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The effect of bolus advisors on glycaemic parameters in adults with diabetes on intensive insulin therapy: A systematic review with meta-analysis

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Abstract

Aim: To conduct a systematic review with meta-analysis to provide a comprehensive synthesis of randomized controlled trials (RCTs) and prospective cohort studies investigating the effects of currently available bolus advisors on glycaemic parameters in adults with diabetes.

Materials and Methods: An electronic search of PubMed, Embase, CINAHL, Cochrane Library and ClinicalTrials.gov was conducted in December 2022. The risk of bias was assessed using the revised Cochrane Risk of Bias tool. (Standardized) mean difference (MD) was selected to determine the difference in continuous outcomes between the groups. A random-effects model meta-analysis and meta-regression

were performed. This systematic review was registered on PROSPERO (CRD42022374588).

Results: A total of 18 RCTs involving 1645 adults (50% females) with a median glycated haemoglobin (HbA1c) concentration of 8.45% (7.95%–9.30%) were included. The majority of participants had type 1 diabetes ($N = 1510$, 92%) and were on multiple daily injections ($N = 1173$, 71%). Twelve of the 18 trials had low risk of bias. The meta-analysis of 10 studies with available data on HbA1c showed that the use of a bolus advisor modestly reduced HbA1c compared to standard treatment (MD −011%, 95% confidence interval −0.22 to −0.01; $I^2 = 0\%$). This effect was accompanied by small improvements in low blood glucose index and treatment satisfaction, but not with reductions in hypoglycaemic events or changes in other secondary outcomes.

Conclusion: Use of a bolus advisor is associated with slightly better glucose control and treatment satisfaction in people with diabetes on intensive insulin treatment. Future studies should investigate whether personalizing bolus advisors using artificial intelligence technology can enhance these effects.

KEYWORDS

bolus advisor, diabetes type 1, diabetes type 2, glycaemic control, insulin therapy

1 | INTRODUCTION

Self-management is the cornerstone of diabetes treatment for people with type 1 or type 2 diabetes on intensive insulin treatment. To achieve optimal glycaemic control, people with diabetes are required to adjust their insulin dose based on multiple dynamic and personal parameters, including glucose concentrations and the carbohydrate content of their meals. The efforts needed for such insulin dose adjustments in people's everyday life are considered time-consuming, challenging, and error-prone,[1–5] with limited health literacy and fear of hypoglycaemia posing potential obstacles.[2,3,6]

To overcome these barriers, bolus advisors have been developed to assist people with diabetes in calculating their mealtime insulin boluses.[7] Although initially introduced as a new feature of insulin pumps, bolus advisors are now also available for individuals on multiple daily injections (MDI) in the form of mobile applications, standalone devices, or as integrated parts of glucose meters.[7] Parameters included in standard bolus advisors are the carbohydrate content of a meal (by self-assessment), the insulin-to-carbohydrate ratio, the current and target glucose levels, and the insulin-sensitivity factor, whereas insulin-on-board is incorporated in bolus advisors for insulin pumps.[8] Standard bolus advisors have been reported to improve bolus estimation,[1] increase patient satisfaction,[9–11] improve quality of life,[11,12] and reduce hypoglycaemic events,[11,13] although the effect on glycated haemoglobin (HbA1c) values or time in range (TIR) is less clear.[5,12,14,15] Importantly, the success of bolus advisors very much depends on the frequency of glucose monitoring,[16] adjustment of dynamic insulin parameters (e.g., insulin sensitivity factor),[16] the accuracy of carbohydrate calculation, and integration of the outcome with planned activities.[17] More recently, adaptive bolus advisors have been developed, which include features of artificial intelligence (AI),[14,18,19] advanced nutrient calculators,[20,21] wireless and automated transfer of treatment-related (glucose, insulin) data, and/or physical activity tracking.[14,21,22] Although these additional features might increase the potential for achieving greater accuracy, their effect in optimizing glycaemic control remains to be established.[23]

Two prior systematic reviews on a small number of studies, one of which included a meta-analysis, failed to show an effect of (adaptive) bolus advisors on glycaemic control in people with type 1 diabetes.[24,25] Our study builds upon these previous reports by incorporating a broader range of glycaemic endpoints and more diverse populations, including patients on MDI therapy, and with type 2 diabetes. In addition, new evidence on bolus advisors has emerged since the publication of the meta-analysis.[25] Therefore, the purpose of this systematic review and meta-analysis was to summarize all available evidence from randomized controlled trials (RCTs) and prospective cohort studies on the effects of currently available bolus advisors on or their associations with glycaemic parameters and quality of life in adults with type 1 or type 2 diabetes on insulin treatment.

2 | MATERIALS AND METHODS

This systematic review was conducted according to the updated recommendations in the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2020 statement, along with its extensions, and the Cochrane Handbook for Systematic Reviews of

Interventions.[26,27] The protocol was registered in PROSPERO (CRD42022374588).

The electronic search, screening of relevance by abstract and title, assessment of eligibility of full-text articles, data extraction and risk of bias assessment were independently performed by two authors (E.J.D.B. and C.H.S.). Any inconsistencies were discussed until consensus was obtained. If necessary, the senior authors (U.P.-B. and B.E.d.G.) were consulted to make the final decision.

