Clinical and Translational Report

Cell Metabolism

CGMap: Characterizing continuous glucose monitor data in thousands of non-diabetic individuals

Graphical abstract

Highlights

- CGMap, a characterization of CGM data collected from over 7,000 non-diabetic individuals

- First map of reference values of CGM-derived measures, a tool for future CGM research

- CGM-derived measures are associated with clinical parameters, some from fundus imaging

- CGM-derived measures differ in associations with clinical parameters in wake and sleep

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In brief

Keshet et al. present CGMap, a characterization of CGM data from over 7,000 non-diabetic individuals, providing reference values for future research. They show that CGM-derived measures progress differently with age and gender and are significantly associated with clinical parameters, presenting new research directions for glucose effects on human health.

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SUMMARY

Despite its rising prevalence, diabetes diagnosis still relies on measures from blood tests. Technological advances in continuous glucose monitoring (CGM) devices introduce a potential tool to expand our understanding of glucose control and variability in people with and without diabetes. Yet CGM data have not been characterized in large-scale healthy cohorts, creating a lack of reference for CGM data research. Here we present CGMap, a characterization of CGM data collected from over 7,000 non-diabetic individuals, aged 40–70 years, between 2019 and 2022. We provide reference values of key CGM-derived clinical measures that can serve as a tool for future CGM research. We further explored the relationship between CGM-derived measures and diabetes-related clinical parameters, uncovering several significant relationships, including associations of mean blood glucose with measures from fundus imaging and sleep monitoring. These findings offer novel research directions for understanding the influence of glucose levels on various aspects of human health.

INTRODUCTION

Diabetes is a major health issue worldwide. With rising prevalence over the past decade, no country is free of diabetes, and its prevalence is expected to continue rising in the future. Estimates predict that by 2030 more than 7% of the adult population, 400 million adults, will be diagnosed with diabetes, with an increase of 69% of adults with diabetes in developing countries and 20% increase in developed countries. Aside from the individual short- and long-term complications of diabetes, such as higher risk for coronary heart disease and cardiovascular events, the rising prevalence of the disease has a colossal economic burden on the healthcare system. In the US alone, the national cost of diabetes and pre-diabetes in 2007 reached 218 billion dollars, and this cost will inflate as diabetes prevalence rises. Currently, diabetes diagnosis relies on blood tests results: elevated levels of fasting glucose; random glucose in the presence of diabetes-related symptoms; glycated hemoglobin (HbA1c), which provides an index of average blood glucose measurement over a period of 2–3 months; or glucose levels measured in an oral glucose tolerance test (OGTT). Despite their low cost and simplicity, they fail to provide information on glycemic variability or rapid changes in glucose values throughout the day. These tests have additional disadvantages: fasting blood glucose can vary substantially between days and HbA1C is not reliable in certain conditions (such as anemia, iron deficiency, or during pregnancy) and has many existing assays used to evaluate it, causing variability in test results. Moreover, current clinical diagnoses of pre-diabetes and diabetes are defined by a single threshold of HbA1C test higher than 5.7% and 6.5%, although it has been shown that the progression from health to disease occurs on a “continuum” that involves different cellular mechanisms. All the above stress the need to move beyond blood glucose levels and HbA1C and find better tools to diagnose, treat, and manage patients with pre-diabetes and diabetes.

Continuous glucose monitoring (CGM) devices became commercially available in the year 2000, and since then their accuracy has improved, while their size, weight, and cost decreased. Several studies have already shown that the use of CGM contributes to a decrease of HbA1C and an increase of time in range (TIR) in patients with type 1 and type 2 diabetes. The growing availability and lower costs of CGM have also broadened its use beyond these traditional studies to more general applications. One such work revealed specific
patterns of glycemic response, which were named “gluco-types,” revealing heterogeneity within traditional diagnostic categories of glucose regulation. Other works, using CGM data in healthy individuals, showed that the dips in postprandial glucose can predict postprandial self-reported hunger and that glycemic response to identical meals is highly variable among healthy individuals. Yet in spite of its growing use both in the clinic and in research, CGM data lack a definition of standardized metrics, or standardized advice on how to best use the information it provides, particularly in healthy individuals. Moreover, the relationships, and as a result redundancies, of the many CGM-derived metrics still require characterization. The lack of large-scale prospective studies on CGM data, publicly available implementation software, and public CGM datasets presents difficult challenges delaying this important task.

Here, we present the characterization of CGM data collected as part of the 10K—a large-scale, prospective, longitudinal study. In this study, CGM was measured in more than 7,000 non-diabetic adults aged 40–70 years, between the years 2019 and 2022. We analyze previously defined glycemic measures, calculated using the iglu R package, and present a reference map of their values and distributions in a non-diabetic population. Further, we incorporate additional clinical measures obtained in the 10K cohort, to explore the relationship between CGM-derived measures and pre-selected variables indicating an individual health state in several aspects such as cardiovascular health, nutritional habits, and sleep quality. This work, which we term CGMap, aims to provide a useful resource for both clinicians and scientists, providing an open, available source of reference that can be used in any future work involving CGM data.

