Sex differences in cigarette smoking following a mindfulness-based cessation randomized controlled trial

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Abstract

Some interventions for smoking cessation such as quit smoking aids show sex-specific effects on outcomes, but behavioral interventions such as mindfulness-based interventions (MBIs) for smoking cessation lack formal reporting of sex-intervention tests of interaction to date. To address this gap, we conducted a secondary analysis of a RCT dataset (N=213), recruiting participants from California, to statistically test a sex-intervention interaction effect on complete 7-day point prevalence abstinence (PPA), proportion of days abstinent, and daily cigarettes smoked. Smoking was assessed using the timeline follow back method spanning the four weeks following a daily 14-day app-based intervention and a planned smoking quit date immediately following the intervention phase. All models adjusted for baseline nicotine dependence. The study groups had comparable sex proportions (MBI: 56% female; control: 55% female) and the ratio of outcome assessment completion by group was not dependent on sex. Intent-to-treat analysis revealed a significant sex-intervention interaction effect for daily cigarettes smoked ([female coded 1]: two-way interaction effect IRR=0.59, 95% CI: 0.46-0.77, p<.0001; effect for female: IRR=0.68, 95% CI: 0.57-0.81, effect for male: IRR=1.14, 95% CI: 0.95-1.37), but not for complete 7-day PPA ([female coded 1] two-way interaction effect OR=1.24, 95% CI: 0.31-4.89, p=0.76) or proportion of total days abstinent ([female coded 1] two-way interaction effect OR=1.97, 95% CI: 0.53-7.37, p=0.31). Females, but not males, allocated to a daily app-based MBI with a quit plan and quit aid workbook smoke fewer cigarettes per day compared to females in the control group. Males, but not females, showed significantly less use of the MBI app compared to the control app.

Keywords: mindfulness, smoking, cessation, sex, interaction, subgroup, NCT05440903**Introduction**

Subgroup analyses of randomized controlled trials (RCTs) may play a role in discerning differences in intervention outcomes between demographic groups. Among these, an essential focus is on exploring the heterogeneity in intervention effects between males and females. (1) This investigation is pertinent due to the known hormonal, phenotypic, social, and drug response differences between sexes, which could potentially influence the direction and magnitude of effects generated by biological or behavioral interventions. (2-4) While a main effect analysis indicates an intervention's overall impact across a sample, subgroup analysis can unveil nuanced patterns, such as one sex driving the observed effect or even worsening after the intervention.

Smoking cessation is a research area where sex differences are relevant. Among the sex-intervention tests identified in the smoking cessation literature, 82 tests suggested that women were significantly less likely to quit than men while the opposite pattern was seen in only 16 tests. (5) In network meta-analyses examining intervention effects on cessation outcomes, it was also observed that females show less success at quitting than males, irrespective of treatment type (6), but the effectiveness of select pharmacotherapies is also larger for women than for men in some cases. (7) Taken together, there appears to be heterogeneity in response to smoking cessation interventions by sex and the disparity appears to vary by treatment type. Even less is known about sex-intervention interaction effects focusing on non-pharmacological interventions such as mindfulness-based interventions (MBIs).

In terms of general wellness outcomes, meta-analyses indicate that MBIs may produce the largest effect sizes in the general population, with the point estimate (Hedges' g=0.42, CI:0.29-0.55) surpassing eight other evidence-supported behavioral programs (e.g., Cognitive Behavioral Therapy, Acceptance and Commitment Therapy, and multi-component psychological and social support interventions). (8) However, there is a noticeable sex-based self-selection evident in the overall MBI literature, with females being overrepresented in most samples. For

example, a systematic review of 117 RCTs testing MBIs on a variety of outcomes, not just specific to smoking cessation, revealed that male participants constituted only 29% of the total 9,820 participants enrolled in RCTs. (9) Only 16 (14%) of those 117 RCTs reported outcomes stratified by sex. Although the review did indeed note the need for tests of sex-intervention interaction effects generated by RCTs, there was no analysis conducted in that review focusing in on the 16 studies identified as having conducted subgroup analyses.

