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Continuous glucose monitoring versus self-monitoring of blood glucose in the management of cystic fibrosis related diabetes: A systematic review and meta-analysis

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ABSTRACT

Background: Treatment of cystic fibrosis related diabetes (CFRD) can improve outcomes and use of continuous glucose monitoring (CGM) can positively impact glycemic control. We conducted a systematic review to assess current evidence on CGM compared to self-monitoring of blood glucose (SMBG) in the management of CFRD to determine its effect on glycemic, pulmonary, non-pulmonary and quality of life outcomes.

Methods: Using pre-defined selection criteria, we searched MEDLINE, Embase, CENTRAL, Evidence-Based Medicine Reviews, grey literature and six relevant journals for studies using CGM and/or SMBG in CFRD with greater than 6 weeks of follow-up and reported change in HbA1c. The primary outcome was weighted mean difference (WMD) in plasma HbA1c between CGM and SMBG groups. Secondary outcomes included exploring interrelationships between CGM metrics and effects on disease-specific pulmonary, non-pulmonary and quality of life outcomes.

Results: A total of 1671 references were retrieved, 862 studies screened and 124 full-texts assessed for eligibility. No studies directly compared CGM to SMBG. A meta-analysis of seventeen studies of 416 individuals (CGM = 138, SMBG = 278) found CGM group had 4.1 mmol/mol (95% CI -7.9 to -0.30, $p = 0.034$) lower HbA1c compared to SMBG group. Most studies demonstrated moderate-to-high risk of bias. Publication bias was also present. Heterogeneity was high and meta-regression identified duration of follow-up in SMBG group as main contributor.

Conclusion: Our findings suggest use of CGM may be associated with improved glycemic control compared to SMBG in CFRD, however evidence of benefit on pulmonary, non-pulmonary and psychosocial outcomes are lacking.

1. Introduction

Due to the improved life expectancy of individuals diagnosed with cystic fibrosis (CF), there has been a rise in co-morbidities such as cystic fibrosis related diabetes (CFRD) [1,2]. Up to half of all adults with CF may have CFRD which is associated with adverse pulmonary outcomes [3–6]. This is of great consequence given respiratory disease remains the commonest cause of mortality. Studies have demonstrated that individuals with CFRD have lower baseline lung function [7], faster rate of pulmonary decline [5], altered lung microbiome [8], prolonged pulmonary exacerbations [9] and increased mortality [3] when compared to individuals without diabetes. The predominant underlying pathophysiology in CFRD is insulin deficiency [10]. Hyperglycemia due to insulin resistance is also important and may accelerate β-cell dysfunction and loss [11]. Insulin resistance may increase during glucocorticoid use, puberty [12], pregnancy [13] and in the presence of inflammatory cytokines [10]. In addition, defects in substrate utilisation, dysregulated hepatic gluconeogenesis and presence of liver disease may also impact insulin resistance [14]. Exocrine pancreatic dysfunction often accompanies endocrine dysfunction perhaps due to shared pathogenesis [11,15]. The transient and unpredictable effects of these vari-

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ables contribute to significant glycemic instability in CFRD which requires intensive monitoring of blood glucose levels to ensure optimal treatment with insulin.

Insulin therapy in CFRD can have multifaceted benefits including enabling weight gain, minimising hyperglycemia-induced lung dysfunction and reducing microvascular complications [16,17]. It is also associated with increased risk of hypoglycemia. Insulin use in CFRD varies depending on the setting, with studies reporting over 80% of hospitalised individuals use insulin [18,19] compared to less than 50% in the community [20]. For those treated with insulin, uptake of an insulin pump is reportedly low with estimates ranging between 4–14% [19,21]. Monitoring and managing insulin therapy in CFRD can be challenging and this has led to increased utilisation of continuous glucose monitoring (CGM). These are devices worn by a user and provide real-time sensor glucose measurements and trends allowing immediate decision-making by the individual and review of comprehensive historical reports; insights not provided with standard multiple daily finger prick self-monitoring of blood glucose (SMBG) [22–24]. Use of CGM in the management of type 1 diabetes has been demonstrated to improve glycemic control, increase hypoglycemic confidence and reduce diabetes distress [23,25].

Guidelines recommend quarterly monitoring of HbA1c in people with confirmed CFRD with a treatment target <53mmol/mol (<7%) to reduce risk of microvascular complications [26]. There appears to be strong correlation between plasma HbA1c and mean glucose concentrations [27] and average sensor glucose [28] on CGM in people with CFRD. However, plasma HbA1c in people with CF may be impacted by high red cell turnover, iron deficiency and/or anaemia leading to inaccuracies [29,30]. Prevalence estimates of iron deficiency anaemia in CF range between 44–60% [31,32] and the magnitude and direction of change in HbA1c associated with iron deficiency and/or anaemia remains unclear [33]. As a result, HbA1c is not recommended for the diagnosis of CFRD, however in CFRD confirmed using other methods, HbA1c is currently the best standardised measurement tool available to assess longitudinal glycemic control [26,28,34].

It is unclear whether benefits of CGM demonstrated in people with type 1 diabetes are transferable to individuals with CFRD. The primary objective of this systematic review was to assess the current evidence on CGM (intervention) compared to SMBG (standard care) in the management of people with confirmed CFRD to determine if CGM use improves glycemic control as measured by longitudinal change in plasma HbA1c during follow-up. Secondary objectives were to evaluate interrelationships between CGM metrics and pulmonary and non-pulmonary outcomes in CFRD, explore quality of life outcomes and identify gaps in the evidence and areas where further research is required.

