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Socioeconomic Status and Glycaemic Variability in People with Type 2 Diabetes: A Baseline Analysis of the GP-OSMOTIC Study

Degree Project in Medicine

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ABBREVIATIONS

CGM	Continuous Glucose Monitoring
CONGA	Continuous Overall Net Glycaemic Action
CV	Coefficient of Variation
eGFR	estimated Glomerular Filtration Rate
FGM	Flash Glucose Monitoring
GP-OSMOTIC	General Practice Optimising Structured MOnitoring To achieve Improved Clinical Outcomes
GV	Glycaemic Variability
IQ range	Interquartile range
IRSD	Index of Relative Soceioeconomic Disadvantage
MAGE	Mean Amplitude of Glucose Excursions
r-CGM	retrospective Continuous Glucose Monitoring
RCT	Randomised Controlled Trial
REDCap	Research Electronic Data Capture
SD	Standard deviation
SEIFA	Socio-Economic Indexes For Areas
SES	Socioeconomic status
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TAFE	Technical And Further Education

ABSTRACT

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Socioeconomic Status and Glycaemic Variability in People with Type 2 Diabetes: A Baseline Analysis of the GP-OSMOTIC Study

Introduction

WHO has estimated that 422 million people have diabetes worldwide, of which approximately 90% have type 2 diabetes (T2D). Glycaemic management is central in diabetes care. HbA1c is the gold-standard to assess long-term hyperglycaemia. HbA1c has been linked to diabetes-related complications, such as cardiovascular disease. Additionally, HbA1c levels has been shown to be inversely associated with socioeconomic status (SES). Research has suggested that glycaemic variability (GV), short-term fluctuations in blood glucose, is a risk factor of diabetes-related complications independent of HbA1c. However, the relationship between SES and GV has not been explored.

Aim

To explore the relationship between GV and SES in people with T2D attending general practice in Victoria, Australia.

Methods

This secondary analysis used baseline data from the General Practice Optimised Structured MOnitoring To Improve Clinical outcomes (GP-OSMOTIC) trial. The analysis included 279 people with T2D. GV was quantified by coefficient of variation (CV), calculated using readings

from continuous glucose monitors. SES was measured by educational attainment and Index of Relative Socioeconomic Disadvantage (IRSD) deciles. An increase in IRSD decile inidicates lower levels of disadvantage. Multivariable mixed-effects linear regressions controlling for covariates were performed to explore the relationship between GV and SES.

Results

The mean (SD) CV in the study population was 30.0% (8.3) and 57 (20.4%) participants experienced high GV (defined as CV≥36%). The median (interquartile range) IRSD decile was 5 (2, 7). The educational attainment was similar to the Victorian population, based on the Australian census. No associations were found between CV and educational attainment/IRSD decile.

Conclusions

In contrast to the proven associations between HbA1c and SES, this study did not show any links beween SES and GV. This is the first study exploring this relationship. The evidence is still insufficient and more studies need to be conducted to completely evaulate this possible association.

Keywords

Type 2 diabetes, socioeconomic status, glycaemic variability, primary care

INTRODUCTION

Diabetes in numbers

The world has seen an almost fourfold increase in diabetes prevalence since 1980. The WHO now estimate that 422 million adults, or 8.5% of the adult population, live with diabetes(1). The two main types of diabetes are type 1 diabetes (T1D) and type 2 diabetes (T2D), with the latter accounting for around 90% of all diabetes cases(2). In Australia, diabetes has been recognised as a national health priority area since 1996(3). The prevalence of T2D in the Australian population is 4.1%(4) and the annual cost impact has been estimated at AU$14.6 billion(5). Diabetes was ranked as the seventh leading cause of death in Australia in 2017(6).

What is diabetes?

Physiological regulation of blood glucose

Diabetes is heterogenous condition associated with chronic hyperglycaemia. In people without diabetes, blood glucose levels are strictly controlled and only varies within a narrow interval. The two key hormones involved in this process are insulin and glucagon. Under normal physiological conditions, insulin is secreted from pancreatic β-cells in response to an increase in blood glucose concentrations, for instance after a meal. Insulin increases glucose uptake, e.g. by muscle cells and adipocytes, thereby providing the cells with an energy substrate while also decreasing blood glucose levels(7, 8). Low blood glucose concentrations, for instance while sleeping or between meals, trigger glucagon secretion from the pancreatic α-cells. Glucagon stimulates glucose release from the liver into the bloodstream(9). The interaction between insulin and glucagon is vital to maintain normoglycaemia.

Patophysiology of diabetes

T1D is caused by an autoimmune destruction of the insulin-producing β-cells in the pancreas. This deterioration leads to an inability to produce insulin, which causes hyperglycaemia(10). Two important pathophysiological mechanisms behind the development of T2D are insulin resistance and β-cell exhaustion(11). However, additional mechanisms have been described to contribute to the glucose intolerance(12). Insulin resistance is a phenomenon where tissues gradually become less sensitive to insulin. As a consequence to this inadequate response to normal insulin levels, cellular uptake of glucose decrease while blood glucose levels increase. The hyperglycaemia triggers a compensatory hyperinsulinaemia, where the secretion of insulin from the pancreas into the bloodstream increases to maintain normoglycaemia(7). Eventually the β-cells get exhausted because of this high strain(13). As the body cannot compensate for the insulin resistance any longer, blood glucose levels rises(7). The major aim of T2D management is to improve blood glucose levels. Lifestyle changes such as physical activity, dietary changes and weight loss, together with diabetes self-management education are important parts of diabetes treatment(14). If this is not sufficient to manage the hyperglycaemia, anti-diabetic drugs should be added to the regime(14). There are several different medication options available and treatment should be individualised(15). As the condition progresses, there is often a need to intensify the treatment, e.g. by increasing the dosage or adding another anti-diabetic drug. Eventually, some people with T2D need to implement exogenous insulin to the treatment regime because of the progressive β-cell dysfunction(11, 13, 14).

Diabetes-related complications

Apart from the day-to-day challenges of living with a chronic condition, diabetes is also associated with a substantial risk of developing complications as the condition progresses. The long-term complications are generally categorized into two main groups: microvascular and

macrovascular complications. Macrovascular complications refer to coronary artery disease, stroke and peripheral artererial disease. Microvascular complications refer to retinopathy, nephropathy and neuropathy(16). Because of the increased risk of macrovascular events, treatment of T2D also include management of other risk factors for cardiovascular disease, such as regulation of blood pressure and blood lipids(14). The risk of complications has repeatedly been associated with the level of chronic hyperglycaemia. Multiple studies have documented that treatment aimed to improve glycaemic levels reduces the risk of complications(17-20). Hence, it is important to frequently monitor blood glucose levels. Moreover, research has also shown that if the glycaemic management is too strict, there is an increased risk of hypoglycaemia. Hypoglycaemia is when blood glucose levels decreases to a level beneath the normal physiological threshold. The risk of hypoglycaemic events is particularly associated with the use of exogenous insulin(11). In addition to symptoms such as sweating, nausea, palpitations, drowsiness and confusion, it could also lead to harmful events such as seizures and coma if left untreated(21).

