Efficacy and safety of flash glucose monitoring in patients with type 1 and type 2 diabetes. A systematic review and meta-analysis.

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ONLINE-ONLY SUPPLEMENTAL MATERIAL

Supplemental Table S1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplemental Table S2. Search strategy for PubMed.

(((((flash) AND glucose) AND monitoring)) OR ((freestyle) AND libre)) OR (((free) AND style) AND libre)

Supplemental Table S3. Risk of bias summary: review of authors' judgements about each risk of bias item for each included observational study.

	1	2	3	4	5	6	7	8	9	10	11	Total
Al Hayek, 2017	Yes	Yes	No	Yes	Yes	No	Yes	No	Uncl	Yes	Yes	7
Al Hayek, 2019	Yes	Yes	No	Yes	Yes	No	Yes	No	Uncl	Yes	Yes	7
Campbell, 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	8
Gernay, 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Uncl	Yes	Yes	8
Kramer, 2019	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	7
Landau, 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9
Messaaoui, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	10
Moreno-Fernandez, 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	8
Paris, 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9

Questions:
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
3. Was a sample size justification, power description, or variance and effect estimates provided?
4. Was the test/service/intervention clearly described and delivered consistently across the study population?
5. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
6. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between intervention and outcome if it existed?
8. Were the outcome assessors blinded to the intervention status of participants?
9. Was loss to follow-up after baseline 20% or less?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?
11. Was study free of funding bias?

Supplemental Table S4. Risk of bias summary: review of authors' judgements about each risk of bias item for each included randomized controlled trial.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Funding
Bolinder, 2016	Unclear	Low	High	High	Low	Low	High
Haak, 2017	Unclear	Low	High	High	High	Low	High
Yaron, 2019	Unclear	Unclear	High	High	Low	Low	High

Supplemental Table S5. Additional characteristics of included studies.

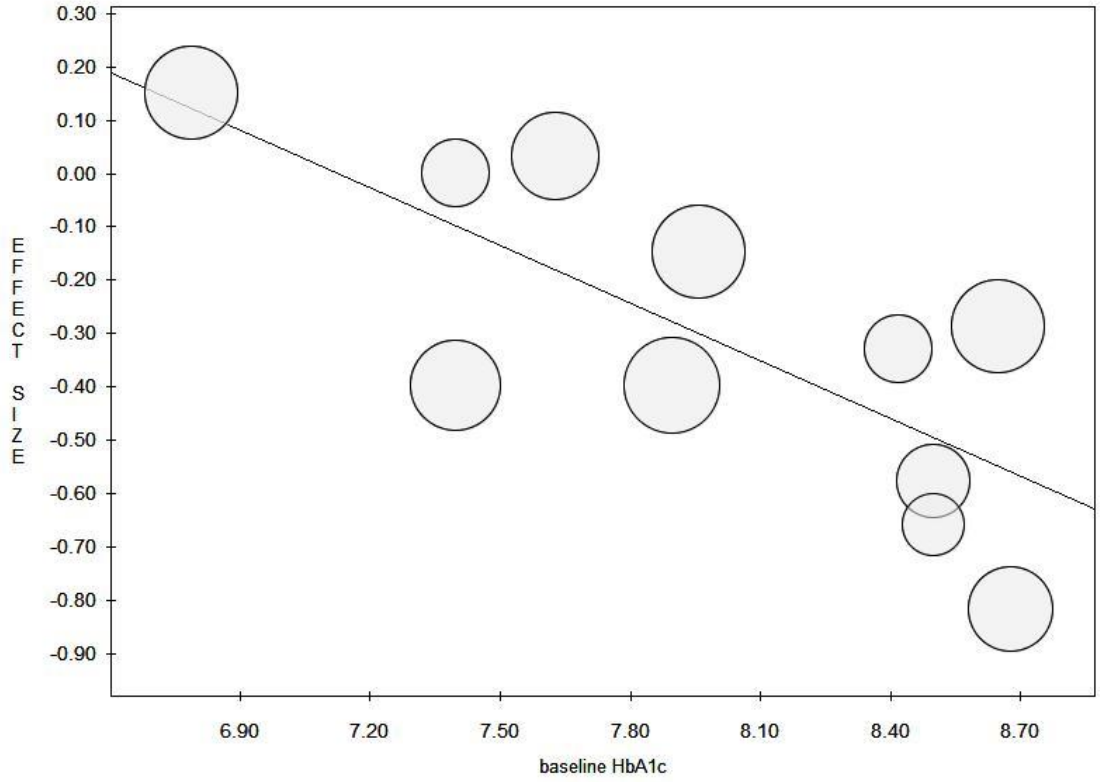
First Author, year	Age (years)	Diabetes duration (years)
Type 1 diabetes mellitus		
Al Hayek, 2017	18 patients aged 13-16 29 patients aged 17-19	18 patients <5 29 patients ≥10
Al Hayek, 2019	30 patients aged 17-19 17 patients aged 20-21	13 patients ≤5 34 patients >5
Bolinder, 2016	43.7 ± 13.9	median 20 (range 13–27) in FGM arm median 20 (range 12–32) in SMBG arm
Campbell, 2018	10.3 ± 4.0	5.4 ± 3.7
Kramer, 2019	50.9 ± 13.3	21.9 ± 15.1
Landau, 2018	13.4 ± 4.9	median 3.2 (range 1-7.4)
Messaaoui, 2019	13.7 ± 3.4	6.3 ± 3.6
Moreno-Fernandez, 2018	mean 38.2 (range 22--55)	20.9 ± 7.8
Paris, 2018	40.1 ± 13.1	16.8 ± 10.9
Type 2 diabetes mellitus		
Haak, 2017	59.2 ± 10.2	17.3 ± 8
Yaron, 2019	66.7 ± 7.5	21.8 ± 7.6
Mixed		
Gernay, 2018	50 ± 14	26 ± 12

