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Assessing the potential for precision medicine in body weight reduction with regard to type 2 diabetes mellitus therapies: A meta-regression analysis of 120 randomized controlled trials

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Abstract

Aims: To assess the potential for precision medicine in type 2 diabetes by quantifying the variability of body weight as response to pharmacological treatment and to identify predictors which could explain this variability.

Methods: We used randomized clinical trials (RCTs) comparing glucose-lowering drugs (including but not limited to sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and thiazolidinediones) to placebo from four recent systematic reviews. RCTs reporting on body weight after treatment to allow for calculation of its logarithmic standard deviation (log[SD], i.e., treatment response heterogeneity) in verum (i.e., treatment) and placebo groups were included. Meta-regression analyses were performed with respect to variability of body weight after treatment and potential predictors.

Results: A total of 120 RCTs with a total of 43 663 participants were analysed. A slightly larger treatment response heterogeneity was shown in the verum groups, with a median log(SD) of 2.83 compared to 2.79 from placebo. After full adjustment

in the meta-regression model, the difference in body weight log(SD) was −0.026 (95% confidence interval −0.044; 0.008), with greater variability in the placebo groups. Scatterplots did not show any slope divergence (i.e., interaction) between clinical predictors and the respective treatment (verum or placebo).

Conclusions: We found no major treatment response heterogeneity in RCTs of glucose-lowering drugs for body weight reduction in type 2 diabetes. The precision medicine approach may thus be of limited value in this setting.

KEYWORDS

body weight reduction, GLP-1 receptor agonist, meta-regression analysis, obesity, precision medicine, SGLT2 inhibitor, type 2 diabetes mellitus

1 | INTRODUCTION

Randomized clinical trials (RCTs) are fundamental to guide clinical recommendations and reduce morbidity and mortality worldwide. They are, however, conducted under controlled conditions, assuming that enrolled participants have a common phenotype and thus contributing to a 'one-size-fits-all' approach.[1] In addition, they report on average treatment effects from large groups of participants, with study results commonly extrapolated to the treatment of single individuals. However, the variability of clinical outcomes within these groups is an important source of information which could be used to assess the potential for precision medicine.[2]

Precision medicine proposes a shift from the current system of medical care to a more patient-centred approach, considering genetic data and environmental and social factors that may influence disease susceptibility.[3,4] Precision medicine may be particularly well suited for the medical treatment of type 2 diabetes mellitus where the wide variety of clinical phenotypes could account for differential responses to established and newer glucose-lowering drugs.[5] However, before significant resources are invested, the potential for precision medicine in the field of diabetes should first be evaluated. This could be achieved by secondary analysis of placebo-controlled randomized trial results in which two key principles are fulfilled.[6] First, treatment response heterogeneity must be demonstrated; that is, variability in response to different treatment in the same participants should be present. In parallel group trials, the variability of clinical outcomes would then be larger in the verum groups as compared to that in the placebo groups. Second, it should be possible to characterize and estimate the treatment response variability associated with predictor variables such as age, sex or type of glucose-lowering therapy.[6] To this end, interaction of clinical predictors and treatment could be explored. So far, little evidence is available on the potential of precision medicine in the treatment of diabetes.[2,7]

Body weight is an important outcome in trials of glucose-lowering medications.[8] Knowing whether certain therapies for type 2 diabetes are more amenable to a precision medicine approach than others may have important implications for the management of obese diabetic patients. Notably, glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to have substantial effects on body weight[9]; however, it remains unknown which patients benefit the most. Thus, we aimed to assess the potential for precision medicine in body weight reduction with the medical treatment of type 2 diabetes.

2 | METHODS

2.1 | Study selection and data extraction

We included RCTs from four recent systematic reviews that evaluated the relative efficacy of glucose-lowering drugs (sodium-glucose cotransporter-2 [SGLT2] inhibitors, GLP-1 receptor agonists, thiazolidinediones, metformin, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 [DPP-4] inhibitors, sulphonylureas, combination therapies) for type 2 diabetes in comparison to a placebo group for a duration of 24 weeks or longer, and which reported on body weight after treatment.[8,10–12] Drug regimens with add-on treatments were included if reported as a verum arm. We excluded trials that did not compare a glucose-lowering drug to placebo, as well as studies not reporting on body weight either at baseline or at end of trial follow-up. No language restrictions were applied.

