Handling missing data, selection bias, and measurement error in observational studies

Choi, J.

Chapter 5

Estimating medication effects using routinely collected electronic health records: changes in blood glucose and HbA1c levels after glucose-lowering medication prescription in the Netherlands Epidemiology of Obesity study participants

Ready to be submitted

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Abstract

Background

Measurements affected by medication use, such as glucose levels alleviated after glucose-lowering medication, are commonly encountered in epidemiological studies. Potential methods for validly handling these measurements affected by medication use are incorporating the information of the mean medication effect and, sometimes, its standard deviation. In this study, we aim to describe changes in blood glucose and HbA1c levels after glucose-lowering medication prescription from routinely collected data.

Method

Participants from the Netherlands Epidemiology of Obesity (NEO) study who developed type 2 diabetes during the follow-up period were included. The patients were identified using general practitioners' Electronic Patient Records (EPR). The EPRs were also used to obtain repeated measurements of blood glucose and HbA1c. We fitted linear mixed models with glucose and HbA1c as the outcomes. Time as a categorical variable was added as a fixed effect and random effect.

Results

In total, 127 incident diabetes cases were included in the analyses. In general, we observed a sharp increase in glucose and HbA1c levels shortly before the medication prescription. After the prescription, levels of both decreased. The lowest values were observed at 6-12 months after prescription, which were 1.76 mmol/L lower in glucose [CI: -2.54, -0.99] and 0.80% lower in HbA1c [CI: -1.61, -0.45] than 6-12 months before prescription. After one year, glucose and HbA1c levels increased, but even after two years, levels were significantly lower than before starting medication. Variation in medication effect between individuals was large.

Conclusion

The sharp increase in glucose and HbA1c shortly before medication prescription likely reflects random high values. Considering a longer period before the medication prescription is needed to obtain a better estimate of the medication effect. The estimated medication effects were smaller than observed in RCTs, yet on average, treatment remained effective for more than two years after prescription. Routinely collected data can provide insights into medication effects in the real-world which may not be easily obtained from RCTs.

1. Introduction

Population-based observational studies are often used to provide insight into the real-world relationships between clinical measurements and the effects of various treatments. Population-based studies, by their nature, include a wide range of individuals with various clinical features. Thus, in a population-based cohort, it is common to encounter that some measurements are affected by medication use in a subgroup of the study population. Examples are cholesterol levels controlled by cholesterol-lowering medication or blood pressure levels lowered by antihypertensive medication.

Glucose-lowering medication is a commonly used treatment for (pre)diabetes to regulate blood glucose levels. It was recently reported that 10.2% of the US population had diabetes (1). From 2007 to 2010, 88% of people aged ≥ 20 years with diagnosed diabetes were reported to be treated with insulin and/or oral medications (2). In the database of the UK Biobank, a widely known prospective cohort recruited from the general UK population aged 40–69 years (3), approximately 4% reported using glucose-lowering medication for type 2 diabetes (T2D) (4).

Medication use is not of concern when one is interested in measurements as observed regardless of whether medication is used. Sometimes, however, researchers may be interested in the measurements if untreated so that the estimated result would reflect the natural relationship between the variables of interest. However, the untreated values cannot be observed for those who are on medication. Consequently, appropriate methods to correctly adjust for medication effects would be needed.

Several studies have shown that effect estimates can be substantially biased if the measurements affected by medication use are handled with invalid methods (5-8). When the affected measurement is an outcome variable, adding an estimated mean medication effect to the treated values is an appropriate method (5, 7). When the exposure is affected, a valid method could be a regression calibration approach (7). To apply these methods, information on the mean (and standard deviation) of the medication effect, acquired from external information, is needed.

The mean medication effect and standard deviation may be acquired from randomized controlled trials (RCTs). Meta-analyses of RCTs on glucose-lowering medication showed that using a single type of medication reduced HbA1c levels by, on average, 0.66% to 1.11% (values aligned to the assay used in the Diabetes Control and Complication Trial; DCCT), depending on the drug classes (9) or approximately 1% over the course of the studies (10, 11). Trials on glucose-lowering medication found an effect of 2-4 mmol/L lowering blood glucose on average (12-14).

Although the effects of glucose-lowering medication are known from RCTs, these may not reflect how blood glucose and HbA1c levels change before and after medication prescription in real-world settings. Populations eligible for trials may not represent the population of interest in an observational cohort study. Eligibility criteria and the recruitment process of population-based cohort studies could be vastly different from RCTs, where study participants are usually recruited in a restrictive manner. Furthermore, randomization of treatment by no means reflects how medications are prescribed and administered in real-world settings. Additionally, follow-up in RCTs generally starts shortly before or at the start of the prescription, and the follow-up period is often less than one year (10), providing limited information on long-term medication effects. A possible approach to circumvent these issues is to estimate the medication effect directly from the population of interest in a real-world setting.