RESULTS

Participant characteristics and study design
CGM data of the 7,578 participants that have been recruited to the 10K project at the time of writing this study were analyzed. Excluding invalid CGM connections and connections of individuals who did not meet the inclusion criteria (see study population section in Method details), 7,104 individuals were included, 45.7% males and 54.3% females, with an average age of 52.7 years and mean BMI of 25.9 kg/m². CGM-derived measures of glucose control and glucose variability were calculated using the iglu R package. Participants in the 10K study also underwent blood tests and measurements of anthropometry, vital signs, liver ultrasound, body composition obtained by a DXA (dual-energy X-ray absorptiometry) scan, continuous real-time food intake logging, and continuous sleep monitoring for 3 nights (Figures 1A and 1B). We focused on 34 selected clinical measures that have been shown to be related to glucose control or diabetes that were divided into 6 categories: (1) measures of body composition, (2) measures from blood lipid profile, (3) vascular measures, (4) liver-related measures, (5) measures related to sleep disorders, and (6) measures of nutritional habits (see quantification and statistical analysis).
Reference values of CGM-derived measures

Using the iglu R package, all available 49 CGM-derived summary measures were calculated for each of the 7,104 eligible CGM connections in the study population (Figure 1C). A short description of the calculated measures can be found in Table S2. For each measure, percentiles for the entire study population, and for males and females separately, were calculated using Lowess regression, for every age from 40 to 70 years old, and can be found at https://github.com/ayya-keshet/CGMap. Additionally, we provide a simple-to-use online interface in which users can upload pre-measured CGM data, calculate all iglu measures, and place the measured individual on the age-gender reference values calculated from our non-diabetic population.

Relationship between CGM-derived measures

To characterize the relationships between CGM-derived measures, pairwise Pearson correlations were calculated and clustered using hierarchical clustering (Figure S2). This resulted in 5 clusters of CGM-derived measures, which we term as follows: (1) mean-glucose measures, (2) variability measures, (3) in-range measures, (4) high glucose level measures, and (5) low glucose level measures. The full list of CGM-derived measures, with division to clusters, can be seen in Table S3. Measures of glucose variability were divided between three clusters—cluster II and cluster IV, with two variability measures, ADRR (average daily risk range) and IGC (index of glycemic control), which were more correlated with measures of low glucose level measures, in cluster V. A previous work that examined the relationships between CGM-derived metrics, calculated using iglu, also found several clusters of the measures. Similar to the clusters found here, most measures of mean glucose (mean, eA1C, GMI, median, and J_index) clustered together.

To further analyze CGM-derived measures, we chose to focus on 8 key measures: TIR as percent time in range 70–180 mg/dL, eA1C, MAGE (mean amplitude of glycemic excursions), MODD (mean of daily differences), CV (coefficient of variation), J_index, LBGI (low blood glucose index), and HBGI (high blood glucose index) (summarized in Table 1). These 8 key measures were chosen to represent the different clusters, and they include measures currently used in clinic and research when reporting CGM data as TIR and eA1C, along with less studies metrics such as MODD and MAGE. Though some key measures represent identical aspects of glucose control, they were chosen because they capture differing biological aspects. For example, MAGE and MODD both summarize glucose variability, yet while the MODD is a measure that looks at day-to-day variability, the MAGE reflects the within-day glycemic variability. All further analyses will be shown on these selected measures and are available for all other measures in the CGMap repository at https://github.com/ayya-keshet/CGMap.