Based on trials previously identified in published systematic reviews, (10, 11) we are aware of 16 RCTs specifically testing a MBI on smoking cessation outcomes. (12-27) See Table 1 citing these studies. Among these, one trial consisted exclusively of females. (18) Further, we found that only one of these published RCT reports included a test, and the result was null, for a sex-treatment interaction, (22) but the analytic strategy was not detailed and the smoking outcome for the analysis not clarified. Our study represents one of the first reported analysis of a formal sex-intervention interaction within a RCT designed to evaluate the effect of a MBI on smoking outcomes during a self-directed quit attempt. The main effect of intervention group in the published trial was the outperformance of the MBI compared to the control on abstinence days (OR=2.00, 95% CI: 1.03-3.87, p=.04) and daily cigs smoked (IRR=0.81, 95% CI: 0.71-0.92, p=.002) but not 7-day PPA (OR=1.60, 95% CI: 0.81-3.18, p=.18). (28) Drawing from the literature indicating that females show lower success in quitting smoking compared to males, irrespective of treatment type, (6) in this exploratory analysis, we hypothesized that females would show less favorable outcomes than males in terms of abstinence and harm reduction (reduced cigarette smoking) during the four weeks following a quit date. The contribution of this work is to determine whether a MBI generates differential effects on smoking in males and females by study group.

Method

Study design

This was a parallel-group RCT recruiting human subjects across California counties using online media advertisements. The main trial objective was to test the efficacy of daily, app-based behavioral interventions (i.e., Headspace versus Tedtalks, both with NCI quit smoking workbook education on making a quit attempt) in helping people who smoke daily to quit smoking and/or reduce their smoking. Mindfulness training involved using the Headspace app, which provided prerecorded introductory mindfulness meditation guided by experienced teachers. The attention control used TED Talk audio recordings to provide psychoeducation on various popular culture topics. The sessions were chosen to avoid content on meditation, smoking, or behavior change. Participants were instructed to listen with full attention, ensuring they remained engaged with the material. All participants were instructed to complete 10 minutes of either app twice daily for 14 days, totaling 280 minutes. All participants received the National Cancer Institute's smoking cessation workbook, "Clearing the Air," (https://www.cancer.gov/publications/patient-education/clearing-the-air) to support their quit attempt. The pre-trial protocol was published, (29) and full details for the trial (e.g., intervention descriptions, compensation, power calculation) and the trial data set are publicly available with the journal publication of the main outcomes. (28) The first day of the quit attempt, known as the “quit day,” was on the day that followed the fourteenth day of the intervention phase. The outcome assessment occurred 28 days after the quit day. The trial took place from July 2021 to December 2022 and was registered with clinicaltrials.gov (NCT05440903) and approved by a university Institutional Review Board (UP-20-00900).

Participants and procedures

Study protocols and interviews were conducted remotely from participants’ preferred locations using a secure online videoconferencing platform. Individuals who saw the study

advertisement were instructed to follow a link to complete an online survey indicating their interest, after which they voluntarily requested to be contacted by the study team. A 15-minute phone screening was used to assess initial eligibility and to schedule baseline interviews for qualifying candidates. Upon passing screening, participants received electronic informed consent documents to sign and return after a phone-based verbal informed consent process, led by a trained staff. To qualify for the study, individuals had to be 18 years of age or older, had smoked at least 5 cigarettes daily for the past 2 years, be willing to make a self-directed cigarette quit attempt, and be current residents of California. Ineligibility criteria included lack of English fluency, no access to remote video capability, mindfulness or meditation practices exceeding 5 minutes daily within the past 30 days, or use of smoking quit aids within the past 30 days.

