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Original article

Feasibility of digital phenotyping based on continuous glucose monitoring to support personalized lifestyle medicine in type 2 diabetes

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ABSTRACT

Objectives: Type 2 diabetes is a highly prevalent age-related chronic condition, with complex and heterogeneous pathogenesis. A 5-point oral glucose tolerance test can identify type 2 diabetes subtypes or "diabetypes" based on the degree of insulin resistance in muscle and/or liver, and beta-cell dysfunction. Due to its costly and invasive nature, the oral glucose tolerance test is not scalable. Presuming that differences in glucose and insulin dynamics manifest in continuous glucose monitoring profiles, we explore the potential of continuous glucose metrics to replace the oral glucose tolerance test for diabetyping.
Study design: In a prospective intervention study, 41 people with type 2 diabetes on lifestyle and/or metformin treatment wore a continuous glucose monitor during 3 control periods of 4 days. During each control period, participants underwent a 5-point oral glucose tolerance test after an overnight fast.
Main outcome measures: Continuous glucose monitoring data from the control periods, excluding the day of the oral glucose tolerance test, was retrospectively analyzed for associations with diabetypes, as well as Spearman correlations between bootstrapped continuous glucose features, including physiology-based and other time-series features, and oral glucose tolerance metrics.
Results: Significant associations were observed between continuous glucose metrics (e.g., low and high blood glucose index, eA1c, and glucose excursions) and oral glucose tolerance metrics (e.g., 2-h glucose, disposition index, insulinogenic index). Furthermore, data-driven metrics (e.g., maximum shift, lumpiness) showed more selective correlations, indicating that data-driven metrics may contain additional information associated with oral glucose tolerance metrics.
Conclusions: These results indicate the potential of continuous glucose monitoring to replace the oral glucose tolerance test for diabetyping, driving proactive and personalized (lifestyle) treatment.
Netherlands trial register: NL7848

1. Introduction

Type-2 diabetes (T2D) is a chronic condition, associated with diffuse complications [1] and an increased risk of premature death [2], and affecting nearly 500 million people globally in 2021 [3]. The prevalence of T2D is projected to rise to over 700 million people in 2045. The introduction of continuous glucose monitoring (CGM) has been a game changer allowing real-time and continuous insight into glucose dynamics in relation to diabetes management. Utilization of CGM was shown to improve clinical and economical outcomes through improved diabetes management, in particular for people with T1D and T2D treated with multiple daily insulin injections [4]. Not surprisingly, CGM has recently been included in the American Diabetes Association guidelines to serve as a minimally invasive solution to enhance diabetes management [5].

Indeed, CGM allows for more granular insight into glycemic health

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and diabetes monitoring than traditional fasting glucose and HbA1c measurements can provide. Insight in CGM parameters, including time in range (TIR) and average glucose, can support self-management and shared decision making for people with diabetes and their healthcare professionals. In addition, integration of CGM and consumer-generated lifestyle data can drive personalized lifestyle management. Interestingly, CGM has the potential to identify novel T2D subgroups based on temporal glucose patterns [6]. In 2018, Ahlqvist et al. identified and characterized five phenotypes and their association with disease progression and complications in age-related diabetes [7]. This was based on six variables, i.e., glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, β-cell function and insulin resistance. Insulin resistance is an early metabolic disturbance that precedes the development of diverse metabolic diseases. Due to heterogeneity in the primary organ affected by insulin resistance different metabolic phenotypes can be distinguished [8]. These T2D subgroups, or 'diabetypes', based on their different underlying etiology in insulin resistance and beta-cell function, respond differently to lifestyle interventions, highlighting the importance of personalization [9–11]. A 5-point oral glucose tolerance test (OGTT) can identify twelve diabetypes, by analyzing hepatic insulin resistance (HIR), muscle insulin resistance (MIR) and beta-cell dysfunction and using these data combined with fasting insulin to assign participants to one of these diabetypes [12,13].

Unfortunately, the OGTT is costly and time consuming for the, and intrusive and invasive for the subject, therefore, difficult to implement in health care at scale. Moreover, it only provides an episodic assessment and has shown to have a significant inter-test variation [14]. Presuming that the different glucose and insulin dynamics manifest in CGM profiles, we here aim to explore the potential of CGM-based digital biomarkers for diabetyping following post-hoc analysis of the Gluco-Insight trial. Taking OGTT data from this trial, we defined the diabetypes according to the methods described earlier [12,13] to explore the differences in CGM-based metrics among them. Additionally, correlation analyses were performed to compare the underlying OGTT-metrics with the CGM-metrics. This study anticipates providing a first indication for future CGM-based diabetyping, which after further validation could be used to support personalized (lifestyle) treatment.

2. Methods

2.1. Clinical study and data selection for retrospective analysis

Data from the Gluco-Insight study were used for retrospective analysis. In short, 41 individuals with T2D using lifestyle and/or metformin for diabetes management were included. Eligibility criteria included a body mass index (BMI) below 40 kg/m^2 and no previous insulin treatment. The study consisted of eleven 4-day self-monitoring periods, which included 3 control periods and 8 lifestyle intervention periods, each separated by a 7-day washout period. The control periods consisted of self-monitoring during habitual daily life. During each self-monitoring period participants used a CGM system (Dexcom G6, Dexcom Inc., San Diego, USA), which measured the amount of glucose in interstitial fluid every 5 min and transformed these data into estimated blood glucose levels. Participants applied the CGM sensor one day before the start of each monitoring period. During each control period (week 2, 13 and 24), participants came to the clinic after an overnight fast for an OGTT. The study protocol was approved by the Medical Ethics Committee Brabant (NL70771.028.19), performed in accordance with the Declaration of Helsinki and good clinical practice and registered at the Netherlands Trial Register: NL7848. All participants provided written informed consent.

