Received: 24 August 2023 | Accepted: 20 October 2023

DOI: 10.1111/dme.15249

DIABETIC Medicine

RESEARCH ARTICLE

Intermittently scanned continuous glucose monitoring in adults with type 1 diabetes: A subgroup analysis from the FLASH-UK study

Lalantha Leelarathna[1,2] | **Christopher J. Sutton**[3,4] | **Mark L. Evans**[5] | **Sankalpa Neupane**[6] | **Gerry Rayman**[7] | **Sarah Lumley**[8] | **Iain Cranston**[9] | **Parth Narendran**[10] | **Ashma Krishan**[3] | **Vicky P. Taxiarchi**[11] | **Katharine Barnard-Kelly**[12] | **Rachel A. Elliott**[13] | **Matthew Burns**[4] | **Maisie Camm**[1] | **Hood Thabit**[1,2] | **Emma G. Wilmot**[14,15] | **on behalf of the FLASH-UK Trial Study Group**

[1]Manchester Diabetes Centre, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

[2]Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

[3]Centre for Biostatistics, Division of Population Health, Health Services Research & Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

[4]Manchester Clinical Trials Unit, Division of Population Health, Health Service Research & Primary Care, University of Manchester, Manchester, UK

[5]Wellcome Trust-MRC Institute of Metabolic Science, NIHR Cambridge Biomedical Research Centre, Cambridge University Hospitals and University of Cambridge, Cambridge, UK

[6]Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

[7]The Diabetes and Endocrine Centre, Ipswich Hospital, East Suffolk and North Essex NHS Foundation Trust, Ipswich, UK

[8]The Adam Practice, Dorset, UK

[9]Academic Department of Diabetes and Endocrinology, Queen Alexandra Hospital, Cosham, Portsmouth, UK

[10]Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, UK

[11]Centre for Women's Mental Health, Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

[12]Barnard Health, BHR Limited, Hampshire, UK

[13]Manchester Centre for Health Economics, Division of Population Health, Health Service Research & Primary Care, University of Manchester, Manchester, UK

[14]University of Nottingham, Nottingham, UK

[15]University Hospitals of Derby and Burton NHS Foundation Trust, Royal Derby Hospital, Derby, UK

Correspondence
Lalantha Leelarathna, Manchester Diabetes Centre, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester M13 9WL, UK.

Abstract

Aims: The FLASH-UK trial showed lower HbA1c with intermittently scanned continuous glucose monitoring (isCGM), as compared with self monitoring of blood glucose (SMBG), in adults with type 1 diabetes and HbA1c ≥58 mmol/mol (≥7.5%). Here, we present results from the pre-specified subgroup analysis

Clinical Trials Registry No. NCT03815006.

Email: lalantha.leelarathna@manchester.ac.uk

Funding information
Diabetes UK

for the 24-week HbA1c (primary outcome) and selected sensor-based secondary outcomes.

Methods: This was a multi-centre, parallel-design, randomised controlled trial. The difference in treatment effect between subgroups (baseline HbA1c [≤75 vs. >75 mmol/mol] [≤9.0 vs >9.0%], treatment modality [pump vs injections], prior participation in structured education, age, educational level, impaired awareness of hypoglycaemia, deprivation index quintile sex, ethnic group and Patient Health Questionnaire-9 [PHQ-9] detected depression category) were evaluated.

Results: One hundred fifty-six participants (females 44%, mean [SD] baseline HbA1c 71 [9] mmol/mol 8.6 [0.8%], age 44 [15]) were randomly assigned, in a 1:1 ratio to isCGM ($n=78$) or SMBG ($n=78$). The mean (SD) baseline HbA1c (%) was 8.7 (0.9) in the isCGM group and 8.5 (0.8) in the SMBG group, lowering to 7.9 (0.8) versus 8.3 (0.9), respectively, at 24 weeks (adjusted mean difference −0.5, 95% confidence interval [CI] −0.7 to −0.3; $p<0.001$]. For HbA1c, there was no impact of treatment modality, prior participation in structured education, deprivation index quintile, sex or baseline depression category. The between-group difference in HbA1c was larger for younger people (a reduction of 2.7 [95% CI 0.3–5.0; $p=0.028$] mmol/mol for every additional 15 years of age). Those with HbA1c 76–97 mmol/mol (>9.0%–11.0%) had a marginally non-significant higher reduction in HbA1c of 8.4 mmol/mol (3.3–13.5) compared to 3.1 (0.3–6.0) in those with HbA1c 58–75 mmol/mol ($p=0.08$). For 'Time in range' (% 3.9–10 mmol/L), the difference was larger for those with at least a bachelor's degree. For 'Time below range' (% <3.9 mmol/L), the difference was larger for those using injections, older people and those with less than bachelor's degree.

Conclusions: Intermittently scanned continuous glucose monitoring is generally effective across a range of baseline characteristics.

KEYWORDS
continuous blood glucose monitoring, deprivation, insulin, type 1 diabetes

1 | INTRODUCTION

Type 1 diabetes (T1D) involves lifelong insulin therapy, usually through multiple daily injections or an insulin pump. Regular monitoring of blood glucose levels is necessary to adjust insulin doses and maintain stable glucose levels. Still, many struggle to self monitor blood glucose (SMBG) by finger pricks at the frequency needed to guide insulin dose adjustment, often due to pain and inconvenience.[1–3] Consequently, glycaemia remains above target values in most people living with T1D;[4] this increases the risk of longer term complications such as nephropathy, neuropathy and retinopathy. The development of continuous glucose monitoring (CGM) systems has enabled glucose to be monitored without fingerprick tests.[5] The FreeStyle Libre System (FSL) (Abbott Diabetes Care, Oxon, UK) is an intermittently scanned continuous glucose monitoring (isCGM) allowing the use of a mobile phone or reader to scan ('flash') a subcutaneously placed sensor.[6] Launched in Europe in 2020, the FreeStyle Libre 2 (FSL2) includes optional threshold alarms to alert users of hypoglycaemia and/or hyperglycaemia.

What's new?

- When using is CGM, There was no impact of treatment modality, of prior participation in structured education, deprivation, sex or depression category on HbA1c.
- Younger participants had a larger reduction in HbA1c, "time above range", and mean glucose.
- "Time in range" was greater for more educated participants.

We recently conducted a randomised controlled trial (RCT), 'The FLASH-UK study',[7] to investigate the efficacy and safety of isCGM with optional alarms in adults

with Type 1 diabetes and high HbA1c (≥58 mmol/mol [≥7.5%]) compared with traditional SMBG. Results of the trial[8] showed improved HbA1c (adjusted mean difference −5 mmol/mol, 95% confidence interval [CI] −8 to −3 mmol/mol; [−0.5%, 95% CI −0.7 to −0.3; $p < 0.001$]) and sensor-based metrics with the use of isCGM. This analysis assesses the heterogeneity of treatment effects in HbA1c and key sensor-based metrics between a range of pre-specified subgroups, including baseline HbA1c category (≤75 vs >75 mmol/mol] [≤9.0 vs >9.0%], age, gender, treatment modality, educational attainment, economic deprivation (measured using deprivation index quintile) and depression status and may provide useful information about the impact of isCGM in different subgroups, driving future research and hypothesis generation.[9]

2 | METHODS

'FLASH-UK' was an open-label, multi-centre, randomised (1:1), parallel-group trial conducted at seven UK specialist diabetes clinics and one primary care centre (a list of participating centres and investigators is provided in Appendix S1). The trial design, funding and conduct were independent of the device manufacturer and conducted in accordance with the Declaration of Helsinki Ethical Principles for Medical Research involving Human Subjects (October 2000) with oversight from Trial Steering and Independent Data Monitoring Committees. The protocol was approved by Greater Manchester West Research Ethics Committee on 21/03/2019 (Reference 19/NW/0081). The study protocol and key HbA1c and sensor results have been previously published.[7,8]

2.1 | Participants

People ≥16 years, with T1D for at least 1 year and HbA1c 58 mmol/mol (7.5%) to 97 mmol/mol (11.0%) either on continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI) were eligible. Key exclusion criteria were current users of CGM or isCGM, pregnancy/planned pregnancy or complete loss of hypoglycaemia awareness. A full list of inclusion and exclusion criteria is provided in Appendix S1. Participants were provided with oral and written information about the trial before written informed consent was obtained.

