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Original investigation

Differential Efficacy of Nicotine Replacement Among Overweight and Obese Women Smokers

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Abstract

Introduction: Rates of obesity are higher among more dependent smokers and 37%–65% of smokers seeking cessation treatment are overweight or obese. Overweight or obese smokers may possess metabolic and neurobiological features that contribute to difficulty achieving cessation using front-line nicotine replacement products. Attention to factors that facilitate effective cessation treatment in this vulnerable population is needed to significantly reduce mortality risk among overweight and obese smokers.

Method: This secondary analysis of 2 large trials of transdermal nicotine replacement in general medical practices evaluated the hypothesis that higher body mass index (BMI) would moderate the efficacy of the nicotine patch. We examined the potential for gender to further moderate the relationship between BMI and treatment efficacy.

Results: In the placebo controlled trial (N = 1,621), 21-mg patch was no more effective than placebo for assisting biochemically verified point prevalence abstinence up to 1 year after quitting for women with higher BMI, but appeared to be effective for men at normal or high BMI (gender × BMI beta = –0.22, p = .004). We did not find differential long-term cessation outcomes among male or female smokers in the 15-mg patch trial (n = 705). However, we observed significantly higher rates of early lapse among women with higher BMI treated with nicotine patch across both trials.

Conclusion: These results suggest that increased BMI may affect the efficacy of nicotine patch on reducing risk of early lapse in women. Additional research is needed to explore mechanisms of risk for decreased efficacy of this commonly used cessation aid.

Introduction

Tobacco use continues as the leading cause of premature death worldwide, killing 6 million people each year.[1] Tobacco related impact on morbidity is compounded by frequent comorbid health conditions. Obesity is an epidemic in the United Kingdom and United States and adds to health problems experienced by tobacco users.[2] Both obesity and tobacco use are associated with increased risk of cardiovascular disease, pulmonary disease, diabetes,[3] reduced health-related quality of life, and increased health care and medication spending.[4] Although smoking has been associated with lower body weight, rates of obesity are higher among heavier smokers[5] and 37%–65% of smokers seeking cessation treatment are overweight or obese.[6] Attention to factors that may facilitate effective cessation treatment in this vulnerable population is needed to significantly reduce mortality risk among overweight and obese smokers.[7]

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In both the United Kingdom and United States, nicotine replacement therapy (NRT) has consistently been the most frequently used cessation aid, with 43% of UK smokers[8] and 32% of US smokers[9] using NRT products when making quit attempts. However, few studies have examined the impact of obesity on the efficacy of NRT. Persistent tobacco and obesity may arise from shared etiology. For example, differential metabolism of nicotine[10] has been linked both with heavy smoking and adiposity.[11] Disruptions in emotion regulation[12] and reward system function[13] both promote obesity and tobacco use. These co-occurring risks may suggest candidate pathways for differential response to NRT among overweight and obese smokers.

NRT products are designed to promote cessation by ameliorating nicotine-withdrawal symptoms such as craving, negative affect,[14] and changes in brain reward systems that may affect the hedonic value of tobacco use.[15] Evaluation of primary mechanisms suggest NRT's ability to promote abstinence can in part be explained by NRT's effect on lowering craving during early abstinence.[16] NRT does not appear to prevent risk for relapse through changes in negative affect or hedonic responsiveness during early abstinence.[17]

Direct examination of response to NRT among overweight and obese smokers is limited. Hypothesized dysfunction in reward responsiveness in obese smokers led to examination of NRT's designed to provide rapid and maximally reinforcing delivery of nicotine. When compared to the slower transdermal NRT, a rapid delivery nicotine nasal spray was more effective in promoting abstinence among obese smokers.[18] Individual differences in nicotine metabolism significantly impact effectiveness of NRT[19] and lower concentrations of nicotine with standardized dosing have been observed in obese smokers.[20] Given potential decreased nicotine delivery from nicotine patches, potential lower nicotine metabolism, and higher prevalence of vulnerabilities in hedonic responsiveness, overweight and obese smokers may evidence differential benefit from the nicotine patch. This study examines the primary hypothesis that nicotine replacement with transdermal patch will be less effective among overweight or obese smokers relative to their normal weight counterparts. We will follow examination of this primary hypothesis with exploratory analyses of the potential moderating impact of gender in two transdermal nicotine replacement trials based in UK general medical practices.