HbA1c: An important part of diabetes management

Several tools are being used to evaluate the effect of diabetes management and the progression of the condition. This includes physical assessment and pathology tests such as HbA1c, glycated haemoglobin(14). HbA1c is a proxy measure of the mean glycaemic levels over the last three months and it has been shown to have a strong correlation with the actual mean glucose values(22). HbA1c is considered the gold-standard to assess glycaemic management. According to current Australian guidelines, the general target for optimal glycaemic levels in people with T2D is a HbA1c of less than 7% (≤53 mmol/mol)(14). The recommendation is based on previous studies that have shown that tight glucose management prevent

complications, but also that there is an increased risk of hypoglycaemic events and increased mortality rates if treatment is too intensive(23). There are however several individual factors, such as age, presence of other conditions and history of hypoglycaemic events, that must be taken into account. Because of this, the HbA1c target can be set higher as well as lower than the general recommendation of 7%(23).

Glycaemic variability

Chronic hyperglycaemia does not seem to be the sole cause of diabetes-related complications. The large Diabetes Control and Complications (DCCT) study assessed the long-term risk of developing diabetic retinopathy in people with T1D and found that the risk could not be completely explained by HbA1c alone. The authors of the article therefore suggested that other measures of glycaemia could be of importance(17). It has now been proposed that there are three important factors in the impaired glucose metabolism of diabetes, referred to as the glycaemic triumvirate. In addition to chronic hyperglycaemia, this model adds hypoglycaemia and glycaemic variability (GV) to the deleterious components of diabetes-related dysglycaemia(24). GV refers to the acute fluctuations in blood glucose. GV has been found to be higher in people with T2D, compared to people without diabetes(25).

Various studies have linked micro- and macrovascular complications to GV, independent of the level of chronic hyperglycemia(26-28). Hyperglycaemia is known to cause vascular damage through different methabolic pathways. These have been shown to be derived from an overproduction of mitochondrial reactive oxygen species, referred to as oxidative stress(29). Activation of oxidative stress has also been linked to glucose fluctuations(30, 31) and research has suggested that GV could induce higher levels of oxidative stress than chronic hyperglycaemia(32). Additionally, a higher frequency of the glucose oscillations and a larger

amplitude of the hyperglycaemic excursions seem to generate even more oxidative stress, which ultimately could lead to the development of long-term complications(30, 33).

The abovementioned findings have raised the question if a marker of GV should be incorporated into a clinical setting as a tool to monitor the condition, but potentially also as a therapeutic target(34). Since HbA1c is a measure of the long-term mean glucose, daily fluctuations in glucose levels are not taken in consideration. This is a possible limitation in the routine assessment of glycaemic management. A person could for instance have low mean glucose levels and thereby optimum HbA1c levels, but still have high GV(34). A great level of fluctuations around a low mean value, indicates a risk of intermittent blood glucose excursions within the hypoglycaemic range, which is potentially dangerous and would not be captured by the clinician using only HbA1c. Additionally, it could imply that the risk of long-term complications is greater than what HbA1c indicates.

How should glycaemic variability be quantified?

GV is a broad term that has been used to describe variations within a day (intraday fluctuations) as well as variations between days (interday fluctuations). Moreover, several different indices has been used to quantify GV, e.g. the mean amplitude of glucose excursions (MAGE), standard deviation (SD) and continuous overall net glycaemic action (CONGA)(34). Each index has its own strengths and limitations. Some common difficulties are that most indices are based on complex equations and that the actual value can be hard to interpret for the clinician as well as the person with diabetes. The level of heterogeneity in how GV is described complicates the comparison of the aggregated research results. But with the increasing evidence of the relationship between GV and diabetes-related complications(26, 27, 30, 35-38), a need for a gold-standard method to describe GV arose. In 2017, an international expert panel at the

Advanced Technologies and Treatments for Diabetes (ATTD) congress came to the conclusion that coefficient of variation (CV) should be the primary measure of GV(39). CV is calculated by dividing the SD of glucose by the mean glucose, multiplied by 100 to get a percentage. Compared to only using SD, CV has the advantage of adding mean glucose to the calculation. The combination of mean and SD makes it more descriptive of hypoglycaemic excursions(38). To put CV in a clinical setting, a threshold of 36% has been suggested to distinguish between high and low GV. The reason behind this is that the risk of hypoglycaemic events increases significantly beyond the point of 36%(38, 39).

Continuous glucose monitoring

Measurements of GV has become more accessible to researchers and clinicians with the introduction of continuous glucose monitoring (CGM). CGM devices monitor and display glucose levels continuously to the person wearing the sensor. The FreeStyle Libre Flash Glucose Monitoring (FGM) system (Abbott Diabetes Care, Alameda, California), is another variant of CGM device. It is using a technology which requires that the sensor is scanned for glucose readings to be displayed(40). The FreeStyle Libre measures interstitial glucose levels with a filament that is inserted into subcutaneous tissue of the upper arm. The interstitial glucose concentration is representative of the blood glucose concentration, but with a time delay(40). A study published in 2015 reported this lag time to be 4.5 ±4.8 minutes(41). Glucose levels are automatically read every 15 minutes and data is stored in the device for 8 hours. The sensor can be worn for a maximum of 14 days(42). The FreeStyle Libre Pro is a version of the FGM system that stores all glucose readings to be analysed after the full 2-week period, a technology called retrospective continuous glucose monitoring (r-CGM). During this time, the readings are inaccessible to the person wearing the sensor until they are reviewed, e.g. at the general practice.

These readings can be used to calculate mean glucose levels and SD for the period the sensor is worn.

Socioeconomic status

The increasing availability of FGM technology has led to new opportunities to study the relationships between GV and other variables. One of certain importance is socioeconomic status (SES), which has been demonstrated to be associated with multiple health inequities such as differences in mortality risk(43) and onset of multimorbidity(44). Inequities can be regarded as differences in health according to social groupings that are unjust and avoidable(45). The interest in SES in health is driven by a concern for social justice and the notion that health and health care opportunities, experiences and outcomes should not be dependent on a person's social position. The study of SES inequities in health has a long tradition and aims to identify, expose, monitor, address and reduce health inequity. SES is a multidimensional concept, often defined by various variables within three main domains: social, economic and work status(46). It can be used as an individual and as an area-based measure. A lack of consensus on how to best capture SES has led to a great variety in the variables used in previous research. Individual SES has been estimated by factors such as income, level of education and occupational status. Regional SES is often estimated with the use of indices based on censuses(47). These indices generally take several variables in account, for instance the proportion of unemployment and one-parent families in an area.

Socioeconomic status and diabetes

SES has been associated with several diabetes-related outcomes. The Australian Institute for Health and Welfare has reported that lower SES is associated with a higher prevalence of diabetes, an increased rate of hospitalisations and higher diabetes-related mortality rate in the

Australian population(48). Furthermore, an inverse association between HbA1c levels and SES has been identified by several studies(49-51). This was recently confirmed by a meta-analysis investigating the association between SES and HbA1c(52). Increased risk of hypoglycaemic events is another diabetes-related outcome associated with lower SES(53). Various lifestyle factors related to an increased risk of developing diabetes, e.g. physical inactivity and being overweight(54), have also been reported to have an association with SES. People with higher SES has been shown to have a lower BMI, healthier diets and a greater probability of engaging in leisure physical activity, compared to people with lower SES(55-57). No research has been conducted on the relationship between GV and SES to my knowledge, even though several associations between SES and diabetes-related outcomes have been established. As GV has been shown to be a risk factor for long-term complications independent of HbA1c(26, 27, 37) and as GV has a potential role as a clinical tool(34), this missing piece in the research needs to be addressed.

