Glucose control, sulphonylurea, and insulin treatment in elderly people with type 2 diabetes and risk of severe hypoglycemia and death: an observational study

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Abstract

Objective: To estimate the relative and absolute risk of severe hypoglycemia and mortality associated with glucose control, sulphonylurea and insulin treatment in elderly people with type 2 diabetes.

Research Design and Methods: We identified elderly subjects (≥70 years) with type 2 diabetes between 2000 and 2017 in the UK CPRD primary care database with linkage to hospitalization and death data. Subjects with three consecutive HbA_{1c} <7% (53 mmol/mol) while on insulin and/or sulphonylurea within 60 days prior to the third HbA_{1c} (exposed) were matched to not exposed. Hazard ratios (HRs) and absolute risks were estimated for hospitalizations for severe hypoglycemia and cardiovascular and non-cardiovascular-related mortality.

Results: Among 22,857 included subjects (6288 [27.5%] exposed, of which 5659 [90.0%] on sulphonylurea), 10,878 (47.6%) deaths and 1392 (6.1%) severe hypoglycemic episodes occurred during the follow-up. Compared to non-exposed, the adjusted HR in exposed was 2.52 (95% CI: 2.23, 2.84) for severe hypoglycemia; 0.98 (0.91, 1.06) for cardiovascular mortality; and 1.05 (0.99, 1.11) for non-cardiovascular mortality. In a 70-, 75-, 80- and 85-year-old subject, the 10-year risk of severe hypoglycemia was 7.7%, 8.1%, 8.6%, and 8.4% higher than non-exposed while differences for non-cardiovascular mortality ranged from 1.2% (-0.1, 2.5) in a 70-year-old to 1.6% (-0.2, 3.4) in an 85-year-old subject. Sulphonylurea and insulin were more relevant predictors of severe hypoglycemia and death than glucose levels.

Conclusions: Elderly subjects with type 2 diabetes and low HbA_{1c} on sulphonylurea or insulin treatment experienced a substantially higher risk of hospitalization for severe hypoglycemia but had no clear evidence of increased risks of mortality.

Glucose control in people with type 2 diabetes plays an important role in reducing the risk of cardiovascular disease (CVD).(1) While there is robust epidemiological evidence of a progressive association between glucose levels and risk of long-term vascular complications,(2) intensive glucose control aiming at normal glucose levels has not been consistently associated with a reduced risk of cardiovascular events or mortality in randomized controlled trials (RCTs) of subjects with type 2 diabetes.(3-5) Conversely, intensive glucose control could increase the short- and long-term risk of hypoglycemia-related complications.(6) Combined with the emerging observational evidence showing a higher mortality in patients experiencing severe hypoglycemic episodes,(7; 8) the results of these RCTs raised a greater awareness on the risk associated with an excessive glucose control and contributed to the development of the clinical concept of "diabetes overtreatment", whereby an intense glucose control may result in more harms than benefits, particularly in elderly patients.(9)

A definition of "overtreatment" based on the combination of glucose (HbA_{1c}), treatment (medications associated with a higher risk of hypoglycemia), and demographic (age, given the higher risk of hypoglycemia and hypoglycemia-associated complications in elderly patients) criteria has been adopted in many observational studies,(10) particularly those using electronic health records,(11; 12) although other definitions have been reported in the literature.(13) In particular, HbA_{1c} lower than 7% (53 mmol/mol) in subjects older than 65 years who are at risk of hypoglycemia while on insulin and/or sulfonylurea have been suggested as criteria to identify patients at risk of potential overtreatment.(11; 14) To date, the available epidemiological studies have mainly described the incidence and risk factors of overtreatment;(10-13; 15; 16) to what extent overtreatment is associated with the relative and absolute risk of severe hypoglycemia and cause-specific mortality remains, however, largely unknown. At the same time, there is limited evidence on the comparative relevance of the

defining elements of overtreatment on long-term outcomes, which may contribute to its heterogeneous definitions.

To help clarify the evidence, we used UK primary care data to investigate the presence and the magnitude of the association of potential overtreatment, and of its defining elements age, HbA_{1c}, and glucose-lowering agents, with the relative and absolute risk of hospitalization for severe hypoglycemia and CVD- and non-CVD-related mortality in elderly people with type 2 diabetes.