2. Methods

2.1. Search strategy

The present systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) reporting guidelines [35] and the full search protocol has been published on Prospero [36]. A concept map (*see Supplementary Material)* was developed using MeSH terms and text words to maximise sensitivity: “cystic fibrosis” AND “diabetes” AND “continuous glucose monitoring” OR “self-monitoring”. A systematic search, based on pre-defined selection criteria combining MeSH terms and text words was developed using the OVID platform and translated to other databases with the search carried out on 15th April 2021 (*see Supplementary Material).* The following electronic databases were used to identify relevant published literature; Medline & Medline in-process and other non-indexed citations, EMBASE and Emcare, All EBM Reviews, CENTRAL (Cochrane Central Register of Controlled Trials) and Web of Science. The International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/) was also searched to identify ongoing trials. Monash Health search engine was used to search the grey literature using British Library, Google Scholar and Open Grey. Abstracts from six relevant conferences were hand-searched where they were published as supplements in journals including Diabetes UK Abstracts (*Diabetic Medicine)*, American Diabetes Association Scientific Session Abstracts (*Diabetes)*, European Association for the Study of Diabetes Annual Meeting (*Diabetologia)*, European Cystic Fibrosis Society (*Journal of Cystic Fibrosis)*, Annual North American Cystic Fibrosis Conference (*Pediatric Pulmonology)* and Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (*Pediatric Diabetes).* Reference lists were searched to find additional articles by notable authors.

2.2. Inclusion and exclusion criteria

Children and adults of any gender with a confirmed diagnosis of CFRD as per current American Diabetes Association criteria who used CGM for at least 72 hours and/or SMBG and had at least 6 weeks of follow-up with HbA1c available at baseline and follow-up were considered. There were no restrictions on the type of CGM used, treatment for CFRD or co-interventions. Due to anticipated paucity of studies in the field, all study designs were included. Additional limits included human studies only and English language papers published after year 2000.

2.3. Data collection

All search results were exported for storage to Endnote and transferred to Covidence, a web-based platform for screening. A single reviewer (SK) screened the titles, abstracts and keywords of every article retrieved by the search strategy to assess eligibility according to the selection criteria. Subsequently, two reviewers (SK, MP) independently reviewed all full text articles to be included in the study, with discrepancies resolved by a third investigator (HT).

2.4. Data extraction

Pre-designed templates were filled with extracted data by SK. Information extracted included a) General study details (title, authors, reference, year of publication, setting), b) Study information (selection criteria, study design and methods, number of participants), c) Participant demographics (age, gender), d) Index test (type of CGM used, average duration of wear), e) Outcomes of interest including HbA1c, CGM metrics, adverse effects of CGM use and consumer satisfaction, pulmonary (change in forced expiratory volume in one second FEV1, frequency of pulmonary exacerbations, isolation of multi-resistant organisms) and non-pulmonary (body mass index [BMI], weight) outcomes [37]. The author’s definitions of each of the reported variables was accepted.

2.5. Risk of bias assessment

Assessment of risk of bias was performed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [38]. A list of confounding domains and co-interventions were identified and signalling questions created to grade each study using the ROBINS-1 tool into low, moderate, serious or critical risk of bias *(See supplementary material).*

2.6. Outcomes

The primary outcome was weighted mean difference (WMD) in plasma HbA1c in individuals with confirmed CFRD who were using CGM (intervention) versus SMBG (standard care) over follow-up of at least 6 weeks. Secondary outcomes included (i) CGM metrics (mean glucose, clinically significant hypoglycemia [< 3.0 mmol/L], percentage time in target range [< 3.9 – 10.0 mmol/L], clinically significant hyperglycemia [> 13.9 mmol/L], glycemic variability, estimated A1c [mmol/mol and %]), (ii) Pulmonary outcomes (frequency of pulmonary exacerbations, change in FEV1, isolation of multi-resistant organisms), (iii) Non-pulmonary outcomes (change in BMI or weight) and (iv) consumer satisfaction with CGM and impact on quality of life.

2.7. Statistical analysis

We synthesized a quantitative analysis for the primary outcome of WMD in plasma HbA1c between the CGM (intervention) and SMBG (standard care) groups. All secondary outcomes were exploratory. Each study was labelled as either evaluating CGM or SMBG with or without a co-intervention. From each study the reported baseline and follow-up HbA1c values were (a) converted to IFCC (mmol/mol) if DCCT (%) values were reported (b) standard deviation and confidence intervals were collected or estimated from equations if not reported (c) absolute and percentage difference in mean HbA1c during the follow-up period was calculated and (d) a random effects model was used to calculate the WMD with 95% CI for each study which was then pooled in a meta-analysis to derive an overall WMD between the two groups. We also evaluated the differential implications of CGM use without co-interventions by performing a subgroup meta-analysis. A 2-sided *P*value < 0.05 was considered statistically significant. Publication bias was assessed using Eggers graphical test [39]. Stata was used for all quantitative analysis.

2.7.1. Assessment of heterogeneity

Heterogeneity between studies was assessed using I^2 index with an I^2 greater than 50% indicative of significant heterogeneity. A meta-regression to examine the source of heterogeneity was planned.

3. Results

3.1. Search results

A flow diagram Fig. 1 shows 1671 total references were retrieved by the original search and after removal of duplicates, 862 studies were title and abstract screened by SK. Subsequently 124 full-texts were assessed for eligibility by SK and MP. In total, 24 studies met our inclusion and exclusion criteria of which 11 evaluated CGM and 13 evaluated SMBG. Of the 24 studies meeting our protocol criteria, 12 also reported pulmonary, non-pulmonary or consumer satisfaction and quality of life outcomes.

3.2. Study characteristics

Characteristics of studies that met our review protocol criteria are presented in Table 1. We found no randomised controlled studies assessing the glycemic effects of CGM versus SMBG in the management of CFRD. Seven studies [40–46] met our protocol inclusion criteria however were case reports describing individual outcomes. Grancini et al. [47] and Grover et al. [48] compared outcomes in two groups using SMBG with and without a co-intervention. The average follow-up period was 21.2 months (CGM group 5.9 ± 2.9 months vs SMBG 31.8 ± 61.9 months, $p = 0.24$). The baseline HbA1c in the CGM group was significantly higher compared to SMBG group (64.3 ± mmol/mol vs 52.1 ± mmol/mol, $p = 0.007$) *(See Supplementary material for weighted mean baseline HbA1c for the two groups).* The Freestyle Libre was the most commonly used CGM device.

3.3. Risk of bias

Figs. 2 and 3 summarise the risk of bias according to ROBINS-1 tool for studies meeting protocol inclusion and exclusion criteria evaluating CGM and SMBG in the management of CFRD respectively. Due to the large number of studies having co-interventions and/or retrospective design most were graded at being serious to critical risk of bias.

