

Gender differences in weight gain during attempted and successful smoking cessation on dulaglutide treatment: a predefined secondary analysis of a randomised trial

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ABSTRACT

Background Women seem to have more difficulty quitting smoking than men. This is particularly concerning as smoking puts women at a higher risk of developing smoking-associated diseases. Greater concerns about postcessation weight gain in women have been postulated as a possible explanation.

Methods Predefined secondary analysis of a placebo-controlled, double-blind, parallel-group, superiority randomised trial including 255 adults who smoke daily (155 women, 100 men). Participants received weekly dulaglutide (1.5 mg) or placebo (0.9% sodium chloride) in addition to standardised smoking cessation care (varenicline 2 mg/day plus behavioural counselling) over 12 weeks. We aimed to investigate gender differences in weight change after dulaglutide-assisted smoking cessation. Weight change between baseline and week 12 was analysed as absolute and relative weight change and as substantial weight gain (defined as >6% increase).

Results No gender differences were observed in absolute or relative weight change neither on dulaglutide nor placebo treatment. However, substantial weight gain (defined as >6% increase) in the placebo group was almost five times more frequent in females than males (24% vs 5%). Female patients were less likely to have substantial weight gain on dulaglutide compared with placebo (1% (n=1/83) vs 24% (n=17/72); p<0.001), while this dulaglutide effect was less pronounced in males (0% (n=0/44) vs 5% (n=3/56); p=0.333).

Conclusion Dulaglutide reduced postcessation weight gain in both genders and was very effective in preventing substantial weight gain, which seems to be a specific observation in females.

Trial registration number NCT03204396.

INTRODUCTION

Smoking cessation needs to be a priority in healthcare, and a special focus should be placed on females who smoke: while the smoking prevalence in men is decreasing in many places, these trends are declining slower or even rising in women.¹ This is

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Women seem to have more difficulty quitting smoking than men and there seem to be greater concerns about postcessation weight gain in women.

WHAT THIS STUDY ADDS

⇒ Substantial weight gain (defined as >6% increase) in the placebo group was almost five times more frequent in females than males (24% vs 5%). Dulaglutide, compared with placebo, significantly prevented substantial weight gain in females (1% vs 24%).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results underline the efficacy of dulaglutide in preventing postcessation weight gain in both genders and particularly in women who appear to be more prone to substantial weight gain than men.

particularly concerning as smoking puts women at higher risk of developing diseases such as lung cancer^{2,3} or coronary heart disease than men.⁴⁻⁶ Furthermore, women seem less successful in quitting smoking than men showing higher relapse rates.⁷⁻¹⁰ One possible reason could be postcessation weight gain, which is a major barrier to smoking cessation and seems to be a greater concern for women.¹¹ In a recent retrospective cohort study, weight gain during smoking cessation was associated with failed abstinence in women but not in men.¹² Moreover, young females who smoke heavily seem at particular risk of pronounced weight gain after cessation,¹³ and postcessation weight gain seems to persist longer in women than in men.¹⁴⁻¹⁶ However, postcessation weight gain and negative effects such as the risk of

