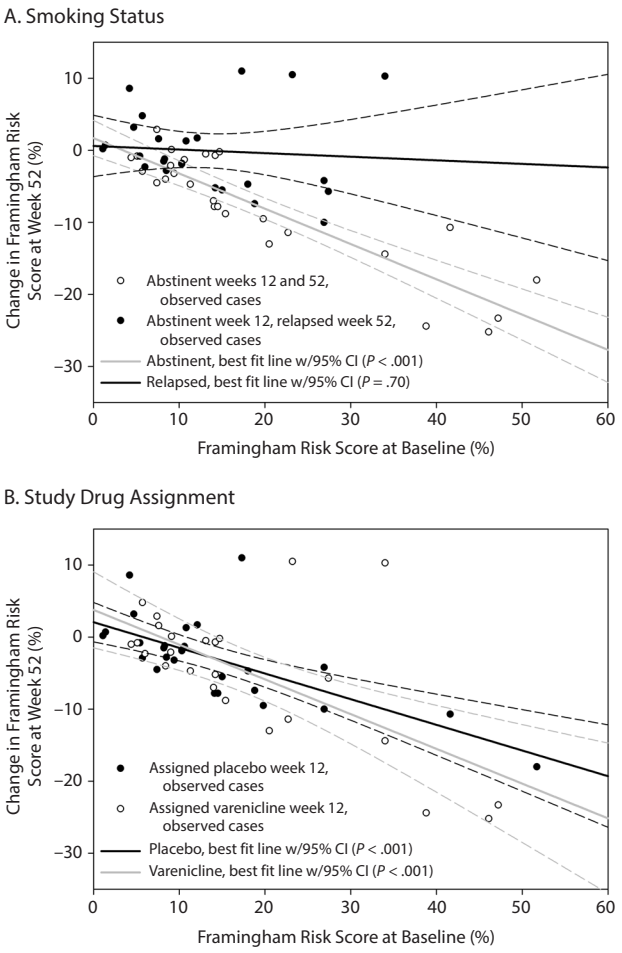


Figure 2. Change in Framingham Risk Score at 52 Weeks by Baseline Risk Score, Comparing by Smoking Status and Study Drug Assignment[a]



[a]Framingham 10-year General Cardiovascular Disease risk score was calculated for each randomized participant at baseline and week 52.[37] The risk score included gender, age, total cholesterol, high-density lipoprotein cholesterol, and systolic blood pressure, as well as yes/no indicators for treatment of systolic blood pressure, diagnosis of diabetes, and smoking status.

DISCUSSION

This is the first study to assess the impact of 1-year sustained tobacco abstinence on weight gain and cardiovascular risk among adult outpatients with serious mental illness. Despite the relatively young age of participants, one-third had diabetes, one-third had hypertension, more than half had hyperlipidemia, and the majority was obese. The study results clearly demonstrate that quitting smoking substantially reduced 10-year cardiovascular risk. However, sustained tobacco abstinence was associated with significant weight gain over 1 year. In contrast to studies of abstinence-associated weight gain among smokers in the general population, the trajectory of postcessation weight gain in this cohort of adults with serious mental illness continued throughout the 12 months of abstinence rather than stabilizing after 3 months.[28] The increases in weight that we observed among those who remained abstinent are predictive of future risk for even higher rates of diabetes, hypertension, and cardiovascular disease in the following years.

Physicians are less likely to provide pharmacotherapeutic or behavioral smoking cessation treatment to their patients who have psychiatric illnesses.[32,38,39] Although increasingly robust clinical trial evidence demonstrates safety and effectiveness of nicotine replacement therapy, bupropion, and varenicline in smokers with serious mental illness,[40–47] provider and patient concerns about adverse events and drug interactions when using pharmacotherapeutic cessation treatments in persons with psychiatric illness reduce the likelihood that smokers receive these interventions.[32,48] Most people with serious mental illness have frequent contact with the health care system and are accustomed to taking multiple medications, and, in our sample, 80% of smokers believed that quitting would improve their health "very much." These factors suggest that smokers with serious mental illness would be receptive to more widespread, long-term prescription of smoking cessation medications and that this would lead to significant reductions in tobacco use and related cardiovascular mortality in this vulnerable population.