Progression of CGM-derived measures with age

To examine the progression of CGM-derived measures with age in a non-diabetic population, we used a robust linear regression model for each CGM-derived feature, examining a model fitted on the entire study population and additional separate models for males and females. Figure S3 displays the coefficients obtained for age in each model. We found variability in age-related changes of CGM-derived measures. The maximum glucose value showed the largest change, rising each year by 0.5 mg/dL (0.55 mg/dL in females; 0.54 mg/dL in males). Several measures do not change with age—for example, most of the TIR measures for several pre-defined glucose ranges. While some CGM-derived measures behave similarly in males and females, such as the SD (standard deviation) and different SD subtypes (SDw, SDhmm, SDdm, and SDwsh), some measures differ in their change with age in males and females. The minimum glucose value rises each year by 0.11 mg/dL in males, while in females the rise is almost double: 0.18 mg/dL each year. Age-gender reference plots for eA1C, MAGE, and MODD can be seen in Figure 2, and age reference plots for these measures as well as age and age-gender reference plots for J_index, HBGI and LGBI, CV, and TIR can be seen in Figures S4–S6. We found that eA1C obtained through CGM rises by 0.007% with each 1-year increase in age, with similar rises of 0.007% and 0.009% for each 1-year increase in age in males and females, respectively. All 8 key measures were found to have significant changes with age (Table S4), with MAGE showing the largest change with age: rising by 0.130 mg/dL with each 1-year increase in age, with an increase of 0.144 mg/dL in males and 0.117 mg/dL in females. Previous studies have shown that glucose variability in patients with diabetes, and the MAGE in particular, is affected by nutritional habits, such as carbohydrate consumption. Utilizing the real-time food logging reported by participants in the 10K cohort, we calculated the median percentage of daily carbohydrate consumption from the total caloric intake per participant, which in the entire cohort had a median value of 42.42% (8.98). Using the same analysis as for the CGM-derived measures, we analyzed whether carbohydrate consumption changes with age and found that carbohydrate consumption is slightly reduced with age in the entire population by 0.01% with every 1-year increase in age. To examine whether the changes of MAGE with age are affected by these changes in nutritional habits, we fitted a robust linear regression model for age, adjusting for the median daily carbohydrate consumption percent, and found that the increase of MAGE with age remained the same in males but was somewhat smaller in females and in the entire study population (Table S4). This small reduction in changes with age when adjusting for carbohydrate consumption was also observed for eA1C and J_index, and a summary of all results for the 8 key measures can be seen in Table S4.

Correlations of CGM-derived measures to other clinical measures

Thirty-four clinical measures related to glycemic control or diabetes, based on prior knowledge and previous research, were chosen from the 10K measures (see quantification and statistical analysis). The relationships between CGM-derived measures and these measures were analyzed using an age- and gender-adjusted correlation. Excluding HbA1C, which was analyzed separately, we divided all other 33 clinical measures into 6 categories: anthropometry and body composition, lipids, vascular, liver, sleep, and nutrition. Figure 3 shows the correlation coefficients for the 8 key CGM measures with the clinical measures in the above 6 categories. BMI, waist circumference, and total fat mass obtained through DXA showed very similar correlation patterns to all 8 key
measures, with statistically significant correlations to all measures but the MAGE, which was found to be significantly correlated only to BMI. This is partly in line with results from a study on a smaller population, which found that higher BMI and waist circumference were associated with higher mean-glucose levels and slightly higher levels of the MODD, but not the MAGE.29

Variable correlation patterns were found in the lipid category, inspecting measures of blood lipid profile obtained through blood tests. While total cholesterol and LDL cholesterol did not seem to be associated with any of the 8 CGM-derived measures, triglycerides showed significant correlations to all 8 key measures except CV, with positive correlations to all but the LBGI. HDL had a different pattern than all other lipid measures and was negatively correlated with TIR, eA1C, MODD, J_index, and HBGI; positively correlated with the LBGI and CV; and uncorrelated with the MAGE.

Clinical measures in the vascular category, which were obtained through varying methods, showed diverse correlations to the 8 CGM-derived measures. Systolic and diastolic sitting blood pressure (BP) were similarly correlated with the 8 CGM measures, with positive correlations to all but the LBGI. Carotid intima media thickness, which is obtained through an ultrasound test, showed an opposite pattern: a positive correlation to LBGI and a negative correlation to all other key measures. eGFR was positively and significantly correlated only to HBGI. The three vascular measures obtained through fundus imaging, average vessel width, vessel density, and fractal dimension, showed lower correlations than other measures in the vascular category, yet some were statistically significant. Fractal dimension showed a similar correlation pattern to the intima media thickness and was significantly correlated with eA1C and J_index, and average vessel width was significantly correlated with the MODD.

Many significant correlations were found between the 8 key CGM measures and liver-related clinical measures. ALT/GPT (alanine aminotransferase/glutamate pyruvate transaminase) and AST/GOT (aspartate aminotransferase/glutamate oxaloacetate transaminase) showed significant correlations to all but the LBGI. Carotid intima media thickness, which is obtained through an ultrasound test, showed an opposite pattern: a positive correlation to LBGI and a negative correlation to all other key measures. eGFR was positively and significantly correlated only to HBGI. The three vascular measures obtained through fundus imaging, average vessel width, vessel density, and fractal dimension, showed lower correlations than other measures in the vascular category, yet some were statistically significant. Fractal dimension showed a similar correlation pattern to the intima media thickness and was significantly correlated with eA1C and J_index, and average vessel width was significantly correlated with the MODD.

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transaminase) showed a similar correlation pattern, with ALT/GPT showing more significant correlations. Liver attenuation describes the weakening of the ultrasound beam as it passes through the liver and has been described to be related to clinical measures of liver state. 30 We found it was significantly correlated with all key measures but LBGI, with the highest correlation to the MODD. Liver elasticity, also obtained in liver ultrasound, 31 did not show significant correlations to any of the 8 key measures.

