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Do continuous glucose monitoring (CGM) metrics predict macrovascular and microvascular complications in diabetes? The FACULTY protocol of a retrospective real-world cohort study

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ABSTRACT

Introduction Glycated haemoglobin (HbA1c) is currently the gold standard for assessing glycaemic control in diabetes, given the established relationship with microvascular and macrovascular complications in this condition. However, HbA1c is affected by non-glycaemic factors, while also failing to provide data on hypoglycaemic exposure and glucose variability, which are associated with adverse vascular outcomes. Continuous glucose monitoring (CGM)-derived glucose metrics provide a more comprehensive assessment of glycaemia, but their role in predicting future vascular complications remains unclear. Here, we present the protocol for a real-world cohort study, aiming to establish the relationship between CGM-derived glycaemic metrics and the incidence of macrovascular and/or microvascular complications in people with diabetes.

Methods and analysis This cohort study will use data from all CGM new users (FreeStyle Libre system) in France who uploaded their glycaemic values onto the LibreView cloud-based system, linked with data from the French nationwide *Système National des Données de Santé* claims database. The study is expected to include a minimum of 70 000 individuals with diabetes with a first date of glucose data upload to the LibreView platform after 1 January 2018 and with a 6-year follow-up period. The primary outcomes are the first occurrence of new macrovascular or microvascular complications, analysed as a composite outcome and separately. Secondary outcomes will include all-cause mortality and hospital admissions for any cause. This longitudinal study will provide key data on the relationship between CGM-derived glycaemic metrics and micro/macrovascular complications in diabetes. This will have an impact on routine clinical practice by setting targets for the different glycaemic markers, based on robust outcome data, thus helping to optimise glucose management in diabetes.

Ethics and dissemination The study data-collection protocol is approved by the French National Commission for Informatics and Liberties, including approval from the *Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé*. This study complies with French and European regulations, including those relating to the General Data Protection Regulation. This study uses pseudonymous information, not requiring informed consent. Dissemination plans include full publication of the study outcomes in peer-reviewed journal(s) with open access and presentations at national and international diabetes and cardiovascular conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The *Système National des Données de Santé* (SNDS) is a comprehensive nationwide healthcare claims database linked to the national hospital discharge summaries database that covers approximately 99% of the French population, and the linked LibreView data provides granular and standardised glucose measurements for detailed analysis.
⇒ There is limited risk of study selection bias, other than the requirement for FreeStyle Libre users to also be LibreView users, which could impact generalisability.
⇒ Confounding bias is minimised by adjusting Cox models for baseline covariates, and residual or unmeasured confounders will be tested using negative control outcomes.
⇒ The SNDS claims database provides only limited clinical data and no biological results describing the severity or stage of the disease or risk factors, such as diet, environmental exposure, obesity, alcohol, family history and smoking status.

INTRODUCTION

Diabetes is a complex metabolic disorder with a higher risk of complications and premature death compared with the general population without diabetes.[1] In most high-income countries, diabetes is a leading cause of vascular disease, including macrovascular and microvascular complications, responsible for

increasing diabetes-related costs.[1] The risk of these long-term complications of hyperglycaemia is also to be counterbalanced by the shorter-term risk of hypoglycaemia,[2] secondary to diabetes therapies, which is also associated with adverse vascular outcomes.[3–7]

For people with diabetes on insulin therapy, frequent glucose monitoring is a prerequisite for adequate glycaemic control. Self-monitoring of blood glucose (SMBG) using capillary glucose tests was the standard of care reference tool for glucose monitoring in insulin-treated individuals with diabetes.[2] Unfortunately, for many people with diabetes, inadequate engagement with SMBG represents a barrier to optimal glucose control,[8] as it can be painful, difficult to maintain in the long term and inconvenient to conduct in public.[9] Moreover, SMBG provides sporadic glucose measurements that, in many cases, are not enough to allow for effective and safe treatment changes. These barriers to the use of SMBG suggest a need for wider application of newer innovations in glucose testing, such as continuous glucose monitoring (CGM). Unlike the sporadic nature of SMBG testing, CGM allows a more comprehensive analysis of glucose profile, including glycaemic excursions and hypoglycaemic exposure, which can inform immediate therapy decisions and/or lifestyle modifications. In addition to this real-time therapeutic benefit for people with diabetes, CGM metrics collected over a period of time can historically be analysed by healthcare providers. Whatever the reporting platform used, CGM metrics and targets have been agreed[10] and provide precise information regarding hypoglycaemia and hyperglycaemia exposure, glucose variability and daily glucose patterns.[11] In contrast to the wealth of glycaemic data provided by CGM, glycated haemoglobin (HbA1c), the current gold-standard surrogate parameter for glucose control and endpoint for diabetes clinical studies[12 13] only reflects average glucose levels over the last 2–3 months. In trials, this makes the assessment of response to a particular intervention lengthy and incomplete as HbA1c fails to address hypoglycaemia and glucose variability, both of which are associated with adverse vascular outcomes.[11]