2.2 | Trial procedures

Participants were randomised (1:1) to isCGM or SMBG using stochastic minimisation. The intervention was the CE marked FreeStyle Libre 2 (FSL2, Abbott Diabetes Care, Oxon, UK) isCGM device with optional alerts. The control group continued with their usual SMBG monitoring. The study consisted of six visits for those in the isCGM arm and seven visits in the SMBG arm (Appendix S1). Due to the COVID-19 pandemic, study visits were conducted in person or virtually. All participants underwent pre-randomisation-blinded CGM (using the Freestyle Libre Pro CGM device for between 10 and 14 days). Education about utilising sensor and fingerprick glucose data and treatment optimisation were provided at randomisation, 4 and 12 weeks to both arms equally. HbA1c was measured at screening, 12 and 24 weeks. Sensor-based outcomes were calculated using GStat software, version 2.3 (University of Cambridge, Cambridge, UK).

2.3 | Outcomes

The primary outcome of the FLASH-UK trial was the HbA1c level at 24 weeks post-randomisation. Pre-specified sensor-based secondary outcomes included percentage time in the target range of 3.9–10 mmol/L (TIR), percentage time in hypoglycaemia (TBR) (<3.9 and 3.0 mmol/L), percentage time above range >10 mM (TAR) and glucose variability (standard deviation and coefficient of variation). A full list of trial outcomes is included in Appendix S1, and the results have been previously published.[8]

2.4 | Planned subgroups

Pre-specified subgroup analyses included a comparison between the following categories:

- Baseline HbA1c category: 58–75 mmol/mol (7.5%–9.0%); >75–97 mmol/mol (>9.0%–11.0%)
- Treatment modality: Continuous Subcutaneous Insulin Infusion (CSII), also known as insulin pump; Multiple Daily Injections (MDI);
- Prior participation in any structured education course (DAFNE, BERTIE or any other local course): Yes; No
- Age group at recruitment: 16 to <30; 30 to <45; 45 to <60; ≥60 years
- Educational level: <Bachelor's degree; ≥Bachelor's degree
- Impaired awareness of hypoglycaemia: No (Clarke score ≤3); Yes (Clarke score >3);
- Deprivation Index Quintile (The English Index of Multiple Deprivation) (a measure of socio-economic status) includes the following domains: income, employment, education, skills and training, health and disability, crime, barriers to housing and services and

living environment. Quintile range from 1 to 5, with lower quintiles indicating a higher level of deprivation. For example, quintile 1 pertains to (approximately) 20% of the English population with the highest levels of deprivation[10]
- Sex: Male; Female
- Ethnic group: white; non-white
- PHQ-9: Mild or no depression (items sum score <10); Moderate or severe depression (items sum score ≥10).

2.5 | Statistical analysis

Analyses included only those participants who had provided data for the corresponding outcome at 24 weeks. Outcomes were analysed with the use of a linear mixed model, with the trial group, baseline HbA1c level, treatment modality (pump vs injections), previous participation in a structured education programme regarding diabetes, current use of a bolus calculator and, unless otherwise included, the baseline value of that outcome measure as fixed effects and with the trial centre as a random effect. For each subgroup separately, the subgroup and its interaction with the treatment modality were added to the model as fixed factors. If a potential linear trend was observed across age groups or deprivation quintile, the variable was considered as a linear term in the linear mixed model. No imputation was used for the primary outcome as the amount of missing data was low and similar between trial arms and secondary outcome analysis were post hoc and exploratory. A two-sided alpha level of 0.05 was used for testing with 95% confidence intervals are presented throughout: There was no adjustment applied for multiplicity. Descriptive analysis by subgroup using mean, median, standard deviation (SD), inter-quartile range (IQR) and range was performed for key sensor-use variables (average number of scans per full 24 h [per day] and percentage use) to explore the possible impact of sensor usage on the findings. (Table 1)

3 | RESULTS

3.1 | Characteristics of the participants (Table 1)

Between December 2019 and March 2021, 313 patients were screened, and 185 were recruited. Subsequently, 156 participants were randomly assigned to the isCGM group ($n = 78$) or SMBG group ($n = 78$), of which 72 (92%) in the isCGM group and 69 (88%) in the SMBG group provided primary outcome data. The isCGM and SMBG groups had similar baseline characteristics (Table 1), with a mean (SD) age of 44 (15) years, the duration of diabetes 21 (13) years and the baseline HbA1c 71 (9.0) mmol/mol (8.6% [0.8]). Almost all (97%) participants were of white ethnicity, 44% were female, 35% were in manual occupation and 68% had lower than undergraduate degree educational achievement.

3.2 | Subgroup analysis for the primary outcome, HbA1c at 24 weeks

Results of the subgroup analysis for HbA1c at 24 weeks are shown in Figure 1 and Table S1. There was no impact of treatment modality, prior participation in structured education, deprivation index quintile, sex or Patient Health Questionnaire-9 (PHQ-9) detected depression category. A trend was noted in age categories, with between-group differences in HbA1c decreasing approximately linearly with increasing age. When investigated as a linear effect, the effect of the use of isCGM significantly reduced with increasing age ($p = 0.028$); the size of the reduction in effect with age was 2.7 (95% CI 0.3–5.0) mmol/mol for every additional 15 years of age. Those with HbA1c between 76 and 97 mmol/mol (9.1%–11.0%) had a marginally non-significant higher reduction in HbA1c 8.4 mmol/mol (3.3–13.5) compared to 3.1 (0.3–6.0) in those with HbA1c between 58 and 75 mmol/mol ($p = 0.08$). The effect of educational level was unclear, with an estimated treatment effect of isCGM of a 4.3 (95% CI 1.4–7.1) reduction among those educated to less than degree level compared to a reduction of 8.1 (4.0–12.2) among those educated to degree level or higher.

3.3 | Subgroup analysis for the time in range (TIR) (% 3.9–10 mmol/L)

Results of the subgroup analysis for TIR at 24 weeks are shown in Figure 2 and Table S2. There was no impact of HbA1c category, treatment modality, prior participation in structured education, sex or deprivation category. In keeping with the larger between-group difference in HbA1c, the estimated between-group difference in TIR was larger for younger people, decreasing by 4.1 (95% CI −0.2 to 8.4) percentage points for every additional 15 years of age, although the confidence interval just spanned 0. Those with at least a bachelor's degree achieved higher between-group increase in TIR (16.5 percentage points;95% CI 9.1–24.0) compared to those less than a bachelor's degree (5.9 percentage points;95% CI 0.8–11.0). A trend of higher between-group difference in TIR was also noted in those with moderate or severe depression based on PHQ-9.