Sleep-related measures were obtained using continuous sleep monitoring, performed with a home apnea test for 3 nights. 18 The largest correlation from the 8 key measures was found between the mean oxygen saturation and eA1C, showing a negative correlation of $-0.15 (-0.17, -0.12)$ ($p < 10^{-6}$). MAGE and MODD, two measures of glycemic variability, showed different correlations to sleep-related measures: while the MAGE did not seem to be correlated with any sleep measure, MODD was significantly correlated with all sleep measures, with positive correlations to RDI (respiratory disturbance index), ODI (oxygen desaturation index), AHI (apnea-hypopnea index), and the total wake time and negative correlations to total sleep time and mean oxygen saturation. A previous study examining sleep-related measures of non-diabetic individuals found that AHI was significantly correlated with the mean glucose values obtained from CGM, but not with the SD or CV. 32 We found similar results showing that both the eA1C, a linear transformation of the mean glucose value, 33 and the mean glucose value itself were positively correlated with AHI, while the SD and CV were not.

When examining the relationship between measures summarizing nutritional information from real-time food logging and the 8 key CGM measures, we found that measures of macronutrients’ median daily consumption from the total caloric intake were more correlated with CGM measures than the median daily caloric intake. The percent of carbohydrate consumption was positively correlated with all measures but the LBGI, with the highest correlations to the MODD and CV, and a slightly lower correlation to the MAGE, despite the fact that the MAGE was designed as a measure for glycemic excursions directly related to meals. 34

Investigating the correlation patterns presented in Figure 3, we can observe that certain CGM-derived measures are more correlated with certain categories of clinical measures. Clinical measures of anthropometry and body composition show significant correlations to CGM-derived measures related to mean glucose—TIR, eA1C, and J_index—while clinical measures related to liver and sleep phenotypes are more correlated with CGM-derived measures of glucose variability as the MODD. TIR showed similar correlation patterns to those of eA1C and J_index, though the correlations were weaker and less significant. This might stem from the fact that our study population is non-diabetic and as such most glucose values measured are in the normal range, causing the TIR to be less variable.

Correlations between all 49 CGM-derived measures and the 34 clinical measures can be found in the CGMap repository at https://github.com/ayya-kehat/CGMap.

CGL-derived measures during sleep and wake
CGL-derived measures were calculated separately for wake, sleep, and all times, while only considering CGM measures overlapping with data obtained from continuous sleep monitoring devices (Figure 1A). Age- and gender-adjusted correlations were then calculated between each clinical measure and CGM-derived measures during wake, sleep, and all times. Many of the correlations between CGM-derived measures and clinical measures showed different patterns during sleep and wake times.

All anthropometry and body composition measures showed a higher correlation to eA1C, J_index, LBGI, and HBGI during sleep time as opposed to wake time. BMI showed a correlation of 0.16 (0.13, 0.19) ($p = 1.2 \times 10^{-23}$) and 0.12 (0.09, 0.15) ($p = 3.2 \times 10^{-14}$) to eA1C and J_index during sleep, while during wakefulness these correlations were 0.004 (−0.07, 0.08) ($p = 0.97$) and 0.02 (−0.06, 0.1) ($p = 0.80$) (Figure 4). These differences in correlations between wakefulness and sleep were apparent in clinical measures from other categories as well. Results for 6 such measures, one from each category, are shown in Figure 4. Triglycerides, from the lipids category, were significantly correlated with eA1C, J_index, HBGI, and LBGI only during sleep and not in wakefulness. Liver attenuation obtained through ultrasound, ODI from continuous sleep monitoring, and BP were significantly correlated with eA1C, J_index, and LBGI only during sleep, while in HBGI the differences between sleep and wake were less apparent. Additional sleep-related measures, AHI and RDI, also showed more apparent correlations to eA1C, J_index, HBGI, and MODD during sleep. A previous study integrating CGM and sleep monitoring in patients with type 2 diabetes found similar results showing that the correlation between obstructive sleep apnea (OSA), defined by the number of ODI events in an hour, and mean glucose value obtained through CGM was more pronounced during sleep compared to wakefulness. 35 Nutrition information-related clinical measures did not show clear differences in associations during sleep and wake, aside from the median daily carbohydrate intake (%), which showed higher correlations during wakefulness (Figure 4) and not during sleep.

