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CONTINUOUS GLUCOSE MONITORING FOR THE DETECTION OF PREDIABETES AND EARLY DYSGLYCEMIA

Ph.D. Thesis

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***“An investment in knowledge, always pays the best
interest.”***

Benjamin Franklin

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS	5
2. STUDENT PROFILE.....	6
2.1. Vision and mission statement.....	6
2.2. Specific goals	6
2.3. Scientometrics.....	6
2.4. Future plans.....	7
3. SUMMARY OF THE THESIS.....	8
4. GRAPHICAL ABSTRACT	9
4.1. Study 1	9
4.2. Study 2 [29]	9
5. INTRODUCTION	10
5.1. Prediabetes as a growing global health challenge.....	10
5.2. Limitations of current approaches for identifying prediabetes	10
5.3. Continuous glucose monitoring	11
5.4. Knowledge gap and rationale	12
6. OBJECTIVES.....	13
6.1. Study 1	13
6.2. Study 2	13
7. METHODS.....	14
7.1. Study 1	14
7.1.1. Eligibility criteria	14
7.1.2. Search strategy and information sources.....	14
7.1.3. Study selection and data extraction.....	14
7.1.4. Risk of bias assessment.....	15
7.1.5. Statistical methods.....	15
7.2. Study 2	16
7.2.1. Study design	16
7.2.2. Setting.....	16
7.2.3. Participants and eligibility criteria	16
7.2.4. Variables and outcome definitions	17
7.2.5. Efforts to minimize bias	17
7.2.6. Statistical methods.....	17
8. RESULTS	19

8.1. Study 1	19
8.1.1. Search and selection	19
8.1.2. Basic characteristics of the included studies and participants.....	19
8.1.3. Primary outcome (MAGE).....	24
8.1.4. Secondary outcomes.....	24
8.1.5. Risk of bias assessment	24
8.1.6. Additional analyses	26
8.2. Study 2	28
8.2.1. Selection	28
8.2.2. Basic characteristics of the included studies and participants.....	29
8.2.3. Discordance between HbA1c and FPG.....	30
8.2.4. Relationship between CGM Metrics and Laboratory Markers	31
8.2.5. Classification performance of individual and combined CGM metrics.....	32
8.2.6. Relative contribution of CGM metrics.....	35
8.2.7. Additional analyses	36
8.2.8. Bias and quality assessment	37
9. DISCUSSION.....	38
9.1. Summary of findings	38
9.2. Comparison with previous studies	38
9.3. Discordance between HbA1c and FPG	39
9.4. Physiological interpretation of CGM-derived metrics.....	39
9.5. Why was classification performance moderate rather than high?	40
9.6. Public health and clinical implications	41
9.7. Strengths	41
9.7.1. Study 1.....	41
9.7.2. Study 2.....	41
9.8. Limitations	42
9.8.1. Study 1.....	42
9.8.2. Study 2.....	42
10. CONCLUSIONS	44
10.1. Study 1	44
10.2. Study 2	44
11. IMPLICATIONS FOR PRACTICE	45
11.1. Study 1	45

11.2. Study 2	45
12. IMPLICATIONS FOR RESEARCH.....	46
12.1. Study 1	46
12.2. Study 2	46
13. IMPLICATIONS FOR POLICYMAKERS	47
13.1. Study 1	47
13.2. Study 2	47
14. FUTURE PERSPECTIVES	48
15. REFERENCES	49
16. BIBLIOGRAPHY	55
16.1. Publications related to the thesis.....	55
16.2. Publications not related to the thesis.....	55
17. ACKNOWLEDGEMENTS.....	56

1. LIST OF ABBREVIATIONS

ADA	American Diabetes Association
ADAG	A1C-derived average glucose
BMI	Body mass index
CGM	Continuous glucose monitoring
CI	Confidence interval
CV	Coefficient of variation
EASD	European Association for the Study of Diabetes
FPG	Fasting plasma glucose
GMI	Glucose management indicator
HbA1c	Hemoglobin A1c
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
MAGE	Mean amplitude of glycemic excursions
MARD	Mean absolute relative difference
MD	Mean difference
OGTT	Oral glucose tolerance test
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
SD	Standard deviation
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAR	Time above range
TITR	Time in tight range
TIR	Time in range

2. STUDENT PROFILE

2.1. Vision and mission statement

My vision is to reduce the global incidence of diabetes mellitus through earlier detection and targeted prevention strategies. My mission is to identify and address dysglycemia at its earliest stages, before it progresses to overt diabetes, by utilizing data-driven and personalized approaches to metabolic monitoring and risk assessment.



2.2. Specific goals

The overall aim of my PhD projects was to investigate the utility of continuous glucose monitoring (CGM) in the detection and characterization of early dysglycemia. Specifically, the project aimed to: (1) compare CGM-derived glycemetic metrics between individuals with prediabetes and normoglycemia; (2) quantify the degree of discordance between conventional laboratory markers used for prediabetes detection, particularly hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG); and (3) evaluate the diagnostic performance of selected CGM metrics relative to these established glycemetic markers. Ultimately, the projects aimed to explore the potential role of CGM as a complementary tool for the early identification of dysglycemia and support more personalized, prevention-oriented approaches to metabolic risk assessment.

2.3. Scientometrics

Number of all publications:	3
Cumulative IF:	14.4
Av IF/publication:	4.8
Ranking (SCImago):	1 D1, 2 Q1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	9.5
Av IF/publication:	4.75
Ranking (SCImago):	1 D1, 1 Q1
Number of citations on Google Scholar:	3

Number of citations on MTMT (independent):	1
H-index:	1

The student's detailed bibliography can be found on page 55.

2.4. Future plans

My future plans include continuing my research in early dysglycemia detection and prevention, with a particular focus on advancing the clinical application of continuous glucose monitoring in nondiabetic populations. I aim to expand my work through prospective and interventional studies and to further develop CGM-based risk stratification and personalized lifestyle interventions.

As part of these efforts, I have been invited to join Stanford University as a visiting researcher in 2027 for a five-month research period under the supervision of Professor Michael Snyder, one of the pioneers of precision health and continuous glucose monitoring research. This opportunity will provide a unique environment to further investigate the role of CGM in early metabolic dysfunction, strengthen international collaborations, and accelerate the translational impact of my research.

My long-term goal is to contribute to the development of evidence-based strategies that enable earlier identification, prevention, and reversal of dysglycemia through personalized and data-driven approaches.

In parallel with my own research activities, I intend to contribute to the development of future clinical researchers through my role as a methodology supervisor at the Centre for Translational Medicine. By supporting study design, evidence synthesis, and clinical research methodology, I hope to facilitate high-quality translational research and promote the application of rigorous scientific principles in healthcare research.

3. SUMMARY OF THE THESIS

Prediabetes affects approximately one in three adults worldwide, yet most affected individuals remain undiagnosed. As an intermediate state of dysglycemia, prediabetes is associated with an increased risk of progressing to type 2 diabetes mellitus (T2DM) and its associated complications. Early identification is therefore essential to enable timely preventive intervention.

Current clinical guidelines recommend HbA1c, FPG, and oral glucose tolerance test (OGTT) measurements. However, these methods provide only static or averaged assessments of glycemic status and may fail to capture early disturbances in glucose regulation. Furthermore, as demonstrated in the second study of this thesis, HbA1c and FPG identify substantially different subgroups of individuals with prediabetes, which may contribute to underdiagnosis and delayed preventive care.

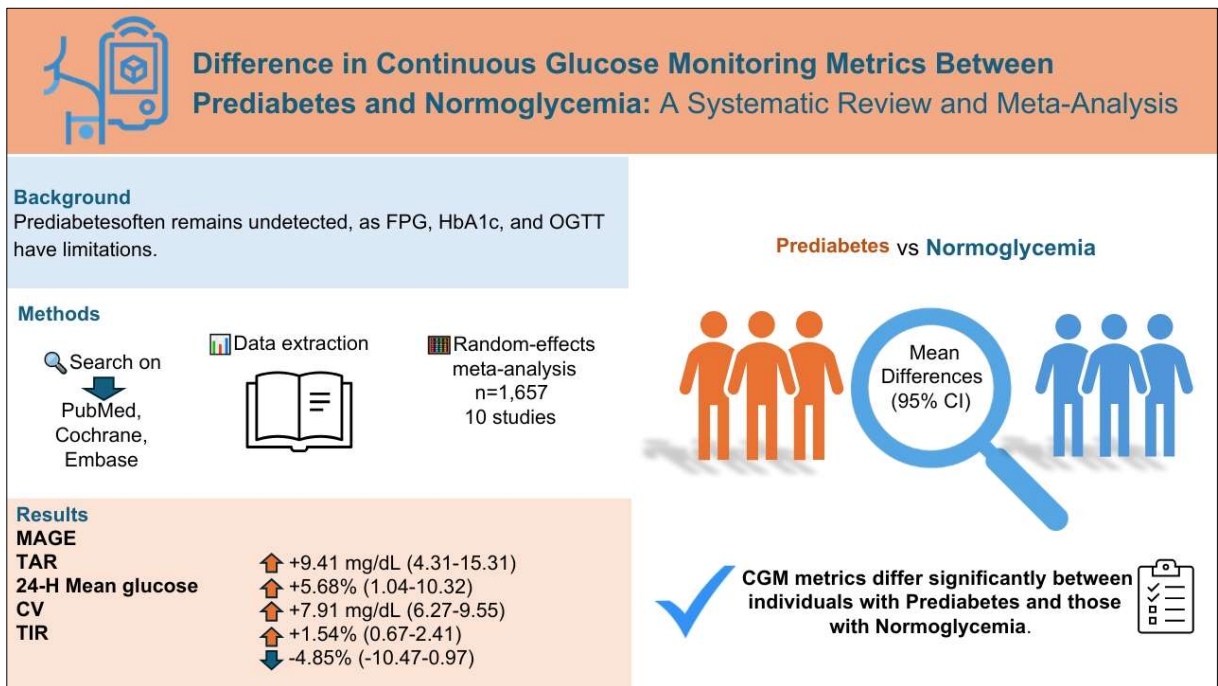
CGM, originally developed for glucose management in type 1 diabetes mellitus (T1DM), has recently emerged as a promising tool for evaluating glycemic patterns in nondiabetic populations. Unlike conventional glycemic markers, CGM provides continuous, high-resolution measurements of glucose dynamics and may offer additional insight into early metabolic dysregulation.

The first study demonstrated that several CGM-derived metrics can effectively differentiate prediabetes from those with normoglycemia. The second study further revealed substantial discordance between conventional glycemic markers (HbA1c and FPG) and showed that selected CGM metrics achieved diagnostic performance comparable to these traditional measures when evaluated against an independent glycemic reference standard.

