The factors predicting glucose and weight response to injectable semaglutide (Ozempic): real-world data from the Association of British Clinical Diabetologists' audit programme

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Abstract

Background: Previous randomised controlled trials have observed individual differences in response to Glucagon-Like Peptide-1 Receptor Agonists (GLP1RA) according to baseline characteristics such as glycated haemoglobin (HbA_{1c}) and weight. The Association of British Clinical Diabetologists (ABCD) launched a nationwide UK audit in January 2019 to assess the clinical utility, efficacy and safety of injectable semaglutide in routine practice. The aim of this analysis was to investigate associations between baseline characteristics and HbA_{1c} and weight reductions with semaglutide in real-world use.

Methods: Data were extracted from the secure online tool and individuals who had baseline and follow-up data available within a defined 6 (3-9) month window were included. Variables were assessed as both continuous variables and categorical variables in a multivariate regression model. Missing data were multiply imputed.

Results: In total, 620 individuals were included. Baseline characteristics: (mean±SD) age was 58.7±10.7 years, HbA_{1c} 81.6±18.5 mmol/mol (9.5±1.7%), weight 108.2±24.2 kg and body mass index (BMI) 37.6±7.6 kg/m^2. Median diabetes duration was 11.2 years (IQR 6.6-16) and 50.5% (313/620) of subjects were male. The median follow-up time was 0.5 years. HbA_{1c} reduced by 14.9 mmol/mol (95% CI 13.5, 16.1) [-1.4% (95% CI -1.2, -1.5)]; p<0.001; and weight reduced by 4.2kg (95% CI 3.6, 4.8; p<0.001). Higher HbA_{1c}, younger age and GLP1RA naïvety were associated with larger HbA_{1c} reduction. Higher baseline weight/BMI and GP1RA naïvety were associated with larger weight reduction.

Conclusion: In this real-world study, baseline HbA_{1c} and weight were important predictors of HbA_{1c} and weight reduction outcomes following initiation of semaglutide in routine clinical practice. Our data mirror existing randomised controlled trial data, but further evidence is being collected over a longer follow-up period.

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Introduction

Type 2 diabetes (T2DM) is estimated to affect 3.4 million people in England and 537 million worldwide.[1,2] It is increasingly recognised as a heterogenous condition.[3-5] Individuals with different clinical phenotypes may have different responses to the range of therapies currently available and there is increasing interest in utilising precision medicine approaches to stratify individuals towards the best treatment option for them.[6,7] Whilst work is ongoing to identify potential biomarkers and genetic factors, their cost may prohibit their wide use in public-funded healthcare systems.[8] Routinely measured clinical data may be useful to stratify individuals, identifying those who are most likely to benefit from a given treatment, though evidence in this area is remains limited.[5]

Glucagon-like peptide 1 receptor agonists (GLP1RAs) are increasingly used in the management of T2DM, with greater emphasis on their use in recent national and international

guidelines.[9-11] Semaglutide is a once-weekly injectable GLP1RA licensed for the treatment of T2DM; it is also available as a once-daily oral preparation.[12]

The SUSTAIN series of randomised controlled trials consistently demonstrated efficacy of semaglutide, with mean weight loss of 4.11 kg and HbA_{1c} reductions of 15 mmol/mol at the maximally titrated 1mg dose when results were pooled by meta-analysis.[13] Reductions in major adverse cardiovascular events have also been reported across the trials.[14,15] Although SUSTAIN-6 reported increased rates of retinopathy, these findings were not observed across the trials by meta-analysis.[16,17] However, the trials included were of relatively short duration: work is ongoing to understand retinopathy risk with more prolonged follow-up.[18]