TABLE 1 Demographic and clinical characteristics at baseline.

	isCGM ($n=78$)	SMBG ($n=78$)	Total ($n=156$)
Mean (SD) Age, years	44 (14)	44 (15)	44 (15)
Gender			
Male	45 (58)	42 (54)	87 (56)
Female	33 (42)	36 (46)	69 (44)
Ethnic group			
White	77 (99)	75 (96)	152 (97)
Non-white	1 (1)	3 (4)	4 (3)
Educational level			
Lower than bachelor's degree	56 (72)	50 (64)	106 (68)
Bachelor's degree or higher	22 (28)	28 (36)	50 (32)
Occupational type			
No occupation	12 (15)	15 (19)	27 (17)
Office based	35 (45)	40 (51)	75 (48)
Manual occupation	31 (40)	23 (29)	54 (35)
Deprivation Index quintile			
1	18 (23)	14 (18)	32 (21)
2	8 (10)	9 (12)	17 (11)
3	16 (21)	21 (27)	37 (24)
4	19 (24)	19 (24)	38 (24)
5	17 (22)	15 (19)	32 (21)
Mean (SD) Weight, kg	80.1 (15.7)	83.7 (16.8)	82.0 (16.3)
Mean (SD) BMI, kg m^2	27.2 (4.5)	28.2 (4.9)	27.7 (4.7)
Mean (SD) Duration of diabetes	20 (12)	23 (13)	21 (13)
Mean (SD) HbA1c (%)	8.7 (0.9)	8.5 (0.8)	8.6 (0.8)
Mean (SD) HbA1c (mmol/mol)	71.6 (9.5)	69.9 (8.5)	70.8 (9.0)
HbA1C category			
7.5%–9.0% (58–75 mmol/mol)	58 (74)	59 (76)	117 (75)
>9.0%–11.0% (>75–97 mmol/mol)	20 (26)	19 (24)	39 (25)
Prior participation in structured education			
Yes	47 (60)	44 (56)	91 (58)
No	31 (40)	34 (44)	65 (42)
Bolus calculator use			
No	52 (67)	51 (65)	103 (66)
Yes	26 (33)	27 (35)	53 (34)
Insulin treatment modality			
CSII	20 (26)	24 (31)	44 (28)
MDI	58 (74)	54 (69)	112 (72)

Note: Values are presented as number (%), unless stated otherwise.

3.4 | Subgroup analysis for the time below range (TBR) (%) (<3.9 mmol/L) (Figure 3; Table S3) and TBR (%) (<3.0 mmol/L) (Figure S1; Table S7)

TBR <3.9 mmol/L: No impact of prior participation in structured education, deprivation category, sex, or PHQ-9 detected depression category on the between-group difference in TBR <3.9 mmol/L. Those treated with multiple daily injections had a larger between-group difference (−3.9 percentage points [−5.8 to −2.0]) compared to those on insulin pump therapy (−0.8 percentage points [−3.1 to 1.5]). Investigated as a linear effect, the between-group difference in TBR was larger for older people, increasing

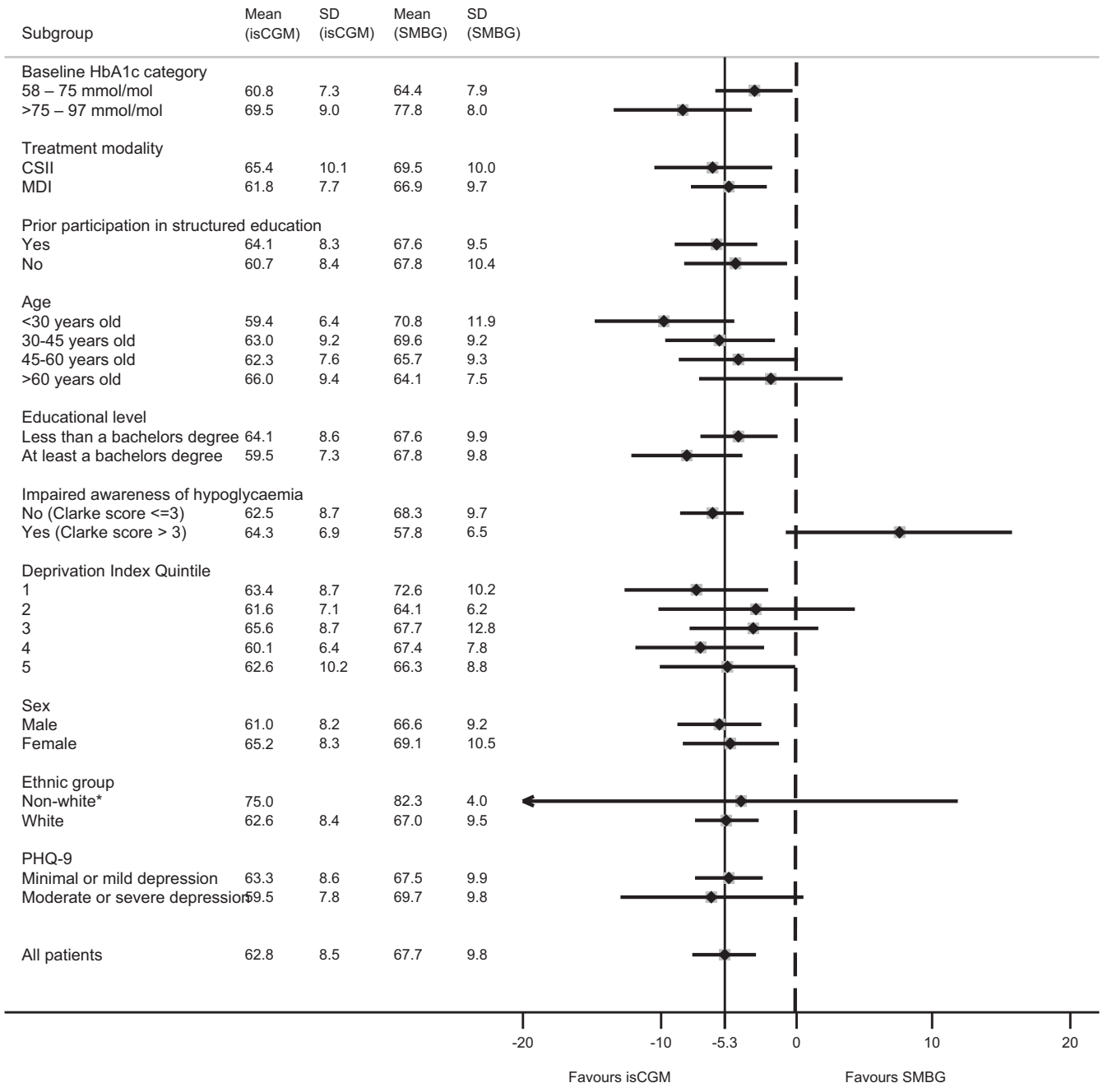

FIGURE 1 Subgroup analyses for HbA1c at 24 weeks. The vertical solid line represent the overall effect of isCGM. *SD not calculable for isCGM non-white category as $n = 1$. isCGM, intermittently-scanned continuous glucose monitoring; SMBG, self monitoring of blood glucose.

by 1.9 (95 CI% 0.2–3.7) percentage points for every additional 15 years of age. Similarly those less than a bachelor's degree had a larger between-group difference (−4.0 percentage points [−5.9 to −2.2]) compared to those with at least a bachelor's degree (−0.6 percentage points [−3.2 to 2.1]).

TBR <3.0 mmol/L: In keeping with the above observations, those treated with multiple daily injections had a larger between-group difference in TBR <3.0 mmol/L as well as those with less than a bachelor's degree.