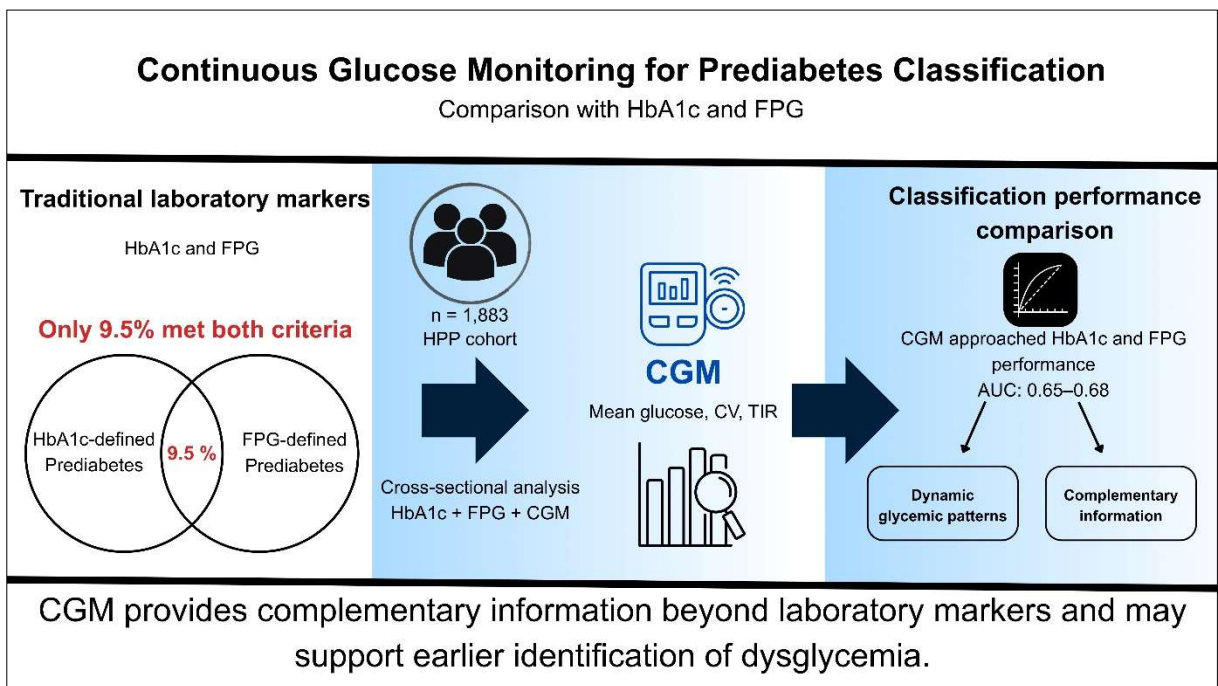
Together, these findings support the potential role of CGM as a complementary tool for the earlier detection and characterization of dysglycemia. They provide a strong rationale for future longitudinal and interventional studies investigating the integration of CGM into prediabetes screening and risk-stratification strategies, with the ultimate goal of enabling earlier and more personalized preventive care.

4. GRAPHICAL ABSTRACT

4.1. Study 1



4.2. Study 2 [29]



5. INTRODUCTION

5.1. Prediabetes as a growing global health challenge

Prediabetes is an intermediate metabolic state characterized by glucose levels above the normal range but below the diagnostic threshold for T2DM [1]. It affects more than one-third of adults worldwide and has emerged as a major public health challenge due to its high prevalence, asymptomatic nature, and association with future metabolic and cardiovascular complications [2,3]. Importantly, most affected individuals remain unaware of their condition until more advanced metabolic abnormalities develop [4].

Prediabetes is associated with an increased risk of progression to T2DM, cardiovascular disease, chronic kidney disease, neuropathy, and premature mortality [5–7]. However, progression from normoglycemia to T2DM typically occurs over several years, providing a valuable opportunity for preventive interventions [2]. Lifestyle modification programs have consistently demonstrated that early identification and treatment can significantly reduce the risk of future diabetes development [9,10]. Consequently, accurate identification of individuals with early dysglycemia remains a major clinical priority.

5.2. Limitations of current approaches for identifying prediabetes

Current clinical guidelines recommend FPG, HbA1c, and OGTT for the identification of prediabetes [1]. Although these tests are widely used, each captures different aspects of glucose physiology and has important limitations.

FPG reflects fasting glycemia at a single time point and may fail to detect abnormalities occurring predominantly in the postprandial period [15]. HbA1c reflects average glycemia over the preceding two to three months and does not require fasting [6]; however, it may be influenced by factors unrelated to glucose metabolism, including erythrocyte turnover, anemia, ethnicity, and certain medical conditions [16]. OGTT is generally considered the most sensitive conventional method because it directly evaluates the physiological response to a standardized glucose challenge [17]; however, its time-consuming and resource-intensive nature limits its routine use in clinical practice [15].

Importantly, growing evidence suggests that dysglycemia develops gradually along a biological continuum rather than a discrete transition from health to disease [11]. Metabolic abnormalities involving insulin sensitivity, beta-cell function, hepatic glucose

metabolism, and postprandial glucose regulation may begin years before conventional diagnostic thresholds are reached [5]. Consequently, individuals with similar HbA1c or FPG values may exhibit markedly different patterns of glucose regulation and future metabolic risk [12]. One of the major challenges in prediabetes detection is the limited agreement between conventional laboratory markers. Numerous studies have demonstrated substantial discordance between HbA1c-, FPG-, and OGTT-based classifications of prediabetes [18–20]. Because these markers reflect different physiological processes, individuals identified as having prediabetes by one diagnostic criterion are frequently not classified as prediabetic by another [18-20]. This discordance may contribute to inconsistent prevalence estimates, delayed diagnosis, and uncertainty regarding optimal screening strategies [21].

5.3. Continuous glucose monitoring

CGM enables near-continuous measurement of interstitial glucose concentrations throughout daily life [22]. Modern CGM systems provide glucose readings every few minutes, generating detailed information regarding glucose patterns, glycemic variability, and responses to meals, physical activity, sleep, and other environmental influences [23].

Unlike conventional laboratory markers, CGM captures dynamic aspects of glucose regulation. Metrics such as mean glucose, time above range (TAR), time in range (TIR), coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE) offer insight into early metabolic abnormalities that are not reflected by HbA1c or FPG alone [23].

Although CGM was initially developed for individuals with diabetes mellitus [22, 24], increasing attention has focused on its potential application in nondiabetic populations. Numerous randomized clinical trials have demonstrated improvements in glycemic control, reductions in hypoglycemia, and enhanced quality of life among individuals using CGM [25]. Several observational studies have reported higher glycemic variability, greater postprandial glucose excursions, and greater hyperglycemic exposure among individuals with prediabetes compared with normoglycemic controls [26–28].

5.4. Knowledge gap and rationale

Despite increasing interest in CGM, its role in prediabetes detection remains incompletely understood.

First, no comprehensive quantitative synthesis had evaluated whether CGM-derived metrics consistently differ between individuals with prediabetes and normoglycemia across the available literature.

Second, although substantial discordance exists between HbA1c and FPG-based definitions of prediabetes, relatively little is known about how CGM-derived metrics perform in relation to these conventional laboratory markers in large real-world populations.

Addressing these knowledge gaps may clarify whether CGM provides clinically meaningful information beyond traditional diagnostic approaches and may contribute to improved strategies for identifying individuals at increased metabolic risk. Therefore, the present thesis aimed to investigate the potential role of CGM in the detection and characterization of prediabetes and early dysglycemia through a systematic review and meta-analysis and a large real-world cohort study.

6. OBJECTIVES

6.1. Study 1

To systematically evaluate differences in CGM-derived metrics between individuals with prediabetes and normoglycemia, thereby providing evidence to support the potential role of CGM in individuals without diabetes [28].

6.2. Study 2

To quantify the discordance between HbA1c and FPG in prediabetes identification, and to investigate the diagnostic performance of selected CGM-metrics relative to these conventional glycemic markers [29].

7. METHODS

The first study was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024608658) and conducted in accordance with the Cochrane Handbook [30] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [31].

The second study was a cross-sectional registry analysis of the Human Phenotype Project (HPP) cohort [32] and was reported in accordance with the STROBE guidelines [33].

7.1. Study 1

7.1.1. Eligibility criteria

The PECO (Population, Exposure, Comparator, Outcome) framework was used to construct the eligibility criteria. Observational studies and randomized controlled trials enrolling nondiabetic individuals undergoing CGM measurements were eligible for inclusion. CGM metrics of prediabetics (HbA1c 5.7–6.5%, fasting glucose 100–125 mg/dL, or 2-h OGTT 140–199 mg/dL) were compared with normoglycemic individuals [1]. Studies including patients with diabetes, severe comorbidities, pregnancy, or glucose-lowering therapy were excluded.

7.1.2. Search strategy and information sources

A systematic search was conducted in PubMed, EMBASE, and CENTRAL on September 3, 2025 without any language restrictions. The following search key was used: ((“continuous” AND “glucose” AND “monitoring”) OR “CGM”) AND (“HbA1c” OR (“Hemoglobin A1c”) OR (“fasting” AND “blood” AND “glucose”) OR “FBG” OR “OGTT” OR (“oral” AND “glucose” AND “tolerance” AND “test”)). Additional studies were identified through reference and citation screening of the included articles.

7.1.3. Study selection and data extraction

Records from the systematic search were imported to EndNote 21, where duplicates were removed. The selection process was subsequently conducted using the Rayyan Intelligent Systematic Review program. Each stage of the selection process was performed independently by four reviewers. The primary investigator (G.R.) screened all records, while the other reviewers (J.N., Sha.J., and Shi.J.) each independently screened a part of

the dataset, ensuring that each record was assessed by at least two reviewers. After each stage of the selection process, inter-reviewer agreement was evaluated by calculating the Cohen's Kappa coefficient (κ).

Relevant data from the eligible studies were extracted independently by four authors (G.R., J.N., Sha.J., and Shi.J.). All extracted data were recorded in a standardized Excel spreadsheet (Office 365, Microsoft, USA). The following data were extracted: study characteristics, demographics, and CGM metrics (MAGE, TAR, TIR, CV, mean glucose).

Any disagreements were resolved by consensus or with the help of a fourth reviewer (E.S.).

7.1.4. Risk of bias assessment

Three authors (G.R., Sha.J., and Shi.J.) independently assessed the risk of bias using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [34]. The ROBINS-I tool evaluates bias across seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Each domain was judged as having low, moderate, serious, or critical risk of bias, or no information. An overall risk-of-bias judgment was assigned to each study according to ROBINS-I guidance. Any disagreements were resolved by consensus or with the help of a fourth reviewer (J.L.).

7.1.5. Statistical methods

Effect sizes were expressed as mean differences (MDs) with 95% confidence intervals (CIs). For each study, sample size, mean, and standard deviation (SD) were extracted or derived separately for prediabetes and normoglycemia groups, and MDs were calculated as the difference between group means. When necessary, means and standard deviations were estimated from reported summary statistics using established methods. [35,36]

Pooled estimates were generated using inverse-variance random-effects models when at least two studies contributed data. Between-study variance (τ^2) was estimated using the restricted maximum-likelihood method, and heterogeneity was quantified with I^2 . Confidence intervals for τ^2 were obtained using the Q-profile approach.

Subgroup analyses were performed by device type, ethnicity, and monitoring duration, and sensitivity analyses excluded high-risk studies. Additional subset analyses were conducted, including only studies published from 2019 onward.