2.1 | Outcomes of interest

Our primary outcome measure was the post-intervention difference in HbA1c between experimental and control groups. Secondary outcomes included the frequency of hypoglycaemic events, TIR, time below range (TBR), time above range (TAR), mean and postprandial glucose, low blood glucose index (LBGI), high blood glucose index (HBGI), mean amplitude of glycaemic excursions (MAGE), glycaemic variability expressed as coefficient of variation (CV) or standard deviation (SD), total, basal and bolus insulin, and body weight. In addition, the effect of bolus advisors on patient-reported outcomes was investigated.

2.2 | Data source and search strategy

A sensitive electronic search of MEDLINE (PubMed), Embase (Ovid), Cochrane Library (Wiley), CINAHL (EBSCO) and ClinicalTrials.gov was conducted in December 2022. All articles available online in the databases were included for assessment, resulting in a database coverage from 2003 to 2022. The final search included a combination of title/abstract words and Medical Subject Headings (PubMed) and Emtree (EMBASE) terms. No language or date limitations were applied to the search strategy. To identify future relevant articles, alerts in all four databases were created. Full details of the search strategy are available in the Supplementary Appendix.

2.3 | Eligibility criteria

All peer-reviewed RCTs and prospective cohort studies assessing the effect of a bolus advisor alone and combined with other support systems (e.g., continuous glucose monitoring [CGM]) on glycaemic parameters (TIR, HbA1c, glucose variability, hypoglycaemia) and patient-reported outcomes in adults with diabetes on intensive insulin therapy were included. *In silico* studies or studies involving children or participants with types of diabetes other than type 1 or type 2, for example, maturity-onset diabetes of the young, were excluded. In addition, 'grey literature' or publications from unidentified sources (conference papers, reports, etc.) and observational studies other than prospective cohort studies, were disregarded.

2.4 | Study selection

Studies identified by the search strategy were imported into COVIDENCE software, version 1.0 (www.covidence.org). The COVIDENCE software automatically removed duplicates from the two searches. Next, articles were independently screened for eligibility based on title and abstract against the inclusion and exclusion criteria. When in doubt, the full text of the article was read. All potentially relevant articles identified after title and abstract review underwent full-text reading. To identify other possible relevant trials, a backward and forward citation search of included articles was conducted through the PubMed interface in December 2022. If study reports were not publicly available, authors were contacted with the request to share their article.

2.5 | Data extraction

A standardized data extraction template was designed within the COVIDENCE software, collecting desired information from each included article regarding report, study treatment and participant characteristics, results, and conflicts of interest. More information on the data extraction can be found in the Supplementary Appendix (Data S1). If data were missing, the original investigators were contacted with the request for additional information. For some studies, estimated means and SD were calculated (e.g., from five-number summary values or confidence intervals [CIs]). Mean HbA1c levels expressed in mmol/mol in one study[5] were converted to %. As it was not possible to convert an SD expressed in mmol/mol to %, an SD was imputed based on the average SDs of the studies included in the meta-analysis.[26]

2.6 | Risk of bias assessment

The risk of bias was assessed using the revised Cochrane 'Risk of Bias' tool for randomized trials (RoB 2.0), employing the additional guidance for cluster-randomized and crossover trials.[28] Supporting information and justification for judgements of risk of bias (low risk of bias; some concerns; or high risk of bias) were recorded. For each study, an overall risk of bias judgement across the five domains using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) was made (Table S1).

2.7 | Statistics

As the effects of bolus advisors were deemed to vary according to patient age, carbohydrate-counting skills, and the type of bolus advisor used, the random-effects model was chosen. A restricted maximum likelihood random-effects variance estimator