The aim of this study

The aim of this secondary data analysis is to explore the relationship between GV and SES. In addition to contributing to a broader understanding of this emerging marker of glycaemia, it could also lead to an increased clinical consideration of the impact SES has on diabetes and diabetes management.

Research question

What is the relationship between glycaemic variability, measured by coefficient of variation, and socioeconomic status in people with type 2 diabetes attending general practice in Victoria, Australia?

Hypothesis

There is an inverse relationship between socioeconomic status and glycaemic variability in people with type 2 diabetes attending general practice in Victoria, Australia.

METHODS

Study design and study population

This is a secondary analysis of baseline data from the General Practice Optimising Structured MOnitoring To achieve Improved Clinical outcomes (GP-OSMOTIC) study, a randomised controlled trial (RCT)(58). The aim of GP-OSMOTIC is to investigate how the intermittent use of r-CGM could impact the care of people with T2D in general practice. The two main aims are to investigate [1] if the use of r-CGM could improve HbA1c levels in people with T2D not reaching their individual target and [2] if the use of r-CGM is cost-effective for this purpose.

Inclusion criteria for the GP-OSMOTIC trial were: age between 18 to 80 years, ≥1 year of T2D diagnosis, active patient of the practice (defined as ≥3 visits in the last 2 years) the most recent HbA1c level 0,5% (5,5 mmol/mol) above the individualised target (with the latest HbA1c measured in the previous month), stable anti-hyperglycaemic treatment for the last 4 months with at least 2 non-insulin hyperglycaemic agents and/or insulin.

Exclusion criteria for the GP-OSMOTIC trial were: any debilitating medical condition (e.g. unstable cardiovascular disease and end-stage cancer), an estimated glomerular filtration rate (eGFR) <30 ml/min/1,73 m^2, proliferative retinopathy, lactation, pregnancy or planning pregnancy, inability to speak english or give informed consent, unwillingness to use r-CGM or follow the study protocol, allergy to the adhesive tape needed for attaching the r-CGM and conditions that make monitoring of glucose control with HbA1c unreliable (e.g. iron deficency anaemia and haemoglobinopathy).

Additional exclusion criteria for this secondary analysis were: missing r-CGM data (e.g. if the sensor malfunctioned or was lost by the participant or clinic) and less than 5 days of r-CGM data. This is because the manufacturer of the r-CGM device states that at least 5 days of readings is required to obtain enough readings for the results to be reliable(42).

In the GP-OSMOTIC trial, participants were randomised to either an intervention arm or a control arm. Participants in the intervention group wore the r-CGM for 2 weeks every 3 months (baseline, 3, 6, 9 and 12 months) while those in the control group only wore the r-CGM for 2 weeks at baseline and at 12 months. Regardless of study arm, all participants were recommended to meet with their health professional for clinical review every 3 months. This is consistent with current clinical guidelines in Australia(14). In addition to the usual clinical care, the intervention group viewed and discussed the reports from the r-CGM together with their health professional at these quarterly meetings. In the control group, the baseline r-CGM-report was blinded to the participant and the health professional. However, the r-CGM data from 12 months could be viewed as this marked the end of the data collection for the trial.

Data collection

The data was collected from people with T2D attending general practice in Victoria, Australia. A total of 299 participants were recruited from 25 general practices between October 2016 and November 2017. All participants gave their written consent before enrolling in the study.

The r-CGM device that was used to collect data on glucose levels was the FreeStyle Libre Pro Flash Glucose Monitoring System. The sensor was applied to the participant's upper arm by a health professional (general practicioner or practice nurse) and was then activated using the appurtenant reader. When activated, the sensor records interstitial glucose levels every 15 minutes. After application, the device could be worn for a maximum of 14 days. All glucose

readings were inaccessible to the participant while wearing the device. After this period, the sensor was returned to the general practice where the health professional downloaded the data to a computer and onto *Microsoft Office Excel 2013* (Microsoft Corporation, Seattle, Washington, USA).

Baseline data collection also included pathology tests (e.g. blood lipids and creatinine) and biometric measures such as blood pressure, weight and height. If the HbA1c had not been measured during the last month, it was included in the baseline pathology tests collected by research assistants. Information about medicines and other medicial conditions was obtained from the participants' electronic medical records. Participants also completed a survey with the help of research assistants. The survey included questions on smoking status, dietary and exercise habits, educational attainment, psychological well-being and frequency of self-monitoring of blood glucose. Written consent, data from the survey and clinical data was collected and managed in *REDCap* (Research Electronic Data Capture)(59), hosted at a secure server at the University of Melbourne.

Variables

Glycaemic variability

The readings from the r-CGM devices was used to calculate GV. The chosen measurement was coefficient of variation (CV), as international consensus recommendations states that CV should be the primary measure of GV(39). CV was calculated using the formula $CV = ([SD\ of\ glucose] / [mean\ glucose]) \cdot 100$. All calculations of the mean and SD of glucose were performed using the software *EasyGV version 9.0.R2* (Oxford University Innovation, Oxford, United Kingdom). EasyGv is an Excel workbook that uses the recordings from r-CGM

devices to calculate various measurements of GV. Calculations of CV were then performed in *STATA version 15.0* (StataCorp, College Station, Texas, USA).

Socioeconomic status

Area-based socioeconomic status

The Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socioeconomic Disadvantage (IRSD) score was used as the measurement of area-based SES. Participants were matched with an IRSD score based on the residual postcode they reported in the baseline survey. The IRSD index is based on the 2011 Australian census. It includes 16 different economic, social and political variables which indicate a relative disadvantage(60). These include factors such as unemployment rate, the proportion of one-parent families and the proportion of people with a yearly income of less than $20,800. All variables are summarised to a score. The score is used to compare the relative difference in disadvantage between areas in Australia. The lower the score, the higher proportion of relatively disadvantaged people in that area. Based on the score, the areas can also be ordered into deciles. The first decile consists of the 10% of the areas with the lowest scores and the tenth decile consists of the 10% of the areas with the highest scores(60).

Individual socioeconomic status

Educational attainment was used as the measurement of individual SES. Participants answered the question "*What is the highest level of education you have completed*?" in the baseline and were given the following five options to choose from: "*never attended"*, "*primary education"*, "*secondary education"*, "*trade/TAFE"* and "*university degree/diploma"*.

In Australia, primary education stretches from Kindergarten to year 6 or 7 and secondary education from year 7 or 8 to year 12. TAFE (Technical And Further Education) is a form of

tertiary education. The education is vocational and the training mainly gives the student practical skills in a specific employment field, such as business or tourism(61). Trade school is generally shorter than TAFE and is often part of an apprenticeship, where working is combined with training for a profession, e.g. electrical and plumbing.

Covariates

The following variables were identified as potential covariates for this analysis: age, diet and exercise habits, BMI, multimorbidity condition count, insulin prescription and HbA1c. Age was used instead of duration of diabetes, since the two variables show a collinear relationship and duration of diabetes was poorly recorded in the electronic medical records. Two questions from the baseline survey was used to assess diet and exercise habits: [1] "*On how many of the last seven days did you space carbohydrates evenly during the day?*' and [2] "*On how many of the last seven days did you participate in at least 30 minutes of physical activity? (Total minutes of continuous activity, including walking)*". The BMI was calculated using the biometric measures recorded at the baseline study assessment visit. The multimorbidity condition count was based on information from the electronic medical records. A total of 40 possible chronic conditions (other than T2D) were included in this count, based on previous research on multimorbidity(44, 62-65). The full list of the chronic diseases is provided in *Appendix A*. Information on insulin prescription was also retrieved from the electronic medical records. For the HbA1c, baseline measures were used.

