Review

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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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Abstract: Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder that poses a significant public health challenge. Prioritising its prevention is essential for enhancing health at both individual and community levels. With the burgeoning interest in wearable health technologies and individualised nutrition, continuous glucose monitoring systems (CGMs) have expanded their scope, transitioning from exclusive use in diabetes management to lifestyle enhancement for individuals without diabetes (PNLD). 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 PNLD, 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. The current literature inadequately supports the clinical relevance and lasting impact of these interventions. Moreover, a glaring paucity of research exists on the potential negative consequences of CGM usage, such as obsessive symptom tracking and potential onset of disordered eating behaviours, like orthorexia. This highlights a pressing need to refine CGM regulation in the UK, especially concerning its 'off-label use'. Addressing these research gaps and regulatory issues may enhance the role of CGMs in T2DM prevention strategies and non-communicable diseases among PNLD, ensuring a more unified and effective approach. Current evidence suggests caution in endorsing CGMs as a holistic instrument for T2DM prevention through lifestyle refinement is warranted.

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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 [1]. Predominantly Type 2 DM (T2DM), comprising 80-90% of all cases, is characterised by persistent hyperglycaemia interspersed with sporadic glucose fluctuations [1]. The imperative of early detection and prediction of this dysglycaemia is underscored by its capacity to preserve beta-cell (β-cell) function, achievable through lifestyle modifications such as weight management, which is integral to delaying T2DM's onset [1].

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; 42-47mmol/mol range) or fasting plasma glucose (FPG;

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5.5-6.9mmol/L) [2]. Nonetheless, the fidelity and comprehensiveness of these parameters for risk demarcation are contested, given findings highlighting their potential shortfall in pinpointing latent T2DM cases [2,3], thereby necessitating alternative diagnostic modalities.

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 [4]. Originating for diabetes management, CGMs' relevance has evolved, with recent inquiries delving into their potential as preventive tools for people not living with diabetes (PNLD). Unlike conventional HbA1c tests, CGMs provide a comprehensive insight into glucose dynamics, potentially refining risk categorisation through glycaemic variability (GV) parameters [5–7].

Presently, clinical guidelines do not recommend CGMs outside of type 1 diabetes (T1DM) or insulin-administered T2DM contexts [8]. Notwithstanding, commercial companies advocating CGMs to the broader public have flourished, particularly to the health-conscious. Commercial rhetoric advertises CGMs as central to mitigating non-communicable disease risks, encompassing T2DM, while advancing holistic wellness [9]. The pivotal challenge remains: discerning the validity of such assertions. With studies [10] underscoring dietary modifications and increased physical exertion (leading to weight loss) as crucial, potentially reducing T2DM risk by up to 71%, CGMs might be pivotal tools for bespoke interventions within PNLD. Although numerous studies support CGMs in T1DM regimes [11], their potential in PNLD remains to be comprehensively explored. This narrative review seeks to synthesise existing research on CGM application within PNLD, examining current regulatory directives and ascertain their prospective contribution to T2DM prevention and overall health betterment.

Continuous Glucose Monitors overview

CGMs exhibit diverse design functionalities and accuracy levels. Present models can measure glucose for up to 14 days, accurately documenting durations and frequencies of both hypo- and hyperglycaemic episodes (Table 1) [12–14], in addition to postprandial spikes [5]. CGMs are typically categorised into real-time CGM (rtCGM) and intermittently scanned CGM (isCGM). The former comprises a sensor and transmitter, continuously relaying data to a display, such as the Dexcom G6. Regular calibration through self-monitoring blood glucose (SMBG) is often mandated, at least bi-daily, although recent models eliminate this requirement [15]. Contrarily, isCGMs lack transmitters; users manually scan sensors using devices like the FreeStyle Libre paired with smartphones.

For optimal dysglycaemia detection, CGMs must maintain high accuracy, provide unambiguous glycaemic assessment metrics, and set definitive clinical benchmarks for the specific user group. Absence of these attributes potentially compromises the tangible benefits to the user.

Table 1. Glycaemic target levels for people living with diabetes and people living without[1].

Glycaemia target levels by type (mmol/L)	Preprandial	Postprandial
T1DM	3.9-7.0	<7.8
T2DM	3.9-7.0	<8.5
People not-living with diabetes	3.9-5.9	5.0-9.0

CGM accuracy

The efficacy of CGMs has experienced significant progress over recent decades, with the Mean Absolute Relative Difference (MARD) reducing from 25% to a respectable 10%, especially in the context of T1DM [16]. Accuracy metrics for CGMs encompass point, trend, and threshold alarm accuracies [17]. For PNLD, given the relatively benign glucose fluctuations compared to T1DM and T2DM, point accuracy becomes the pre-eminent criterion [17]. This metric appraises the alignment

[1] Postprandial, 90 minutes after meals; mmol/L, millimoles per litre; T1DM, Type 1 diabetes; T2DM, Type 2 diabetes.

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between an isolated glucose reading and an established reference benchmark [17]. However, the application of this to PNLD is mired in challenges due to the lack of specific target ranges and accuracy data, hindering commercial adaptation.

Relying on comprehensive metrics like MARD may overshadow inaccuracies specifically within the hypoglycaemic domain, potentially introducing unwarranted alarm in PNLD [18]. Furthermore, metrics devoid of agreement rates obscure the proportion of clinically relevant readings, thus potentially endorsing CGMs with respectable averages yet erratic excursions [19].

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 stipulated target ranges allied with agreement rates [20]. Within these benchmarks, the point accuracy criteria elucidate the least proportion of readings required to align with the Advanced Technologies & Treatments for Diabetes (ATTD) consensus guidelines [20]. Presently compliant devices include the Freestyle Libre 2, Freestyle Libre 3, Dexcom ONE, Dexcom G6, and Dexcom G7 [21]. However, for PNLD, the precision for reaping CGM benefits might deviate from the stringent isCGM criteria, and the dearth of this data renders diabetic target benchmarks potentially inapplicable.