Measures

Sex. Biological sex assigned at birth was self-reported at baseline with the item: What sex were you assigned at birth, on your original birth certificate? [response options: male, female, prefer not to answer]. *Cigarette dependence*. Dependence was assessed at baseline using the self-report method on the Fagerström Test for Cigarette Dependence (FTCD) measure. (30) Items on the measure included questions regarding the number of cigarettes smoked per day, the urge to smoke upon waking, difficulty refraining from smoking in specific situations, smoking even when ill, smoking frequently in the morning, and the importance of the first cigarette of the day. Higher scores indicate a greater level of cigarette smoking dependence. *Contemplation Ladder.* Readiness to consider smoking cessation was measured using the Contemplation Ladder, (31) which visually quantifies an individual's quit motivation and is provided to give baseline information on motivation to quit smoking by sex. The lowest score of 0 represents "no thought of quitting", whereas the highest score of 10 represents "taking action to quit (e.g., cutting down, enrolling in a program)". *Cigarette smoking*. Smoking

behavior was assessed using the timeline follow back (TLFB) calendar measure, completed by each participant on day 28 following the quit date. The recall period covered 28 days (i.e., 4 weeks). Variables derived from the TLFB for the behavioral dimensions of smoking included complete 7-day point prevalence abstinence (PPA; i.e., defined as not smoking a single cigarette in 7 days for the final fourth week of assessment), (32) proportion of days abstinent, and daily cigarettes smoked.(33)

Statistical analysis

This pre-registered trial was originally designed on an estimated power calculation to detect a between-group contrast effect of smoking cessation outcomes at the threshold of $p<.05$ using a prior of medium effect size. (29) All models we used to test the joint sex-intervention interaction term applied the intention-to-treat (ITT) analytic principle to include all participants randomized by the trial regardless of protocol adherence . FTCD cigarette smoking dependence score at baseline and sex were included terms in all estimated models, as this was also done in our analysis of the trial main effects. (28) The two-way sex-intervention interaction term was added to the exact trial outcome models without further alteration. The analytic outcome was *cigarette smoking* on dimensions of abstinence (complete 7-day PPA as a binary variable [0 or 1]; proportion of days abstinent [range of 0 to 1]) and daily cigarettes smoked is the count of cigarettes smoked for each participant, repeatedly measured daily for 28 days. Logistic regression modeling was used for the 7-day PPA and generalized Binomial modeling was used for the proportion of days abstinent. Generalized estimating equations with a Poisson random count variable and log link function was used for the daily cigarettes smoked, appropriately adjusting for the correlation of the repeatedly measured daily cigarettes smoke within participant. Those n=51 participants who did not complete the final smoking assessment were not included in each model because they did not have data to contribute to any of the three smoking outcomes. Model results are described in odds ratio (OR) for 7-day PPA and for

proportion of days abstinent (based on binomial [0/1] modeling of abstinence), or in incidence rate ratio (IRR) for daily cigarettes smoked, with associated 95% confidence intervals (CI) and p-values. Sex-specific estimates (and 95% CIs) of the intervention effect on smoking outcomes were obtained using contrasts and linear hypothesis regarding the appropriate regression model parameters. All statistical computations were done in Stata/SE 18.0 (StataCorp, College Station, TX). Statistical significance was claimed at the $p<0.005$ threshold, given the nature of the exploratory secondary analysis for testing interaction as well as newer recommendations for setting stringent thresholds of statistical significance. (34)

Results

Sex characteristics in relation to the randomized controlled trial

Out of 545 individuals inquiring about the study, 213 received random assignment and enrolled in the trial, and the follow-up smoking outcome assessment completion rate was 76% for each study group (77/101 in MBI group and 85/112 in control group completed outcomes assessment). There were no statistical differences in sex proportions by group assignment (MBI: 56% female; control: 55% female, $p=.89$). Table 2 shows select demographic and baseline smoking variables categorized by sex. There were no sex differences in any of the variables shown in the table (all p's >.01).

Attrition results showed that the effect of intervention on outcome assessment completion was not significantly different by sex (interaction $p=.08$). In terms of the counts of outcomes assessment completers by sex, the MBI group had 40 females and 37 males out of 77 total completers. The control group contained 49 females and 36 males out of 85 total completers. Protocol adherence (based on binary [0/1]) to intervention results also showed that the effect of intervention on adherence was not significantly different by sex (interaction $p=.06$).