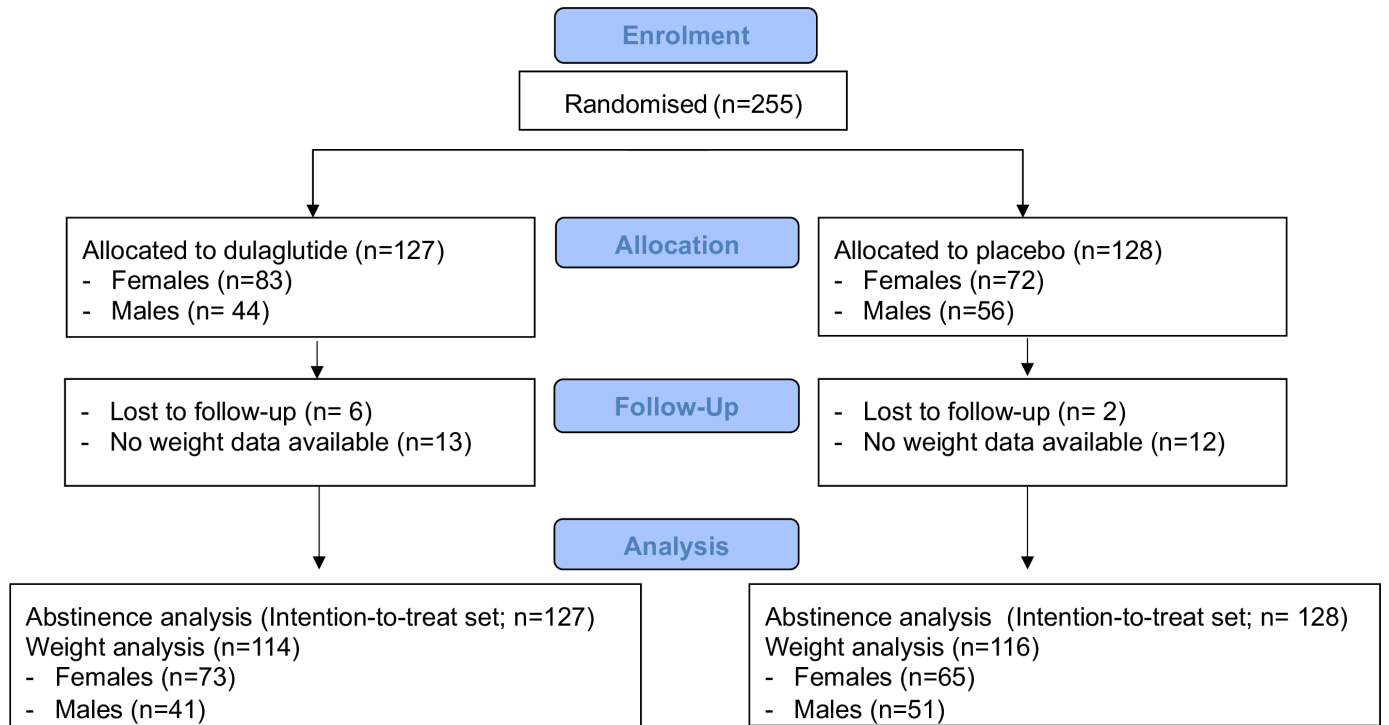


Figure 1 Participant flow diagram.

developing type 2 diabetes are present in both women and men.¹⁷

Glucagon-like peptide 1 (GLP-1) is a gut hormone released on food intake that potentiates glucose-dependent insulin secretion, inhibits glucagon secretion, slows gastric emptying and decreases appetite.¹⁸ Its analogues (GLP-1a) are cornerstones in the treatment of type 2 diabetes mellitus and obesity due to their glucose and weight-lowering properties.¹⁹ Moreover, GLP-1a have attracted attention as a potential smoking cessation therapy as several preclinical and one pilot clinical trial suggested reduced nicotine consumption on GLP-1a treatment.^{20 21} In contrast, the main and previously published results of this randomised controlled trial provided no evidence of a beneficial effect of dulaglutide on abstinence rates after a 12-week treatment compared with placebo.²² Nevertheless, dulaglutide was very effective in reducing postcessation weight gain compared with placebo.²² In this predefined secondary analysis, we aimed to investigate gender differences in postcessation weight change in dulaglutide-treated and placebo-treated females and males.

Assuming that females show greater weight gain after smoking cessation than males which may affect abstinence rates, we hypothesised that they might profit more from the weight-lowering effect of dulaglutide treatment both in terms of weight control and smoking abstinence.

METHODS

Study design and population

This is a predefined secondary analysis of a placebo-controlled, double-blind, parallel-group, superiority,

single-centre randomised trial including 255 participants, conducted at the University Hospital Basel, Switzerland, from 2017 to 2022. The aim of the main study was to investigate dulaglutide as a new smoking cessation therapy. The primary outcomes of the study were point prevalence abstinence rate and postcessation weight at week 12. These primary results as well as full details of the studies' rationale, design, test protocol and statistical analysis have been published previously.²³ Briefly, adults between the age of 18 and 75 years were included if they smoked either ≥ 10 cigarettes per day *or* exhibited at least moderate cigarette dependence (defined by a Fagerstrom²⁴⁻²⁶ score of ≥ 5 points) and agreed to receive concomitant behavioural counselling and pharmacotherapy with varenicline. Participants were excluded if they had pre-existing treatment with GLP-1a, a history of pancreatitis, severe renal insufficiency, unstable psychiatric conditions or anorexia nervosa. In addition to the study medication (see below), participants received standard of care according to current national guidelines²⁷ including pharmacotherapy with the nicotinic receptor partial agonist varenicline of 2 mg/day and behavioural counselling.