In this study, we explore how observational routinely collected data can be used to describe and estimate changes in blood glucose and HbA1c levels change over time before and after glucose-lowering medication prescription. Therefore, we use data from the Netherlands Epidemiology of Obesity (NEO) study and its follow-up data routinely collected by general practitioners. Using these data, we estimate the effect of medication use on blood glucose and HbA1c levels and discuss the results and the advantages and pitfalls of using observational routinely collected data to estimate the effect of glucose-lowering treatments.

2. Method

Study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study designed to investigate pathways leading to obesity-related conditions and diseases. The study recruited men and women aged 45 to 65 years living in the greater area of Leiden, the Netherlands, with an oversampling of individuals with a BMI of 27 kg/m^2 or higher. Details of the design and inclusion criteria of the NEO study can be found elsewhere (15). The first wave of data collection started in September 2008 and was completed in September 2012.

Follow-up of the NEO study participants

During the follow-up of the NEO study participants, clinical endpoints were collected thorough electronic patient records (EPR) of general practitioners (GP). The EPR contains basic data of care provided and recorded by general practitioners, such as disease diagnosis, treatment prescription, test results, and referrals. The records are encoded with International Classification of Primary Care (ICPC) codes. Medication prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC)

classification. We used the EPRs extracted in October 2017 - May 2018 to obtain repeated measurements of blood glucose and HbA1 and diagnosis of T2D of the NEO study participants.

From the EPR, those who were not diagnosed with T2D at the first NEO visit but were diagnosed during the follow-up (i.e., incident diabetes cases) were identified. Ascertainment of T2D was performed based on three components: 1) the presence of ICPC code T90 or T90.02, and/or 2) a prescription of glucose-lowering medication, defined by ATC codes starting with A10, and/or 3) the presence of keywords for glucose-lowering medication, such as insulin, metformin, or any generic names in free text (complete list of keywords is provided in a Appendix 1). The general practitioner was contacted if it remained unclear whether a participant was correctly diagnosed with T2D. We then excluded participants i) whose medication prescription date was unknown, ii) who did not have blood test results for glucose or HbA1c, or iii) whose blood test results were only available more than 12 months before the first medication prescription date.

Statistical analysis

HbA1c levels were standardized to HbA1c DCCT (%) values. Biologically unrealistic low values (HbA1c < 4% or blood glucose=0 mmol/L) were set to be missing. Time was centralized to the first prescription date of the antidiabetic treatment (time 0: date of the first prescription).

Descriptive statistics of the participants' characteristics at the NEO visit were presented as the mean and standard deviation for continuous variables and frequencies for categorical variables. To explore the change in glucose and HbA1c over time, we used spaghetti plots to display individual-level data and box plots to visualize all data.

We fitted linear mixed models to estimate changes in glucose and HbA1c levels over time after starting medication. Dependent variables were repeated blood glucose and HbA1c measurements. Time was added as a fixed effect with the following categorization: (up and until) 6 to (less than) 12 months *before* the first prescription/ 3 to 6 months *before*/ 0 (including the date of a first prescription) to 3 months *before*/ (more than) 0 to (up an until) 3 months *after*/ 3 to 6 months *after*/ 6 to 12 months *after*/ 12 to 24 months *after*/ more than 24 months *after*. Categorization was done such that the mean value at each time category contrasts with the mean value at 6 to 12 months *before* the prescription. As random effects, we added a random person effect plus a random effect for different periods after medication prescription categorized as follows: (more than) 0 to 3 (up and until) months *after the first prescription*/ 3 to 6 months *after*/ 6 to 12 months *after*/ 12 to 24 months *after*/ more than 24 months *after*. Figure 1 visualizes the timeline of the glucose and HBA1c measurements and the NEO visit.

We further explored whether the mean changes in glucose and HbA1c after medication prescription were dependent on age, BMI, or sex. For this, we fitted three models, where we respectively added BMI at the NEO visit (continuous), sex, or age at the first prescription date (continuous) as fixed effects, with an interaction term with medication prescription.

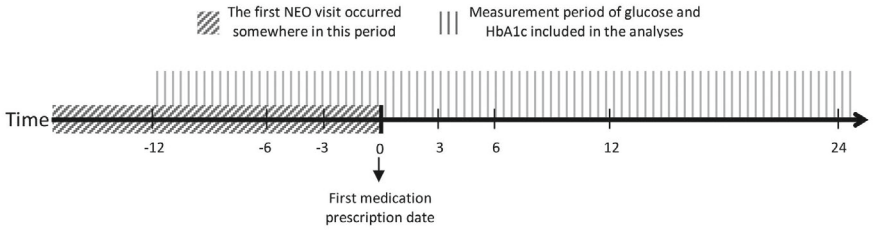


Figure 1. Timeline of the glucose and HBA1c measurements and the NEO visit. Time 0 is the date of the first prescription. The date of the first NEO visit, which was before time 0, varies between individuals (for some individuals, it was less than 12 months before the first prescription). In the analyses, glucose and HbA1c measures from 12 months before the first prescription were used.