The FreeStyle Libre system and the second-generation FreeStyle Libre 2 system with optional high- and low-glucose alarms, are sensor-based, discreet and easy-to-use glucose monitoring systems that continuously measure glucose levels in the interstitial fluid for up to 14 days per sensor. These FreeStyle Libre systems have been reimbursed in France since June 2017 and provide a valuable alternative to SMBG testing for adults and children (aged 4 and older) with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). In addition to the FreeStyle Libre systems, individuals and healthcare professionals can access LibreView, which is a secure telemonitoring platform for consulting, analysing and assessing the history of interstitial glucose values, in order to implement effective management of people with diabetes. The information is available in LibreView in the form of ambulatory glucose profile (AGP) reports,[14] which present standardised CGM metrics that help with interpreting the dense continuously monitored glucose data. At least 10 CGM-derived metrics, including time in range (TIR), glucose variability and measures of hypoglycaemic exposure, are standardised with agreed targets for effective management of glycaemia in diabetes mellitus.[10] Just as importantly, these have now also been formally recommended as endpoints in clinical trials in diabetes.[15]

Among CGM-derived measures, TIR is emerging as a relevant surrogate endpoint for microvascular complications of T1DM and T2DM, with increased TIR being associated with decreased rates of retinopathy,[16 17] nephropathy,[16] painful diabetic neuropathy[18] and preserved peripheral nerve function.[19] In terms of macrovascular outcomes, increased TIR is associated with reduced occurrence of surrogate vascular risk markers,[20 21] lower risk of all-cause and CVD mortality,[22] as well as reduced incidence of peripheral artery disease[23] and diabetic foot ulcers.[24] Overall, in T2DM, there is a consistent association between higher TIR and fewer macrovascular and microvascular complications[19 20 25–30] with similar findings documented in T1DM.[30 31]

However, studies linking CGM metrics to incident diabetes complications remain relatively limited, as most have been conducted on small numbers of individuals and over a short period of follow-up, while some only involved specific ethnic groups. Therefore, there is an urgent need for large studies over longer follow-up periods to fully understand the link between new glycaemic measures and vascular complications of diabetes.

We describe here the design, data collection and analysis of a longitudinal study aiming to assess the prognostic value of CGM-derived metrics in real-life settings for determining the risk of developing macrovascular or microvascular complications in individuals with diabetes, using data collected from the LibreView system linked to the French nationwide *Système National des Données de Santé* (SNDS) claims database.[32]

Study design

This retrospective cohort study will include all new users of the FreeStyle Libre system with a first date of glucose data upload to the LibreView platform in the study period and for whom data will be linked to their healthcare information from the SNDS database. The study period will be from 1 January 2018 to 31 December 2022, and the date of the first glucose data loaded into the LibreView system will be defined as the index date (figure 1). All individuals will be followed in the SNDS for a minimum of 1 year and up to 6 years after the index date or until their death. Their treatment and outcomes following the FreeStyle Libre index date will be extracted from the SNDS database, along with their history of claims for a 5-year period prior to the index date (figure 1). The study protocol was designed in association with the Bordeaux PharmacoEpi, INSERM CIC-P 1401, a French Academic Research Organisation specialised in pharmacoepidemiology.