All analyses were performed in R (version 4.3) [37] using the meta and dmetar packages [38,39].

7.2. Study 2

7.2.1. Study design

A cross-sectional analysis was conducted to investigate the classification performance of HbA1c and FPG for identifying prediabetes, and to evaluate the comparative performance of individual and combined CGM metrics using six clinically selected parameters. The discriminative ability of these CGM-derived metrics was compared with that of HbA1c and/or FPG for identifying dysglycemia in a real-world cohort [29].

7.2.2. Setting

All data used in this study were derived from the HPP, a large-scale, prospective, longitudinal cohort established by the Weizmann Institute of Science to investigate determinants of human health and disease. Participants undergo extensive phenotyping including laboratory assessments, CGM, lifestyle questionnaires, microbiome profiling, and additional clinical measurements. Detailed descriptions of the cohort design and recruitment procedures have been published previously [32].

7.2.3. Participants and eligibility criteria

Participants were selected from the HPP, a prospective population-based cohort established by the Weizmann Institute of Science. Eligible individuals were required to have at least 7 consecutive days of CGM data and available HbA1c and FPG measurements obtained within 90 days of the CGM monitoring period. Individuals were excluded if they had diabetes mellitus, defined as HbA1c $\geq 6.5\%$ or FPG ≥ 126 mg/dL [1], were using glucose-lowering medication, or were pregnant at the time of CGM monitoring [29].

7.2.4. Variables and outcome definitions

Prediabetes status was defined using four laboratory-based reference definitions: (1) impaired HbA1c (5.7–6.4%), (2) impaired FPG (5.6–6.9 mmol/L), (3) the intersection of these definitions (both HbA1c and FPG in the prediabetes range), and (4) the union of these definitions (HbA1c or FPG in the prediabetes range) [29]. These reference definitions were used as analytical classification criteria with increasing diagnostic stringency, ranging from the least restrictive definition (HbA1c or FPG) to the most restrictive definition (HbA1c and FPG), rather than as clinical diagnostic criteria. The union definition is consistent with current ADA recommendations, in which either HbA1c or FPG is sufficient for prediabetes classification [1].

Predictor variables included HbA1c, FPG, individual CGM-derived metrics, and a combined CGM metric set. The combined CGM metric set was selected based on clinical relevance and consisted of mean glucose, CV, TITR, TAR, GMI, and MAGE. The TITR range (63–140 mg/dL) was defined according to the standardized HPP analytical pipeline and was consistent with previous analyses performed in the same cohort [29].

In addition to evaluating each CGM metric individually, a combined model incorporating all six CGM-derived metrics was constructed to assess their joint classification performance.

7.2.5. Efforts to minimize bias

The broad catchment of the registry, limited selection bias, and standardized on-site measurements minimized measurement bias. Only complete-case records were analyzed; missingness was <5 % for all variables [29].

7.2.6. Statistical methods

Binary classification models were developed using multiple machine learning algorithms to evaluate the ability of HbA1c, FPG and CGM metrics to classify prediabetes across four laboratory-based reference definitions. Both individual CGM metrics and combined CGM-based models were evaluated. Model performance was assessed using repeated cross-validation to estimate discrimination in independent test samples [29].

Classification performance was quantified using the area under the receiver operating characteristic curve (AUC). Correlations between CGM metrics and laboratory markers were assessed using Pearson correlation coefficients.

Analyses were performed using Python (version 3.10), scikit-learn (version 1.4.1), and optbinning (version 0.20.1) [40].

8. RESULTS

8.1. Study 1

8.1.1. Search and selection

In the first study, we identified 21,764 studies. After duplicate removal and eligibility screening, 12 studies remained. An additional four studies were included after citation tracking. In total, 16 studies were selected for the systematic review, with ten of these studies included in the meta-analysis (**Figure 1**) [28].

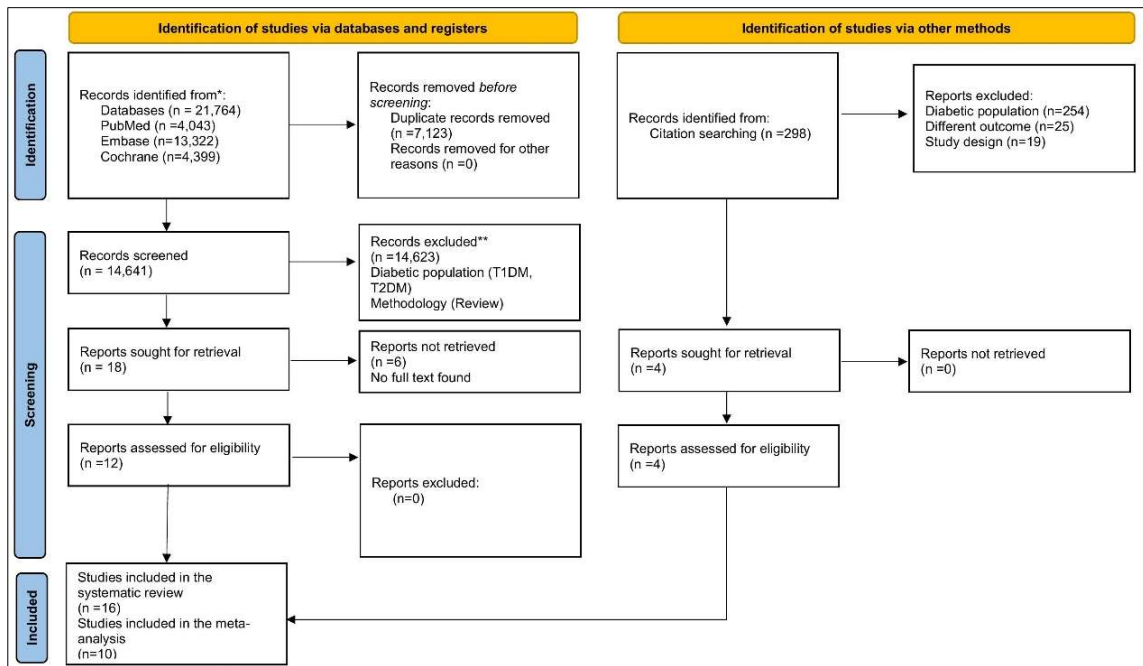


Figure 1. PRISMA 2020 flowchart representing the detailed systematic search and study selection process [28]

8.1.2. Basic characteristics of the included studies and participants

Sixteen studies (2010–2024) were included, totalling 1,657 participants in the quantitative synthesis. Most used prospective cross-sectional designs with CGM over defined monitoring periods were conducted in the USA, Japan, Spain, China, Greece, and Sri Lanka. All studies used ADA/EASD-approved devices (Abbott Freestyle Libre, Dexcom G6/G7, Medtronic Guardian). The main characteristics of the included studies are presented in **Table 1** [28].

Table 1. Characteristics of the included studies and participants [28]

Author (year)	Study site	Total number of patients (female%)	Age in years (SD or min- max) ‡	Prediabetes group number of patients (female %)	Prediabetes group BMI (SD)	Normoglycemia group number of patients (female%)	Normogly- cemia group BMI	Calibration method (F/N) ¹	MARD value range ²	High- risk cohort (Y/N) ³	CGM mode (blinded/ unblinded) ⁴
Rizos et al. 2024 [41]	Greece	36 (61.1)	51 (31.3- 76.3)	18 (61.1)	27.34 (3.8)	18 (61.1)	21.13 (3.2)	N	9.1- 16.3	N	U
Spartano et al. 2024 [42]	USA	1,023 (64.5)	58.5 (NA)	463 (45.8)	29.3 (5.1)	560 (64.1)	26.5 (4.8)	F	8.2- 10.1	N	B
Kashiwagi et al. 2023 [43]	Japan	40 (50)	40.3 (NA)	14 (43)	21.5 (2.1)	26 (54)	21.1 (2.8)	F	7.8-9.2	N	NA
Dorcely et al. 2022 [27]	USA	15 (20)	50 (14)	8 (0)	NA	7 (43)	31.14 (5.7)	F	7.8-9.2	Y	U

Author (year)	Study site	Total number of patients (female%)	Age in years (SD or min- max) ‡	Prediabetes group number of patients (female %)	Prediabetes group BMI (SD)	Normoglycemia group number of patients (female%)	Normogly- cemia group BMI	Calibration method (F/N) ¹	MARD value range ²	High- risk cohort (Y/N) ³	CGM mode (blinded/ unblinded) ⁴
Rodriguez- S et al. 2018 [26]	Spain	322 (57.5)	44 (13)	68 (57.4)	NA	254 (57.5)	26.3 (4.2)	N	9.1- 16.3	N	U
Hanefeld et al. 2014 [44]	USA	80 (34)	NA	42 (21.42)	28.87 (4.12)	28 (53)	28.35 (3.47)	N	9.1- 16.3	N	NA
Madhu et al. 2013[45]	Sri Lanka	60 (65)	46.3 (8.8)	20 (65)	28.92 (2.42)	20 (65)	29.01 (4.2)	N	9.1- 16.3	Y	U
Xu et al. 2012[46]	China	40 (55)	38 (8)	29 (55)	NA	11 (NA)	NA	N	9.1- 16.3	N	NA
Nomura et al. 2011[47]	Japan	29 (14)	38 (6.9)	7 (14)	NA	22 (14)	25 (2.3)	N	9.1- 16.3	N	NA

Author (year)	Study site	Total number of patients (female%)	Age in years (SD or min- max) ‡	Prediabetes group number of patients (female %)	Prediabetes group BMI (SD)	Normoglycemia group number of patients (female%)	Normogly- cemia group BMI	Calibration method (F/N) ¹	MARD value range ²	High- risk cohort (Y/N) ³	CGM mode (blinded/ unblinded) ⁴
Chakarova et al. 2019[48]	Bulgaria	42 (NA)	NA (NA)	NA	30,3 (5.3)	18 (77.7)	24,8 (6.9)	F	7.8-9.2	Y	B
DuBose et al. 2022[49]	USA	39 (51)	4.4 (1.4)	NA	NA	NA	NA	F	8.2- 10.1	N	NA
Sundberg et al. 2016[50]	Sweden	15 (66.6)	5.4 (1.6)	NA	NA	NA	NA	F	8.2- 10.1	Y	NA
Fox et al. 2010[51]	USA	74 (69)	(9-65)	NA	NA	NA	NA	F, N	8.2- 16.3	Y	B
Shah et al. 2019[52]	USA	153 (101)	31 (21)	NA	NA	NA	NA	F	8.2- 10.1	Y	B

Author (year)	Study site	Total number of patients (female%)	Age in years (SD or min- max) ‡	Prediabetes group number of patients (female %)	Prediabetes group BMI (SD)	Normoglycemia group number of patients (female%)	Normogly- cemia group BMI	Calibration method (F/N) ¹	MARD value range ²	High- risk cohort (Y/N) ³	CGM mode (blinded/ unblinded) ⁴
Shilo et al. 2024[53]	Israel	8315 (54.4)	51.3 (7.58)	NA	NA	NA	NA	F	7.8-9.2	N	NA
Borg et al. 2010[54]	USA, Europe, Africa	80 (69)	41 (13.8)	NA	NA	NA	NA	N	9.1- 16.3	N	NA

‡ Parameters are presented as mean ± standard deviation, or median with minimum–maximum values.