3. Results

In total, 6671 individuals were included in the NEO study. Among the participants who did not use any antidiabetic medication at the NEO visit, 297 participants were identified as incident type 2 diabetes cases from the EPR. Participants who did not have information on the medication prescription date (n=126), did not have laboratory measurements for glucose or HbA1c (n=41), or had only laboratory measurements more than 12 months before the medication prescription (n=3) were excluded. In total, 127 individuals remained. The mean number of repeated measurements for blood glucose was 12 (IQR: [7, 20]; maximum: 105), and for HbA1c was eight (IQR: [5, 14]; maximum: 58). Figure 2 illustrates a flow chart of the selection of the study sample.

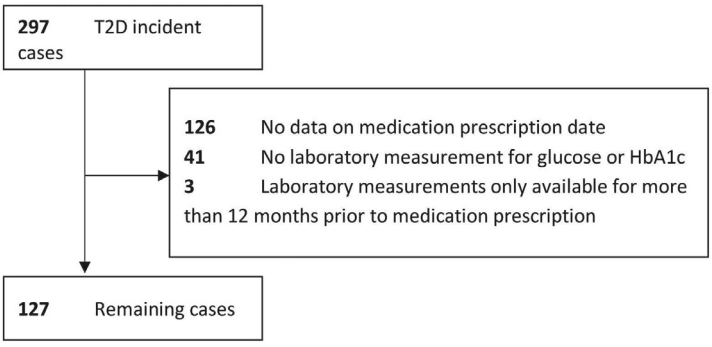


Figure 2. Sample selection process and the number of individuals included in the analyses

Table 1 summarizes the general characteristics of the 127 individuals measured at the first visit of the NEO study. Mean fasting glucose (7.0 mmol/L, SD: 1.8), HbA1c level (6.0 %, SD: 0.9), and HOMA-IR (6.0, SD: 3.8) indicated that a large number of the included participants were already prediabetic, defined as fasting glucose level between 5.6–6.9 mmol/L or HbA1c level between 5.7–6.4% (18), at the first NEO visit. The selected individuals also had high mean BMI (33.6 kg/m2, SD: 5.4), and many were hypertensive (50%). Time from first measurement to prescription varied largely between individuals (121 days, IQR: [7, 260]). Types of first-prescribed glucose-lowering medication are summarized in Table 2. Metformin was most often prescribed as the first glucose-lowering medication.

Table 1. Participants' characteristics at the first NEO visit. Mean and standard deviation was used for continuous variables [mean (sd)]. Frequency and percentage were used for categorical variables [N (%)]

Measurements at the NEO visit (N=127)	
Sex	
Male	65 (51.2%)
Age in years	56.0 (5.8)
Age in years at the date of prescription	60.6 (6.2)
Education	
High	50 (39.4%)
Hypertension	
Yes	63 (49.6%)
BMI (kg/m2)	33.6 (5.4)
Glucose (mmol/L)	7.0 (1.8)
Insulin (mU/L)	19.5 (11.8)
HOMA1-IR	6.0 (3.8)
HbA1c (%)	6.0 (0.9)
Total cholesterol (mmol/L)	5.7 (1.1)
Triglycerides (mmol/L)	1.9 (1.3)
HDL (mmol/L)	1.3 (0.3)
LDL (mmol/L)	3.6 (1.0)
Lipid-lowering drugs use	
Yes	19 (15.0%)
Hypertension drugs use	
Yes	54 (42.5%)
Time from NEO visit to prescription (days)	121 (IQR: 7, 260)