Studies highlight a congruence between CGM and plasma glucose levels (PGL) in PNLD. However, CGM precision can vary depending on user characteristics, predominantly body composition [22–25]. 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 [23–25]. This underscores the necessity for considering body composition in CGM interpretation, particularly for people living with obesity.

In concordance with earlier findings in non-athletic people living with diabetes (PLWD) [26], higher device bias during physical exertion in PNLD has been documented, implying potential blind spots in early hypoglycaemic episode detection during activity, restricting device reliability to sedentary periods [27]. Mechanisms for this reduced accuracy include microcirculation perturbations caused by localised movement, increased body temperature, and rapid glucose shifts, termed "sensor drift" [27]. Thus, PNLD partaking in physical activity may receive skewed data, potentially resulting in undue concerns or misinformed lifestyle adjustments.

Furthermore, certain concurrent medications can adversely influence CGM precision. Notably, devices like Medtronic Guardian Sensors and Dexcom G4 Platinum have recorded potential accuracy reductions, possibly due to electrochemical interferences from specific agents like lisinopril and albuterol [28,29]. Nevertheless, emerging nanotechnological solutions aim to counteract these interferences [28,30], yet it remains imperative for current CGM users, especially PNLD, to remain vigilant of such potential drug interactions when interpreting CGM readings.

Another salient factor is the discrepancy between glucose concentrations in the ISF and PGL. Given the intricate dynamics of ISF glucose, influenced by blood glucose transitions and glucose metabolism rates, several CGMs utilise algorithms to adjust for physiological variances between ISF and blood glucose, endeavouring to approximate glucose levels. Such computational models insinuate that displayed readings might not genuinely correspond to either ISF or capillary glucose values [12], emphasizing the need for rigorous calibration processes and precise reference standards to ensure the reliability of CGM outputs for PNLD, an aspect currently amiss.

Parameters for measuring glycaemia

Evaluating glycaemic control employs various methodologies, with HbA1c being predominant, reflecting the average blood glucose (BG) over the preceding three months [31]. However, precision is contingent upon several physiological variables such as glucose uptake, red blood cell lifespan, and episodic BG spikes [31,32]. Notably, the same HbA1c readings might denote intra-variability in both PLWD and PNLD [31], highlighting the limitation of exclusively leaning on singular metrics. As a result, alternative measures have been proposed to document glucose excursions, emphasising glycaemic variability. GV represents the intensity and frequency of glycaemic changes [33] and is

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pivotal in anticipating both micro- and macrovascular complications, aligning with elevated HbA1c, FPG, postprandial glycaemia, and insulin resistance [34,35]. Through GV measurement, CGMs delineate glucose dysregulation phases, identifying phenotypes like impaired glucose tolerance (IGT), impaired fasting glucose (IFG), T1DM, and T2DM [5–7]. Thus, harnessing CGMs to discern initial glycaemic anomalies via GV could pave innovative pathways to prevent or mitigate T2DM and its subsequent complications.

GV is encapsulated by a variety of metrics [36], summarised in Table 2 [33]. Each GV index distinctively records varying dimensions of glycaemic fluxes, including amplitude, frequency, duration, or pattern [33]. 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 [33]. For PNLD, 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 PNLD complicates both academic research and clinical or commercial implementations [33].

Table 2. Continuous glucose monitoring metrics[2].

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.

Composite metrics (CM) may provide a composite vantage for glycaemic assessment. Hall et al. (2018) championed spectral clustering of CGM readings to identify glucotypes indicative of IGT [37]. Such CMs encapsulate multiple "variability" metrics, potentially yielding a comprehensive view of GV and early dysglycaemia detection in PNLD [37]. Yet, more exhaustive research is essential to validate such models' appropriateness for T2DM risk categorisation. Although CMs are increasingly adopted commercially to guide lifestyle adjustments and optimise 'metabolic health' in PNLD [9], there is currently a scarcity of peer reviewed studies corroborating the efficacy and validity of such CM utilisations. A shared understanding on the integral components of CM for CGM, ideal scoring procedures, empirical outcome linkages, and PNLD benchmarks remains pending [38]. Nevertheless, companies continue to monetize these concepts, prompting questions regarding enhanced regulatory scrutiny.

The International Diabetes Center introduced the Ambulatory Glucose Profile (AGP) which amalgamates standard glycaemic metrics, GV indices, and a summarised glycaemic exposure [39]. This framework facilitates a consistent comparison of glucose data across diverse CGMs, enhancing clinical analysis and therapeutic interventions. However, a limitation arises in differentiating between pre-prandial and postprandial glycaemia [39]. When appraising Time in Range (TIR), it is imperative to delineate a specific glucose bracket. Per the International Consensus on TIR, for PLWD, a universal standard recommends at least 70% within the designated range, with levels below 3.0

[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; HbA1c, glycated heamoglobin;

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mmol/L not exceeding 1%, and those surpassing 10mmol/L capped at 25% [37,40]. Although AGP utility in diabetes management is evident, its relevance may diminish in PNLD due to its alignment with diabetes-specific directives. More recently, The Diabetes Technology Society unveiled the Glycaemic Risk Index (GRI) [41] - a composite metric gauging glycaemia quality 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. In summary, the development of bespoke benchmarks or innovative methodologies specific to PNLD remains essential for optimising CGM data accuracy and applicability.

Establishing clinical targets: What is "normal glycaemia"?

To establish a reference for a 'standard' glucose profile, researchers have investigated glucose patterns in healthy individuals utilising CGMs. In PNLD or prediabetes data shows the percentage of time below 4.0mmol/L during masked CGM to have a median of 1.92% (27.6 minutes) and a mean of 3.54% (51.0 minutes) across a day [42]. 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 [39]. This disparity is likely attributed to glucose fluctuations linked to meal intakes [42]. 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 [42] to facilitate a nuanced comprehension of GV and its related implications in PNLD.

