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Posted Date: 1 February 2024

doi: 10.20944/preprints202309.2075.v2

Keywords: Continuous Glucose Monitor; People not living with diabetes; Regulations



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Review

# Innovative Solution or Cause for Concern? The Use of Continuous Glucose Monitors in People Not Living with Diabetes: A Narrative Review

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## What's new

- With the growing interest in wearable health technologies, continuous glucose monitoring systems (CGMs) have expanded their scope, transitioning from exclusive use in diabetes management to lifestyle enhancement for individuals without diabetes.
- This narrative review summarises current knowledge and discusses regulation of CGMs and critically assesses the benefits of CGMs for individuals without diabetes, as presented in the 'health and wellness' sector.
- Given the increasing adoption of CGMs by individuals without diabetes, this review shows there is a dearth of compelling evidence for the utility of CGM in this group. We emphasise the importance of refining CGM regulation in the UK, particularly when considering its 'off-label' use.

**Abstract:** Type 2 diabetes mellitus (T2DM) poses a significant public health challenge. Prioritising its prevention is essential. With the growing interest in wearable health technologies continuous glucose monitoring systems (CGMs) have expanded their scope, transitioning from exclusive use in diabetes management to lifestyle enhancement for individuals without diabetes. While CGMs primarily target glycaemic stabilization, their potential role in mitigating noncommunicable conditions, including T2DM, warrants exploration. This review examines the regulation of CGMs and critically assesses the purported benefits of CGMs for individuals without diabetes, as presented in the 'health and wellness' sector: (1) early dysglycaemia detection through glucose variability observation; (2) refining glycaemic control by tailoring nutrition according to postprandial glucose response; and (3) promoting and fine-tuning physical activity based on instantaneous data feedback. We find a lack of compelling evidence for the utility of CGMs in PNLD, including accuracy, data analysis and interpretation metrics, and user acceptability markedly under-researched. A paucity of research exists on the unanticipated negative consequences of CGM usage, such as obsessive symptom tracking and potential onset of disordered eating, like orthorexia. Given the increasing adoption of CGMs by individuals without diabetes, this review underscores the need of addressing these research gaps to ensure safety and reliability of CGMs in novel contexts. We emphasise the importance of refining CGM regulation in the UK, particularly when considering its 'off-label' use. Marrying robust scientific evidence with effective regulation is pivotal in fortifying the coherence, equity, and effectiveness of diabetes prevention initiatives, while protecting the wellbeing of CGM users.

**Keywords:** continuous glucose monitor; people not living with diabetes; CGM regulations; wearable technology

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## Introduction

Diabetes mellitus (DM) remains a predominant metabolic condition, with figures indicating that approximately 415 million individuals worldwide have been diagnosed. By 2045 the number is expected to escalate to nearly 700 million.<sup>1</sup> Predominantly Type 2 DM (T2DM), comprising 80-90% of all cases, is characterised by persistent hyperglycaemia interspersed with sporadic glucose fluctuations.<sup>1</sup> In the UK, the National Health Service (NHS) has pioneered the Diabetes Prevention Programme (DPP), championing measures to avert T2DM amongst adults deemed high-risk; identified using metrics like glycated haemoglobin (HbA1c; 42-47 mmol/mol range) or fasting plasma glucose (FPG; 5.5-6.9 mmol/L).<sup>2</sup> Nonetheless, the fidelity and comprehensiveness of these parameters for risk stratification are contested, given findings highlighting shortfalls in pinpointing latent T2DM cases thereby necessitating alternative diagnostic modalities<sup>3-4</sup>.

Prominently, wearable technologies, spearheaded by continuous glucose monitors (CGMs), offer promise. These transcutaneous electrochemical devices continually track glucose levels in the interstitial fluid (ISF) via a subdermal sensor electrode.<sup>4</sup> Present models can measure glucose for up to 14 days, accurately documenting durations and frequencies of both hypo- (glucose<3.9 mmol/L) and hyperglycaemic (glucose>10.0 mmol/L) episodes in addition to postprandial spikes.<sup>4-5</sup> Glycaemic data can be obtained using either a transmitter for real-time CGMs such as Dexcom G6 or smartphone applications for intermittently scanned CGMs (isCGMs) such as the LibreLink for Freestyle Libre 2 and 3 sensors.<sup>6</sup>

Originating for diabetes management, devices' relevance has now evolved, with recent inquiries delving into their utility for people not living with diabetes (PNLD). Unlike conventional HbA1c tests, CGMs allow a comprehensive insight into glucose dynamics, potentially refining risk categorisation through glycaemic variability (GV) parameters.<sup>7-8,41</sup> Extracting such CGM-based digital biomarkers of early dysglycaemia to allow timely intervention may present a novel strategy for diabetes prevention.<sup>9</sup> The imperative of early detection and prediction of dysglycaemia is underscored by its capacity to preserve beta-cell ( $\beta$ -cell) function, with lifestyle modifications such as weight management, being integral to delaying T2DM's onset.<sup>7</sup> By addressing inter-individual physiological differences in glycaemic responses to foods,<sup>10</sup> CGMs are well-positioned as potential tools for providing personalised nutritional advice. Easy access and continuity of instantaneous glycaemic data feedback suggests further functionality of CGMs to motivating and fine-tuning physical activity for optimised glycaemic control.<sup>11</sup> At present clinical guidelines do not recommend CGMs outside of type 1 diabetes (T1DM) or insulin treated T2DM contexts.<sup>12</sup> Despite this, CGM's are being increasingly adopted by PNLD – a trend catalysed by the 'health and wellness' market advertising and distributing the CGMs to the broader public, particularly to the health-conscious<sup>13</sup> and those that afford them. The working model for disease prevention using CGMs in PNLD is yet to be comprehensively explored. This narrative review seeks to synthesise and critically analyse existing research on CGM application within PNLD, particularly devices' performance and outcomes achieved in detecting early dysglycaemia, personalised nutrition and behavioural interventions. We further examine current regulatory directives and ascertain their prospective contribution to T2DM prevention and overall health improvement.