2.2. Diabetyping

During the OGTT, venous blood samples were collected before and at 30, 60, 90 and 120 min after consumption of a water solution containing 75 g glucose. The glucose and insulin response were used to calculate three indices: (1) hepatic insulin resistance index (HIRI); (2) muscle insulin sensitivity index (MISI); and (3) disposition index (DI) as a measure of pancreatic beta-cell function (BCF) [15,16]. See Supplementary File 1A for calculations. Taking these indices (HIRI, MISI, and DI) and combining this with fasting insulin results in a total of 12 distinct diabetypes (Fig. 1) [11]. For data analysis, only diabetypes with sample sizes $n > 10$ were included.

2.3. CGM feature extraction

To create features from CGM data, we processed the raw CGM data and extracted a wide range of features. For this, we only retained control period days with a full set of 288 data points per day (5 min sample frequency). The CGM data was then organized by subject and date. We applied a series of functions to each group to calculate various physiology-based and other time-series features. The physiology-based features are clinically-validated metrics of glucose and glucose variability and encompass the average daily risk range (ADRR), estimated A1c (eA1c), interday coefficient of variation, interday standard deviation, J-index, mean amplitude of glycemic excursions (MAGE), low blood glucose index (LBGI), high blood glucose index (HBGI), time in range (TIR), time outside range (TOR), percentage in range (PIR), percentage out range (POR). Physiology-based features were extracted using the cgmquantify package [17]. As CGM devices can measure a rich time-series dataset of interstitial glucose levels, time-series features were calculated to capture information about glucose variability and dynamics that may not be represented by traditional clinically validated measures. Time-series features were calculated using the R package *tsfeatures* [18]. Details on the extracted features are provided in Supplementary File 1B.

2.4. Statistics

All statistical analysis and visualizations were performed in R, version 4.1.2. *ggplot2* was used for all visualizations [19,20].

2.5. Ambulatory glucose profiles

To visualize ambulatory glucose profiles, we employed quantile regression (package *quantreg*) with periodic B-splines (package *pbs*), which are particularly suited for modeling cyclical glucose fluctuations [21,22]. Our plots show median glucose values and variability across the selected diabetypes with a sample size >10.

2.6. Bootstrapped Dunn-test

We included CGM data within an 8-day period surrounding each OGTT test date, while excluding CGM readings from the exact days of OGTT tests. This led to a dataset where each OGTT-derived metric was associated with several days of CGM data. We utilized a bootstrapping method to manage the multiple CGM data points corresponding to a single OGTT metric. This involved repeatedly resampling and analyzing randomly selected matched pairs of CGM and OGTT data, enabling statistical examination of relationships between the two datasets. Each subset included only one pair of CGM and OGTT data per subject, to maintain independence between samples. This process was replicated 500 times, each time creating a distinct data subset for analysis.

For each subset, we employed the a non-parametric pairwise statistical (package *rstatix*) to evaluate differences in metrics among the selected diabetypes ($n > 10$) within our dataset [23]. Each diabetype classification of a subject was associated with several days of CGM metrics. Mirroring the approach used for correlation analysis, we generated 500 subsets by randomly selecting a unique pair of data points for each subject for every subset. We then calculated the mean test statistics and associated *p*-values from the generated Dunn tests.

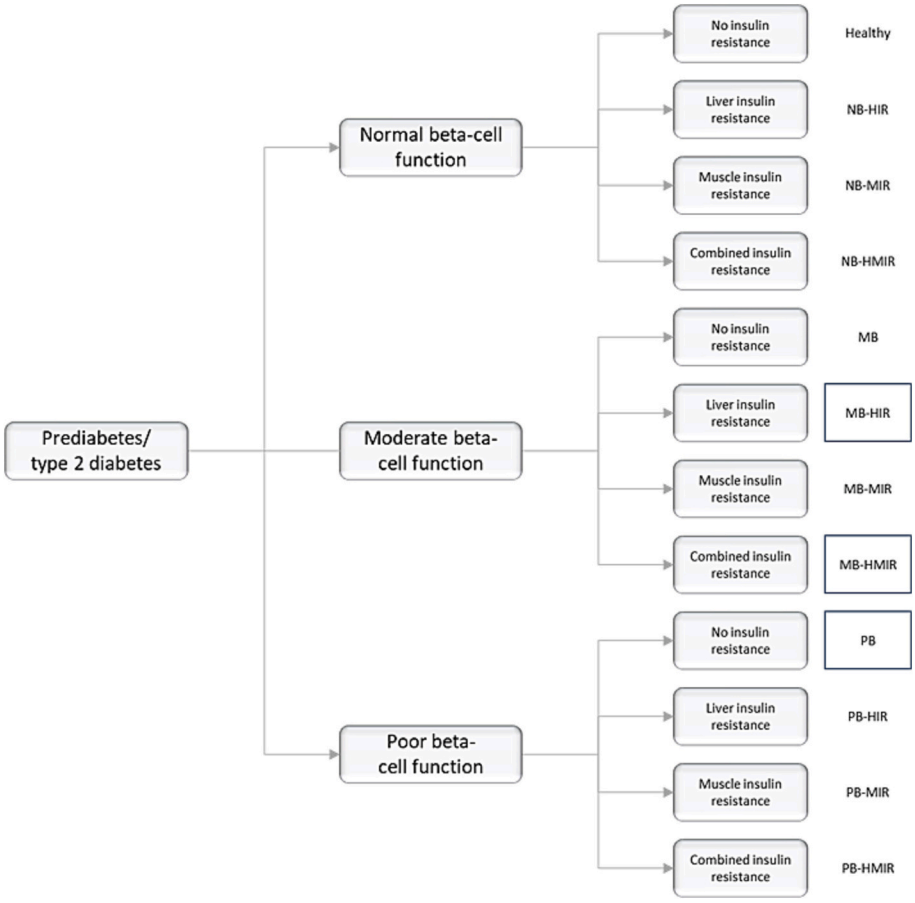

Fig. 1. Overview of the determination of the 12 distinct diabetypes. Marked diabetypes were selected for data analysis. NB: normal beta-cell function; MB: moderate beta-cell function; PB: poor beta-cell function; HIR: hepatic insulin resistance; MIR: muscle insulin resistance; HMIR: hepatic and muscle insulin resistance.