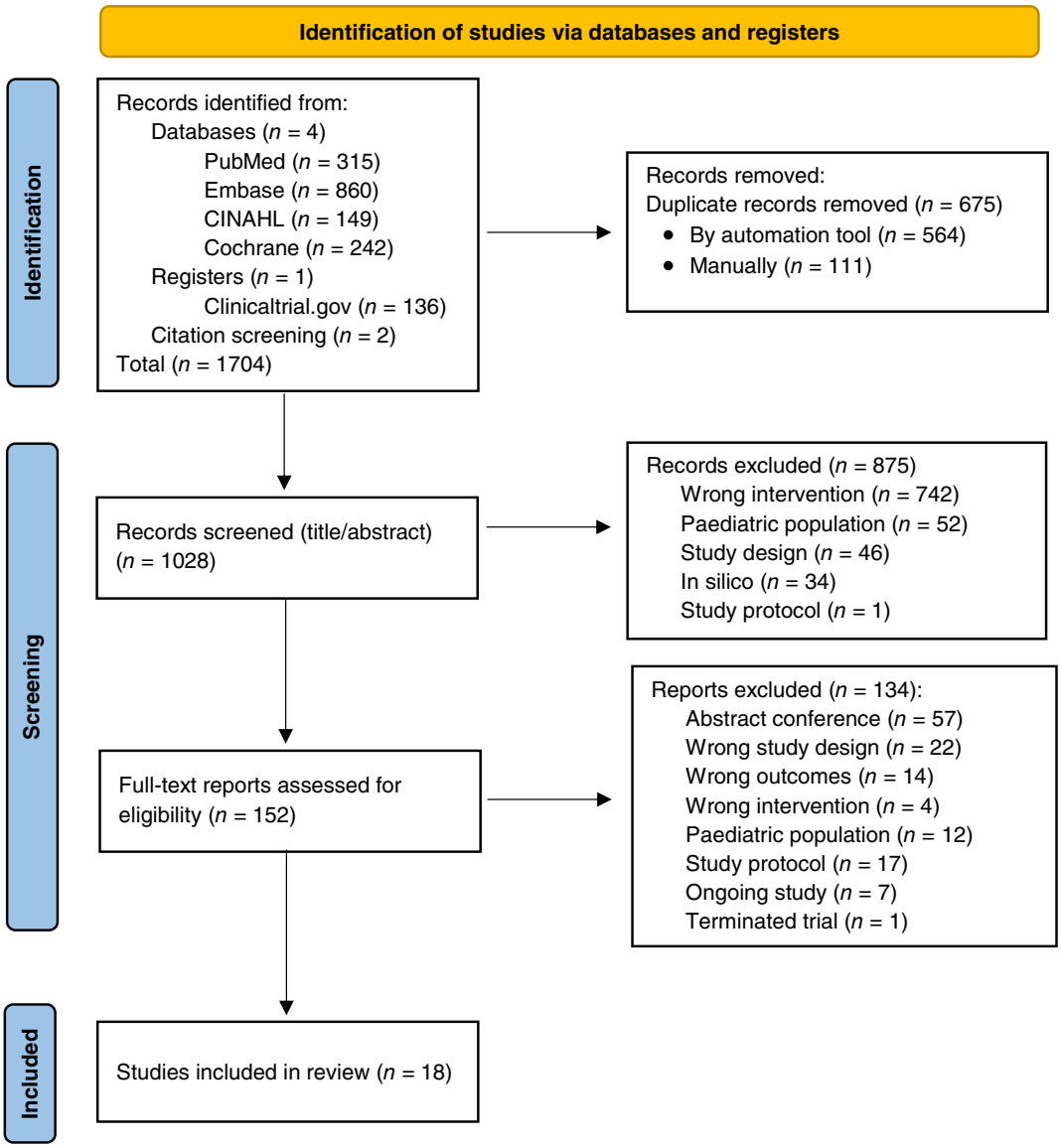

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for the identification of studies included in the systematic review.

was used to estimate the heterogeneity variance.[26] The threshold for substantial heterogeneity was considered ≥50%, quantified as Higgin's I^2.[26] In addition, the impact of heterogeneity was explored by performing a meta-regression. Potential publication bias was assessed via funnel plot asymmetry. Several subgroup and sensitivity analyses were performed to explore the influence of study characteristics on the effect size. The meta-regression, the analysis of potential publication bias, and the sensitivity and subgroup analyses were only performed on outcomes with a minimum of 10 studies included in the meta-analysis as recommended by the Cochrane Handbook.[26] *p* values of <0.05 were taken to indicate statistical significance. The statistical program R version 4.2.3 and its environments were used for data analysis.

3 | RESULTS

A total of 1702 studies were identified by the literature search on PubMed (315), Embase (860), Cochrane (242), CINAHL (149) and ClinicalTrials.gov (136), 675 of which were duplicates (Figure 1). After removing duplicates, 1028 articles remained, of which 835 articles were excluded based on title and abstract screening (reasons for exclusion are listed in Figure 1). The full texts of the remaining 152 articles were retrieved and reviewed, after which another 134 articles were deemed irrelevant. By citation screening of the included studies, another two relevant articles were identified. Overall, 18 RCTs were included in the analysis.[5,6,9–15,20,21,29–35] No observational studies matching the inclusion criteria were identified.

TABLE 1 Characteristics of included studies.