Method

Patch Trial and Patch II Study Participants

The study was a double-blinded, randomized, placebo-controlled trial of NRT patches for smoking cessation (N = 1,686). Treatment seeking heavy smokers between the ages of 25 and 65 years who smoked ≥15 cigarettes/day were recruited from 19 UK general practices in Oxfordshire and randomized into one of four equal groups to receive active NRT patch 21 mg/day in reducing doses over 12 weeks or a placebo patch, in combination with a specific Health Authority smoking cessation support booklet or a standard Health Education Authority leaflet. Abstinence at 1, 4, 8, 12, 24, and 52 weeks was assessed using self-report combined with exhaled carbon monoxide (CO) < 10 ppm to confirm abstinence since the previous visit and also with salivary cotinine ≤20 ng/ml at 24 and 52 weeks. Primary outcomes were biochemically confirmed point prevalence abstinence at each follow-up assessment. The final study sample was composed of 1,621 individuals who completed all study required baseline assessments (65/1,686, 3.9% had missing data preventing computation of body mass index [BMI]). Ethical approval was obtained from the Anglia and Oxford Multicentre Research Ethics Committee and from the 86 Local Research Ethics Committees covering the areas of residence of the patients. Details of this trial are available in the primary clinical trial outcome paper.[21]

Patch In Practice Trial Participants

This study[22] was an open-label randomized trial of behavioral support intensity for smoking cessation in smokers 18 years and older who smoked more than 10 cigarettes/day using 15-mg NRT patches (N = 925). Participants were recruited from 26 UK general practices in Oxfordshire and Buckinghamshire and randomized to one of two equal groups: Basic support (pre-cessation counseling and support visits by trial nurses in general practice surgeries at 1 and 4 weeks after the initial appointment) or weekly support (basic support plus telephone calls at 10 days and 3 weeks after the initial appointment and an additional visit at 2 weeks to motivate adherence to NRT patch and renew quit attempts). Treatment consisted of 15 mg/16 hr patches for 8 weeks. Abstinence at 1, 4, 12, 26, and 52 weeks from quit day was assessed using self-report combined with exhaled CO < 10 ppm and salivary cotinine < 15 ng/ml. Primary outcomes were biochemically confirmed sustained abstinence at each follow-up assessment. Given interest in early lapse, we did not include an additional grace period for initial abstinence as was reported in the original trial.[22] The final patch in practice (PIP) study sample was composed of 705 individuals who completed all study required baseline assessments (225/930, 25% had missing data preventing computation of BMI).

Measures

Measured domains available from both studies included (a) descriptive measures, (b) level of nicotine dependence, and (c) smoking outcomes. Participants provided background information including age, gender, height, and weight. BMI was computed by dividing the participants' weight (kg) by height^2 (m). Severity of nicotine dependence was assessed using the Horn-Russell[23] nicotine dependency scale, a nine-item measure with total scores ranging from 0 to 27, with scores >18 indicating high levels of nicotine dependence. We then examine point-prevalence abstinence at 1-, 4-, 8-, 12-, 24-, and 52-week assessments. Results from single marker genetic variants and patch response at these end points have been reported in subsamples of these data in previous publications.[21]