Statistical methods

All baseline data was downloaded from *REDCap* onto *Microsoft Office Excel*. It was then uploaded to the statistical software *STATA version 15.0*, which was used for all data analyses. Multivariable mixed-effects linear regressions were used to explore the relationships between

[1] IRSD decile and CV and [2] educational attainment and CV. The statistical model also included random intercepts for general practices to account for the clustering of patients within clinics and adjustment for age, diet, exercise, BMI, insulin prescription, multimorbidity condition count and HbA1c.

Continuous measures with a normal distribution are summarised using mean and standard deviation (SD). Continuous measures with a skewed distribution are summarised using median and interquartile range (IQ range). Categorical variables are summarised using frequencies (n) and percentages (%).

In the analysis of the relationship between educational attainment and CV, participants who answered "*never attended*", "*primary education*" and "*secondary education*" in the baseline survey were merged and used as a reference group. The two remaining education levels, "*trade/TAFE*" and "*university degree/diploma*", were compared to the reference group. The IRSD deciles of the study population were not normally distributed. Log and square root transformations of this variable were therefore considered. However, the distribution did not improve when comparing the original data to the transformed data. As neither log or square transformation resulted in an improvement of data distribution, the original data was used for my analysis.

Power calculation

No power calculation was performed for this secondary data analysis. This is because there was [1] no pilot study [2] no known data on the mean difference and standard deviation of GV in a population of people with T2D in a general practice setting to base a power calculation on. The GP-OSMOTIC trial was powered to detect a 0.5% (5.5 mmol/mol) difference in mean HbA1c

between the control and the intervention arm and may not have been powered to detect differences in GV.

ETHICS

Ethics approval for the GP-OSMOTIC trial has been obtained from the University of Melbourne Health Sciences Human Ethics Sub Committee (amendment ID 1647151.6). The ethics approval also includes this secondary analysis. All participants signed a consent form before enrolment in the study.

RESULTS

Study population: Recruitment

The study population consisted of 279 participants, as a total of 20 of the 299 participants from the GP-OSMOTIC trial met the exclusion criteria set for this secondary data analysis. Data from the r-CGM was missing for 8 of the participants and another 12 had less than 5 days of r-CGM readings, which is insufficient to obtain reliable glucose profiles(42). A flowchart of the recruitment of participants for the GP-OSMOTIC and this secondary analysis is displayed in *Figure 1*.

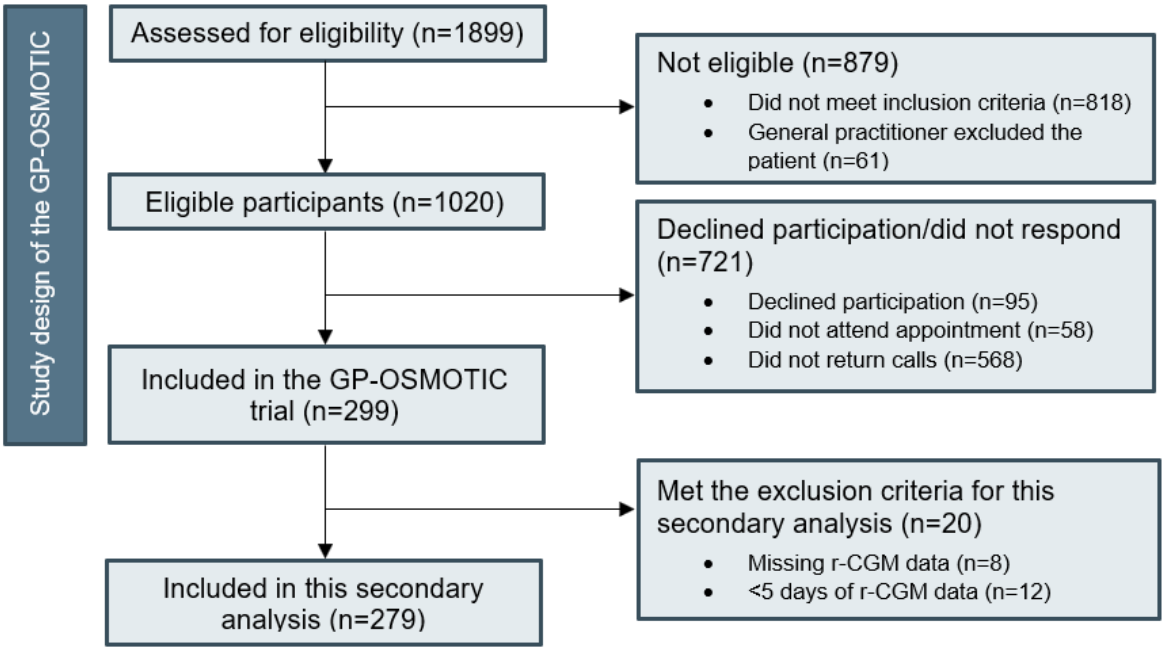

Figure 1. Flowchart of the recruitment of the study population of GP-OSMOTIC and this secondary data analysis.

Study population: Characteristics and glycaemic measures

The characteristics of the study population are summarised in *Table 1*. Comparison of the included and the excluded participants showed no major differences in the key characteristics. The full list of the characteristics of the excluded participants is provided in *Appendix B*. Information on the IRSD deciles, educational attainment and CV of the study population are summarised in *Table 2*. The mean (SD) duration of r-CGM use by the 279 included participants was 12.3 (2.4) days. No hypoglycaemic events were recorded by the r-CGM devices during this period. The mean (SD) CV in the cohort was 30.0% (8.3) and 57 (20.4%) of the participants experienced high GV (CV ≥36%(38, 39)). The distribution of CV in the cohort is displayed in *Figure 2*.

Table 1. Characteristics of the study population.

Characteristics	n = 279	Missing data, n (%)
Age (in years), mean (SD)	60.4 (9.9)	-
Female, n (%)	114 (40.9)	-
Years of diabetes, median (IQ range)	12 (9, 20)	13 (4.7)
Currently smoking[a], n (%)	39 (14.0)	12 (4.3)
Insulin prescription, n (%)	143 (51.3)	-
Diet[b], median (IQ range)	3 (1, 5)	1 (0.4)
Exercise[c], median (IQ range)	5 (3, 7)	1 (0.4)
BMI (kg/m^2), mean (SD)	33.9 (7.8)	-
Multimorbidity condition count[d], n (%)		
Diabetes only	30 (10.8)	
Diabetes + 1 condition	70 (25.1)	
Diabetes + 2 conditions	68 (24.4)	-
Diabetes + 3 conditions	42 (15.1)	
Diabetes + ≥4 conditions	69 (24.7)	
HbA1c, mean (SD)		
mmol/mol	74.1 (13.3)	-
%	8.9 (1.2)	

[a]= One or more cigarettes per day in the past 12 months
[b]= How many days in the last week that participants spaced carbohydrates evenly through the day
[c]= How many days in the last week in which participants engaged in ≥30 minutes of physical activity
[d]= Based on a total of 40 possible conditions, listed in *Appendix A.*

Table 2. Measurements of socioeconomic status and glycaemic variability in the study population.