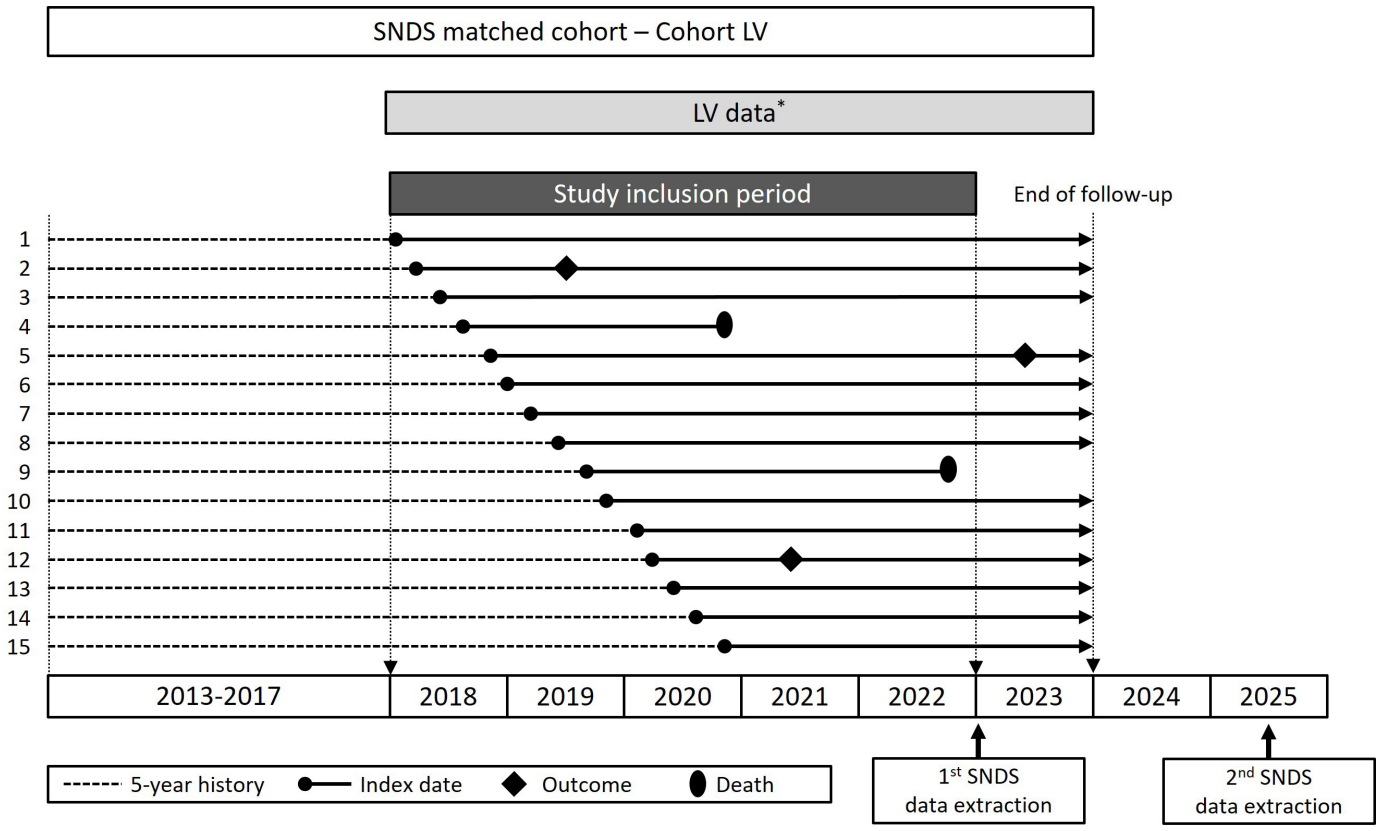

Figure 1 Study design of LibreView cohort (with LibreView data). *Throughout the study period, time-stamped LV glucose metrics will be reported regularly for defined time windows. The primary analysis will use 90-day windows to enable comparison with HbA1c metrics. LV, LibreView; SNDS, Système National des Données de Santé.

Data source

SNDS database

The SNDS is the comprehensive reimbursement claims database of the French national health insurance system. It currently covers around 99% of the total French population from birth (or immigration) to death (or emigration).[32] All beneficiaries are identified by a unique national pseudonymised identifier, with which healthcare resource consumption can be tracked over their lifetime. The SNDS compiles data on all reimbursed healthcare consumption in the public and private sectors, including in the hospital and community settings. Diagnoses of medical conditions are classified based on the International Classification of Diseases, 10th Revision (ICD-10). If the beneficiary dies, the cause of death can be accessed through a link to the national deaths register.

Access to the SNDS is carefully regulated by French law with an authorisation process by the French data protection commission after a scientific and ethics evaluation by the *Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé* (CESREES).

LibreView system

The LibreView system is a secure, regionally located and General Data Protection Regulation (GDPR)-compliant, cloud-based data storage platform for all CGM data collected from individuals using FreeStyle Libre sensors with either the FreeStyle reader, the FreeStyle LibreLink application, the FreeStyle Libre Pro and other readers. The CGM data are reported as standardised metrics (table 1).[10 14] The LibreView system also contains information on the user's age and sex. At the end of 2021, approximately 166 000 individuals with diabetes were using LibreView in France.

Data linkage

Data linkage between the LibreView system and SNDS will be performed employing a deterministic linkage and recording personal information of patients (first name, last name, sex, birth date) obtained from the LibreView system. This deterministic linkage uses a 2-step procedure defined by the French Data Protection Commission to reconstruct the personal national identifier of individuals from the information defined above, and then to generate a unique national pseudonymised identifier with erasure of all personal identifiers. A probabilistic linkage, based on several common parameters in both databases, such as sex, month and year of birth and the provision date of FreeStyle Libre reader, can complete the deterministic linkage if the procedure has failed for some patients. The quality of the linkage will be assessed by the use of a metric (similarity index) which is specified *a priori* to measure the dissimilarity, which will be compared with a threshold of the decision to link.[33–37]

Table 1 CGM-derived glucose metrics to be collected and analysed in the study

Metric	Interpretation
Mean glucose	A measure of the average 24-hour glucose concentration calculated across all of the recorded glucose readings.
Time in range (TIR):	Measures the % of time spent in consensus target glucose range 70–180 mg/dL (3.9–10.0 mmol/L). In pregnancy, this range is 63–140 mg/dL (3.5–7.8 mmol/L).
Time below range (TBR):	Measures the % of time spent with glucose <70 mg/dL (<3.9 mmol/L), including readings <54 mg/dL (<3.0 mmol/L), which may also be reported separately.
Time above range (TAR):	Measures the % of time spent with >180 mg/dL (>10.0 mmol/L), including readings >250 mg/dL (>13.9 mmol/L), which may also be reported separately.
Glucose variability	Measures the % coefficient of variation (CV). This is the reflection of a dynamic process characterised by the amplitude, the frequency and the duration of the fluctuation that contribute to assess the risks of complications coming from the variation of glucose.
Time In tight range (TITR):	Measures the % of time spent in target glucose range 70–140 mg/dL (3.9–7.8 mmol/L).
Glucose management indicator (GMI)	A measure of short-term glucose levels that can be used to predict long-term glucose exposure. GMI is expressed in the same units as HbA1c (% or mmol/mol) for comparative purposes, but they are usually not identical.