While noticeable differences were observed in the connections of eA1C, J_index, HBGI, and LBGI to clinical measures, this was not the case for the MODD and the MAGE, which showed very similar correlations in sleep and wakefulness. Since sleep and wake correlations were calculated only using CGM measures overlapping with sleep monitoring data (Figure 1A), and some participants were only measured for 2 consecutive nights, only 1 day of CGM information was available for them. The MODD, which calculates the mean difference between

Figure 2. Age-gender reference plots
(A) eA1C.
(B) MAGE.
(C) MODD.
Orange, females; blue, males. Dots show data points. Dotted black lines show the 3rd, 10th, 50th, 90th, and 97th percentiles obtained using Lowess regression. Robust regression equation is shown in black.
Figure 3. Correlation of key CGM-derived measures with other clinical measures

Dots present the correlation coefficient, with lines marking the 95% CIs. Asterisk marks correlations with significant FDR-corrected p value.
glucose values obtained at the same time of day on different days, could not be calculated for these participants, leaving a smaller number of participants to calculate its correlations during wakefulness, which creates the large CIs for the MODD during wakefulness.

Results for all CGM-derived measures and all clinical measures during sleep, wakefulness, and all times can be found in the CGMap repository at https://github.com/ayya-keshet/CGMap.

DISCUSSION

In this work we analyzed a unique dataset of CGM measures, collected on more than 7,000 non-diabetic individuals. To the best of our knowledge, this is the first work that presents results on a large-scale cohort of non-diabetic individuals measured using CGM. As such, it holds the potential to serve as a fundamental reference for future research on CGM data. To construct this reference, which we termed CGMap, we first summarized CGM data using previously defined clinical measures, which could provide a comparable index for future work utilizing it, as one of the current issues when working with CGM data is the lack of standardized measures. We have made this information accessible at https://github.com/ayya-keshet/CGMap. The many previously defined clinical measures, and the relationships between them, have yet to be fully characterized in a healthy non-diabetic population, and as a result their redundancies are unknown. Analyzing 49 CGM-derived measures, we found that they could be clustered into 5 groups: (1) mean-glucose measures, (2) variability measures, (3) in-range measures, (4) high glucose level measures, and (5) low glucose level measures. Some of the measures showed very high correlations within our defined clusters, emphasizing the possible redundancies in them. While measures of mean glucose, in-range, hypoglycemia, and hyperglycemia clustered together, glucose variability measures were present in several different clusters, perhaps due to their divergent nature. The partition of CGM-derived measures presented here could be used in future work to focus only on a few relevant measures by choosing representative measures from each cluster, avoiding the use of redundant and highly correlated measures.

Analyzing the relation of the CGM-derived measures with age, in the entire study population and separately for males and females, we discovered diverse patterns of progression of CGM-derived measures with age. eA1C showed a slight increase with age, a result compatible with known changes of HbA1c, obtained through a blood test. MAGE, on the other hand, showed a larger increase with age. This increase remained even when accounting for the median daily percent of carbohydrate consumption from the total caloric intake, which in our study population slightly decreased with age. This might imply that the changes of MAGE with age do not stem from behavioral changes as we age but from biological mechanism changes, but
verifying this will require further explorations. CGM changes with age might just reflect the changes of glucose metabolism throughout the human life course; nevertheless, quantifying these changes could help clinicians estimate the expected change and identify abnormal changes. To facilitate the use of CGM to analyze longitudinal progression, standardized by age and sex, we must first determine which CGM-derived measures change with age and could be used for this purpose. Previous work partly investigated changes in glucose control with age both from blood tests and from CGM, yet here we present a comprehensive investigation, determining which CGM-derived measures change with age and at what scale. Further investigation is required to give clinical meaning to changes of CGM-derived measures with age and their possible association to health deterioration.

Exploiting the wealth of clinical measures taken as part of the 10K cohort, we sought to explore their connections to CGM-derived measures. We chose 34 clinical measures and divided 33 of them into 6 categories: anthropometry and body composition, lipids, vascular, liver, sleep, and nutrition. Many of the links between CGM-derived measures and the clinical measures analyzed here have not been previously studied, and less so in a non-diabetic population. Anthropometry and body composition measures have been shown to be related to glycemic variability, as well as mean blood glucose levels. Our analyses demonstrate that different correlation patterns exist between anthropometry and body composition measures and CGM-derived measures. While eA1C and the J_index, two relatively simple summary measures obtained through CGM, show very similar correlations to BMI, waist circumference, and body composition metrics obtained from DXA scan, the MODD and the MAGE—two glucose variability measures—display differing correlation patterns. This contrast between the MAGE and the MODD emphasizes the importance of feature selection and design, and moreover construction of clearer guidelines and metrics, when working with CGM data.

We found that clinical measures representing different body systems or phenotypes correlate with different CGM-derived measures: measures of body composition are associated with measures of mean glucose while measures of liver and sleep phenotypes are more associated with measures of glucose variability. These patterns emphasize the importance of choosing the relevant CGM summary measures according to the phenotype of interest and could assist clinicians and researchers to better choose which measures to examine according to the physical aspect they wish to investigate. Moreover, the choice of CGM measures might differ when working with non-diabetic as opposed to individuals with diabetes, as we found that widely used measures, such as TIR, showed weaker correlations to clinical phenotypes in our non-diabetic population.