3.4. Primary outcome

Seventeen studies that assessed the effect of CGM versus SMBG on longitudinal change in HbA1c among 416 individuals with CFRD (CGM = 138 and SMBG = 278) were pooled into a meta-analysis (See Fig. 4). From baseline to follow-up, the weighted mean difference in HbA1c for the CGM group was -3.9 mmol/mol (95% CI -5.9 to -2.0, $p < 0.0001$) compared to the SMBG group of -3.0 mmol/mol (95% CI -7.5 to 1.5, $p = 0.93$). The overall WMD favoured improved glycemic control in the CGM group with a 4.1 mmol/mol lower HbA1c (95% CI -7.9 to -0.30, $p = 0.034$) which equated to approximately 0.4% (DCCT/NGSP) reduction in HbA1c in the CGM group compared to the SMBG group.

3.4.1. Subgroup meta-analysis

A forest-plot of meta-analysis for HbA1c was also derived from studies with no co-interventions and low to moderate risk of bias evaluating CGM ($n = 4$) ([49,52,55,56]) and SMBG ($n = 2$) ([47,58]) *(See Supplementary Material).* These results also favoured improved glycemic control in the CGM group with WMD in HbA1c of -3.7 mmol/mol (95% CI -5.6 to -1.7, $p = 0.89$) in the CGM group compared to +7.7 mmol/mol (95% CI 2.3 to 13.0, $p = 0.24$) in the SMBG group.

The small numbers and inadequate information regarding insulin regimens in the studies prohibited analyses that compared individuals with CFRD using multiple daily insulin injections versus insulin pump therapy.

3.4.2. Heterogeneity

There was considerable heterogeneity attributed to the SMBG group ($I^2 = 95.7\%$) contributing to the high heterogeneity in the overall WMD.

3.4.3. Publication bias

There was evidence of publication bias according to Egger's test for small-study effects ($p = 0.014$) *(See Supplementary material).* We used a random-effects model to investigate the study-level covariates that may have accounted for the heterogeneity as demonstrated by the funnel-plot asymmetry.

3.4.4. Meta-regression

The heterogeneity in the SMBG group was very high ($I^2 = 95.7\%$), however there was no evidence for heterogeneity in the CGM group ($I^2 = 0\%$). A meta-regression with duration of follow-up and presence of co-intervention as covariates was performed *(See supplementary material).* We found the main source contributing to overall heterogeneity was the *duration of follow-up* in the SMBG group ($p = 0.019$).

Table 1
Characteristics including presence of co-interventions, baseline and follow-up HbA1c and duration of follow-up of studies meeting protocol inclusion and exclusion criteria.

Author	Year	Study Design	n	Age (yrs)	CGM used	Follow-up (months)	Outcomes reported	Co-intervention	Baseline HbA1c (mmol/mol	Follow-up HbA1c (mmol/mol)	Δ HbA1c (%)
Studies evaluating Continuous Glucose Monitoring (CGM)											
Balzer(49)	2014	Case Series	7	n/a	iPRO2	6	HbA1c, FEV1, BMI, CGM metrics	Nil	66.6	55.3	-17%
Campbell* [40]	2015	Case Report	1	16	Libre	> 3	HbA1c	Insulin pump	81.4	69.4	-15%
Casas* [41]	2007	Case Report	1	2	NS	12	HbA1c	Insulin pump	41.0	37.7	-8%
Dyce [50]	2015	Retrospective	9	27.7	NS	> 3	HbA1c, FEV1, weight, CGM metrics	Pre/post initiation of degludec	65.2	54.5	-16%
Dyce [51]	2013	Retrospective	11	n/a	NS	> 3	HbA1c, weight (kg), FEV1, CGM metrics	Specialist diabetic service	57.4	49.7	-13%
Gnanapragasam* [43]	2020	Case report	1	21	Libre	3	HbA1c, Weight	Semaglutide + insulin titration	76.0	50.8	-33%
Hagan [52]	2020	Retrospective	12	NS	Libre	> 3	HbA1c	Nil	58.5	51.9	-11%
Muniandy [53]	2012	Prospective	5	28	NS	>3	HbA1c, FEV1, BMI	Exercise program	83.6	73.8	-12%
Ng [54]	2020	Prospective	5	12.4	DexG6	6	HbA1c, Weight, FEV1	Insulin Initiation	62.6	42.7	-32%
Shimmin [55]	2020	Retrospective	78	n/a	Libre	3	HbA1c, BMI, CGM metrics and QOL	Nil	58.5	55.0	-6%
Stackhouse [56]	2017	Prospective	11	n/a	iPro2	> 3	HbA1c	Nil	62.3	57.5	-8%
Studies evaluating Self-monitoring of Blood Glucose Levels (SMBG)											
Bonnette [57]	2020	Retrospective	10	24		12	HbA1c, FEV1, BMI	Lung transplantation	59.6	44.3	-26%
Christian* [42]	2019	Case Report	1	34		72	HbA1c, weight, FEV1	Ivacaftor	41.0	46.4	13%
Denis [58]	2015	Retrospective	119	n/a		216	HbA1c	Nil	35.5	44.3	25%
Grancini [47]	2019	Prospective	9	NS		> 3	HbA1c	Carbohydrate counting vs No intervention	57.4	48.6 58.5	-15% 2%
Grover [48]	2007	Prospective	19	34		3	HbA1c, weight, SMBG	Insulin initiation Glargine vs NPH	47.5	46.4 48.6	-2% 2%
Hardin [59]	2009	Retrospective	9	27		6	HbA1c, SMBG	Insulin pump	66.1	54.1	-18%
Hasan[60]	2020	Retrospective	24	28.7		27.2	HbA1c, FEV1	CFTR modulators	46.4	41.0	-12%
Hubert[61]	2011	Retrospective	25	27		12	HbA1c	Repaglinide	49.7	39.9	-20%
Kettley [62]	2017	Retrospective	35	NS		> 3	HbA1c	Quality improvement initiative	55.4	54.9	-1%
Pirgon* [44]	2012	Case Report	1	4		24	HbA1c	Insulin initiation	86.9	55.2	-36%
Rayanagoudar* [45]	2011	Case Report	1	35		24	HbA1c	Enteral feeds	63.9	55.2	-14%
Reali* [46]	2006	Case Report	1	23		6	HbA1c, SMBG, FEV1, BMI	Insulin pump	86.9	46.4	-47%
Sullivan [63]	2013	Retrospective	16	38.2		3	HbA1c	Quality improvement initiative	50.6	46.4	-8%

* Case reports excluded from meta-analysis FEV1 = forced expiratory volume in one second, BMI = body mass index, CFTR = cystic fibrosis transmembrane conductance regulator, NPH = neutral protamine hagedorn insulin, QOL = quality of life NS = not specified.