Supplemental Table S6: Training and compliance to FGM.

First Author, year	Reported training on the interpretation of glucose-sensor data	Sensor adherence (mean [SD])	Number of sensor scans/day (mean [SD])
Type 1 diabetes mellitus			
Al Hayek, 2017	No	NR	NR
Al Hayek, 2019	No	NR	NR
Bolinder, 2016	No	93 ± 7%	15.1 ± 6.9
Campbell, 2018	No	91 ± 8%	12.9 ± 5.7
Kramer, 2019	Yes	NR	11.9 ± 7.7
Landau, 2018	Unclear	NR	Median 12 (range 8 to 16.5)
Messaaoui, 2019	Yes	NR	7.5 ± 4.2
Moreno-Fernandez, 2018	Yes	94%	17.8 ± 9.9
Paris, 2018	No	NR	8.9 ± 7.7
Type 2 diabetes mellitus			
Haak, 2017	No	89 ± 9%	8.3 ± 4.4
Yaron, 2019	No	NR	11.4 ± 7.8
Mixed			
Gernay, 2018	NR	85 ± 18%	8.8 ± NR

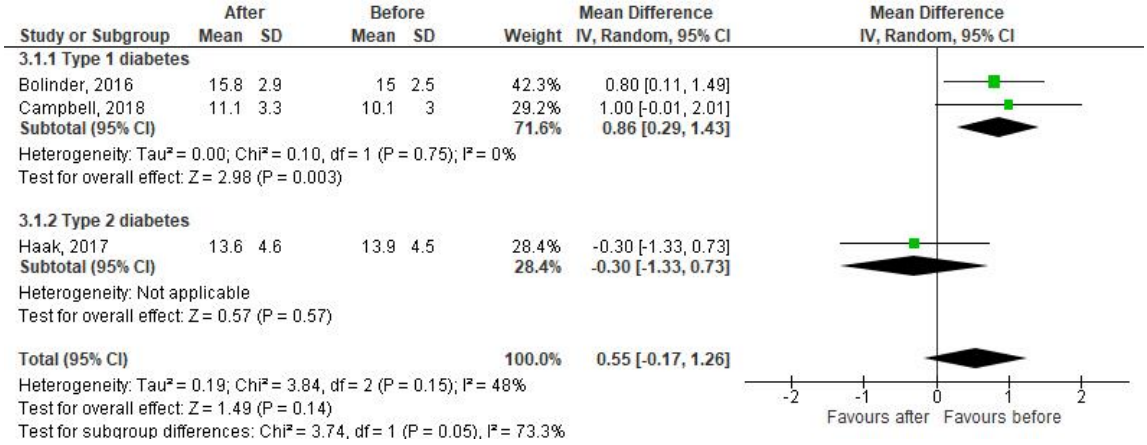
Legend – NR, not reported.