Existing research on CGMs in PNLD indicates 73% of normoglycemic participants exhibit PG that surpasses these thresholds aligning with prediabetic patterns [43]. This assertion gains credence with data illustrating that normoglycemic subjects often achieve glucose excursions paralleling IGT and diabetic levels [44], insinuating a potential onset of prediabetes [43]. However, it is crucial to note that these elevated glucose excursions might be normal physiological responses to increased carbohydrate or sugar consumption or other external stressors [45]. Current data is fragmented concerning the proposition that innate GV elevations, akin to those in prediabetes or diabetes, correlate with heightened T2DM risks, bypassing elevated HbA1c or other health concerns [46]. While the significance of GV in PLWD is documented, the absence of research on the repercussions of lifestyle interventions in reducing GV in PNLD necessitates further study [46]. Hence, any current assertions about prioritising these responses in PNLD should be approached with caution.

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 β-cell dysfunction, can be achieved through lifestyle modifications [47,48]. Dietetic interventions aimed at weight reduction and BG moderation are fundamental in precluding T2DM [47]. The efficacy of the NHS DPP, which entails an intensive lifestyle intervention emphasising dietary modifications and energy restriction, was varied, even though it substantially reduced diabetes risk [48]. Distinct T2DM subgroups, informed by diverse aetiologies, have shown varied responses to lifestyle interventions [49]. A recent study identified four T2DM subcategories based on age of onset, obesity, and poor glycaemic control, each manifesting unique responses to lifestyle changes [49]. Importantly, discernible inter-individual differences in postprandial glycaemic responses (PPGRs) to the same foods have been observed in PNLD, accentuating the importance of such variations in formulating intervention strategies [50,51]. This positions CGMs as potential tools for providing personalised nutritional advice by addressing these disparities [50,51].

Personalised nutrition (PN) represents a dietary protocol fashioned in accordance with an individual's genetic, microbiotic, metabolic, alimentary, and other inherent factors [52]. While a multitude of studies support PN's potential for metabolic health improvement [53,54], scant research, to our knowledge, has delved into the clinical benefits of using CGMs within the PNLD [55].

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The aforementioned study [50] discerned individual PPGRs, characterised the individual variabilities, and identified associated determinants. For uniform food items, significant inter-personal PPGR variations were noted. For example, the mean PPGR for bread registered at 2.4±1.8mmol/L*h, though this ranged from <0.8 to >4.4mmol/l*h. An innovative machine learning (ML) model, incorporating a variety of data sets including blood tests, microbiome evaluations, dietary diaries, and anthropometrics, surpassed conventional dietary guidance in predicting responses [50], an achievement echoed in a subsequent study [51]. However, the long-term success of this model remains to be authenticated, with benchmarking against traditional diagnostics or PPGR-modulating dietary interventions outstanding [52]. Interestingly, contemporary research juxtaposing PN interventions with generic dietary advice revealed little effect on pivotal indices such as HbA1c or GV [53,55].

The Personalised Responses to Dietary Composition Trial-1 (PREDICT-1) trial, employing CGMs, assessed glycaemic responses to eight varied macronutrient meals also considering lipid and C-peptide concentrations [56]. Lifestyle determinants like physical activity, sleep, and microbiome data were assimilated. The findings mirrored prior studies and received validation from an independent US cohort of 100 participants [56]. PREDICT 2 and 3 seek to reaffirm these insights in more expansive cohorts [54].

A recent observational analysis within the PNLD devised predictive glucose models using CGM data, smartwatch data for physical activity and sleep, and food intake via mobile application [57]. This algorithm showcased notable precision, suggesting plausible forecasts of food-induced glucose variations and the influence of lifestyle elements on glucose [57]. These pioneering studies accentuate the promise of CGMs in PN. Nonetheless, the dearth of long-term studies casts a speculation over the therapeutic implications of such models.

Recent debates have challenged the idea of predominantly inter-individual variability in PPGR, as opposed to intra-individual variability in PN [58]. Poor reliability of PPGR to multiple duplicate meals were reported, with intraindividual variability similar to variability across various meals [58]. Even under controlled conditions, obtaining only two measurements was insufficient to accurately estimate PPGR, though determining the number of CGM readings for estimates remains ambiguous [58]. While previous studies [50,51,55,56] demonstrated consistent PPGR to simple meals, like bread or muffins, only one [55] encompasses real-life multicomponent meals. Furthermore, the efficacy of CGM-driven meal assessments within PN may be device-dependent, given observed variances in inter-personal PPGR with distinct devices [59], prompting reflections on genuine personalisation and use in T2DM prevention.

However, some criticisms highlight potential methodological oversights. Ad-libitum feeding could compromise sensor accuracy, especially during glycaemic extremes [60]. Ambiguously composed meals might distort meal classification. Supportively, reduced variability indices were documented for carbohydrate-rich meals (>25 g) [60]. The PREDICT 1 study data reinforces the consistency of CGMs in charting glycaemic responses across disparate metrics [60].

Given these conflicting observations, deeming CGMs as the definitive tools for PN in PNLD seems premature. Fundamental determinants, encompassing device variation, energy consumption, and meal composition, necessitate meticulous examination. Such insights are instrumental in enhancing the reliability and efficiency of CGM-facilitated PN in the context of PNLD.

Behavioural Change

Effective glycaemic regulation is intrinsically linked to diet, physical activity, and mood. CGMs can elucidate these interrelations by graphically associating lifestyle determinants with blood glucose variations, thus fostering healthier practices, as observed in prediabetes, T1DM, and T2DM cohorts [61]. Significantly, the Freestyle Libre Pro has shown enhanced HbA1c outcomes and treatment contentment in PLWD T2 [62]. The use of Dexcom G6 CGM has resulted in significantly greater improvement in HbA1c levels as compared with traditional blood glucose monitoring in PLWD T2 treated only with basal insulin [63]. No significant differences in the daily insulin dose or diabetes medications between the groups suggest that glycaemic improvements are likely due to behaviour

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change following CGM adoption, rather than therapy adjustments [63]. CGM-associated improvements in glycaemic outcomes were also shown in PLWD T2 not using insulin [64]. The IMMEDIATE study revealed that using a special diabetes self-management education (DSME) programme along with CGMs resulted in higher TIR and greater reduction in HbA1c, as well as increased patient satisfaction, compared to DSME use alone [64]. An uptick in CGM usage has also been associated with better glycaemic outcomes [65]. CGMs may therefore also foster beneficial behavioural changes in PNLD by increasing accountability thereby improving glycaemic control and anticipating diabetes onset. While robust data on behavioural shifts post-CGM introduction in PNLD is limited, similar trajectories are expected.

