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Once-Weekly Semaglutide in Adults With Daily Cigarette Use
A Randomized Clinical Trial

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Abstract

IMPORTANCE People who smoke cigarettes face increased risk of morbidity and mortality, in part due to elevated rates of cardiometabolic disease. Preclinical and early clinical data indicate that glucagon-like peptide-1 receptor agonists (GLP-1RAs) warrant consideration for smoking cessation and prevention of associated cardiometabolic risks.

OBJECTIVE To evaluate the effects of semaglutide vs placebo on cigarette smoking, craving, and weight outcomes in people who smoke.

DESIGN, SETTING, AND PARTICIPANTS This parallel-arm phase 2a randomized clinical trial with embedded human laboratory sessions was conducted at an academic medical center, with enrollment occurring from October 2022 to April 2024. Participants were non–treatment-seeking adults consuming at least 5 cigarettes per day. Data were analyzed in 2025.

INTERVENTION Nine weeks of subcutaneous of semaglutide (0.25 mg for 4 weeks, 0.5 mg for 4 weeks, 1.0 mg for 1 week) vs placebo.

MAIN OUTCOMES AND MEASURES The co–primary outcomes were laboratory measures of smoking resistance and reinstatement and self-administration, assessed before and after treatment. Changes in cigarette use, cigarette craving, body weight, and other outcomes were assessed weekly.

RESULTS Of 45 participants enrolled, 24 participants (mean [SD] age, 44 [12] years; 20 [83%] female; mean [SD] body mass index, 33.5 [7.2]; mean [SD] cigarettes per day, 15.4 [7.9]) were randomized to placebo (12 participants) or semaglutide (12 participants), of whom 21 participants (88%) completed the primary outcome assessment. Primary treatment-by-time interactions on laboratory measures of smoking resistance (23 participants; β = 0.16 [95% CI, −0.07 to 0.40]; $P = .16$) and number of cigarettes (22 participants; β = −0.08 [95% CI, −0.25 to 0.08]; $P = .30$) were not significant. Supplementary change score analyses indicated significantly greater reductions in laboratory smoking (β = −0.69 [95% CI, −1.26 to −0.13]; $P = .02$; $d = 0.67$) in the semaglutide group vs the placebo group after treatment. Semaglutide reduced cigarette craving (treatment-by-time interaction: β = −0.11 [95% CI, −0.20 to −0.03]; $P = .01$) and body weight (β = −0.04 [95% CI, −0.05 to −0.03]; $P < .001$) over treatment weeks. Exploratory effect size analyses indicated potential effects on withdrawal symptoms.

CONCLUSIONS AND RELEVANCE In this phase 2a randomized clinical trial, semaglutide monotherapy did not significantly increase laboratory smoking resistance or reduce weekly cigarettes per day but reduced nicotine craving and body weight. Larger trials should evaluate effects

(continued)

Key Points

Question Does semaglutide reduce cigarette use, craving, and body weight in people who smoke cigarettes but are not attempting cessation?

Findings In this randomized clinical trial including 24 participants, the effects of semaglutide on laboratory cigarette smoking and resistance to smoking were not significant in primary interaction tests, but change score analyses indicated that semaglutide significantly reduced laboratory smoking from before to after treatment. Semaglutide led to significant reductions in weekly cigarette craving, body weight, and hemoglobin A_{1c} relative to placebo, without significantly reducing number of cigarettes smoked per day.

Meaning These findings suggest that glucagon-like peptide-1 receptor agonist monotherapy may alter some nicotine outcomes in people who smoke, irrespective of cessation treatment.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

of GLP-1RA therapies on cessation, postcessation weight gain, and cardiometabolic outcomes in people who smoke.

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Introduction

Cigarette smoking remains the leading cause of preventable morbidity and mortality worldwide, accounting for more than 8 million deaths and 220 million disability-adjusted life-years annually.[1] Despite overall declines in smoking prevalence, smoking-related deaths are increasing alongside global population growth.[1] Smoking increases the risk of cardiovascular diseases,[2] type 2 diabetes,[3,4] and cancer-related deaths.[5] Smoking rates are often higher in psychiatric populations, including those with co-occurring substance use disorders[6,7] and other serious mental illnesses.[8]

While smoking is associated with lower mean body weight,[9,10] people who smoke with overweight or obesity are a high-risk subgroup,[11] and evidence suggests a positive association between body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and number of cigarettes per day (CPD) among people who smoke.[11] Importantly, most people who smoke experience postcessation weight gain,[12,13] which is a known barrier to cessation.[14] Additionally, the elevated risk for new-onset type 2 diabetes following smoking cessation is proportional to the extent of weight regain.[15]

With only 3 US Food and Drug Administration–approved smoking cessation medications available (nicotine replacement therapy [NRT], bupropion, and varenicline), identifying new therapies with novel mechanisms of action is imperative.[16] Considering elevated rates of cardiometabolic disease in people who smoke, treatments that support cessation while simultaneously reducing cardiometabolic risks, including weight regain and new-onset diabetes, may significantly improve morbidity and mortality outcomes in people who smoke. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), now under evaluation for numerous conditions beyond the primary indications of diabetes and obesity,[17] improve cardiometabolic outcomes and reduce prospective risk for negative cardiovascular events.[18] GLP-1RAs are increasingly under investigation for neuropsychiatric[19-21] and substance use disorders.[22-25]