In the MBI group, 43.9% of females and 48.7% males were adherent; in the control group, 56.1% of females and 51.3% of males were adherent. Group differences on the number of app sessions completed were significantly different by sex (interaction *p*=.003). In females, completed app sessions did not differ by study group (median MBI=20.0, IQR=10-26; control=22.0, IQR=17-26, *p*=.28), while in males, app sessions completed differed by study group (median MBI=13.0, IQR=6-18; control=21.5, IQR=17-26, *p*=.004).

Sex-intervention interaction effect on cigarette smoking dimensions

Table 3 presents the results of the analyses testing the two-way sex-intervention interaction term on smoking abstinence and daily cigarettes smoked Days with completed daily cigarette smoked outcome (27 days with a range [23 to 28] days per participant) were included in GEE model, excluding 51 participants with missing data for all outcomes. Results revealed a significant sex-intervention interaction effect for daily cigarettes smoked ([female coded 1]: two-way interaction effect IRR=0.59, 95% CI: 0.46-0.77, p<.0001; effect for female: IRR=0.68, 95% CI: 0.57-0.81, effect for male: IRR=1.14, 95% CI: 0.95-1.37), but not for complete 7-day PPA ([female coded 1] two-way interaction effect OR=1.24, 95% CI: 0.31-4.89, *p*=.76) or proportion of total days abstinent ([female coded 1] two-way interaction effect OR=1.97, 95% CI: 0.53-7.37, *p*=.31). Figures 1a-c shows the estimated effects by sex and group for all smoking outcomes, with the interaction effect only significant for the daily cigs outcome. Females in the MBI group smoked statistically fewer cigs per day relative to females in the control group. Males in MBI group and control group smoked a similar number of daily cigarettes.

Discussion

Our analysis contributes a formal testing of sex-intervention interaction effects on smoking cessation outcomes in a RCT testing a behavioral-focused MBI. Our additional findings

offer support for the possible existence of a nuanced sex difference in the cigarette smoked per day dimension following an app-based MBI, although findings do not support this subgroup effect for smoking abstinence dimensions (i.e., 7-day PPA and proportion of days abstinent). This finding contextualizes our previously reported RCT main effect of intervention on number of daily cigarettes smoked that favored the MBI group over the control group (OR=0.81, 95% CI: 0.71-0.92). Much of the intervention effect can be attributed to females in the MBI group smoking fewer daily cigarettes than females in the control group. The similar number of daily cigarettes smoked for males in both study groups contributed less to the overall intervention effect size. This new finding of a sex-intervention interaction effect should be validated in future studies of previous trial datasets or newly completed trials to determine if this effect can be replicated in independent trials. Among the MBI trials for smoking cessation that we identified in the existing literature, none we are aware of reported results from formal sex-intervention interaction testing. This highlights the potential significance of such analyses in future trial investigations, especially considering the sex differences observed in the broader cessation literature that vary by treatment type.(5, 6)

We had originally hypothesized that if a sex difference was detected in this RCT, females would show poorer cessation outcomes, consistent with previous reviews and network meta-analyses.(5, 6) Our findings showed that MBI males relative to control males and MBI females relative to control females did not show statistically different abstinence outcomes (i.e., 7-day PPA and proportion of days abstinent).. However, contrary to our prediction, females in the MBI group fared better in terms of statistically fewer daily cigarettes smoked relative to females in the control group. For males, daily cigarettes smoked did not appear to differ by study group. When considering the previously identified sex-based disparity in cessation outcomes after intervention,(6) MBIs may provide an approach revealing greater intervention

effect for females relative to females in certain control groups, pertaining to fewer daily cigarettes (i.e., a harm reduction outcome).