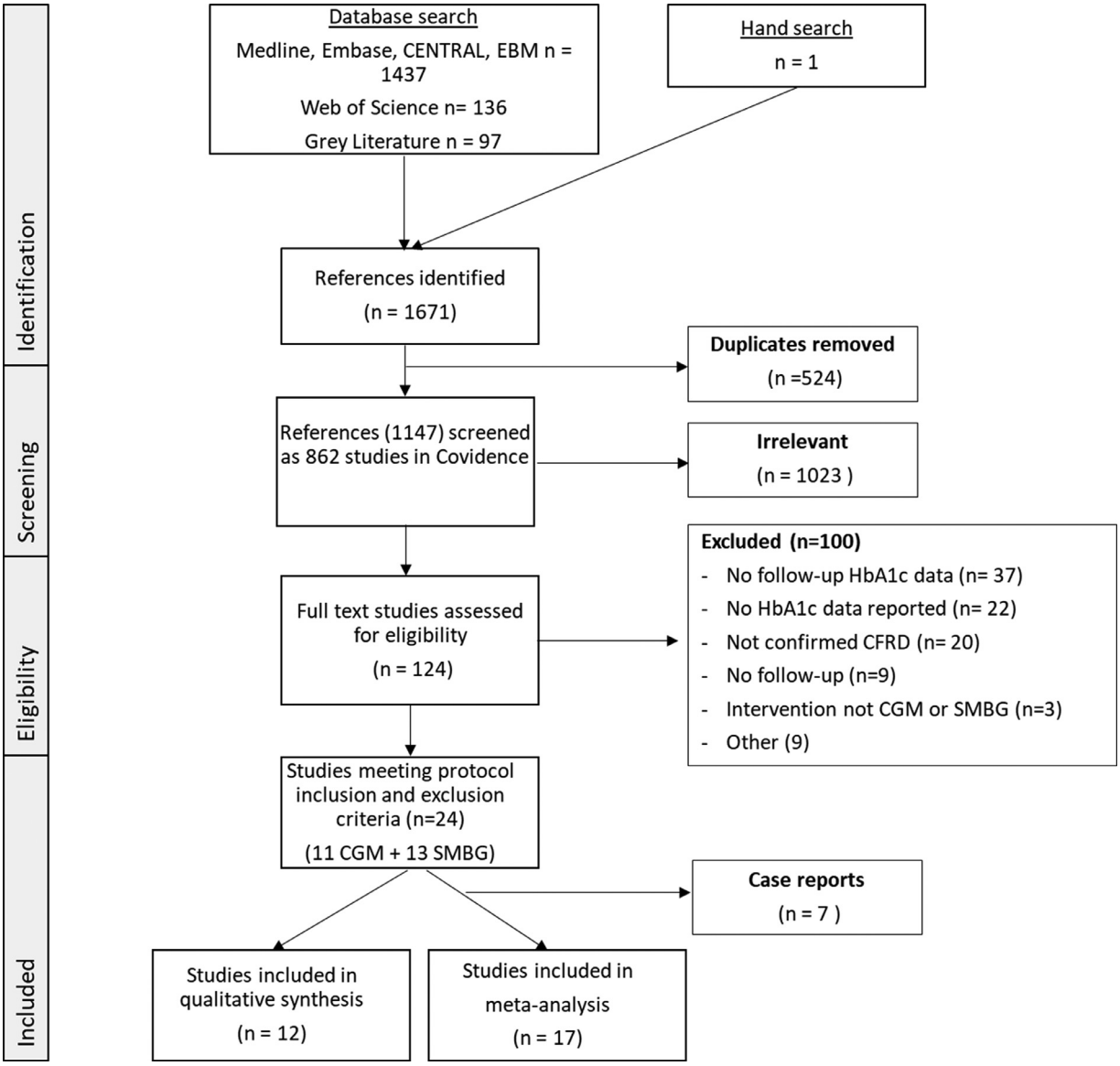

Fig. 1. PRISMA Study Flow diagram.

3.4.5. Subgroup meta-analysis according to duration of follow-up

Fig. 5 demonstrates that there was a trend towards improved glycemic control with longer duration of follow-up in the CGM group. At 2-3 months WMD was -3.5 mmol/mol (95% CI -5.6 to -1.5, $p = 0.60$), and at 4–6 months -8.0 mmol/mol (95% CI -15.6 to -0.3, $p = -0.96$). However, one study evaluating >7 months follow-up had a WMD of -4.8 mmol/mol (95% CI -17.2 to 7.6).

3.5. Secondary outcomes

3.5.1. Pulmonary outcomes

Balzer et al. [49] reported an overall reduction in FEV1 of 4% during the follow-up period in seven individuals with CFRD using CGM. In contrast, Dyce and colleagues reported overall improvement in FEV1 by 8.4% (mean FEV1 improved from 59 to 64%) in 78% ($n = 14/18$) of adults with CFRD using CGM to aid glycemic control over a 12-month period. They also reported 53% of their group required less intravenous antibiotics and 38% required fewer oral antibiotics [64] compared to pre-CGM use period.