3.5 | Subgroup analysis for the time above range (TAR) (>10 mmol/L) (Figure 4; Table S4)

The between-group difference in the reduction of TAR was significantly larger for younger people, with the effect relative to SMBG decreasing by 5.9 (95% CI 0.8–10.9) percentage points for each additional 15 years of age. Those with at least a bachelor's degree achieved a larger between-group reduction in TAR than those without a bachelor's degree.

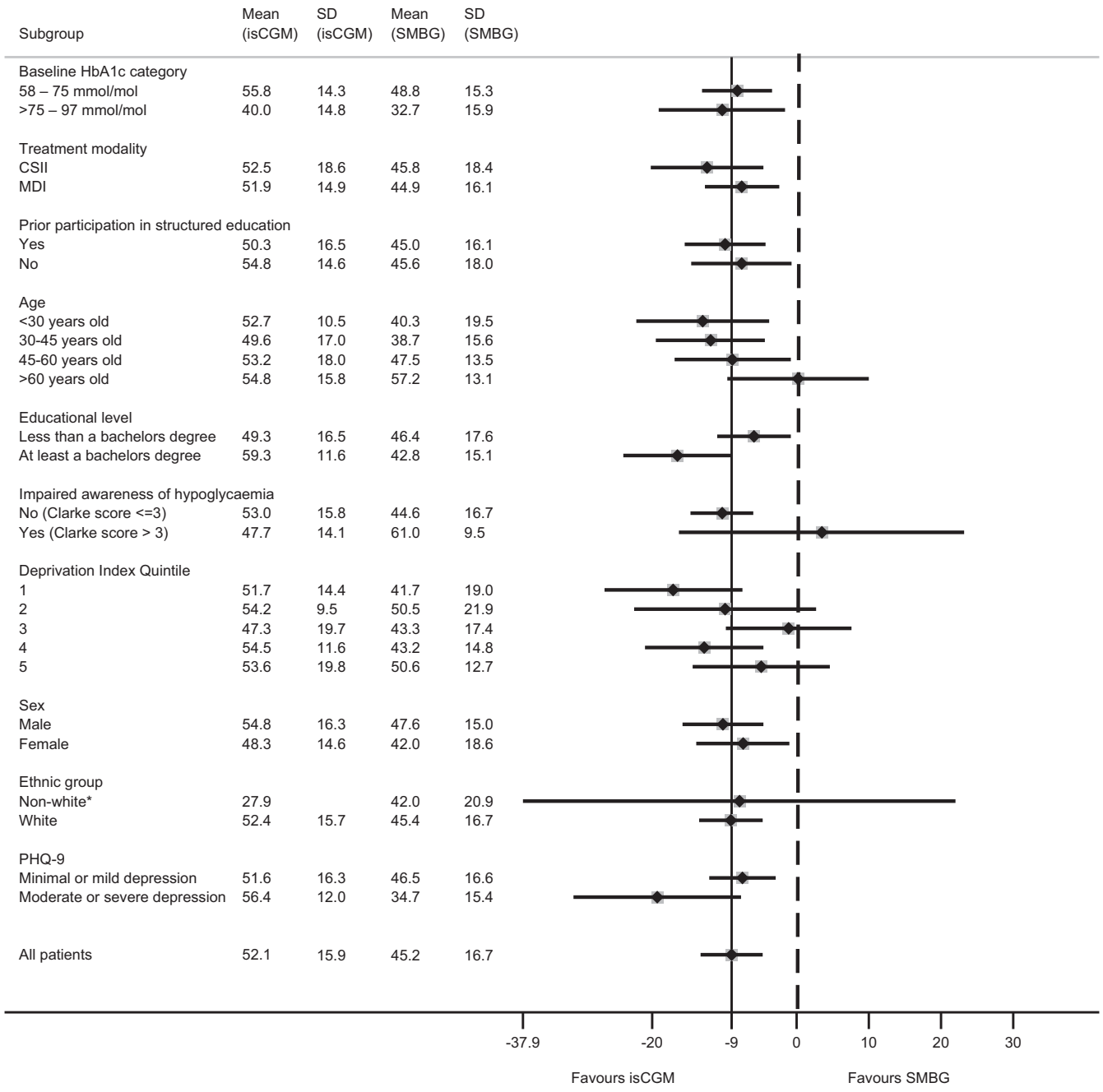

FIGURE 2 Subgroup analyses for time (%) in range (3.9–10 mm/L) (70–180 mg/dL). The vertical solid line represent the overall effect of isCGM. Between-group differences were calculated as SMBG – isCGM for consistency with other Figures (to ensure that negative differences can be interpreted as favouring isCGM). *SD not calculable for isCGM non-white category as n = 1. isCGM, intermittently-scanned continuous glucose monitoring; SMBG, self monitoring of blood glucose.

3.6 | Subgroup analysis for mean glucose (Figure 5; Table S5)

In keeping with HbA1c change, the between-group difference in mean glucose was significantly larger for younger people, with the effect decreasing by 0.7 (95% CI 0.2–1.3) mmol/L for every additional 15 years of age. Those with at least a bachelor's degree achieved larger reduction in mean glucose with isCGM compared to those with less than a bachelor's degree. There was also a non-significant differences in effects between the higher HbA1c category 75–97 mmol/mol (−1.5 [−2.6 to −0.4] mmol/L) compared to those with HbA1c 58–75 mmol/mol (−0.3 [−0.9 to 0.3] mmol/L).

3.7 | Subgroup analysis for the glucose variability (CV%) (Figure 6; Table S6)

The between-group difference (reduction) in glucose variability as measured by the coefficient of variation (CV) of

