

The measurement and consequences of daily glucose variability

Citation for published version (APA):

Foreman, Y. D. (2021). *The measurement and consequences of daily glucose variability: a meaningful addition to the mean?* [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20211020yf>

Document status and date:

Published: 01/01/2021

DOI:

[10.26481/dis.20211020yf](https://doi.org/10.26481/dis.20211020yf)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Chapter 10

Scientific and societal impact

This chapter reflects on the scientific and societal impact of this thesis by identifying—in the context of the research field and current clinical practice—the different short- and long-term contributions of its findings.

Research field and main objectives of this thesis

Diabetes mellitus is a metabolic disease that is characterized by elevated blood glucose values¹. At present, approximately 463 million individuals are affected by diabetes worldwide; a figure that is expected to rise to 700 million by 2045^{2,3}. This is problematic because diabetes lowers life expectancy⁴⁻⁶ and strongly increases the chances of several diseases, including cardiovascular disease⁷, eye, kidney, and nerve disease^{8,9}, and dementia¹⁰. More and more studies show that having prediabetes, which is the stage between normal glucose metabolism and diabetes, is also unhealthy⁹⁻¹². This is concerning because the number of individuals with prediabetes is increasing worldwide as well^{13,14}.

Diabetes and its related diseases have a negative effect on quality of life¹⁵ and represent a large share of the global health spending^{16,17}. Prevention of these diseases will, thus, benefit the individual as well as society. However, this requires knowledge of the ways through which diabetes and prediabetes can cause disease. While decades of stellar research have led to great insights, and consequently have improved treatment and prevention¹⁸, much is still unclear. Relatively recently, daily glucose fluctuations, also known as daily glucose variability, were suggested to be harmful¹⁹. Hence, a main objective of this thesis was to study whether daily glucose variability is indeed related to cardiovascular disease, eye, kidney, and nerve disease, and cognitive decline.

At the start of this century, a new device was introduced to improve diabetes care²⁰. This device enables continuous glucose monitoring (CGM) and, thus, is able to record hundreds of glucose values per day. This allows for detailed study of daily glucose patterns. Hence, it is a device that is particularly suited to assess the degree of daily glucose variability²¹. Partly because of this, it is increasingly being used in scientific research and clinical practice. Studies have shown that use of CGM can improve diabetes care²⁰, and that the specific values calculated with CGM, in particular the intuitive index time in range, are important to individuals with diabetes²². However, several important aspects of CGM and the measurement of daily glucose variability have been insufficiently studied. Therefore, a main objective of this thesis was to do so in order to improve both future studies and clinical practice.

Relevance of the key findings

Continuous glucose monitoring and daily glucose variability measurement

In this thesis, we studied how many days are needed to get a reliable CGM recording. This is relevant because CGM is quite expensive and undergoing it can be a burden²³,

especially when daily fingerpricks are required to calibrate the device²⁰. Regarding short-term scientific value, knowledge of the minimum number of days needed can prevent both too short or too long recording periods, which would enhance measurement quality and limit participant strain in future studies, respectively. This information may also be used to reduce such burden in the clinical care of individuals with diabetes who intermittently wear a CGM. We believe that these findings can be used to improve the next *International Consensus Report on Clinical Targets for CGM Data Interpretation*²¹.

CGM is also used in closed-loop insulin delivery systems, which can dose insulin based on the glucose values measured with CGM^{24,25}. These systems are a very promising option to improve diabetes care in the near future²⁶⁻²⁹. These devices may be improved by addressing certain inherent shortcomings related to CGM, such as sensor delay and brief periods of sensor malfunction^{24, 30, 31}. In this thesis, we developed a model to predict future glucose values in order to improve the CGM part of closed-loop insulin delivery systems. Our model was able to accurately and safely predict glucose values at 15- and 60-minute intervals, which could be useful in case of short periods of CGM malfunction. Our aim is to explore the possibility of further optimizing these prediction models in cooperation with companies that are specialized in diabetes care.

A large number of values can be measured with CGM, such as the average glucose and degree of daily glucose variability²³. In this thesis, we studied, using data of participants with normal glucose metabolism, what the normal ranges of these values are. Interestingly, the daily glucose variability target that is currently recommended by the *International Consensus Report* lies much higher than the normal values found²¹. Future research should assess whether the target values should be lowered to more reflect the normal values by establishing whether daily glucose variability is harmful, and if so, at what point it becomes too damaging or unsafe.