Data extraction was carried out independently by two investigators (T.R., B.S.) with disagreements resolved by consensus with a third investigator (O.K.). We collected information on age, sex, glycated haemoglobin (HbA1c) values, duration of disease, glucose-lowering medication from the verum group, year of publication and, importantly, mean body weight values at baseline and after treatment, as well as standard deviation (SD) and natural logarithm of the SD (log [SD]) of body weight after treatment.

2.2 | Study outcome

The primary outcome was the variability of body weight as expressed by the log(SD) in each trial arm. If this measure was not immediately reported, but only the respective standard error (SE), we used the

formula SE = SD/√(sample size) to calculate the SD for body weight values. In case only a 95% confidence interval (CI) for the mean body weight was available, the SD was calculated using the formula:

$$\text{CI} = (\text{population mean}) \pm 1.96 \times \text{SE}.$$

In case only medians, quartiles minimal/maximal values of body weight values were reported, the formulas proposed by Luo et al.[13] and McGrath et al[14] were applied to determine the SDs.

Clinical trials may have reported two types of body weight log (SD): raw and baseline-corrected. Raw log(SD) uses body weight values as measured after treatment for the individual participant. Baseline correction refers to body weight before treatment for each included participant being subtracted from the body weight value after treatment. Results for the raw log(SD) values are given in this main text and those for baseline-corrected values are provided in the Supporting Information.

2.3 | Statistical analysis

To compare log(SD) between the verum and placebo arms, we used the arm-based model proposed by Nakagawa et al.[15] This entails computing weighted meta-regression models with a bias-corrected outcome of [log(SD) + 1/[2(n−1)], where 'n' represents the sample size in each study arm and '1/[2(n−1)]' represents the bias correction.[15]

The first condition, existence of treatment effect heterogeneity, was assessed using a weighted meta-regression model with the fixed-effect covariates treatment (placebo or verum) and the log(mean) of body weight values in the respective arm. A random intercept was used to allow for correlations between the individual arms within a trial. The different sample sizes in the study arms were adequately taken into account by means of inverse-variance weighting; the respective weight for a trial arm was 2(n−1).

The second condition, existence of clinical predictors for treatment effect heterogeneity, was analysed analogously to the meta-regression model of the first condition with only an additional covariate: the interaction term of treatment (placebo or verum) with the respective clinical predictor (mean age at baseline, proportion of male participants at baseline, mean HbA1c at baseline, mean duration of disease at baseline, duration of treatment, year of publication, mean body weight at baseline, or drug class).

All analyses were performed using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Overall, 1942 RCTs were identified. Following screening based on titles and abstracts, 1519 studies were excluded due to duplications and five due to missing outcome of interest. From the remaining 418 studies, 193 did not provide results on the log(SD) of body weight after treatment, 89 only reported on adjusted log(SD) after treatment, 13 did not report on mean body weight, and three trials did not provide information on sample size. After exclusions, 120 clinical trials were eligible for meta-regression analyses (Figure 1). These were divided (Figure S1) into 73 trials with raw log(SD) and 47 with baseline-corrected log(SD). From those with raw log(SD), 102 treatment arms (17 963 participants) and 75 placebo arms (14 356 participants) were identified. From RCTs with baseline-corrected log(SDs), 69 treatment arms (3751 participants) and 47 placebo arms (7603 participants) were found. In total, 43 663 participants were included in the final analyses (Figure S1). A description of the included trial arms (stratified by placebo and verum arms) is shown in Table 1. Populations in both groups were similar with respect to baseline mean age, proportion of male participants, mean known disease duration and mean body weight, indicating an overall adequate randomization process.