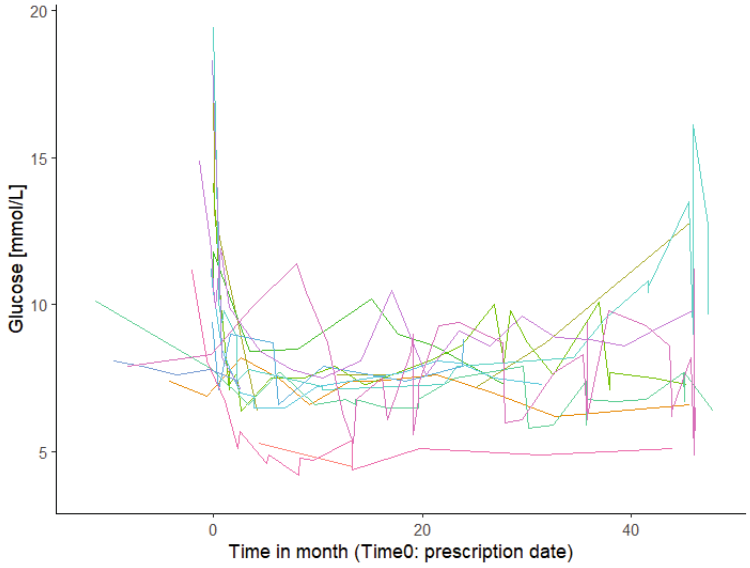
Table 2. Types of medication prescribed at the first prescription date for 127 individuals

Prescribed medication types*	**Frequency**
Gliclazide	2
Glimepiride	1
Insulin injection pen	4
Metformin	117
Sitagliptin	1
Tolbutamide	3
Others/ unknown	5
Total	**133**

* Six individuals have been prescribed two types of medication on their first prescription date.

Appendix 2 compares the characteristics of the individuals included (n=127) and excluded (n=170) from the analyses. Glucose and HbA1c levels were on average lower (0.4 mmol/L and 0.2%, respectively) in the excluded individuals compared to those included.

Figure 3 displays changes in blood glucose and HbA1c levels of 15 randomly chosen individuals, showing considerable variation in patterns over time. The observed overall means over time are visualized in Figure 4. The figures indicate that glucose and HbA1c levels peaked near the first medication prescription date.



3a.

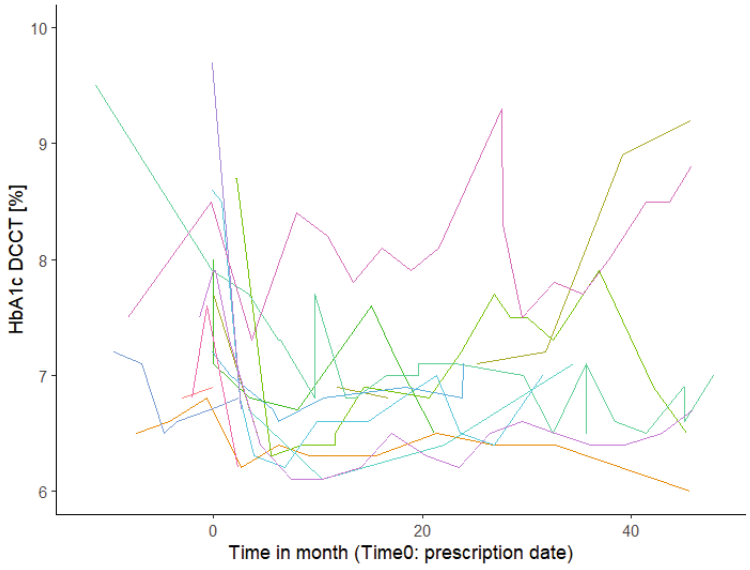


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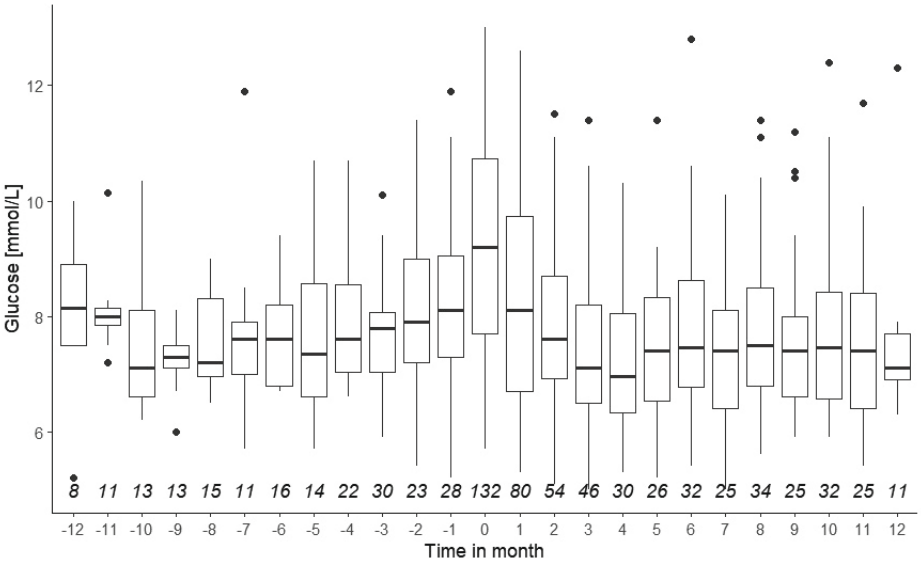
Figure 3. Spaghetti plots for glucose (a) and HbA1c (b) levels of 15 randomly chosen individuals