Methods

Data source

In conducting and reporting this study, we followed the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.(17) We used the Clinical Practice Research Datalink (CPRD) to identify a cohort of elderly subjects with type 2 diabetes in the UK. CPRD is a primary care database of anonymized electronic health records from general practices, with approximately 7% of the UK population of which is broadly representative in terms of age and sex, which has been validated and extensively used for epidemiological research during the last 30 years.(18; 19) CPRD routinely collects data on demographics, laboratory tests, diagnoses, referrals, prescriptions, and health-related behaviors.(18) We used Hospital Episodes Statistics (HES) Admitted Care to define the medical history of included subjects and the Office for National Statistics (ONS) Death Registration to obtain date and cause of death. The patient-level linkage is carried out by a trusted third party using a 8-stage stepwise deterministic methodology.(20) This study has been approved by the Independent Scientific Advisory Committee (ISAC; protocol number: 18_156R2). The code lists used in the study are available at https://github.com/supingling/overtreatment.

Population

We included all elderly subjects (≥70 years) with diagnosis code(s) of type 2 diabetes between Jan 1, 2000 and Dec 31, 2017 and randomly assigned a day and month of birth to each subject as they are not available in CPRD due to the anonymization process. All subjects were considered at risk of being exposed to overtreatment since the 70th birthday, if diagnosed with

type 2 diabetes before 70 years old; or since the date of diagnosis, if it occurred after 70 years old. Subjects had also to be registered within an up-to-standard practice for a minimum of one year before the diagnosis of type 2 diabetes; those without linkage to HES or ONS death registration were not eligible for this study.

Exposure

In line with the available evidence from previous epidemiological studies using electronic health records and the clinical recommendations about the definition of "overtreatment",(11-14) we defined the exposure based on the glycemic control and the concurrent use of glucose-lowering agents associated with a higher risk of hypoglycemia. The exposed group included subjects with three consecutive values of HbA_{1c} <7% (53 mmol/mol) while on insulin and/or sulphonylurea within 60 days prior to the third HbA_{1c} measurement date; index date was identified as the first occurrence of these criteria. Up to 3 non-exposed subjects were matched to those exposed by year of birth ± 1 year, year of type 2 diabetes diagnosis, gender, number of HbA_{1c} measurements since being at risk of overtreatment until index date, and the length of the time frame from being at risk of overtreatment to index date ± 6 months. The non-exposed group included all subjects with type 2 diabetes aged ≥70 years between Jan 1, 2000 and Dec 31, 2017 who did not meet the criteria for the exposure. We further excluded subjects with history of severe hypoglycemia before index date in both the exposed and non-exposed group.

Outcomes

Outcomes included hospitalization for severe hypoglycemia and CVD- and non-CVD-related death. Severe hypoglycemia was defined as an admission to the hospital reporting the ICD-10 code of "E16.0", "E16.1" or "E16.2" in HES Admitted Care; date and the underlying cause of

death, defined using ICD-10 codes, were ascertained via linkage to ONS Death Registration. For severe hypoglycemia, subjects were followed-up until the first hospitalization for severe hypoglycemia, death, or Dec 31, 2017 (HES linkage date), whichever occurred first; for mortality, they were followed-up until death or Feb 14, 2018 (ONS linkage date).

Covariates

Socio-demographic factors included: age at index date, gender, ethnicity (White, non-White, obtained from HES and CPRD), diabetes durations, and deprivation (Townsend score in 2001: quintile 1 - most affluent; quintile 5 - most deprived). BMI, alcohol consumption (no drinker, ex-drinker, yes but unknown units, yes with ≤14 units/week, yes with >14 units/week), smoking status (no smoker, ex-smoker, current smoker), HbA_{1c}, blood pressure, total, HDL, and LDL cholesterol, and estimated glomerular filtration rate (CKD-EPI equation) were identified in CPRD using the closest value to the index date. Glucose-lowering medications, ACE inhibitors, angiotensin II receptor blockers, and statins were identified through prescriptions in CPRD within 60 days prior to the index date. Heart failure, stroke, myocardial infarction, cancer, peripheral arterial disease, chronic kidney disease, non-traumatic lower limb amputation, dementia, anemia, and depression were assessed by the presence of at least one diagnosis (or procedure) code in CPRD or HES before the index date.

Statistical analysis

We reported the characteristics of included subjects stratified by exposure status as median and interquartile range (IQR) for continuous and number and percentage for categorical variables. We used the Royston-Parmar-Lambert parametric survival model, with time into the study (i.e., from index date) as time scale;(21) the index date of the non-exposed subjects was the same

calendar date of the matched exposed subjects. The advantage of this model over the Cox regression is the possibility to investigate relative (hazard ratio, HR) as well as absolute effects. Accounting for competing risk, we used standardized cause-specific cumulative incidence functions to quantify the 5-year and 10-year absolute risk in severe hypoglycemia, CVD- and non-CVD-related death in exposed and non-exposed subjects and their difference.(22; 23) To allow the effect of the exposure to change across age, we tested a non-linear interaction between a restricted cubic spline transformation of age and the exposure. We further adjusted for socio-demographic and lifestyle factors, laboratory tests, medications, and previous medical conditions. To account for missing data, we performed multiple imputation and combined estimates using Rubin's rules across 10 imputed datasets;(24) we also conducted a complete-case analysis. To assess the robustness of our results, and investigate the comparative role of glucose control and therapies on the risk of the three outcomes, we performed several supplemental analyses (details reported in the Supplemental Material).