Several trials reported no difference in HbA_{1c} and weight response to semaglutide across individuals with different baseline clinical characteristics,[19] but two reported differential responses across baseline characteristics. First, SUSTAIN-8 demonstrated larger HbA_{1c} reductions in individuals with higher baseline BMI and HbA_{1c} levels.[20] Second, real-world evidence from an Italian clinic found HbA_{1c} reductions were greatest at six months in individuals with higher baseline HbA_{1c}, greater weight loss and longer diabetes duration.[21] This latter study also found that higher baseline BMI predicted greater weight loss and that GLP1RA-naïve individuals reached similar end-points to those switching from alternative GLP1Ras. Previous Association of British Clinical Diabetologists (ABCD) audit programme has also reported the additional benefits of switching to semaglutide from alternative GLP1RA preparations.[22] Only minor differences have been observed in terms of race or ethnicity across the SUSTAIN trails.[23]

The nationwide ABCD injectable semaglutide audit was launched in January 2019 with the aim to collect routine clinical data on individuals using semaglutide in the UK and to assess outcomes in real-world clinical practice. The aim of this analysis was to assess the clinical characteristics which may predict HbA_{1c} and weight responses associated with semaglutide in the real world, using data from the ABCD audit.

Methods

Participating centres were invited to collect anonymised, routinely collected, clinical data on individuals commenced on injectable semaglutide (0.25-1 mg, Ozempic) to a secure online tool. De-identified data were then extracted for analysis in this cohort study. All individuals with baseline data and at least one follow-up entry for HbA_{1c} and/or weight were included. Individuals with large amounts of missing data in key covariates of imputation (e.g. age, gender) were excluded (n=14). The follow-up period was defined as 6 months, with a window of 3-9 months. Key co-variates were identified as follows: baseline HbA_{1c}, baseline weight, age, gender, duration of diabetes and previous GLP1RA use. Ethnicity could not be assessed due to missing data. For all other variables, missing data were multiply imputed with 10 imputations, and Rubin's rules were applied for the analysis.[24]

HbA_{1c} and both absolute and relative weight change from

Table 1. Baseline characteristics of the included individuals, reported as mean±SD or median (IQR)

Characteristic		n=620
Age, years ± SD		58.7 ± 10.7
Male, % (N)		50.5% (313)
Median diabetes duration, year (IQR)		11.2 (6.6-16)
Mean HbA_{1c},	% ± SD	9.2 ± 1.3
	mmol/mol ± SD	81.6 ± 18.5
Mean BMI, kg/m^2 ± SD		37.6 ± 7.6
Mean weight, kg ± SD		108.2 ± 24.2
Mean serum creatinine, umol/L ± SD		79.8 ± 27.6
Mean systolic BP, mmHg ± SD		133.4 ± 14.6
Mean diastolic BP, mmHg ± SD		78.2 ± 9.8
Total cholesterol, mmol/L ±SD		4.3 ± 1.1
ALT, u/L ±SD		31.1 ± 17.5
Previous GLP1 use, %		23.5%

BMI, body mass index; eGFR, estimated glomerular filtration rate; BP, blood pressure; IQR, interquartile range; ALT, alanine aminotransferase; SD, standard deviation

Table 2. Multivariate linear regression models and coefficients for both change in HbA_{1c} (mmol/mol) and weight (kg).

Outcome	Covariate	β (95% CI)†	P value
-ΔHbA$_{1c}$, mmol/mol	Age, years	-0.01 (-0.14, 0.13)	0.874
	Gender, male	-0.39 (-3.13, 2.37)	0.783
	Baseline HbA$_{1c}$, mmol/mol	6.8 (6.05, 7.64)	**<0.001**
	Baseline weight, kg	-0.08 (-0.15, -0.02)	**0.007**
	Diabetes duration, years	-0.17 (-0.37, 0.03)	0.096
	Previous GLP1RA use*	-4.05 (-7.42, -0.69)	**0.018**
ΔWeight, Kg	Age, years	0.02 (-0.04, 0.09)	0.482
	Gender, male	-0.71 (-1.97, 0.55)	0.270
	Baseline HbA$_{1c}$, mmol/mol	-0.01 (-0.01, 0.01)	0.792
	Baseline weight, kg	0.04 (0.01, 0.07)	**0.004**
	Diabetes duration, years	-0.06 (-0.16, 0.04)	0.245
	Previous GLP1RA use*	-1.39 (-2.98, 0.19)	0.084
-ΔWeight, % baseline	Age, years	0.01 (-0.54, 0.06)	0.861
	Gender, male	-0.67 (-1.81, 0.47)	0.249
	Baseline HbA$_{1c}$, mmol/mol	-0.02 (-0.08, 0.04)	0.594
	Baseline weight, kg	-0.01 (-0.31, 0.02)	0.584
	Diabetes duration, years	-0.06 (-0.15, 0.03)	0.208
	Previous GLP1RA use*	-1.14 (-2.57, 0.29)	0.119