3.5.2. Non-pulmonary outcomes

Only two studies using CGM with no co-interventions reported changes in BMI [49,55]). Baseline BMI in these studies were 21.7 ± 2.2 kg/m^2. Balzer reported mixed outcomes in their seven study participants with 71% ($n = 5/7$) demonstrating 4% increase in BMI with remaining 29% ($n = 2/7$) showing a 5% reduction in BMI over the 6-month follow-up period [49]. Shimmin reported no significant change in BMI in their study [55]. Ng reported four individuals managed with CGM and aggressive insulin up-titration had 4.1% improvement in body weight over 6 months [54]. Dyce reported 72% ($n = 13/18$) of their cohort had weight gain with mean weight increase from 59 to 60 kg noted over 12 months [64]. None of the studies provided body composition data.

3.5.3. Consumer satisfaction

Only one study assessed consumer satisfaction with the Freestyle Libre device in 48 adults (mean age 37 years, 20 male) with 88% of respondents agreeing or strongly agreeing that the Freestyle Libre device was easy and comfortable to use [55]. Almost all (98%) respondents recommended CGM use in the future

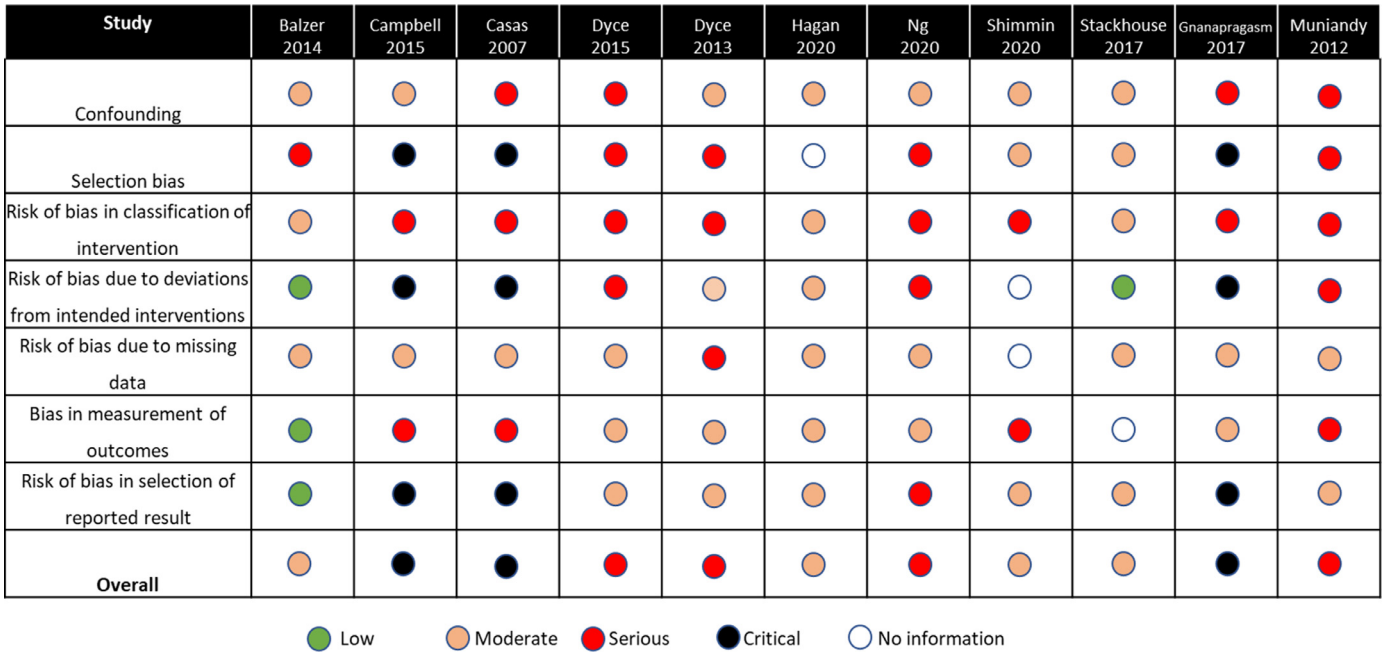

Fig. 2. Risk of bias of studies evaluating CGM in CFRD according to ROBINS-I tool criteria.

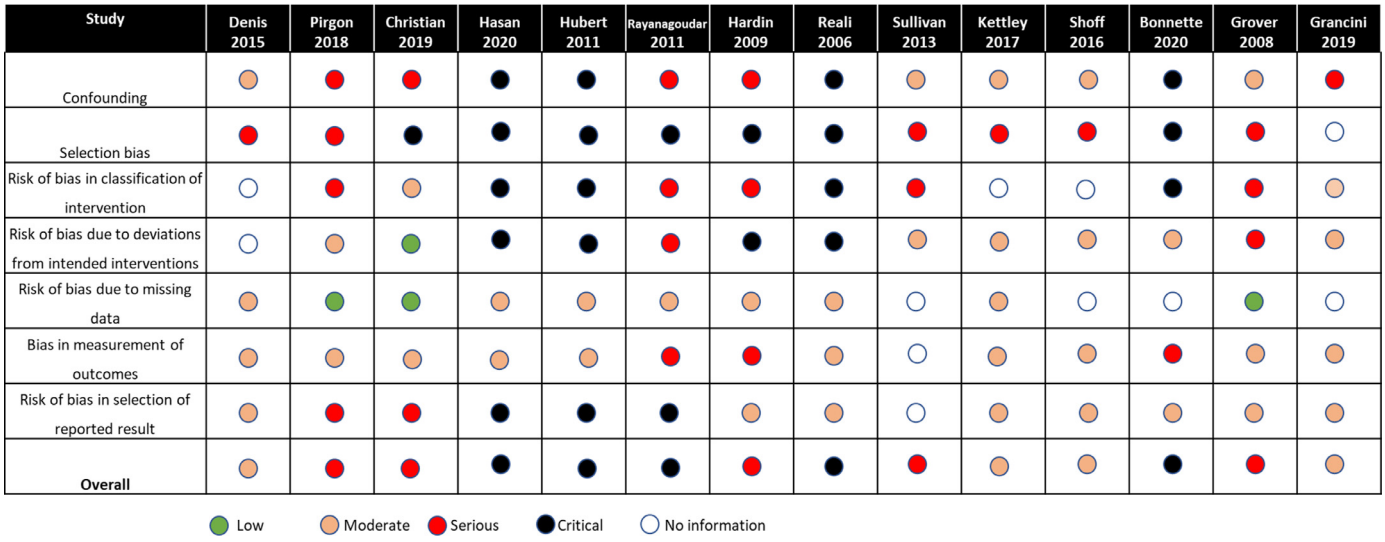

Fig. 3. Risk of bias of studies evaluating SMBG in CFRD according to ROBINS-I tool criteria.

and found the glucose trend arrows and scanning function of the Freestyle libre highly useful.