Accumulating evidence points to GLP-1RAs as a candidate therapeutic class for smoking cessation.[26,27] In preclinical studies, GLP-1 receptor activation decreases nicotine self-administration,[28,29] reduces nicotine-evoked dopamine response,[30,31] modulates nicotine reward and avoidance,[28] and prevents withdrawal-related hyperphagia.[26,27,29] Two early clinical trials suggested that GLP-1RAs—administered adjunctively with smoking cessation therapies—are safe and efficacious for weight control[13,32] and may improve cessation rates.[13] Preliminary findings further indicate that GLP-1RAs may reduce cigarette intake in the context of other substance use disorders.[24] To our knowledge, no clinical trials have evaluated the efficacy of GLP-1RA monotherapy in people who smoke[26] or the effects of GLP-1RAs on smoking outcomes in a noncessation context. This phase 2a trial evaluated effects of semaglutide monotherapy on smoking-related outcomes in people who smoke who were not attempting cessation.

Methods

This investigator-initiated randomized clinical trial involved an Investigational New Drug Exemption from the US Food and Drug Administration and received institutional review board approval from the University of North Carolina-Chapel Hill. All participants provided written informed consent. The trial

protocol and statistical analysis plan are provided in Supplement 1. This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Trial Design

This trial incorporated a hybrid clinical trial/human laboratory design[24] to examine effects of semaglutide on laboratory smoking, weekly cigarette use, and associated outcomes in non–treatment-seeking people who smoke. Following baseline assessments and randomization, participants received subcutaneous semaglutide or placebo injections for 9 weeks. Laboratory smoking sessions occurred at pretreatment and after 8 treatment weeks.

Participant Sample

Participants were recruited from October 2022 to April 2024 via public and social media advertisements. Primary inclusion criteria included age 21 to 65 years; reporting 5 CPD or more in the past year with no period of abstinence more than 90 days; baseline biochemical verification of smoking, based on expired carbon monoxide 8 ppm or greater; and willingness to receive semaglutide and complete clinic and laboratory smoking visits. Primary exclusion criteria included past-month use of NRT, current smoking cessation attempt or treatment, regular (weekly) e-cigarette use, current illicit drug use (cannabis excepted) based on self-report and toxicological screen, prior GLP-1RA use, weight loss medications, BMI less than 23, meeting criteria for alcohol or other substance use disorders (mild cannabis use disorder excepted), and history of diabetes or related diagnoses. Self-reported race and ethnicity were provided by participants as Asian, Black or African American, Hawaiian or Pacific Islander, other or multiracial, and White. Race and ethnicity data were collected for purposes of describing the study sample. Full inclusion and exclusion criteria are provided in the eAppendix in Supplement 2.

Study Procedures

Participants provided signed informed consent at the eligibility screening. Following a baseline screening (week 0) visit, participants completed a laboratory smoking session. Participants were then randomized and returned for 9 weeks of semaglutide or placebo injections (week 1-9 visits). Clinic visits included assessments of cigarette use, craving, withdrawal, weight, vital signs, and adverse events. A posttreatment laboratory smoking session occurred between weeks 8 and 9, with discharge occurring at week 10.

Study Medication

A research nurse administered semaglutide weekly (weeks 1-4: 0.25 mg/wk; weeks 5-8: 0.5 mg/wk; week 9: 1.0 mg). The 1.0-mg dose was administered if no adverse events or scheduling events precluded a dose increase. The limited trial duration precluded use of higher doses. As a noncessation trial, NRT or other smoking cessation interventions were not provided.

Outcomes Assessment

Laboratory smoking sessions involved a validated medication screening procedure[33,34] designed to model 2 stages of a smoking lapse: the initial decision to smoke (reinstatement) and subsequent self-administration (eAppendix and eFigure 1 in Supplement 2). Participants arrived in the morning after receiving instructions for overnight abstinence; adherence was confirmed based on carbon monoxide less than 6 ppm (or ≥50% reduction from the baseline value). Next, participants received a package of their preferred cigarettes, an ashtray, and lighter. During the lapse phase participants could delay smoking for up to 50 minutes in exchange for nominal compensation. Once electing to smoke (or once reaching 50 minutes of delay), participants then received a tray containing 8 of their preferred cigarettes and were allowed to smoke ad libitum for 60 minutes. Subjective responses to smoking were assessed after the first cigarette and at subsequent intervals. The a priori co–primary outcomes were smoking resistance (delay time in minutes) and cigarettes smoked.[33,34]

Weekly Outcomes

Past-week smoking (secondary outcome) was assessed at each visit[35] and converted to mean CPD in the prior week. Other weekly outcomes (included as exploratory outcomes) were cigarette craving (Brief Questionnaire of Smoking Urge),[36] smoking withdrawal (Wisconsin Smoking Withdrawal Scale [WSWS]),[37] self-efficacy (confidence) for resisting smoking (Smoking Abstinence Self-Efficacy Questionnaire]),[38] and motivation and readiness to quit smoking, assessed via a contemplation ladder.[38] Measures of subjective responses to laboratory smoking (exploratory outcomes) included the Cigarette Evaluation Scale,[39] Drug Effects Questionnaire,[40] and visual analogue scales assessing drug effects (eg, dizzy, tired), including supplemental items to capture aversive responses (eg, nauseous, sick).