Characteristics	n = 279	Missing data, n (%)
IRSD decile[a], median (IQ range)	5 (2, 7)	4 (1.4)
Educational attainment, n (%)		
Never attended	1 (0.4)	
Primary education	20 (7.2)	
Secondary education	129 (46.2)	12 (4.3)
Trade/TAFE[b]	51 (18.3)	
University degree/diploma	66 (23.7)	
Glycaemic variability (CV[c]), mean (SD)	30.0 (8.3)	-
High glycaemic variability (CV ≥36%)		-
Yes, n (%)	57 (20.4)	
No, n (%)	222 (79.6)	

[a]= Index of Relative Socioeconomic Disadvantage. The first decile is the most deprived, the tenth decile is the least deprived
[b]= Technical And Further Education
[c]= Coefficient of variation ([SD of glucose] / [mean glucose] · 100)

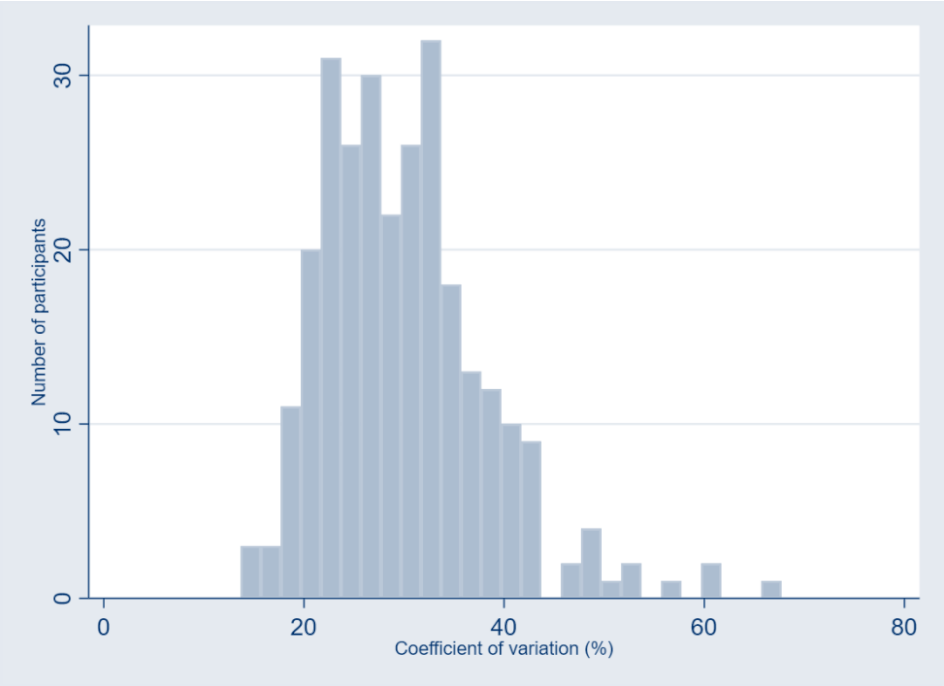

Figure 2. Histogram displaying the distribution of glycaemic variability (quantified by coefficient of variation) in 279 people with type 2 diabetes in Victoria, Australia.

Relationship between glycaemic variability and IRSD

The distribution of participants in the IRSD deciles are displayed in *Figure 3*. The median (IQ range) IRSD decile was 5 (2, 7). The correlation between GV (quantified by CV) and IRSD deciles are shown in *Figure 4*.

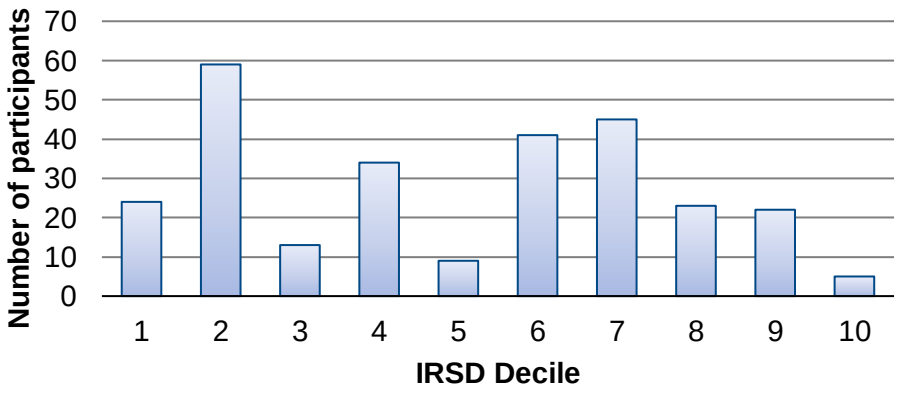

Figure 3. Bar chart displaying the number of individuals in the deciles of Index of Relative Socioeconomic Disadvantage (IRSD) scores. The IRSD scores of the entire Australian population are grouped into 10 equally sized groups (deciles). The first decile contains the most deprived areas and the tenth decile contains the least deprived areas. Information on IRSD was missing for 4 out of 279 participants.

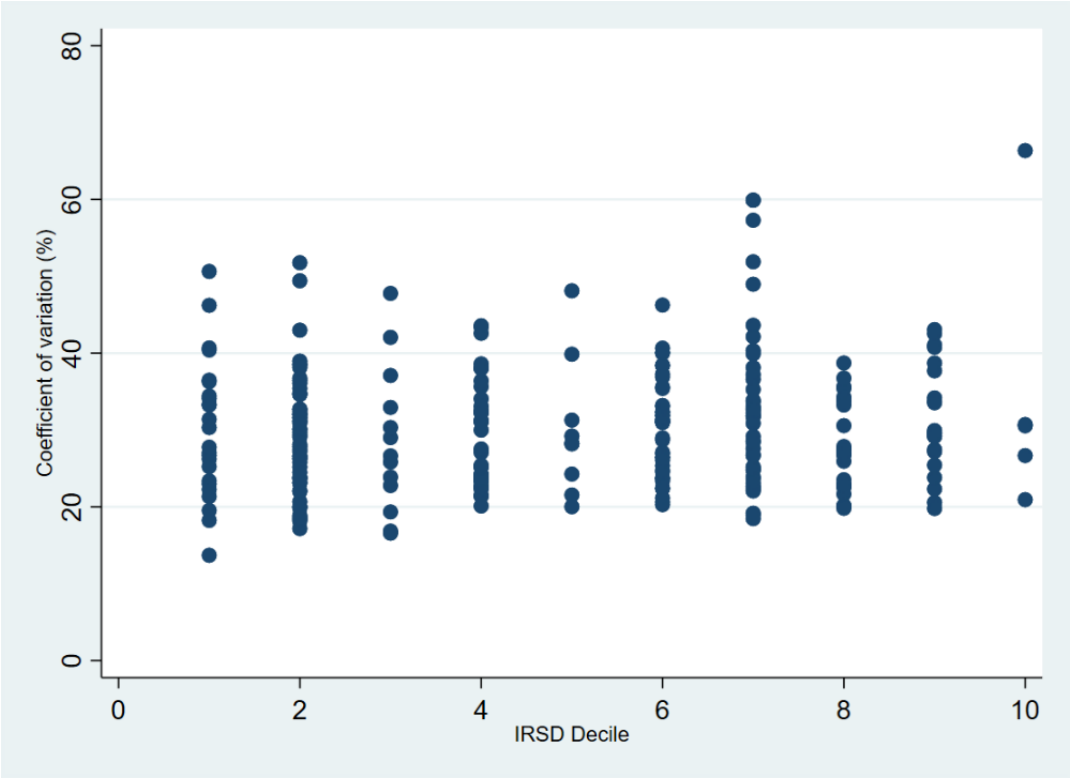

Figure 4. Scatter plot of the correlation between glycaemic variability (quantified by coefficient of variation) and the Index of Relative Socioeconomic Disadvantage (IRSD) deciles in 275 people with type 2 diabetes in Victoria, Australia. Information on IRSD was missing for 4 participants.