Author and year	Country	Study design RCT	Duration study, weeks	Analysis	Sample size, N[a]	Type of BA	Name BA	Standard care	Diabetes	Insulin regimen	Age, years		Diabetes duration, years		HbA1c (%) at baseline	
											Intervention	Control	Intervention	Control	Intervention	Control
Franc 2020,[31]	France	Cluster	52	ITT	665	Adaptive	DIABEO	Standard care	Type 1 and type 2	MDI and CSII	39.1 ± 13·6	38.3 ± 14.6	17.8 ± 10.2	17.8 ± 10.0	9.1 ± 1.1	9.1 ± 1.0
Maurizi 2011,[32]	Italy	Parallel	26	ITT	40	Standard	Calsulin	Standard care	Type 1	NA	34.5 ± 15	39.3 ± 13	14.4 ± 10.8	13.4 ± 7	7.9 ± 1.0	7.8 ± 1.6
Christensen 2021,[5]	Denmark	Parallel	24	ITT	79	Standard	Accu-check Connect diabetes management + app	Advanced carbohydrate counting	Type 2	MDI	64.1 ± 9.9	61.0 ± 9.2	18.1 ± 7·8	19.3 ± 7.4	8.7 ± 1.0	8.7 ± 1.1
Di Folco 2014,[29]	Italy	Parallel	16	ITT	64	Standard	NA	Standard care	Type 1	MDI	NA	NA	16 ± 2	14 ± 8	8.32 ± 1.47	8.85 ± 1.43
Gross 2003,[6]	United States	Crossover	2	NA	49	Standard	Medtronic MiniMed	Standard care	Type 1	CSII	43 ± 15[b]		22 ± 16[b]		NA	NA
Schmidt 2012,[10]	Denmark	Parallel	16	ITT	51	Standard	Aviva Expert	Standard care with traditional blood glucose metre	Type 1	MDI	42 ± 10	46 ± 9	21 ± 9	14 ± 12	8.8 ± 0.7	9.1 ± 0.7
Rossi 2013,[21]	Italy	Parallel	26	ITT	127	Adaptive	Diabetes Interactive Diary (DID)	Standard care	Type 1	MDI	38.4 ± 10.3	34.3 ± 10.0	16.2 ± 10.0	15.0 ± 8.4	8.4 ± 0.79	8.5 ± 0.8
Ziegler 2013,[9]	UK and Germany	Parallel	26	ITT	218	Standard	Aviva Expert	Standard care	Type 1 and type 2	MDI	42.7 ± 13.5	42.0 ± 14.5	18.1 ± 10.5	17.3 ± 11.6	8.90 ± 1.13	8.87 ± 1.26
Vallejo-Mora 2017,[13]	Spain	Parallel	16	PP	70	Standard	Aviva Expert	Standard care	Type 1	MDI	30.7 ± 12.56	34.2 ± 12.69	14.8 ± 10.08	16.2 ± 8.91	8.4 ± 0.83	8.3 ± 0.94
Gonzalez 2016,[11]	Spain	Crossover	36	ITT	53	Standard	Aviva Expert	Standard care	Type 1	MDI	38.7 ± 11[b]		16.6 ± 7.9[b]		8.13 ± 1	8.05 ± 0.7
Hommel 2017,[15]	Denmark	Parallel	52	ITT	168	Standard	Aviva Expert	Advanced carbohydrate counting	Type 1	MDI	46.9 ± 14.4	47.1 ± 12.7	23.4 ± 13.9	22.0 ± 13.9	8.9 ± 0.7	9.0 ± 0.8
Pańkowska 2017,[20]	Poland	Crossover	3.14	PP	13	Adaptive	VoiceDiab	Standard care	Type 1	CSII	NA	NA	NA	NA	NA	NA
van Meijel 2018,[34]	Netherlands	Parallel	16	ITT	32	Standard	NA	Standard care	Type 1	CSII	48 ± 15	45 ± 15	28 ± 14	27 ± 12	8.1 ± 1.0	8.0 ± 1.3
Breton 2018,[36]	United States	Crossover	8.29	PP	24	Standard	UVA decision support system (DSS)	Standard care	Type 1	MDI and CSII	37 ± 11[b]		21 ± 11.1[b]		7.2 ± 1.0[b]	
Fabris 2020,[31]	United States	Crossover	46	PP	15	Adaptive	Insulin sensitivity informed smart bolus calculator	Standard bolus advisor	Type 1	CSII	44.4 ± 12.7[b]		25.9 ± 13.4[b]		6.9 ± 0.9[b]	

(Continues)

TABLE 1 (Continued)

Author and year	Country	Study design RCT	Duration study, weeks	Analysis	Sample size, N[a]	Type of BA	Name BA	Standard care	Diabetes	Insulin regimen	Age, years		Diabetes duration, years		HbA1c (%) at baseline	
											Intervention	Control	Intervention	Control	Intervention	Control
Avari 2021,[14]	UK and Spain	Crossover design	32	ITT and PP	50	Adaptive	Predictive Personalised Decision Support (PEPPER)	Standard bolus advisor within the PEPPER handset	Type 1	MDI and CSII	41.5 (32.3–49.8)[b]		21.0 (11.5–26.0)[b]		7.7 (7.5–8.2)[b]	
Secher 2021,[12]	Denmark	Parallel	26	ITT and PP	83	Standard	mySugar	Standard care	Type 1	MDI	47.2 ± 25.1	44.6 ± 13.5	16.5 (8–26)	16 (10–27)	8.0 (7.6–8.6)	8.2 (7.9–8.6)
Montanari 2022,[33]	Spain	Parallel	24	ITT and PP	111	Standard	GLIC APP	Standard care	Type 1	MDI and CSII	26.81 ± 7.06	27.82 ± 5.98	16.86 ± 6.07	18.41 ± 6.54	9.6 ± 1.5	9·0 ± 0.5

Note: Data are presented as means ± SD or medians with interquartile range.

Abbreviations: BA, bolus advisor; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin; ITT, intention-to-treat; MDI, multiple daily injections; NA, not available; RCT, randomized controlled trial; PP, per-protocol.

[a]Sample size across all treatment arms.

[b]Data presented for all participants.