4. Discussion

4.1. Main findings

To our knowledge, this is the first systematic review to report outcomes of CGM compared to SMBG in the management of CFRD. Our findings suggest CGM can result in improved glycemic control compared to standard care with SMBG as evidenced by a 4.1mmol/mol (-0.4%) reduction in HbA1c after at least 6 weeks of use, however the quality of the studies included in the meta-analysis were poor. We found effects on pulmonary and non-pulmonary outcomes were conflicting. Consumer feedback on the Freestyle Libre demonstrated high user acceptability and overwhelmingly positive experiences.

4.2. Comparison to type 1 diabetes studies

Our findings are consistent with multiple systematic reviews evaluating data from randomised controlled trials in type 1 diabetes which have demonstrated that use of CGM is associated with improved glycemic control as evidenced by reduction in HbA1c when compared to SMBG [65–72]. However, the magnitude of difference in HbA1c between CGM and SMBG groups was greater in our study than those reported in type 1 diabetes cohorts (-0.4% vs -0.26%) [65] which indicate that our findings likely over-estimate CGM effect. Nevertheless, CFRD has distinct epidemiology, pathophysiology and management compared to type 1 diabetes, which could partly explain the observed differences.

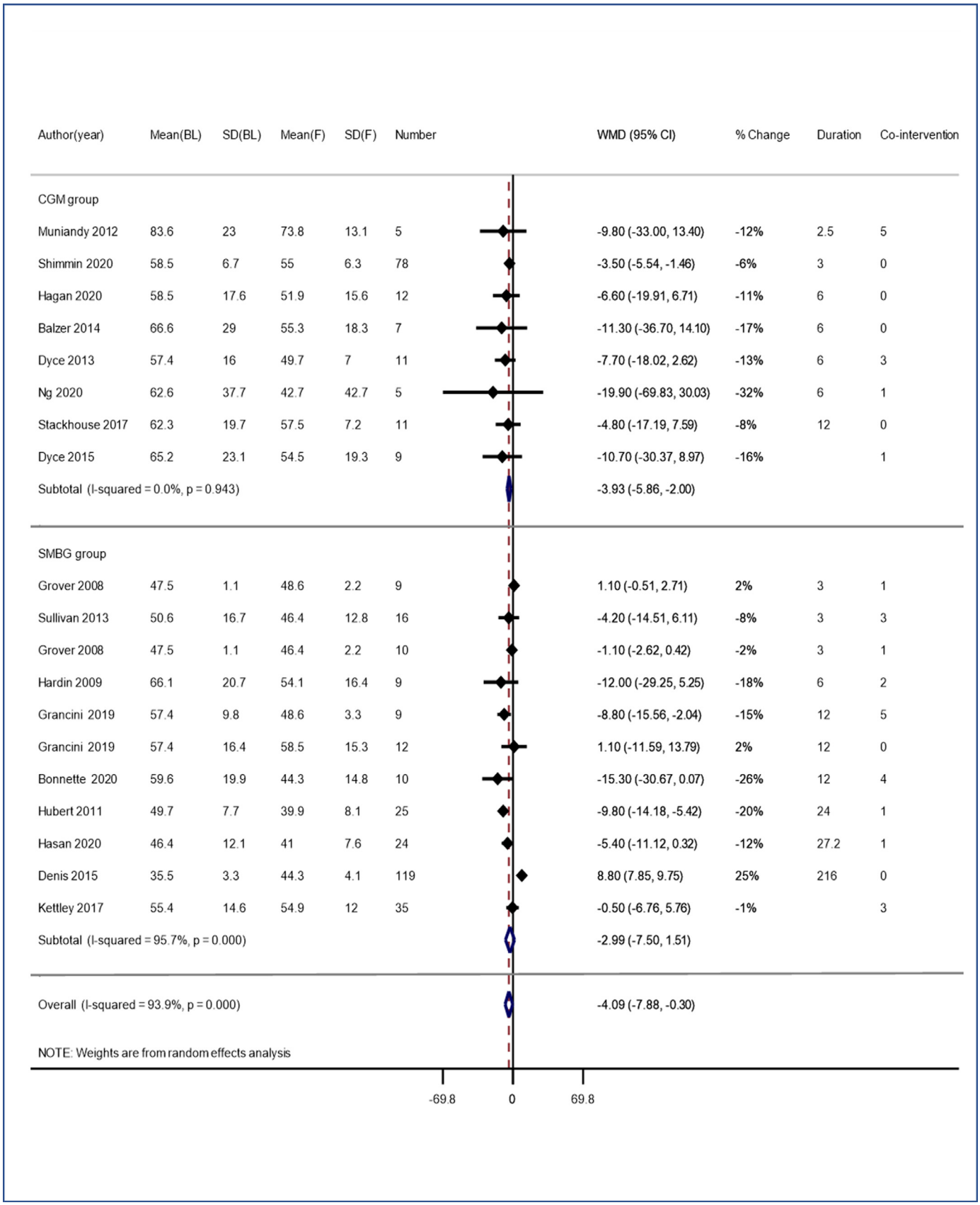

Fig. 4. Forest plot of meta-analysis for HbA1c expressed as weighted mean difference (WMD) in CGM (intervention) and SMBG (standard care) groups[1].