Supplemental Figure S1. Meta-regression on change in HbA1c from baseline to the last available follow-up on FGM based on baseline HbA1c.

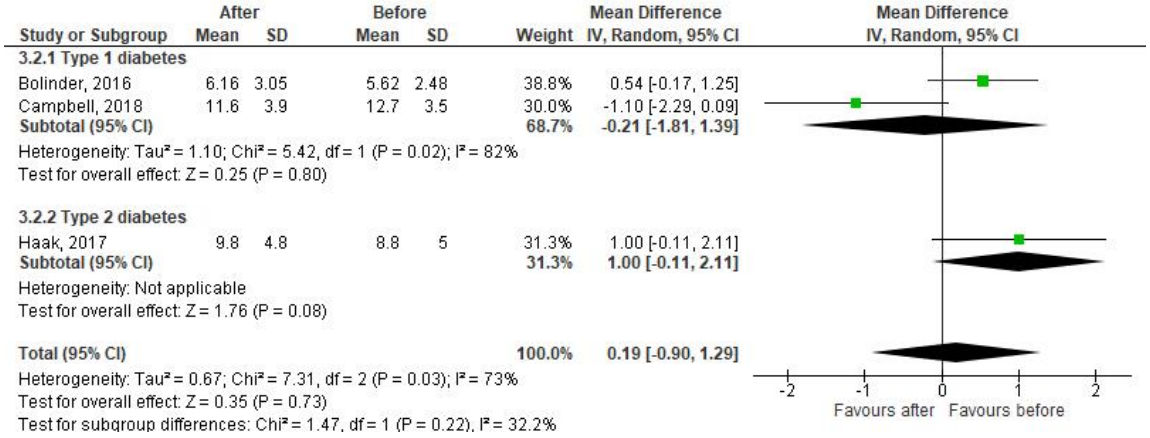


y=2.58-0.36x

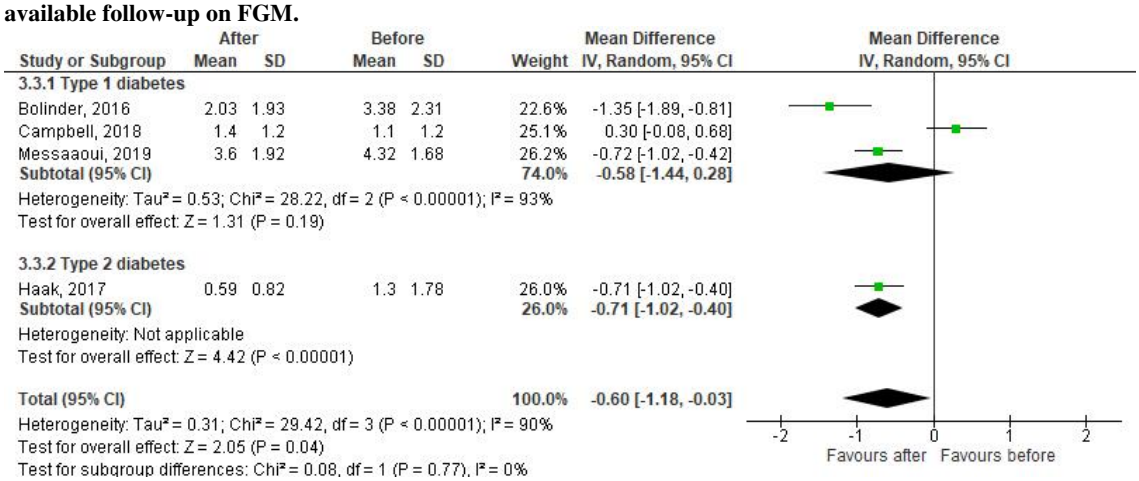
Supplemental Figure S2. Forest plot of meta-analysis for change in time in range from baseline to the last available follow-up on FGM.