Abbreviations: BMI: body mass index; CGM: continuous glucose monitor; MARD: mean absolute relative difference; USA: United States of America

¹F = factory-calibrated CGM, N = manually calibrated CGM.

²The MARD values were not reported in the listed studies but were added based on validation and pivotal trials of the respective CGM devices [25,55, 56]

³High-risk (risk-enriched) cohort = intentional recruitment based on baseline risk: family history of diabetes (≥1 first-degree relative) and/or obesity (BMI ≥30 kg/m²).

⁴B = blinded (professional CGM; participants cannot view readings), U = unblinded (real-time CGM), NA = not available.

8.1.3. Primary outcome (MAGE)

Eight studies (n = 602) showed significantly higher MAGE in prediabetes compared with normoglycemia, with a pooled MD of 9.81 mg/dL (95% CI: 4.31–15.31) (**Figure 2A**). Although heterogeneity was high ($I^2 = 77\%$), all studies reported elevated MAGE in prediabetes [28].

8.1.4. Secondary outcomes

Other CGM metrics generally demonstrated worse glycemic profiles among individuals with prediabetes than among those with normoglycemia. Five studies (n = 1,484) reported TAR >140 mg/dL, showing significantly greater hyperglycemic exposure in prediabetes (MD = 5.68%; 95% CI, 1.04–10.32; $I^2 = 90\%$) (**Figure 2B**). Similarly, eight studies (n = 1,606) reported significantly higher mean 24-hour glucose levels in prediabetes (MD = 7.91 mg/dL; 95% CI, 6.27–9.55; $I^2 = 10\%$) (**Figure 2C**) [28].

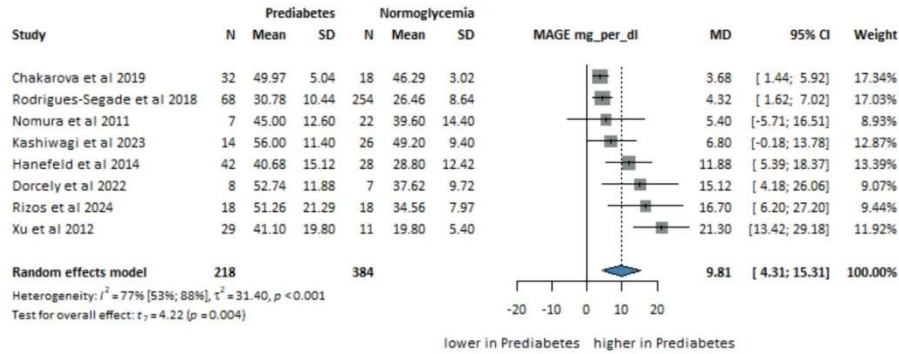
Six studies (n = 557) evaluating glycemic variability found significantly higher CV values among individuals with prediabetes (MD = 1.54%; 95% CI, 0.67–2.41; $I^2 = 0\%$) (**Figure 3A**). In contrast, four studies (n = 1,421) reported a non-significant trend toward lower TIR (70–140 mg/dL) in prediabetes compared with normoglycemia (MD = -4.75%; 95% CI, -10.47 to 0.97; $I^2 = 89\%$) (**Figure 3B**) [28].

8.1.5. Risk of bias assessment

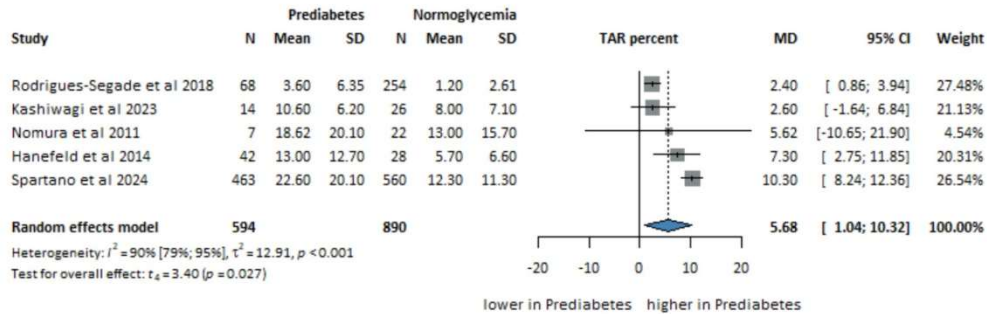
Using ROBINS-I [34], three studies were rated as low risk, six as moderate, and one as serious, primarily due to participant selection and intervention classification. Excluding this single high-risk study [27] from the sensitivity analysis did not meaningfully alter the pooled estimates, indicating the robustness of the results. Variability in CGM monitoring duration (3–14 days) may also have contributed to between-study differences.

Publication bias could not be assessed because fewer than ten studies were included. Heterogeneity was moderate to high in several studies. To explore potential sources, we conducted subgroup analyses [28].

2A



2B



2C

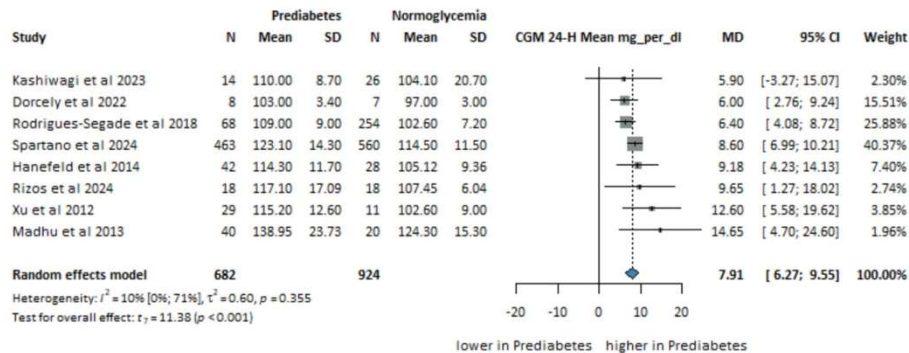


Figure 2. Mean Difference in (A) MAGE (mg/dL, n=602), (B) TAR (%; n=1,484) and (C) 24-h CGM mean (mg/dL, n=1,606) between individuals with Prediabetes and Normoglycemia [28]. *MAGE*: mean amplitude of glycemic excursions; *MD*: mean difference; *SD*: standard deviation; *TAR*: time above range

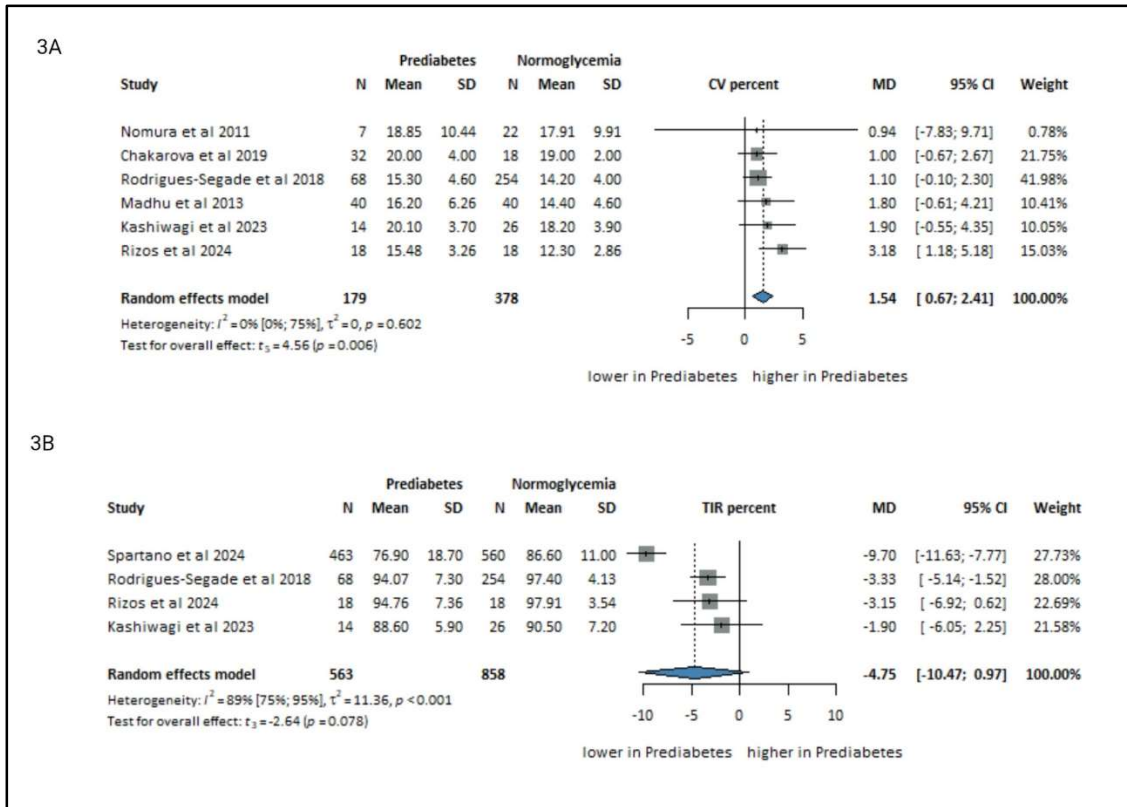


Figure 3. Mean Difference in (A) CV (%; $n=557$) and (B) TIR (%; $n=1,421$) between individuals with Prediabetes and Normoglycemia [28]. *CV*: coefficient of variation; *MD*: mean difference; *SD*: standard deviation; *TIR*: time in range.

8.1.6. Additional analyses

Additional analyses included subgroup and sensitivity analyses to explore sources of heterogeneity. For MAGE, neither device type ($p = 0.816$; $I^2 = 79\%$) nor race ($p = 0.660$; $I^2 = 74\%$) explained heterogeneity, while monitoring duration showed a significant effect (<7 days: MD 14.01 mg/dL vs. ≥ 7 days: 5.80 mg/dL; $p = 0.034$; $I^2 = 51\%$). Leave-one-out analyses identified blinded CGM studies as major contributors to between-study heterogeneity (**Figure 4**) [28]. Excluding the blinded study by Spartano et al. reduced heterogeneity for TIR from $I^2 = 92\%$ to $I^2 = 0\%$ while preserving the direction of the pooled effect. Because standalone CGM systems became widely available after 2018, an additional sensitivity analysis restricted to studies published from 2019 onward was performed. This confirmed the robustness of the primary findings, with 24-hour mean glucose remaining statistically significant (MD 7.84 mg/dL; 95% CI 5.51–10.17). Excluding high-risk studies resulted in only minor changes in the pooled estimates.