The absence of a sex difference in the smoking abstinence dimensions by group, alongside positive evidence of a sex difference in daily cigarettes smoked by group, may be partially explained by addiction theory. One prominent theory posits that drug use is more likely to occur during acute states of negative affect, wherein the selection of cigarettes strengthens, (35) thus overriding competing abstinence goals. Previous laboratory studies show that females report higher negative affect than males following an acute stressor task(36) and report higher negative affect and greater preference for immediate smoking after a smoking cue.(37) It is plausible that females smoked fewer daily cigarettes after a MBI compared to control females, as the intervention emphasized daily practices aimed at modulating sympathetic nervous system functions associated with negative affect.(38, 39) Thus, MBIs hypothetically may decrease the frequency of occurrence of acute negative affect states that elicit smoking. Select MBIs previously adapted for smoking cessation indeed target affective states, such as craving, during a quit attempt.(40) This postulation is supported by some empirical results in a previous RCT, which assessed negative affect following an acute stressor task before and after the MBI among individuals (80% female sample) with a history of negative affect.(41) The study observed a significant reduction in acute negative affect response during the task following a MBI, in contrast to a waitlist control.

It is also possible that daily cigarettes smoked may serve as a more sensitive measure of changes in smoking behavior compared to complete cessation outcomes, such as PPA, especially when an intervention is brief and delivered at low dose. While measures like PPA are a standard for determining the efficacy of a treatment approach for long-term cessation, the observed reduction in the average number of cigarettes smoked in the current study can be considered as meaningful. The observed effect for the sex-intervention interaction was small but

appears relevant as a marker of harm reduction, commonly used in smoking cessation trials, and may be associated with enhanced cessation outcomes in the future.(42, 43) The effect is also further substantiated by an observed difference in app use by sex and group. Males showed a difference in app use by group (less app use among males in MBI group compared to control) and females show similar app use regardless of app group. Future studies might examine potential sex-intervention interaction effects in abstinence outcomes in the context of a cessation trial that includes a more intensive MBI paired with an evidence-based pharmacotherapy (e.g., varenicline).

There are limitations to our interpretation of sex differences resulting from this secondary statistical analysis of variables measured in a RCT. One is that trials of MBIs may recruit participants with a positive expectancy bias elicited by the assigned intervention. It is unknown in our sample whether such bias is more common in females. If so, females participating in an MBI might report more positively on assessments, particularly since behavioral interventions become noticeable once the intervention phase commences. Previous research supports this biasing effect in the context of substance use outcomes.(44) This bias could wield influence, given that females appear more inclined to self-select into MBI trials than males. Thus, females might be more likely to report smoking fewer cigarettes, knowing the study personnel had highlighted a quit date, which sets an expectation for reduced smoking behavior. The observed differences in app use by sex and the proportion of missing data on smoking outcomes may have affected interaction analyses in unpredictable ways. Additionally, the current study did not assess select psychological (e.g., self-efficacy) or social (e.g., social networks of smokers) factors that might influence smoking cessation and may be differentially impacted by sex. We welcome independent replication attempts of our sex-intervention interaction effect in additional datasets of past and future RCTs. It is important to balance these findings with empirical work

showing that most claims for subgroup differences related to sex lack strong statistical support and corroboration outside the field of smoking cessation.(46)

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Table 1. Reporting of sex differences test result in RCTs of MBIs for smoking cessation

Citation	**N**	**% female**	**Sex differences effect result**
Araujo 2021	113	64%	Not on record
Black 2023	213	54%	Reported herein as a secondary analysis
Bowen 2009	123	27%	"No significant moderating effects were found for gender" [no model or outcome clarified for this test]
Brewer 2011	88	38%	Not on record
Davis 2013	55	29%	Not on record
Davis 2014	135	47%	Not on record
Davis 2014	196	48%	Not on record
de Souza 2020	86	82%	Not on record
Garrison 2020	325	72%	Not on record
Goldenhersch 2020	120	48%	Not on record
Rogojanski 2011	61	41%	Not on record
Ruscio 2016	44	50%	Not on record
Singh 2014	51	20%	Not on record
Tang 2013	27	Not reported	Not on record
Vidrine 2016	412	55%	Not on record
Weng 2021	213	100%	Not applicable, female-only sample

Note. A sex-intervention interaction effect or subgroup stratification analysis by sex was not reported in the article cited or from additional searches of secondary analyses of the RCTs.