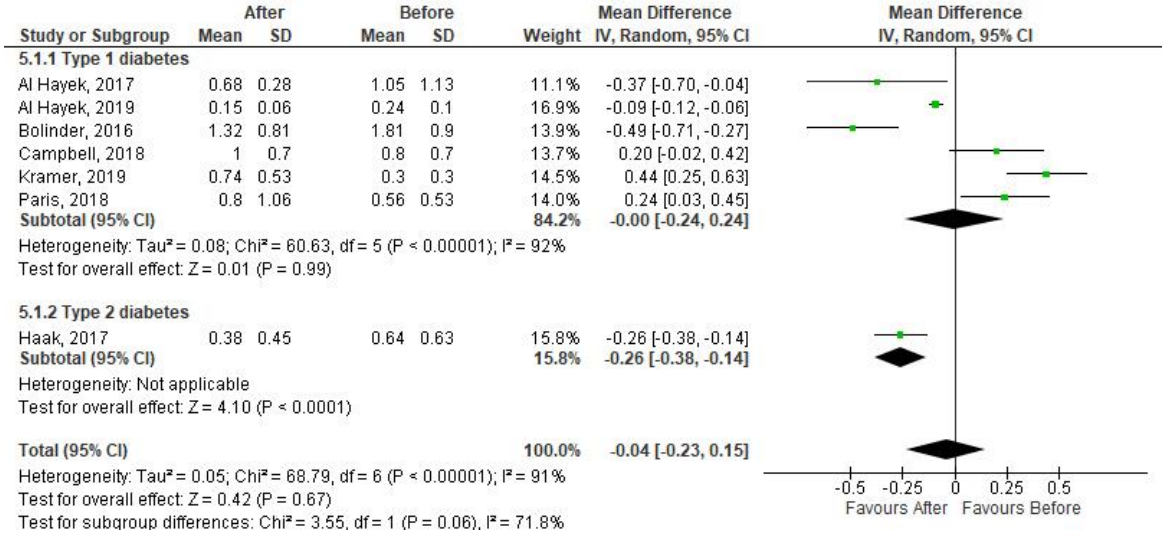
Supplemental Figure S3. Forest plot of meta-analysis for change in time above 180 mg/dl from baseline to the last available follow-up on FGM.



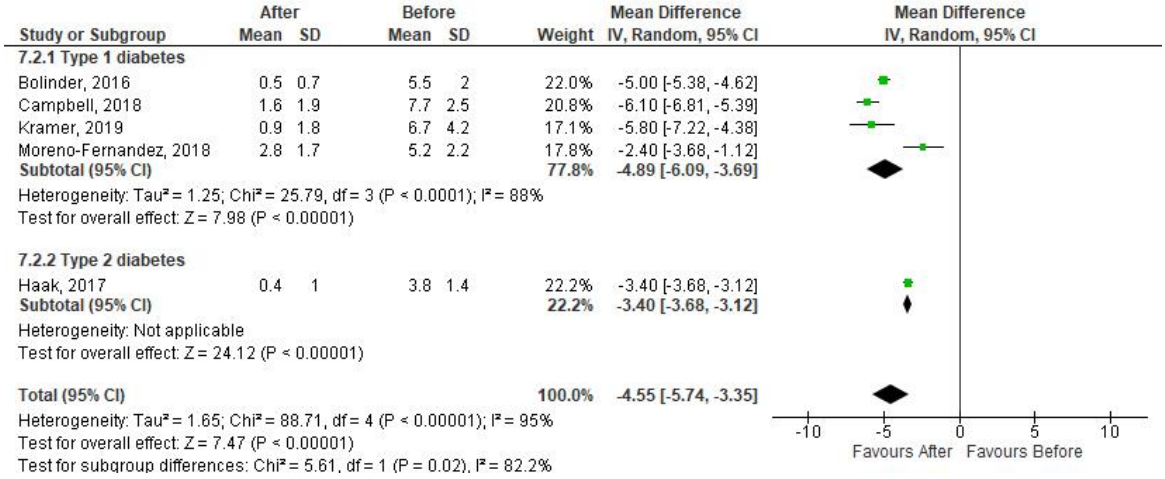
Supplemental Figure S4. Forest plot of meta-analysis for change in time below 70 mg/dl from baseline to the last available follow-up on FGM.