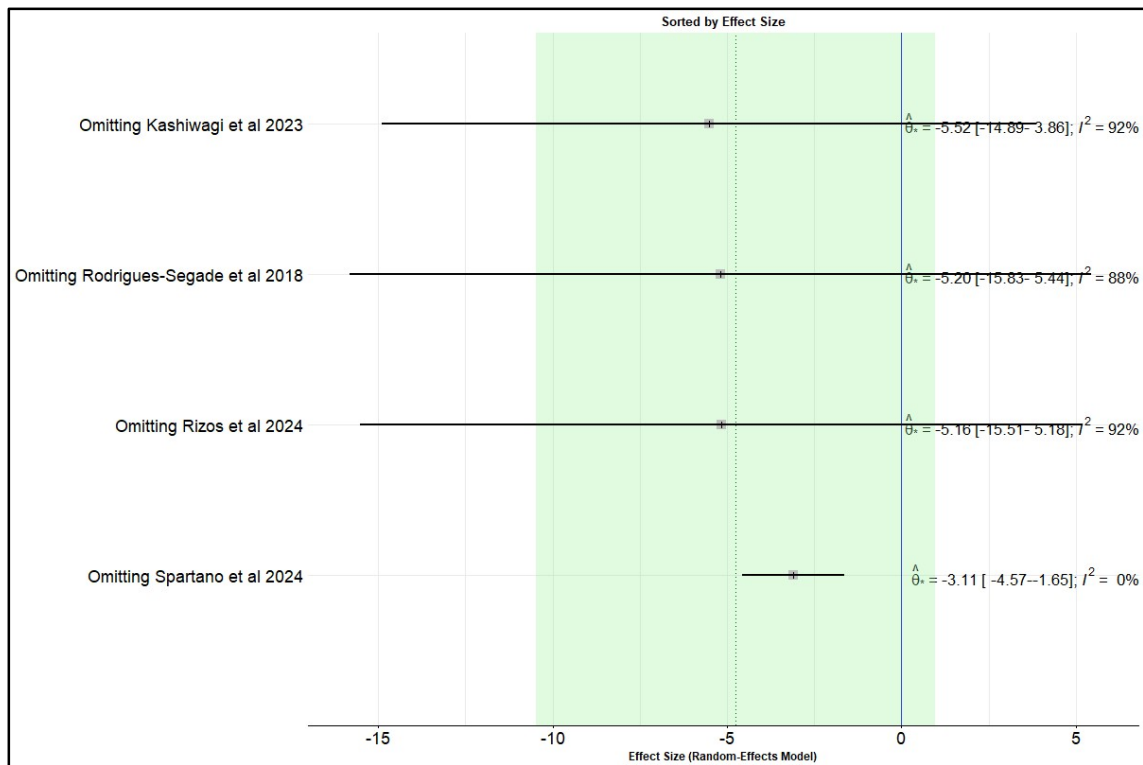


Figure 4. Leave-one-out analysis for time TIR (time in range) [28].

8.2. Study 2

8.2.1. Selection

A total of 9,497 individuals were screened for eligibility. Of these, 7,614 were excluded for one or more of the following reasons: HbA1c and/or FPG measurements obtained more than 90 days from the CGM monitoring period, fewer than seven consecutive days of CGM data, or a diagnosis of diabetes based on HbA1c and/or FPG. The final analytic cohort consisted of 1,883 participants with complete HbA1c, FPG, and CGM data. The participant selection is shown in **Figure 5** [29].

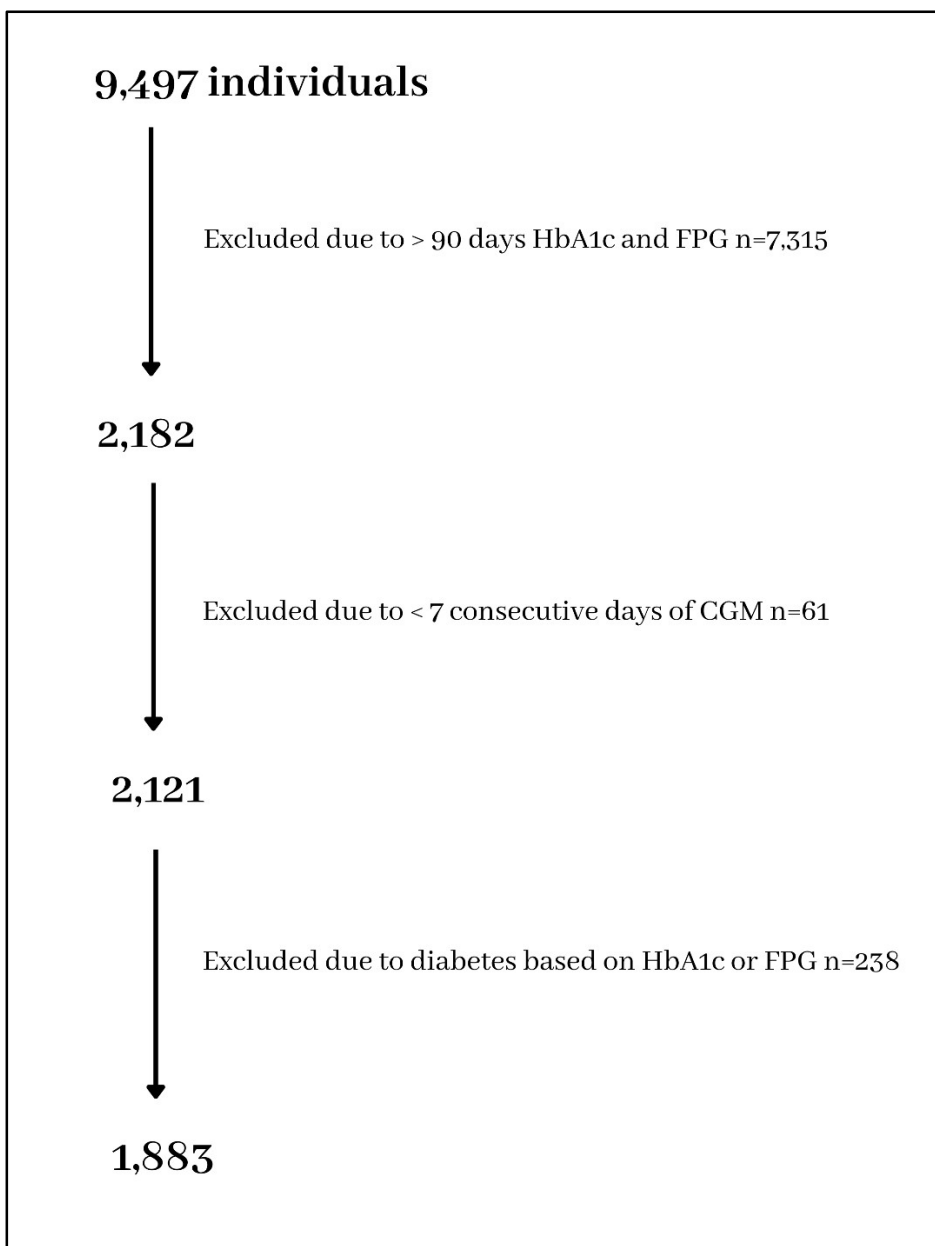


Figure 5. Participant selection flowchart [29]

8.2.2. Basic characteristics of the included studies and participants

Baseline characteristics of the second study population are summarized in **Table 2**. Participants (n = 1,883) classified as prediabetic by both HbA1c and FPG (dual-marker group) tended to be older and exhibited higher BMI, HbA1c, and FPG levels than those identified by either marker alone. Partial discordance was observed between HbA1c- and FPG-defined prediabetes groups, indicating incomplete overlap in classification. CGM-derived TAR, MAGE, and CV values were lowest in the normoglycemic group and highest in the dual-marker prediabetes group [29].

Table 2. Baseline characteristics of study participants [29]

	All	Prediabetes based on HbA1c	Prediabetes based on FPG	Prediabetes based on HbA1c or FPG	Prediabetes based on HbA1c and FPG
Number of patients	1,883	441	445	708	178
Age, years	50.2 (45.0, 56.8)	55.2 (49.2, 61.9)	52.8 (46.5, 59.8)	53.6 (47.2, 60.1)	56.0 (50.0, 62.2)
Female, %	52.5	57.8	44.0	50.8	51.1
BMI	25.5 (23.1, 28.3)	26.9 (24.0, 30.2)	26.8 (24.4, 30.0)	26.7 (24.0, 29.8)	28.0 (25.0, 31.2)
HbA1c, %	5.4 (5.1, 5.6)	5.8 (5.7, 6.0)	5.6 (5.3, 5.8)	5.7 (5.5, 5.9)	5.9 (5.8, 6.1)
FPG (mmol/L)	5.16 (4.83, 5.5)	5.38 (5.05, 5.83)	5.83 (5.66, 6.11)	5.61 (5.27, 5.94)	5.88 (5.72, 6.27)
CGM: 63-140, %	97.2 (94.4, 98.8)	96.3 (93.0, 98.2)	96.7 (93.7, 98.6)	96.7 (93.8, 98.6)	95.4 (91.0, 97.7)
CGM > 140, %	0.8 (0.2, 2.4)	1.9 (0.6, 4.7)	1.4 (0.4, 4.5)	1.4 (0.4, 4.1)	3.2 (0.9, 6.5)
MAGE mmol/L	1.97 (1.7, 2.37)	2.20 (1.84, 2.72)	2.07 (1.72, 2.61)	2.12 (1.76, 2.60)	2.32 (1.87, 2.92)
CV, %	15.8 (13.7, 18.4)	16.8 (14.2, 19.7)	15.6 (13.3, 18.8)	16.2 (13.8, 18.9)	16.7 (14.1, 20.0)

	All	Prediabetes based on HbA1c	Prediabetes based on FPG	Prediabetes based on HbA1c or FPG	Prediabetes based on HbA1c and FPG
GMI, mmol/L	5.5 (5.4, 5.7)	5.6 (5.5, 5.8)	5.6 (5.5, 5.8)	5.6 (5.4, 5.8)	5.7 (5.6, 5.9)
Mean CGM, mmol/L	5.12 (4.8, 5.49)	5.32 (4.98, 5.73)	5.36 (5.01, 5.75)	5.31 (4.95, 5.68)	5.59 (5.21, 5.95)
Time between HbA1c and CGM measurement, days	32.0 (16.0, 56.0)	35.0 (19.0, 59.0)	35.0 (18.0, 63.0)	35.0 (18.0, 60.2)	36.5 (20.0, 63.8)
Time between FPG and CGM measurement, days	32.0 (16.0, 56.0)	35.0 (19.0, 58.0)	35.0 (18.0, 62.0)	35.0 (18.0, 58.2)	37.0 (20.2, 63.0)

Data are presented as median (interquartile range) or percentage, where indicated.

HbA1c-defined prediabetes: HbA1c 5.7–6.4% with normal FPG (<5.6 mmol/L).

FPG-defined prediabetes: FPG 5.6–6.9 mmol/L with normal HbA1c (<5.7%).

HbA1c OR FPG: participants meeting either criterion; HbA1c AND FPG: participants meeting both criteria.

CGM-derived metrics are based on at least seven consecutive days of valid sensor data recorded with the Abbott Freestyle Libre Pro system under free-living conditions.