CGM, continuous glucose monitoring.

Study cohort selection

To be included in the cohort study, all individuals from the linkage between the LibreView system and the SNDS, and with a first date (index date) of LibreView glucose data between 1 January 2018 and 31 December 2022, must be aged ≥18 years, have a follow-up period of 1–6 years and a 'look-back' period of 5 years in the SNDS database, in order to define the presence of comorbidities and absence of the defined outcomes prior to the index date. Diagnosis of diabetes will be identified in the SNDS based on a validated algorithm,[38–40] using specific ICD-10 codes from hospitalisations, long-term disease registration, and reimbursements of specific medications within the 5-year history period. A subgroup of individuals without any micro- or macro-vascular complication at baseline will be identified within this cohort and analysed separately.

Patient and public involvement

The planned study will be a retrospective observational study using pseudonymised data; therefore, neither patients nor the public will be involved in the study design or analysis. The study steering committee will invite patient representatives to monitor the study progress, help with data interpretation from the patient perspective and contribute to the dissemination of study findings.

CGM-derived glucose metrics

The cohort will be assessed on time-stamped CGM metrics from the LibreView system, starting at the index date to the end of follow-up. Throughout the study period, time-stamped glucose metrics will be reported regularly for defined time windows. The primary analysis will use a 90-day window to enable comparison with HbA1c metrics. Additionally, time-windows covering 14-day periods, as well as 1, 6 and 12 months will be included in a subsequent sensitivity analysis on the distribution of CGM measures over time. CGM measures will be assessed according to the criteria listed in table 1.[10 41 42]

Individuals with CGM data capture that is below the minimum defined threshold recorded in the LibreView system will be excluded. The international consensus minimum data capture recommendations for making clinical decisions are >70% of data over a 14-day period.[10] The FACULTY study is centred on making robust correlations between CGM-derived metrics and the observed incidence of macrovascular and microvascular events rather than active clinical decision-making. Therefore, the Scientific Committee agreed on the following inclusion criteria for a given time-window analysis; that is, having >50% CGM data capture per 14-day period, for more than 50% of the 14-day periods included in the time-window and without two consecutive 14-day periods with ≦50% CGM data capture. As such, an individual may contribute to all time-window analyses, to some but not all, or to none of the time-window analyses. Sensitivity analyses will be performed with different thresholds. These criteria will be subject to updates according to the recommendations current at the time of the study's analysis.

Outcomes

The primary outcome will be the first occurrence of a macrovascular or microvascular complication during the follow-up period, analysed both as a composite outcome and separately. Primary outcome analysis will be stratified according to the absence (to assess incident complication)/presence (to assess recurrent complication) of any macrovasuclar or microvascular complications within the 5-year period prior to the index date. Macrovascular complications are defined by hospitalisation with a diagnosis of myocardial infarction, stroke, heart failure or peripheral artery disease. Microvascular complications are defined by the first occurrence of diabetic retinopathy, diabetic neuropathy or diabetic nephropathy during follow-up. Death from any cause will also be counted.

Incident macrovascular complications are: new myocardial infarction or stroke occurring during follow-up, heart failure or peripheral artery disease diagnosed during follow-up, in the absence of these outcomes within the 5-year period prior to the index date. Incident

Table 2 Primary and secondary outcomes to be investigated in the study (LibreView cohort)

Primary outcome measures		Objectives to be achieved
Microvascular complication (first occurrence)	► Diabetic retinopathy ► Diabetic neuropathy ► Diabetic nephropathy	► Description of baseline characteristics ► Description of hospital admission for any cause during follow-up ► Description of the glucose metrics over the defined follow-up ► Description of the different continuous glucose monitoring (CGM) metrics ► Incidence rates of each event occurring during the study period ► Estimation of the cumulative incidence of death to be considered as a competing risk; ► An identification of predictive factors, including CGM metrics, associated with the clinical outcomes
Macrovascular complication (first occurrence)	► Heart failure (HF) ► Myocardial infarction (MI) ► Ischaemic stroke ► Peripheral artery disease (PAD) .	
Secondary outcome measures		
All-cause mortality Hospital admission for any cause		

microvascular complications are the first occurrence of diabetic retinopathy, diabetic neuropathy and diabetic nephropathy during follow-up. These diagnoses will be identified based on validated algorithms (provided in online supplemental table 1) and/or a combination of relevant ICD-10 diagnosis codes related to hospitalisation.[43–47]

Secondary outcomes will include all-cause mortality and hospital admission for any cause, which will be assessed at 1 and 3 years after the index date and over the overall follow-up period. All study variables are detailed in table 2.

Covariates

Several covariates will be identified at the index date and over the 5-year history period.

From the LibreView system

- Gender, birth date and the provision date of the FreeStyle Libre reader.