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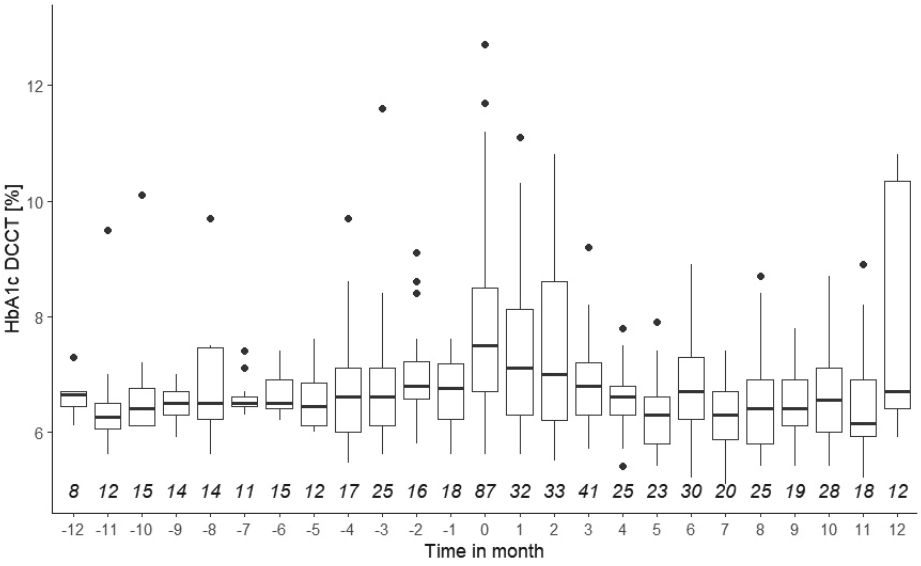


4b.

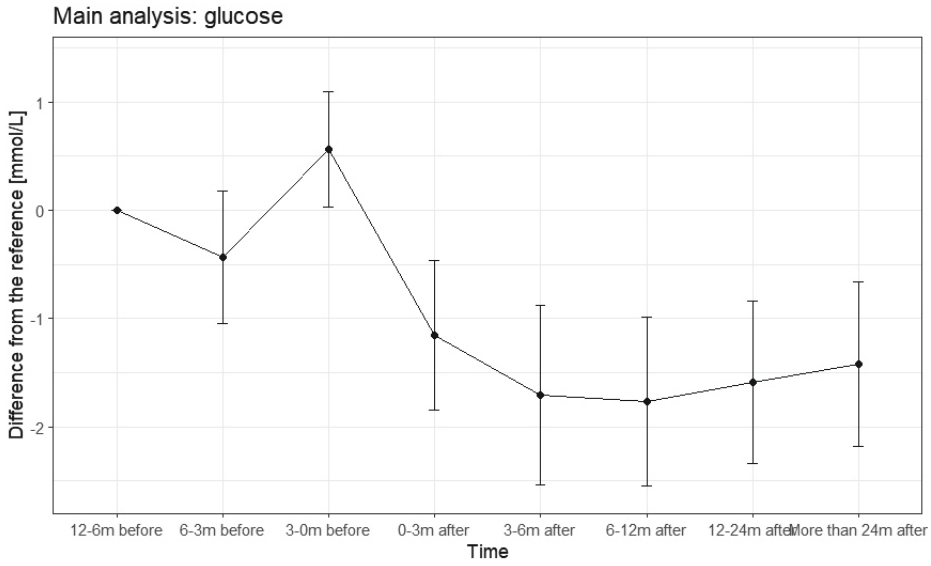
Figure 4. The median and interquartile range of glucose (a) and HbA1c (b) measurements at each time on a monthly scale. Numbers in italic fonts represent the number of available observations at each point.