Statistical Analyses

We used maximum likelihood estimation of generalized linear mixed effects logit models (GLMM) when model repeated binary smoking outcomes that were biochemically verified self-reports of abstinence at 1, 4, 8, 12, 24, and 52 weeks after quit day. In this intention to treat (ITT) analysis, all assessments falling above established CO threshold (>8 ppm) and unobserved assessments were considered smoking in all analyses. We included a random effect for participants repeated assessments and fixed effects for age, gender, level of nicotine dependence, and the effect of time as planned covariates in all analyses. Models were evaluated using a likelihood ratio test for the inclusion of terms reflecting: (a) time as a categorical set of indicators using the end of treatment at week 12 as a reference; (b) time as a linear trend; or (c) time with both linear and quadratic time centered to reflect difference in the rate of change in abstinence from within treatment to long-term follow-up. We assessed

our primary moderation hypothesis using an interaction of baseline BMI and treatment assignment in primary outcome assessments. We followed primary hypothesis tests with exploration of gender as a further moderating effect of the relationship between BMI and treatment assignment. Analyses of the PIP trial with GLMM included planned covariates and follow-up assessments at 1, 4, 8, 12, 26, and 52 weeks. Moderation hypotheses were evaluated with interaction terms of baseline BMI and gender. All statistical analyses, tables, and figures were generated using R statistical software (http://www.r-project.org/) using packages rms,[24] LME4,[25] and ggplot2.[26]

Results

Participant Characteristics

In the patch trial there were 1,621 participants with complete baseline characteristics for analysis. We omit 65 cases from the ITT sample of 1,686 given missing information on baseline height or weight. Baseline characteristics (sex, age, BMI) were similar across active and placebo treatment groups (Table 1). The sample was 59% female (n = 447), mean age of 43 (SD = 10) and mean Horn-Russell[23] nicotine dependency score of 15 (SD = 5). Rates of overweight or obesity (BMI ≥ 25 kg/m^2) were higher ($X^2(1) = 9.27$, p = .002) among women (43.4%) than men (36.2%). Levels of nicotine dependence were similar for normal weight (mean = 14.8 ± 4.6) and overweight or obese (mean = 14.8 ± 4.8) smokers (p = .945). There were 807 participants randomized to active patch (50%) and 814 to placebo patch. After removing cases with missing covariates (8 in placebo, 10 in active), 1,621 in final models of point prevalence abstinence (PPA). Failure to collect BMI (n = 65, 3.9%) was more likely among women (b = –0.51, SE = 0.26, p = .046) and smokers with higher nicotine dependence (b = 0.06, SE = 0.03, p = .020) and missing BMI was unrelated to smoking outcomes at the end of treatment (p = .16). Adherence to patch treatment as evidenced by the return of a used product at the 12-week assessment (43%) was not significantly related to level of BMI (b = 0.01, SE = 0.02, p = .69). Rates of response to follow-up at the 12-week (91%) or 52-week (86%) assessments were not related to level of BMI in repeated measures GLMM (b = 0.01, SE = 0.02, p = .556).

In the PIP trial, there were 705 participants with complete baseline characteristics for analysis. We omitted 225 cases from the ITT sample of 930 given missing BMI. Rates of overweight or obesity (BMI ≥ 25) were similar ($X^2(1) = 0.12$, p = .73) for women (53.5%) and men (51.2%). Levels of nicotine dependence were similar for normal weight (mean = 5.0 ± 2.2) and overweight or obese (mean = 5.1 ± 2.2) smokers (p = .296). Failure to collect BMI was associated with higher nicotine dependence (b = 0.08, SE = 0.04, p = .048) and was not associated with demographic characteristics (p = .12) or smoking outcomes at the end of treatment (p = .80). Adherence to treatment as evidenced by self-reported use of patches (54%) at the week-4 final dispensing visit was not significantly associated with level of BMI (b = –0.07, SE = 0.15, p = .64). Levels of BMI were not significantly related (b = –0.04, SE = 0.03, p = .21) to response to follow-up (90.5%).