## Methods

Electronic searches of the online databases PubMed (MEDLINE), EMBASE and Cochrane Library between January 1980 to August 2023 were conducted for studies examining aspects of CGM utility and performance in PNLD. Search terms used included 'Continuous glucose monitoring', 'healthy', 'without diabetes'. The references of the included articles were also screened manually to access relevant articles that were not identified during the database search. Search was narrowed to studies with primary focus on adult populations only. Overall, 25 eligible studies were identified (Supplementary Table S1-5). The obtained results and analysis are presented in a logical sequence, structured around the three objectives: 1) evaluation of CGM performance as a tool for early dysglycaemia detection; 2) in personalised nutrition; and 3) in behavioural interventions.

## Evaluation of CGM performance as a tool for early dysglycaemia detection

To confirm the utility of CGMs for optimal dysglycaemia detection in PNLD, CGMs should 1) maintain high accuracy; 2) provide unambiguous glycaemic assessment metrics; 3) set definitive clinical benchmarks for this specific user group.<sup>5</sup> Absence of these attributes may at best compromise the tangible benefits, and at worst lead to adverse health outcomes in PNLD.

### 1. Accuracy

The efficacy of CGMs has significantly progressed over recently, with the Mean Absolute Relative Difference (MARD) reducing from 25% to a respectable 10%, especially in the context of T1DM.<sup>14</sup> Accuracy metrics for CGMs encompass point, trend, and threshold alarm accuracies.<sup>15</sup> For PNLD, given the relatively benign glucose fluctuations compared to T1DM and T2DM, point accuracy becomes the pre-eminent criterion.<sup>15</sup> This metric appraises the alignment between an isolated glucose reading and an established reference benchmark.<sup>15</sup> However, relying on comprehensive metrics like MARD may overshadow inaccuracies specifically within the hypoglycaemic domain, inducing unreasonable anxiety in PNLD.<sup>16</sup> MARD values are reported to depend on glucose ranges (diabetic versus normo-glycaemic), as well as on the model of the CGM sensor.<sup>17</sup> Furthermore, metrics devoid of agreement rates obscure the proportion of clinically relevant readings, thus potentially endorsing CGMs with respectable averages yet erratic excursions.<sup>18</sup>

Currently, the standards ratified by the United States Food and Drug Administration (FDA) for iCGMs serve as the exclusive published regulatory benchmarks delineating minimal accuracy prerequisites, leveraging specified target ranges associated with agreement rates.<sup>19</sup> Within these benchmarks, the point accuracy criteria explain the least proportion of readings required to align with the Advanced Technologies & Treatments for Diabetes (ATTD) consensus guidelines.<sup>19</sup> Presently compliant devices include the Freestyle Libre 2, Freestyle Libre 3, Dexcom ONE, Dexcom G6, and Dexcom G7.<sup>20</sup> However, for PNLD, the precision for reaping CGM benefits might deviate from the stringent isCGM criteria, and the dearth of this data makes diabetic target benchmarks potentially unsuitable.

The available studies on CGM accuracy in PNLD exhibit overarching limitations, including small and unrepresentative sample sizes,<sup>21-25,28</sup> use of outdated device models<sup>27-28</sup> and low generalisability. Analysis is rarely supported with confidence intervals, thereby effect size, precision and reliability of the findings are uncertain.<sup>21-23,25,28</sup> Highly variable accuracy measured with MARD across contexts highlights the need for nuanced understanding of device performance in the target population (Table S1 in supplementary materials).

CGM precision can vary depending on user characteristics, predominantly body composition.<sup>17, 21-22</sup> Facets like overall body fat, body fat percentage, and Body Mass Index (BMI) are inversely associated with CGM precision. Factors stemming from shifts in subcutaneous fat and capillary networks, characteristic of obesity, potentially affect the diffusion impediment and subsequently CGM precision across different BMI categories.<sup>21-22</sup> This underscores the necessity for considering body composition in CGM interpretation, particularly for people living with obesity. Given obesity is the leading driver of T2DM and people with the condition present the key PNLD subgroup to uptake CGMs, further optimization of device accuracy to account for the outlined limitations remains imperative.