With respect to our primary outcome and first prerequisite, the median body weight after treatment was 85.2 kg in the placebo group and 86.2 kg in the verum group, which showed a similar body weight reduction in the placebo groups as compared to the verum groups (−0.6 kg/−0.4 kg). The median log(SD) of body weight was 2.79 in the placebo group and 2.83 in the verum groups. Considering the complete distribution of the log(SD) values of body weight between placebo and verum (Figure 2), a relatively homogeneous distribution pattern was seen in the placebo groups (median 2.79; min: 1.47; max: 3.64; Q1: 2.45; Q3: 2.96) and in the verum groups (median 2.83; min: 1.29; max: 3.67; Q1: 2.49; Q3: 2.97). After full adjustment for the log (mean), the correlations of the arms within trials, and the different sample sizes in the study arms, the treatment effect on the log(SD) was −0.026 (95% CI −0.044; −0,008), indicating a numerically larger log(SD) in the placebo groups. Boxplots with baseline-corrected log (SD) values of body weight are presented in Figure S2.

Figure 3 shows there were no differences in log(SD) values versus placebo for any of the separate drug classes. In subgroup analyses in GLP-1 receptor agonist trials, we found no difference in body weight log(SD), with −0.008 (95% CI −0.072; 0.056) in raw log(SD) trials, however, there was a signal in the subgroup with baseline-corrected log(SD) towards larger variability in the verum groups, with 0.063 (95% CI −0.005; 0.132) at higher baseline HbA1c levels (Figure 4). In further exploratory analyses (Figures S6–S13) of interactions of treatment with seven clinical predictors for the two outcomes of raw and baseline-corrected log(SD) for all other drug classes of GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors and thiazolidinediones, we found no clear pattern supporting precision medicine potential.

A description of the included trial arms (stratified by placebo and verum arms) for the trials reporting on baseline-corrected log(SD) of body weight is given in Table S1. Baseline-corrected log(SD) versus placebo for all drug classes showed a slight positive mean difference of 0.13 (0.01–0.24) for GLP-1 receptor agonists and 0.28 (0.09–0.48) for thiazolidinediones (Figure S3).

The results from meta-regression models for assessing the second condition are shown in Figure S4 (scatterplots of the log[SD] of body weight after treatment against continuous predictors) and Table S2 (clinical predictors for the log[SD] of body weight after treatment). Scatterplot diagrams showing the interaction between the clinical predictor and the respective treatment (verum or placebo) are shown in