Abstinence Outcomes

Figure 1 displays the observed differences in rates of abstinence for normal weight (BMI < 25 kg/m^2) and overweight/obese (BMI ≥ 25 kg/m^2) men and women allocated to active or placebo patch treatment conditions in the patch trial. For demonstration purposes, we classified patch trial participants with normal weight (BMI < 25 kg/m^2, $n_{placebo}$ = 481, n_{active} = 499) and overweight or obese smokers (BMI ≥ 25 kg/m^2, $n_{placebo}$ = 333, n_{active} = 308) and present PPA for smokers allocated to active or placebo arms.

We used GLMM assess our primary hypotheses that higher BMI would be related to reduced efficacy of active compared to placebo patch, that reduced efficacy of the active patch among smokers with higher BMI may be more pronounced among women compared to men. We included planned covariates (age, sex, nicotine dependence) and treatment group assignment in all models. We found support for models using a categorical indicator, rather than linear ($X^2(4) = 236.1$, p < .001) or quadratic ($X^2(3) = 29.3$, p < .001) indicators, for abstinence over time. We observed higher rates of abstinence during treatment (effect of time at 1, 4, 8, and 12 weeks) and a stabilizing of overall rates across long-term follow-up (24- and 52-weeks). Treatment related differences in rates of PPA differed across active and placebo conditions were highest during weeks 4 and 52 and were similar across other assessment points (treatment × time interaction). We included terms in the model (effects of time × treatment) to reflect these changes in the rate of abstinence over time (p < .05). We assessed our primary moderating hypothesis by combining the treatment assignment in interaction terms with gender and BMI and examined the relationship with smoking outcomes (Table 2). For models of continuous BMI, we centered the values at a value of 25 kg/m^2, the clinical cutoff for overweight status. We observed a statistically significant interaction between BMI and gender (p = .004) but not BMI with treatment (p = .267). Both normal and overweight women and men demonstrated increased rates of verified abstinence when given active relative to placebo patch. We observed lower rates of abstinence among overweight women compared to men.

Table 1. Participant Characteristics Patch Trial

	Patch trial placebo, n = 807		Active (21-mg), n = 814		Patch in practice active (15-mg), n = 705	
	Mean	*SD*	Mean	*SD*	Mean	*SD*
Age	42.83	10.04	42.35	9.89	44.01	12.35
Female (%)	60.3%		59.7%			
Nicotine dependence	14.94[a]	4.41	14.69	4.73	5.05[b]	2.18
Body mass index (BMI)	25.09	4.32	24.68	3.94	25.95	4.8
Percent overweight or obese (BMI ≥ 25)	0.205		0.19		0.53	

[a]Nicotine dependence assessed with Horn-Russell score in patch trial.
[b]Fagerstrom Test for Nicotine Dependence in the patch in practice trial.