Another salient factor is the discrepancy between glucose concentrations in the ISF and blood glucose. This is particularly problematic with rapid glucose fluctuations such as during high intensity exercise or following the consumption of highly-glycaemic foods.<sup>23-24</sup> CGM overestimation of ISF glucose after glucose loading has been previously highlighted.<sup>23</sup> During activity, studies in both PLWD and PNLD show higher CGM bias with blind spots in early hypoglycaemic episode detection therefore restricting device reliability to sedentary periods.<sup>24</sup> Mechanisms for this reduced accuracy may also include microcirculation perturbations caused by localised movement, increased body temperature, and rapid glucose shifts, termed "sensor drift".<sup>24</sup> Thus, PNLD partaking in physical activity may receive skewed data, potentially resulting in undue concerns or misinformed lifestyle adjustments. In fact, Wong and colleagues (2021) report overall lower accuracy of the Freestyle Libre sensor in PNLD comparing to previous studies in people with T1DM or T2DM. This may be because people living with diabetes have comprised tissue glucose uptake, which is associated with higher

ISF, making it more sensitive to changes in blood glucose levels.<sup>25</sup> Therefore, the difference between ISF and blood glucose might be smaller than in PNLN, both in fasting and postprandial states. This speculation, however, is yet to be tested in human trials.<sup>25</sup>

Several CGMs utilize algorithms to adjust for these physiological variances between the two compartments, aiming to approximate glucose levels. Such computational models insinuate that displayed readings might not genuinely correspond to either ISF or capillary glucose values.<sup>26</sup> CGM measurements also suffer from lower inter-day reproducibility in PNLN, especially among younger individuals as established using functional data analysis.<sup>27</sup> This emphasizes the need for rigorous calibration processes and precise reference standards to compile best practice guidelines ensuring reliability of CGM outputs. For PNLN, this aspect is visibly amiss.

Furthermore, certain concurrent medications can adversely influence CGM precision. Notably, devices like Medtronic Guardian Sensors and Dexcom G4 Platinum have recorded accuracy reductions due to electrochemical interferences from specific agents like lisinopril and albuterol.<sup>28-29</sup> It is possible for these interferences to have a bigger role in accounting for the implausible CGM data than users and even clinicians assume. Despite this, there is scarcity of publications addressing this limitation with the majority testing outdated systems. While regulatory requirements mandate manufacturers to conduct interference studies for each new CGM model and generation, considerable proportion of the data generated from these studies remains unpublished.<sup>30</sup> As CGMs are increasingly utilised by PNLN, clinical studies examining potential interferences specific to this group are urgently required.

While the emerging nanotechnological solutions aim to account for this,<sup>26,31</sup> it currently remains imperative for CGM users to be vigilant of potential drug interactions when interpreting CGM readings. At present, the judgment of nocturnal hypoglycemia and postprandial hyperglycemia as determined CGM in PNLN is inappropriate. Use of more reliable devices such as self-monitoring of BG and subsequent calibration is recommended.<sup>23</sup>

## 2. Provide unambiguous glycaemic assessment metrics

Evaluating glycaemic control employs various methodologies, with HbA1c being predominant, reflecting the average blood glucose (BG) over the preceding three months.<sup>31</sup> However, precision is contingent upon several physiological variables such as glucose uptake, red blood cell lifespan, and episodic BG spikes.<sup>32-33</sup> Notably, the same HbA1c readings might denote intra-variability in both PLWN and PNLN highlighting the limitation of the metric.<sup>32</sup> As a result, alternative measures have been proposed to document glucose excursions, emphasising glycaemic variability. GV represents the intensity and frequency of glycaemic changes<sup>34</sup> and is pivotal in anticipating both micro- and macrovascular complications, aligning with elevated HbA1c, FPG, postprandial glycaemia, and insulin resistance.<sup>35-36</sup> Through GV measurement, CGMs were shown to delineate glucose dysregulation phases, identifying phenotypes like impaired glucose tolerance (IGT), impaired fasting glucose (IFG), T1DM, and T2DM.<sup>7-8</sup> Thus, harnessing CGMs to discern initial dysglycaemia via GV could pave innovative pathways to prevent or mitigate T2DM and its subsequent complications.

GV is encapsulated by a variety of metrics,<sup>37</sup> summarised in Table 1.<sup>37-38</sup> Each GV index distinctively records varying dimensions of glycaemic fluxes, including amplitude, frequency, duration, or pattern.<sup>34</sup> For instance, conventional glycaemic metrics, such as mean glucose (MG), standard deviation (SD), and coefficient of variation (CoV) fail to fully capture GV, often leaning towards hyperglycaemic overemphasis.<sup>34</sup> For PNLN, emphasising general glycaemic stability is typical; therefore, metrics evaluating glucose amplitude and frequency are relevant. However, the absence of a universally accepted GV standard for PNLN complicates both research and clinical implementations<sup>34</sup> while also questioning their commercial utility.

**Table 1.** Continuous glucose monitoring metrics.

Metric	Description
MAGE	Measure of magnitude of glycaemic excursions that exceed 1 SD from the mean.

SD	Measure of variation of all glucose measurements.
CoV	Magnitude of variability relative to mean blood glucose. CoV=(SD)/(mean glucose) x 100
TIR, TBR, TAR	Proportion of time spent within, below or above blood glucose levels within the target range.
CONGA	Combined measurement of timing and magnitude of blood glucose level fluctuations at specific time periods.
GMI	Estimate of HbA1c, based on average glucose.
eA1C	A linear transformation of the mean glucose value, meant to estimate the HbA1c blood test. Calculated: $(46.7 + \text{mean}(\text{Glucose}))/28.7$
J_index	Index designed to stress the importance of the mean level and the variability of glycaemia. Calculated: $0.001 * [\text{mean}(\text{Glucose}) + \text{SD}(\text{Glucose})]^2$

MAGE, mean amplitude of glycemic excursions, SD, Standard deviation of blood glucose levels; CoV, coefficient of variation for glucose; TIR, time in range. TBR, time below range; TAR, time above range; CONGA, continuous overall net glycemic action; GMI, glucose management indicator; eA1C, estimated A1c glycated haemoglobin; J\_index, Youden's index; HbA1c, glycated haemoglobin.