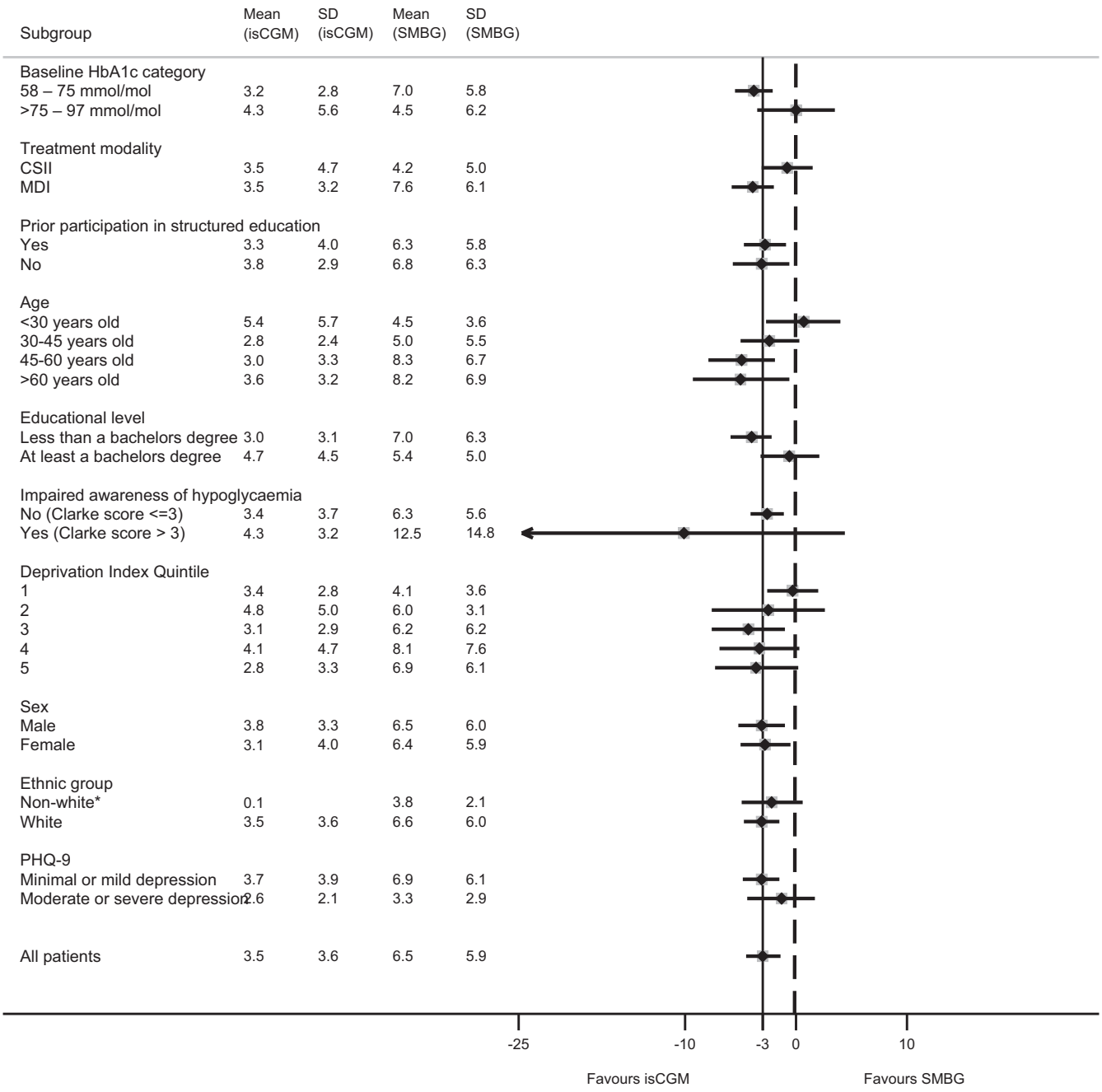

FIGURE 3 Subgroup analyses for time (%) below range (<3.9 mmol/L). The vertical solid line represent the overall effect of isCGM. *SD not calculable for isCGM non-white category as $n = 1$. isCGM, intermittently-scanned continuous glucose monitoring; SMBG, self monitoring of blood glucose.

glucose (%) was significantly larger for older people, with the effect increasing by 2.2 (95% CI 0.5–4.0) percentage points for every additional 15 years of age. The between-group difference was also larger for those with lower deprivation (higher quintile). When investigated as a linear function, the effect increased by 1.5 (95% CI 0.2–2.7) percentage points for every additional Deprivation Index quintile.

3.8 | Sensor usage

Mean percentage sensor usage (wear) was high (over 90%) in almost all subgroups, with only those ($n = 8$) with impaired awareness of hypoglycaemia having mean usage <90% over their last 2 weeks of isCGM wear (Table S8). There were some observed differences in mean average daily number of scans performed between subgroups,

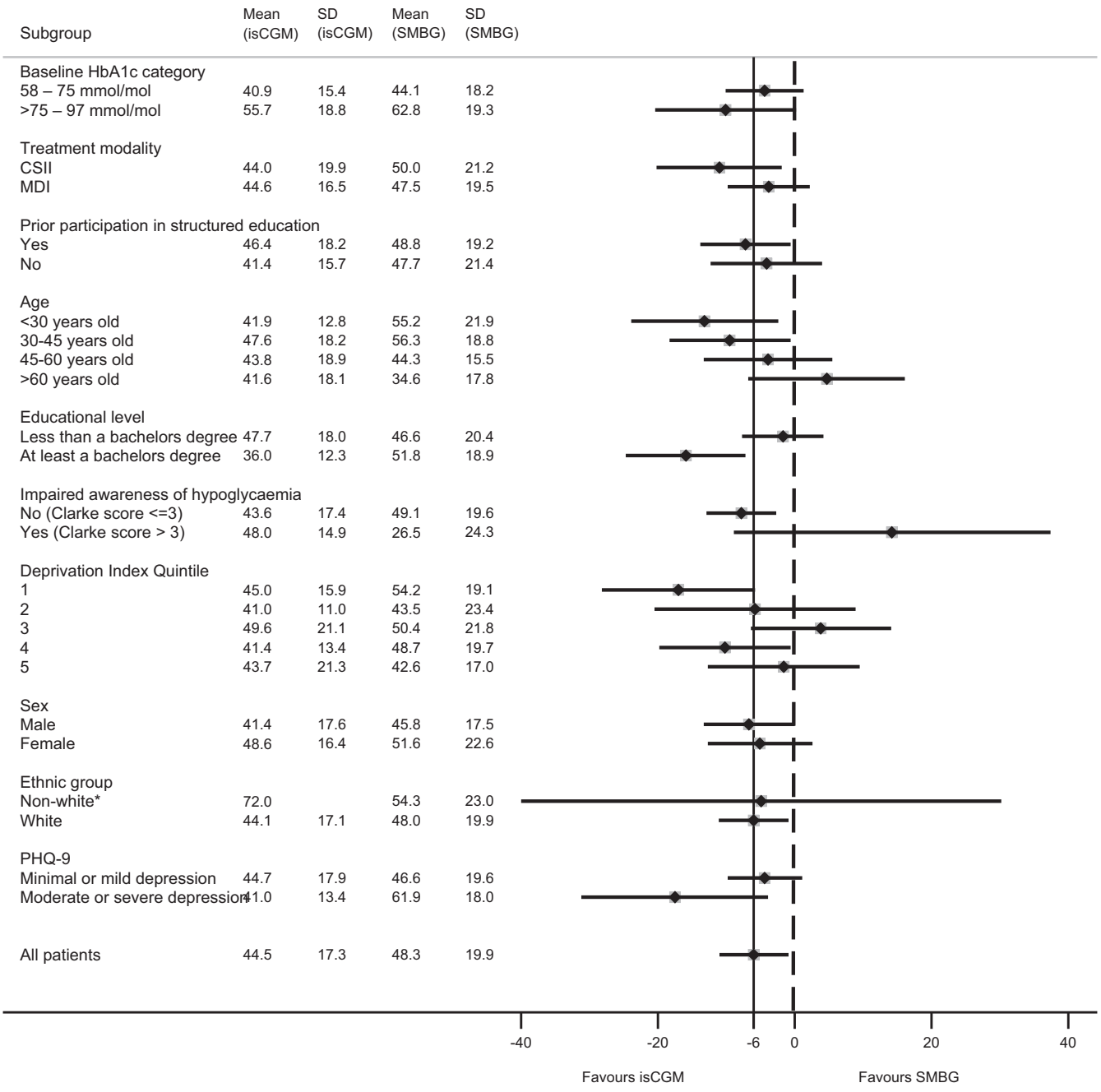

FIGURE 4 Subgroup analyses for time (%) above range (>10 mmol/L). The vertical solid line represent the overall effect of isCGM. *SD not calculable for isCGM non-white category as $n = 1$. isCGM, intermittently-scanned continuous glucose monitoring; SMBG, self monitoring of blood glucose.

with older participants or those with lower baseline HbA1c levels tending to perform more scans than younger participants or those with higher baseline HbA1c levels. Scanning frequency was similar for those educated to less than degree level (mean 10.9/day) and those educated to at least degree level (11.4). Participants with self reported moderate or severe depression had greater scanning frequency (14.2 vs 10.5).