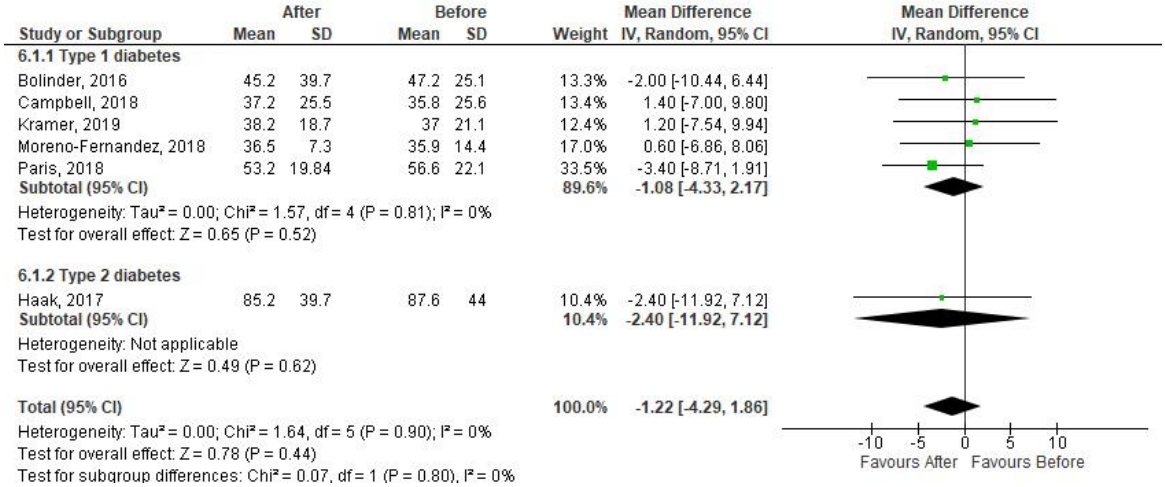
Supplemental Figure S5. Forest plot of meta-analysis for change in frequency of hypoglycemic events from baseline to the last available follow-up on FGM.



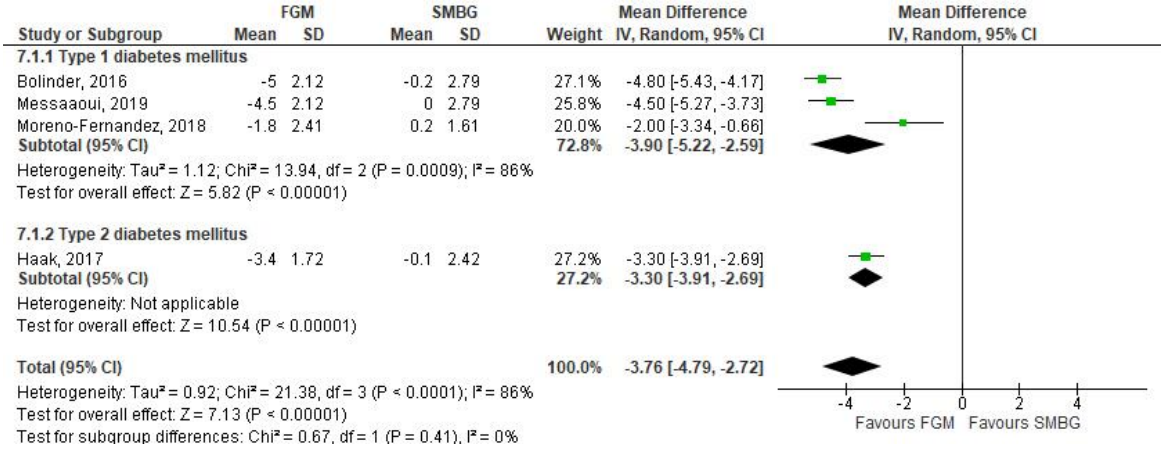
Supplemental Figure S6. Forest plot of meta-analysis for change in number of SMBG measurements per day from baseline to the last available follow-up on FGM.