BMI – body mass index, CGM – continuous glucose monitoring, CV – coefficient of variation, FPG – fasting plasma glucose, GMI – glucose management indicator, HbA1c – hemoglobin A1c, MAGE – mean amplitude glycemic excursions

8.2.3. Discordance between HbA1c and FPG

HbA1c- and FPG-based classifications showed marked discordance, with only 9.5% of participants meeting both prediabetes criteria (**Figure 6**). These findings indicate that HbA1c and FPG capture partially distinct subgroups of individuals at metabolic risk [29].

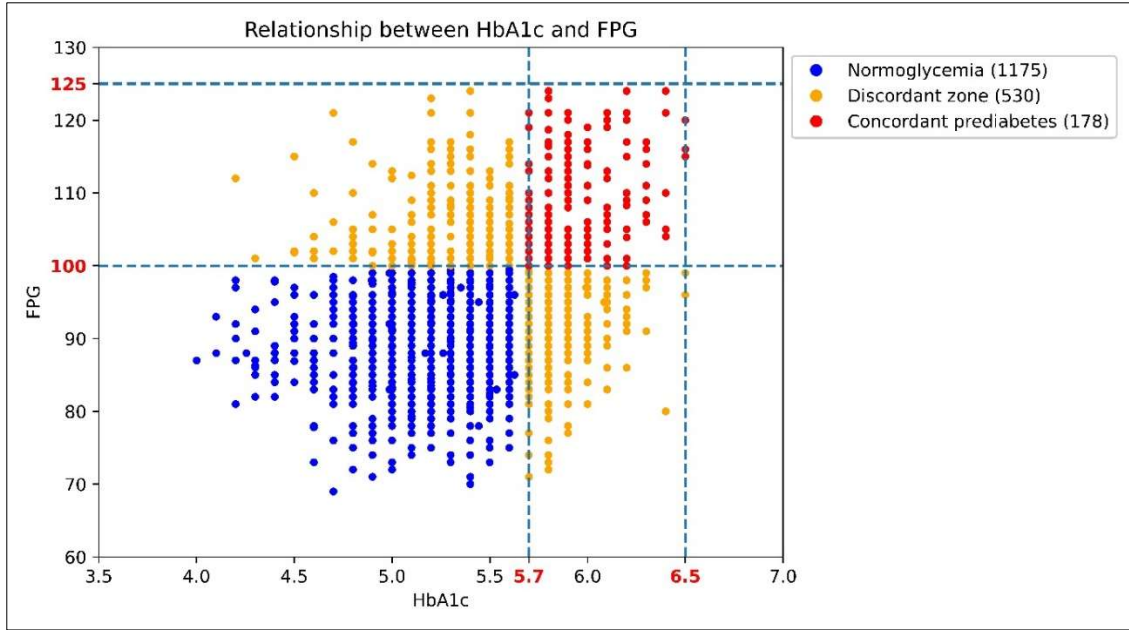


Figure 6. Relationship between HbA1c (%) and FPG (mmol/L) in identifying prediabetes. Scatterplot illustrating partial overlap and discordance between HbA1c (%) and FPG (mmol/L) in identifying prediabetes [29]. *FPG* – *fasting plasma glucose*, *HbA1c* – *hemoglobin A1c*.

8.2.4. Relationship between CGM Metrics and Laboratory Markers

CGM metrics showed moderate correlations with HbA1c and FPG, indicating partial overlap but also distinct glycemic information not captured by laboratory markers (**Figure 7**). Mean glucose, GMI, TAR, and MAGE demonstrated stronger associations with laboratory measures than variability metrics such as CV or TIR [29].

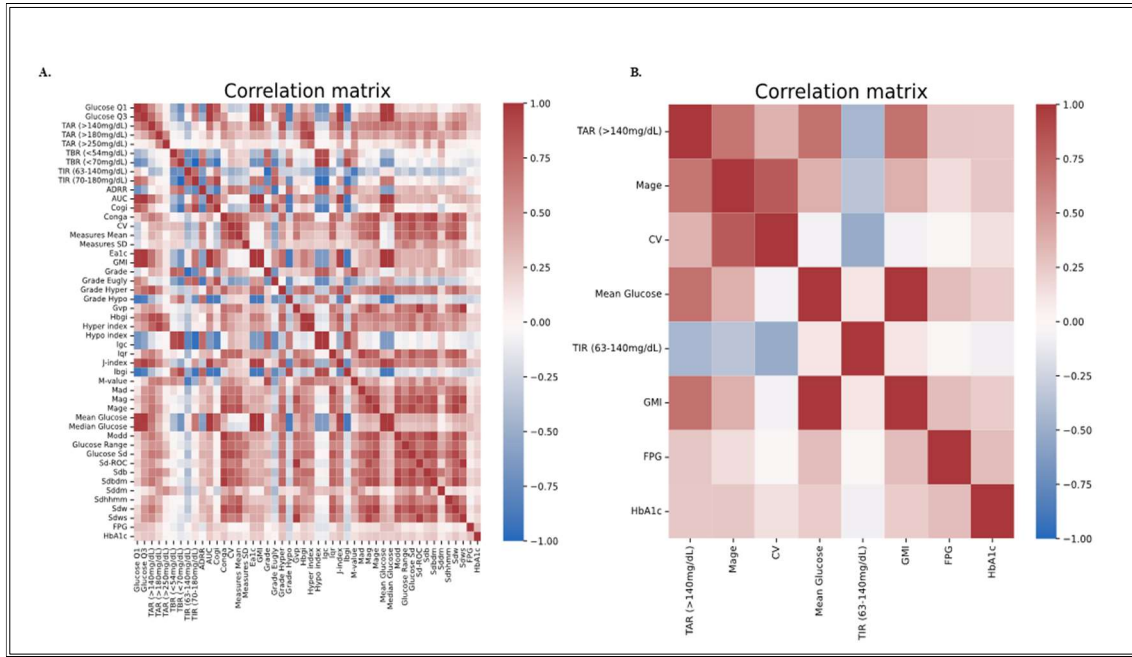


Figure 7. Correlation matrix showing associations between HbA1c, FPG, and (A) all CGM metrics, and (B) 6 selected CGM metrics included in classification models [29]. *AUC* – area under the curve, *CGM* – continuous glucose monitoring, *CONGA* – continuous overall net glycemic action, *CV* – coefficient of variation, *FPG* – fasting plasma glucose, *GMI* – glucose management indicator, *HbA1c* – hemoglobin A1c, *Hyper index* – hyperglycemia index, *Hypo index* – hypoglycemia index, *IQR* – interquartile range, *MAGE* – mean amplitude of glycemic excursions, *Mean glucose* – mean glucose, *SD* – standard deviation, *TAR* – time above range, *TBR* – time below range, *TIR* – time in range

8.2.5. Classification performance of individual and combined CGM metrics

Across reference definitions, several individual CGM metrics achieved classification performance approaching that of HbA1c and FPG when each laboratory marker was evaluated against the alternative prediabetes definition. Among clinically interpretable CGM metrics, mean glucose, TAR >140 mg/dL, MAGE, and GMI demonstrated the strongest classification performance across reference definitions. AUC values generally ranged from approximately 0.65 to 0.68, approaching the discrimination achieved by conventional laboratory markers when evaluated against one another (**Table 3**) [29].

Combined CGM-based models incorporating six CGM metrics (TAR > 140 mg/dL, MAGE, CV, TIR, GMI, and mean glucose) did not substantially outperform individual

CGM metrics, indicating that clinically interpretable single CGM measures capture most of the discriminative information available from glucose monitoring profiles. When prediabetes was defined using both HbA1c and FPG criteria, classification performance improved across all methods, including laboratory markers and CGM-metrics, reflecting more advanced dysglycemia [29].

Table 3. Classification performance of individual and combined CGM metrics compared with HbA1c and FPG across alternative laboratory-based reference definitions of prediabetes [29]

Predictor	HbA1c	FPG	"AND"	"OR"
Age	0.6798	0.5958	0.6824	0.6445
Glucose Q1	0.6131	0.6595	0.7109	0.6323
Glucose Q3	0.6547	0.6494	0.7378	0.6464
TAR (>140mg/dL)	0.665	0.6217	0.7292	0.6361
TAR (>180mg/dL)	0.6044	0.5779	0.6543	0.5835
TAR (>250mg/dL)	0.5031	0.5016	0.5039	0.5023
TBR (<54mg/dL)	0.5396	0.5804	0.584	0.5614
TBR (<70mg/dL)	0.5786	0.627	0.6567	0.6006
TIR (63-140mg/dL)	0.5963	0.546	0.6338	0.5602
TIR (70-180mg/dL)	0.5543	0.6041	0.6116	0.5809
ADRR	0.5108	0.5728	0.5449	0.5478
AUC	0.6465	0.6609	0.7392	0.6485
Cogi	0.5661	0.616	0.6338	0.591
Conga	0.649	0.5914	0.6891	0.6152
CV	0.5904	0.514	0.5692	0.5331
Measures Mean	0.5937	0.5185	0.5721	0.5311
Measures SD	0.5651	0.5011	0.5542	0.5292
Ea1c	0.6456	0.6607	0.7378	0.6482
GMI	0.6456	0.6607	0.7378	0.6482
Grade	0.5876	0.5392	0.6299	0.5498
Grade Eugly	0.5196	0.5311	0.5134	0.5139
Grade Hyper	0.659	0.6255	0.7233	0.6366
Grade Hypo	0.618	0.6507	0.7033	0.6319
Gvp	0.5922	0.5273	0.6146	0.5496

Predictor	HbA1c	FPG	"AND"	"OR"
Hbgi	0.6706	0.6278	0.7356	0.6427
Hyper index	0.6617	0.6184	0.7261	0.6322
Hypo index	0.5791	0.6312	0.6573	0.604
Igc	0.559	0.6139	0.623	0.5879
Iqr	0.6283	0.5321	0.6388	0.5721
J-index	0.6688	0.6526	0.7503	0.6551
lbgi	0.6141	0.6559	0.7086	0.631
M-value	0.6125	0.5588	0.6599	0.5729
Mad	0.6307	0.5525	0.6437	0.5878
Mag	0.6483	0.5636	0.6731	0.5991
MAGE	0.6535	0.5673	0.6757	0.605
Mean Glucose	0.6456	0.6607	0.7378	0.6482
Median Glucose	0.6342	0.6678	0.7335	0.6465
Modd	0.654	0.5935	0.6921	0.6196
Glucose Range	0.6292	0.5505	0.6543	0.5814
Glucose Sd	0.6507	0.5537	0.6676	0.5953
Sd-ROC	0.5914	0.5294	0.6157	0.5503
Sdb	0.6549	0.5902	0.6881	0.6192
Sdbdm	0.6538	0.5875	0.6904	0.6154
Sddm	0.5716	0.5421	0.5731	0.5604
Sdhhmm	0.5934	0.5346	0.5596	0.523
Sdw	0.6464	0.5449	0.6615	0.5876
Sdws	0.6115	0.5367	0.6337	0.5647
BMI	0.6167	0.6267	0.6758	0.6225
FPG	0.6703	1	0.9404	0.8541
HbA1c	1	0.663	0.9418	0.8464
6 CGM	0.6777	0.663	0.7504	0.6569

AUC – area under the curve, BMI – body mass index, CGM – continuous glucose monitoring, CONGA – continuous overall net glycemic action, CV – coefficient of variation, FPG – fasting plasma glucose, GMI – glucose management indicator, HbA1c – hemoglobin A1c, Hyper index – hyperglycemia index, Hypo index – hypoglycemia index, IQR – interquartile range, MAGE – mean amplitude of glycemic excursions, Mean glucose – mean glucose, SD – standard deviation, TAR – time above range, TBR – time below range, TIR – time in range

8.2.6. Relative contribution of CGM metrics

Analyses of relative metric contribution showed that mean glucose and MAGE contributed more strongly to classification than variability metrics such as CV and TIR (Figure 8), consistent with their higher discriminative performance observed in receiver operating characteristic analyses (Figure 9) [29].