Table 2. Demographic and cigarette smoking variables by sex

Variable	**Total (N=213)**	**Male (n=96)**	**Female (n=117)**
Age, M (SD)	41.18 (13.51)	40.17 (13.32)	42.02 (13.66)
Race/ethnicity, n (%)			
White	123 (57.75)	52 (54.17)	71 (60.68)
Black or African American	14 (6.57)	7 (7.29)	7 (5.98)
Hispanic	41 (19.25)	20 (20.83)	21 (17.95)
Asian (Philippine Islands, Southeast Asia, India)	5 (2.35)	3 (3.12)	2 (1.71)
American Indian or Alaskan Native	4 (1.88)	3 (3.12)	1 (0.85)
Multiracial	17 (7.98)	6 (6.25)	11 (9.40)
Other	7 (3.29)	4 (4.17)	3 (2.56)
Not reported	2 (0.94)	1 (1.04)	1 (0.85)
Education, n (%)			
Less than high school	7 (3.29)	1 (1.04)	6 (5.13)
High school diploma or GED	47 (22.07)	22 (22.92)	25 (21.37)
Some college completed or current enrollee	103 (48.36)	45 (46.88)	58 (49.57)
College degree or higher completed	56 (26.29)	28 (29.17)	28 (23.93)
Income, n (%)			
< $15,000	57 (26.76)	20 (20.83)	37 (31.62)
≥ $15,000 - $29,999	60 (28.17)	25 (26.04)	35 (29.91)
≥ $30,000 - $44,999	30 (14.08)	13 (13.54)	17 (14.53)
≥ $45,000 - $59,999	27 (12.68)	14 (14.58)	13 (11.11)
≥ $60,000 - $74,999	12 (5.63)	9 (8.33)	4 (3.42)
≥ $75,000 - $89,999	12 (5.63)	6 (6.25)	6 (5.13)

≥ $90,000 - $104,999	4 (1.88)	1 (1.04)	3 (2.56)
≥ $105,000 - $119,999	6 (2.82)	6 (6.25)	0 (0)
≥ $120,000	5 (2.35)	3 (3.12)	2 (1.71)
FTCD smoking dependence score at BL, M (SD)	4.68 (2.00)	4.70 (1.90)	4.66 (2.09)
Daily cigarettes smoked at BL, M (SD)	12.33 (6.07)	12.98 (6.13)	11.79 (6.00)
Contemplation Ladder at BL, M (SD)	6.89 (2.42)	6.51 (2.49)	7.22 (2.32)
Outcomes variables of the trial			
Complete 7-day PPA, n (%)	50 (23.5)	21 (21.9)	29 (24.8)
Proportion of days abstinent, M (SD)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
Daily cigarettes smoked per day overall, M (SD)	5.3 (7.3)	5.6 (7.9)	5.1 (6.8)