4 | DISCUSSION

4.1 | Key findings

In this subgroup analysis from the FLASH-UK study, we evaluated the impact of a range of clinical and demographic factors on HbA1c and selected sensor-based metrics. Overall, our results suggest isCGM is generally

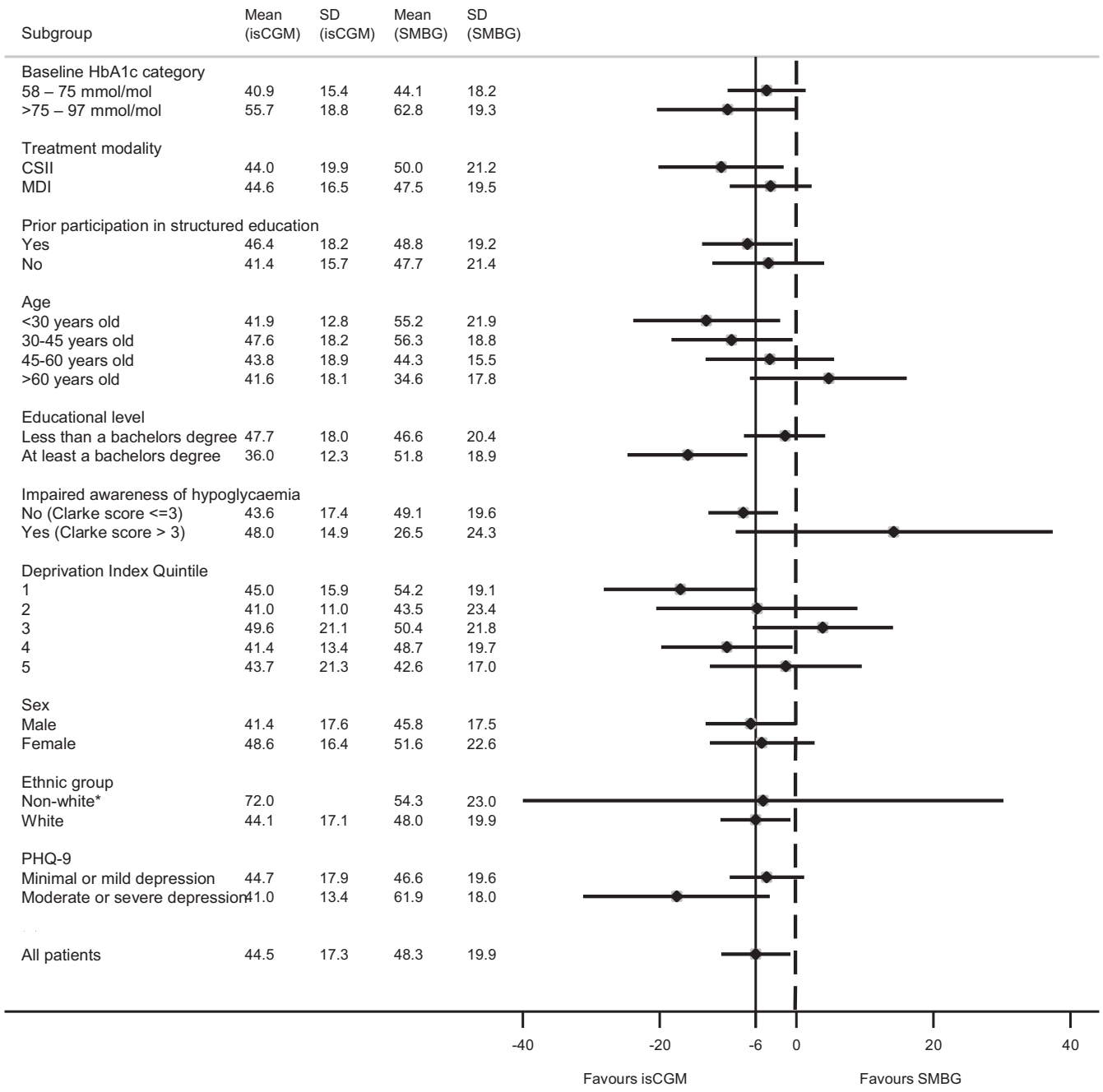

FIGURE 5 Subgroup analyses for mean glucose (mmol/L). The vertical solid line represent the overall effect of isCGM. *SD not calculable for isCGM non-white category as $n = 1$. isCGM, intermittently-scanned continuous glucose monitoring; SMBG, self monitoring of blood glucose.

effective across a range of clinical and demographic characteristics. In particular, there was no impact of prior participation in structured education, treatment modality, sex deprivation index quintile or baseline Patient Health Questionnaire-9 (PHQ-9)-detected depression category on the primary outcome (HbA1c reduction). Our results suggest that younger participants had a greater reduction in HbA1c, TAR (>10 mmol/L) and mean glucose with a non-significant increase in TIR (3.9–10 mmol/L) compared to older participants. In contrast, older participants had a larger reduction in sensor-detected hypoglycaemia. Importantly, neither prior participation in structured education nor gender-influenced treatment effect in HbA1c or sensor-based metrics. Insulin treatment modality (pump vs multiple daily injections) had no impact on HbA1c reduction, TIR or TAR. In contrast, those treated with multiple daily injections had a larger reduction in hypoglycaemia when using isCGM at both 3.9 and 3.0 mmol/L thresholds. Interestingly, those with at least a bachelor's degree had greater increase in TIR, a larger reduction