Clinical and Safety Outcomes

A standardized scale[41] captured side effects and adverse events. Weight and vital signs were assessed weekly. Depression symptoms[41] and hemoglobin A_{1c} (HbA_{1c}) were assessed monthly (baseline, week 4, week 8).

Statistical Analyses

The a priori analysis plan specified linear mixed models (LMM) to test treatment-by-time interactions for both primary laboratory outcomes (delay time and cigarettes smoked) and weekly outcomes (eg, CPD). LMMs included a random effect for participant (random intercept), within-participant fixed effects of time, between-participants effects for group (semaglutide vs placebo), and treatment-by-time interactions, with full information maximum likelihood estimation to accommodate missing data (using lme4 package version 1.1-37[42] for RStudio version 2024.04.2 + 764[43] [R Project for Statistical Computing]). Results were considered statistically significant at 2-sided $P < .05$. Power analyses called for a final sample of 36 participants (eAppendix in Supplement 2). Due to logistic delays following the pandemic and associated budgetary constraints, a final sample of 24 participants was randomized before the project ended, providing insufficient power for planned interaction tests. To improve statistical power, planned LMM were followed by analyses testing baseline-to-posttreatment changes on laboratory and weekly outcomes, with estimates of medication effect size to guide future studies. Effect sizes (Cohen *d*) for change from baseline at each dose and treatment month (0.25 mg/week and 0.5 mg/week) were computed with the lsr package version 0.5.2 for R[44]. Values of $d = 0.20$, $d = 0.50$, and $d = 0.80$ reflect small, medium, and large effects, respectively. Data were analyzed in 2025.

Results

Sample Characteristics and Retention

Of 45 participants enrolled, 24 participants (mean [SD] age, 44 [12] years; 20 [83%] female; mean [SD] BMI: 33.5 [7.2]; mean [SD] cigarettes per day 15.4 [7.9]) were randomized to medication (12 participants) or placebo (12 participants) (**Table**). A total of 22 participants completed visits through week 8 prior to primary outcome assessments, and 21 participants completed the posttreatment laboratory session (**Figure 1**; eAppendix in Supplement 2.

Laboratory Smoking Outcomes

Laboratory analyses excluded observations from participants who were verified as nonadherent with overnight abstinence (2 participants, 3 observations) or did not engage in smoking (3 participants, 4 observations) (eAppendix in Supplement 2). The preplanned LMMs for delay time and laboratory cigarettes smoked yielded no significant treatment-by-time interactions (delay time: β = 0.16 [95% CI, −0.07 to 0.40]; $P = .16$; cigarettes smoked: β = −0.08 [95% CI, −0.25 to 0.08]; $P = .30$), and the medication condition effect failed to reach significance for delay time β = −0.24 [95% CI −0.67 to 0.18]; $P = .25$) and cigarettes consumed (β = 0.34 [95% CI −0.04 to 0.73]; $P = .08$) (eTable 2 in

Supplement 2). In change score analyses (**Figure 2**; eTable 3 in Supplement 2), semaglutide-treated participants showed a mean (SD) increase in delay time of 10.30 (27.60) minutes vs a mean (SD) reduction in delay time of −2.89 (13.80) minutes in the placebo group, a difference that was not statistically significant (β = 0.46 [95% CI, −0.09 to 1.02]; *P* = .11; *d* = 0.60). However, semaglutide-treated participants had a significantly greater reduction in cigarettes consumed (mean [SD] change, −0.89 [0.60] cigarettes) from before to after treatment vs the placebo group (mean [SD] change, −0.44 [0.73] cigarettes) (β = −0.69 [95% CI, −1.26 to −0.13]; *P* = .02; *d* = 0.67). Laboratory craving and supplemental subjective response analyses are shown in the eAppendix and eFigure 2 in Supplement 2.

Weekly Smoking, Craving, and Associated Outcomes

The preplanned LMM for weekly craving (Brief Questionnaire of Smoking Urge score) yielded a significant treatment-by-time interaction (**Figure 3**A), indicating greater craving reduction in the semaglutide group vs the placebo group (β = −0.11 [95% CI, −0.20 to −0.03]; *P* = .01). The LMM for CPD showed overall significant reductions in cigarettes per day across groups (β = −0.10 [95% CI, −0.13 to −0.07]; *P* < .001) but no treatment-by-time interaction (β = −0.01; [95% CI, −0.04 to 0.03]; *P* = .65). Full results are presented in eTable 4 in Supplement 2.