The unadjusted and adjusted results exploring the association between CV and IRSD are presented in *Table 3* together with the full list of covariates. The unadjusted linear regression showed that one increase in IRSD decile, meaning a higher level of socioeconomic advantage, was associated with a 0.04% increase in CV (95% confidence interval -0.39, 0.47, p-value 0.86). Following adjustment for the covariates (age, diet, exercise, BMI, insulin prescription, multimorbidity condition count and HbA1c), an increase in IRSD decile was associated with a 0.03% increase in CV (95% confidence interval -0.35, 0.40, p-value 0.89). The results were not statistically significant.

Table 3. Association between glycaemic variability and IRSD deciles in the unadjusted and adjusted model, including the results for all covariates.

CV[a]	β-coefficient (95% CI)	p-value
Unadjusted model		
IRSD[b] decile	0.04 (-0.39, 0.47)	0.86
Adjusted model with covariates		
IRSD[b] decile	0.03 (-0.35, 0.40)	0.89
Age in years	0.15 (0.06, 0.25)	<0.01
BMI (kg/m^2)	-0.11 (-0.22, 0.01)	0.06
HbA1c (%)	-1.03 (-1.74, -0.33)	<0.01
Multimorbidity condition count[c]	-0.37 (-1.07, 0.33)	0.30
Insulin prescription	6.83 (5.07, 8.60)	<0.01
Exercise[d]	-0.31 (-0.69, 0.06)	0.10
Diet[e]	-0.11 (-0.47, 0.25)	0.54

[a]= Coefficient of variation, ([SD of glucose] / [mean glucose] · 100)
[b]= Index of Relative Socioeconomic Disadvantage. The first decile is the most deprived, the tenth decile is the least deprived
[c]= Based on a total of 40 possible conditions, listed in *Appendix A.*
[d]= How many days in the last week in which participants engaged in ≥30 minutes of physical activity
[e]= How many days in the last week that participants spaced carbohydrates evenly through the day

Relationship between glycaemic variability and educational attainment

Out of the 279 participants, 1 (0.4%) had never attended school, 20 (7.2%) had finished primary education and 129 (46.2%) had finished secondary education. These 150 (53.4%) participants constituted the reference group for the anlysis. Of the remaining participants, 51 (18.3%) had an education in trade/TAFE and 66 (23.7%) had a university diploma or degree. Information on educational attainment was missing for 12 (4.3%) participants. The educational attainment of the study population is displayed in *Figure 5*. The correlation between GV (quantified by CV) and educational attainment is shown in *Figure 6.*

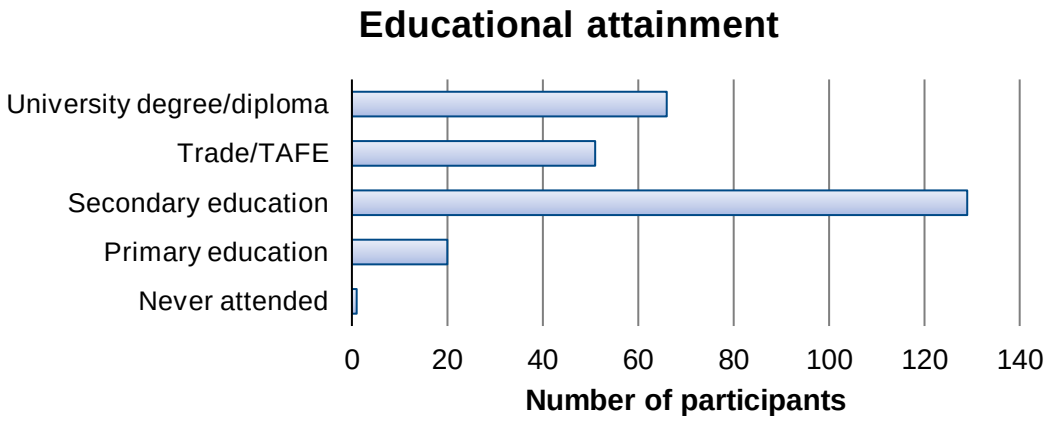

Figure 5. Bar chart showing the distribution of educational attainment among 257 people with type 2 diabetes in Victoria, Australia. Information on educational attainment was missing for 12 participants.

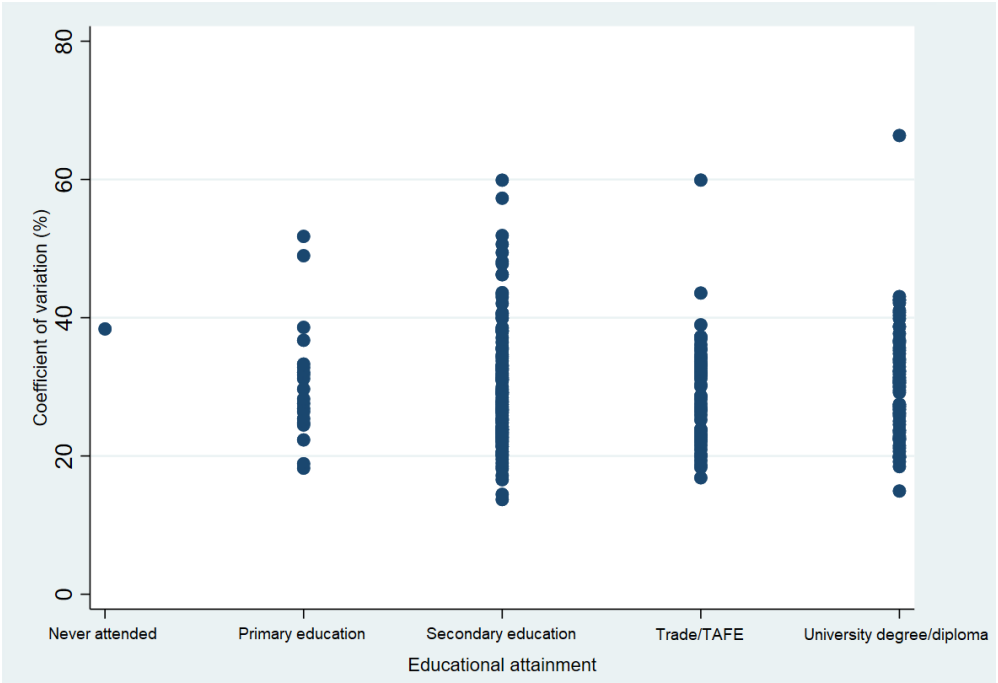

Figure 6. Scatter plot of the relationship between glycaemic variability (quantified by coefficient of variation) and the educational attainment in 267 people with type 2 diabetes in Victoria, Australia. Information on educational attainment was missing for 12 participants.