The "Sugar Challenge" study unravelled glucose patterns in 665 participants [66]. Using CGMs alongside a smartphone application, participants discerned glucose dynamics relative to elements like dietary composition and physical exertion. Instantaneous feedback spurred them to avoid foods with a high glycaemic index, leading to an optimised TIR [66]. Yet, the long-term ramifications of these modifications remain speculative.

Food consumption is multifaceted, moulded by social, habitual, and psychological facets [67]. Emotional eating can predispose individuals to weight gain and T2DM [67]. One investigation on "hunger training" assessed the alignment between perceived hunger and CGM data. Those guided to eat based on pre-meal glucose metrics registered noteworthy weight reduction, regardless of the glucose assessment technique [67].

Physical activity, paramount for modulating post-meal glucose fluctuations and T2DM risk, may be enhanced by CGMs [68]. Witnessing the immediate glycaemic benefits of exercise can stimulate activity adherence [69,70]. An 8-week investigation contrasting traditional exercise regimes with a CGM-enhanced regimen revealed superior fitness outcomes and attendance displayed by the latter group [69]. Paired with fitness trackers, CGMs also prompted improved motivation to change behaviour in people living with overweight [70]. Yet, research constraints curtail the generalisability of these outcomes, with scant evidence in PNLD [71].

While CGMs' benefits seem evident in PLWD, their assimilation in PNLD demands scrutiny [72]. One study indicated 90% of users found the CGM easy to use and enlightening, but only 40% foresaw its health utility [72]. 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 [72]. In contrast, another study emphasised CGMs' pedagogic capacity in PNLD, with the majority recognising their dietary and lifestyle guidance potential [73].

CGMs seem poised to bolster glycaemic awareness and regulation, particularly regarding lifestyle choices. However, their widespread uptake, especially in PNLD, is contingent on enhancing user interaction and understanding their comprehensive influence on behaviour change.

CGM regulation

Continuous Glucose Monitors (CGM) have witnessed extensive application both in clinical scenarios and the broader commercial sphere, engendering debates regarding the regulatory strictures overseeing their usage. As it stands, CGMs gain market entry in Europe post-acquisition of the Conformité Européenne (CE) marking, among other global validations [21]. 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 [21]. For instance, variances have been detected in the MARD values of a CGM apparatus between company-backed studies and independent research [74,75].

Post the EU Medical Devices Regulation (MDR) 2017/745, CGMs must sport a CE marking for UK marketability [76]. Yet, post-Brexit regulations indicate that CE-labelled medical tools will only have access to the UK market until 31 December 2024 [21]. 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 [21]. Therefore, manufacturers bear the onus of presenting and substantiating clinical evidence in line with overarching safety and efficacy

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parameters [77], although these directives are primarily diabetes-centric, often sidelining PNLD considerations.

Exceptions do exist, such as the Abbott Libre Sense Glucose Sport Biosensor (Supersapiens) which obtained a CE marking solely for athletic applications [78]. The manufacturer delineates that this tool is not crafted for diagnosis, treatment, or any medical ailment management [78]. The designated utility and categorisation intrinsically steer the evidence threshold for CE marking attainment [76]. Nonetheless, a budding trend shows CGMs, originally designated for distinct functions, gaining traction among PNLD, surpassing their CE certificatory bounds [79]. 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 nutritional guidance in PNLD, engendering a regulatory quagmire [9,80].

This presents a regulatory puzzle, amplifying apprehensions over CGM distribution controls and the latent risks for PNLD utilising devices outside of prescribed parameters. While the EU MDR 2017/745 sketches out the regulations for distributors and post-market observation, it remains reticent on the consequences of unsanctioned medical device distribution. This leaves a cloud of uncertainty over matters of accountability, liability, and patient safety [77]. Importantly, the term 'off-label use' remains nebulous within EU MDR 2017/745, given its circumscribed emphasis on manufacturers identifying, but not clearly defining, such use [81]. Observing that certain med-tech companies have retailed CGMs for 'off-label use' since 2017 reveals a clear regulatory oversight [21].

The Medicines and Healthcare products Regulatory Agency (MHRA) undertook a 2022 public consultation endeavouring to rearticulate the 'intended purpose' for medical devices, CGMs included [82]. Considering the escalating adoption of CGMs outside their prescribed remits, 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 [83].

Despite CGMs not being officially endorsed for detecting dysglycaemia and shaping behavioural changes in PNLD, marketing narratives suggesting the converse abound [79]. Such proclamations risk being labelled 'misleading' in the face of conspicuous evidential voids. 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. Preliminary analyses underscore a dearth of compelling evidence for the utility of CGM in PNLD [24,50,66,67]. Disturbingly, these devices often transcend their designated uses without stringent regulatory oversight.

Recent literature posits that dietary strategies informed by CGM metrics surpass traditional carbohydrate-centric diets in modulating glycaemic responses and maintaining blood glucose equilibrium. However, amongst extensive studies utilising CGMs for PN, none have rigorously contrasted their clinical efficacy with, say, Self-Monitoring Blood Glucose (SMBG). Aggravating matters employed test meals in extant research often lack ecological validity [55], and the predictive algorithms employed leverage variables not ubiquitously available, casting aspersions on their universal utility. Enhanced accuracy in dietary predictions is plausible when merging diverse datasets with CGM metrics [84]. Yet, prior to the mainstreaming of these advanced glycaemic data analysis techniques, robust validation is mandated. The conspicuous absence of transparent academic scrutiny into proprietary methods of med-tech companies accentuates the urgency for independent assessments before global adoption.