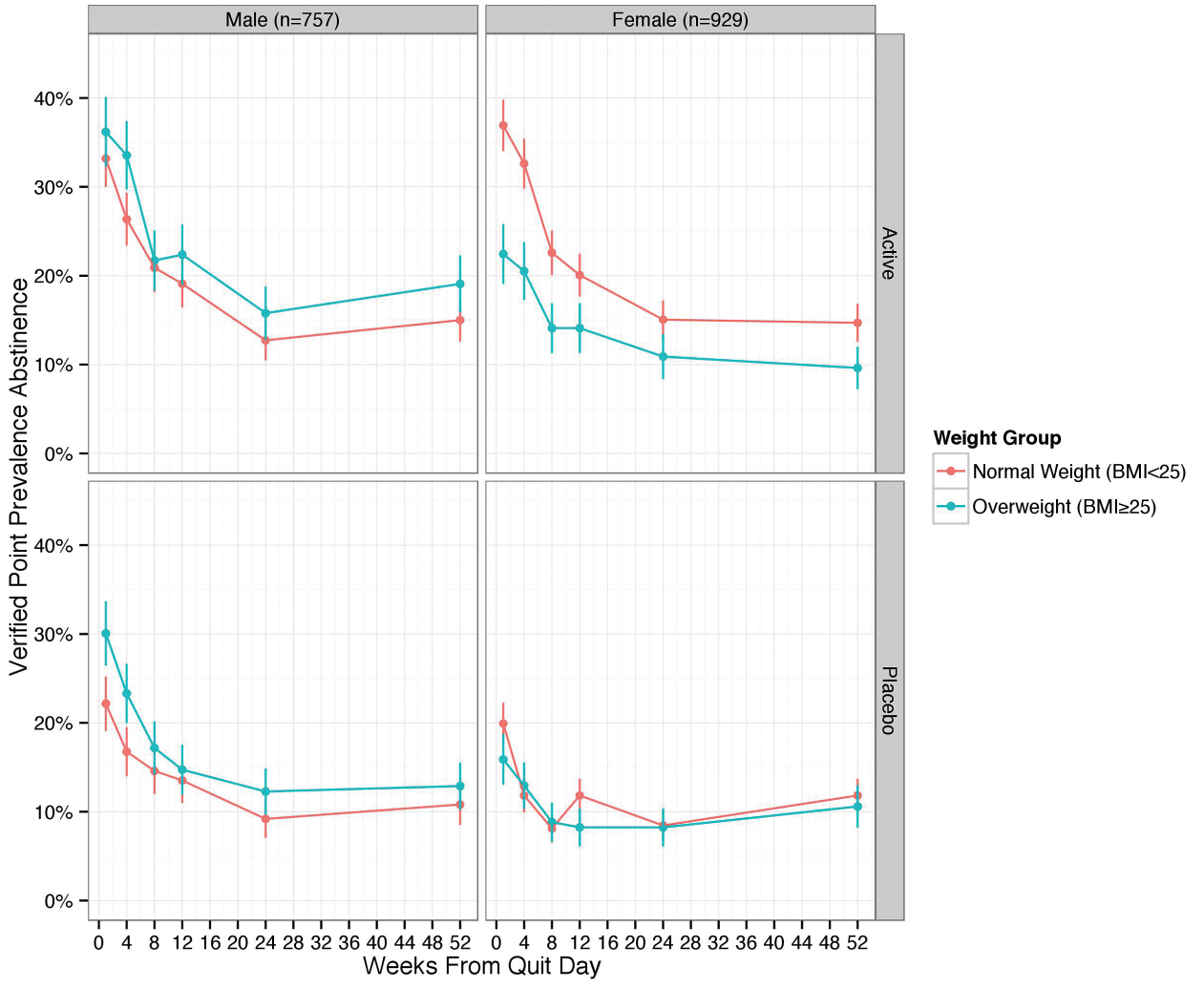

Figure 1. Rates of biochemically verified 7-day-point prevalence abstinence and standard errors at 1-, 4-, 8-, 12-, 24-, and 52-week assessments during treatment for normal weight and overweight/obese smokers receiving active or placebo patch treatment.

Table 2. Results From Generalized Linear Mixed Effects Models of Biochemically Verified Abstinence at 1, 4, 8, 12, 24, and 52 Weeks After the Assigned Quit Date in the Patch Trial

	Model of effects		
Examined variable	Beta	*SE*	*p* value
Main effects			
Horn-Russel	−0.02	0.03	.435
Sex (female)	−0.63	0.26	.015
Patch (active)	0.12	0.06	.071
Time 1 vs. 12	1.84	0.23	.000
Time 4 vs. 12	0.77	0.24	.001
Time 8 vs. 12	−0.12	0.25	.619
Time 24 vs. 12	−0.74	0.26	.005
Time 52 vs. 12	−0.12	0.25	.619
Body mass index (BMI)	0.12	0.06	.071
Two-way interactions			
Patch:time 1 vs. 12	0.05	0.30	.869
Patch:time 4 vs. 12	0.61	0.30	.047
Patch:time 8 vs. 12	0.32	0.32	.315
Patch:time 24 vs. 12	−0.22	0.34	.520
Patch:time 52 vs. 12	−0.66	0.33	.043
Sex:BMI	−0.22	0.08	.004