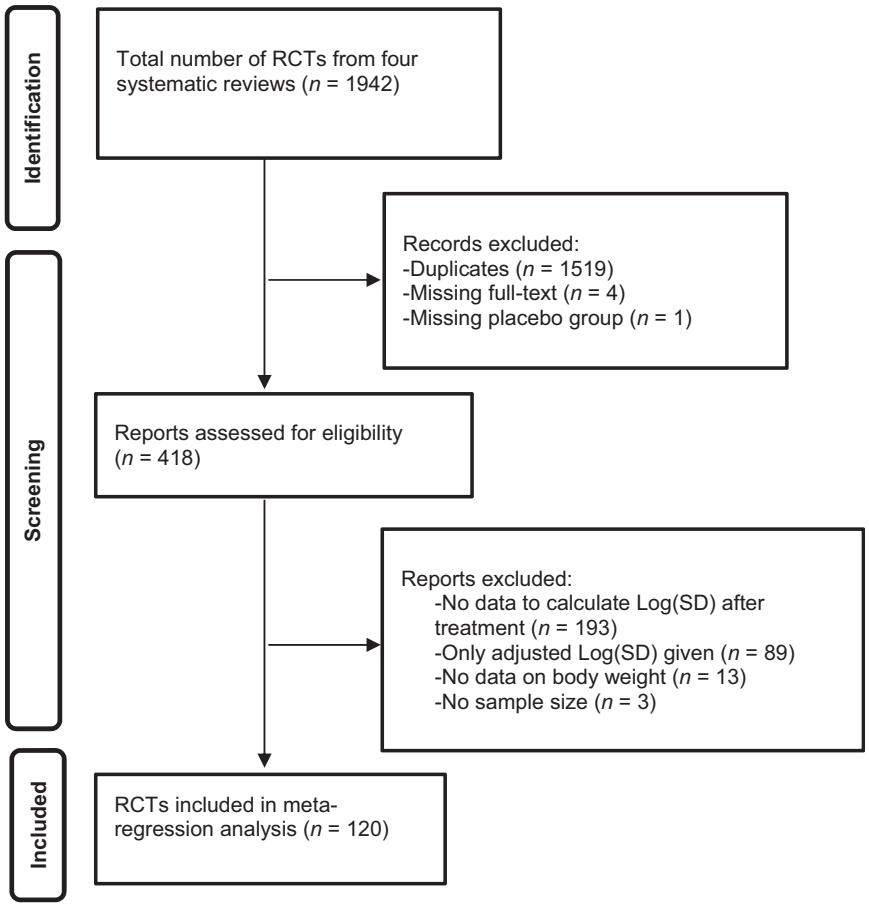

FIGURE 1 Flow diagram of the screening and selection of the included randomized clinical trials (RCTs). Log(SD), natural logarithm of the standard deviation.

Figure S4. Scatterplots were adjusted for weighting of the different sample sizes, but not for treatment strength and the correlations within studies. In brief, interaction would be demonstrated by a difference in the slopes of the two regression lines. We found no relevant differences between slopes of clinical predictors.

Figure S5 shows the baseline-corrected log(SD) of body weight after treatment against continuous predictors. Table S2 shows the fully adjusted slopes of the regression lines and their differences.

4 | DISCUSSION

The results of this meta-regression analysis can be summarized as follows: (1) for the first condition, the fully adjusted log(SD) of body weight after treatment was −0.026 (95% CI −0.044; −0.008), which demonstrates a nonrelevant variability difference of body weight after treatment, with greater variability in placebo groups; and (2) no clinical predictors could be found to explain a potential variability of the primary outcome of interest. In consequence, no potential for the precision medicine approach in body weight reduction could be demonstrated with medical therapies for type 2 diabetes mellitus.

In a recent publication and, for the first time, our research team applied this methodology of detecting treatment response heterogeneity or evidence of clinical predictors based on variability of HbA1c between verum and placebo groups in the treatment of type 2 diabetes.[2] The study showed only minor differences in the variability between placebo and verum groups, and no clinical predictors to explain treatment interaction could be identified. Thus, a limited potential for precision medicine to lower HbA1c with established therapies of type 2 diabetes could be demonstrated. However, new markers from the field of epigenetics or proteomics could be investigated in future evaluations of potential for precision medicine. In addition, new glucose-lowering therapies may well show possible treatment response heterogeneity in the future.

The disadvantages of evaluating RCTs and their significance for treatment heterogeneity and individual patient−treatment interactions have been discussed previously.[2] As an alternative, further N-of-1 studies or repeated crossover clinical trials will likely provide more precise assessments.[16] The TriMaster study was the first three-period randomized crossover trial able to assess the within-person differential responses to several therapies for type 2 diabetes. It demonstrated that clinical characteristics such as body mass index (BMI) or estimated glomerular filtration rate could be suitable for therapy adjustment.[17] The study showed that pioglitazone lowered HbA1c more than sitagliptin (−1.5 mmol/mol) in those with a BMI >30 kg/m^2. In those with a BMI ≤30 kg/m^2, sitagliptin was more effective (−1.4 mmol/mol).[17] This suggests that if subgroups are available, a stratified therapy approach adapted to the respective group could be applied in type 2 diabetes.

Regarding body weight reduction, we were unable to find a clear potential for precision medicine in our data, irrespective of drug class (Figure 3). In the subset of trials with the variability outcome of

TABLE 1 Description of included trial arms, separated by placebo and verum arms, for the trials reporting on the raw natural logarithm of the standard deviation of body weight.