2.7. Bootstrapped Spearman correlations

Following a similar rationale and procedure as used for Dunn test, we calculated Spearman correlations between the CGM and OGTT metrics on the full dataset. In each iteration, we also generated a set of null correlations, which were compared with the actual correlations to determine if the observed relationships were statistically significant. This was achieved by randomly shuffling the values within each subset prior to correlation calculation. The shuffling of data removes any original relationships between variables, creating a baseline of 'null' correlations.

Finally, we aggregated actual and null correlations from all iterations and then calculated the mean correlations and their corresponding *p*-values. In this context, a p-value represents the chance of observing an equally strong correlation under the hypothesis that CGM and OGTT metrics are uncorrelated. Thus, a low p-value indicates that a correlation is unlikely to be coincidental.

2.8. Mutual information heatmap

Mutual information between all pairs of time series features was calculated using the *infotheo* package [24]. A shrinkage estimator was used for increased robustness against noisy estimates. A distance matrix was calculated from the mutual information matrix by subtracting each element of the mutual information matrix from the maximum value in the matrix. Density-based spatial clustering of applications with noise (DBSCAN) was performed on this distance matrix using the *dbscan* package to identify clusters of features with high mutual information [25]. DBSCAN was chosen because it is robust to noise and does not force all points into a cluster, allowing for the identification of features with unique information content.

3. Results

3.1. Study population

Table 1 shows baseline characteristics of the study population included for retrospective data analysis. The study population comprised 41 participants with an average age of 62 years and 46 % being female. BMI was 29.1 kg/m^2 (SD 3.8 kg/m^2) and average diabetes duration since diagnosis was 9.7 years (SD 6.5 years). A total of 118 OGTTs were available for retrospective analysis, with an associated 3 valid CGM days per OGTT on average (Table 2). Diabetypes with a total sample size >10 (from all three visits) included the MB-HIR phenotype ($n = 54$; moderate beta cell function and liver insulin resistance, but not muscle insulin resistance), MB-HMIR phenotype ($n = 16$; moderate beta cell function, liver insulin resistance, and muscle insulin resistance combined), and PB phenotype ($n = 20$; poor beta cell function, without organ insulin resistance). Albeit that the sample sizes at baseline are too small to allow for statistical comparison, notable differences in baseline characteristics between the MB-HIR and MB-HMIR phenotypes, as compared to the PB phenotype were the duration of diabetes (8.9 and 9.5 vs. 13.0 years) and BMI (31.0 and 28.2 vs. 24.3 kg/m2) (Table 1). Baseline HbA1c concentrations were 48.8 (SD = 6.08), 67.3 (SD = 23.8), and 74.4 (SD = 13.5) mmol/mol in the MB-HIR, MB-HMIR and PB phenotypes, respectively.

Differences in OGTT profiles in the total data sample were observed among the selected diabetypes, with a faster decline in glucose in the

Table 1
Baseline characteristics.

	Total sample (n = 41)	MB-HIR (n = 18)	MB-HMIR (n = 6)	PB (n = 4)
Demographics				
Age [years], mean (SD)	62.3 (7.2)	59.3 (6.3)	66.5 (7.1)	63.2 (9.0)
Female, n (%)	19 (46.3 %)	7 (39 %)	2 (33 %)	1 (25 %)
Clinical characteristics				
BMI [kg/m^2], mean (SD)	29.1 (3.8)	31.0 (3.4)	28.2 (2.5)	24.3 (3.1)
Duration of diabetes [years], mean (SD)	9.7 (6.5)	8.9 (6.8)	9.5 (6.4)	13.0 (8.5)
Treatment, n (%)				
Exercise and diet	16 (39 %)	4 (22 %)	3 (50 %)	1 (25 %)
Metformin	14 (34 %)	7 (39 %)	2 (33 %)	2 (50 %)
Both	11 (27 %)	7 (39 %)	1 (17 %)	1 (25 %)

MB-HIR: moderate beta-cell function and liver insulin resistance; MB-HMIR: moderate beta-cell function and liver and muscle insulin resistance; PB: poor beta-cell function, without organ insulin resistance.

Table 2
Total data sample characteristics.

	Sample (n = 118)
Observational	
Total number of OGTT observations, N	118
Total number of OGTT observations per person, median (min, max)	3 [2,3]
Total number of CGM days per person, median (IQR)	8 [6, 10]
Number of included CGM days per OGTT, within 8 days from OGTT, median (IQR)	3 [3, 4]
Diabetypes, > ± 10 prevalence, n (%)[a]	
Moderate beta-cell function and liver insulin resistance (MB-HIR)	54 (46 %)
Moderate beta-cell function and liver and muscle insulin resistance (MB-HMIR)	16 (14 %)
Poor beta-cell function, without organ insulin resistance (PB)	20 (17 %)

[a] For statistical comparison of CGM-features among the different diabetypes, only diabetypes with a sample size >10 were selected to ensure enough power. Therefore, the total number of diabetypes does not add up to 118.