The International Diabetes Centre introduced the Ambulatory Glucose Profile (AGP) which combines standard glycaemic metrics, GV indices, and a summarised glycaemic exposure.<sup>39</sup> This framework facilitates a consistent comparison of glucose data across diverse CGMs, enhancing clinical analysis and therapeutic interventions. Although AGP utility in diabetes management is evident, its relevance may diminish in PNLD due to its alignment with diabetes-specific directives. Recently, The Diabetes Technology Society unveiled the Glycaemic Risk Index (GRI)<sup>40</sup> - a composite metric (CM) assessing glycaemic control based on hypoglycaemia and hyperglycaemia durations and severities from two weeks of CGM data. Its correlation with comprehensive clinical evaluations of glycaemic profiles is noteworthy. For PNLD, such a unified measure would be invaluable.

CGMs have been developed characterising CGM-derived measures from over 7,000 PNLD using previously defined diabetes related clinical parameters including anthropometry body composition, lipid, vascular, liver, sleep, and nutrition.<sup>38</sup> GV measures spanned across multiple identified cluster groups with MODD and MAGE displayed differing correlation patterns with anthropometry and body composition (Table S2 in supplementary materials). These in turn were strongly associated with measures of mean glucose, whereas liver and sleep showed greater association with GV. Markers for early detection of diabetic retinopathy such as fractal dimension displayed significant associations with eA1C and J\_index, potentially presenting a digital biomarker for early IGT in PNLD.<sup>38</sup> Widely used metrics such as TIR showed weaker correlations to clinical parameters in PNLD. This emphasizes the importance of choosing the relevant CGM summary measures according to the parameter of interest.<sup>38</sup> For instance, Hall et al. (2018) championed spectral clustering of CGM readings to identify glucotypes indicative of IGT in PNLD.<sup>41</sup> Such CMs encapsulate multiple "variability" metrics, potentially yielding a comprehensive view of GV and early dysglycaemia detection in PNLD.<sup>41</sup> A web interface was developed for PNLD to upload CGM data for classification.<sup>41</sup> CMs are also being increasingly developed and adopted commercially to guide lifestyle adjustments and optimise 'metabolic health' in PNLD.<sup>42</sup> To confirm their validity in health assessment in PNLD, long-term prospective outcome studies are warranted for objective cross-comparison of CM and their predictive power for disease progression.<sup>24</sup> Further construction of clear guidelines for feature selection, design and metrics for working with CGMs data specifically for PNLD is warranted. Importantly, research addressing the biological and mechanistic meaning of these associations is vital, otherwise, clinical relevance and real-world applicability of the findings are uncertain.

### 3. Set definitive clinical benchmarks for this specific user group: What is "normal glycaemia"?

Definitive clinical benchmarks are necessary to establish a reference point for interpreting CGM data in PNLD to enable appropriate and timely interventions (Table S3 in supplementary material). Data in PNLD shows CGM-measured mean average glucose of 5.4 – 5.5 mmol/L for ages 7-60 years, with those older averaging 5.8 mmol/L.<sup>44</sup> The percentage of time below 4.0mmol/L during masked CGM showed a median of 1.92% (27.6 minutes) and a mean of 3.54% (51.0 minutes) across a day.<sup>45</sup> Concurrently, the TIR stood at 97.0%, with an SD of 1.0mmol/L and a CoV of 20.0%. Notably, GV was elevated during the day compared to night, though other glycaemic metrics remained consistent irrespective of time of day.<sup>45</sup> This disparity is likely attributed to glucose fluctuations linked to meal intakes.<sup>45</sup> Given the data skewness, median durations in hypoglycaemia (<3.9mmol/L) and severe hypoglycaemia (<3.0mmol/L) (1.6% and 0% respectively) are proposed as the most precise indicators. Despite medians being less influenced by outliers, means encompass all values, potentially offering a more holistic view of an individual's glucose profile. Therefore, future CGM evaluations should incorporate these mean times to facilitate a nuanced comprehension of GV and its related implications in PNLD.<sup>45</sup>

Existing research on CGMs in PNLD indicates 73% of normoglycemic participants exhibit PG that surpasses thresholds aligning with prediabetic patterns.<sup>46</sup> Normoglycemic subjects often achieve glucose excursions paralleling IGT and diabetic levels,<sup>47</sup> insinuating a potential onset of prediabetes.<sup>46</sup> Current data is overly fragmented to suggest that natural GV, akin to those in prediabetes or diabetes, correlate with heightened T2DM risks, bypassing elevated HbA1c or other health concerns.<sup>48</sup> While the clinical significance of GV in PLWD is documented, the absence of research on the outcomes of lifestyle interventions in reducing GV in PNLD necessitates further study.<sup>48</sup>

### **CGMs for predicting postprandial glycaemic responses to food as part of personalised nutrition.**

Optimising glycaemic control, especially during the early stages of dysglycaemia before pronounced  $\beta$ -cell dysfunction, can be achieved through lifestyle modifications.<sup>49-50</sup> Dietetic interventions aimed at weight reduction and glycaemic control are fundamental in precluding T2DM.<sup>49-50</sup> In PNLD, greater postprandial glycaemia (PPGR) is associated with reduced insulin sensitivity and impaired  $\beta$ -cell function.<sup>51</sup> Importantly, discernible inter-individual differences in PPGRs to the same foods have been observed in PNLD, which are not considered by traditional carbohydrate or calorie-centric dietetic approaches.<sup>10,52</sup> This positions CGMs as potential tools for providing personalised nutritional advice by addressing these disparities, optimising PPGRs and preventing deleterious metabolic consequences.