Variable	Placebo ($N = 75$ arms)		Verum ($N = 102$ arms)	
	Number of missing arms	Median (Min/Q1/Q3/Max)	Number of missing arms	Median (Min/Q1/Q3/Max) or *n* (%)
Mean age at baseline, years	4	57.2 (44.0/54.3/59.8/74.4)	4	56.1 (47.6/53.8/59.0/74.0)
Proportion of male participants at baseline, %	7	54.5 (21.2/48.7/63.1/100.0)	9	55.0 (19.0/48.3/63.0/100.0)
Mean HbA1c at baseline, mmol/mol	0	65 (43/60/69/105)	0	65 (43/61/69/104)
Mean known disease duration at baseline, years	21	7.9 (0.5/5.0/10.0/18.0)	32	7.9 (0.5/4.6/9.4/16.3)
Year	0	2013 (1988/2007/2015/2020)	0	2013 (1988/2007/2015/2020)
Treatment (drug class)				
Alpha-glucosidase inhibitors	—	—	0	9 (9)
DPP-4 inhibitors	—	—	0	17 (17)
GLP-1 receptor agonists	—	—	0	18 (18)
Metformin	—	—	0	10 (10)
SGLT2 inhibitors	—	—	0	19 (19)
Sulphonylureas	—	—	0	2 (2)
Thiazolidinediones	—	—	0	21 (21)
Combination therapies	—	—	0	3 (3)
Others	—	—	0	3 (3)
Duration of treatment, weeks	0	24 (24/24/52/260)	0	24 (24/24/52/260)
Number of treated individuals	0	54 (7/25/108/7998)	0	67 (9/25/130/8078)
Mean body weight at baseline, kg	0	85.8 (60.8/76.0/91.1/117.8)	0	86.6 (60.7/78.4/93.0/119.3)
Mean body weight after treatment, kg	0	85.2 (60.0/75.1/91.0/117.8)	0	86.2 (59.9/77.0/93.0/119.3)
Log(mean) of body weight after treatment, kg	0	4.4 (4.1/4.3/4.5/4.8)	0	4.5 (4.1/4.3/4.5/4.8)
SD of body weight after treatment, mmol/mol	0	16.3 (4.3/11.6/19.2/38.0)	0	16.9 (3.6/12.1/19.5/39.4)
Log(SD) of body weight after treatment, mmol/mol	0	2.79 (1.47/2.45/2.96/3.64)	0	2.83 (1.29/2.49/2.97/3.67)

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; log(SD), natural logarithm of the standard deviation; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2.

baseline-corrected log(SD), there was a discernible signal towards higher variability in thiazolidinediones and GLP-1 receptor agonist studies in participants with higher baseline HbA1c levels (Figure 4 and Figure S3). This contrasts with results from three other studies on the efficacy of semaglutide, a GLP-1 receptor agonist, which showed consistent body weight reduction across different patient subgroups.[18–20] However, those results, as well as our results, were derived from exploratory subgroup analyses from clinical trials, and it is possible that results were positive at random due to multiple testing. Thus, further studies considering the effect of GLP-1 receptor agonists and thiazolidinediones on the variability of body weight reduction as a primary outcome of interest would provide more conclusive results.

The future of precision medicine keeps many possibilities open. Important steps have already been taken in the analysis of subgroups by means of subdivision based on clinical parameters. Furthermore, studies have already identified genetic mutations and changes in loci being associated with increased risk of the disease or changes in the effectiveness of glucose-lowering drugs.[21,22] It is important to build on these findings to enable their integration into clinical practice. The challenge ahead will be to correlate this multitude of mutations with clinical subgroups in order to allow for reliable decision making.[23] The current findings do not reject the potential of precision medicine in diabetes and/or body weight reduction in the future, but should encourage us to dig deeper. There may be other factors (genetic, environmental or socioeconomic) that are true clinical predictors for treatment effect heterogeneity. In addition, new glucose-lowering therapies might have a greater potential for precision treatment.

This study has some limitations. Consideration of first and second conditions could be regarded as indirect evidence. Identical variances

or SDs cannot be interpreted as synonymous of absence of possible treatment response heterogeneity. Treatment response heterogeneity could still be present despite the same variances in both the verum and placebo groups. This may occur if subgroups of studies showed exactly the same divergent effects with both verum and placebo. Nevertheless, the use of an arm-based statistical model with weighting of each individual treatment arm could be considered a strength of this study.