Inherent variables like calibration issues, 'sensor drift', or drug interactions can compromise CGM accuracy. Appraising the clinical implications of such deviations within PNLD is complicated

due to scant research. Distinctly, when transitioning CGM utility from PLWD to PNLD, their clinical ramifications are set to diverge markedly. Disconcertingly, such nuances are frequently neglected by industry stakeholders, complicating assessments of CGM's accuracy and efficacy in disease prevention in PNLD.

Further concern emerges regarding unanticipated psychological ramifications of CGM use in non-medical settings. The repercussions of CGM data on exacerbating anxiety, compulsive behaviours, or disordered eating patterns remain sparsely explored. Albeit eating disorders being an exclusion commercially for CGM in PNLD, research links regular calorie and fitness monitoring with eating disorder including anorexia or orthorexia [85]. Thus, 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.

Finally, there exists an urgent need for regulatory entities to amplify post-market clinical follow-up (PMCF) oversight. Equally, there is a clarion call to educate both practitioners and end-users about interpreting CGM data, fostering a well-rounded adoption paradigm. As such, marrying rigorous research, stringent regulation, and informed end-user engagement is paramount, to ensure CGMs' merits outweigh the associated risks [86].

Conclusion

This review critically evaluates the available literature concerning the utility of CGMs in PNLD. Currently, the evidence suggests that CGMs, in their present form, may not be wholly 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. Several salient areas, including accuracy, data analysis metrics, user acceptability, and potential adverse effects of CGMs in PNLD, remain markedly under-researched. This dearth of knowledge restricts our understanding of CGMs' potential efficacy in improving health. With the surging interest in personalised nutrition solutions and wearable technologies, it is incumbent upon regulatory authorities to delineate clear guidelines encompassing CGM validation, transparency, and safety in novel applications including PNLD. 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.

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References

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci 2020; 21(17):6275. doi:10.3390/ijms21176275
2. Penn L, Rodrigues A, Haste A, et al. NHS Diabetes Prevention Programme in England: formative evaluation of the programme in early phase implementation. BMJ Open 2018;8:e019467. doi:10.1136/bmjopen-2017-019467
3. Sitasuwan T, Lertwattanarak R. Prediction of type 2 diabetes mellitus using fasting plasma glucose and HbA1c levels among individuals with impaired fasting plasma glucose: a cross-sectional study in Thailand. BMJ Open 2020;10(11):e041269. doi: 10.1136/bmjopen-2020-041269
4. Kumar Das S, Nayak KK, Krishnaswamy PR, Kumar V, Bhat N. Review- Electrochemistry and Other Emerging Technologies for Continuous Glucose Monitoring Devices. ECS Sens Plus 2022;1 031601. doi:10.1149/2754-2726/ac7abb

5. Acciaroli G, Sparacino G, Hakaste L, et al. Diabetes and Prediabetes Classification Using Glycemic Variability Indices From Continuous Glucose Monitoring Data. J Diabetes Sci Technol 2017;12(1):105–113. doi:10.1177/1932296817710478
6. Goel P, Parkhi D, Barua A, Shah M, Ghaskadbi S. A Minimal Model Approach for Analyzing Continuous Glucose Monitoring in Type 2 Diabetes. Front Physiol 2018;9: 673. doi:10.3389/fphys.2018.00673
7. Longato E, Acciaroli G, Facchinetti A, Maran A, Sparacino G. Simple Linear Support Vector Machine Classifier Can Distinguish Impaired Glucose Tolerance Versus Type 2 Diabetes Using a Reduced Set of CGM-Based Glycemic Variability Indices. J Diabetes Sci Technol 2020;14(2):297–302. doi:10.1177/1932296819838856
8. NHS King's College Hospital, NHS Foundation Trust. Flash and real time continuous glucose monitoring: NICE diabetes guidance update 2022; https://www.kch.nhs.uk/wp-content/uploads/2023/01/pl-1038.1-flash-and-real-time-continuous-glucose-monitoring-nice-diabetes-guidance-update.pdf. Accessed September 22, 2023.
9. Corindia A. Introducing Metabolic Healthspan 2023. https://www.veri.co/learn/introducing-metabolic-healthspan. Accessed September 22, 2023.
10. Diabetes Prevention Program Research Group. Long-term Effects of Lifestyle Intervention or Metformin on Diabetes Development and Microvascular Complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015; 3(11):866-875. doi:10.1016/S2213-8587(15)00291-0
11. Teo E, Hassan N, Tam W, Koh S. Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis. Diabetologia 2022;65(4):604-619. doi:10.1007/s00125-021-05648-4
12. Ceriello A, Colagiuri S. International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. Diabet Med 2008;25(10):1151-6. doi: 10.1111/j.1464-5491.2008.02565.x
13. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management 2015. https://www.nice.org.uk/guidance/ng17. Accessed September 24, 2023.
14. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management 2015. https://www.nice.org.uk/guidance/ng28. Accessed September 24, 2023.
15. Meurant R, Freckmann G, Pleus S. Regulatory Profile for glucose self-monitoring tools 2021.https://haiweb.org/wp-content/uploads/2021/10/Self_Monitoring-Devices-Regulatory-Profile-1.pdf. Accessed September 22, 2023.
16. Bailey TS, Alva S. Landscape of continuous glucose monitoring (CGM) and integrated CGM: Accuracy considerations. Diabetes Technol Ther 2021;23(S3):S5–S11. doi: 10.1089/dia.2021.0236
17. CLSI. Performance Metrics for Continuous Interstitial Glucose Monitoring. 2nd ed. CLSI guideline POCT05. Clinical and Laboratory Standards Institute 2020. https://clsi.org/media/tqkj5mmn/poct05ed2_sample.pdf. Accessed September 23, 2023.
18. Heinemann L, Schoemaker M, Schmelzeisen-Redecker G, et al. Benefits and Limitations of MARD as a Performance Parameter for Continuous Glucose Monitoring in the Interstitial Space. J Diabetes Sci Technol 2020;14(1):135–150. doi: 10.1177/1932296819855670
19. Freckmann G, Pleus S, Grady M, Setford S, Levy B. Measures of Accuracy for Continuous Glucose Monitoring and Blood Glucose Monitoring Devices. J Diabetes Sci Technol 2019;13(3):575-583. doi:10.1177/1932296818812062
20. Food and Drug Administration. CFR - Code of Federal Regulations Title 21 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=862.1355. Accessed September 23, 2023.
21. Pemberton JS, Wilmot EG, Barnard-Kelly K, et al. CGM accuracy: Contrasting CE marking with the governmental controls of the USA (FDA) and Australia (TGA): A narrative review. Diabetes Obes Metab 2023;25(4):916–939. doi:10.1111/dom.14962
22. Akintola AA, Noordam R, Jansen SW. Accuracy of Continuous Glucose Monitoring Measurements in Normo-Glycemic Individuals. PLoS ONE 2015;0(10):e0139973. doi: 10.1371/journal.pone.0139973.
23. Ghane N, Broadney MM, Davis EK, et al. Estimating plasma glucose with the FreeStyle Libre Pro continuous glucose monitor during oral glucose tolerance tests in youth without diabetes. Pediatr Diabetes 2019;20(8):1072-1079. doi:10.1111/pedi.12910