All participants signed a written informed consent form before participation, and the study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. The trial was registered at ClinicalTrials.gov (NCT03204396).

Objectives and hypotheses

The main objective was to evaluate gender differences in postcessation weight change after 12 weeks of dulaglutide or placebo treatment.

Table 1 Baseline characteristics

	Females (155)	Males (100)
Age at baseline: median (IQR)	42 (32, 53)	44 (34, 53)
Baseline metabolic parameters		
Weight (kg): mean (SD)	72.1 (13.3)	92.6 (17.0)
BMI (kg/m ²): mean (SD)	26.0 (5.0)	28.9 (4.9)
HbA1c (%): mean (SD)	5.3 (0.5)	5.6 (0.7)
Baseline smoking habits		
Cigarettes/day: median (IQR)	20 (14, 20)	20 (15, 28)
Pack years: median (IQR)	19 (10, 33)	22 (13, 40)
Past cessation attempts: median (IQR)	2 (1, 3)	2 (1, 3)
Fagerstrom score: median (IQR)	7 (6, 8)	7 (6, 8)
Main arguments for cessation: n (%)		
Health in general	119 (77)	80 (80)
Specific health problems	38 (25)	33 (33)
Saving money	47 (30)	29 (29)
Symptoms of smoking	12 (8)	11 (11)
Social pressure	18 (12)	16 (16)
Dependence	30 (19)	13 (13)
Self-concept	34 (22)	15 (15)
Be a model for children	31 (20)	15 (15)
Tobacco-associated disease: n (%)		
Pulmonary disease	37 (24)	20 (20)
Cardiovascular disease	33 (21)	32 (32)
Cerebrovascular disease	7 (5)	3 (3)
Cancer	9 (6)	8 (8)
Gastrointestinal disease	16 (10)	12 (12)
Osteoporosis	9 (6)	1 (1)
Medication: n (%)		
Antihypertensive drugs	23 (15)	28 (28)
Aspirin	7 (5)	12 (12)
Oral anticoagulation	6 (4)	5 (5)
Statins	14 (9)	15 (15)
Oral antidiabetic drugs	3 (2)	2 (2)
Insulin	1 (1)	4 (4)
Proton pump inhibitor	13 (8)	13 (13)
Antipsychotics	15 (10)	8 (8)
Contraceptives	25 (16)	0 (0)

Data are presented in median (IQR), mean (SD) and numbers (%). BMI, body mass index.;

We hypothesised that females compared with males (1) experience greater postcessation weight gain, (2) show lower abstinence rates on placebo treatment and (3) profit more from weight-lowering effects of dulaglutide treatment both in terms of weight control and abstinence rates. Accordingly, we aimed to explore gender-specific dulaglutide effects and gender-specific abstinence rates according to treatment arm. A further outcome included

gender differences in time to quit on dulaglutide and placebo treatment.

Intervention

Participants were 1:1 randomised to dulaglutide or placebo according to a computer-generated randomisation list. The trial medication, consisting of either 0.5 mL dulaglutide or 0.5 mL of 0.9% sodium chloride as placebo, was subcutaneously injected at the study site once weekly during a 12-week treatment phase. Dulaglutide was acquired as Trulicity²⁸ pen 0.75 mg, used for the first injection, and 1.5 mg, injected in the following visits. Participants, healthcare providers and the study team were blinded to treatment allocation. As injection devices of dulaglutide and placebo were not identical, injections were performed by unblinded study staff otherwise not involved in the trial, and participants wore blindfolds during the drug injection. For more detailed methodology, please refer to our previous publications.^{22 23}

Assessments

At baseline, demographic data, haemoglobin A1c (HbA1c), cigarette dependence (Fagerstrom test^{24–26}) and reasons for smoking cessation (by a predefined list of 12 items) were assessed (online supplemental material page 2). Nicotine exposure was assessed by end-expiratory carbon monoxide (CO) measurement (Micro+ Smokerlyzer²⁹) at baseline and on every weekly visit. Weight was assessed at baseline and week 12 using a standard electronic scale. For weight measurements, participants were asked to remove shoes, jackets and extra clothing as well as items in their pockets to achieve comparable circumstances for each measurement using the same electronic scale at each study visit. At week 12, smoking abstinence was recorded as self-reported 7-day smoking abstinence and biochemically confirmed by end-expiratory exhaled CO measurement of ≤10 ppm.