Personalised nutrition (PN) is a dietary protocol tailored to an individual's genetic, microbiotic, metabolic, alimentary, and other key factors.<sup>53</sup> Scant research, to our knowledge, has delved into the clinical benefits of using CGMs for PN within the PNLD (Table S4 in supplementary materials).<sup>55</sup>

The aforementioned study<sup>10</sup> discerned individual PPGRs, characterised the individual variabilities, and identified associated factors. For uniform food items such as bread, significant inter-personal PPGR variations were noted serving basis to the development of a predictive machine learning (ML) model. Incorporating data gathered from participants' blood tests, microbiome evaluations, dietary diaries, and anthropometrics, the ML model's ability to predict individual PPGR was comparable to dietary guidance based on expert analysis of CGM data only.<sup>10</sup> Results were echoed in a subsequent study<sup>52</sup> to suggest potential application of the algorithm in PNLD. The authors reported a continuous relationship between PPGRs and risk factors for T2DM such as BMI, HbA1c and wakeup (fasting) glucose and proposed its potential clinical utility.<sup>10</sup> However, without reported confidence intervals, the precision and reliability of these associations are difficult to ascertain raising concerns about the external validity and generalisability of the findings. The predictions made require validation in appropriately powered longitudinal studies. The long-term success of the ML model remains to be confirmed,<sup>10</sup> with benchmarking against traditional diagnostics or PPGR-modulating dietary interventions still outstanding.<sup>53</sup> Ultimately, a large proportion of the predictive features in these studies is related to the faecal microbiome with the underlying mechanisms currently elusive.<sup>10</sup> Further research is essential to decipher the connections

between the gut microbiome and glycaemic outcomes, guiding the formulation of appropriate and evidence-based PN interventions.

High inter-personal variability in PPGRs was also supported by the findings from The Personalised Responses to Dietary Composition Trial-1 (PREDICT-1) trial with further validation from an independent US cohort of PNLD.<sup>54</sup> The study identified higher variability in postprandial triglyceride and glucose rather than fasting values, suggesting the former to be a better indicator of metabolic health. However, PPGRs were less informative than fasting glucose as a biomarker predicting IGT (7.8–11.0 mmol/L 2 hours after an OGTT) and atherosclerotic cardiovascular disease (ASCVD) 10yr risk score.<sup>54</sup> Therefore, the clinical decisions based solely on fasting glucose may already capture a reasonable proportion of the relevant information as indicated by only a minor improvement in ASCVD risk prediction being reported when PPGR was added (ROC AUC = 0.69 vs 0.72, respectively).<sup>54</sup> Furthermore, while the study emphasises the larger role of individual glucose in impacting the incremental area under the curve (iAUC) than the macronutrient composition of a meals (16.73% vs. 18.74%), whether this difference is clinically meaningful depends on the specific clinical context and the extent to which such variations translate into health outcomes in PNLD. Contrastingly to its name, PREDICT 1 study did not establish long-term predictive values of higher PPGR variation and does not show its relevance in better discrimination of metabolic tolerance. Current evidence does not provide compelling evidence that PN is a superior strategy for disease prevention, but instead show correlations which should not in themselves be taken as sufficient grounding for a population-wide intervention. PREDICT 2 and 3 are set out to reaffirm the findings of PREDICT 1 in more expansive cohorts.<sup>55</sup> However, unless PPGR predictions are translated into clinical outcomes it is unclear as to how these studies will significantly update the working model meaningfully enough to increase the confidence in the true value of PN in PNLD.

The key assumption of PN studies is that an individual's unique response to the same meal is reproducible<sup>54</sup> has now been challenged.<sup>56</sup> With recent data showing poor reliability of PPGR to multiple duplicate meals, with intra-individual glucose variability similar to that seen across various meals.<sup>56</sup> Even under controlled experimental conditions, obtaining two measurements was insufficient to accurately estimate PPGR, however determining the number of CGM readings needed for accurate estimates remains ambiguous.<sup>56</sup> Furthermore, the efficacy of CGM-driven meal assessments within PN may be device-dependent, given observed variances in inter-personal PPGR with different devices,<sup>57</sup> prompting reflections on genuine personalisation and use in T2DM prevention. The discrepancies could, however, have arisen due to potential methodological challenges. Ad-libitum feeding could have compromised sensor accuracy, especially during glycaemic extremes, with ambiguously composed meals distorting meal classification.<sup>58</sup> Supportively, reduced variability indices were documented for carbohydrate-rich meals (>25g)<sup>58</sup>, though results were not replicated in an independent data set.

Given these inconsistent findings, the transition of CGMs from a medical device measuring glucose dynamics in diabetes management to a comprehensive tool for PN seems premature. Merely demonstrating inter-individual variations in PPGRs<sup>10,54</sup> appears insufficient to substantiate the claims of PN using CGMs as a superior dietetic approach capable of optimising metabolic health in PNLD.