We hypothesized a moderating effect of BMI such that the efficacy of the active patch would be attenuated among smokers with higher BMI. For descriptive purposes, we display rates of PPA among women and men classified as normal weight and overweight or obese (Figure 1). The formal test of three-way interaction of treatment, continuous levels of BMI, and gender was not significant statistically (b = −0.18, SE = 0.15, p = .242). In post-hoc exploratory analyses, we conducted subgroup analyses within active patch and placebo patch groups. We found that the interaction term evaluating the effect of BMI on the odds of abstinence differed for women and men (BMI × gender interaction) in active (b = −0.30, SE = 0.10, p = .003) and not in placebo patch (b = −0.14, SE = 0.13, p = .29) subgroups. Among smokers who received active patch, the odds ratio was higher (OR = 1.3, 95% CI = 1.1, 1.5) for men and lower (OR = 0.7, 95% CI = 0.6, 0.9) for women who increased by one-half of a standard deviation unit on BMI (1.8 kg/m^2). Among smokers who received placebo patch, the odds ratio was 1.2 (95% CI = 1.0, 1.5) for men and 0.93 (95% CI = 0.8, 1.2) for women, suggesting no significant difference in abstinence rates for smokers who increased by one-half of a standard deviation BMI unit.

Figure 2 presents descriptive plots of observed PPA for PIP participants classified as normal (BMI < 25 kg/m^2 = 333, BMI ≥ 25 kg/m^2 = 372) and overweight/obese using baseline BMI. In GLMM models, we evaluated unconditional models with categorical, linear, and quadratic effects for time. We found support for models using categorical indicators of time (with week 12 as the reference) rather than linear ($X^2(3)$ = 109.4, p < .001) or quadratic ($X^2(2)$ = 92.3, p < .001) indicators for abstinence over time. In analyses using continuous BMI (centered at BMI = 25) along with planned covariates we again observed higher rates abstinence in 1-, 4-, and 8-week assessments compared with 12-weeks (ps < .001) and lower rates at 26- and 52-week assessments (ps < .001).

When assessing the potential moderating effect of baseline BMI on PPA we observed a significant interaction effect of continuous levels of BMI and gender (Table 3), an effect that was stronger the first week of treatment for women (gender × BMI × time interaction, p = .001). Women who were classified as overweight or obese (BMI ≥ 25 kg/m^2) lapsed earlier, with 74% smoking within the first week compared to 65% of their normal weight counterparts (BMI < 25). Also reflected in the magnitude of the gender × BMI × time interaction effects was the higher rate of abstinence at the end of treatment (week 12, p = .037) among men with lower baseline BMI. Long-term abstinence rates were similarly low (<10%) for all participants.

Discussion

This re-analysis of a randomized placebo controlled trial of the efficacy of transdermal NRT among heavy smokers confirmed our hypothesis that heavy smokers with higher BMI had higher rates of lapsing in the first week of treatment and lower rates of biochemically verified point prevalence abstinence up to 1 year after quitting. However, this result was only observed among women. In a second trial using a lower dose nicotine patch, we observed overall lower rates of abstinence and a similar pattern of early lapse and poor outcomes for women with higher BMI. In both standard and low-dose patch trials, the differential relationship between higher BMI and lower odds of abstinence was significant after adjustment for level of tobacco dependence. Although our reliance on existing trials limited our ability to evaluate proposed mechanisms to help explain the potential moderating effect of BMI on early lapse among women, this study suggests the merits of exploring mechanisms of risk for decreased efficacy of this commonly used cessation aid. Given the rising rates of obesity and that 36%–68% of smokers seeking treatment are overweight or obese, clinicians and consumers will need guidance in optimizing cessation treatment recommendations.

Why Might Overweight or Obese Women Smokers be at Risk for Early Lapse to Smoking?