The results exploring the association between CV and educational attainment are presented in *Table 4* together with the full list of covariates. In the unadjusted model, participants with the educational level "*trade/TAFE*" had 0.93% lower CV (95% confidence interval -3.50, 1.64, p-value 0.48) than the reference group consisting of participants answering "*never attended*",

"*primary education*" and "*secondary education*" in the baseline survey. Participants with the educational level "*university degree/diploma*" had a 0.78% lower CV (95% confidence interval -3.24, 1.67, p-value 0.53) than the reference group. After adjusting for the covariates, both educational levels were associated with an increase in CV compared to the reference group. The increase was 0.70% in the trade/TAFE group (95% confidence interval -1.62, 3.02, p-value 0.56) and 0.33% in the university degree/diploma group (95% confidence interval -1.87, 2.53, p-value 0.77). The results were not statistically significant.

Table 4. Association between CV and educational attainment in the unadjusted and adjusted model, including the results for all covariates.

CV[a]	β-coefficient (95% CI)	p-value
Unadjusted model		
Never attended, primary education, secondary education (reference)	-	-
Trade/TAFE[b]	-0.93 (-3.50, 1.64)	0.48
University degree/diploma	-0.78 (-3.24, 1.67)	0.53
Adjusted model with covariates		
Never attended, primary education, secondary education (reference)	-	-
Trade/TAFE[b]	0.70 (-1.62, 3.02)	0.56
University degree/diploma	0.33 (-1.87, 2.53)	0.77
Age in years	0.17 (0.08, 0.27)	<0.01
BMI (kg/m^2)	-0.11 (-0.22, 0.01)	0.07
HbA1c (%)	-1.02 (-1.75, -0.30)	<0.01
Multimorbidity condition count[c]	-0.45 (-1.18, 0.28)	0.23
Insulin prescription	6.87 (5.04, 8.71)	<0.01
Exercise[d]	-0.34 (-0.72, 0.04)	0.08
Diet[e]	-0.16 (-0.54, 0.21)	0.39

[a]= Coefficient of variation, ([SD of glucose] / [mean glucose] · 100)
[b]= Technical And Further Education
[c]= The count is based on a total of 40 possible conditions, listed in *Appendix A*.
[d]= How many days in the last week in which participants engaged in ≥30 minutes of physical activity
[e]= How many days in the last week that participants spaced carbohydrates evenly through the day

DISCUSSION

Summary of the results

This secondary analysis on baseline data from the GP-OSMOTIC trial(58) aimed to explore the relationship between GV and SES in people with T2D attending general practice in Victoria, Australia. This study cohort consisted of 279 participants from 25 general practices. The mean (SD) CV of the participants was 30.0% (8.3) and 57 (20.4%) of the participants experienced high GV (CV ≥36%(38)). No associations were found between GV and SES, which was quantified by the IRSD deciles(60) on an area-level and by educational attainment on an individual level. This was in contrast to the hypothesis of the study. Moreover, the small changes in mean CV observed between the groups of different SES in the analyses can not be considered clinically significant.

Relation to previous research

The mean CV in this study population was slightly higher than what has been reported by some of the previous studies using CV as a measure of GV in people with T2D(26, 38, 66). The cohorts in these previous studies were recruited from outpatient clinics and not from primary care. Moreover, 51.3% of the participants in the GP-OSMOTIC cohort were prescribed insulin, which is a higher proportion than in the abovementioned studies. This may explain the higher mean CV observed in this population. A previous study has demonstrated GV to be higher in people prescribed insulin(38). Exogenous insulin is often implemented after years of progressive β-cell exhaustion, one of the important pathophysiological pathways of T2D(11), which has been linked to increasing GV(67).

To my knowledge, this is the first study on the relationship between GV and SES. The absence of a relationship in this specific study is however in contrast to what has been demonstrated

regarding the association between SES and other glycaemic parameters in people with T2D. Previous research have suggested that those with lower SES are associatied with higher HbA1c levels(52) and are at an increased risk of hypoglycaemic events(53). Additionally, lower SES has been associated with a higher prevalence of T2D(49) and outcomes such as a greater probability of diabetes-related complications(68) and a higher frequency of diabetes-related hospital admissions(69).

SES is a multifaceted concept that consists of several different variables influencing the overall health. The relationship between separate social factors and downstream complications is complex and not fully understood. Former studies has pointed out differences in multiple health behaviours along the socioeconomic gradient, such as nutrition(55), physical activity(57) and smoking(70). Moreover, psychosocial factors linked to SES, such as stress, can also impact health behaviours. Higher levels of stress has for instance been associated with higher rates of smoking and less exercise(71). It has been suggested that all these factors contribute to various physiological changes with effects on the endocrine systems(72). This could be part of the reason behind the previously demonstrated differences in HbA1c levels between groups of different SES. One possible explanation why no associations were found between GV and SES in this study is that the various social factors do not impact the short-term blood glucose levels to the same extent as they influence long-term blood glucose levels (which is reflected by HbA1c). There is also a possibility that wearing a r-CGM device caused behavioural changes in diet habits, physical acivity and the use of anti-diabetes medications in the study participants. This could in turn have improved the overall GV of the cohort and reduced possible differences in GV between the various socioeconomic groups.

Strenghts and limitations

One of the strenghts of this study is that it included r-CGM data from a large study population consisting of 279 participants. It also has the advantage of using 2-week r-CGM, which generates more data than the 3-day CGM that has often been used in previous research, with a mean (SD) duration of 12.3 (2.4) days in the cohort. Furthermore, there is no gold-standard for measuring SES. Therefore this study included one individual and one area-based measure to better assess the SES in the cohort. The educational attainment in the study cohort was also found to be similar to the general Victorian population after comparison based on the 2016 census(73).

There are some noteworthy limitations. Firstly, this is a secondary analysis of baseline data of the GP-OSMOTIC trial, which was designed to have the statistical power to detect differences in mean HbA1c levels, not GV. This could have affected the results of this project. Secondly, the cohort had a skewed distribution of the participants within the deciles of IRSD score, which could have influenced the statistical validity. Transformation of the data was considered but neither log nor square root transformtation improved the distribution. Thirdly, the study cohort consists only of people attending primary care in Victoria. With such a strong regional focus, it is hard to generalise any results to other settings. Fourthly, it is important to be aware of the risk of ecological fallacy in this study. There is a risk of misinterpretation of the data as GV is measured on an individual level while the IRSD measures the average SES of all the people within a certain area. The assumption about an individual's SES based on aggregate data is not necessarily accurate. Fifthly, there is a risk of sampling bias. It is possible that people who are dissatisfied with their blood glucose levels and management are not as interested in

volunteering in a study concerning blood glucose monitoring as those with more stable glycaemic parameters. This could have influenced the level of GV in the cohort.