*GLP1RA, Glucagon-like peptide-1 receptor agonist
†Negative values represent smaller changes from baseline per one-unit change in covariate. Positive values represent larger changes from baseline

baseline were assessed using a multivariate linear regression analysis incorporating the above characteristics into the model as continuous covariates. The overall model co-efficient and significance levels were also calculated and reported. Subgroup analyses were then performed by classifying these characteristics into groups as follow:

- Age – <60 years; ⩾60 years
- Gender
- Duration of diabetes – <10 years; ⩾10 years
- HbA_{1c} – 48-64 mmol/mol [6.5-8%]; 64.1-80 mmol/mol [8-9.5%]; >80 mmol/mol [>9.5%]
- BMI – <30 kg/m^2; 30-40 kg/m^2; >40 kg/m^2
- Previous GLP1RA use

Statistical significance was defined as p<0.05. When including multiple groups pairwise comparisons were adjusted for multiple comparisons using a Bonferroni correction. All analyses were performed in Stata 16.

The ABCD audit programme is approved by the Confidentiality Advisory Group and a Caldicott Guardian.[25]

Results

In total 620 individuals were included in this analysis. The flow diagram for inclusion in this analysis is available in Appendix 1 (online at www.bjd-abcd.com. The baseline characteristics are summarised in table 1.

Over a median follow-up time of 0.5 years (0.4-0.7), across the entire population HbA_{1c} reduced by 14.9 mmol/mol (95% CI 13.5, 16.1; p<0.001) [-1.4% (95%CI -1.2, -1.5)]. Absolute weight reductions of 4.2kg (95% CI 3.6-4.8; p<0.001) and relative weight reductions of 3.9% (95% CI 3.4-4.5%; p<0.001) were observed.

The models and coefficients calculated for baseline characteristics when used in continuous data format are displayed in table 2. The coefficients represent the difference in HbA_{1c} reduction per-one unit change in the covariate assessed (for continuous values) or compared to reference (for categorical i.e. GLP1RA-naïve vs previous GLP1RA use). Baseline

Figure 1. Forest plot showing change in HbA_{1c} amongst different subgroups. Results non-significant unless other stated. *P<0.05