Statistical analysis

Baseline characteristics are summarised using descriptive statistics. Discrete variables are expressed as frequencies (percentage (%) and number of participants (n)). Continuous variables are expressed as median and IQR (25th–75th percentiles) or mean and SD. All analyses were performed using the statistical program R (V.4.2.1 or higher). A two-sided significance level of 0.05 was used for every analysis. No adjustment for multiple testing was performed.

The analyses assessed the difference between females and males in absolute (in kilograms) and relative (in percentage) weight change and abstinence rates (individuals who continued smoking vs individuals who quit smoking) from baseline to week 12 of treatment (dulaglutide vs placebo) according to the intention-to-treat principle (lost participants were counted as individuals who continued smoking). The difference in abstinence was assessed by using logistic regression models, and weight change was assessed by using linear regression models.

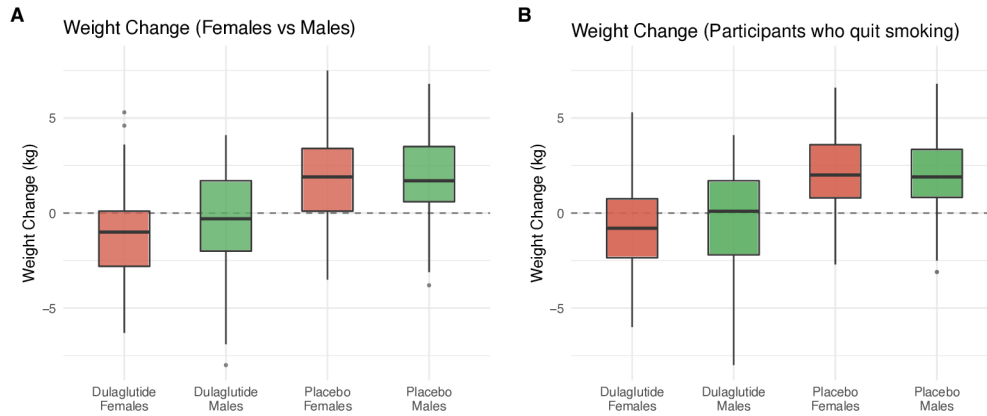


Figure 2 Weight change after 12 weeks in all participants (A) and the subgroup of participants who quit smoking (B).

Estimates were presented with their 95% CI. The models included abstinence or weight change as the dependent variable and gender (females vs males) as a categorical predictor and treatment arm (dulaglutide vs placebo) as an adjusting covariate. In case of significant interaction, the models were analysed and reported for each subgroup separately. The time to quit was analysed descriptively by estimating Kaplan-Meier curves according to gender and treatment. The differences in time to quit were assessed using the log-rank test. As a supplementary analysis, the given outcomes were also assessed only in a subgroup of participants defined as abstinent by the end of the treatment phase of 12 weeks, referred to as individuals who quit smoking. Furthermore, we assessed the proportion of participants experiencing substantial weight gain (post hoc defined as a clinically meaningful increase of >6% within the 12 weeks of treatment) and compared the groups using the χ^2 or Fisher's exact test, respectively. The analysis plan for the present study was not pre-registered.

RESULTS

Baseline characteristics

Of the 255 participants, 155 (61%) were female and 100 (39%) were male (figure 1). The median (IQR) age was 42 (32, 53) in females and 44 (34, 53) in males. Mean (SD) weight was 72.1 (13.3) kg in females and 92.6 (17.0) kg in males, while body mass index (BMI) was 26.0 (5.0) kg/m² and 28.9 (4.9) kg/m², respectively. At inclusion, females smoked a median of 20 (IQR 14, 20) cigarettes per day and had cumulated 19 (10, 33) pack years, while males smoked 20 (15, 28) cigarettes per day and had 22 (13, 40) pack years. Arguments for smoking cessation were balanced between genders, most commonly *general health* (77% in females vs 80% in males), followed by *financial reasons* (30% vs 29%) and *specific health problems* (25% in females vs 33% in males). No gender differences in tobacco-associated diseases or previous cessation attempts were observed. Baseline characteristics are presented in table 1.