MB-HIR phenotype as compared to the MB-HMIR phenotype, and the highest glucose peak in the PB phenotype (Fig. 2). The MB-HIR phenotype showed the highest insulin release, followed by the MB-HMIR phenotype.

3.2. CGM profiles differ among diabetypes

Significant differences in CGM profiles and metrics were observed among the selected diabetypes. The MB-HMIR phenotype showed increased glucose levels and glycemic variability (Fig. 3, upper panel) as compared to the MB-HIR phenotype. This observation was confirmed by significantly higher levels of ADRR, eA1c, HBGI, J-index, and MAGE, and lower levels of LBGI (Fig. 3, lower panel, $p < 0.05$), suggesting that muscle insulin resistance influences these parameters by increasing glucose fluctuations, but also basal glucose levels in the context of moderate beta cell function and hepatic insulin resistance. The PB phenotype presented with higher basal glucose levels, and even more elevated levels during the night (Fig. 3, upper panel). The resulting CGM metrics were positioned between the other two diabetypes, showing a significant increase of eA1c, HBGI, and MAGE, and decrease in LBGI as compared to the PB-HIR phenotype (Fig. 3, lower panel, $p < 0.05$). Other features did not significantly differ among the diabetypes.

3.3. CGM features correlate with OGTT-derived metrics

Further exploration of physiology-based CGM features revealed significant Spearman correlations in the bootstrapped datasets (also including diabetypes with $n < 10$) with several OGTT-derived metrics, including disposition index, insulinogenic index, and insulin AUC, as well as standard clinical glycemic markers such as fasting glucose, 2-h glucose, and HbA1c (Fig. 4).

Among the features, ADRR, eA1c, HBGI, J-index, MAGE, and LBGI stood out due to their consistent correlations with many OGTT metrics and clinical glycemic variables. ADRR, eA1c, HBGI, J-Index and MAGE all showed significant positive correlations with fasting glucose, 2-h glucose, and HbA1c, and negative correlations with disposition index, insulinogenic index, and insulin AUC. Contrastingly, LBGI (Low Blood Glucose Index) was found to be significantly negatively correlated with fasting glucose ($\rho = -0.654$, $p < 0.001$), 2-h glucose ($\rho = -0.540$, $p < 0.001$), and HbA1c ($\rho = -0.577$, $p < 0.001$), indicating its sensitivity to lower glucose values. It also showed positive correlations with the disposition index ($\rho = 0.313$, $p = 0.038$), insulinogenic index ($\rho = 0.401$, $p = 0.012$), and insulin AUC ($\rho = 0.510$, $p = 0.004$). Intraday SD only showed a significant correlation with HbA1c ($\rho = 0.36$, $p = 0.02$). Interestingly, both TIR and CV, core CGM metrics that are recognized in diabetes guidelines, showed no significant association with OGTT metrics ($p > 0.05$).

On the other hand, specific non-physiology-based time-series

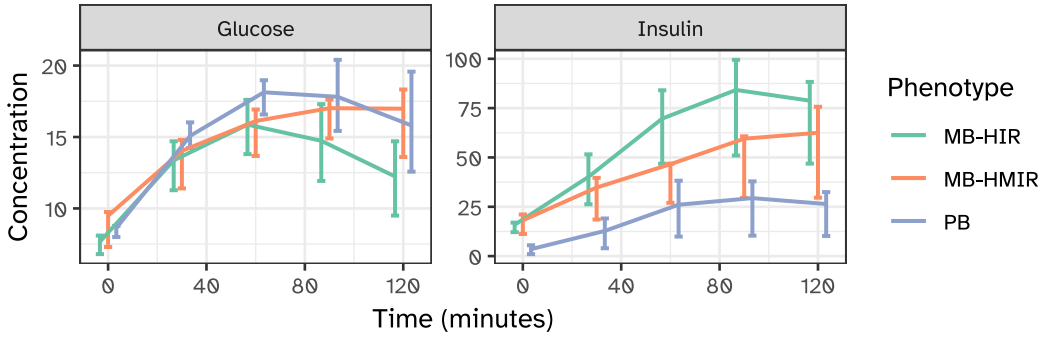

Fig. 2. Glucose (mmol/L) and insulin (mU/L) responses after OGTT administration in three diabetypes (MB-HIR, MB-HMIR, and PB). Only diabetypes with a sample size >10 were included in the analysis. Data is presented as the mean concentration at each time point during the OGTT, with error bars representing the interquartile range. MB-HIR = moderate beta cell function & liver insulin resistance; MB-HMIR = moderate beta cell function, liver insulin resistance & muscle insulin resistance; PB = low.