One-year tobacco abstinence in our study was associated with an increase in mean BMI and with a large proportion

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(58%) of participants gaining more than 5 kg. Serum glucose increased in both groups, but in the abstinent group, the week 52 measurement had increased by 17 mg/dL compared to baseline. In a secondary analysis[29] of a randomized study of 5 smoking cessation pharmacotherapies in 1,504 smokers without serious mental illness, those who were abstinent for 3 years had higher weight gain, fasting serum glucose levels, and incident diabetes than continuous smokers. Another secondary analysis[30] of a randomized trial of bupropion in 392 smokers hospitalized for myocardial infarction found that those who quit gained more weight, had increased blood pressure, and required more hypoglycemic medications than continuous smokers at 1 year. These studies suggest that the higher BMI and worsening glucose levels we observed are likely to be associated with increases in diabetes and hypertension with continued abstinence in the next 3 years.

Addressing weight gain and lifestyle modification in people with serious mental illness is essential for reducing risk of cardiovascular disease.[11,25,49] However, there are several barriers for making changes in diet and physical activity, including cognitive impairment and negative symptoms, low socioeconomic status contributing to poor access to healthy foods and exercise facilities, and lack of access to organized dietary and exercise programs.[11,50,51] Lifestyle intervention trials, similar to smoking cessation trials, have typically excluded people with serious mental illness,[11] but recent randomized controlled trials have demonstrated that lifestyle interventions delivered to people with serious mental illness in the community setting resulted in weight loss,[51–53] increased fitness,[54] and decreased fasting glucose levels.[52] Another double-blind, randomized study found that 16 weeks of metformin plus diet and exercise counseling produced modest reductions in weight, triglycerides, and hemoglobin A1c among outpatients with serious mental illness.[55] Although these study interventions did not address tobacco use, adding cognitive-behavioral smoking counseling and other tobacco treatment to individual and group-based diet and exercise interventions could lead to more significant improvements in cardiovascular risk, and an exercise component could help promote tobacco cessation as well as weight loss.[56–58]

This study has limitations. The trial was not designed to detect differences in weight and cardiovascular risk, although these outcomes were defined a priori for secondary analyses. Approximately 25% of participants enrolled in the randomized phase did not complete 1-year follow-up and were not included in this study. However, there were no differences detected between those who did and did not complete the study in baseline demographics, cardiovascular risk factors, or psychiatric diagnoses. Sixty-eight percent who did not complete follow-up had been assigned to placebo, and a majority who discontinued the study did so because they had relapsed. Participants in the abstinent group were older than those in the relapsed group, and this contributed to baseline differences in Framingham risk score. However, the difference in age did not influence the benefit of quitting smoking, as demonstrated in the sensitivity analysis of the Framingham risk score that assumed all participants were "never" smokers.

The results of this study highlight the urgent need for better treatment for tobacco use and obesity among adults with serious mental illness in order to reduce the wide disparity in cardiovascular mortality compared to the general population. Unfortunately, the current health delivery model for people with serious mental illness segregates behavioral and medical care, and this creates significant barriers for providing effective and sustainable treatments for smoking and lifestyle modification.[49,59] Future efforts to deliver integrated behavioral and medical care will be critical to address unhealthy lifestyle behaviors in the context of complex medical and psychiatric diagnoses.

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Drug names: bupropion (Zyban and others), clozapine (Clozaril, FazaClo, and others), varenicline (Chantix).

Potential conflicts of interest: **Dr Achtyes** is an employee of Pine Rest Christian Mental Health Services and Michigan State University and consults for Cherry Health and Network180, all in Grand Rapids, Michigan; he has also received research funding from Otsuka, Vanguard Research Group, National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism, Centers for Medicare and Medicaid Services, and National Institute of Mental Health. **Dr Evins** has served as a consultant for Pfizer and has received research support from Pfizer and Forum Pharma. The remaining authors have no competing interests to disclose.

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