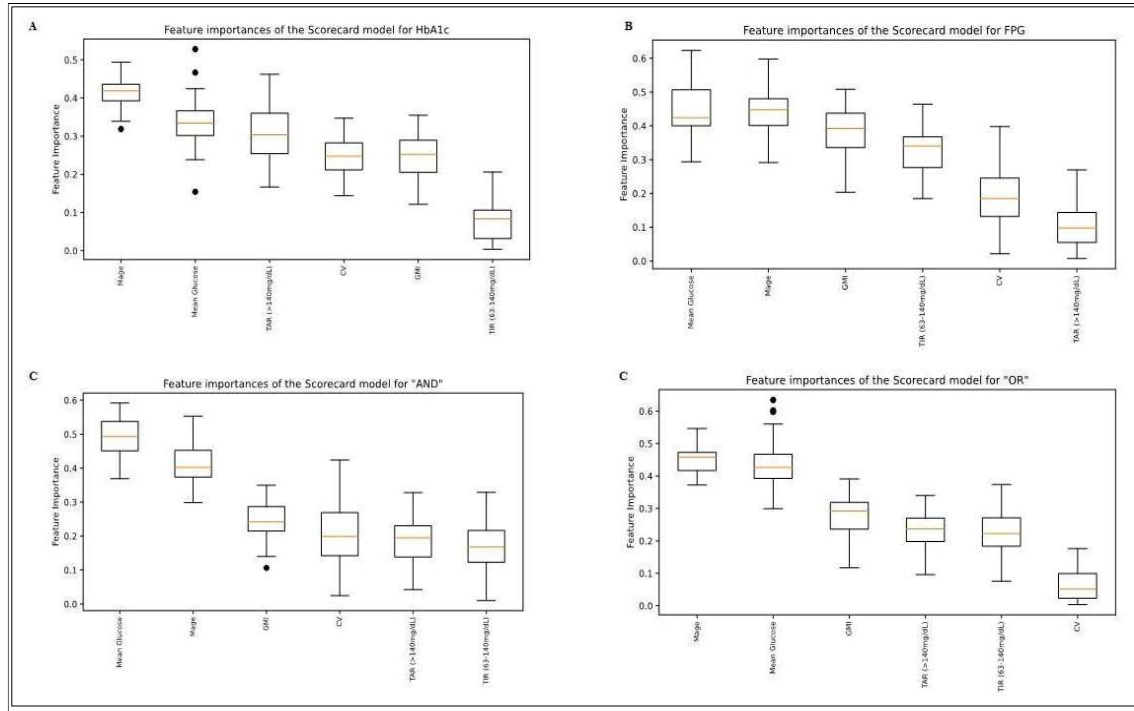


Figure 8. Feature importances box plots of the scorecard model for prediction of (A) HbA1c-defined prediabetes, (B) FPG-defined prediabetes, (C) HbA1c and FPG-defined prediabetes, and (D) HbA1c or FPG-defined prediabetes [29]. *CGM* – continuous glucose monitoring, *CV* – coefficient of variation, *FPG* – fasting plasma glucose, *GMI* – glucose management indicator, *MAGE* – mean amplitude glycemic excursions, *ROC* – receiver operating characteristic curve, *TAR* – time above range, *TIR* – time in range.

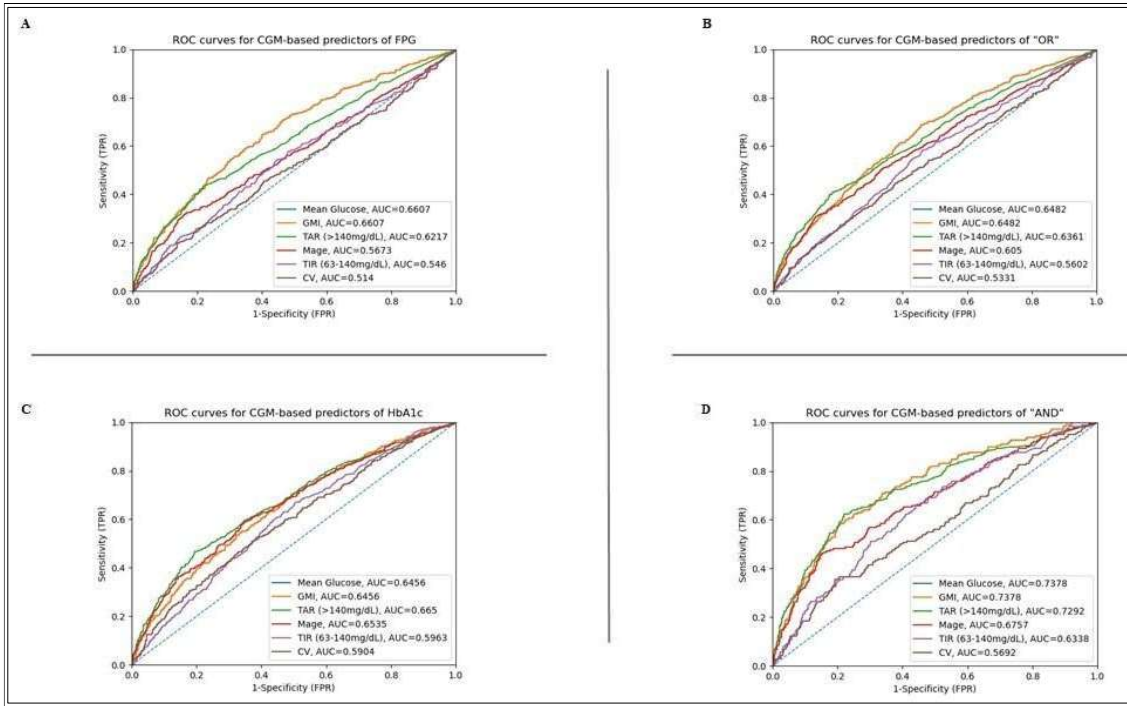


Figure 9. ROC curves for CGM-based predictors for classification of prediabetes defined by (A) FPG, (B) HbA1c OR FPG, (C) HbA1c, and (D) HbA1c AND FPG [29]. *CGM* – continuous glucose monitoring, *FPG* – fasting plasma glucose, *ROC* – receiver operating characteristic curve.

8.2.7. Additional analyses

Sensitivity analyses using alternative CGM cutoffs, model specifications, a ≤ 30 -day lab–CGM interval, and restriction to participants with 13–14 days of CGM monitoring produced results consistent with the primary analysis, supporting the robustness of the classification models. Similar discrimination was observed across all sensitivity analyses, indicating that model performance was not substantially influenced by alternative analytical assumptions. Adjustment for age and BMI further improved model performance across all four laboratory-based reference definitions, increasing AUC across all outcomes and both TITR- and TIR-based models (**Table 4**) [29].

Table 4. Performance of the combined CGM classification model with and without adjustment for age and BMI across four laboratory-based reference definitions. Values are presented as AUC (95% CI) [29].

Model	HbA1c	FPG	„AND”	„OR”
within 90 days, TITR 63–140 mg/dL	0.668 (0.597–0.740)	0.655 (0.600–0.710)	0.725 (0.653–0.796)	0.648 (0.587–0.709)
within 90 days, TITR 63–140 mg/dL + age and BMI	0.746 (0.688–0.804)	0.693 (0.640–0.747)	0.804 (0.749–0.859)	0.715 (0.664–0.765)
within 90 days, TIR 70–180 mg/dL	0.677 (0.608–0.747)	0.661 (0.606–0.717)	0.749 (0.674–0.824)	0.656 (0.595–0.717)
within 90 days, TIR 70–180 mg/dL + age and BMI	0.745 (0.688–0.803)	0.692 (0.639–0.745)	0.802 (0.747–0.858)	0.713 (0.663–0.764)

TIR: time in range (70–180 mg/dL).

TITR: tight time in range (63–140 mg/dL).

8.2.8. Bias and quality assessment

Bias and quality were addressed through the registry’s broad catchment, standardized on-site measurements, and minimal selection bias, with missing data <5% across variables and complete-case analysis applied. However, potential selection bias cannot be excluded, as participants may have been more health-conscious than the general population, and generalizability may be limited due to the single-country (Israel) cohort.

9. DISCUSSION

9.1. Summary of findings

This thesis investigated the potential role of CGM in the detection and characterization of prediabetes and early dysglycemia. Through a systematic review and meta-analysis and a large-scale real-world cohort analysis, the findings consistently suggest that CGM captures clinically relevant aspects of glucose regulation that are not fully reflected by conventional laboratory markers.

The first study demonstrated that individuals with prediabetes exhibit significantly altered CGM-derived glycemic profiles compared with normoglycemic individuals. Prediabetes was associated with a higher mean glucose levels, greater glycemic variability, higher TAR, and lower TIR, indicating that measurable differences in glucose regulation are already present before the onset of overt diabetes.

The second study demonstrated substantial discordance between HbA1c- and FPG-based definitions of prediabetes. Importantly, several CGM-derived metrics achieved classification performance approaching that of conventional laboratory markers, highlighting the potential role of CGM in the detection and characterization of early dysglycemia. Together, these findings support the concept that dysglycemia develops along a continuum and that CGM may offer additional insight into early metabolic dysfunction beyond conventional diagnostic approaches.

9.2. Comparison with previous studies

Several individual studies have previously reported that glucose patterns differ substantially between individuals with prediabetes and those with normoglycemia. Rodriguez-Segade et al. [26] demonstrated that CGM identified glycemic abnormalities that were not captured by HbA1c or fasting glucose alone. Similarly, Dorcely et al. reported that CGM-derived measures and one-hour glucose responses revealed metabolic abnormalities even among individuals with apparently normal HbA1c values [27].

More recently, studies from the Human Phenotype Project and related cohorts have highlighted considerable heterogeneity in glucose regulation among individuals traditionally classified as normoglycemic [32]. These observations support the concept

that dysglycemia develops gradually and may be detectable before conventional diagnostic thresholds are exceeded [57].

The findings of the present thesis are consistent with these earlier observations. However, unlike previous individual studies, the first study provides the first quantitative synthesis of available evidence comparing CGM metrics between prediabetes and normoglycemia. Across multiple populations and study settings, prediabetes was consistently associated with less favorable CGM profiles, supporting the biological plausibility of CGM as a tool for identifying early metabolic dysfunction.

9.3. Discordance between HbA1c and FPG

A major finding of the cohort study was the substantial discordance between HbA1c- and FPG-based definitions of prediabetes. Although both markers are recommended by current clinical guidelines, they identified considerably different subgroups of individuals.