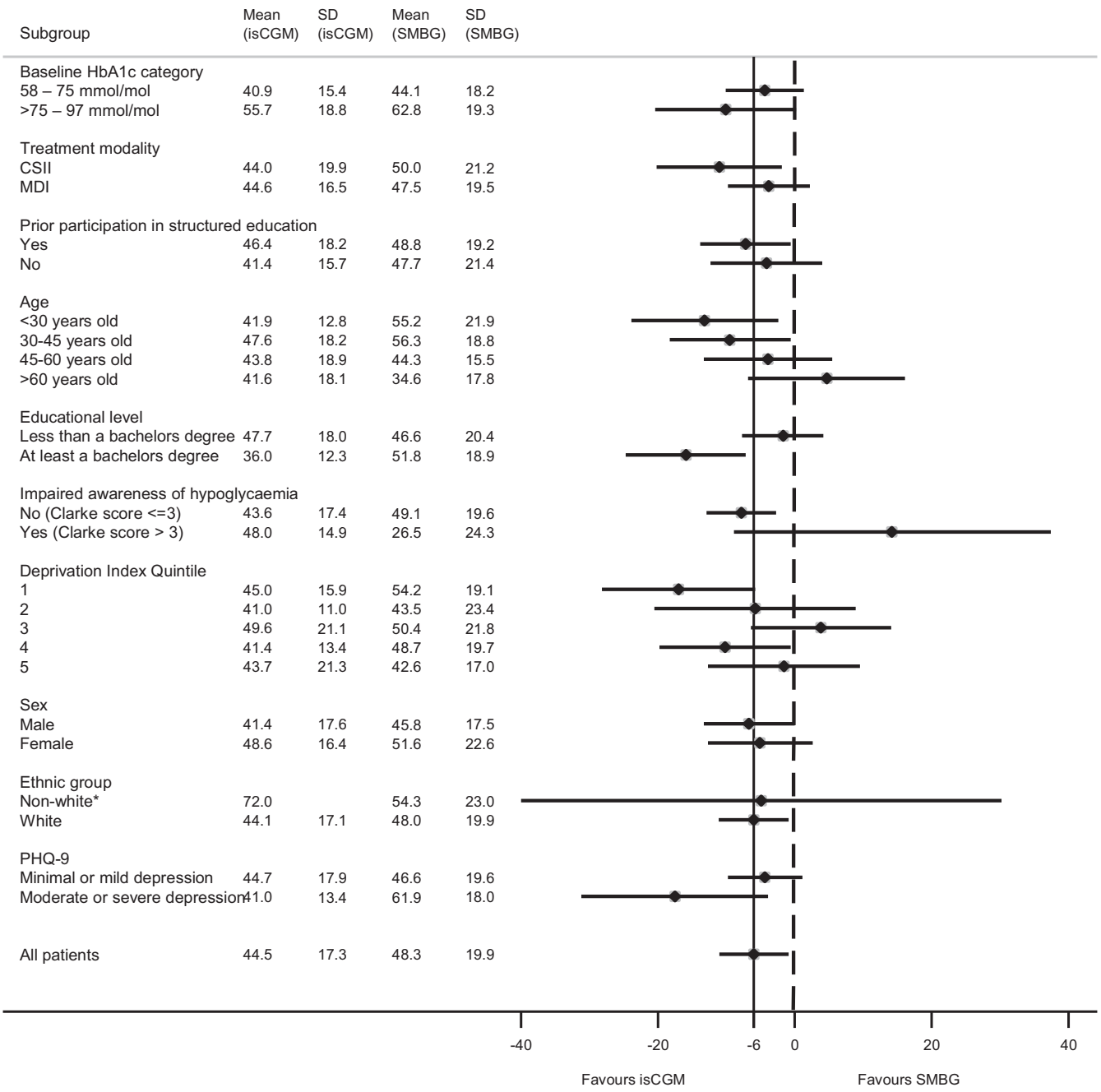

FIGURE 6 Subgroup analyses for coefficient of variation of glucose (%). The vertical solid line represent the overall effect of isCGM. *SD not calculable for isCGM non-white category as $n = 1$. isCGM, intermittently-scanned continuous glucose monitoring; SMBG, self monitoring of blood glucose.

in TAR and lower mean glucose on using isCGM, with non-significantly greater reduction in HbA1c. In contrast, those with less than a bachelor's degree had a larger reduction in hypoglycaemia at both 3.9 and 3.0 mmol/L thresholds. A non-significant trend of higher HbA1c reduction was seen in those with baseline HbA1c >75–97 mmol/mol (>9.0%–11.0%) and a non-significant trend of a larger reduction in TBR (both below 3.9 and below 3.0 mmol/L) were seen in those with baseline HbA1c 58–75 mmol/mol (7.5%–9.0%). Deprivation status did not impact the effect of isCGM on HbA1c reduction or sensor-based metrics such as TIR, TAR or TBR, but those with lower deprivation (higher Deprivation Index quintiles) had a greater reduction in glucose variability. Importantly, scanning frequency and overall sensor usage was broadly similar across various subgroups.

Our results suggest that younger participants had a greater reduction in HbA1c, TAR (>10 mmol/L) and mean glucose with a non-significant increase in TIR (3.9–10 mmol/L) compared to older participants. While our

study cannot provide a definite interpretation of these observations, it is possible, that the reason for high HbA1c and high TAR in younger participants, was mainly due to non-testing of glucose, whereas in older participants, it may have been for more complex reasons, not necessarily helped by having more glucose information (e.g. fear and burden of hypoglycaemia and co-existent co-morbidities). As a result, having easier access to glucose data helped younger participants more than older participants. Older participants are likely to have longer duration of diabetes which is associated with higher burden of hypoglycaemia. It is of note in older participants had a larger benefit in terms of hypoglycaemia reduction compared to younger participants which may suggest hypoglycaemia avoidance may have been a more important priority for this group. We noted those with at least a bachelor's degree had greater increase in TIR, a larger reduction in TAR and lower mean glucose on using isCGM. Based on this observation, it might be useful to provide additional training to those without at least a bachelor's degree to harness the full potential of this device. As noted before, scanning frequency and overall sensor usage was broadly similar across various subgroups.

4.2 | Comparison with previous studies

To put these findings in context, it is useful to compare with other UK-based studies of isCGM users. The real-world data set from the UK Association of British Clinical Diabetologists (ABCD) FreeStyle Libre audit provides insight into the relationship between some key baseline characteristics prior to FSL initiation and outcomes at follow-up. For example, in keeping with our observations, ABCD follow-up data from 6446 individuals on isCGM identified higher baseline HbA1c as a significant predictor of HbA1c response.[11] The ABCD study identified 'other' non-DAFNE-structured education as a predictor of response in contrast to previous completion of 'DAFNE structured education', which was not. Overall, age, gender, ethnicity, duration of diabetes, BMI and treatment modality did not predict HbA1c response.[12]

For time-in-range outcomes, ABCD data from 3250 individuals with follow-up data found that those who achieved TIR% 50–70 and TIR% >70 at 7.9 months were more likely to be older, have a lower HbA1c and lower diabetes-related distress at baseline.[13,14] In addition, duration of diabetes, baseline Gold score and structured education completion had a significant but limited absolute effect on the attainment of TIR% 50–70 and TIR% >70 at follow-up, with a significant negative correlation between the TIR% and pre-FSL HbA1c.

Real-world data from Scotland provides further context for our results. Baseline HbA1c was a strong predictor of HbA1c response, with those with the highest HbA1c values experiencing the greatest reduction in HbA1c.[15] Similar to our findings, while a reduction in HbA1c was observed in all age groups, there were smaller changes in the older (>64 years) group with the greatest HbA1c reductions in the 19–24-year subgroup. There were no differences in outcomes by gender, deprivation status or prior structured education. Those with prior pump use had greater HbA1c reduction than those without prior pump use, even when baseline HbA1c was accounted for.

ALERTT1 randomised controlled trial study showed that switching from intermittently scanned continuous glucose monitoring (isCGM) without alerts to real-time CGM (rtCGM) with alert functionality improved time in range (3.9–10 mmol/L), HbA1c, time <3.0 mmol/L and Hypoglycaemia Fear Survey score after 6 months in adults with type 1 diabetes.[16] A recent post hoc analysis from this study has also not shown any impact of 14 baseline characteristics on HbA1c or time in range.[17]

4.3 | Strengths and limitations

A strength of the FLASH-UK subgroup analysis is that this was the first RCT to investigate the effects of isCGM with optional alarms (Freestyle Libre 2) in adults with Type 1 diabetes and high HbA1c. Other strengths include the independent study conduct and pre-specified subgroup analysis. Limitations include small number of participants with impaired awareness of hypoglycaemia and non-White ethnicity. We were not able to analyse alarm data, as at the time of the study, Libreview software did not capture alarm data. Some subgroup factors are likely to be related—for example, educational status and deprivation status. Our study was not powered for subgroup analysis and only subgroup analyses for HbA1c were preplanned (and detailed in the statistical analysis plan). Subgroup analyses for secondary outcomes are post hoc, although we applied the subgroups and methods used for the primary outcome measure consistently across secondary outcomes. Moreover, while percentages of missing data were low (<10%) and similar between isCGM and SMBG groups for the primary outcome measure, this was not the case for secondary outcome measures. Hence our findings, particularly for secondary outcome measures, should be interpreted cautiously. We have not corrected for multiplicity in subgroups or outcomes, but our interpretation focuses on findings that appear consistent across primary and most secondary outcomes. Further research is needed to explore the findings from our study,

for example, to understand the reasons behind why younger participants achieve larger reduction in HbA1c or those with at least bachelor's degree achieve larger improvement in TIR.