Table 2 Change in weight according to the treatment group and smoking status

Weight change (kg), dulaglutide versus placebo			Weight change (kg), individuals who quit versus who continued smoking according to treatment groups		
Estimate (95% CI)	P value	Comparison group	Estimate (95% CI)	P value	Comparison group
-3.1 (-3.9, -2.3)	<0.001	Females Dulaglutide versus placebo	-2.8 (-3.8, -1.7)	<0.001	Females who quit smoking Dulaglutide versus placebo
-2.5 (-3.7, -1.4)	<0.001	Males Dulaglutide versus placebo	-2.6 (-4.1, -1.1)	<0.001	Males who quit smoking Dulaglutide versus placebo
-0.6 (-0.4, 1.7)	0.240	Dulaglutide Females versus males	0.3 (-0.6, 1.2)	0.506	Individuals who quit smoking Females versus males
0.1 (-0.8, 1.0)	0.841	Placebo Females versus males	1.3 (-0.1, 2.6)	0.068	Individuals who continued smoking Females versus males

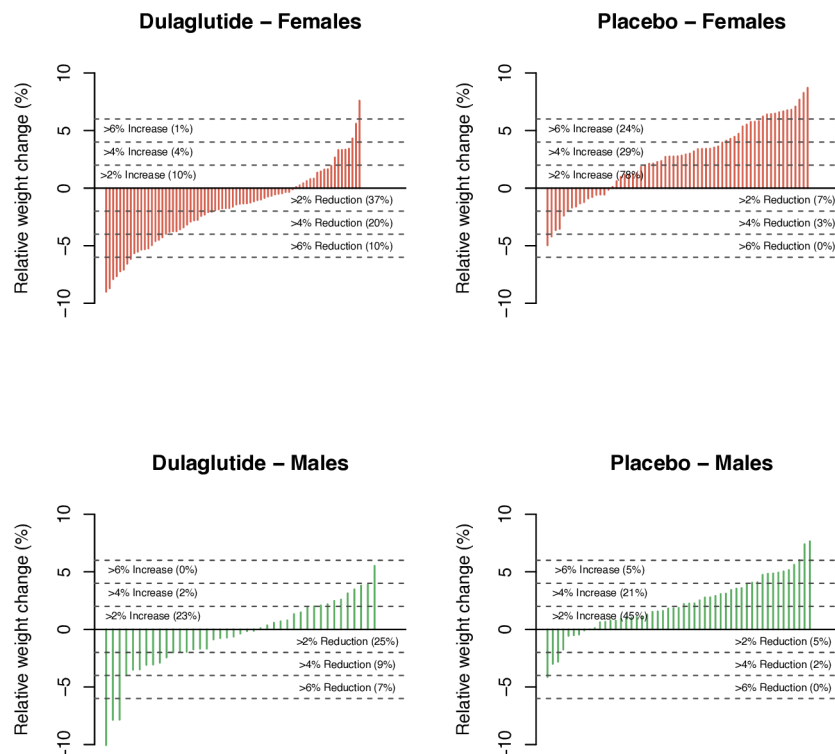


Figure 3 Weight change after 12 weeks relative to initial body weight in females and males, separated by treatment arm.

Weight change from baseline to week 12

Absolute and relative weight changes in females and males were similar according to treatment group and smoking status. In females, weight decreased by -1.2 (2.5) kg/ -1.8 (3.4) % on dulaglutide compared with $+1.9$ (2.4) kg/ $+2.6$ (3.3) % gained on placebo (difference: -3.1 kg, 95% CI $(-3.9, -2.3)$; $p < 0.001$ / -4.3% , 95% CI $(-5.4, -3.2)$; $p < 0.001$) after 12 weeks of treatment. In males, it decreased by -0.6 (3.1) kg/ -0.6 (3.3) % on dulaglutide compared with $+1.9$ (2.3) kg/ $+2.1$ (2.5) % gained on placebo (difference: -2.5 kg, 95% CI $(-3.7, -1.4)$; $p < 0.001$ / -2.7% , 95% CI $(-5.4, -3.2)$; $p < 0.001$) (figure 2, table 2).

Dulaglutide was equally effective in reducing absolute weight gain in females and males (difference: 0.6 kg, 95% CI $(-0.4, 1.7)$; $p = 0.240$). Analysis of relative weight change lacked evidence for higher effectiveness of dulaglutide in females (difference: 1.2%, 95% CI $(-0.1, 2.5)$; $p = 0.073$).