Exploratory change-from-baseline analyses were conducted for CPD, craving, withdrawal (WSWS), self-efficacy (Smoking Abstinence Self-Efficacy Questionnaire), and readiness to change (contemplation ladder) by dose and treatment month (weeks 1-4 and weeks 5-8). Results indicated

Table. Pretreatment Characteristics by Treatment Arm for Randomized Participants

Characteristic	Mean (SD)		
	Placebo (n = 12)	Semaglutide (n = 12)	Total (N = 24)
Sex, No. (%)			
Female	10 (83)	10 (83)	20 (83)
Male	2 (17)	2 (17)	4 (17)
Age, y	44 (13)	44 (11)	44 (12)
Race, No. (%)			
Asian	0	0	0
Black or African American	2 (17)	2 (17)	4 (17)
Hawaiian or Pacific Islander	0	0	0
Other or multiracial	0	0	0
White	10 (83)	10 (83)	20 (83)
Hispanic ethnicity, No. (%)	2 (17)	2 (17)	4 (17)
Nicotine dependence (FTND score)	12.2 (6.5)	11.9 (4.7)	12.0 (5.6)
Tobacco consumption			
Cigarettes per day	18.8 (8.6)	12.0 (5.6)	15.4 (7.9)
Percentage of smoking days	100 (0)	99.4 (1.3)	99.7 (1.0)
Laboratory posttreatment smoking abstinence verification			
Arrival CO reading, ppm	9.9 (6.0)	7.2 (4.9)	8.6 (5.0)
Smoking abstinence, h	12.5 (6.7)	13.2 (1.5)	12.8 (4.9)
Alcohol consumption, No. (%)[a]	7 (29)	8 (25)	15 (27)
Drinks per day	1.6 (1.0)	0.8 (0.7)	1.5 (0.9)
Weight, kg	88.6 (17.4)	98.2 (20.6)	93.4 (19.3)
BMI	31.5 (5.6)	35.6 (8.1)	33.5 (7.2)
Blood pressure, mm Hg			
Systolic	133.9 (15.5)	121.3 (19.1)	127.6 (18.2)
Diastolic	88.7 (12.5)	81.5 (9.8)	82.0 (13.7)
Heart rate, bpm	83.5 (13.1)	82.0 (13.7)	82.8 (13.1)
HbA_{1c}, %	5.25 (0.37)	5.19 (0.50)	5.22 (0.43)
Depression (CES-D score)	8.1 (5.6)	8.1 (6.8)	8.1 (6.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); bpm, beats per minute; CES-D, Center for Epidemiologic Studies Depression scale; CO, carbon monoxide; FTND, Fagerström Test for Nicotine Dependence; HbA_{1c}, hemoglobin A_{1c}; ppm, parts per million.

SI conversion factor: To convert HbA1c to proportion of total hemoglobin, multiply by 0.01.

[a] Alcohol consumption was defined as drinking at least 1 alcohol drink during the 28-day baseline period. Drinks per day were calculated for participants who reported alcohol consumption only.

Figure 1. Participant Enrollment Flowchart

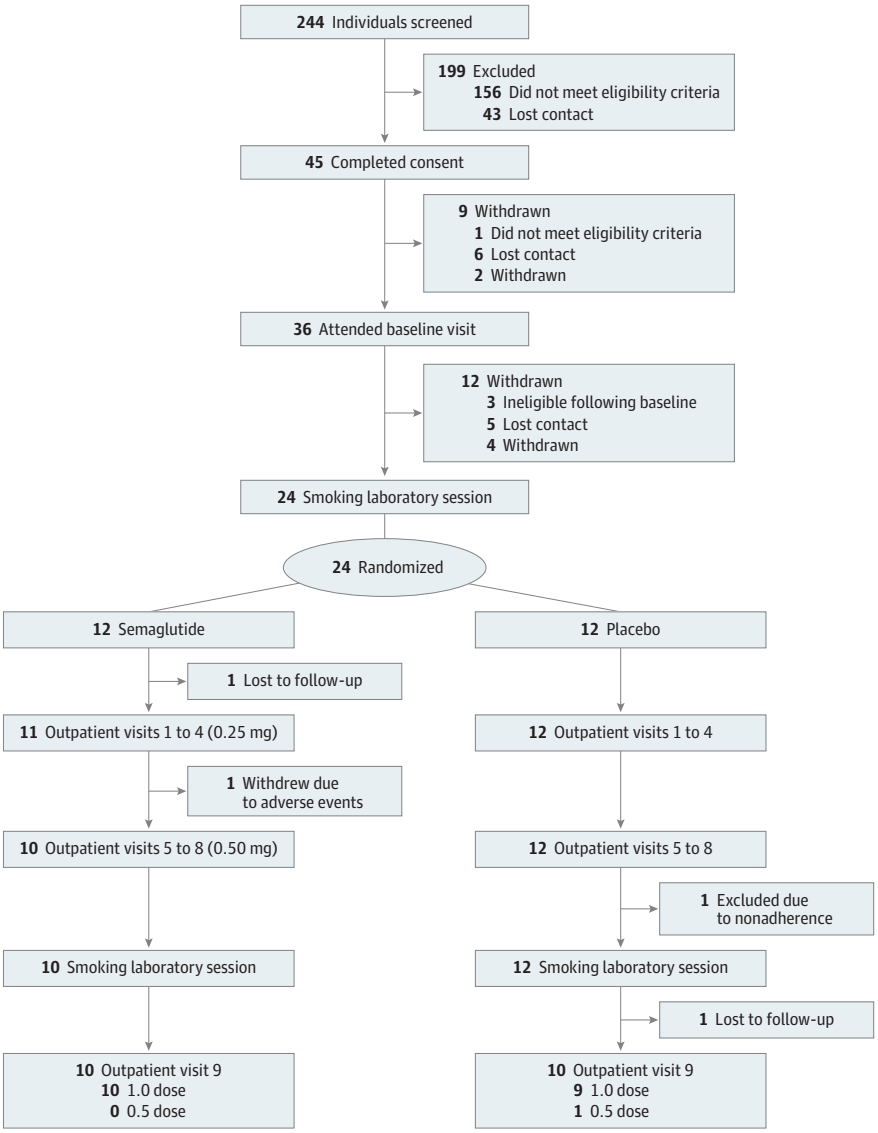
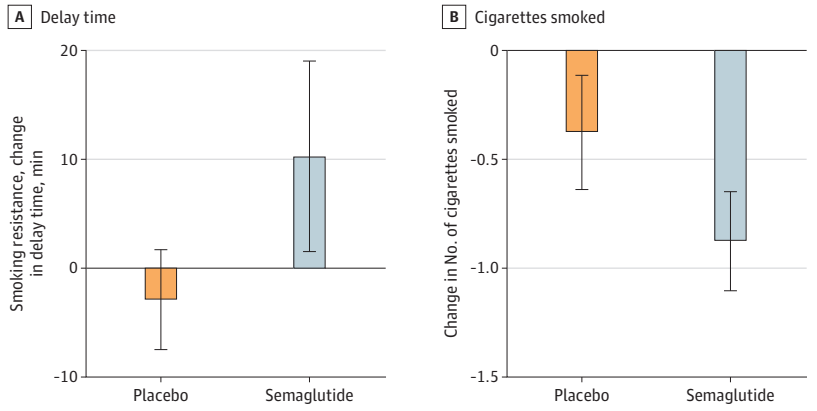