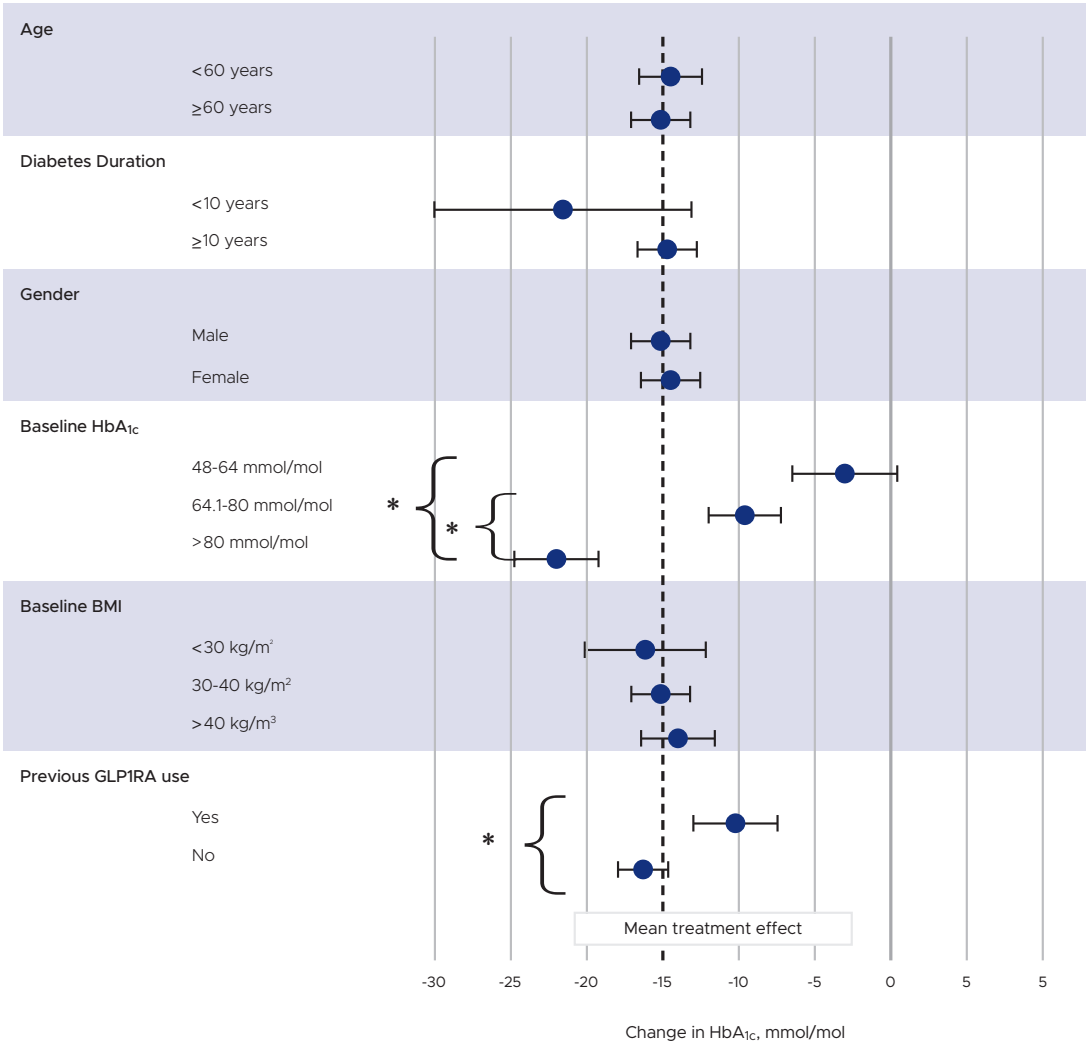