From SNDS

- General characteristics with gender, year of birth, residence area and the French Deprivation Index.
- Provision date of the FreeStyle Libre sensor, type and date of provision of other telemonitoring devices.
- Main comorbidities based on disease algorithms developed by the CNAM and synthesised in a single Disease Risk Score (DRS), see online supplemental table 1.
- Use of glucose-lowering and/or cardiovascular drugs, antipsychotic and antidepressant medications: glucose-lowering therapies (insulins, metformin, meglitinides, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium–glucose cotransporter 2 inhibitors, α-glucosidase inhibitors), cardiovascular disease risk treatment (low-dose aspirin or other antiplatelets, anticoagulants, cholesterol-lowering or other lipid agents, antihypertensives, antianginal (non-hydropyridines calcium channel inhibitors, nitrates, β-blockers, ranolazine and others), heart failure treatments (angiotensin-converting enzyme inhibitors, angiotensin receptor/neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, diuretics), corticosteroids, prescribed weight loss drugs, dopamine antagonists, serotonin antagonists and reuptake inhibitors, monoamine oxidase inhibitors and tricyclic antidepressants.

Statistical analysis

Study size

For the LibreView cohort, the study will aim to recruit a minimum of 70 000 individuals with diabetes. The incidence of macrovascular and microvascular complications among individuals newly diagnosed with T2DM was estimated in a study using data from a US-integrated healthcare system.[48] This showed incidence rates for heart failure (7.1 per 1000 person-years, 95% CI 6.9 to 7.3); stable angina (7.1, 95% CI 7.0 to 7.3); cardiovascular disease (11.9, 95% CI 11.7 to 12.2); chronic kidney disease (21.2, 95% CI 20.9 to 21.6) and peripheral neuropathy (26.9, 95% CI 26.5 to 27.3). Based on these data, table 3 shows the 95% CI of similar incidence rates observed with a sample size between 50 000 and 200 000 and an average 3-year follow-up period. With 70 000 individuals from the LibreView cohort matched with SNDS data, the precision of IR 95% CI will be 6% and 2% for IR=5 and 30 per 1000 person-years, respectively.

Data analysis

For descriptive analyses, qualitative and ordinal variables will be summarised by frequencies and proportions of each modality, taking into account missing data as a modality. Continuous variables will be summarised by size, number of individuals with missing data, arithmetic mean, standard deviation (SD), median, interquartile ranges (IQRs) and extreme values. A Cox proportional hazards model will be used to assess the prognosis value of each CGM criteria for each outcome: outcome will be the dependent variable, CGM criteria will be a fixed independent variable, while DRS and time-varying drug exposure

Table 3 CI for incidence rates (normal approximation) according to different sample sizes with a 3-year follow-up period

Sample size	True rate					
	5/1000 PY	10/1000 PY	15/1000 PY	20/1000 PY	25/1000 PY	30/1000 PY
50 000	(4.66; 5.37)	(9.51; 10.52)	(14.40; 15.63)	(19.30; 20.72)	(24.22; 25.80)	(29.15; 30.88)
70 000	(4.71; 5.31)	(9.58; 10.43)	(14.49; 15.53)	(19.41; 20.61)	(24.34; 25.68)	(29.28; 30.74)
100 000	(4.75; 5.26)	(9.65; 10.36)	(14.57; 15.44)	(19.51; 20.51)	(24.45; 25.57)	(29.40; 30.62)
120 000	(4.77; 5.24)	(9.68; 10.33)	(14.61; 15.40)	(19.55; 20.46)	(24.50; 25.52)	(29.45; 30.56)
140 000	(4.79; 5.22)	(9.70; 10.31)	(14.64; 15.37)	(19.58; 20.43)	(24.53; 25.48)	(29.49; 30.52)
160 000	(4.80; 5.20)	(9.72; 10.29)	(14.66; 15.35)	(19.61; 20.40)	(24.56; 25.45)	(29.52; 30.49)
180 000	(4.82; 5.19)	(9.74; 10.20)	(14.68; 15.33)	(19.63; 20.38)	(24.59; 25.42)	(29.55; 30.46)
200 000	(4.82; 5.18)	(9.75; 10.26)	(14.70; 15.31)	(19.65; 20.36)	(24.61; 25.40)	(29.57; 30.43)

For the nested case-control approach, the expected study size to estimate an IR with sufficient precision depends on the number of events identified in the cohort (number of cases) and the number of matched controls. Selecting a sufficient number of controls per case will play an important part in minimising the power loss, particularly, for studies with few case-control sets and small relative risk.[55]
IR, incidence rate; PY, person-years.

will be adjustment covariates. CGM-derived glucose data will summarise all glucose time-stamped metrics available within a relevant time window. They will be calculated over a given period from the index date to 90 days (as primary analysis) and to 14 days,1 month, 6 months or 12 months (sensitivity analysis) and included in the Cox model as fixed covariates. Only drug exposure during follow-up will be time-varying covariates. A DRS is an approach to controlling for a large number of confounding variables by summarising them in a single score.[49] It estimates the probability of disease (eg, macrovascular complication), considering adjustment for potential confounders during the non-exposed historical period. It will be computed from a multivariable logistic regression model considering confounding factors during the 1-year period without CGM measurement before index date. These factors will be detailed in the statistical analysis plan, which is currently under development by Bordeaux PharmacoEpi and will be finalised before data lockdown and start of any analysis. The difference between prognosis value of the different diabetes CGM criteria will be assessed by comparing the predictive ability of the models adjusted for each of these criteria independently, using the Concordance Index (c-index),[17 22] sensitivity, specificity, time-dependent AUC,[23 24 50] Integrated Brier Score[20] and/or other metrics. Primary analyses will be stratified according to the presence/absence of microvascular or macrovascular complication at baseline.