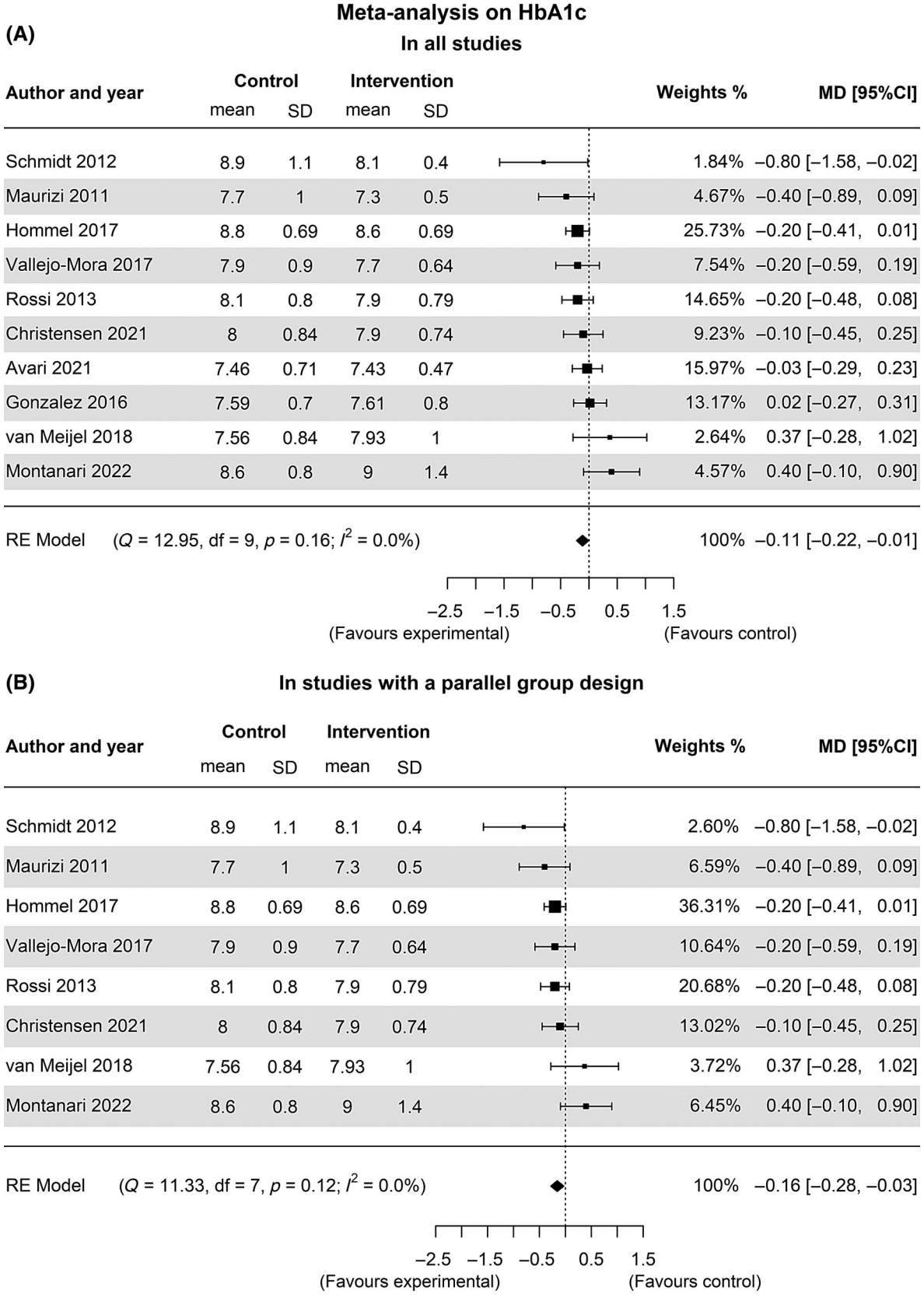

FIGURE 2 Mean difference (MD) and 95% confidence interval (CI) of glycated haemoglobin (HbA1c; %). Random-effects (RE) model meta-analysis with restricted maximum likelihood model. (A) Analysis in all studies disregarding study design. (B) Analysis in studies with a parallel group design.; *Q*, Cochrane's Q test for heterogeneity; I^2, heterogeneity statistics.

Characteristics of the 18 included RCTs are presented in Table 1. The 18 trials comprised a total of 1645 adults, the majority of whom had type 1 diabetes ($N = 1510$), with only a few studies enrolling participants with type 2 diabetes. The median (interquartile range [IQR]) HbA1c at baseline averaged 69 (63-78) mmol/mol 8.45% (7.95%–9.30%), the median (IQR) age was 42 (37–44) years, and the median (IQR) diabetes duration was 18 (16–21) years. The studies included an equal number of males and females, of whom the majority were on MDI therapy ($N = 1173$). Study length ranged from 2 to 52 weeks. Only five studies examined an adaptive bolus advisor (i.e., Diabetes Interactive Diary [DID],[21] Predictive Personalised Decision Support [PEPPER],[14] VoiceDiab,[20] smart bolus calculator[30] and DIABEO[31]), of which two compared the adaptive bolus advisor to a standard bolus advisor.[14,30]

The effect of bolus advisors on HbA1c was reported in 14 studies, 11 with a parallel, two with a crossover, and one with a cluster design. Ten trials (eight parallel and two crossover studies) were included in the meta-analysis, as four studies did not report data on post-intervention HbA1c levels. The meta-analysis of these 10 studies showed a significant, albeit limited, effect of bolus advisors on HbA1c levels compared to standard treatment (mean difference [MD] −0.11%, 95% CI −0.22 to −0.01; $I^2 = 0\%$ [Figure 2]). The effect on HbA1c slightly increased (MD −0.16%, 95% CI −0.28 to −0.03; $I^2 = 0\%$ [Figure 2]), although the effect size remained modest when only studies with a parallel design were included in the analysis. Neither analysis exhibited substantial heterogeneity. The meta-regression identified no study characteristics that had a potential modification effect on the primary outcome.

The analysis of the primary outcome in studies with a parallel group design, excluding studies with potential for a high risk of bias,[33] showed bolus advisors to significantly lower HbA1c (MD −0.19%, 95% CI −0.32 to −0.0.06; $I^2 = 0\%$ [Figure S4]). This effect did not change (MD −0.19%, 95% CI −0.34 to −0.05; $I^2 = 0\%$ [Figure S5]) when only parallel studies without high risk of bias assessing only a standard bolus advisor were included in the analysis.