Main analyses

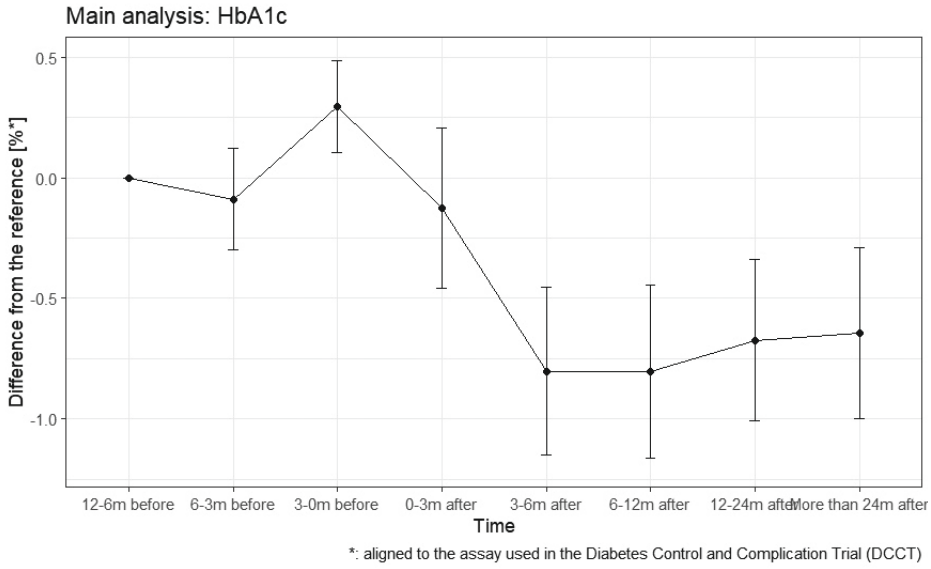
Table 3 summarizes the results of the fitted linear mixed models. Figure 5 visualizes the estimated mean differences in glucose and HbA1c at each time category compared to the level at 6-12 months *before* the prescription and their confidence intervals.

For glucose, the mean level increased shortly before the first medication prescription; that is, the level at 0 to 3 months before prescription was 0.56 mmol/L *higher* [CI: 0.03, 1.10] compared to 6-12 months before prescription. The mean level decreased in 0-3 months *after* prescription, which was 1.15 mmol/L *lower* [CI: -1.85, -0.46] than 6-12 months before prescription. The decrease in glucose levels was the largest 6-12 months *after* prescription; the levels were on average 1.76 mmol/L *lower* [CI: -2.54, -0.99] compared to 6-12 months before prescription. Glucose levels slightly increased after 12 months and more than 24 months after prescription, the level was after 24 months 1.42 mmol/L *lower* [CI: -2.18, -0,66] than 6-12 months before prescription. The effect of medication on glucose varied largely between the individuals, with the standard deviation equal to 2.30 mmol/L at 0-3 months *after* prescription and 3.09 mmol/L at more than 24 months after prescription. Between-individual before medication and within-individual variability were also relatively large (SD: 3.23 mmol/L and 1.63 mmol/L, respectively).

The trend was similar for the HbA1c measurements. The mean level at 0-3 months *before* the prescription was 0.30% *higher* [CI: 0.10, 0.49] than 6-12 months before prescription. The HbA1c level decreased after the prescription. The largest decrease was shown at 3-6 months *after* prescription, which was 0.80% lower than 6-12 months *before* prescription, [CI: -1.15, -0.45] and 6-12 months *after prescription* [CI: -1.16, -0.45]. The mean HbA1c level slightly increased at later time points. At more than 24 months *after* prescription, the mean level was 0.65% *lower* [CI: -1.00, -0.29] than 6-12 months before treatment. Variations in the prescription effect were large and tended to be larger when the follow-up time increased.



5a.



5b.

Figure 5. Change in glucose (a) and HbA1c (b) levels at each time point compared to the levels at 6 to 12 months before medication use

Table 3. Results of fitting linear mixed models where the outcome was glucose or the HbA1c measurement. Time as a categorical variable was added as a fixed effect, and medication use was added as a random effect

	Glucose (mmol/L)	HbA1c (%)
Fixed effects (estimate [CI])		
Intercept (mean at time 0)	9.45 [8.71, 10.18]	7.36 [7.05, 7.67]
6 - 12m before prescription	-	-
3 - 6m before prescription	-0.44 [-1.05, 0.18]	-0.09 [-0.3, 0.12]
0 - 3m before prescription	0.56 [0.03, 1.10]	0.30 [0.10, 0.49]
0 - 3m after prescription	-1.15 [-1.85, -0.46]	-0.13 [-0.46, 0.21]
3 - 6m after prescription	-1.71 [-2.54, -0.88]	-0.80 [-1.15, -0.45]
6 - 12m after prescription	-1.76 [-2.54, -0.99]	-0.80 [-1.16, -0.45]
12 - 24m after prescription	-1.59 [-2.34, -0.84]	-0.67 [-1.01, -0.34]
More than 24m after prescription	-1.42 [-2.18, -0.66]	-0.65 [-1.00, -0.29]
Random effects (SD)		
Between-person variation	3.23	1.45
Variation in the mean difference		
at 0 - 3m after prescription	2.30	1.24
at 3 - 6m after prescription	3.30	1.52
at 6 -12m after prescription	3.06	1.61
at 12 - 24m after prescription	3.07	1.51
More than 24m after prescription	3.09	1.55
Within-person variation	1.63	0.53