Statistical analysis will be performed using SAS™ (SAS Institute, latest current version, North Carolina, USA) and R software.

Secondary analyses

This cohort involves several time-sensitive variables that need to be recomputed at every new time point of follow-up, while the incidence of the outcomes observed during the follow-up may be low. Consequently, a nested case-control design will also be used. Cases will be new FreeStyle Libre users who present an outcome during the follow-up. Each case will be matched with up to six controls on age, sex, FreeStyle Libre initiation date of the case and the DRS (see above). Controls will not have an outcome recorded within the same follow-up period that corresponds with the case. In case-control studies, DRS matching has been proven to increase statistical efficiency, particularly when the outcome is rare, which may be the case for new macrovascular and microvascular complications.[19] Comparison of baseline characteristics between cases and controls will be performed using standardised differences. A conditional logistic regression model will be used to compare CGM metrics between cases and controls. In this nested case-control approach, the CGM measures will be calculated within the time-window of 30 days before the date of case identification (the same date will be used for controls) for main analysis and 3, 6 and 12 months for sensitivity analyses. Additionally, a negative control outcome analysis will be implemented to assess the possibility of residual confounding.

Data protection and privacy of the study population

The study data-collection protocol has been approved by the French National Commission for Informatics and Liberties (CNIL) under the reference number 923 194 on 5 October 2023, including already-obtained approval from CESREES on 15 June 2023. This study complies with French and European regulations, including those relating to GDPR. Given this study will be using SNDS analysis with individual pseudonymous information, informed consent is not required.

Study registration

This study will be registered on the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) EU-PAS website (ENCePP checklist, Annex 1) and on the BORDEAUX PHARMACOEPI website.

DISCUSSION

We have described the scientific rationale, specific aims and the protocol for a retrospective analysis of two datasets, using a unique strategy for record linkage between clinical data collected by a medical device and healthcare data from the SNDS claims database. Using a longitudinal study design and combining LibreView cloud-based platform for all FreeStyle Libre data, together with outpatients claims and national hospital-discharge summaries contained within the SNDS claims database in France, we will be able to determine the associations between measures of CGM-defined glucose control with the incidence of macrovascular and microvascular complications of diabetes. The data will help to assess the predictive link between standardised CGM-derived glucose metrics, independent of HbA1c, and the longitudinal risk of macrovascular and microvascular diseases.

The size and scope of the SNDS database, covering about 99% of the French population (67 million individuals), allows the recruitment of a minimum of 70 000 individual users for analysis. In previous studies, the size and scope of the SNDS have been central to enabling the identification of FreeStyle Libre users for further study in the context of hospital admission episodes.[51–54] This present study will link the extensive information about healthcare resource use in the SNDS, including episodes of macrovascular and microvascular disease, with established measures of glucose control collected by FreeStyle Libre users. This will allow us to define additional and more-dynamic risk-assessment criteria for diabetes complications beyond HbA1c. Ultimately, CGM metrics could be more easily used as outcomes in clinical trials[15] and considered by healthcare regulatory authorities in the same way as HbA1c.

This work will be the largest longitudinal study to investigate the relationship between key CGM-derived metrics and the risk of future macrovascular and microvascular complications in individuals with T1DM or T2DM. This, in turn, will help to refine the role of HbA1c in predicting diabetes complications, particularly as the accuracy of this marker can be affected by non-glycaemic factors. Moreover, this study will help to set CGM standards of care for managing individuals with T1DM and T2DM, based on robust outcome data.

In summary, results from the FACULTY study will help healthcare professionals to target the most important modifiable glycaemic marker(s) in order to reduce the unacceptably high risk of vascular complications in individuals with diabetes, consequently improving outcomes and reducing health costs in this high-risk population.

ETHICS AND DISSEMINATION

The study data collection protocol has been approved by the French CNIL under reference number 923 194 on 5 October 2023, including already-obtained approval from the *Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé* (CESREES) on 15 June 2023. This study complies with French and European regulations, including those relating to GDPR. Given this study will be using SNDS analysis with individual pseudonymous information, informed consent is not required. Dissemination plans include full publication of the study outcomes in peer-reviewed journal(s) and ensuring open access while also presenting the findings in national and international diabetes and cardiovascular conferences. Please also see the previous statement on patient and public involvement.