### **Behavioural Change**

Effective glycaemic regulation is intrinsically linked to diet, physical activity, and mood. CGMs can reveal these interrelations by graphically associating lifestyle factors with corresponding blood glucose results, thus fostering healthier practices, as observed in prediabetes, T1DM, and T2DM cohorts.<sup>59-62</sup> For instance, the use of Dexcom G6 CGM has resulted in significantly greater improvement in HbA1c levels as compared with traditional blood glucose monitoring in people with T2DM treated only with basal insulin.<sup>63</sup> Despite this, no significant differences in the daily insulin dose or diabetes medications between the groups was found, suggesting that glycaemic improvements may have been due to behavioural changes following CGM adoption, rather than therapy adjustments.<sup>63</sup> Similarly, CGMs may also foster beneficial behavioural changes in PNLD by

increasing accountability thereby improving glycaemic control and anticipating diabetes onset (Table S5 in supplementary materials).

The "Sugar Challenge" study assessed glucose patterns in 665 participants.<sup>64</sup> Using CGMs alongside a smartphone application, participants glucose dynamics relative to factors like dietary composition and physical activity were measured. Among PNLD with poor baseline TIR (time spent in range 3.3-7.8 mmol/L less than 83 %), 91.7% displayed TIR improvement by an average 23.2%. The authors suggested this effect was primarily attributed to avoidance of foods with high glycaemic index.<sup>64</sup> While the ATTD consensus for TIR is 3.9-10mmol/L for T1DM, the study defined TIR for PNLD as glucose levels 3.0 mmol/L-7.8 mmol/L, as PNLD can have non-pathologic Level 1 (below 3.8 mmol/L) hypoglycaemia.<sup>64</sup> Given discrepancies in TIR definitions, the addition of percentages of TIR including euglycaemia, hypoglycaemia and hyperglycaemia in conjunction with GV metrics would have been beneficial for greater clarity on clinical benefit.

Food consumption is multifaceted, moulded by a combination of physiological, social and psychological facets,<sup>65</sup> for instance, emotional eating can predispose individuals to weight gain and T2DM.<sup>65</sup> On the other hand, glucose dips 2-3 hours postprandially has been shown to be the best predictor of hunger and subsequent energy intake than any other temporal aspect of iAUC.<sup>66</sup>

One investigation on "hunger training" assessed the alignment between perceived hunger and CGM data. Participants who were instructed to eat based on pre-meal glucose metrics saw noteworthy weight loss, regardless of the glucose assessment technique used,<sup>65</sup> despite this no significant differences in acceptability, adherence or behaviour change were noted between the two methods. Qualitative data, however, hints at a more positive experience and a greater inclination to explore a variety of foods in the CGM group. Conversely, the discomfort inherent in finger pricking may have motivated greater mindfulness of eating behaviours.<sup>67</sup> By associating glucose dynamics with subsequent eating behaviour and making this data visible CGMs may thus enable PNLD to tailor interventions that address both the physiological and behavioural aspects of weight management.

Physical activity, paramount for controlling post-meal glucose fluctuations and T2DM risk, may be enhanced by CGMs.<sup>68</sup> Witnessing the immediate glycaemic benefits of exercise may help to stimulate activity adherence.<sup>69-70</sup> An 8-week investigation contrasting traditional exercise with a CGM-enhanced regimen revealed superior fitness outcomes and attendance in the latter group.<sup>69</sup> Paired with fitness trackers, CGMs also prompted improved motivation for weight loss in people living with overweight.<sup>69</sup> Though the sustainability of these behavioural improvements is uncertain given the short-term nature of the studies available.<sup>69</sup> Further randomised controlled trials exploring the prolonged effect of physical activity on CGM based glycaemic measures are warranted.<sup>70</sup>

While CGMs' benefits seem evident in PLWD, their integration in PNLD demands scrutiny.<sup>71</sup> One study indicated 90% of users found the CGM easy to use and enlightening, but only 40% foresaw its health utility.<sup>71</sup> This diminished adoption could stem from gaps in understanding CGM data, deterring full engagement. Crucially, this research did not probe the CGM's potential behavioural influence or conduct qualitative assessments to enhance comprehension in PNLD.<sup>71</sup> In contrast, another study emphasised CGMs' educational capacity in PNLD, with the majority recognising their dietary and lifestyle guidance potential.<sup>45</sup> Future behavioural studies using CGMs in PNLD should consider provision of concise information sessions on how dietary choices and physical activity impact glycaemia and how it reflects in CGM data. This could help motivate users by bridging gaps in understanding and fostering greater engagement. Ultimately, the effect size and relevance of CGM-enhanced interventions will depend on the specific needs of the target user. It is therefore crucial to carry out qualitative assessments of PNLD experiences of using CGM to better understand the unique demands and objectives of this user group.

### **CGM regulation**

Valued at 138 billion pounds in 2019, the global digital health market is poised to surge to an estimated 522 billion pounds by 2025, with a compound annual growth rate (CAGR) of 25%. This trajectory underscores the increasing importance of technology-driven solutions in influencing both

individual and population health.<sup>72</sup> In this climate, ensuring regulatory frameworks evolve accordingly with the rapid advancements in health technology is imperative to promote innovation while also protecting end-user safety. Given CGMs have witnessed extensive application in the broader commercial setting, despite the absence of according guidelines, concerns arise regarding the regulatory strictures overseeing their usage in PNLD.