The results were similar in the placebo group showing no statistically significant gender difference in absolute or relative weight change (difference: 0.1 kg, 95% CI $(-0.8, 1.0)$; $p = 0.841$ / -0.4% , 95% CI $(-1.5, 0.7)$; $p = 0.442$).

In the subgroup of females who quit smoking, weight decreased by -0.7 (2.5) kg/ -1.1 (3.4) % on dulaglutide compared with $+2.1$ (2.3) kg/ $+2.9$ (3.1) % gained on placebo (difference: -2.8 kg, 95% CI $(-3.8, -1.7)$; $p < 0.001$ / -4.0% , 95% CI $(-5.3, -2.7)$; $p < 0.001$). Among males who quit smoking, it decreased by -0.5 (3.6) kg/ -0.4 (3.7) % on dulaglutide compared with $+2.1$ (2.3) kg/ $+2.3$ (2.4) % gained on placebo (difference: -2.6 kg, 95% CI $(-4.1, -1.1)$; $p < 0.001$ / -2.7% , 95% CI $(-4.2, -1.1)$; $p = 0.001$) (online supplemental figure S1, table 2). Our

data found no gender differences among individuals who quit smoking in absolute or relative weight change neither on placebo (difference: 0.0 kg, 95% CI $(-1.0, 1.0)$; $p = 0.954$ / -0.6% , 95% CI $(-1.8, 0.6)$; $p = 0.340$) nor on dulaglutide (difference: 0.2 kg, 95% CI $(-1.2, 1.6)$; $p = 0.762$ / 0.7% , 95% CI $(-0.9, 2.3)$; $p = 0.382$).

Substantial weight gain (defined as $>6\%$ increase) was almost five times more frequent in females than males on placebo (24% vs 5%) (figure 3). Of note, substantial weight gain in females on dulaglutide was significantly less frequent compared with placebo (1% (n=1/83) vs 24% (n=17/72); $p < 0.001$), while no such dulaglutide effect was observed in males (0% (n=0/44) vs 5% (n=3/56); $p = 0.333$) (figure 3). This was consistent in the subgroup of individuals who quit smoking, that is, substantial weight gain was significantly less frequent on dulaglutide compared with placebo (2% (n=1/51) vs 21% (n=10/47); $p = 0.007$) in females, while no such dulaglutide effect was observed in males (0% (n=0/29) vs 8% (n=3/36); $p = 0.319$) (online supplemental figure S2).

Absolute values for BMI, weight at baseline and week 12 stratified by smoking status and treatment can be found in online supplemental tables S1 and S2.

Abstinence rates and time to quit

We found similar abstinence rates between females and males, irrespective of treatment (figure 4). After 12 weeks, 63% (n=98/155) of females and 65% (n=65/100) of males were abstinent. Sixty-five per cent (n=47/72) of females on placebo and 61% (n=51/83) of females on dulaglutide were abstinent. Similarly, 64% (n=36/56) of males on placebo and 66% (n=29/44) of males on