Interaction effects

When adding *BMI at the first visit* and its interaction with medication use in the model, we observed that people with higher BMI at the NEO visit had a larger decrease in both glucose and HbA1c levels after medication prescription; 0.13 mmol/L [CI: 0.03; 0.23] *lower* for glucose and 0.05% *lower* [CI: 0.00; 0.09] for HbA1c per 1kg/m^2 increase in BMI. We did not observe an interaction effect between *sex* and medication use. When adding age at the first prescription date, we observed different directions of the effect for HbA1c and glucose; people who were older, on average, had a higher decrease in glucose but a smaller decrease in HbA1c after medication prescription.

4. Discussion

This study explored changes in blood glucose and HbA1c levels before and after glucose-lowering medication prescription from observation study data. We used the data from the NEO study and the routinely collected electronic health record data of its participants. We observed that glucose and HbA1c levels sharply increased shortly before prescription. The decrease in the outcome levels was the largest at 6-12 months after prescription; on average, 1.76 mmol/L lower in glucose and 0.80% lower in HbA1c compared to 6-12 months before starting medication. After one year, glucose and HbA1c levels increased slightly. The levels of both, however, remained significantly lower than before medication use. Similar to previous studies, we observed considerable within-person variations (17). The effect of medication on glucose and HbA1c varied largely between the individuals. The effects of the medication were larger in people with higher BMI.

Our results showed that the estimated medication effect depends on the period before medication use is chosen as a reference. The effect of medication would seem larger when considering 0-3 months before medication use as the reference, because an increase in glucose and HbA1c levels was observed shortly before medication prescription. It is known that the variability of glucose is large (17), and it might have occurred that a randomly high measurement of blood glucose level led to a decision to prescribe medication for some patients. Only comparing the last measurement before the start of medication to the measurements after the start of medication could lead to a regression to the mean effect, i.e., the phenomenon that extreme observations are followed by observations closer to the mean (19, 20). Thus, to not overestimate the medication effect, it is important to consider trends in measurements over a longer period. In our study, HbA1c and glucose measurements in 6-12 months before the treatment seemed to better reflect the clinical condition of an individual compared to the measurements shortly before the medication prescription and thus more appropriate to be set as the reference.

Advantages and pitfalls of estimating the effect of medication use from observational data

The average reduction in glucose and HbA1c after the first prescription estimated in our study was somewhat lower than the medication effects obtained from RCTs, which varied between 2-4mmol/L lower values for glucose and 0.66-1.5% for HbA1c depending on medication types (10, 12-14). These discrepancies may reflect the differences between observational settings and RCTs.

Compared to RCTs, routinely collected data better reflects how the population of interest behaves in practice, which has a consequence on the effectiveness of medication in the real world. It is known that the adherence rate of the routinely administered oral

treatment for chronic diseases, such as diabetes, is low (25, 26), likely leading to a lower average reduction in glucose and HbA1c in this study than shown in RCTs. Such tendency was also, in part, reflected when looking at long-term effects. Although the mean levels also after the first year remained significantly below the levels before medication use, the levels increased after the first year of medication use. Between-individual behavioral variations might have contributed to the large standard deviations in medication effect. As the variability in the real world is well-represented, routinely collected data may provide more realistic information about the medication effect in one's population of interest.

However, several considerations should be made when utilizing routinely collected data. The main concern is that clinical decisions made in real-world settings are often not clearly known and the recording of data may have been done selectively or inaccurately. For instance, some individuals in our study had much more frequent measurements of glucose and HbA1c than others. This suggests that a selected group of T2D patients were much more closely monitored than others.

We also observed that many individuals did not have information on medication prescriptions even though they were identified as type 2 diabetes patients. This could indeed reflect the diagnosis and prescription process of the real world. In the Netherlands, for example, the initial action of a GP when a person is diagnosed with T2D is lifestyle intervention, where individuals are advised to change their behaviors by exercising or controlling their diet. The fact that the average glucose and HbA1c levels were lower in the individuals excluded from the analyses (see Appendix 2) may indicate that medication use was not needed for some of these individuals. On the other hand, it may be that medication prescriptions were not recorded and that the date of the first prescription was wrong or missing in some individuals. Discrepancies in medical recordings, such as omitting prescribed medication or wrongly recording administration timing, commonly occur (27, 28). It is challenging to know what appears in the data is whether a true reflection of the real world or an error in the recording process.

Insufficient contextual knowledge introduces challenges in knowing to what extent the effect estimates in our study can be generalized. Hence, more detailed knowledge of how GPs prescribed medication in routine care would greatly help in modelling medication effects and understanding the generalizability of the estimated effects.