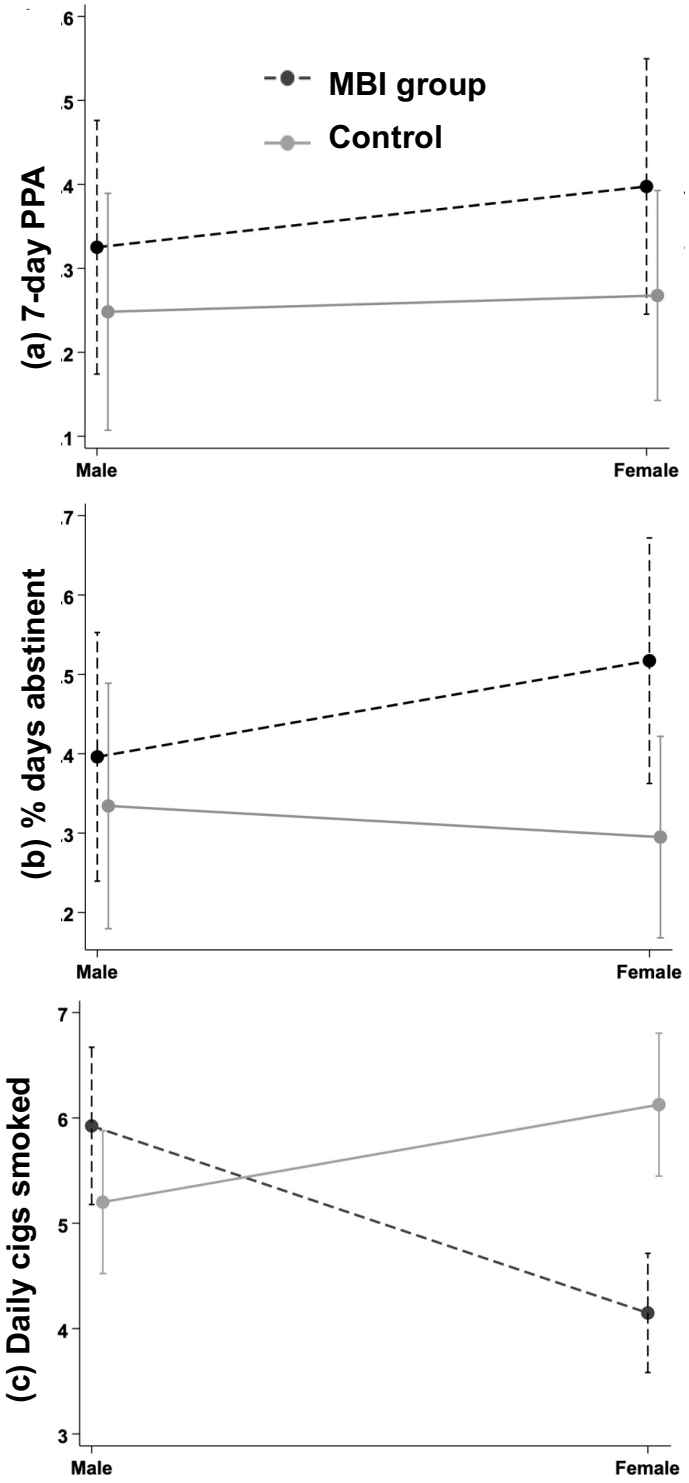
Note. FTCD = Fagerström Test for Cigarette Dependence; M = mean; SD = standard deviation; BL = baseline; There were no sex differences in any of the variable scores shown in the table (all p's >.01).

Table 3. Sex-intervention interaction effect on cigarette smoking and effect size by sex

Smoking dimension	**Sex-intervention interaction**	**95% CI**	***p***	**Male ES**	**Female ES**
7-day PPA	OR = 1.24	0.31-4.89	.76	1.46 (0.52-4.06)	1.81 (0.73-4.46)
Proportion of days abstinent	OR = 1.97	0.53-7.37	.31	1.31 (0.50-3.43)	2.58 (1.06-6.27)
Daily cigarettes smoked	IRR = 0.59	0.46-0.77	<.0001	1.14 (0.95-1.37)	0.68 (0.57-0.81)

Note. The analytic sample of n=162 is due to 51 participants not completing the final smoking assessment; PPA = complete 7-day point prevalence abstinence during final week of follow up; ES= effect size by sex; CI = confidence interval; Female is coded as 1 for the two-way sex-intervention interaction. Tables inclusive of all estimates for all model predictors are provided as supplementary material.

Figure 1a-c. Cigarette smoking values during a quit attempt by sex and intervention



Note. The analytic sample of n=162 is due to 51 participants not completing the final smoking assessment Adjusted models predicting cigarette smoking dimensions following a quit date,

covarying for baseline FTCD smoking dependence and sex; vertical lines are 95% confidence intervals