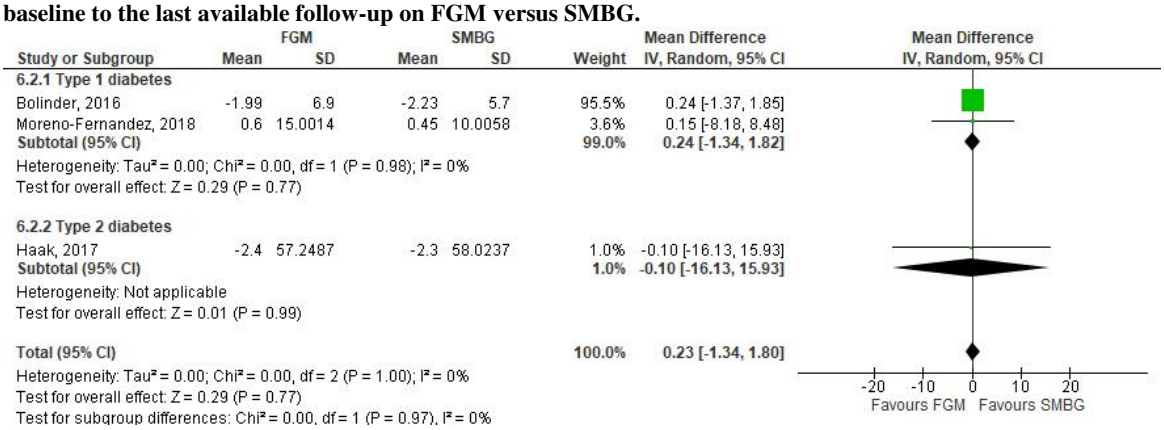
Supplemental Figure S7. Forest plot of meta-analysis for change in total daily insulin dose from baseline to the last available follow-up on FGM.



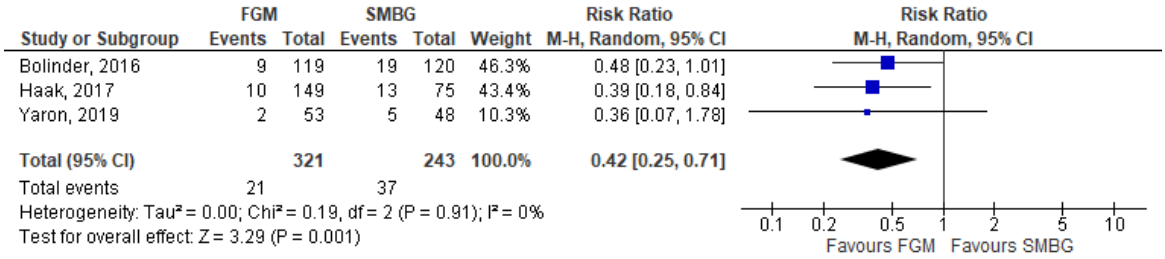
Supplemental Figure S8. Forest plot of meta-analysis for difference in change in SMBG measurements from baseline to the last available follow-up on FGM versus SMBG.



Supplemental Figure S9. Forest plot of meta-analysis for difference in change in total daily insulin dose from baseline to the last available follow-up on FGM versus SMBG.



Supplemental Figure S10. Forest plot of meta-analysis for relative risk of discontinuation on FGM versus SMBG.



Supplemental Table S7. Efficacy of FGM on patient-reported outcomes.