Fractal dimension, obtained from fundus imaging, has been previously established as a potential marker for early detection of diabetic retinopathy in study populations with diabetic retinopathy or early signs of it. We have discovered that even in a non-diabetic population, the fractal dimensions display significant associations with measures of blood glucose control, such as eA1C and J_index, presenting its potential as an early marker for impaired glucose control even in healthy individuals.

On the other hand, we did not find any significant correlation between vessel density, another important measure in diabetic retinopathy, and CGM-derived measures.

Several previous studies have investigated the association between CGM-derived measures and sleep disorder measures such as AHI, ODI, and RDI, yet most have focused on individuals with type 2 diabetes or included a small population of non-diabetic individuals. Moreover, these studies did not focus on the differences in association between CGM-derived measures and sleep disorder measures in wakefulness and sleep times. We found, in a large population of non-diabetic individuals, that several key CGM-derived measures present different associations with several health-related measures, as well as sleep disorder measures, during wakefulness and sleep. This was most apparent in the association of eA1C and J_index to measures related to body composition such as fat mass, VAT mass, and BMI, which were more correlated during sleep. On the other hand, the MAGE and HbA1C were more correlated during wakefulness, perhaps due to the nature of the MAGE index, which was designed to evaluate meal-related glycemic excursions. Glucose levels during the day are affected by many behavioral factors such as meals, exercise, or medication intake, which might explain the changes in associations between CGM-derived measures and other clinical measures in wakefulness and sleep. The results found here could serve as a tool to distinguish which CGM-derived measures are better suited for future research involving sleep and CGM data.

Though most previous studies investigating CGM measures focused mainly on individuals with diabetes, a recently published study focused on characterizing CGM measures in a non-diabetic population. Despite the smaller sample size of 153 individuals, with a larger age span (7–80 years old), this study showed, similar to the results presented here, that measures of mean glucose and glucose variability (SD and CV) rise with age.

In summary, we present a comprehensive characterization of CGM measures on a large non-diabetic population. As the use of CGM in research and in the clinic is expanding, the reference values for CGM-derived measures provided here, and their relationship to other clinical measures, will serve as a key tool for researchers and clinicians: evaluating the health status of patients measured with CGM compared to a non-diabetic population, evaluating results of clinical trials utilizing CGM, and raising new research hypotheses regarding CGM and relevant health outcomes. We believe that the summaries and results we presented here may assist future research involving CGM data and hope it will inspire additional initiatives to expand this reference and knowledge base in the future.

Limitations of study

Our study has some limitations, one of them being CGM accuracy. While previous studies found its accuracy adequate, the FreeStyle Libre Pro Flash CGM device could be less accurate in hypoglycemia ranges, which needs to be considered when interpreting results involving CGM measures of hypoglycemia. Additionally, there is still no long-term follow up for the 10K participants, which prevents us from associating CGM measures and long-term health outcomes. To link CGM characteristics with future health outcomes, future studies are...
required, once 10K participants have been followed for several years. Moreover, further research is required to understand the biological and mechanistic meaning of the associations found in this study between CGM-derived measures and clinical measures.

**STAR METHODS**

Detailed methods are provided in the online version of this paper and include the following:

- **KEY RESOURCES TABLE**
- **RESOURCE AVAILABILITY**
  - Lead contact
  - Materials availability
  - Data and code availability
- **EXPERIMENTAL MODEL AND SUBJECT DETAILS**
  - Human participants
- **METHOD DETAILS**
  - Data
  - Covariates definitions
- **QUANTIFICATION AND STATISTICAL ANALYSIS**
- **ADDITIONAL RESOURCES**

Supplemental information can be found online at https://doi.org/10.1016/j.cmet.2023.04.002.

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**AUTHOR CONTRIBUTIONS**

A.K. conceived the project, designed and conducted the analyses, interpreted the results, and wrote the manuscript. S.S. interpreted the results and wrote the manuscript. A.G. conducted the analyses. Y.T.-B. and Y.A. interpreted the results. E.S. and H.R. conceived and directed the project and analyses, designed the analyses, interpreted the results, wrote the manuscript, and supervised the project.

**DECLARATION OF INTERESTS**

H.R. is an employee in Pheno.AI, Ltd, a biomedical data science company from Tel-Aviv, Israel. A.K. and E.S. are paid consultants to Pheno.AI, Ltd.

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**REFERENCES**


STAR METHODS

KEY RESOURCES TABLE

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RESOURCE AVAILABILITY

Lead contact
Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Hagai Rossman (hagai.rossman@weizmann.ac.il).