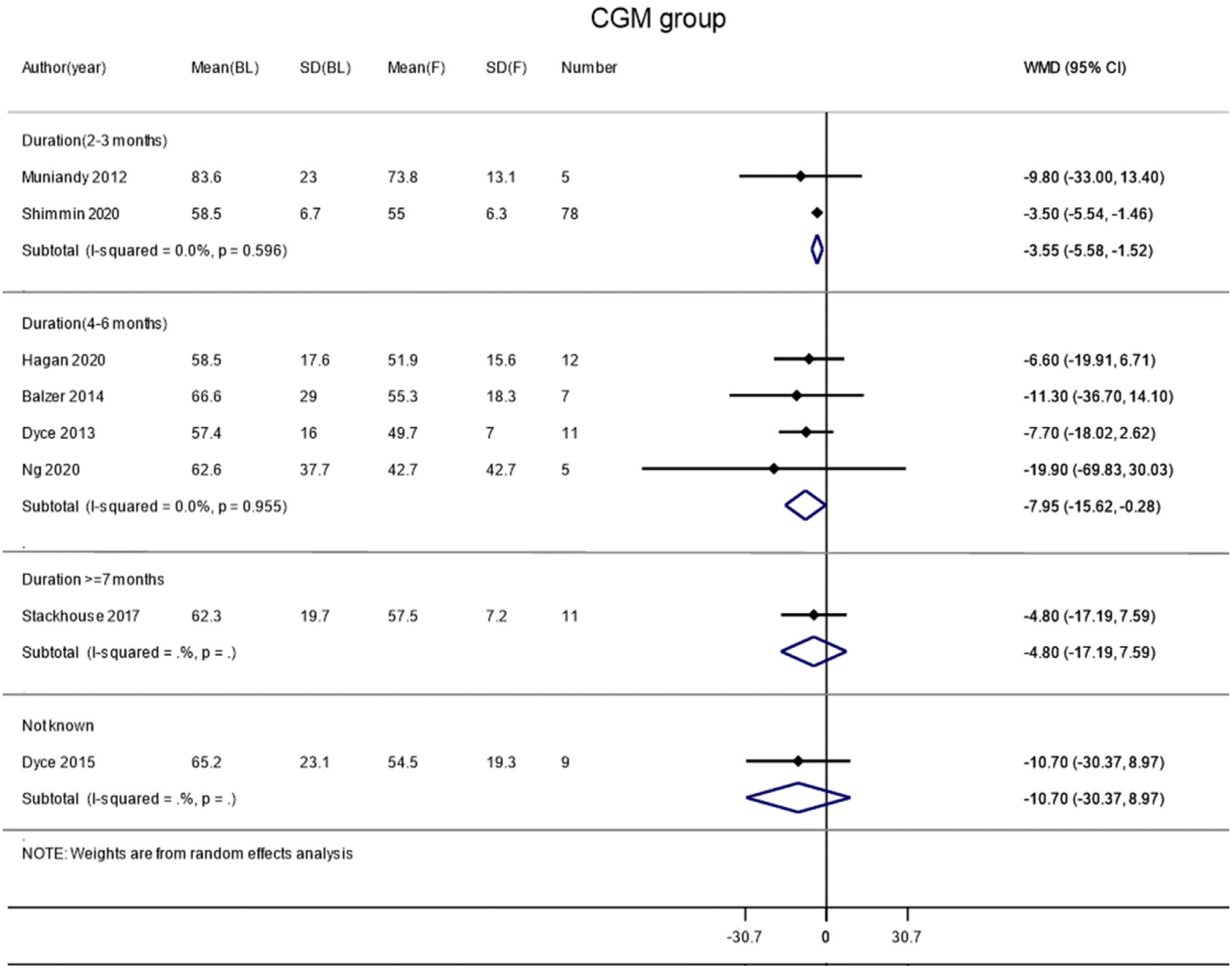

Fig. 5. Forest plot of meta-analysis for HbA1c expressed as weighted mean difference (WMD) in CGM (intervention) group according to duration of follow-up.

4.3. Clinical implications

Improved glycemic control in CFRD can reduce mortality [6]. The proposed mechanisms underlying poorer outcomes in CFRD are multifactorial including hyperglycemia-induced lung dysfunction through disruption of the airway surface liquid layer [73], effect on colonisation and proliferation of microbes implicated in pulmonary exacerbations, impact on immune function and increased production of advanced glycation end-products [16,17]. Evidence linking hyperglycemia detected on CGM to declining pulmonary function [74,75] and weight [76] together with altered microbiome [74] in CF exists. If use of CGM can improve glycemic control in CFRD then clarity around CGM targets are also needed. There is consensus on key CGM metrics and targets in type 1 diabetes [77] with one of the core metrics being time in range specified as 70–180 mg/dL (3.9–10 mmol/L). Microvascular complications are the principal disease-specific outcome in type 1 diabetes and studies have demonstrated correlations between time in range on CGM and complications [78]. Although increasing life expectancy may influence diabetes-related manifestations, at present microvascular complications remain less common in CF [79]. Therefore, we propose that pulmonary function should be considered the primary outcome and we found currently there is insufficient evidence to support disease-specific CGM targets in CFRD.

Evidence linking blood glucose levels ≥7.8 mmol/L with impaired function of the airway surface liquid layer [16] resulting in altered microbiome [80,81] and reduced defence against infection [82] exists. Prescription of insulin therapy based on sensor glucose levels on CGM >7.8 mmol/L for >4.5% time has also been shown to improve disease-specific outcomes (FEV1 and weight) in individuals with CFRD [83]. Our group found dysglycemia on CGM defined as percentage of time >7.8 mmol/L was associated with poorer recovery of pulmonary function following an exacerbation [18]. Such findings suggest a time in range CGM target of 70–180 mg/dL (3.9–10 mmol/L) utilised in type 1 diabetes may not be directly transferable to CFRD. Whether more conservative thresholds such as those utilised in pregnant women with diabetes with time in range of 63–140 mg/dL (3.5–7.8 mmol/L) [77] may be more appropriate for individuals with CFRD requires further evaluation.