The subgroup analysis revealed no difference in the reduction of HbA1c levels when adaptive bolus advisors (MD −0.11%, 95% CI −0.30 to 0.08; $I^2 = 0\%$ [Figure S6]) were compared to standard bolus advisors (MD −0.10%, 95% CI −0.26 to 0.05; $I^2 = 20\%$ [-Figure S6]). This finding should be interpreted with caution, as only two studies with different study designs assessing an adaptive bolus advisor were available for the meta-analysis. The (additional) sensitivity analyses are shown in the Supplementary Appendix.

Large variability was found in the data collection and reporting of hypoglycaemic events. Only five studies explicitly reported quantitative data (e.g., mean with SD or 95% CI, or median with IQR) on hypoglycaemic events based on patient reports and/or glucose meter downloads. Furthermore, the units used to express and the definition of hypoglycaemia varied, making it difficult to compare the trials. Therefore, a standardized mean difference (SMD) was used in the meta-analysis. No significant effect was found in the number of hypoglycaemic events between the experimental and control group (SMD −0.09, 95% CI −0.28 to 0.11; $I^2 = 0\%$ [Figure S7]).

The effect of bolus advisors on LBGI was reported in five studies, one with a parallel and four with a crossover study design. For LBGI, the SMD was pooled since both self-monitored blood glucose (one study) and CGM (four studies) were used to evaluate the outcome. Based on this limited number of studies, the use of a bolus advisor was associated with a lower LBGI than in the control arm (SMD −0.24, 95% CI −0.47 to −0.01; $I^2 = 0\%$ [Figure 3]).

There was no significant difference between the bolus advisor group and the control group in terms of TIR, TBR, TAR, glycaemic variability expressed as CV, HBGI, MAGE, SD, mean glucose and postprandial glucose, bolus, basal and total insulin, and body weight (Figures S13–S25).

Several questionnaires were used in the different clinical trials to assess quality of life, fear of hypoglycaemia, and treatment satisfaction (Figures S26–S29). In the meta-analysis, only the status version of the Diabetes Treatment Satisfaction Questionnaire (DTSQs) showed a significant improvement in the experimental group versus the control group, both in the analysis including all five studies (SMD 0.26, 95% CI 0.09 to 0.44; $I^2 = 0\%$ [Figure 3]) and in the analysis including only the RCTs with a parallel group design (SMD 0.31, 95% CI 0.12 to 0.50; $I^2 = 0\%$ [Figure S23]).

Twelve of the 18 trials had low risk of bias, three fell into the 'some concern' category and three showed high risk of bias (Figures S1–S3). The more frequent concerns were related to bias arising from the randomization process, bias due to missing results and bias in the selection of the reported results. The overall quality of evidence for each domain and for the cluster-randomized trial is shown in Figures S1–S3.

Limited information was available about the intensity of bolus advisor use during the study period. In general, a moderate adherence to bolus advisor usage was maintained; on average, participants in the intervention group requested 3.8 bolus recommendations per day.

The contour-enhanced funnel plot indicated no significant asymmetry, suggesting that publication bias is unlikely (Figure S30).

4 | DISCUSSION

This systematic review comprehensively synthesized evidence on the effect of currently available bolus advisors on glycaemic parameters in adults with type 1 or type 2 diabetes on intensive insulin therapy. In the meta-analysis, the use of a bolus advisor demonstrated a statistically significant reduction in HbA1c compared to continuation of standard care. The use of a bolus advisor was also associated with a modest decrease in LBGI and an improvement in treatment satisfaction, but not with improvements in any other glycaemic parameter, including hypoglycaemic events, times in, above or below range or glucose variability, or in other patient-reported outcomes.

Whereas previous systematic reviews failed to show an effect of bolus advisors on HbA1c, our findings now demonstrate these tools to significantly reduce HbA1c. However, the effect size was smaller than what is usually regarded as clinically relevant.[35] We also found use of a bolus advisor to be associated with somewhat lower LBGI, but not with lower incidence of hypoglycaemic events, even though one study had an integrated stop-before-low function integrated in the device, and two studies followed a strict hypo-/hyperglycaemia