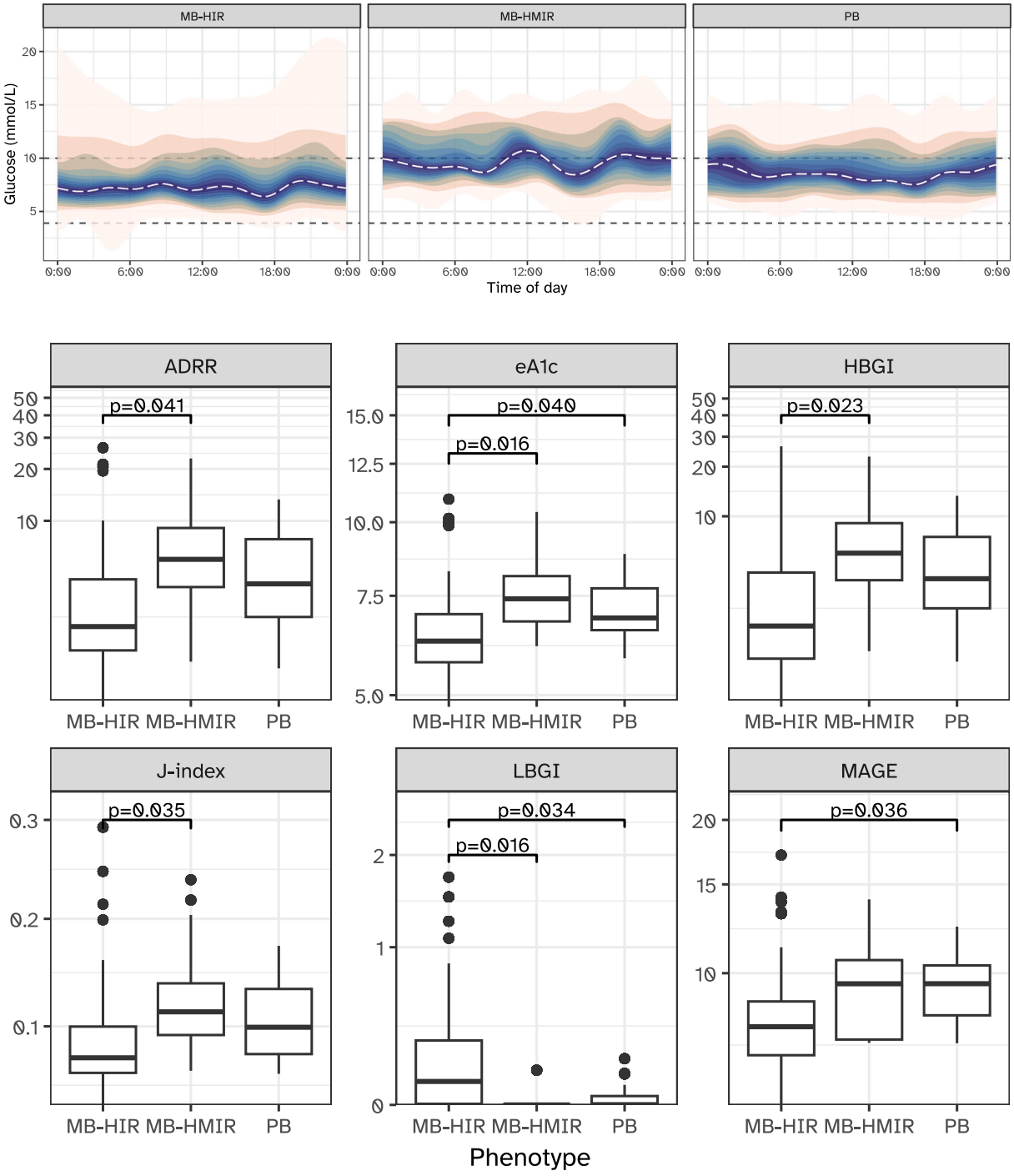

Fig. 3. Differences of CGM profiles and features in comparison to diabetypes. Only diabetypes with a sample size >10 were included in the analysis. The upper plots show 24-h CGM profiles for the different diabetypes within 8 days from the OGTT, with shaded bands indicating the range between pairs of quantiles. The lower plots show statistically significant differences among the diabetypes in six CGM-derived features based on bootstrapped 24-h CGM profiles. MB-HIR = moderate beta cell function & liver insulin resistance; MB-HMIR = moderate beta cell function, liver insulin resistance & muscle insulin resistance; PB = low beta cell function without organ insulin resistance. ADRR: average daily risk range; eA1c: estimated A1c; HBGI: high blood glucose index; J-index: calculated from the mean blood glucose and SD, LBGI: low blood glucose index; MAGE: mean amplitude of glycemic excursions.

features such as Lumpiness and Max_KL_shift showed more selective correlations (Fig. 5). Lumpiness was significantly correlated with disposition index ($\rho = 0.35$, $p = 0.03$) and 2-h glucose ($\rho = -0.364$, $p = 0.018$), indicating its relevance in assessing these specific metrics. Max_KL_shift, instead was correlated with 2-h glucose ($\rho = -0.329$, $p = 0.034$) and HbA1c ($\rho = -0.29$, $p = 0.05$). A substantial number of time-series features, such as Time KL shift and Max var. shift, show no significant correlation with OGTT-derived standard clinical glycemic metrics, and physiology-based features. For instance, the correlation between J-index and Time KL shift is very close to zero ($\rho = -0.0995$), indicating no meaningful relationship.

These findings show the potential of certain CGM features, like ADRR, eA1c, HBGI, J-index, and MAGE, as indicators for a range of OGTT-derived and standard clinical glycemic metrics, while features like Lumpiness and Max_KL_shift may provide more targeted insights. A substantial number of other time-series features, such as Time KL shift