Among overweight or obese women smokers in the patch trial who received active 21-mg patch, 78% were unable to obtain abstinent during the first week of cessation compared with 63% of their normal weight counterparts. We replicated this observation in the PIP trial where rates of early lapse were 74% and 65% among overweight and normal weight women receiving 15-mg active patch. We did not observe BMI-related differences in rates of early lapse among men in either trial. Men with lower BMI in the PIP trial had lower rates of lapse at the end of treatment and no differences were observed for long-term outcomes. We know that the efficacy of transdermal NRT is in part explained by a reduction in cravings after quitting. Lapse events in the week after initial cessation are strongly linked to the intensity of cravings, particularly on quit day.[16] This is a natural process to examine when exploring why overweight or obese women smokers may have higher risk for early lapse. Given

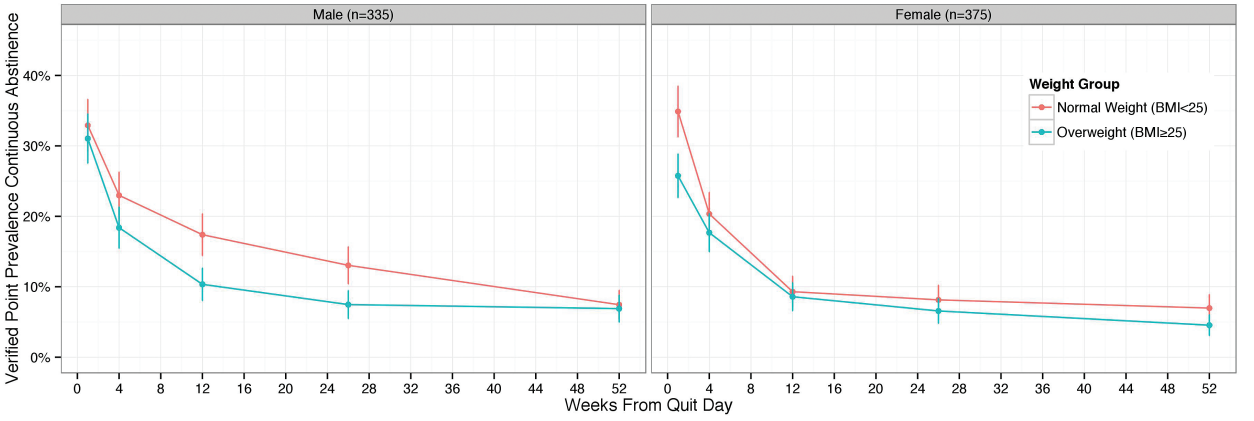

Figure 2. Rates of biochemically verified 7-day-point prevalence abstinence and standard errors at 1-, 4-, 12-, 26-, and 52-week assessments during treatment for normal weight and overweight/obese smokers receiving active patch treatment in the patch in practice trial.

Table 3. Results From Generalized Linear Mixed Effects Models of Biochemically Verified Abstinence at 1, 4, 8, 12, 24, and 52 Weeks After the Assigned Quit Date in the Patch In Practice Trial

	Model of effects		
Examined variable	**Beta**	***SE***	***p* value**
Main effects			
FTND	−1.01	0.25	.000
Sex (female)	−2.43	1.45	.093
Group (weekly)	0.06	1.07	.954
Time 1 vs. 12	7.16	0.98	.000
Time 4 vs. 12	3.42	0.72	.000
Time 26 vs. 12	−2.40	0.75	.001
Time 52 vs. 12	−4.99	1.01	.000
BMI	−0.24	0.24	.323
Two-way interactions			
Sex:time 1 vs. 12	2.34	1.27	.066
Sex:time 4 vs. 12	2.09	1.08	.053
Sex:time 26 vs. 12	1.03	1.05	.329
Sex:time 52 vs. 12	1.93	1.30	.139
BMI:time 1 vs. 12	0.40	0.20	.049
BMI:time 4 vs. 12	0.19	0.17	.270
BMI:time 26 vs. 12	0.14	0.20	.491
BMI:time 52 vs. 12	0.48	0.22	.030
Sex:BMI	0.30	0.30	.326
Three-way interactions			
Sex:BMI:time 1 vs. 12	−0.64	0.25	.011
Sex:BMI:time 4 vs. 12	−0.26	0.22	.224
Sex:BMI:time 26 vs. 12	−0.21	0.24	.393
Sex:BMI:time 52 vs. 12	−0.61	0.29	.037