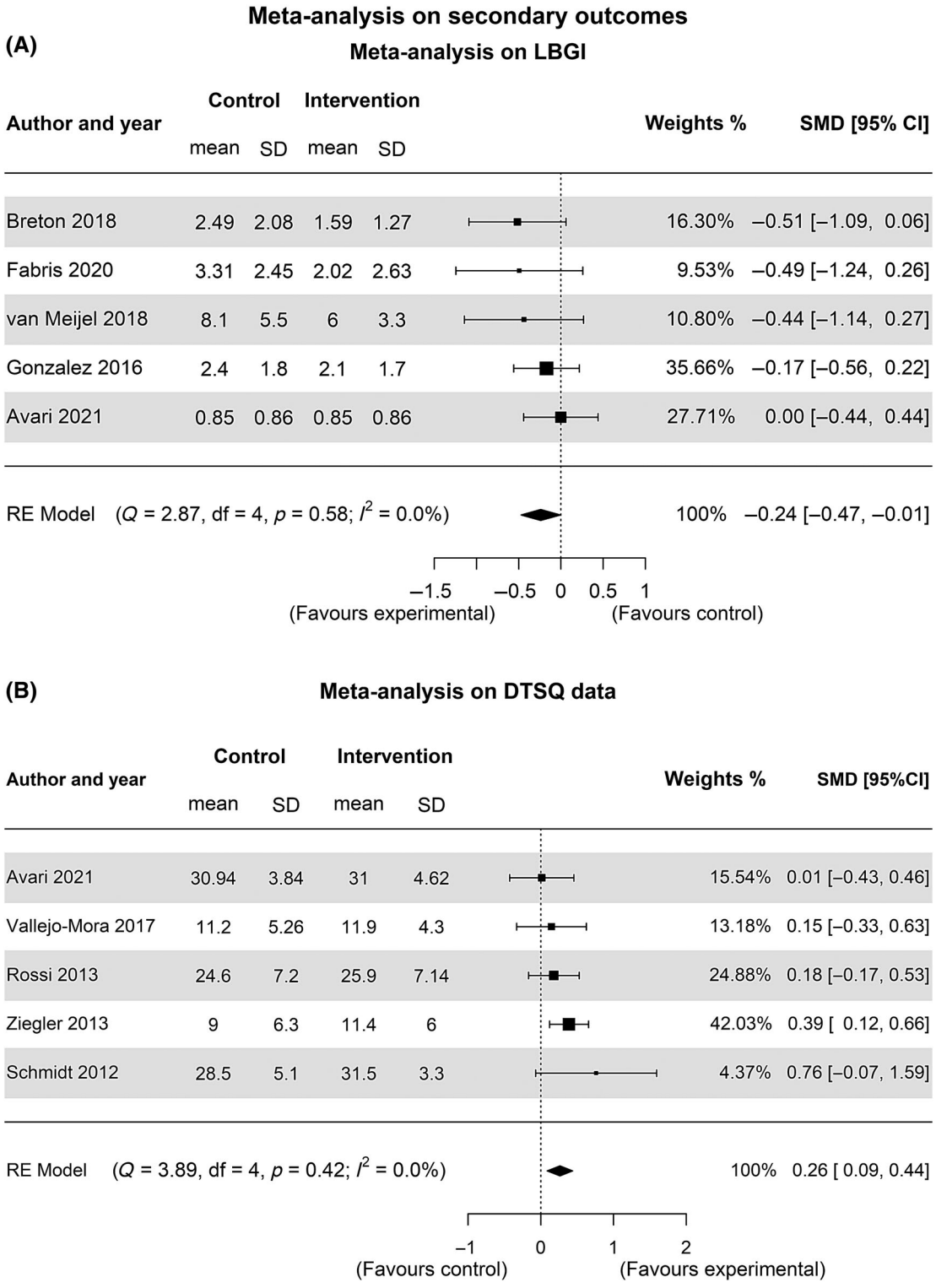

FIGURE 3 Standardized mean difference (SMD) and 95% confidence interval (CI) of low blood glucose index (LBGI) and Diabetes Treatment Satisfaction Questionnaire (DTSQ). Random-effects (RE) model meta-analysis with restricted maximum likelihood model. (A) Meta-analysis on LBGI in all studies. (B) Meta-analysis on DTSQ in all studies.

safety protocol.[14,30,36] Analogously, a previously published meta-analysis demonstrated a small, although not significant, decrease in hypoglycaemic events among a smaller number of study participants.[25] Although the clinical relevance of the observed reduction in LBGI may be called into question, even minor improvements in mitigating the risk of hypoglycaemia could benefit treatment satisfaction and should be viewed in the context of glycaemic control that did not deteriorate or even improved. Indeed, it is reassuring that the reduction in HbA1c, albeit modest, was not associated with increased TBR or more hypoglycaemic events.

The limited benefits associated with bolus advisors can be attributed to several factors that necessitate consideration. First, the clinical effectiveness of bolus advisors is highly dependent on the accuracy of the user input.[17] People with diabetes are required to regularly monitor their glucose levels, precisely calculate the carbohydrate content of their meals, and provide sufficient and accurate data on personal and dynamic parameters. Carbohydrate counting plays a crucial role in diabetes self-management, requiring people with diabetes to gain knowledge about the macronutrient content of their meal, read and understand food labels, and possess sufficient numerical skills to calculate the bolus insulin dose.[37] Several systematic reviews and meta-analyses have demonstrated the beneficial effect of carbohydrate counting on glycaemic control.[38–40] However, there is limited information available regarding the accuracy of carbohydrate counting in adults with diabetes. A study conducted by Meade et al.[2] found that individuals with type 1 diabetes had an average test score of 59% when assessing their carbohydrate-counting skills. Similarly, a study by Brazeau et al.[3] revealed that inaccurate carbohydrate counting is common among the diabetes population and associated with suboptimal glycaemic control.

Treatment adherence is another crucial factor in maximizing the benefits of using a bolus advisor. Achieving and maintaining the behaviour modifications necessary for treatment compliance has proven challenging.[41] Seeking insulin dose suggestion may also be perceived as burdensome as people with diabetes must possess the necessary technical skills to operate bolus advisors.[10,14] It is important to note that limited health literacy is not uncommon among the diabetes population,[42–44] which can pose challenges in effectively utilizing these tools. Furthermore, the refusal to use a bolus advisor could also be attributed to a lack of trust in its advice or reluctance to make changes in customary behaviours.