Figure 2. Bar Graphs of Change in Laboratory Smoking Resistance and Cigarette Smoking Before vs After Treatment



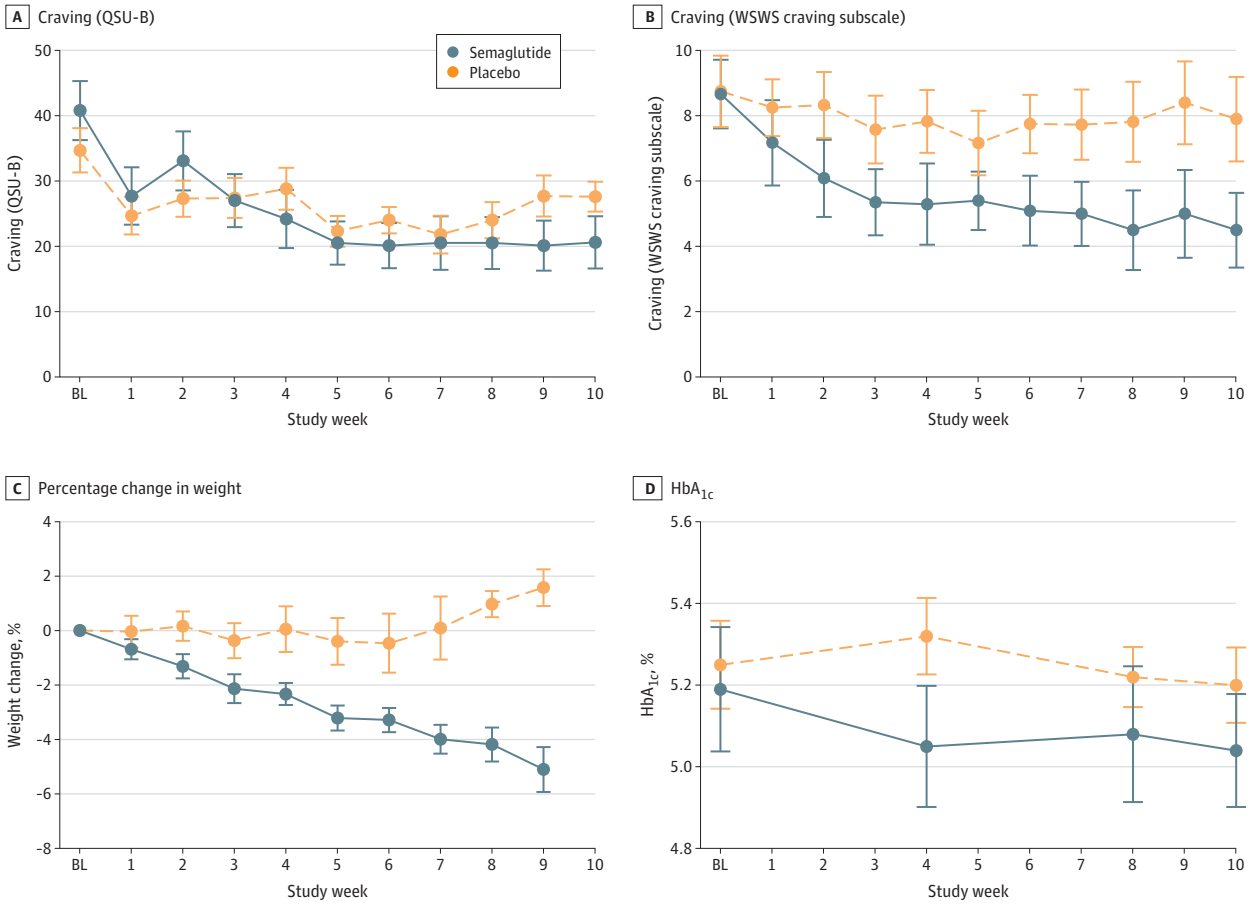
Bars depict group means for pre-to-post-treatment change in laboratory smoking resistance, as measured by delay time in minutes (A) (n = 19) and cigarettes smoked (B) (n = 16). Sample size information is provided in the eAppendix in Supplement 2. Error bars indicate SEs. Posttreatment laboratory sessions occurred following treatment week 8 (semaglutide dose: 0.5 mg/wk).