As medical devices, CGMs gain market entry in Europe post-acquisition of the Conformité Européenne (CE) marking, among other global validations.<sup>20</sup> However, questions surround the robustness of CGM precision evaluations via the CE marking, with criticisms highlighting an absence of unified study methodologies and established performance criteria.<sup>20</sup> For instance, variances have been detected in the MARD values of a CGM apparatus between company-backed studies and independent research.<sup>73-74</sup>

Post the EU Medical Devices Regulation (MDR) 2017/745, CGMs must have a CE marking for UK marketability.<sup>75</sup> Yet, post-Brexit regulations indicate that CE-labelled medical tools will only have access to the UK market until 31 December 2024.<sup>20</sup> Subsequent to this, compliance with the UK Medical Devices Regulation 2002 (UK MDR 2002) and the acquisition of the UK Conformity Assessed (UKCA) marking becomes imperative.<sup>20</sup> Therefore, manufacturers are responsible for presenting and substantiating clinical evidence in line with overarching safety and efficacy parameters,<sup>76</sup> although these directives are primarily diabetes-centric, often sidelining considerations for PNLD.

Exceptions do exist, such as the Abbott Libre Sense Glucose Sport Biosensor (Supersapiens) which obtained a CE marking solely for athletic applications,<sup>77</sup> with the manufacturer outlines that this tool is not crafted for diagnosis, treatment, or any medical purpose.<sup>77</sup> The designated utility and categorisation determine the evidence threshold for CE marking attainment.<sup>75</sup> Nonetheless, CGMs, originally designated for distinct functions in PLWD, are gaining traction among PNLD, surpassing their CE certificatory bounds. A case in point is the Freestyle Libre 2 Flash, CE-certified for ISF glucose measurement in PLWD yet acquired by med-tech companies for providing dietary guidance in PNLD.<sup>13,42,55,77</sup>

This presents a regulatory puzzle, amplifying concerns over CGM distribution controls and the latent risks for PNLD utilising devices outside of intended purposes. While the EU MDR 2017/745 outlines the regulations for distributors and post-market observation, it remains reticent on the consequences of unsanctioned medical device distribution. This creates uncertainty over matters of accountability, liability, and patient safety.<sup>76</sup> Importantly, the term 'off-label use' remains vague within EU MDR 2017/745, given its circumscribed emphasis on manufacturers identifying, but not clearly defining, such use.<sup>78</sup> In fact, the ramifications of this regulatory insufficiency have already adversely impacted the diabetes care market. Following a surge in off-label prescribing of glucagon-like peptide-1 receptor agonists (GLP-1RAs), a National Patient Safety Alert has been declared by the Department of Health and Social Care (DHSC) and the NHS.<sup>79</sup> The current severe shortages of GLP-1RAs compounds are illustrative of the inherent flaws in the regulation, underscoring the pressing need for forward-thinking measures preventive of such crises. Given CGMs are certified for T1DM and insulin-dependent T2DM contexts only, observing that certain med-tech companies have retailed CGMs for 'off-label use' since 2017 reveals a clear regulatory oversight and is a cause for concern.

The Medicines and Healthcare products Regulatory Agency (MHRA) undertook a 2022 public consultation to rearticulate the 'intended purpose' for medical devices, CGMs included.<sup>80</sup> Considering the escalating adoption of CGMs outside their prescribed use, an urgent requirement has arisen to unambiguously term 'off-label' and provide exhaustive guidelines on its implications. Such mandates should encapsulate precision benchmarks, manufacturer duties vis-à-vis device constraints, and responsibility for untoward events stemming from 'off-label use'. Echoing this sentiment, the International Federation of Clinical Chemistry and Laboratory Medicine has advocated for stringent study protocols and performance criteria, as evidenced in a detailed scoping review.<sup>81</sup>

Despite CGMs not being officially endorsed for detecting dysglycaemia, PN or shaping behavioural changes in PNLD, marketing narratives suggesting the opposite abound increasing off-label demand for these devices.<sup>13,42,55</sup> Such proclamations risk being labelled 'misleading' in the face

of significant evidential gaps as outlined in this review. Addressing these regulatory gaps remains imperative to avert the continued misinformation risk to PNLD, potentially leading to deleterious health outcomes.

## Discussion

As the wearable and implantable sensor markets flourish, there is a growing propensity among individuals to personalise health regimens for enhanced well-being and disease prevention. Notwithstanding this trend, a careful appraisal is essential. This preliminary analysis underscores a dearth of compelling evidence for the utility of CGM in PNLD.

PN studies claim that traditional dietary approaches fail to encapsulate the inter-variability in metabolic responses to food, which in turn influence cardio-metabolic disease risk.<sup>10</sup> However, while showing variability in PPGRs based on correlation analysis, how exactly this translates into PN-enabled clinically relevant outcomes in PNLD has not been identified.<sup>10,54</sup> Contrastingly, PPGRs appear to be a poor predictor of such important clinical measures as IGT and ASCVD-10y.<sup>54</sup> Interestingly, contemporary research juxtaposing PN interventions with generic dietary advice revealed little effect on pivotal indices such as HbA1c or GV in prediabetes.<sup>82,83</sup> Until CGM biomarkers that have evidence of causality with diabetes-associated risks are identified, translation of the finding of PN studies in PNLD into meaningful interventions remains challenging. These biomarkers should be easy to extract and interpret for enhanced applicability and adherence.<sup>9</sup> Given the essential role of input data quality (nutrition, sleep, physical activity) on CGM performance, further insights into ensuring accuracy and sufficiency of input data are essential for the overall effectiveness of the device. For instance, a recent observational analysis within the PNLD devised a predictive model able to detect eating moments.<sup>84</sup> Pending validation in a larger cohort, this can potentially support food logging, for example, through artificial intelligence driven notifications, thereby reducing the risk of erroneous reporting.<sup>84</sup> The development of automatic techniques for determining meal macronutrient composition from CGM data would further support seamless use and thus accuracy of predictions.<sup>85</sup>