In this thesis, we also investigated new ways to measure the amount of daily glucose variability. First, we found that the 'glucotype'³², which garnered substantial scientific attention³³⁻³⁶, did not live up to the expectation when used in other studies than the original one. Critical assessment of reproducibility is an important but often overlooked aspect of science³⁷. Second, we showed that the incremental glucose peak during an oral glucose tolerance test (OGTT) as well as the 1-hour OGTT values can be used as measures of daily glucose variability, albeit predominantly in a research setting. This has short-term scientific value because studies that have such data available can immediately start contributing to the study of daily glucose variability. In addition, it puts the results of previous studies on the 1-hour OGTT value in a new light³⁸.

In this thesis, we also extensively reflected on the methods and statistics used in all of its chapters with the aim of providing insights that can help improve future research. For example, we showed that researchers should be especially on their guard for the statistical phenomenon called multicollinearity, which occurs due to a strong

relationship between two or more measures³⁹, when studying the consequences of daily glucose variability.

The consequences of daily glucose variability

In this thesis, we have studied whether daily glucose variability is associated with several measures that precede actual diseases. We show that higher glucose variability is related to higher stiffness of the aorta, which reflects cardiovascular disease and mortality, to lower thickness of the nerves in the eye, which reflects neurodegeneration, and to worse cognitive performance, which reflects cognitive decline. Our findings thereby add to growing evidence that lowering of daily glucose variability (e.g., through lifestyle interventions or specific therapeutic regimens) could be important to prevent disease^{40,41}. However, it is too early to reach such definite conclusions based on our findings. Namely, we assessed precursors of disease rather than actual diseases. In addition, we studied the relationships at one point in time, which makes it difficult to establish cause and effect⁴². As such, the short-term merit of our research lies in the fact that we provide directions for future research on the consequences of daily glucose variability. In the long run—especially if studies convincingly show that daily glucose variability causes future disease and that its treatment can prevent such disease—we hope to be able to state that we have made a meaningful contribution to diabetes care with our initial studies on the effects of daily glucose variability.

Other key findings

In this thesis, we additionally found that prediabetes, diabetes, and measures of average glucose are also related to thickness of the nerves in the eye. This can have several implications for clinical practice. Measurement of the nerves in the eye could help select individuals who are at risk for developing eye or nerve disease. This would be feasible clinically because such measurement is non-invasive, inexpensive, and easy⁴³. In addition, it further indicates early lowering of blood glucose values, possibly already in prediabetes, is key in the early prevention of eye and nerve disease.

Knowledge dissemination to target groups

The impact of this thesis is primarily scientific. Namely, we report multiple ways to improve the quality of scientific research into CGM and daily glucose variability. As such, the scientific community is the main target group of this thesis. Publication of the results in scientific journals is one of the main ways to inform this community. In addition, the results of this thesis have been presented at several national and international conferences (see *Curriculum vitae*). As a result, it seems that these findings are starting to get noticed. For example, the incremental glucose peak has

recently received attention from one of the experts in the glucose variability field⁴⁰. Further, our findings on CGM recording period reliability have been used by other authors to justify their recording period length⁴⁴. In the end, the aim of scientific research is to improve society. If this thesis' suggestions on research quality continue to be applied in the coming years, this thesis will indirectly, positively impact society in the near future.

To a lesser extent, this thesis also has a direct societal impact, predominantly related to healthcare. Namely, certain key findings can have short- and long-term impact on diabetes care, such as reducing CGM burden and altering future therapy. As such, individuals with diabetes and prediabetes, as well as their relatives, are a target group of this thesis. While most of the findings of the current thesis are insufficient to alter the diabetes care of tomorrow, they do make a contribution to a field that can potentially improve the lives of a very large group of people (approximately 700 million in 2045)³. At present, it is debatable whether this target group would profit from being extensively updated on the current results. Regardless, the findings of this thesis have been presented in layman's terms on two separate occasions as part of the popular public symposium that is organized annually for the interested participants of The Maastricht Study.

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