relative reductions in CPD, craving, and withdrawal, along with relative increases in self-efficacy and readiness to change in participants in the semaglutide group vs placebo group (**Figure 4**A-E). Effect size estimates (Cohen's *d*) ranged from small to large, generally increasing in weeks 5 to 8 (0.5 mg/week) vs weeks 1 to 4 (0.25 mg/week). Effect sizes were largest for withdrawal scores, which was unexpected, given that participants were not attempting reduction or cessation. Therefore, follow-up analyses examined WSWS subscales individually, demonstrating that effect sizes were largest for the WSWS craving (Figure 4; weekly changes in WSWS craving scores are provided in Figure 3B) and hunger (eFigure 3 in Supplement 2) subscales. Additionally, medium to large effects were observed for WSWS affective subscales (anger, anxiety, sadness) (eFigure 3 in Supplement 2).

Weight, HbA_{1c}, and Safety Outcomes

The LMM for weight confirmed a significant treatment-by-time interaction (β = −0.04 [95% CI, −0.05 to −0.03]; *P* < .001) (Figure 3C; eTable 5 in Supplement 2). Participants in the semaglutide group lost approximately 5% body weight (mean (SD) change, −5.11% [2.62%]) through week 10, vs a small increase in placebo participants (mean [SD] change, 1.58% [2.13]). Additionally, participants in the semaglutide group had lower HbA_{1c} during treatment vs the placebo group (Figure 3D; eTable 5 in Supplement 2). Group differences in systolic and diastolic blood pressure and Center for Epidemiologic Studies Depression Scale scores were not significant. Adverse events were mostly

Figure 3. Line Graphs of Cigarette Craving, Weight, and Hemoglobin A_{1c} (HbA_{1c}) by Study Week



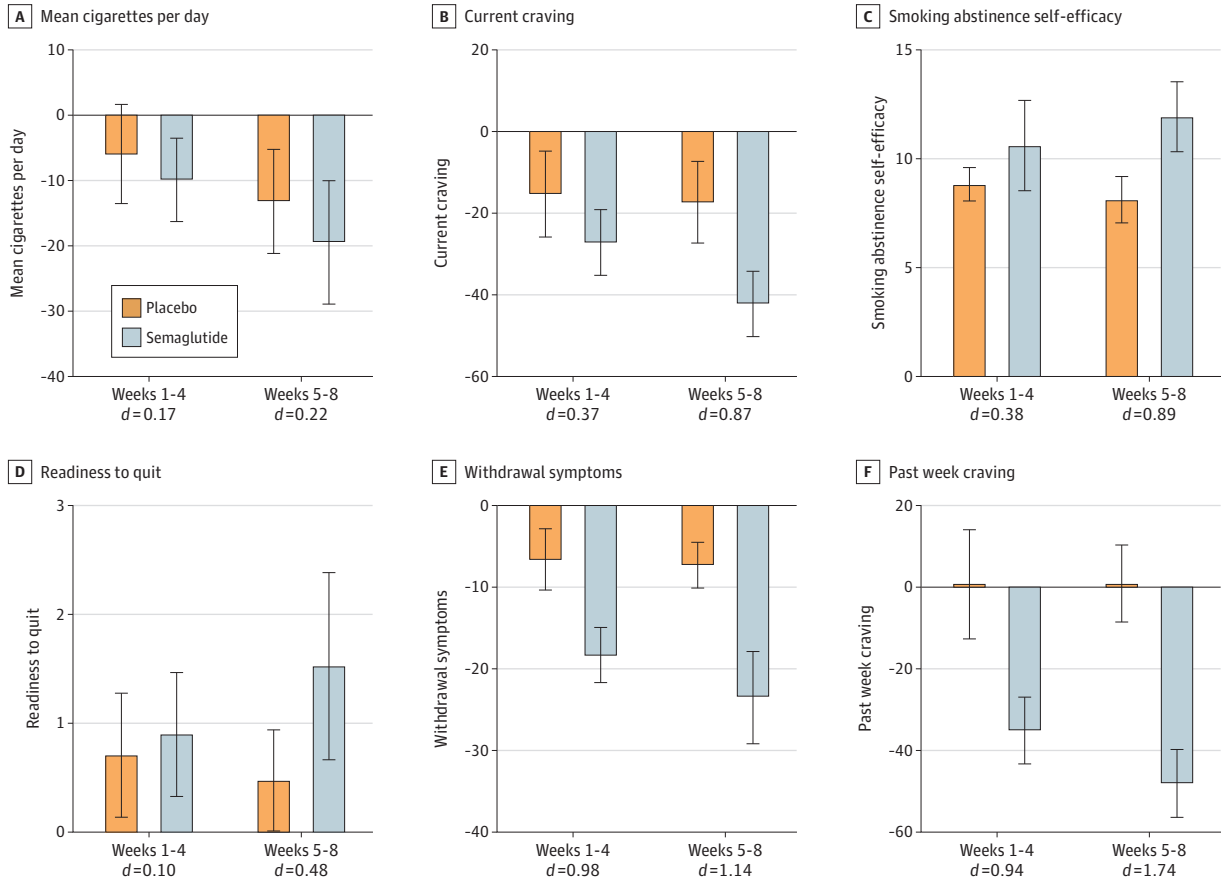
A and B, Craving scores at clinic visits based on the Questionnaire on Smoking Urges-Brief (QSU-B) (A) and Wisconsin Smoking Withdrawal Scale (WSWS) craving subscale (B) by study week. C, Body weight change expressed as percentage change from baseline (BL) (n = 20-24 across weeks [n = 10-12 in the semaglutide group; n = 10-12 in the placebo group]). D, Mean HbA_{1c}, measured at BL and weeks 4, 8, and 10 (n = 17-23 across weeks [n = 9-11 in the semaglutide group; n = 8-12 in the placebo group]). Data points depict group means with SEs (whiskers). To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01.