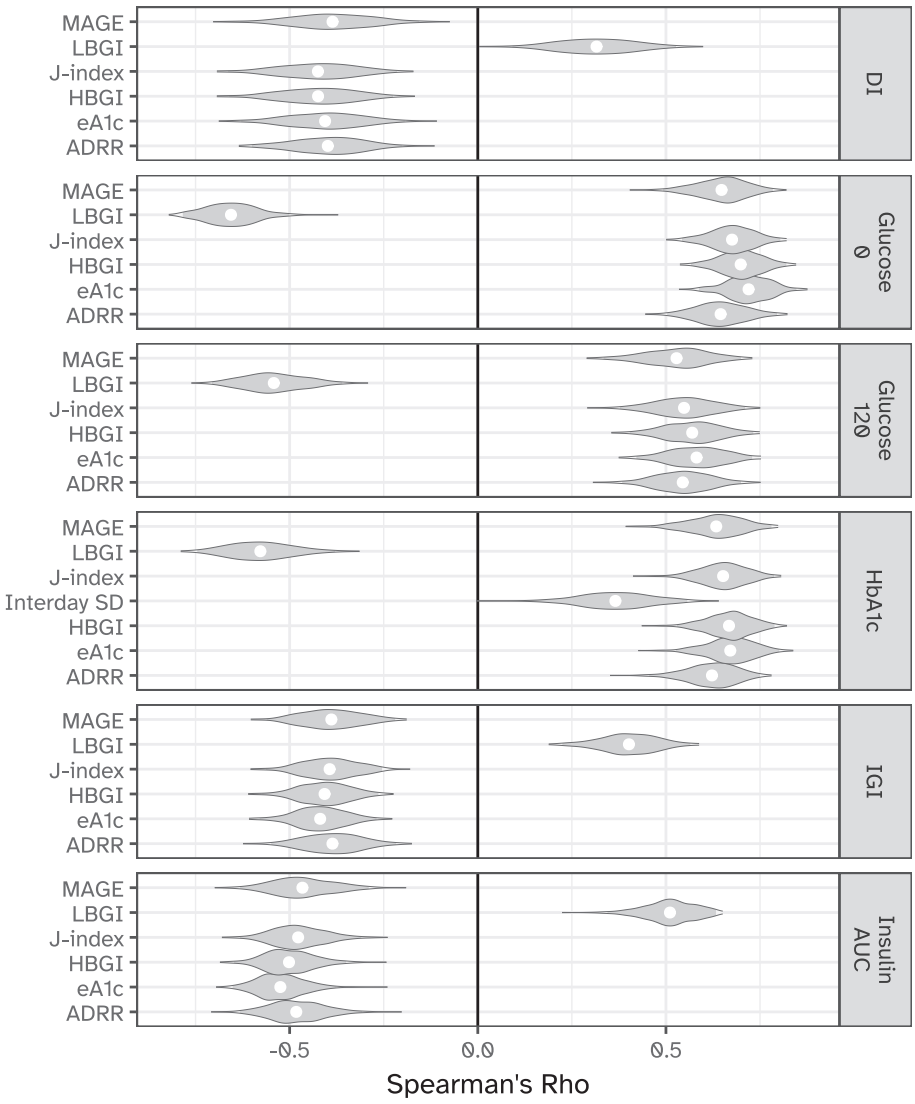

Fig. 4. Significant bootstrapped Spearman correlations between physiology-based time-series CGM features and OGTT derived indices and glycemic biomarkers. DI: disposition index; IGI: insulinogenic index; Interday SD: interday standard deviation; ADRR: average daily risk range; eA1c: estimated A1c; HBGI: high blood glucose index; LBGI: low blood glucose index; MAGE: mean amplitude of glycemic excursions. Unshaded regions encompass 5 % of values, with 95 % of data points in the shaded regions.

and Max var. shift, show no significant correlation with OGTT-derived and standard clinical glycemic metrics.

The large overlap in physiology-based features correlating with OGTT metrics and clinical glycemic variables is reflected by the high mutual information between these physiology-based features, as visualized in a heatmap (Fig. 6), whereas there is much less redundancy in some non-physiology-based features, such as Lumpiness and Max_KL_shift.

4. Discussion

T2D diabetypes differentially respond to lifestyle interventions due to variations in underlying metabolic dysregulation. A five-point OGTT can identify these diabetypes by analyzing hepatic- and muscle insulin resistance in combination with beta-cell dysfunction. However, the OGTT is burdensome and invasive, and therefore difficult to implement at scale. The purpose of this work was to explore the differences in CGM-metrics among different diabetypes and in correlation with indices underlying diabetyping. This supports the potential of less-invasive CGM-based digital phenotyping as an alternative for the OGTT, allowing for continuous and scalable diabetyping in daily contexts. >100,000 CGM data points and 118 OGTT responses were retrospectively analyzed from a total of 41 people with T2D. Significant associations were observed between the diabetypes and OGTT-derived metrics and CGM-based metrics, underlining the potential of CGM as an alternative for OGTT based diagnosis and phenotyping.

The three selected diabetypes, MB-HIR, MB-HMIR and PB showed differential glycemic profiles and OGTT responses. These differences are explained by differences in organ specific insulin resistance and insulin production capacity in the beta-cells between diabetypes [26]. In the MB-HIR diabetype increased basal glucose and insulin levels and a larger initial rise in glucose levels are to be expected, because of increased gluconeogenesis by the liver driven by hepatic insulin resistance. In the MB-HMIR diabetype, both muscle and liver suffer from insulin resistance, resulting in higher basal glucose levels as well as decreased clearance after meals. In this diabetype, glucose may not be sufficiently cleared from the blood before the next meal occurs, resulting in an upwards spiral with a higher steady state after each meal moment. This is also reflected in the significantly higher HBGI, ADRR and eA1c as compared to the MB-HIR diabetype. In the PB-diabetype, not a lack of insulin sensitivity but a severe reduction in insulin production is driving high postprandial glucose responses, which was indeed apparent during