Due to lack of other study designs, parallel-group RCTs were exclusively considered. This has the disadvantage that, as opposed to individual treatment heterogeneity, only general treatment effects and response heterogeneity could be extracted.[24] The individual treatment effect can only be identified in repeated crossover studies or N-of-1 trials, in which each participant is considered individually and receives the treatment and control intervention in random allocation.[25] No authors were contacted to obtain any missing data from the published reports. Furthermore, studies were included from four systematic reviews, and no search strategy for individual studies or risk of bias assessment was conducted. No funnel plots to assess for publication bias were drawn, and the latter may have 'diluted' potential effects together with several other factors (drug aggregation in trials, selection bias, trial heterogeneity). However, the included systematic reviews applied a comprehensive search strategy to major databases. In addition, because only eight clinical predictors were considered, the possibility that other parameters may account for treatment response heterogeneity cannot be excluded.

Factors such as ethnicity[26,27] or treatment adherence may have played a role in the extent of body weight variability. However, due to inconsistent reporting in most of the included trials, these factors were not reported or accounted for as clinical predictors for treatment effect heterogeneity.

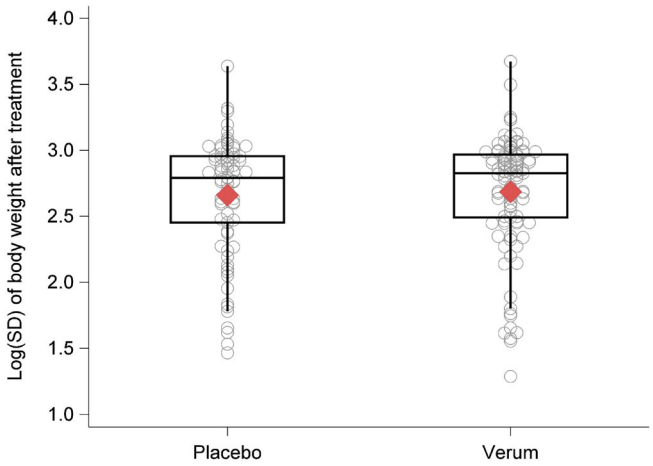

FIGURE 2 Boxplots and observed values for the raw natural logarithm of the standard deviation (log[SD]) of body weight after treatment, separately for verum and placebo arms. Bottom and top edges of a box display the first (Q1) and third (Q3) quartile, the line inside the box indicates the median value. The red diamond within a box shows the mean value. The whiskers that extend from a box indicate the range of values that are outside the middle quartile groups. Note that these boxplots do not adjust for the mean body weight, the sample size or for the correlation within trials.

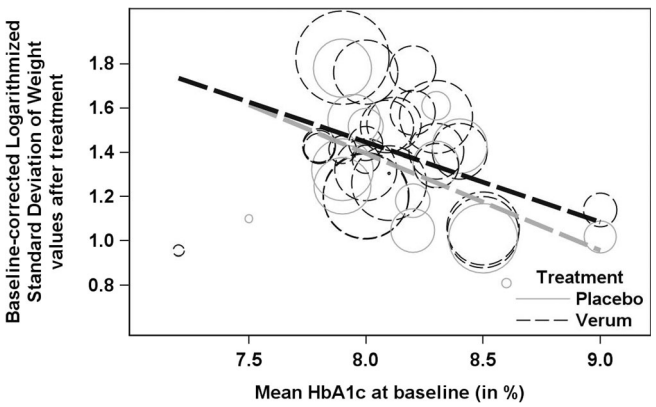

FIGURE 4 Subgroup analysis in trials with glucagon-like peptide-1 receptor agonists: Scatterplot of the baseline-corrected natural logarithm of the standard deviation of body weight after treatment against the continuous predictor mean glycated haemoglobin (HbA1c) at baseline.