mild in severity, including the expected high prevalence of gastrointestinal adverse effects; 1 participant in the semaglutide group discontinued due to adverse effects (eTable 1 in Supplement 2).

Discussion

To our knowledge, this randomized clinical trial is the first registered trial to test GLP-1RA monotherapy in a sample of people who smoke and the first to study semaglutide in this population. Preclinical findings[26-28] and early trials[13,32] suggest that GLP-1RAs warrant consideration for smoking cessation and prevention of postcessation weight gain. Pharmacoepidemiology studies report reduced incidence of tobacco use–related medical codes following exposure to GLP-1 therapies,[45-47] and preliminary evidence indicates that semaglutide may reduce cigarette use in adults with alcohol use disorder.[24] In this study among non–treatment-seeking participants who were not attempting cessation or receiving nicotine replacement therapy, semaglutide did not reduce CPD but significantly reduced nicotine craving, also leading to reductions in body weight and HbA_{1c}. Medication effects on primary laboratory end points were not significant in preplanned interaction tests, although change score analyses indicated greater reductions in laboratory smoking in

Figure 4. Bar Charts of Change From Baseline in Weekly Outcomes by Medication Group and Treatment Period



Bars depict group means with SEs (whiskers) for change from baseline in weekly reports of mean cigarettes per day (A), current cigarette craving (Brief Questionnaire on Smoking Urges) (B), confidence for resisting cigarette smoking (Smoking Abstinence Self-Efficacy) (C), motivation or readiness to quit smoking (contemplation ladder) (D), withdrawal symptoms (Wisconsin Smoking Withdrawal Scale total score) (E), and the Wisconsin Smoking Withdrawal Scale craving subscale (F). Figures depict percentage change from baseline, except D, which depicts raw score for the single-item contemplation ladder. Change scores are presented separately for the first and second months of treatment (0.25 mg/wk for weeks 1-4; 0.5 mg/wk for weeks 5-8). Effect size estimates (Cohen *d*) reflect group differences in pretreatment to posttreatment changes; conventional benchmarks: $d = 0.20$ for a small effect, $d = 0.50$ for a medium effect, and $d = 0.80$ for a large effect. Sample sizes were 20 to 24 participants for all models (placebo: 11 participants in weeks 1-4 and 10 participants in weeks 5-8; semaglutide: 12 participants in weeks 1-4 and 12 participants in weeks 5-8).

semaglutide-treated vs placebo-treated groups. Additionally, exploratory effect size estimates found reductions in withdrawal scores (most prominent for WSWS craving and hunger subscales), and relative increases in reported self-efficacy and readiness to change smoking by the second month of treatment, with effect sizes (*d*) being greater in the second month of treatment. These findings provide early indication that GLP-1RA monotherapy may reduce nicotine craving, and potentially other cessation-relevant cognitive processes, irrespective of smoking cessation or cessation treatments.

These findings complement 2 earlier trials investigating GLP-1RAs in people who smoke. In the first, 6 weeks of exenatide (administered adjunctively with nicotine patch plus behavioral counseling) led to higher rates of abstinence (46%) vs placebo (27%) in a sample of 84 people who smoke.[13] Exenatide also mitigated posttreatment weight gain (mean weight change: 2.96 lb in the placebo group vs −0.49 lb in the exenatide group). A well-powered trial[32] found no effect of dulaglutide (administered adjunctively with varenicline plus behavioral counseling) on abstinence after 12 weeks, also reporting no effect on craving or CPD. The unusually high abstinence rates in the study by Lengsfeld et al[32] (>60%), perhaps reflecting the intensity of the adjunctive treatments, may have limited sensitivity for detecting dulaglutide effects. Nonetheless, dulaglutide mitigated weight regain (mean weight change: 1.9 kg in the placebo group vs −1 kg in the dulaglutide group), reduced HbA_{1c}, and appeared to reduce risk of new-onset prediabetes (placebo group: 7%; dulaglutide group: 1.6%) among participants who quit.