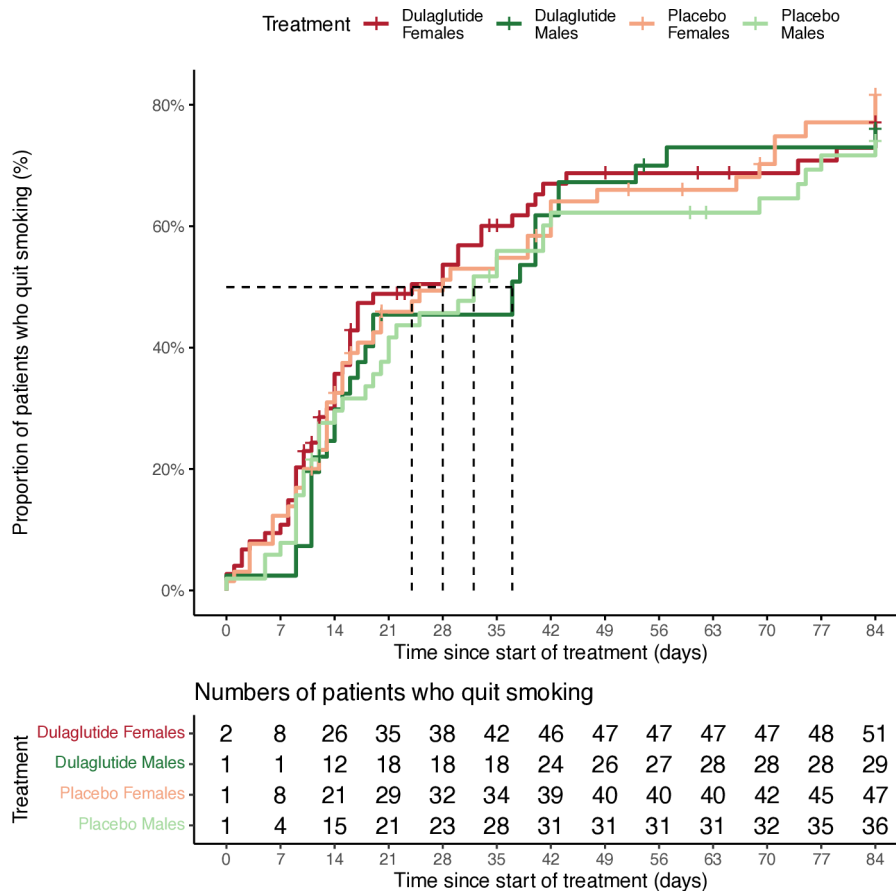


Figure 4 Abstinence rates and time to quit among all participants, separated by gender and treatment arm.

dulaglutide were abstinent. Our data provide no evidence for either a direct association of gender with abstinence (OR 1.04, 95% CI (0.50, 2.17); $p=0.907$) or that the effect of gender-specific abstinence might depend on dulaglutide (interaction term: $p=0.661$).

In females, after 39 and 30 days, 50% of participants in the placebo and dulaglutide group, respectively, had quit smoking and remained abstinent until the end of treatment; whereas in males, after 35 and 40 days, 50% of participants in the placebo and dulaglutide group, respectively, had quit smoking and remained abstinent until the end of treatment. Our data provide no evidence for a difference in time to quit between the four groups (log-rank test: $p=0.98$) (figure 4).

DISCUSSION

Overall, in this predefined secondary analysis of a randomised placebo-controlled trial of dulaglutide during smoking cessation, we observed similar absolute and relative weight changes between genders, but a high rate of substantial weight gain in females treated with placebo. Dulaglutide, compared with placebo, significantly prevented postcessation weight gain in both genders and specifically counteracted substantial weight gain in females. We found no gender-dependent dulaglutide effect on abstinence rates, which were similar in females and males.

The gender effect on postcessation weight is controversially discussed.^{13 15 30–32} In a large randomised clinical trial, both genders showed similar absolute weight gain 1 year after cessation, but women showed more significant relative weight gain than men—which was even more pronounced after 2 years—and were more often affected by a substantial weight gain of $>12\%$.¹⁶ The extent of weight gain may therefore be greater in women, which is also supported by other data³⁰ and our own observation: women in the placebo group showed a higher proportion of substantial weight gain of $>6\%$ increase than men (24% vs 5%). Moreover, the risk of postcessation weight gain may change over time or depend on other factors such as the degree of nicotine dependence or age. This is supported by merged data from two randomised controlled studies, including a total of 750 participants showing the highest risk of postcessation weight gain in young and heavily smoking females while gender per se was not a risk factor.¹³ The decision to add a weight control therapy in the smoking cessation setting could, therefore, be based on an individual risk assessment and our data suggest that an adjunct dulaglutide treatment could be particularly useful for patients facing a high risk of substantial weight gain after smoking cessation such as women. Another target group could be individuals of both genders who failed several cessation attempts due to weight gain.

In terms of GLP-1a treatment, gender is not an important predictor of its action on fasting blood glucose and HbA1c, while the gender effect on weight reduction is less clear.³³ In our study, we observed a trend towards higher effectiveness of dulaglutide on relative weight change in females than males. This aligns with post hoc analyses of seven randomised clinical trials evaluating dulaglutide treatment in patients with diabetes,³⁴ suggesting that the dulaglutide effect on weight loss is more pronounced in women.³⁴ Interestingly, in our study, dulaglutide prevented substantial weight gain particularly in women, supporting the hypothesis of a gender-dependent effect of dulaglutide on weight. Also, in studies with the GLP-1a semaglutide, females experienced greater weight loss than males at a given exposure level of semaglutide.³³