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REFERENCES

1 Cho NH, Shaw JE, Karuranga S, *et al*. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018;138:271–81.
2 Committee A, Draznin B, Aroda VR. Glycemic Targets: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2022;45:S83–96.
3 Elwen FR, Huskinson A, Clapham L, *et al*. An observational study of patient characteristics and mortality following hypoglycemia in the community. *BMJ Open Diabetes Res Care* 2015;3:e000094.
4 Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. *Diabetes Care* 2011;34 Suppl 2:S132–7.
5 Yeh JS, Sung S-H, Huang H-M, *et al*. Hypoglycemia and risk of vascular events and mortality: a systematic review and meta-analysis. *Acta Diabetol* 2016;53:377–92.
6 Pearson SM, Whittam B, Kulavarasalingam K, *et al*. Reduction in cardiovascular mortality following severe hypoglycemia in individuals with type 2 diabetes: the role of a pragmatic and structured intervention : Structured intervention for community hypoglycemia. *Cardiovasc Diabetol* 2021;20:18.
7 Djupsjö C, Kuhl J, Andersson T, *et al*. Admission glucose as a prognostic marker for all-cause mortality and cardiovascular disease. *Cardiovasc Diabetol* 2022;21:258.
8 Ward JEF, Stetson BA, Mokshagundam SPL. Patient perspectives on self-monitoring of blood glucose: perceived recommendations, behaviors and barriers in a clinic sample of adults with type 2 diabetes. *J Diabetes Metab Disord* 2015;14:43.
9 Polonsky WH, Fisher L, Hessler D, *et al*. What is so tough about self-monitoring of blood glucose? Perceived obstacles among patients with Type 2 diabetes. *Diabet Med* 2014;31:40–6.
10 Battelino T, Danne T, Bergenstal RM, *et al*. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care* 2019;42:1593–603.
11 Agiostratidou G, Anhalt H, Ball D, *et al*. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care* 2017;40:1622–30.
12 Stratton IM, Adler AI, Neil HA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
13 The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med* 1993;329:977–86.
14 Bergenstal RM, Ahmann AJ, Bailey T, *et al*. Recommendations for Standardizing Glucose Reporting and Analysis to Optimize Clinical Decision Making in Diabetes: The Ambulatory Glucose Profile. *J Diabetes Sci Technol* 2013;7:562–78.
15 Battelino T, Alexander CM, Amiel SA, *et al*. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol* 2023;11:42–57.
16 Beck RW, Bergenstal RM, Riddlesworth TD, *et al*. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. *Diabetes Care* 2019;42:400–5.
17 Lu J, Ma X, Zhou J, *et al*. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. *Diabetes Care* 2018;41:2370–6.
18 Yang J, Yang X, Zhao D, *et al*. Association of time in range, as assessed by continuous glucose monitoring, with painful diabetic polyneuropathy. *J of Diabetes Invest* 2021;12:828–36.
19 Li F, Zhang Y, Li H, *et al*. TIR generated by continuous glucose monitoring is associated with peripheral nerve function in type 2 diabetes. *Diabetes Res Clin Pract* 2020;166:108289.
20 Lu J, Ma X, Shen Y, *et al*. Time in Range Is Associated with Carotid Intima-Media Thickness in Type 2 Diabetes. *Diabetes Technol Ther* 2020;22:72–8.
21 Zhou H, Wang W, Shen Q, *et al*. Time in range, assessed with continuous glucose monitoring, is associated with brachial-ankle pulse wave velocity in type 2 diabetes: A retrospective single-center analysis. *Front Endocrinol* 2022;13:1014568.
22 Lu J, Wang C, Shen Y, *et al*. Time in Range in Relation to All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes: A Prospective Cohort Study. *Diabetes Care* 2021;44:549–55.
23 Li J, Li Y, Ma W, *et al*. Association of Time in Range levels with Lower Extremity Arterial Disease in patients with type 2 diabetes. *Diabetes Metab Syndr Clin Res Rev* 2020;14:2081–5.
24 Xie P, Deng B, Zhang X, *et al*. Time in range in relation to amputation and all-cause mortality in hospitalised patients with diabetic foot ulcers. *Diabetes Metabolism Res* 2022;38:e3498.
25 Mayeda L, Katz R, Ahmad I, *et al*. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. *BMJ Open Diabetes Res Care* 2020;8:e000991.
26 Guo Q-Y, Lu B, Guo Z-H, *et al*. Continuous glucose monitoring defined time-in-range is associated with sudomotor dysfunction in type 2 diabetes. *World J Diabetes* 2020;11:489–500.
27 Kim MY, Kim G, Park JY, *et al*. The Association Between Continuous Glucose Monitoring-Derived Metrics and Cardiovascular Autonomic Neuropathy in Outpatients with Type 2 Diabetes. *Diabetes Technol Ther* 2021;23:434–42.
28 Guo Q, Zang P, Xu S, *et al*. Time in Range, as a Novel Metric of Glycemic Control, Is Reversely Associated with Presence of Diabetic Cardiovascular Autonomic Neuropathy Independent of HbA1c in Chinese Type 2 Diabetes. *J Diabetes Res* 2020;2020:5817074.
29 Yoo JH, Choi MS, Ahn J, *et al*. Association Between Continuous Glucose Monitoring-Derived Time in Range, Other Core Metrics, and Albuminuria in Type 2 Diabetes. *Diabetes Technol Ther* 2020;22:768–76.
30 Yapanis M, James S, Craig ME, *et al*. Complications of Diabetes and Metrics of Glycemic Management Derived From Continuous Glucose Monitoring. *J Clin Endocrinol Metab* 2022;107:e2221–36.
31 El Malahi A, Van Elsen M, Charleer S, *et al*. Relationship Between Time in Range, Glycemic Variability, HbA1c, and Complications in Adults With Type 1 Diabetes Mellitus. *J Clin Endocrinol Metab* 2022;107:e570–81.
32 Bezin J, Duong M, Lassalle R, *et al*. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug* 2017;26:954–62.
33 Levenshtein VI. Binary codes capable of correcting deletions, insertions and reversals. *Sov Phys Dokl* 1966;10:707–10.
34 Shannon CE. The mathematical theory of communication. *MD Comput Comput Med Pract* 1963;14:306–17.
35 Shannon CE. Prediction and Entropy of Printed English. *Bell Syst Tech J* 1951;30:50–64.
36 Jaro MA. Probabilistic linkage of large public health data files. *Stat Med* 1995;14:491–8.
37 Winkler WE. The state of record linkage and current research problems. *US Census Bureau* 1999.
38 Fosse-Edorh S, Rigou A, Morin S, *et al*. Algorithmes basés sur les données médico-administratives dans le champ des maladies endocriniennes, nutritionnelles et métaboliques, et en particulier du diabète. *Rev Épidémiol Santé Publique* 2017;65:S168–73.
39 Fuentes S, Hrzic R, Haneef R, *et al*. Identifying type 1 / type 2 diabetes in medico-administrative database to improve health surveillance, medical research and prevention in diabetes: Algorithm development and application. *Diabetes Epidemiol Manage* 2023;10:100137.
40 Fuentes S, Cosson E, Mandereau-Bruno L, *et al*. Identifying diabetes cases in health administrative databases: a validation study based on a large French cohort. *Int J Public Health* 2019;64:441–50.
41 Danne T, Nimri R, Battelino T, *et al*. International Consensus on Use of Continuous Glucose Monitoring. *Diabetes Care* 2017;40:1631–40.
42 Bergenstal RM, Beck RW, Close KL, *et al*. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. *Diabetes Care* 2018;41:2275–80.