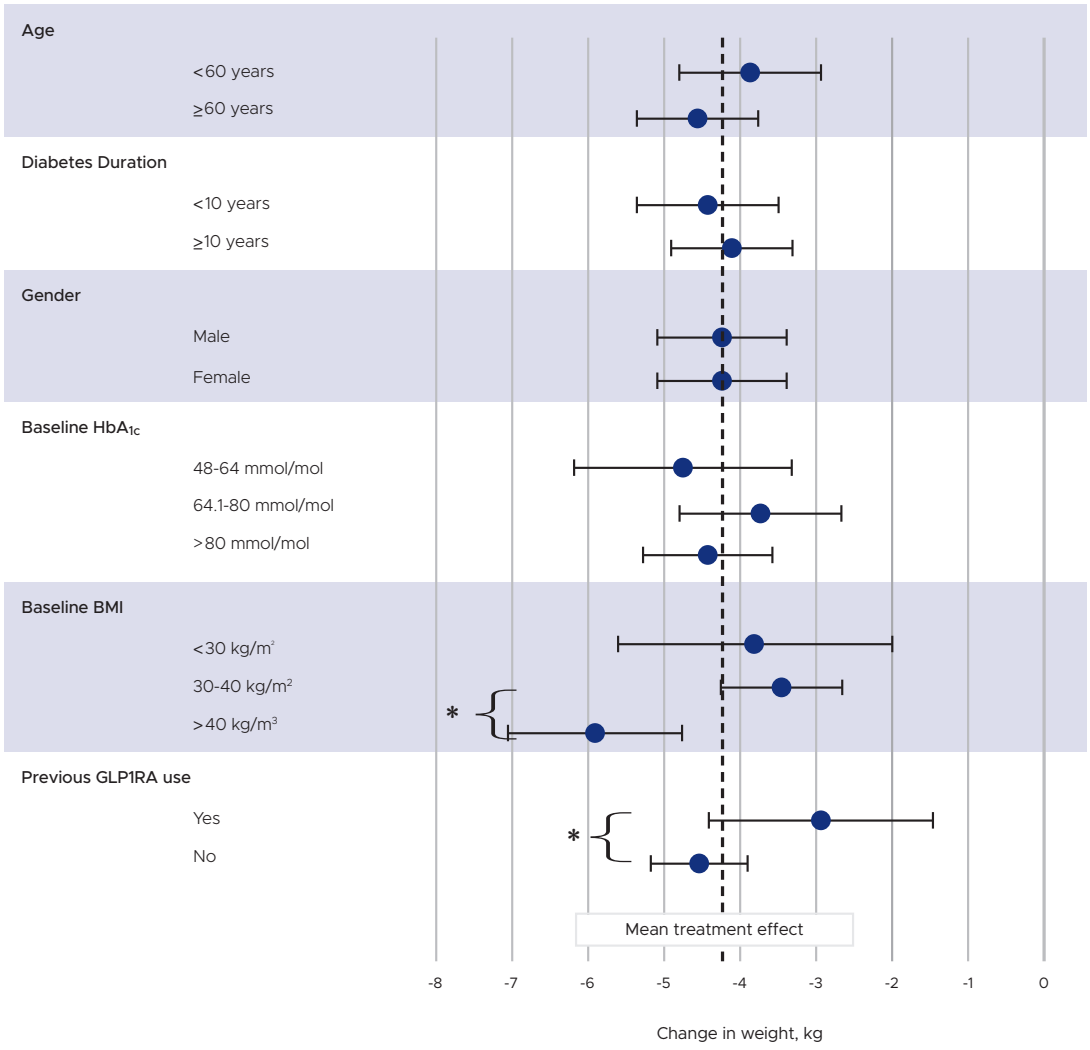