Materials availability
This study did not generate new unique reagents.

Data and code availability

- Data in this paper is part of the Human Phenotype project (THHP) and is accessible to researchers from universities and other research institutions at https://humanphenotypeproject.org/.
- Reference data is available at https://github.com/ayya-keshet/CGMap.
- Data S1 contains the values that were used to create all graphs in the paper (related to Figures 2, 3, and 4).
- Code is available at https://github.com/ayya-keshet/CGMap.
- Any additional information required to re-analyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Human participants
All participants sign an informed consent form upon arrival to the research site. All identifying details of the participants were removed prior to the computational analysis. The 10K cohort study is conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Weizmann Institute of Science. At the time of writing this study 7,578 individuals have been recruited to the 10K project, and recruitment is still ongoing. We analyzed CGM data of the 7,578 recruited individuals, including 8,617,490 glucose measurements, collected between January 2019 and July 2022. Valid CGM connections were considered as connections not containing glucose measures lower than 40 mg/dL or larger than 300 mg/dL. Additional exclusion criteria were reported diagnosis of type-2 diabetes, intermediate hyperglycemia or hypoglycemia without associated diabetes (according to ICD-11 codes 5A11, 5A40 and 5A41 accordingly), and reporting taking diabetes related medications (medications starting with A10 in ATC code). Overall 7,104 individuals were included, 45.7% males and 54.3% females, with an average age of 52.7 years and mean BMI of 25.9 kg/m\textsuperscript{2}. Figure S1 describes eligibility criteria and flow chart of cohort selection, and Table S1 summarizes baseline characteristics of the 7,104 individuals with eligible CGM connections.

METHOD DETAILS

Data
The data for this study was collected as part of the 10K project.\textsuperscript{18} Participants recruited to the study were connected to a FreeStyle Libre Pro Flash continuous glucose monitoring (FSL-CGM) system for two weeks. Data from the first and last days of the CGM
connection were removed prior to the analyses performed here, to maximize data accuracy. Additional measures taken for the participants in the study are blood tests, anthropometry, vital signs, liver ultrasound, body composition measures obtained by a DXA (Dual-energy X-ray absorptiometry) scan, continuous real-time food intake logging, and continuous sleep monitoring for 3 nights. Figure 1A illustrates the integration of CGM measures with information from continuous real-time food intake logging and continuous sleep monitoring. A complete description of the inclusion and exclusion criteria to the study, the measures obtained and the measurement techniques can be found in the original paper describing the 10K cohort.

Covariates definitions

Measures of nutritional habits
Using data from continuous real-time food intake logging, we created summaries of nutritional habits. To assure quality control of the data we first removed individual loggings of food items containing more than 5,000 calories. Following, we aggregated loggings from the same date to create a daily summary of the amount of calories consumed from carbohydrates, proteins and lipids, and the total calories (kcal) consumed. Days containing less than 500 calories reported were discarded. For each remaining day we calculated the percent of calories consumed from carbohydrates, proteins and lipids, and summarized the median of these over all days.

Sleep monitor and sleep staging
The 10K project employs the FDA-approved WatchPAT-300 from Itamar Medical for monitoring sleep. This device comprises five sensors: a wrist-worn actigraph, a finger-worn pulse oximeter and Peripheral Arterial Tone (PAT) probe, and a chest-worn microphone and accelerometer to measure respiratory effort, snoring, and body position. The PAT probe evaluates the modifications in the volume of blood vessels by exerting a consistent pressure over the finger, avoiding the buildup of venous blood and measuring the changes in the displaced volume flow within the probe using a photoplethysmogram (PPG) sensor. The PAT signal reflects changes in the autonomic nervous system (ANS) triggered by respiratory disturbances during sleep. The ANS controls several fundamental functions without conscious control, including blood vessel size and blood pressure regulation, lung airflow, and the heart’s electrical activity and contractility. The WatchPAT’s automatic algorithm analyzes the PAT signal amplitude in conjunction with heart rate and oxygen saturation to identify and classify breathing problems during sleep. Utilizing specific signal patterns, the algorithm provides two indices for diagnosing sleep apnea: Apnea/Hypopnea Index (AHI) and Respiratory Disturbance Index (RDI). The minimal oxygen desaturation for AHl and RDI events is 3%. The snoring sensor aids the clinician in determining if the respiratory events are obstructive, and the body position sensor helps the clinician determine if there is a positional component to the sleep apnea. Additionally, the pulse oximeter calculates the Oxygen Desaturation Index (ODI) based on the number of detected desaturation events per hour of sleep (minimal desaturation: 4%). The accuracy of these algorithms was validated using the gold standard polysomnography (PSG) sleep monitoring. The determination of sleep staging is done by combining multiple sensors. Sleep/wake detection is based on data recorded by the built-in actigraph. The accuracy of these algorithms was validated using the gold standard, manually scored PSG.