Surprisingly and contrary to our assumption, the positive GLP-1a effects of weight had no impact on quit rates neither in females nor males in our study.²² Although unequivocal evidence-based data are lacking, the prevailing opinion in the broader literature is that weight gain is a key factor limiting abstinence in women. Our findings do not support this notion—at least not with regard to short-term abstinence—and rather suggest that (gender-specific) reasons for successful quitting are multi-layered and more complex. In fact, observational study data pointed out biopsychosocial aspects that influence quitting outcomes among genders.⁹ Whether dulaglutide or another weight control treatment would limit relapse rates in females or males at a later time point cannot be answered with our study.

Similar abstinence rates in females and males in our study are in line with a systematic review including eight studies,³⁵ while others showed divergent results. In particular, pooled data from two large randomised smoking cessation trials suggested that women were less likely to be abstinent at 6 months while abstinence rates were less divergent at an earlier point in time of 8 weeks.⁷ In our study, we assessed abstinence rates at 12 weeks. During these 12 weeks, participants were closely monitored (with weekly visits including biofeedback via CO measurements), which could have positively influenced quit rates of both genders. We cannot exclude that women in general may have more difficulties maintaining abstinence in a less guided setting and at later stages. In fact, a study focusing on long-term abstinence (12 months) suggested female sex as a predictor of relapse.¹⁰ Interestingly, the number of previous quit attempts in our female and male participants at baseline was equal and would not give rise to this assumption.

It would have been interesting to know whether and how our participants were concerned about postcessation weight gain. Unfortunately, we did not assess personal barriers to smoking cessation or reasons for relapse. Regarding arguments for smoking cessation, health concerns and financial reasons were among the most often recorded answers, and again no gender differences were found. In the literature, arguments for smoking

cessation vary widely and seem to depend more on different sociocultural norms and expectations than on gender per se.^{36 37}

Lastly, it is important to consider whether gender differences in varenicline efficacy may have influenced our results. Although one study showed a greater benefit of varenicline relative to other smoking cessation medication in women,³⁸ smoking cessation outcomes on varenicline are similar for both genders.³⁹ In terms of weight gain, a meta-analysis showed a modest reduction of postcessation weight gain by varenicline compared with placebo treatment; however, these data were not stratified by gender.⁴⁰

Strength and limitations

This study has the following limitations. First, the prospect of a weight-controlling treatment with GLP-1a may have led to a selection of weight-conscious participants. Second, the study design with weekly visits required a very high motivation of participants. Both factors have most probably influenced the results and our cohort may, therefore, not be directly comparable with others. Third, as discussed above, gender differences in abstinence rates and weight change may develop over time and only be present at a later stage than assessed in this study. Lastly, participants self-identified either as female or male, and no other gender categories were offered; future studies should acknowledge that more than two gender categories exist.

The strength of our study is the prospective randomised design with carefully collected data, including standardised weight measurements. Our results underline the effectiveness of dulaglutide in postcessation weight gain, especially in women prone to substantial weight gain within a short period. This study addresses an important topic and provides knowledge on gender differences in abstinence rates, weight development and dulaglutide action during smoking cessation.

CONCLUSION

In conclusion, our results show that absolute and relative postcessation weight gains after 12 weeks are similar in both genders, while substantial weight gain seems to be a greater problem in females. Dulaglutide was effective in reducing postcessation weight gain in both genders and specifically in preventing substantial weight gain in women. Contrary to our assumption, the weight-controlling effect of dulaglutide did not appear to have a significant impact on short-term abstinence in either females or males. Nevertheless, the possibility of personalised weight control treatment with GLP-1a in the smoking cessation setting is of great interest, and our data suggest that women at greater risk of substantial weight gain may benefit most.

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Contributors FB: investigation, data curation, formal analysis, writing—original draft preparation (lead). CA: formal analysis (lead), visualisation, writing—original draft preparation. SL: investigation, conceptualisation, writing—review and editing. TB and AM: conceptualisation, writing—review and editing. CB: investigation, project administration. MC-C: conceptualisation, supervision, writing—review and editing. BW: conceptualisation, formal analysis, methodology, funding acquisition, project administration, supervision, writing—review and editing. FB, CA and BW are responsible for the overall content as guarantors. All authors edited and approved the final manuscript.

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Patient consent for publication Not applicable.

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Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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