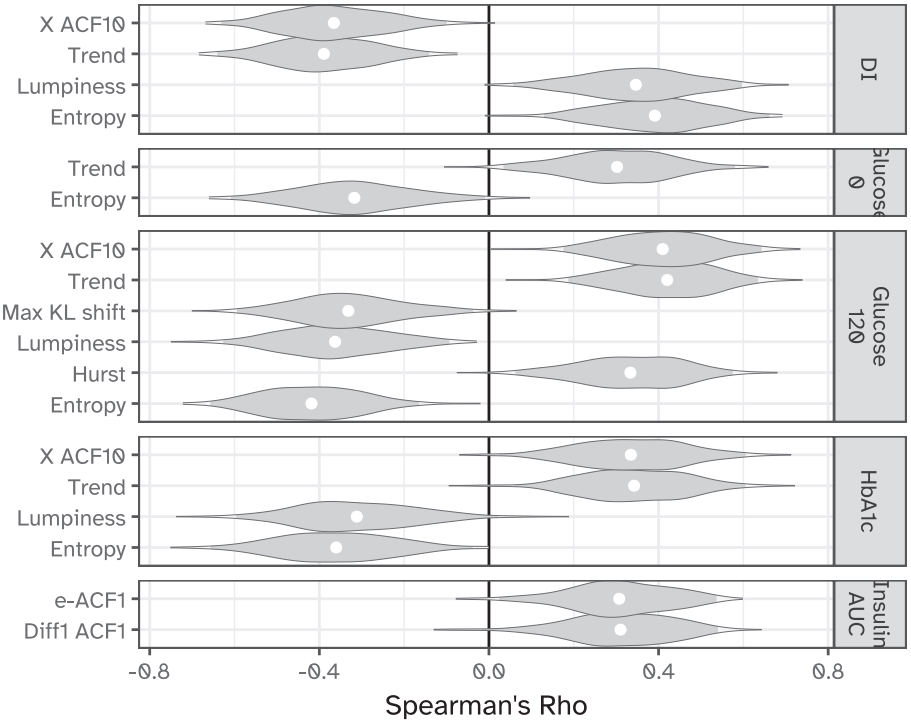

Fig. 5. Significant bootstrapped Spearman correlations between other time-series CGM features and OGTT derived indices and glycemic biomarkers. DI: disposition index; X ACF10: lag 10 autocorrelation function; Max KL shift: largest Kulback-Leibler divergence between two consecutive windows. Unshaded regions encompass 5 % of values, with 95 % of data points in the shaded regions.

the OGTT and reflected by an increased eA1c and MAGE as compared to the MB-HIR diabetype. Also, due to the lack of insulin secretion to keep glucose levels within homeostasis basal glucose levels are high in the PB-diabetype and even increase further during the night.

Various other studies have explored the relationship between OGTT-metrics and CGM-metrics in different populations, including healthy volunteers and type 2 diabetes [27], T1D [28], prediabetes and obesity [29], and gestational diabetes [30]. However, this is the first study to investigate differences in CGM dynamics taking diabetes sub-phenotypes as a starting point. Hall et al. also identified subgroups based on continuous glucose patterns which were associated with clinically meaningful outcomes, such as fasting plasma glucose, 2-h glucose, and HbA1c [31]. In our study, we found a similar correlation between CGM-derived features and fasting and 2-h glucose. Interestingly, in the study by Hall et al., high variability was also observed in normoglycemic and prediabetic people, as diagnosed by traditional biomarkers. The authors argued that this is likely explained by underlying pathophysiology not yet visible in static biomarkers. We connect to existing meaningful metrics related to this underlying pathophysiology, by using OGTT-based indices for insulin resistance and beta-cell functioning and diabetyping. Interestingly, continuous glucose patterns appeared to contain information of insulin dynamics, as disposition index, IGI, and insulin AUC were significantly correlated with CGM-derived features such as ADRR, eA1c, HBGI, J-Index and MAGE. This is also reflected in previous studies, showing significant correlations between glycemic variability, as measured by CV and SD, and fasting C-peptide (as a measure of endogenous insulin secretion) in people with T2D, especially those treated with insulin [32,33]. Although, in our study, no correlations between CV and SD and OGTT-metrics were found. We hypothesize that these metrics, although sensitive to overall glycemic management, they are less discriminative for different etiologies of insulin resistance or beta cell function in our population with relatively well-controlled diabetes. Of note, the positive correlation between LBGI and disposition index and IGI may suggest that people with higher disposition index and IGI are at increased risk of hypoglycemia. However, in this particular population, the LBGI did not exceed a value of 2 (Fig. 2), indicating that hypoglycemia were of no concern Predicting diabetypes may additionally allow for early diagnosis, as insulin sensitivity is already deteriorating before changes in glucose response are observed [34]. Besides, especially diabetypes with isolated muscle insulin resistance, which appears as sustained elevation of glucose levels upon glucose intake, may be misdiagnosed with currently used screening methods that on fasting plasma glucose and HbA1c [35].

It should be noted that this is a retrospective study, and bootstrapping was used to manage the multiple CGM datapoints corresponding to a single OGTT metric. Additionally, variation in the used dataset may be overall small, as the study population consisted of people with T2D using only lifestyle and/or metformin as treatment. Indeed, for the results to be generalized to a larger population, future studies must include normoglycemic people and people with prediabetes as was, for example, been done by Hall et al. [6]. Additionally, only three diabetypes had sufficient sample sizes to be included in data analysis. If CGM data and models can be used to discriminate between all diabetypes will be investigated in a prospective validation study. Lastly, some of the included features are validated for calculation over 14 days, while we used about 3 CGM days per OGTT, which may limit construct validity of these specific features in our study. In future applications it may be advisable to utilize 14-days of CGM data to ensure reliability of included features.

In this study, continuous glucose monitoring data was collected in a real-life, non-controlled setting, whereas OGTTs are performed under highly standardized conditions. In future research or application, it may be considered to introduce some control factors, such as standardized meals or protocols for physical activity. However, such control measures should be well balanced against usability and adherence. Nevertheless, from our results it seems that data collected in a non-controlled setting still holds information with potentially good signal-to-noise. Also, our study included a large dataset with a total number of 118 OGTTs and repeated measures within persons, as well as extensive CGM data.