Direct comparisons between the prior trials and this study are difficult due to divergent methods and populations and different medications examined. However, these 3 studies collectively indicate that GLP-1RAs will likely prove effective for mitigating weight gain in people who smoke, possibly also yielding therapeutic effects on other cardiometabolic outcomes (eg, HbA_{1c}). Because postcessation weight gain is a known barrier to cessation[48] and is associated with greater risk of new-onset type 2 diabetes, preventing weight gain is itself a clinically important objective. As expected, semaglutide-induced weight loss in this study surpassed that observed with exenatide[13] (the first approved GLP-1RA) or dulaglutide[32] (which has a modest weight loss profile relative to semaglutide). An advantage of variable weight loss profiles across GLP-1–based therapies is the ability to prevent postcessation weight gain in people who smoke while maximizing or minimizing weight loss, depending on initial BMI or patient preferences.

A key finding was that semaglutide monotherapy reduced cigarette craving, suggesting that GLP-1–based therapies may reduce craving without concurrent cessation therapies that engage nicotinic acetylcholine receptors. Further trials are needed to determine relative efficacy of GLP-1–based therapies on nicotine craving during monotherapy vs combination treatment (eg, with NRT or varenicline). One possibility is that concurrent NRT augments GLP-1RA–related reductions in craving by preventing withdrawal during nicotine deprivation. Upcoming cessation trials of semaglutide[49] and tirzepatide[50] will inform this question by testing medication both during NRT and after NRT discontinuation. These findings also mirror observed effects of semaglutide on alcohol craving,[24] suggesting that GLP-1RAs may attenuate craving across different addictive drugs.

Exploratory analyses suggested potential effects of semaglutide on other cessation-relevant outcomes. These results indicated greater reductions in withdrawal scores in the semaglutide group, with large effect sizes. Follow-up analyses suggested that these effects appeared driven primarily by WSWS craving and hunger subscales; however, potential reductions on negative mood subscales were also evident. These preliminary results raise the possibility that GLP-1RAs might improve affective symptoms overlapping with common withdrawal symptoms, even in the absence of nicotine deprivation. If replicated in the context of cessation, these findings could imply that GLP-1–based therapies may have protherapeutic effects on withdrawal-type symptoms. Evidence for cognitive-enhancing effects of GLP-1RAs[19-21] may also have implications for withdrawal-associated cognitive deficits, which are implicated in smoking relapse. Exploratory analyses also suggested possible increases in readiness to quit smoking and self-efficacy for resisting cigarettes in semaglutide-treated vs placebo groups, with differences being most pronounced in the second

treatment month. If replicated, these findings raise the interesting possibility that GLP-1–based therapies may lead to changes in cognitive-motivational processes that may increase the likelihood of cessation. While this possibility is speculative, these findings argue for measuring cognitive, motivational, and affective processes in upcoming trials of incretin-based treatments for cessation.

Limitations

These findings should be interpreted in view of study limitations, including the limited sample size. While the sample size limits statistical power and the precision of estimated effects, these effect size estimates provide information for power estimates for future studies, which was a primary aim of this phase 2a trial. While designed as a short-term screening trial, the treatment period is a limitation for estimating medication effects on smoking-related outcomes at higher semaglutide doses. Investigations spanning the full dose range will be important for determining efficacy and safety over longer periods. While sample size precluded examination of BMI as a moderator, initial evidence that GLP-1RAs may differentially change alcohol consumption based on BMI[24,51] make this an important objective for future studies. Additionally, the focus on non–treatment-seeking participants, a common approach in medication screening trials, has both advantages and disadvantages. While less informative for studying smoking cessation, studying non–treatment-seeking people who smoke is relevant for estimating medication effects on smoking-related outcomes in the larger population of people who smoke who are exposed to GLP-1–based therapies outside the context of active cessation attempts.

Conclusions

In this phase 2a randomized clinical trial of non–treatment-seeking people who smoke, semaglutide monotherapy did not significantly improve laboratory smoking reinstatement or reduce weekly CPD but led to greater reductions in laboratory cigarette intake and reduced weekly nicotine craving, also reducing body weight and HbA_{1c}. The potential of GLP-1–based therapies to reduce nicotine craving while preempting negative cardiometabolic outcomes in people who smoke—including postcessation weight gain and risk of new-onset type 2 diabetes—makes it likely that incretin therapies will prove clinically useful for people who smoke.[52] While results of upcoming trials will inform the efficacy of GLP-1–based therapies for cessation, evidence for cardiovascular risk reduction—leading to the recent approval of semaglutide for the prevention of major cardiac events in those with obesity[18]—suggests that incretin-based therapies could offer multifactorial benefits in people who smoke, even irrespective of cessation. This possibility is notable considering the high prevalence of cardiovascular disease in people who smoke and the limited likelihood of long-term cessation following a given quit attempt. From this standpoint, future studies should seek to characterize the long-term cardiometabolic benefits of GLP-1–based therapies in people who smoke and the implications for morbidity and mortality, both within and beyond the context of smoking cessation.

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SUPPLEMENT 1.
Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
eAppendix. Supplementary protocol, analysis and results information
eTable 1. Adverse events by medication condition and dose
eTable 2. Linear mixed models for laboratory outcomes
eTable 3. Change score models for laboratory outcomes
eTable 4. Linear mixed models for weekly cigarettes per day and craving
eTable 5. Linear mixed models for weight and clinical outcomes
eFigure 1. Laboratory smoking lapse procedure
eFigure 2. Pre-to-post-treatment changes in subjective effects to the first cigarette smoked
eFigure 3. Change in Wisconsin Smoking Withdrawal Scale subscale scores

SUPPLEMENT 3.
Data Sharing Statement