43 Bezin J, Girodet P, Rambelomanana S, *et al*. Choice of ICD -10 codes for the identification of acute coronary syndrome in the French hospitalization database. *Fund Clin Pharma* 2015;29:586–91.
44 Bosco-Lévy P, Duret S, Picard F, *et al*. Diagnostic accuracy of the *International Classification of Diseases*, *Tenth Revision*, codes of heart failure in an administrative database. *Pharmacoepidemiol Drug* 2019;28:194–200.
45 Giroud M, Hommel M, Benzenine E, *et al*. Positive Predictive Value of French Hospitalization Discharge Codes for Stroke and Transient Ischemic Attack. *Eur Neurol* 2015;74:92–9.
46 Prat M, Derumeaux H, Sailler L, *et al*. Positive predictive values of peripheral arterial and venous thrombosis codes in French hospital database. *Fund Clin Pharma* 2018;32:108–13.
47 Haviari S, Chollet F, Polazzi S, *et al*. Effect of data validation audit on hospital mortality ranking and pay for performance. *BMJ Qual Saf* 2019;28:459–67.
48 An J, Nichols GA, Qian L, *et al*. Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident type 2 diabetes. *BMJ Open Diabetes Res Care* 2021;9:e001847.
49 Tadrous M, Gagne JJ, Stürmer T, *et al*. Disease risk score as a confounder summary method: systematic review and recommendations. *Pharmacoepidemiol Drug Saf* 2013;22:122–9.
50 Feng Z-Q, Guo Q-Y, Wang W, *et al*. Time in range, especially overnight time in range, is associated with sudomotor dysfunction in patients with type 1 diabetes. *Diabetol Metab Syndr* 2021;13:119.
51 Roussel R, Riveline J-P, Vicaut E, *et al*. Important Drop in Rate of Acute Diabetes Complications in People With Type 1 or Type 2 Diabetes After Initiation of Flash Glucose Monitoring in France: The RELIEF Study. *Diabetes Care* 2021;44:1368–76.
52 Riveline J-P, Roussel R, Vicaut E, *et al*. Reduced Rate of Acute Diabetes Events with Flash Glucose Monitoring Is Sustained for 2 Years After Initiation: Extended Outcomes from the RELIEF Study. *Diabetes Technol Ther* 2022;24:611–8.
53 Guerci B, Levrat-Guillen F, Vicaut E, *et al*. Reduced Acute Diabetes Events After FreeStyle Libre System Initiation in People 65 Years or Older with Type 2 Diabetes on Intensive Insulin Therapy in France. *Diabetes Technol Ther* 2023;25:384–94.
54 Guerci B, Roussel R, Levrat-Guillen F, *et al*. Important Decrease in Hospitalizations for Acute Diabetes Events Following FreeStyle Libre System Initiation in People with Type 2 Diabetes on Basal Insulin Therapy in France. *Diabetes Technol Ther* 2023;25:20–30.
55 Pang D. A relative power table for nested matched case-control studies. *Occup Environ Med* 1999;56:67–9.