5 | CONCLUSION

Findings from the current subgroup analysis suggest that isCGM with optional alarms is effective across a range of baseline characteristics with little or no impact from prior participation in structured education, deprivation status or gender. Our results suggest that, when using isCGM, younger participants had a greater reduction in HbA1c, time above range and mean glucose with a non-significant increase in time in range compared to older participants who had a larger benefit in hypoglycaemia reduction. Those with at least a bachelor's degree had higher TIR (driven by lower TAR) and lower mean glucose when using isCGM compared to those without.

AUTHOR CONTRIBUTIONS

Lalantha Leelarathna, Emma G. Wilmot and Mark L. Evans conceptualised the study. Lalantha Leelarathna, Emma G. Wilmot, Mark L. Evans, Iain Cranston, Parth Narendran, Sankalpa Neupane, Rachel A. Elliott, Christopher J. Sutton and Hood Thabit contributed to the grant application. Matthew Burns was the Lead Clinical Trial Manager. Christopher J. Sutton, Ashma Krishan and Vicky P Taxiarchi were responsible for statistical analysis. Lalantha Leelarathna, Emma G. Wilmot and Mark L. Evans, Iain Cranston, Parth Narendran, Sankalpa Neupane, Hood Thabit, Gerry Rayman, Sarah Lumley, provide site oversight and were responsible for recruitment and study conduct at each site. Maisie Camm contributed to sensor data analysis. Lalantha Leelarathna, Emma G. Wilmot and Christopher J. Sutton wrote the first draft of the article and all authors reviewed and had the opportunity to comment on the content prior to submission. The corresponding author confirms that all coauthors are ICMJE recommendation compliant for the submission of this article. No professional writers were engaged for the preparation of this article.

ACKNOWLEDGEMENTS

We thank independent members of the Trial Steering Committee (Prof R McCrimmon, Dr I Stratton, Prof K Ismail, Dr C Plumpton, Prof C Green, Prof R Agius and Mr N Cahm) and Independent Data Monitoring Committee (Prof H Murphy, Prof J Bolinder and Dr C Campbell). We also thank Prof R Hovorka and Dr MEW Wilinska, University of Cambridge for allowing us to use GStat Software for sensor data analysis.

FUNDING INFORMATION

This work was supported by Diabetes UK grant number 18/0005836. The device manufacturer played no part in design, conduct or any other aspects of the study. The study devices were funded by the National Health Service (NHS) United Kingdom. Work was supported by the NIHR Cambridge Biomedical Research Centre. The University of Cambridge has received salary support for MLE from the National Health Service in the East of England through the Clinical Academic Reserve.

CONFLICT OF INTEREST STATEMENT

EGW has received personal fees from Abbott Diabetes Care, Astra Zeneca, Dexcom, Eli Lilly, Embecta, Glooko, Insulet, Medtronic, Novo Nordisk, Sanofi and Ypsomed. LL has received personal fees from Abbott Diabetes Care, Dexcom, Insulet, Medtronic, Novo Nordisk and Sanofi Diabetes Care. ME has received personal fees from Abbott Diabetes Care, Eli Lilly, Medtronic, Dexcom, Novo Nordisk, Astra Zeneca and Zucara. SN has received personalised fees from QUIN, Roche. PN has acted as a clinical expert for NICE Medtech innovation briefing MIB110 relating to FreeStyle Libre system. GR has received lecture and consultancy fees from Abbott Diabetes UK. MB, KBK, CS, CK, VT, AK and RAE—No competing interests.

DATA AVAILABILITY STATEMENT

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

ORCID

Parth Narendran https://orcid.org/0000-0002-4583-8793
Katharine Barnard-Kelly https://orcid.org/0000-0002-3888-3123
Rachel A. Elliott https://orcid.org/0000-0002-3650-0168
Hood Thabit https://orcid.org/0000-0001-6076-6997

REFERENCES

1. Daneman D. Type 1 diabetes. *Lancet*. 2006;367(9513):847-858.
2. Vincze G, Barner JC, Lopez D. Factors associated with adherence to self-monitoring of blood glucose among persons with diabetes. *Diabetes Educ*. 2004;30(1):112-125.
3. Moström P, Ahlén E, Imberg H, Hansson PO, Lind M. Adherence of self-monitoring of blood glucose in persons with type 1 diabetes in Sweden. *BMJ Open Diabetes Res Care*. 2017;5(1):e000342.
4. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016–2018. *Diabetes Technol Ther*. 2019;21(2):66-72.
5. Avari P, Reddy M, Oliver N. Is it possible to constantly and accurately monitor blood sugar levels, in people with type 1

diabetes, with a discrete device (non-invasive or invasive)? *Diabet Med*. 2020;37(4):532-544.
6. Leelarathna L, Wilmot EG. Flash forward: a review of flash glucose monitoring. *Diabet Med*. 2018;35(4):472-482.
7. Wilmot EG, Evans M, Barnard-Kelly K, et al. Flash glucose monitoring with the FreeStyle Libre 2 compared with self-monitoring of blood glucose in suboptimally controlled type 1 diabetes: the FLASH-UK randomised controlled trial protocol. *BMJ Open*. 2021;11(7):e050713.
8. Leelarathna L, Evans ML, Neupane S, et al. Intermittently scanned continuous glucose monitoring for type 1 diabetes. *N Engl J Med*. 2022;387(16):1477-1487.
9. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189-2194.
10. Gov.uk. *English Indices of Deprivation 2019*. Ministry of Housing, Communities & Local Government; 2020. Accessed August 10, 2023. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019
11. Shah N, Deshmukh H, Wilmot EG, et al. Previous structured education attendance and the relationship with HbA1c and hypoglycaemia awareness in people living with type 1 diabetes mellitus using FreeStyleLibre: insights from the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. *Br J Diabetes*. 2021;21(2):192-197.
12. Deshmukh H, Adeleke KA, Ssemmondo E, et al. Ethnic disparities in people accessing FreeStyle libre in the United Kingdom: insights from the Association of British Clinical Diabetologists audit. *Diabet Med*. 2023;40(8):e15095.
13. Deshmukh H, Wilmot EG, Gregory R, et al. Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the Association of British Clinical Diabetologists (ABCD) nationwide audit. *Diabetes Care*. 2020;43(9):2153-2160.
14. Deshmukh H, Wilmot E, Pieri B, et al. Time in range following flash glucose monitoring: relationship with glycaemic control, diabetes-related distress and resource utilisation in the Association of British Clinical Diabetologists national audit. *Diabet Med*. 2022;39(11):e14942.
15. Jeyam A, Gibb FW, McKnight JA, et al. Flash monitor initiation is associated with improvements in HbA1c levels and DKA rates among people with type 1 diabetes in Scotland: a retrospective nationwide observational study. *Diabetologia*. 2022;65(1):159-172.
16. Visser MM, Charleer S, Fieuws S, et al. Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. *Lancet*. 2021;397(10291):2275-2283.
17. Visser MM, Charleer S, Fieuws S, et al. The impact of baseline user characteristics on the benefits of real-time versus intermittently scanned continuous glucose monitoring in adults with type 1 diabetes: moderator analyses of the ALERTT1 trial. *J Diabetes Sci Technol*. 2022;193229682211283. doi:10.1177/19322968221128315

SUPPORTING INFORMATION

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

How to cite this article: Leelarathna L, Sutton CJ, Evans ML, et al. Intermittently scanned continuous glucose monitoring in adults with type 1 diabetes: A subgroup analysis from the FLASH-UK study. *Diabet Med*. 2023;00:e15249. doi:10.1111/dme.15249