Improvement in plasma HbA1c with utilisation of CGM can also reflect reduced incidence of hypoglycemia [84], however no studies included in our meta-analysis evaluated hypoglycemia as an outcome. Hypoglycemia can occur in CFRD including in people who are insulin naïve, and has been linked to poorer lung function [85]. Hypoglycemia in CFRD may be associated with reduced aware-

ness due to damaged pancreatic alpha cells resulting in absent glucagon and counter-regulatory hormonal responses. Furthermore, treatment of hypoglycemia can be complicated by malabsorption [86]. Use of CGM in type 1 diabetes enabled early detection of hypoglycemia and was associated with significant improvements in diabetes-specific quality of life outcomes such as hypoglycemic confidence, diabetes related anxiety and distress and overall quality of life [25,87]. Assessment of psychosocial outcomes associated with CGM use in CFRD is relevant and should be encouraged.

CGM is a tool that is unlikely to improve glycemic control unless combined with other interventions [88], and our meta-analysis of studies with co-interventions represents a real-world effect. A recent systematic review found currently there is insufficient evidence to determine the impact of insulin therapy guided by CGM compared to standard care in people with CFRD due to a lack of randomised controlled trials [89]. Most individuals with CFRD use multiple daily insulin injections and studies evaluating CGM in people with type 1 diabetes treated with this insulin regimen have reported improved glycemic control which is encouraging [23,24]. Interestingly, we observed a trend towards lower HbA1c with increasing duration of follow-up in the CGM group which might represent a learning curve at the user interface. Clinicians may also use CGM as a decision-making tool to overcome clinical inertia and guide treatment trajectory, particularly if clinical decline is present or suspected [22]. This likely explains the high risk of selection and publication bias noted in our study. The complex matrix of co-interventions that may accompany CGM and contribute to its benefits coupled with heterogenous genetic, epidemiological, pharmacological (such as use of CF transmembrane conductance regulator modulator therapies) and clinical influences on glycemia, present significant barriers to conducting randomised controlled trials in this field. Furthermore, the generalisability of results from such an efficacy trial also warrants consideration and perhaps there is a need to pivot and use pragmatic approaches to evaluate CGM in people with CFRD.

4.4. Strengths and limitations

Our meta-analysis is the first evaluating the effect of CGM compared to SMBG on the longitudinal change in HbA1c in individuals with CFRD. Strengths include comprehensive search of the literature, inclusion of a large range of studies and evaluation of disease-specific outcomes with reference to HbA1c.

Our study had significant limitations including lack of head to head comparisons given absence of high-quality, prospective or randomised controlled trials. Therefore, our meta-analysis and conclusions were drawn from a pool of studies with high risk of bias (confounding, selection and publication bias). Furthermore, most studies did not report inclusion and exclusion criteria, frequency of SMBG, and key CGM metrics [77] therefore evaluation of our stated secondary outcomes was severely restricted. Of particular note is the substantial data contribution by Denis et al. [58] to the SMBG group in the meta-analysis which may have significantly underestimated baseline HbA1c due to inclusion of individuals who were pancreatic insufficient but perhaps had only impaired glucose tolerance together with the very long duration of follow-up which contributed to heterogeneity. Additionally, the significantly higher baseline HbA1c in the CGM group may represent selection of individuals with poorly controlled CFRD for participation in the studies with potential for greater observed reduction in HbA1c. Secondly, absence of studies with non-significant results evaluating CGM contributed to publication bias and potentially inflated the observed benefit. Thirdly, the majority of the studies had co-interventions which could have also amplified CGM effect. And lastly, measurement of the primary outcome of HbA1c could have been impacted by high red cell turnover, iron deficiency, anaemia and machine calibration leading to inaccuracies.

4.5. Future directions

The value of CGM lies in its ability to aid decisions, therefore use of CGM consists of a multifaceted package of clinician and consumer co-interventions. Given there is robust evidence demonstrating benefits of CGM in type 1 diabetes, it would be unethical to design future studies without co-interventions that are provided as part of routine CFRD care. Therefore, it will become increasingly challenging to analyse advantages attributable solely to CGM. With regards to evaluation of CGM, despite potential inaccuracies and shortfalls, HbA1c still remains the most practical and accessible measurement tool currently available for monitoring longitudinal glycemic control in CFRD [26,34] and comparison to estimated A1c (a CGM metric) may be helpful as a point of reference for any CGM study. Secondly glucometric (hyperglycemia and hypoglycemia) and psychosocial outcomes associated with CGM use need further evaluation in CFRD and regardless of design, studies should explore the interrelationships between disease-specific outcomes (e.g. FEV1, weight, pulmonary exacerbations) and CGM metrics in order to clarify targets based on relevant clinical end-points.

Ultimately, integration of CGM and insulin pump therapy to automate glucose monitoring and delivery (sensor and pump therapy) is the future of diabetes technology, with pilot studies in people with CFRD already underway [90,91]. The ability of sensor and pump therapy to minimise glycemic variability by adapting to changing insulin requirements and potentially eliminate need for carbohydrate counting would revolutionise CFRD management. Furthermore, a bio-hormonal (insulin and glucagon) bionic pancreas [91] could have added clinical and psychosocial benefits for individuals susceptible to hypoglycemia. Future evaluation of diabetes technology in CFRD should not be limited to safety and efficacy outcomes but also incorporate a pragmatic approach that assesses implementability. This will ensure that diabetes technology specifically designed for individuals with type 1 diabetes is acceptable to people living with CFRD.

5. Conclusion

Our systematic review findings suggest use of CGM in the management of CFRD may be associated with improved glycemic control as evidenced by a significant reduction in HbA1c after at least 6 weeks of use compared to standard care with SMBG. Despite the detrimental effects of hyperglycemia in CFRD, evidence on CGM benefiting pulmonary and non-pulmonary outcomes in CFRD is lacking, together with consumer and clinician experiences. Future research should evaluate interrelationships between CGM metrics and disease-specific clinical outcomes to elucidate CGM targets based on pulmonary end-points and consider pragmatic approaches to contribute to the evidence-base in this field.

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Author contributions

SK, MP, HT and GS contributed to study design. SK conducted the systematic search, screening, data collection and wrote the first draft of the manuscript. SR conducted formal analysis. MP, GS, SR and HT reviewed/edited the manuscript. SK is the guarantor of this work and takes responsibility for the integrity of the data and accuracy of the analysis.

Declaration of Competing Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.07.013.

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