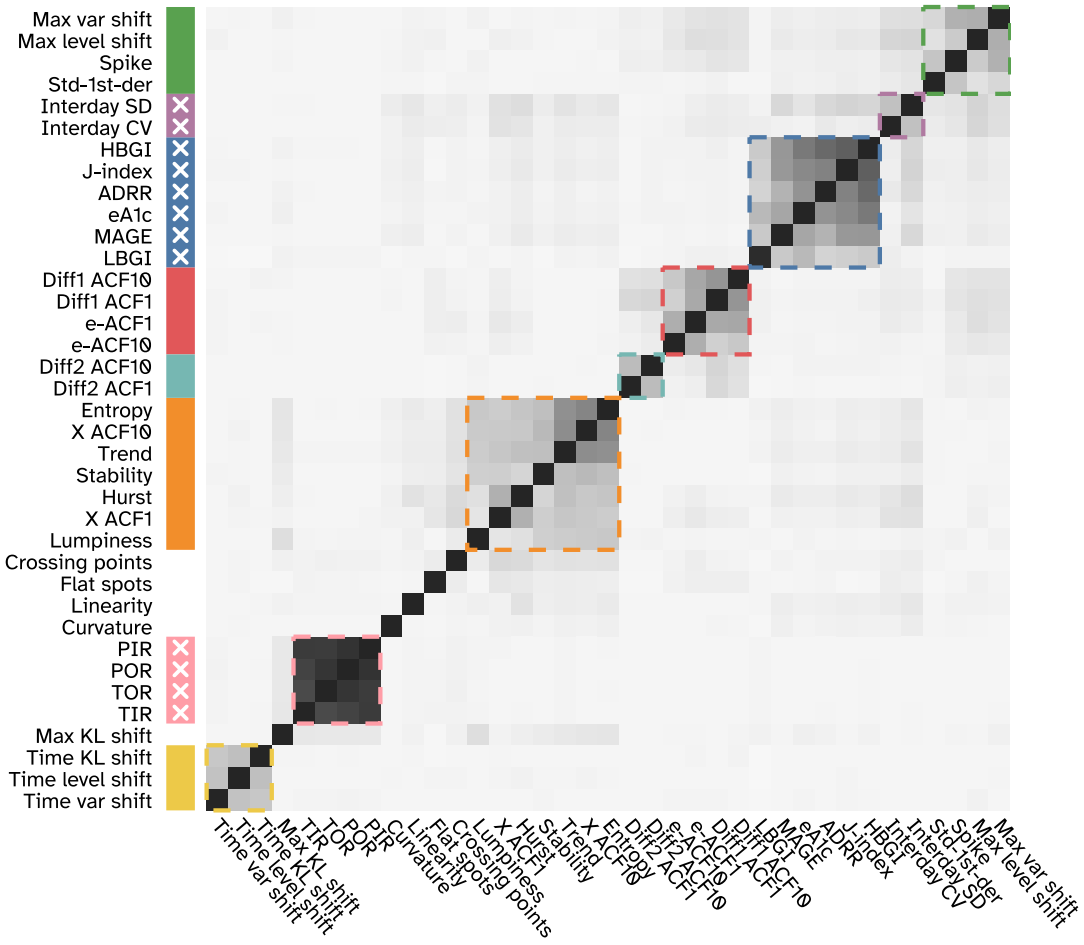

Fig. 6. Heatmap showing the mutual information between pairs of time series features calculated from continuous glucose monitor (CGM) data. Darker squares indicate higher mutual information, suggesting more redundancy in information content for a given feature pair. Dashed boxes and the colored bar indicate clusters of features with high mutual information, identified using density-based spatial clustering (DBSCAN). Features without cluster assignment show very low mutual information with other features. Crosses indicate physiology-based features.

5. Conclusion

Here we explored the potential of non-invasive digital phenotyping based on continuous glucose monitoring as an alternative for OGTT in people with T2D on lifestyle and/or metformin treatment. Pending their prospective validation in a follow-up study, these digital biomarkers may eventually replace non-scalable OGTT for early diagnosis and diabetyping in the home environment driving proactive and personalized (lifestyle) treatment. This would drastically increase the potential impact and accessibility of diabetyping and subsequent personalized treatment, especially anticipating the rapid developments in continuous glucose monitoring allowing for better availability and affordability in the future.

Contributors

Willem J. van den Brink conceived and designed the retrospective data analysis, contributed to the interpretation of the data, wrote the first draft of the manuscript, and reviewed and edited the manuscript.

Tim J. van den Broek conceived and designed the retrospective data analysis, conducted the statistical analyses, contributed to the interpretation of the data, wrote the first draft of the manuscript, and reviewed and edited the manuscript.

Suzan Wopereis contributed to the interpretation of the data, and reviewed and edited the manuscript.

Sonia Difrancesco conducted the statistical analyses, contributed to the interpretation of the data, and reviewed and edited the manuscript.

Frans A.L. van der Horst contributed to the interpretation of the data, and reviewed and edited the manuscript.

Iris M. de Hoogh initiated and coordinated the clinical study, conceived and designed the retrospective data analysis, contributed to the interpretation of the data, wrote the first draft of the manuscript, and reviewed and edited the manuscript.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Ethical approval

The study protocol was approved by the Medical Ethics Committee Brabant (NL70771.028.19), performed in accordance with the Declaration of Helsinki and good clinical practice and registered at the Netherlands Trial Register: NL7848. All participants provided written informed consent for the data analysis as performed in this study.

Provenance and peer review

This article was commissioned and was externally peer reviewed.

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Data sharing and collaboration

There are no linked research data sets for this paper. The datasets generated during and/or analyzed during the current study are not publicly available due to the data being generated as part of a public private partnership and shared intellectual property with partners but are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2024.108188.

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