The limited effects of current bolus advisors may also stem from the fact that they only provide recommendations for prandial insulin, without considering basal insulin needs. In adults, basal insulin usually comprises 45%–60% of the total daily insulin dose and particularly aims to maintain fasting glucose concentrations at consistent levels throughout the day.[45] According to Monnier et al.,[46] the relative contribution of fasting glucose to overall glycaemic control increases with increasing HbA1c levels. In this systematic review, baseline HbA1c levels averaged 69 mmol/mol (8.45%), which may indicate that even substantial improvements in postprandial glucose excursions are unlikely to result in clinically meaningful improvements in overall glycaemic control. In addition, bolus advisors do not adequately account for the variability in insulin requirements that arise from dynamic factors such as insulin sensitivity, physical activity, sleep duration/quality and illness, and ignore the influence of other macronutrients such as protein and fat, which can affect postprandial glucose excursions.[17]

To address the limited effects identified in previous clinical trials, some potential improvements could be considered. One possible advancement is the development of automated algorithms for meal nutrient content estimation based on image or voice recognition algorithms.[20,47] This would alleviate the burden on users to manually input carbohydrate content, promoting accuracy and reducing errors. Advanced AI algorithms could further optimize personalized insulin dose recommendations by incorporating personal and dynamic factors. Additionally, exploring algorithms that have the capability to adjust both bolus and basal insulin and that operate based on real-time data from CGM, connected insulin pens, and insulin pumps without the need for explicit meal announcement have the potential to streamline the process and improve overall user experience.[48]

A strength of this systematic review is that it assessed the effect of both standard and adaptive bolus advisors on multiple glycaemic parameters in adults with type 1 or type 2 diabetes on MDI or continuous subcutaneous insulin infusion. Throughout the entire process of conducting this systematic review, all methodological steps were performed independently by the first two authors, thus minimizing the likelihood of errors and increasing the reliability of findings. Moreover, our carefully designed and comprehensive search strategy maximized the retrieval of relevant articles. To mitigate the potential impact of bias stemming from missing data, study investigators were contacted with the request for additional information.

There are also some limitations. First, the methodological and clinical heterogeneity observed across studies, including variations in intervention, study design and outcome measures, did not enable a direct head-to-head comparison between bolus advisors. Second, the limited number of available RCTs for the meta-analysis of the secondary outcomes further constrained our analyses. Third, the reporting of trial data was sometimes inadequate to facilitate a pair-wise meta-analysis of crossover trials as recommended by the guidelines.[26] The available data on the effects of (adaptive) bolus advisors on glycaemic control in adults with type 2 diabetes mellitus was limited. Further research incorporating a larger body of evidence would be beneficial for a more comprehensive understanding of their potential impact.

In conclusion, use of a bolus advisor is associated with small reductions in HbA1c and LBGI and slight improvement in treatment satisfaction, when compared to standard treatment, in people with diabetes on intensive insulin treatment. Given that even small improvements in glycaemic parameters may still be relevant in the context of diabetes-related complications, these data argue for a more personalized rather than a 'one-size-fits-all' approach to currently available bolus advisors for individuals living with diabetes. Future studies should focus on incorporating additional factors, including automated algorithms for meal nutrient content estimation and basal/bolus titration, and the use of AI with self-learning principles to enhance and optimize the effectiveness of bolus advisors in the management of people with diabetes on intensive insulin treatment.

AUTHOR CONTRIBUTIONS

Elisabeth den Brok, Cecilie Svensson, Ulrik Pedersen-Bjergaard and Bastiaan de Galan designed the study. Elisabeth den Brok and Gregor Franssen designed the search strategy. Elisabeth den Brok and Cecilie Svensson performed the electronic search, selected the articles, appraised the articles and extracted data for the review. Elisabeth den Brok analysed the data with input from Sander van Kuijk. Elisabeth den Brok wrote the first version of the manuscript with input from Cecilie Svensson, Maria Panagiotou, Stavroula Mougiakakou, Ulrik Pedersen-Bjergaard and Bastiaan de Galan. Cecilie Svensson, Maria Panagiotou, Marleen van Greevenbroek, Peter Mertens, Andriani Vazeou, Asimina Mitrakou, Kostantinos Makrilakis, Gregor Franssen, Sander van Kuijk, Stephan Proennecke, Stavroula Mougiakakou, Ulrik Pedersen-Bjergaard

and Bastiaan de Galan contributed to the interpretation of the data, critical reading, and providing comments and edits to the manuscript for important intellectual content. Elisabeth den Brok and Cecilie Svensson are guarantors of the work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval of the version submitted for publication.

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CONFLICT OF INTEREST STATEMENT

Elisabeth den Brok: None. Cecilie Svensson: None. Maria Panagiotou: None. Peter Mertens: None. Andriani Vazeou: None. Konstantinos Makrilakis has served on advisory boards and has received lecture fees from Novo Nordisk, Pharmaserve-Lilly and Sanofi. Asimina Mitrakou: None. Gregor Franssen: None. Sander van Kuijk: None. Marleen van Greevenbroek: None. Stephan Proennecke: None. Stavroula Mougiakakou: None. Ulrik Pedersen-Bjergaard has served on advisory boards for Novo Nordisk, Sanofi-Aventis and Zealand Pharma, and has received lecture fees from Novo Nordisk and Sanofi-Aventis. Bastiaan de Galan has received research support from Novo Nordisk. The authors declare that there are no relationships or activities that might bias, or be perceived as bias, to this work.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15521.

DATA AVAILABILITY STATEMENT

The dataset of the systematic review with meta-analysis, the full standardized data extraction template, the supporting information and justification for judgements of risk of bias and the R scripts are available from the corresponding authors upon reasonable request.

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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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