BMI = body mass index; FTCD = Fagerstrom Test Nicotine Dependence. Time coded categorically with 12 week as the reference.

suggestions that higher BMI may be associated with lower circulating levels of nicotine when using transdermal NRT, obese women smokers may experience reduced control of craving and begin their quit attempts with more volatile withdrawal symptoms. With shared genetic associations between nicotine metabolism and adiposity[11] and general differences in metabolic processes, obese women smokers may also have increased likelihood of being fast metabolizers of nicotine[11] and thus may experience reduced benefit from standard dosing.[18] Exploration of different dosing and different delivery of NRT through gum, lozenge, inhaler or nasal spray may prove to increase efficacy.[27]

There may be an important link between cravings for tobacco and cravings for food that may suggest an additional risk factor that may undermine quit attempts.[28] Nicotine has effects on hedonic properties of food intake and energy expenditure that may help explain the effects of nicotine in regulating appetite and body weight.[29] Disruptions in nicotine's role in homeostatic regulation may differentially impact overweight or obese women smokers relative to their normal weight counterparts, with most notable effects during the first week of cessation when withdrawal effects are most volatile. Concerns about weight may be amplified soon after quitting and may contribute to risk for early lapse to smoking. In treatments designed to address weight concerns directly using cognitive and behavioral skills training, BMI prior to cessation remained predictive of poor smoking outcomes among weight concerned women independent of behavioral counseling.[30] Mixed results from interventions targeting weight concerns suggests the importance of alternative mechanisms of risk for relapse among smokers with higher BMI. However, few studies report differential efficacy of front-line cessation treatments among overweight or obese women smokers.

Other Front-Line Treatments Also Report Differences for Smokers With Higher BMI

In a large trial examining the effect of increasing doses of bupropion together with increasing intensities of behavioral intervention using self-help materials or telephone counseling on cessation outcomes, Swan and colleagues[31] found baseline BMI to be significantly predictive of poor outcomes among women.[31] Although this trial did not include a placebo control, results suggested BMI was an important factor explaining outcomes across examined doses of medication and intensities of behavioral intervention. However, a naturalistic study of quit line counseling using self-reported abstinence showed no significant association between baseline BMI and smoking outcomes.[32] In this observational study, rates of use of the nicotine patch were high, with 67% of overweight and obese smokers reporting using NRT during their current attempt to quit. Behavioral counseling did not improve quit rates across a range of normal, overweight, and obese smokers. These mixed results from large observational studies of behavioral and pharmacotherapy interventions may be due in part to substantial differences in follow-up rates (55% vs. 85%).

Limitations

This secondary analysis did not allow evaluation of proposed mechanism to explain disparate outcomes among women smokers with higher BMI. Future work is needed to replicate these findings in trials capable of examining mediators of treatment outcome. There remains a potential for adherence to be a factor in poorer outcomes observed among women with higher BMI. No information about weight change after cessation was available. The patch trial focused on heavier smokers in clinical settings and thus may reflect a sample with more tobacco dependence. The higher levels of tobacco use may

not represent a broader population of smokers using NRT as a cessation aid. The PIP trial was designed to be generalizable to clinical practice and included a lower smoking rate for entry into the trial. However, the lower dose of the patch limits direct comparison of outcomes across PIP and patch trials.

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Declaration of Interests

PA has done consultancy for McNeil, Pfizer, and Celtic Biotechnology and Sean David has done consultancy with Pfizer—both with regard to smoking cessation.

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