24. Röhling M, Martin T, Wonnemann M, et al. Determination of Postprandial Glycemic Responses by Continuous Glucose Monitoring in a Real-World Setting. Nutrients. 2019;11(10):2305. doi:10.3390/nu11102305
25. Zhang X, Sun F, Wongpipit W, Huang WYJ, Wong SHS. Accuracy of Flash Glucose Monitoring During Postprandial Rest and Different Walking Conditions in Overweight or Obese Young Adults. Front Physiol 2021;12:732751. doi:10.3389/fphys.2021.732751
26. Biagi L, Bertachi A, Quirós C, et al. Accuracy of Continuous Glucose Monitoring before, during, and after Aerobic and Anaerobic Exercise in Patients with Type 1 Diabetes Mellitus. Biosensors 2018;8(1):22. doi:10.3390/bios8010022
27. Clavel P, Tiollier E, Leduc C, Fabre M, Lacome M, Buchheit M. Concurrent Validity of a Continuous Glucose-Monitoring System at Rest and During and Following a High-Intensity Interval Training Session. Int J Sports Physiol Perform 2022; 17(4):627-633. doi:10.1123/ijspp.2021-0222
28. Mian Z, Hermayer KL, Jenkins A. Continuous Glucose Monitoring: Review of an Innovation in Diabetes Management. Am J Med Sci 2019;358(5):332-339. doi: 10.1016/j.amjms.2019.07.003
29. Basu A, Slama MQ, Nicholson WT, et al. Continuous Glucose Monitor Interference With Commonly Prescribed Medications: A Pilot Study. J Diabetes Sci Technol 2017;11(5):936-941. doi:10.1177/1932296817697329
30. Li W, Luo W, Li M. The Impact of Recent Developments in Electrochemical POC Sensor for Blood Sugar Care. Front Chem 2021;9:723186. doi:10.3389/fchem.2021.723186
31. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care 2017;40(8):994-999. doi:10.2337/dc17-0636
32. Xu Y, Bergenstal RM, Dunn TC, Ajjan RA. Addressing shortfalls of laboratory HbA1c using a model that incorporates red cell lifespan. eLife 2021;10:e69456. doi: 10.7554/eLife.69456
33. Olawsky E, Zhang Y, Eberly LE, Helgeson ES, Chow LS. A New Analysis Tool for Continuous Glucose Monitor Data. J Diabetes Sci Technol 2022;16(6):1496-1504. doi: 10.1177/19322968211028909.
34. Lind M, Tuomilehto J, Uusitupa M. The Association between HbA1c, Fasting Glucose, 1-Hour Glucose and 2-Hour Glucose during an Oral Glucose Tolerance Test and Cardiovascular Disease in Individuals with Elevated Risk for Diabetes. PLoS ONE 2014;9(10):e109506. doi:10.1371/journal.pone.0109506
35. Jang JY, Moon S, Cho S, Cho KH, Oh CM. Visit-to-visit HbA1c and glucose variability and the risks of macrovascular and microvascular events in the general population. Sci Rep 2019;9(1):1374. doi:10.1038/s41598-018-37834-7
36. Kovatchev BP. Metrics for glycaemic control — from HbA1c to continuous glucose monitoring. Nat Rev Endocrinol 2017;13(7):425–436. doi:10.1038/nrendo.2017.3
37. Hall H, Perelman D, Breschi A. Glucotypes reveal new patterns of glucose dysregulation. PLoS Biol 2018;16(7):e2005143. doi:10.1371/journal.pbio.2005143
38. Nguyen M, Han J, Spanakis EK, Kovatchev BP, Klonoff DC. A Review of Continuous Glucose Monitoring-Based Composite Metrics for Glycemic Control. Diabetes Technol Ther 2020;22(8):613-622. doi:10.1089/dia.2019.0434
39. Kröger J, Reichel A, Siegmund T, Ziegler R. Clinical Recommendations for the Use of the Ambulatory Glucose Profile in Diabetes Care. J Diabetes Sci Technol 2019;14(3):586–594. doi:10.1177/1932296819883032
40. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care 2019;42(8):1593-1603. doi:10.2337/dci19-0028
41. Klonoff DC, Wang J, Rodbard D, et al. A Glycemia Risk Index (GRI) of Hypoglycemia and Hyperglycemia for Continuous Glucose Monitoring Validated by Clinician Ratings. J Diabetes Sci Technol 2023;17(5):1226-1242. doi:10.1177/19322968221085273
42. Borg R, Kuenen JC, Carstensen B, et al. Real-life glycaemic profiles in non-diabetic individuals with low fasting glucose and normal HbA1c: the A1C-Derived Average Glucose (ADAG) study. Diabetologia 2010;53(8):1608–1611. doi:10.1007/s00125-010-1741-9
43. Rodriguez-Segade S, Rodriguez J, Camiña F, et al. Continuous glucose monitoring is more sensitive than HbA1c and fasting glucose in detecting dysglycaemia in a Spanish population without diabetes. Diabetes Res Clin Pract 2018;142:100–109. doi: 10.1016/j.diabres.2018.05.026
44. Deiss D, Abtahi T, Rastogi R, Kelley EL. Glucose Variability of Individuals without Diabetes Using a Long-Term Continuous Glucose Monitoring System. Diabetes 2018;67(Supplement 1):1542-P. doi:10.2337/db18-1542-P