Recommendations

The estimated changes in blood glucose and HbA1c levels after medication prescription can be used to account for medication use in population cohort studies when untreated glucose or HbA1c values are of interest. For instance, when glucose or HbA1c is used as the outcome in the analysis, excluding individuals on glucose-lowering medication

or adding an indicator variable for medication use would lead to selection bias (21-23). Instead, one can add the values estimated from our study to the outcome values of the individuals using glucose-lowering mediation, an approach recommended in the literature (5, 7, 8). We suggest adding the estimated mean medication effects of this paper to the measurements of the individuals using medication based on their period of medication use. For example, for glucose, one can add 1.15 mmol/L to glucose measurements of the people who were on glucose-lowering medication for 0-3 months and 1.71 to those on medication for 3-6 months.

If glucose or HbA1c is the exposure or a confounding variable, one may either exclude individuals using glucose-lowering medication to estimate results among the non-medication users. As an alternative, researchers may use regression calibration together with adding the mean effect of medication use (7, 24). For this, one can use the estimated mean changes and standard deviations in this paper.

The sample size was limited in our study; therefore, we did not further investigate medication effects in different subgroups. Also, the type of medication used was homogenous, where 90% of the first prescribed medication was metformin. Studies with different populations may show different trends in types of prescribed medication.

5. Conclusion

This study explored changes in blood glucose and HbA1c after glucose-lowering medication prescription using routinely collected electronic health records. We observed that mean glucose and HbA1c levels increased shortly before the first prescription, which may reflect random high values. The medication effects were largest at 6-12 months after the prescription and smaller than what was known from RCTs. Routinely collected observational data allow investigation of real-world effects of medication over a longer period which could not be easily obtained from RCTs. However, challenges remain as clinical decisions and data recording processes in real-world settings are not always clearly known.

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Appendix 1

Keywords used for identifying prescription of glucose-lowering medication

- Keywords used for insulin:

abasaglar; actraphane; actrapid; apidra; fiasp; humalog; humuline; insulatard; insulin; insuman; lantus; levemir; liprolog; mixtard; novomix; novorapid; protaphane; ryzodeg; semglee; suliqua; toujeo; tresiba; xultophy

- Keywords used for other type of glucose lowering medication:

acarbose; actos; aloglip; amaryl; amglidia; avandamet; avandia; bydureon; byetta; canaglif; competact; dapaglif; diamicron; diastabol; dulaglut; ebymect; edistride; efficib; empaglif; enyglid; eucreas; exenat; fertin; forxiga; galvus; glibencl; gliclaz; glidipion; glimepiride; glubrava; glucient; glucobay; glucovance; glustin; glyxambi; icandra; incresync; invokana; jalra; janumet; januvia; jardiance; jentadueto; komboglyze; linaglip; liraglut; metfocell; metform; metnova; miglitol; nateglin; novonorm; onglyza; ozempic; pioglit; prandin; qtern; repaglin; ristaben; ristfor; rosiglit; saxaglip; saxenda; semaglut; sitaglip; starlix; steglujan; synjardy; tandemact; tesavel; tolbutam; trajenta; trulicity; velmetia; victoza; vildaglip; vipdomet; vipidia; vokanamet; xelevia; xigduo; xiliarx; yalformet; zomarist

Appendix 2

A comparison of characteristics at the first NEO visit between the individuals who were included and excluded from the analyses. Mean and standard deviation was used for continuous variables [mean (sd)]. Frequency and the percentage was used for categorical variables [N (%)].

	Included participants (n=127)	**Excluded participants (n=170)**
Sex		
Male	65 (51.2%)	72 (42.4%)
Age in years	56.0 (5.8)	56.7 (5.5)
Education		
High	50 (39.4%)	50 (29.4%)
Hypertension		
Yes	63 (49.6%)	93 (54.7%)
BMI (kg/m2)	33.6 (5.4)	32.6 (4.7)
Glucose (mmol/L)	7.0 (1.8)	6.6 (1.2)
Insulin (mU/L)	19.5 (11.8)	20.8 (23.9)
HOMA1-IR	6.0 (3.8)	6.2 (8.4)
HbA1c (%)	6.0 (0.9)	5.8 (0.7)
Total cholesterol (mmol/L)	5.7 (1.1)	5.6 (1.2)
Triglycerides (mmol/L)	1.9 (1.3)	2.0 (1.2)
HDL (mmol/L)	1.3 (0.3)	1.2 (0.3)
LDL (mmol/L)	3.6 (1.0)	3.5 (1.1)
Lipid-lowering drugs use		
Yes	19 (15.0%)	32 (18.8%)
Hypertension drugs use		
Yes	54 (42.5%)	79 (46.5%)