All analyses were conducted using Stata/IC 16.0 and estimates are reported with 95% confidence interval (CI).

Results

Cohort characteristics

The details of cohort definition are shown in Figure S1. Overall, of 69,993 people with type 2 diabetes aged ≥70 years and with linkage to HES and ONS, 6974 were defined as exposed. After matching, 686 exposed and 46,450 non-exposed subjects were excluded due to no matching or history of severe hypoglycemia, leaving 6288 (27.5%) and 16,569 subjects, respectively, for the analysis.

The pattern of missing data is reported in Table S1. The characteristics of included subjects at index date, stratified by exposure, are shown in Table 1. Compared to non-exposed, exposed subjects had lower HbA_{1c} (6.4% [46 mmol/l] and 6.8% [51 mmol/l]), eGFR, diastolic blood pressure and cholesterol; they were also more likely to be non-drinkers and on thiazolidinedione, ACE inhibitors, angiotensin II receptor blockers and statins. Among the exposed subjects, 90.0% were on a sulphonylurea compared to 75.2% in the non-exposed; corresponding proportions for insulin were 9.2% and 19.7%. Marginal differences were observed for pre-existing comorbidities, ranging from 0.8% for depression (21.5% in the exposed and 22.3% in the non-exposed) to 3.0% for anemia (15.9% and 12.9%, respectively). All other socio-demographic and clinical characteristics were balanced between the two groups.

Hospitalization for severe hypoglycemia

During 121,457 person-years of follow-up (median, 4.9 years), 1392 (6.1%) subjects were admitted to hospital for severe hypoglycemia; hospitalization rates were 17.5 (95% CI: 16.1, 18.9) and 9.2 (8.6, 9.8) per 1000 person-years in exposed and non-exposed subjects,

respectively. Adjusting only for age, the rate of hospitalization for severe hypoglycemia was higher in the exposed compared to non-exposed group (HR: 1.90; 95% CI: 1.71, 2.11). Upon further adjustment for other potential confounders, the HR increased to 2.52 (2.23, 2.84) (Table 2).

Figure 1 shows the absolute risk of severe hypoglycemia in exposed and non-exposed subjects. Regardless of age, the risk of severe hypoglycemia was always higher in the exposed than non-exposed subjects: in a 70-year-old subject, the risk progressively increased up to 6.0% at 5 years and 13.6% at 10 years; corresponding estimates in a 75-, 80- and 85-year-old subject were 6.8% and 14.4%; 7.9% and 15.2%; and 8.5% and 14.8%, respectively. In contrast, in a 70-year-old non-exposed subject, the risk similarly increased over time but to a smaller extent, resulting 2.5% at 5 years and 5.9% at 10 years; corresponding estimates in a 75-, 80- and 85-year-old subject were 2.9% and 6.2%; 3.3% and 6.6%; and 3.6% and 6.4%, respectively. These estimates translated in a 10-year absolute risk difference, comparing exposed to non-exposed, of 7.7% (95% CI: 6.0, 9.4) for a 70-year-old subject; 8.1% (6.7, 9.6) for a 75-year-old subject; 8.6% (7.2, 10.0) for an 80-year-old subject; and 8.4% (6.9, 9.8) for an 85-year-old subject, respectively (Figures 1-2).

Cardiovascular and non-cardiovascular-related mortality

During 125,409 person-years of follow-up (median, 5.2 years), 3670 (16.1%) CVD-related and 7208 (31.5%) non-CVD-related deaths occurred. The crude CVD-related mortality rates were 29.7 (95% CI: 28.0, 31.6) and 29.1 (28.0, 30.2) per 1000 person-years in exposed and non-exposed subjects, respectively; corresponding estimates for non-CVD-related death were 59.6 (57.1, 62.2) and 56.7 (55.1, 58.2). In multivariable models, the adjusted HR was 1.05 (95% CI:

0.99, 1.11) for non-CVD-related and 0.98 (0.91, 1.06) for CVD-related death comparing exposed to non-exposed subjects (Table 2).