Enhanced accuracy in dietary predictions is plausible when merging diverse datasets with CGM metrics.<sup>85</sup> Yet, prior to the mainstreaming of these advanced glycaemic data analysis techniques, robust validation is mandated. Current reproducibility challenges attributable to variation in approaches for metric calculation and lack of algorithms validated on public datasets, result in inconsistent values of the same CGM metrics across software applications. Some metrics often get disregarded due to their inaccessibility rather than clinical value.<sup>9</sup> If CGMs are to be used as a source of digital biomarkers for dysglycaemia, open-source implementation and curation of public CGM datasets for scoring procedures and benchmarking are necessary, but currently pending.<sup>9, 43</sup>

Ensuring accuracy limitations are effectively communicated to the end-user remains the responsibility of the manufacturer. CGM user-manuals align with the intended purpose of the device and thus are generally diabetes-centric. PLWD can also seek professional advice from their clinician for any device-related concerns. This, however, is not the case for PNLD. Therefore, if CGMs are to be used by PNLD for preventative measures, research addressing device accuracy in this context requires mandated. Studies should focus on confirming the practical significance of potential inaccuracies attributed to drug interferences, physical activity or body composition of the user to develop guidelines and support systems tailored to PNLD.

Overall, the body of scientific evidence in support of CGM utility in disease prevention in PNLD is too limited to make definitive conclusions. Notably, a proportion of studies reporting positive results are sponsored or directly affiliated with companies functioning in the realm of PN.<sup>54,57</sup> Thereby, the findings are to be approached with caution. In fact, more than 50% of total research on blood glucose measurement is industry sponsored.<sup>86</sup> Such prevalence underscores the pervasive influence of corporate interests in shaping research output in the field. This highlights the need for independent and diverse studies to establish a more comprehensive understanding of CGM's role in disease prevention for PNLD. Addressing the robustness of CGM studies becomes imperative as the commercial market expands.<sup>86</sup>

Particularly concerning is the lack of studies inquiring into the unanticipated psychological ramifications of CGM use in non-medical settings.<sup>13</sup> Excessive glucose monitoring might unintentionally create maladaptive dietary changes in PNLD (e.g., exclusion of health food to avoid glucose excursion), especially when untrained users grapple with spurious hypo- or hyperglycaemic readings stemming from CGM inaccuracies. While similar calorie and fitness monitoring has been linked to the development of anxiety, compulsive behaviours, or disordered eating patterns, the consequences of CGM data on exacerbating these issues has not been extensively explored.<sup>85</sup> Studies measuring the effect of CGMs on the quality of life, disordered eating and other potential non-clinical factors would provide guidance for PNLD should they want to use the device.<sup>13</sup>

Finally, by presenting the findings in a narrative format this review aims to allow for a broad perspective on the developments in the field. Serving as the first formal attempt to highlight the evidential gap for what appears to be a rapidly expanding off-label use of a medical device, we suggest that the current regulatory frameworks are inadequate to protect wellbeing of both people living with and without diabetes. There exists an urgent need for regulatory bodies to strengthen post-market clinical follow-up oversight for medical devices, including CGMs, to prevent off-label induced widening of health disparities. Equally, there is a clarion call to educate both practitioners and end-users about interpreting CGM data, fostering a well-rounded adoption paradigm. Further inquiry into the topic of CGMs in PNLD in the format of more robust approaches including meta-analyses is recommended in this evolving field. As such, marrying rigorous research, appropriate regulation, and informed end-user engagement is paramount to ensure CGMs' merits outweigh the potential associated risks

## Conclusion

CGMs, in their present form, are not adequate for prevention of T2DM or non-communicable diseases. The available studies lack comprehensive assessments of long-term benefits and fail to prove the clinical significance of the interventions. Aspects including device accuracy, data analysis metrics, user acceptability, and potential adverse effects of CGMs in PNLD, remain under-researched. This dearth of knowledge restricts our understanding of CGMs' potential efficacy in improving health. For CGMs to prove their benefit in PNLD, there is a need for robust experimental and observational studies to help elucidate the relationship between non-diabetic glycaemia and its deleterious health outcomes. With the surging interest in personalised nutrition and wearable technologies, it is incumbent upon regulatory authorities to delineate clear guidelines encompassing CGM validation, transparency, and safety for these novel applications. The ongoing evolution of UK regulatory frameworks presents a timely opportunity to address these gaps, and further investigation into CGMs' role in PNLD is imperative to fortify diabetes prevention initiatives' coherence, fairness, and effectiveness.

**Author contributions:** AB and ZO were responsible for the study conceptualisation. ZO was responsible for original draft. AB and ZO were responsible for the reviewing and editing. AB, ZO and JSP contributed to the final reviewing and editing. All authors agreed the final version.

**Acknowledgements:** We have no acknowledgements.

**Conflict of Interest:** AB reports honoraria from Novo Nordisk, Office of Health Improvement and Disparity, Johnson and Johnson and Obesity UK outside the submitted work and is on the Medical Advisory Board and shareholder of Reset Health Clinics Ltd. JSP is on the Advisory Board for ROCHE Diabetes and has receiver speaker payments from Dexcom. ZO reports no conflicts of interest.

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