This finding is consistent with previous studies demonstrating poor agreement between conventional glycemic markers. Tucker et al. [18]., Ho-Pham et al.[19]., and Aekplakorn et al.[20] all reported substantial disagreement between HbA1c-, FPG-, and OGTT-based classifications. Collectively, these studies suggest that different diagnostic tests identify partially distinct subgroups of individuals at metabolic risk.

The present findings extend this literature by demonstrating that CGM-derived metrics exhibit classification performance approaching that of HbA1c and FPG, while simultaneously capturing aspects of glucose regulation not reflected by either laboratory marker. This observation may be particularly relevant in situations where conventional laboratory results are discordant and clinical uncertainty exists.

9.4. Physiological interpretation of CGM-derived metrics

The observed performance of CGM metrics is biologically plausible and reflects the pathophysiology of early dysglycemia. Prediabetes is characterized not only by modest elevations in average glucose concentration but also by impaired postprandial glucose handling, reduced insulin sensitivity, and progressive beta-cell dysfunction [5, 7].

These alterations often manifest initially as exaggerated glucose excursions following meals rather than persistent fasting hyperglycemia [7]. Consequently, individuals may demonstrate substantial glycemic disturbances despite laboratory values remaining below diagnostic thresholds [12, 57].

CGM provides a unique opportunity to capture these dynamic glucose patterns under free-living conditions [14]. Metrics such as mean glucose, TAR, and MAGE reflect different aspects of glycemic regulation and therefore provide information beyond that available from single laboratory measurements. The finding that metrics reflecting overall glycemic exposure and excursion magnitude generally demonstrated stronger classification performance than variability-based metrics further supports their physiological relevance.

Importantly, these findings do not indicate that CGM functions as a superior diagnostic test. Rather, they suggest that CGM offers complementary physiological information that may improve understanding of an individual's metabolic status.

9.5. Why was classification performance moderate rather than high?

An important observation from the second study is that no individual CGM metric achieved very high discrimination across reference definitions. Several factors may explain this finding.

First, prediabetes is a heterogeneous condition encompassing multiple underlying pathophysiological mechanisms [5]. Individuals may exhibit predominantly fasting abnormalities, predominantly postprandial abnormalities, or a combination of both. Consequently, no single metric is expected to fully capture the entire spectrum of dysglycemia.

Second, the laboratory markers used as reference standards are themselves imperfect [18, 5]. The substantial discordance observed between HbA1c and FPG suggests that these markers do not identify identical populations. Notably, HbA1c and FPG achieved only moderate classification performance when evaluated against each other, indicating that disagreement exists even among conventional diagnostic approaches.

Third, oral glucose tolerance testing was not available in the registry cohort. As a result, classification performance was evaluated relative to alternative laboratory markers rather than against a universally accepted physiological reference standard.

Taken together, these considerations suggest that moderate classification performance should not be interpreted as evidence against the clinical value of CGM. Rather, it reflects the complexity of prediabetes itself and the limitations of current diagnostic frameworks.

9.6. Public health and clinical implications

The growing global burden of prediabetes highlights the need for improved methods of risk identification and stratification [1]. Earlier detection of metabolic dysfunction may facilitate implementation of targeted lifestyle interventions before progression to type 2 diabetes occurs [5].

The present findings suggest that CGM may contribute to this goal by providing a more detailed characterization of glucose regulation than conventional laboratory markers alone. In addition to risk identification, CGM offers immediate behavioral feedback and may support personalized lifestyle modification through visualization of individual glucose responses [12, 14].

Nevertheless, the findings of this thesis do not support the use of CGM as a standalone screening or diagnostic test. Instead, CGM may be most valuable as a complementary tool, particularly among individuals with borderline laboratory findings, discordant HbA1c and FPG results, or elevated clinical risk despite apparently normal laboratory markers.

9.7. Strengths

9.7.1. Study 1

The meta-analysis synthesized data from 1,657 participants across diverse settings and evaluated multiple CGM-derived metrics (MAGE, 24-hour mean glucose, TAR, CV, and TIR). The consistency of findings across these outcomes strengthens confidence in the robustness of the observed differences between prediabetes and normoglycemia.

9.7.2. Study 2

The second study utilized a large, deeply phenotyped real-world cohort with standardized CGM and laboratory measurements. Evaluating multiple CGM metrics against several laboratory-based reference definitions enabled a comprehensive assessment of their potential role in identifying early dysglycemia. In addition, the use of multiple

classification approaches and sensitivity analyses strengthened the robustness and generalizability of the findings.

9.8. Limitations

9.8.1. Study 1

Several limitations should be considered when interpreting the findings of this thesis. Most importantly, oral glucose tolerance test (OGTT) data were not available in the second study, preventing direct comparison with a widely accepted diagnostic reference standard for prediabetes. Consequently, classification performance was evaluated relative to HbA1c and fasting plasma glucose rather than against OGTT-defined dysglycemia.

In the systematic review and meta-analysis, heterogeneity in prediabetes definitions represented an additional limitation. Although most studies used established diagnostic criteria, variability in the application of HbA1c, FPG, and OGTT may have contributed to misclassification and between-study heterogeneity.

9.8.2. Study 2

The cross-sectional design of the registry analysis precludes causal inference and does not allow assessment of future progression to type 2 diabetes. Therefore, the prognostic significance of CGM-derived abnormalities cannot be determined from the present data.

Methodological variability in CGM use may also have influenced the findings. Differences in device generation, monitoring duration, calibration procedures, and study protocols were present across studies included in the meta-analysis. Moreover, there is currently no universally accepted consensus regarding the optimal duration of CGM monitoring for identifying early dysglycemia.

The use of unblinded CGM in some studies may have influenced participant behaviour, potentially attenuating glucose excursions and reducing observed differences between groups. In addition, generalizability may be limited by the characteristics of the registry cohort, which originated from a single country and may represent a relatively health-conscious population.

Despite these limitations, the consistency of findings across complementary study designs supports the overall validity of the conclusions and provides a rationale for future prospective investigations.

10. CONCLUSIONS

10.1. Study 1

This meta-analysis demonstrates that CGM metrics consistently distinguish prediabetes from normoglycemia, capturing dynamic features of glucose regulation beyond conventional markers. These findings support the role of CGM as a complementary tool for refined metabolic risk assessment, with further prospective studies needed to establish standardized thresholds and clinical applicability.

10.2. Study 2

This study highlights the discordance between HbA1c and FPG in prediabetes detection and shows that CGM-derived metrics achieve comparable classification performance while providing additional insight into glycemic patterns. These findings support CGM as a complementary tool for metabolic risk stratification, warranting further prospective validation with clinical outcomes.

11. IMPLICATIONS FOR PRACTICE

11.1. Study 1

CGM-derived metrics are capable of distinguishing individuals with prediabetes from those with normoglycemia, reflecting differences in underlying glucose dynamics not captured by conventional markers. In clinical settings, CGM may provide additional context in individuals with borderline or inconclusive HbA1c or FPG results. These findings support the use of CGM as a complementary tool for more refined metabolic risk assessment.

11.2. Study 2

Given the observed discordance between HbA1c and FPG, CGM may help resolve diagnostic uncertainty in individuals with conflicting laboratory results. CGM-derived metrics offer comparable classification performance while providing additional insight into glycemic patterns, supporting their use as a complementary tool in clinical risk stratification. Implementation in practice will require standardized interpretation frameworks and consideration of cost-effectiveness.

12. IMPLICATIONS FOR RESEARCH

12.1. Study 1

Future research should focus on prospective validation of CGM-derived metrics for the identification of prediabetes, with particular emphasis on establishing standardized thresholds and optimal monitoring duration. Given the heterogeneity observed across studies, consensus on CGM protocols and metric definitions is needed to improve comparability and reproducibility. In addition, further work is warranted to explore dynamic CGM-based features, such as postprandial glucose patterns and duration of hyperglycemia, which may provide deeper insight into early metabolic dysfunction. Integrating CGM data with clinical and phenotypic characteristics may further enhance risk stratification across different stages of dysglycemia.

12.2. Study 2

Future studies should evaluate the predictive value of CGM-derived metrics for progression from prediabetes to T2DM in longitudinal designs incorporating OGTT and clinical outcomes. Given the observed discordance between HbA1c and FPG, research is needed to determine whether CGM can improve classification accuracy when integrated into existing diagnostic frameworks. In addition, studies assessing cost-effectiveness, implementation strategies, and the clinical utility of CGM in nondiabetic populations are essential. The development of standardized interpretation frameworks and validation of digital tools may further support the integration of CGM into preventive care pathways.

13. IMPLICATIONS FOR POLICYMAKERS

13.1. Study 1

Policymakers should support further research aimed at standardizing CGM-based metrics and defining their role in prediabetes identification. Given the heterogeneity in current diagnostic approaches, incorporating CGM into research frameworks may help refine risk assessment strategies. Investment in large-scale prospective studies and the development of standardized protocols will be essential before considering integration into screening recommendations. In addition, supporting education and awareness initiatives may facilitate the appropriate interpretation and use of CGM data in nondiabetic populations.

13.2. Study 2

The observed discordance between HbA1c and FPG highlights limitations in current screening strategies and underscores the need for more comprehensive approaches to metabolic risk assessment. Policymakers should consider supporting the evaluation of CGM as a complementary tool within existing diagnostic pathways, particularly in high-risk or diagnostically uncertain populations. However, broader implementation will require evidence on cost-effectiveness, as well as clearly defined clinical pathways and reimbursement models. Investment in training programs and digital infrastructure may further support the integration of CGM into preventive care and population-level risk stratification.

14. FUTURE PERSPECTIVES

The findings of this thesis support a shift toward more dynamic and individualized approaches to metabolic risk assessment. As continuous glucose monitoring becomes increasingly accessible, its role may extend beyond diabetes management toward earlier identification of dysglycemia and more refined risk stratification in non-diabetic populations.

Rather than replacing conventional diagnostic tools, CGM has the potential to complement existing frameworks by capturing the temporal and context-dependent nature of glucose regulation. This may enable a transition from static, threshold-based classification toward more nuanced, physiology-driven models of metabolic health.

In the longer term, the integration of CGM with digital health technologies, lifestyle data, and biological markers may facilitate the development of personalized prevention strategies. Such approaches could support earlier intervention, improve patient engagement, and contribute to more effective, precision-based metabolic care.

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16.1. Publications related to the thesis

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Differences in Continuous Glucose Monitoring Metrics Between Prediabetes and Normoglycemia: A Systematic Review and Meta-Analysis.

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Rákóczi G, Csányi D, Molontay R, Agócs G, Szentes BL, Lee J, Rancz A, Hegyi P, Sipter E.

Continuous Glucose Monitoring for Prediabetes Classification in a Large Real-World Cohort: Comparison with HbA1c and Fasting Plasma Glucose.

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16.2. Publications not related to the thesis

Rákóczi G, Hegyi P, Sipter E.

Continuous Glucose Monitoring and Early Dysglycemia: Toward an Emerging Stage Preceding Prediabetes.

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