Suggestions for future research

In accordance with the current consensus recommendations, CV was the index used to quantify GV in this study(39). One of the primary reasons behind this recommendation is the capability of CV to capture hypoglycaemic excursions(38). However, no hypoglycaemic events were recorded in the study population during the 2-week period of r-CGM and only 20.4% of the participants experienced high GV (CV ≥36%(38, 39)). This raises the question if the relationship between GV and SES should be explored in another setting, where GV can be assumed to be higher. Age, physical inacitivity, and polypharmacy have been identified as risk factors of higher GV(74) and the use of exogenous insulin is a main cause of hypoglycaemic events in people with T2D(11). Therefore, it would be interesting to conduct a study in an elderely population with high BMI, presence of ≥1 diabetes-related complication, use of insulin and a recorded history of hypoglycaemic events. Additionally, to better explore the relationship to SES and increase the statistical power, future studies could be designed to recruit participants with the aim to achieve a more even distribution within the groups of SES, for instance using IRSD. Altogether, this would provide opportunities to investigate if there are any actual differences in GV along the socioeconomic gradient. There are however some difficulties with stratifying recruitment by SES. As an example, SEIFA reports that the people between 30-49 years are overrepresented in the top IRSD decile and that people >70 years are overrepresented in the lowest deciles and underrepresented in the top deciles(60).

Conclusions

This study did not demonstrate a relationship between GV and area-based SES/individual SES in people with T2D participating in the GP-OSMOTIC study(58), an RCT evaluating the effect of r-CGM on HbA1c levels in a general practice setting in Victoria, Australia. However, given the rising interest in GV and its possible deleterious effects, it is important to explore this relationship more extensively. Once the image is clearer, the aggregative research on the association between various glycaemic parameters and social factors could lead to policy changes to reduce health care inequities e.g. by implementing CGM technology in all general practices. But more research on this novel marker of glycaemia is still needed.

POPULÄRVETENSKAPLIG SAMMANFATTNING

En analys av förhållandet mellan socioekonomisk status och snabba variationer i plasmaglukos hos 279 personer med typ 2-diabetes i Victoria, Australien

Diabetes kan anses vara en av vår tids globala hälsoutmaningar. Det uppskattas att drygt 420 miljoner människor över hela världen lever med diabetes och den siffran beräknas fortsätta stiga. Diabetes karaktäriseras av förhöjda plasmaglukosnivåer (”blodsocker”), vilket har visats kunna ha flertalet skadliga effekter på kroppen med risk för komplikationer såsom njursjukdom, synpåverkan och hjärtinfarkt på längre sikt. Ett viktigt mått för att följa plasmaglukosnivåerna hos individer med diabetes är HbA1c. Det är ett blodprov som speglar medelvärdet av blodsockret under en 3-månadersperiod och används för att utvärdera effekten av behandling samt risken för diabetes-relaterade komplikationer. Tidigare forskning har visat att individer med lägre socioekonomisk status generellt sett har högre HbA1c-nivåer (och därmed högre plasmaglukosnivåer) än individer med högre socioekonomisk status. Forskning har dessutom förslagit att snabba variationer i blodsockret, som på fackspråk kallas glykemisk variabilitet, kan ha skadliga effekter och ge ökad risk för diabeteskomplikationer. Med anledning av detta, samt vad som är känt kring kopplingen mellan socioekonomi och HbA1c, var målsättningen med detta projekt att undersöka det eventuella förhållandet mellan glykemisk variabilitet och socioekonomisk status.

Denna studie baserades på data ifrån 279 personer med typ 2-diabetes i den australiensiska delstaten Victoria, som hade samlats in av en större studie. Varje deltagare i studien fick bära en så kallad *FreeStyle Libre* under 2 veckor. Det är en liten sensor som fästs på baksidan av armen och som mäter glukosnivåerna kontinuerligt, var femtonde minut, utan att individen

behöver göra något. Utifrån dessa mätningar kunde sedan ett mått på den glykemiska variabiliteten beräknas. För att uppskatta den socioekonomiska statusen hos deltagarna användes två olika mått. Dels ett index som jämför den socioekonomiska standarden mellan alla områden i Australien med hjälp av ett poängsystem, baserat på information om flera olika faktorer som erhållits från den australiensiska folkräkningen år 2011 och dels deltagarnas utbildningsnivå.

Studien kunde inte påvisa något samband mellan glykemisk variabilitet och en individs socioekonomiska status i den undersökta populationen. Det behövs emellertid fler och eventuellt större studier som undersöker förhållandet mellan dessa två viktiga faktorer innan några slutsatser kan dras.

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APPENDICES

Appendix A: List of chronic conditions for the multimorbidity condition count

1. Alcohol abuse
2. Anorexia/Bulimia
3. Anxiety and other neurotic stress-related and somatoform disorders
4. Asthma (currently treated)
5. Atrial fibrillation
6. Blindness and low vision
7. Bronchiectasis
8. Cancer diagnosis in the last 5 years
9. Chronic kidney disease
10. Chronic liver disease
11. Chronic obstructive pulmonary disease
12. Chronic sinusitis
13. Constipation (currently treated)
14. Dementia
15. Depression
16. Diverticular disease
17. Epilepsy (currently treated)
18. Gastro-Oesophageal Reflux Disease (currently treated)
19. Glaucoma
20. Hearing loss
21. Hypertension
22. Inflammatory bowel disease
23. Irritable bowel syndrome
24. Ischemic heart disease
25. Learning disability
26. Migraines
27. Multiple sclerosis
28. Neuropathy
29. Other psychoactive substance misuse
30. Painful condition(s) including osteoarthritis, neck/shoulder/knee pain and chronic pain
31. Parkinson's disease
32. Peripheral vascular disease
33. Prostate disorders
34. Psoriasis or eczema
35. Retinopathy
36. Rheumatoid arthritis, other inflammatory polyarthropathies and systemic connective tissue disorders
37. Schizophrenia (and related non-organic psychosis) or bipolar disorder
38. Stroke/TIA
39. Thyroid disorders
40. Viral hepatitis

Appendix B: Characteristics of the excluded participants

Characteristics	n = 20	Missing data, n (%)
Age (in years), mean (SD)	54.9 (10.8)	8 (40)
Gender, n (%)		
Female	6 (30)	8 (40)
Male	6 (30)	
Years of diabetes, median (IQ range)	12.5 (9, 17)	10 (50)
Currently smoking[a], n (%)	4 (20)	5 (25)
IRSD Decile[b], median (IQ range)	5 (3.5, 7.5)	-
Educational attainment, n (%)		
Never attended	-	
Primary	1 (5)	
Secondary	8 (40)	5 (25)
Trade/TAFE	3 (15)	
University degree/diploma	3(15)	
Insulin prescription, n (%)	8 (40)	8 (40)
Diet[c], median (IQ range)	3 (1, 5.5)	-
Exercise[d], median (IQ range)	5 (2, 6.5)	-
BMI (Body Mass Index), mean (SD)	33.8 (4.9)	8 (40)
Multimorbidity condition count[e], n (%)		
Diabetes only	4 (20)	
Diabetes + 1	6 (30)	
Diabetes + 2	3 (15)	-
Diabetes + 3	3 (15)	
Diabetes + ≥4	4 (20)	
HbA1c, mean (SD)		
mmol/mol	74.3 (12.2)	8 (40)
%	8.9 (1.1)	

[a]= One or more cigarettes per day in the past 12 months
[b]= Index of Relative Socioeconomic Disadvantage. The first decile is the most deprived, the tenth decile is the least deprived
[c]= How many days in the last week that participants spaced carbohydrates evenly through the day
[d]= How many days in the last week in which participants engaged in ≥30 minutes of physical activity
[e]= The count is based on a total of 40 possible conditions, listed in *Appendix A*.