Fundus imaging
Fundus imaging is a medical imaging technique that allows for the capturing of detailed, high-resolution images of the back of the eye, including the retina, the optic nerve, and the macula. One of the crucial aspects that can be observed in fundus images is the retinal microvasculature, which refers to the network of small blood vessels that supply blood to the retina. The appearance and structure of the retinal microvasculature can provide insight into the health of the eye and aid in the diagnosis and monitoring of various conditions.

AutoMorph, an open source software package, utilizes deep learning models to aid in the preprocessing of fundus images. The package performs image preprocessing, image quality grading, anatomical segmentation, and the calculation of various morphological features such as vessel caliber, tortuosity density, and fractal dimension. These features are calculated for segmented veins and arteries.

Fractal dimension is a metric that quantifies the complexity of a geometric shape. In the context of the retinal microvasculature, it is used to describe the branching pattern of the blood vessels within the retina. This metric can be determined through methods such as box counting and Minkowski-Bouligand dimension. A high fractal dimension value indicates a complex branching pattern while a lower value indicates a simple pattern. This measurement can be used to detect pathological changes in the retinal vasculature with implications to health and disease.

QUANTIFICATION AND STATISTICAL ANALYSIS
CGM-derived measures of glucose control and glucose variability were calculated using the iglu R package. iglu was chosen since it provides an accessible tool to obtain comprehensive CGM evaluation metrics, as opposed to other packages which only provide reading and organizing capabilities or only partial summary measures compared to iglu. Robust linear regression to assess the relationship between CGM-derived measures and age, and also adjusted by gender, was performed using Hubber regression implemented in the statsmodels python package. Percentiles of the CGM-derived measures at each age were obtained using non-parametric locally weighted scatterplot smoothing (Lowess), using tsmoother. Correlations between CGM-derived measures and other clinical variables measured in the 10K cohort were performed using python pinguin package.

We chose to focus on 34 selected clinical measures which have been shown to be related to glucose control or diabetes: (A) Measures of body composition and (B) blood lipid profile related to metabolic syndrome and glycemic variability. BMI and waist
circumference measured at baseline visit; fat mass, scanned VAT mass and android tissue fat percent obtained using DXA scan; lipid profile obtained from blood tests; (C) Vascular measures such as blood pressure (BP), and measures related to retinopathy - these measures were selected as cardiovascular diseases and retinopathy are known complications of diabetes, and have been shown to be affected by glucose control.\textsuperscript{61–63} Retinopathy features were extracted from fundus images, taken with iCare DRSplus,\textsuperscript{64} using the AutoMorph software.\textsuperscript{53} We also included estimated glomerular filtration rate (eGFR), an important prognostic tool for renal failure, which we calculated from serum creatinine levels using the MDRD equation\textsuperscript{65}; (D) Liver related measures - As non alcoholic fatty liver disease (NAFLD) has been shown to be associated with glucose metabolism,\textsuperscript{66,67} we included ALT\textsuperscript{66,67}/GPT, GGT, AST\textsuperscript{66,67}/GOT, and liver attenuation, viscosity, elasticity and sound speed, from ultrasound tests; (E) Measures related to sleep disorders obtained from continuous sleep monitoring: Oxygen Desaturation Index (ODI), Apnea-Hypopnea Index (AHI), Respiratory Disturbance Index (RDI) along with total sleep and total wake time. These measures were chosen since sleep quality, sleep loss and sleep disorders have been shown to be associated with glucose homeostasis\textsuperscript{68} and diabetes\textbackslash glucose intolerance\textsuperscript{69,70}; (F) measures of nutritional habits were summarized from continuous real-time food intake logging, due to the importance of nutrition in glucose control.\textsuperscript{16} We calculated the median daily caloric intake, and the median percentage of caloric intake of carbohydrates, fats and proteins from the total caloric intake (for further details see covariates definitions under Method details). We also included in our analyses the HbA1C obtained through blood tests, which is one of the current measures used to diagnose diabetes.\textsuperscript{8} Blood tests in the 10K cohort were not measured at baseline and their results were provided by the participants from tests taken at their Health Maintenance Organization. To account only for clinically relevant blood tests, we included only blood test results which were reported to be taken at most 1-year prior to the baseline visit, selecting the most recent blood test for participants who had more than a single test. Not all measures described above were available for all participants, correlations were calculated for the subpopulation of individuals with both measurements correlated available, thus we present correlations with 95\% confidence intervals (CI). Correlations of CGM-derived measures to other variables measured in the 10K were adjusted for age and gender. To address multiple hypotheses we used FDR correction and considered correlations significant only if the FDR corrected p value was lower than 0.05.

**ADDITIONAL RESOURCES**

Human Phenotype Project: https://www.pheno.ai/home.