	Scale	Favorable findings in patient-reported outcomes on FGM at the end of follow-up	Improvement in patient-reported outcomes from baseline to the end of follow-up on FGM	More favorable findings in patient-reported outcomes on FGM versus SMBG
Type 1 diabetes mellitus				
Al Hayek, 2017	Hypoglycemia Fear Survey-Child	-	Yes	NA
	PedsQL 3.0 DM questionnaire	-	Yes	NA
Al Hayek, 2019	Glucose monitoring satisfaction survey	-	Yes	NA
Bolinder, 2016	Diabetes Distress Scale	-	-	No
	Diabetes Quality of Life Questionnaire	-	-	Yes
	Diabetes Treatment Satisfaction Questionnaire	-	-	Yes
	Hypoglycaemia Fear Survey	-	-	No
Campbell, 2018	Diabetes Treatment Satisfaction Questionnaire (teen version)	-	Yes	NA
	Diabetes Treatment Satisfaction Questionnaire (parent version)	-	Yes	NA
Kramer, 2019	Diabetes Treatment Satisfaction Questionnaire change	-	Yes	NA
Landau, 2018	-	-	-	NA
Messaaoui, 2019	Likert-type scale	Yes	-	-
Moreno-Fernandez, 2018	-	-	-	-
Paris, 2018	-	-	-	NA
Type 2 diabetes mellitus				
Haak, 2017	Diabetes Distress Scale	-	-	No
	Diabetes Quality of Life (DQoL)	-	-	No
	Diabetes Treatment Satisfaction Questionnaire status	-	-	Yes
	Diabetes Treatment Satisfaction Questionnaire change	-	-	Yes
Yaron, 2019	Audit of Diabetes Dependent Quality of Life 19	Yes	-	No
	Diabetes Treatment Satisfaction Questionnaire status – Hebrew version	Yes	-	No
	Diabetes Treatment Satisfaction Questionnaire change	Yes	-	No
Mixed				
Gernay, 2018	VAS questionnaire	Yes	-	-

Supplemental Table S8. Adverse events reported on FGM.

	Device-related serious adverse events	Device-related adverse events										Observed anticipated sensor insertion-site symptoms										
		Allergic reaction at sensor insertion site	Diffuse cutaneous reaction	Dry flaky skin	Dry yellow/white collection	Erythema	Infection	Oedema	Rash	Sensor site reaction	Other	Bleeding	Bruising	Contact dermatitis	Erythema	Induration	Infection	Itching	Numbness	Oedema	Pain	Rash
Al Hayek, 2017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Al Hayek, 2019	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bolinder, 2016	0	2	-	-	-	2	-	1	1	2	2	12	4	-	30	3	-	20	-	5	19	12
Campbell, 2018	0	-	1	1	1	-	-	-	-	-	-	15	3	-	14	6	1	4	-	-	21	4
Gernay, 2018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Haak, 2017	0	1	-	-	-	-	1	-	1	3	-	8	4	-	23	3	-	14	-	5	15	8
Kramer, 2019	-	-	-	-	-	-	-	-	-	-	-	13	-	-	13	-	-	-	1	-	-	-
Landau, 2018	-	-	-	-	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-	-	-	-
Messaaoui, 2019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Moreno-Fernandez, 2018	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Paris, 2018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Yaron, 2019	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Supplemental Table S9. Publication bias.

Endpoint	Egger's test
Change in HbA1c (%) on FGM	0.019
Change in time in range (70-180 mg/dl) on FGM (h/day) on FGM	0.681
Change in time above 180 mg/dl on FGM (h/day) on FGM	0.701
Change in time below 70 mg/dl on FGM (h/day) on FGM	0.871
Change in frequency of hypoglycemic events (n/day) on FGM	0.735
Change in SMBG measurements (n/day) on FGM	0.517
Change in total daily insulin dose (IU/day) on FGM	0.192
Difference in change in HbA1c (%) on FGM versus SMBG	0.229
Difference in change in SMBG measurements (n/day) on FGM versus SMBG	0.484
Difference in change in total daily insulin dose (IU/day) on FGM versus SMBG	0.168
Relative risk of discontinuation on FGM versus SMBG	0.657