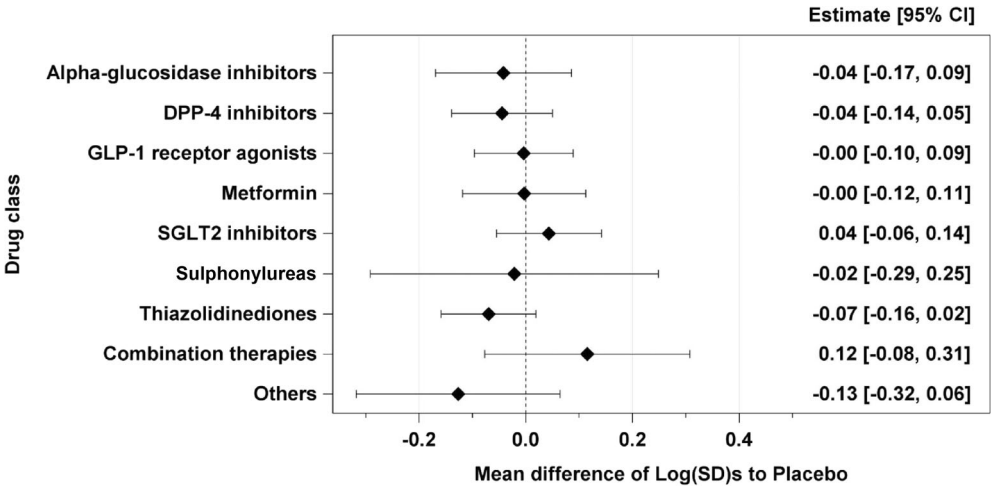

FIGURE 3 Differences in natural logarithm of the standard deviation (log[SD]) against placebo for all treatments (drug classes). DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter-2.

This study shows that the precision medicine approach in the treatment of type 2 diabetes regarding body weight reduction seems to be limited, at least in RCT settings, while real-world treatment may have other influencing factors (such as adherence). However, a homogeneous response to the current glucose-lowering therapy should not be viewed as a disadvantage as it may reflect the fact that no participant is being treated inadequately. In turn, this may translate into greater savings and more affordable therapies for type 2 diabetes.

In conclusion, we found no major treatment response heterogeneity in RCTs of glucose-lowering drugs for body weight reduction in type 2 diabetes. The precision medicine approach may thus be of limited value in this setting.

AUTHOR CONTRIBUTIONS

Kris Vargas, Oliver Kuss, Georg Wolff had the initial idea for the study and wrote the first manuscript draft. Tobias Rütten, Benedikt Siemes and Oliver Kuss performed the statistical analysis. Tobias Rütten and Benedikt Siemes performed the primary data extraction and Oliver Kuss and Sabrina Schlesinger supervised and harmonized the data extraction. Sabrina Schlesinger helped with identification of systematic reviews and relevant studies. Maximilian Brockmeyer, Claudio Parco and Alexander Hoss provided clinical guidance and critically revised the manuscript. Michael Roden, Christian Jung and Malte Kelm were the main supervisors with respect to all clinical issues of this work. All authors contributed to data interpretation, discussion of findings, revision of the manuscript and approval of the final report.

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CONFLICT OF INTEREST STATEMENT

All authors declare: no support from any industry for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work. Maximilian Brockmeyer has received congress travel expenses from Daiichi Sankyo and personal fees from Amgen, Sanofi-Aventis and Novartis. Georg Wolff has received congress travel expenses from Abbott. Oliver Kuss has received honoraria for biostatistical education and consulting from Berlin-Chemie. Michael Roden has received personal fees from Allergan, Astra-Zeneca, Bristol-Myers-Squibb, Eli Lilly, Fishawack Group, Gilead Sciences, Intercept Pharma, Inventiva, Novartis, Novo Nordisk, Pfizer, Prosciento, Sanofi US and Target RWE, and investigator-initiated research support from Boehringer-Ingelheim, Nutricia/Danone and Sanofi-Aventis. Sabrina Schlesinger has received honoraria for lectures from Novo Nordisk.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Zenodo at http://doi.org/10.5281/zenodo.10628482.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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