Figure 2. Forest plot showing change in absolute weight amongst different subgroups. Results non-significant unless other stated. *P<0.05



HbA_{1c}, baseline weight and previous GLP1RA use were significant predictors of HbA_{1c} response to injectable semaglutide. Those with high baseline HbA_{1c} levels had greater HbA_{1c} reductions, and those switching from an alternative GLP1RA to semaglutide had attenuated HbA_{1c} reductions.

Only baseline weight significantly predicted weight loss response to semaglutide, although previous GLP1RA use was trending towards statistical significance. Those with higher weight at baseline lost more weight in association with injectable semaglutide use. For relative weight change, no factors predicted weight loss in response to semaglutide.

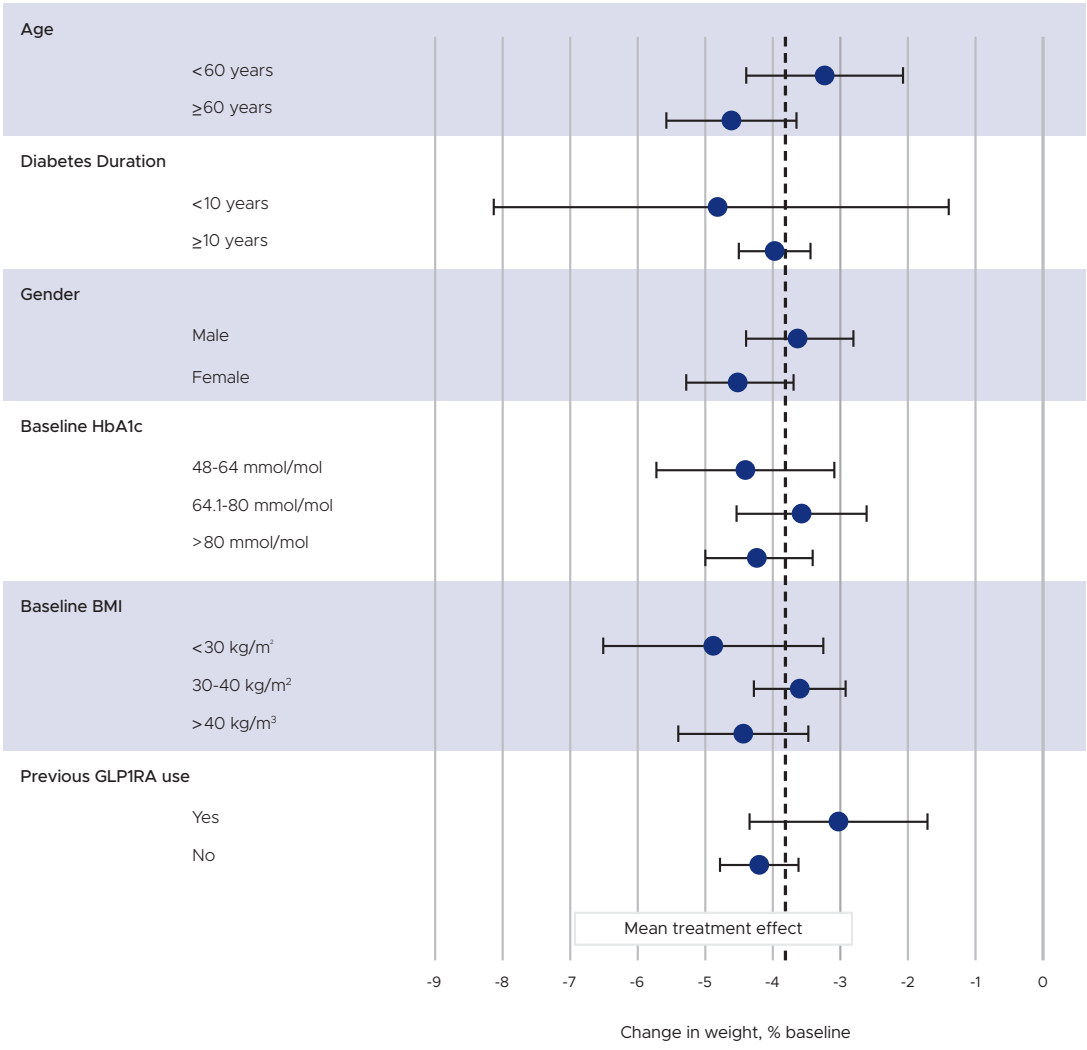
The change in HbA_{1c} from baseline in the subgroup analysis is demonstrated in figure 1. Those with HbA_{1c} ⩾80 mmol/mol (9.5%) had larger HbA_{1c} reductions than those in the lower HbA_{1c} groups, and those switched from alternative GLP1RA drugs had a smaller HbA_{1c} reduction than GLP1RA-naïve individuals. This persisted for relative HbA_{1c} changes, although we have not reported these as we considered they would not be clinically meaningful. In addition, individuals aged <60 years had greater HbA_{1c} reductions than those aged ⩾60 years.