45. Vedantam D, Poman DS, Motwani L, Asif N, Patel A, Anne KK. Stress-Induced Hyperglycemia: Consequences and Management. Cureus 2022;14(7):e26714. doi: 10.7759/cureus.26714
46. Umpierrez GE, Kovatchev B. Glycemic Variability: How to Measure and Its Clinical Implication for Type 2 Diabetes. Am J Med Sci 2018;356(6):518-527. doi: 10.1016/j.amjms.2018.09.010
47. de Hoogh IM, Oosterman JE, Otten W, et al. The Effect of a Lifestyle Intervention on Type 2 Diabetes Pathophysiology and Remission: The Stevenshof Pilot Study. Nutrients 2021;13(7):2193. doi:10.3390/nu13072193
48. de Hoogh IM, Pasman WJ, Boorsma A, van Ommen B, Wopereis S. Effects of a 13-Week Personalized Lifestyle Intervention Based on the Diabetes Subtype for People with Newly Diagnosed Type 2 Diabetes. Biomedicines 2022;10(3):643. doi: 10.3390/biomedicines10030643
49. Bancks MP, Chen H, Balasubramanyam A, et al. Type 2 Diabetes Subgroups, Risk for Complications, and Differential Effects Due to an Intensive Lifestyle Intervention. Diabetes Care 2021;44(5):1203–1210. doi:10.2337/dc20-2372
50. Zeevi D, Korem T, Zmora N, et al. Personalized Nutrition by Prediction of Glycemic Responses. Cell 2015;163(5):1079–1094. doi:10.1016/j.cell.2015.11.001
51. Mendes-Soares H, Raveh-Sadka T, Azulay S, et al. Assessment of a Personalized Approach to Predicting Postprandial Glycemic Responses to Food Among Individuals Without Diabetes. JAMA Netw Open 2019;2(2):e188102. doi: 10.1001/jamanetworkopen.2018.8102
52. Berciano S, Figueiredo J, Brisbois TD, et al. Precision nutrition: Maintaining scientific integrity while realizing market potential. Front Nutr 2022;9:979665. doi: 10.3389/fnut.2022.979665
53. Kharmats AY, Popp C, Hu L, Berube L, et al. A randomized clinical trial comparing low-fat with precision nutrition-based diets for weight loss: impact on glycemic variability and HbA1c. Am J Clin Nutr 2023;118(2):443-451. doi:10.1016/j.ajcnut.2023.05.026
54. Zoe Global Limited. Whitepaper: The PREDICT program 2023. https://zoe.com/whitepapers/the-predict-program. Accessed September 24, 2023.
55. Ben-Yacov O, Godneva A, Rein M, et al. Personalized Postprandial Glucose Response-Targeting Diet Versus Mediterranean Diet for Glycemic Control in Prediabetes. Diabetes care 2021;44(9):1980-1991. doi:10.2337/dc21-0162
56. Berry SE, Valdes AM, Drew DA, et al. Human postprandial responses to food and potential for precision nutrition. Nat Med 2020;26(6):964–973. doi:10.1038/s41591-020-0934-0
57. Van den Brink WJ, van den Broek TJ, Palmisano S, Wopereis S, de Hoogh IM. Digital Biomarkers for Personalized Nutrition: Predicting Meal Moments and Interstitial Glucose with Non-Invasive, Wearable Technologies. Nutrients 2022;14(21):4465. doi: 10.3390/nu14214465
58. Hengist A, Gue J, Hall KD. Imprecision nutrition? Duplicate meals result in unreliable individual glycemic responses measured by continuous glucose monitors across three dietary patterns in adults without diabetes. MedRxiv. Preprint posted online June 15, 2023. doi:10.1101/2023.06.14.23291406
59. Howard R, Guo J, Hall KD. Imprecision nutrition? Different simultaneous continuous glucose monitors provide discordant meal rankings for incremental postprandial glucose in subjects without diabetes. Am J Clin Nutr 2023;112(4):1114–1119. doi:10.1093/ajcn/nqaa198
60. Merino J, Linenberg I, Bermingham KM, et al. Validity of continuous glucose monitoring for categorizing glycemic responses to diet: implications for use in personalized nutrition. Am J Clin Nutr 2022;115(6):1569–1576. doi:10.1093/ajcn/nqac026
61. Ehrhardt N, Al Zaghal E. Behavior Modification in Prediabetes and Diabetes: Potential Use of Real-Time Continuous Glucose Monitoring. J Diabetes Sci Technol 2019;13(2):271-275. doi:10.1177/1932296818790994
62. Ajjan RA, Jackson N, Thomson SA. Reduction in HbA1c using professional flash glucose monitoring in insulin-treated type 2 diabetes patients managed in primary and secondary care settings: A pilot, multicentre, randomised controlled trial. Diab Vasc Dis Res 2019;16(4):385-395. doi:10.1177/1479164119827456
63. Martens T, Beck RW, Bailey R, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Patients With Type 2 Diabetes Treated With Basal Insulin. JAMA 2021;325(22):2262-2272. doi:10.1001/jama.2021.7444
64. Aronson R, Brown RE, Chu L, et al. IMpact of flash glucose Monitoring in pEople with type 2 Diabetes Inadequately controlled with non-insulin Antihyperglycemic ThErapy (IMMEDIATE): A Randomized Clinical Trial. Diabetes Obes Metab 2023;25(4):1024-1031. doi:10.1111/dom.14949

65. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes Res Clin Pract 2018;137:37-46. doi: 10.1016/j.diabres.2017.12.015
66. Dehghani Zahedani A, Shariat Torbaghan S, Rahili S, et al. Improvement in Glucose Regulation Using a Digital Tracker and Continuous Glucose Monitoring in Healthy Adults and Those with Type 2 Diabetes. Diabetes Ther 2021;12(7):1871–1886. doi: 10.1007/s13300-021-01081-3
67. Jospe MR, de Bruin WE, Haszard JJ, Mann JI, Brunton M, Taylor RW. Teaching people to eat according to appetite – Does the method of glucose measurement matter? Appetite 2020;151:104691. doi:10.1016/j.appet.2020.104691
68. Aqeel M, Forster A, Richards EA, et al. The Effect of Timing of Exercise and Eating on Postprandial Response in Adults: A Systematic Review. Nutrients. 2020;12(1):221. doi: 10.3390/nu12010221
69. Bailey KJ, Little JP, Jung ME. Self-Monitoring Using Continuous Glucose Monitors with Real-Time Feedback Improves Exercise Adherence in Individuals with Impaired Blood Glucose: A Pilot Study. Diabetes Technol Ther 2016;18(3):185–193. doi: 10.1089/dia.2015.0285
70. Liao Y, Basen-Engquist KM, Urbauer DL, Bevers TB, Hawk E, Schembre SM. Using Continuous Glucose Monitoring to Motivate Physical Activity in Overweight and Obese Adults Using: A Pilot Study. Cancer Epidemiol Biomarkers Prev 2020;29(4):761-768. doi: 10.1158/1055-9965.EPI-19-0906
71. El Fatouhi D, Héritier H, Allémann C, et al. Associations Between Device-Measured Physical Activity and Glycemic Control and Variability Indices Under Free-Living Conditions. Diabetes Technol Ther 2022;24(3):167-177. doi:10.1089/dia.2021.0294
72. Liao Y, Schembre S. Acceptability of Continuous Glucose Monitoring in Free-Living Healthy Individuals: Implications for the Use of Wearable Biosensors in Diet and Physical Activity Research. JMIR mHealth and uHealth. 2018;6(10):e11181. doi: 10.2196/11181
73. Sofizadeh S, Pehrsson A, Ólafsdóttir AF, Lind M. Evaluation of Reference Metrics for Continuous Glucose Monitoring in Persons Without Diabetes and Prediabetes. J Diabetes Sci Technol 2022;16(2):373-382. doi:10.1177/1932296820965599
74. Zisser H, Wagner R, Pleus S, et al. Clinical performance of three bolus calculators in subjects with type 1 diabetes mellitus: a head-to-head-to-head comparison. Diabetes Technol Ther 2010;12(12):955-61. doi:10.1089/dia.2010.0064.
75. Kölle J, Eichenlaub M, Mende J, et al. Performance Assessment of Three Continuous Glucose Monitoring Systems in Adults With Type 1 Diabetes. J Diabetes Sci Technol 2023;0(0). doi:10.1177/19322968231159657
76. Gov.uk. Regulating medical devices in the UK 2023. https://www.gov.uk/guidance/regulating-medical-devices-in-the-uk. Accessed September 24, 2023.
77. Official Journal of the European Union. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC 2017. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN. Accessed September 24, 2023.
78. Abbott MediaRoom. Abbott Laboratories. Abbott Introduces Libre Sense glucose sport biosensor in Europe, world's first glucose biosensor designed for athletes 2020. https://abbott.mediaroom.com/2020-09-17-Abbott-Introduces-Libre-Sense-Glucose-Sport-Biosensor-in-Europe-Worlds-First-Glucose-Biosensor-Designed-for-Athletes. Accessed September 24, 2023.
79. Jaklevic MC. Start-ups Tout Continuous Glucose Monitoring for People Without Diabetes. JAMA 2021;325(21):2140-2142. doi: 10.1001/jama.2021.3789
80. Abbott MediaRoom. Abbott Laboratories. Abbott's FreeStyle Libre 2, with Optional Real-Time Alarms, Secures CE Mark for Use in Europe 2018. https://abbott.mediaroom.com/2018-10-01-Abbott-s-FreeStyle-R-Libre-2-with-Optional-Real-Time-Alarms-Secures-CE-Mark-for-Use-in-Europe. Accessed September 24, 2023.
81. The European Association of Medical devices Notified Bodies. Team-NB Position Paper. Data generated from 'Off-Label' Use of a device under the EU Medical Device Regulation 2017/745 2022. https://www.team-nb.org/wp-content/uploads/2022/10/Team-NB-PositionPaper-Off-LabelUse-V1-20221005.pdf. Accessed September 24, 2023.
82. Medicines and Healthcare products Regulatory Agency. Government response to consultation on the future regulation of medical devices in the United Kingdom 2022.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1085333/Government_response_to_consultation_on_the_future_regulation_of_medical_devices_in_the_United_Kingdom.pdf. Accessed September 24, 2023.

83. Freckmann G, Eichenlaub M, Waldenmaier D, et al. Clinical Performance Evaluation of Continuous Glucose Monitoring Systems: A Scoping Review and Recommendations for Reporting. J Diabetes Sci Technol 2023;0(0). doi:10.1177/19322968231190941
84. Huo Z, Mortazavi BJ, Chaspari T, Deutz N, Ruebush L, Gutierrez-Osuna R. Predicting the meal macronutrient composition from continuous glucose monitors. 2019 IEEE EMBS International Conference on Biomedical & Health Informatics (BHI), Chicago, IL, USA:1-4. doi:10.1109/BHI.2019.8834488
85. Simpson CC, Mazzeo SE. Calorie counting and fitness tracking technology: Associations with eating disorder symptomatology. Eating Behav 2017;26:89-92. doi: 10.1016/j.eatbeh.2017.02.002
86. Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Hainemann L. Improving the clinical value and utility of CGM systems: issues and recommendations: A joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. Diabetologia 2017;60(12):2319-2328. doi:10.1007/s00125-017-4463-4