The change in absolute weight from baseline in the subgroup analysis is demonstrated in figure 2. Those with BMI >40 kg/m^2 at baseline had larger weight reductions associated with semaglutide than those with BMI 30-40 kg/m^2 at baseline but not those with BMI <30 kg/m^2. Those who switched to semaglutide from an alternative GLP1RA were experienced less weight loss than GLP1RA-naïve individuals. The relative change in weight from baseline is demonstrated in figure 3. No statistically significant differences were noted between subgroups.

Discussion

Our results from the ABCD audit programme demonstrate that HbA_{1c} and both absolute and relative weight reductions with injectable semaglutide translate evidence from randomised controlled trials into real-world clinical practice.

Figure 3. Forest plot showing change in relative weight (percentage of baseline weight) amongst different subgroups. Results non-significant unless other stated. *p<0.05



The HbA_{1c} and weight reductions observed were comparable to those in the SUSTAIN trials.[13,20] Additionally, our results mirrored the findings from SUSTAIN-8 in that those with higher HbA_{1c} and weight baseline achieved larger reductions by follow-up.[20] There was no significant difference noted between individuals with BMI <30 kg/m^2 and those with BMI >40 kg/m^2 .This is likely due to relatively small numbers in the lowest BMI group (n=74).

We did not observe any difference in response across different diabetes durations, in contrast to reports from SUSTAIN-8 and the real-world Italian study highlighted in the introduction.[20,21] We report similar observations to SUSTAIN-8, with a statistically significant impact of baseline weight on HbA_{1c} change, with heavier individuals achieving statistically larger reductions.[20] It should be noted, however, that the coefficient for this is small, and therefore unlikely to be clinically meaningful. The difference across weight did not persist within the subgroup analysis.

GLP1RA-naïve individuals had larger HbA_{1c} and weight reductions than those switching from other GLP1RA medications, although reductions were observed in both groups. This is a finding we have reported previously and that was reported in SUSTAIN-8.[20,22]

Strengths and limitations

The pragmatic real-world study design allows us to observe the use of injectable semaglutide in clinical practice and compare findings in this population to existing RCT data. Our findings confirm that trial results can be generalised to UK clinical practice, despite clinical practice including individuals who are less closely monitored or who perhaps have more extreme baseline characteristics and would therefore have been excluded from trials. In our analysis, baseline HbA_{1c} (81.6 vs 67.2 mmol/mol in SUSTAIN-8) and weight (108 kg vs 90.6 kg in SUSTAIN-8) were higher, and diabetes duration (11.2 years vs 7.5 years in SUSTAIN-8) was longer than in clinical trials. If drug

Key messages

- Injectable semaglutide use in the real world is associated with weight and HbA_{1c} reductions comparable to clinical trial data
- Those with higher HbA_{1c} levels achieve larger HbA_{1c} reductions at follow-up and may benefit most from treatment
- Those with higher weight at baseline achieve larger absolute, but not relative, weight reductions
- This study utilises data from routine UK clinical practice and provides supportive evidence to complement randomised controlled trial data. It may aid in the selection of therapies for individuals seen in clinic

shortages persist these data may help in guiding who may benefit the most from semaglutide.[26]

Real-world data have their limitations. Although the use of multiple imputations may mitigate problems caused by missing data, it does not resolve this completely. Nonetheless, we excluded individuals with high levels of missing data in key covariates. Notably, dose data were not available. Although it is assumed that individuals were maximally titrated, assessment or adjustment for doses was not possible. Additionally, unobserved confounders may impact the results but we are reassured that our findings complement and mirror the existing extensive data on semaglutide well. Ethnicity and deprivation data were not available and further work should focus on uptake and outcomes in these key groups to assess real-world equitability.

Conclusion

In this real-world analysis from the ABCD audit programme, injectable semaglutide was associated with greater HbA_{1c} reduction in those who were younger, vs. older, and in those who had higher, vs. lower, baseline HbA_{1c}. Weight reductions were largest in those who weighed most at baseline. Whilst reductions in weight and HbA_{1c} were observed in individuals switching to semaglutide from other members of the GLP1RA class, these were smaller than in GLP1RA-naïve individuals. Data collection for the ABCD audit is ongoing, and further follow-up will allow us to assess the impact of semaglutide on key outcomes in the long term.

Conflict of interest TSJC has received speaker fees and/or support to attend conferences from NovoNordisk, Lilly, Sanofi, Abbott Diabetes Care, Insulet and Dexcom.
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Ethics statement This study utilises data from a clinic audit and was assessed against health regulatory authority criteria. No ethical approvals were required for this analysis.

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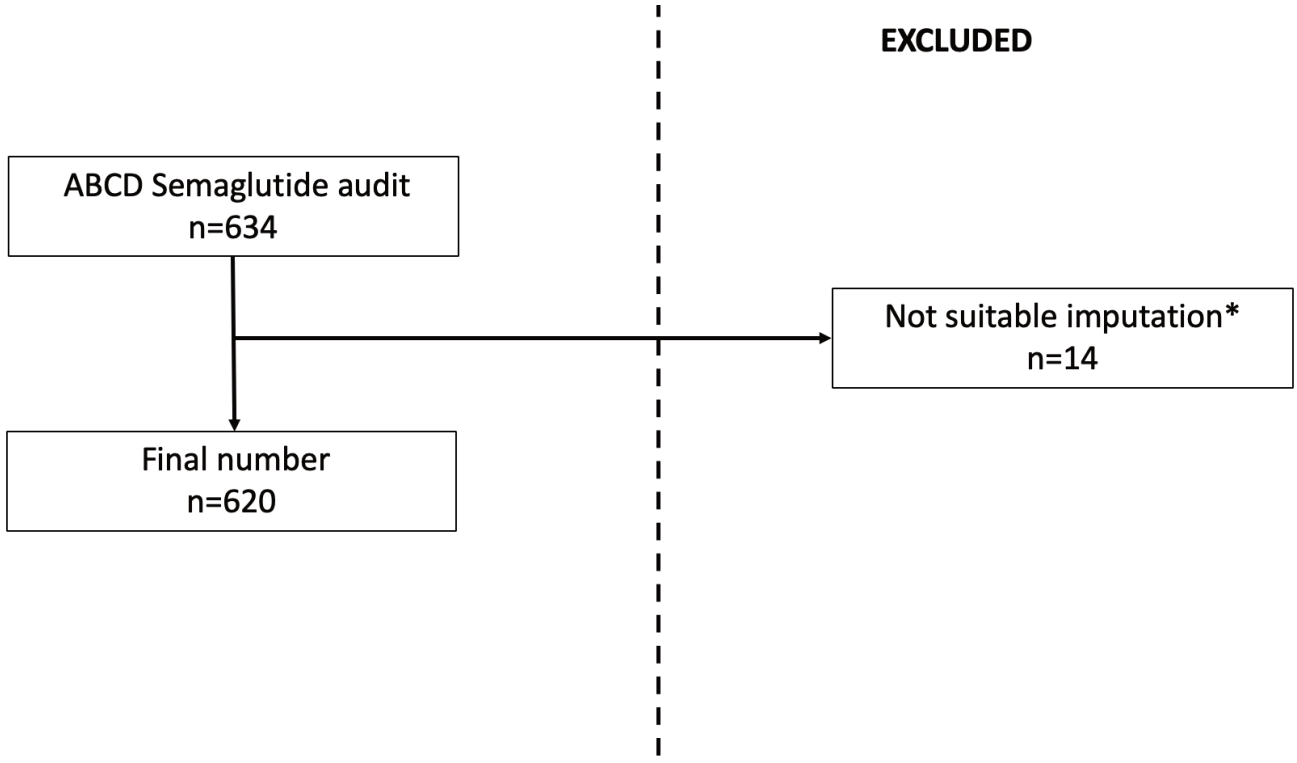
Appendix 1. Flow diagram for numbers included in this analysis



* Due to high levels of missing data in key imputation covariates e.g. age, gender