Figure 1 presents the absolute risk of CVD- and non-CVD-related death over 10 years in exposed and non-exposed subjects. In a 75-year-old non-exposed subject, the risk of CVD- and non-CVD-related death was 8.9% and 16.7% at 5 years and 17.0% and 36.3% at 10 years, respectively; in an 85-year-old subject, corresponding estimates were 16.1% and 28.9% at 5 years and 25.9% and 51.5% at 10 years. In contrast, in a 75-year-old exposed subject, the risk of CVD- and non-CVD-related death was 8.7% and 17.4% at 5 years and 16.6% and 37.7% at 10 years; in an 85-year-old subject, corresponding estimates were 15.7% and 30.1% at 5 years and 25.1% and 53.1% at 10 years. These estimates led to marginal absolute risk differences across ages and over time (Figure 1-2). The 10-year risk of non-CVD-related mortality, comparing subjects exposed to non-exposed, ranged from a minimum increase of 1.2% (-0.1, 2.5) in a 70-year-old subject to a maximum increase of 1.6% (-0.2, 3.4) in an 85-year-old subject (Figure 2). Differences in CVD-related death were smaller: for the same comparison at the same follow-up time, differences ranged from a minimum decrease of 0.3% to a maximum decrease of 0.8%.

Supplemental analyses

Results of the complete-case analysis, shown in Figure S2-S3, were consistent with those of the main analysis.

Supplemental analyses investigating the risk of hypoglycemia and cause-specific death for alternative definitions of the exposure are detailed in the Supplemental Material. When defining overtreatment as three consecutive values of HbA_{1c} <7% (53 mmol/mol) and insulin only or sulphonylurea only (there were only 53 exposed subjects to both medications; Table

1), the estimates for three outcomes were virtually identical to those of the main analysis for the group of subjects on sulphonylurea only. In the group of subjects on insulin only, however, the HRs for hospitalization for severe hypoglycemia (3.91; 95% CI: 2.74 to 5.59) and CVD-related mortality (1.31; 1.01, 1.70) were higher compared to those obtained in the main analysis (Figure S2); these differences in the HRs were mirrored in the absolute risk estimates (Figure S4 and S5). Using three consecutive HbA_{1c} <6.5% (48 mmol/mol) while on insulin and/or sulphonylurea within 60 days prior to the index date did not result in different relative (Figure S2) or absolute (Figure S6 and S7) risks compared to the 7% (53 mmol/mol) threshold. Conversely, in subjects on insulin and/or sulphonylurea within 60 days prior to the index date, people with three consecutive HbA_{1c} <7% (53 mmol/mol) had a lower risk of hospitalization for severe hypoglycemia (HR: 0.71; 0.58, 0.87), CVD-related mortality (0.81; 0.68, 0.96), and non-CVD-related mortality (0.76; 0.68, 0.85) compared to those without (Figure S2). Lastly, when limiting the definition only to the HbA_{1c} criterion (i.e. subjects with three HbA_{1c} <7% (53 mmol/mol) regardless of medications at baseline), compared to no treatment the use of insulin and/or sulphonylurea was associated with a higher risk of admission for severe hypoglycemia (HR: 5.20; 4.44, 6.08), CVD- related (1.15; 1.06, 1.25), and non-CVD-related (1.27; 1.19, 1.34) mortality, while no associations were found with the newer medications sodium-glucose cotransport protein 2 inhibitor (SGLT-2i), dipeptidyl peptidase 4 inhibitor (DPP-4i), or glucagon-like peptide-1 receptor agonist [GLP-1RA]) for all three outcomes (Figure S2).

Stratified analyses by calendar time (to account for changes in clinical recommendations on the management of diabetes), age at diagnosis of type 2 diabetes, diabetes duration, renal function, or prevalent CVD; excluding subjects with previous comorbidities (to reduce the risk of reverse causation); or using alternative statistical methods (robust standard errors or inverse probability of treatment weighting), yielded results consistent with those obtained in the main

analysis (Figure S2, S8, and S9). There was no evidence of severe hypoglycemia as a mediating factor between the exposure and CVD- or non-CVD-related mortality (Table S2).

Discussion

In this retrospective population-based study, we used data of primary care subjects with type 2 diabetes aged ≥70 years and low HbA_{1c} while on insulin and/or sulphonylurea to estimate the relative and absolute risk of hospitalization for severe hypoglycemia, CVD- and non-CVD-related mortality. These subjects, who have been considered as exposed to a potential overtreatment,(11; 14) had a 2.5-fold increased hazard of severe hypoglycemia, translating into a 7-9% higher absolute risk at 10 years, when compared to those not exposed. However, there was no clear evidence of increased risks of mortality associated with the combination of low HbA_{1c} and insulin and/or sulphonylurea. It is important to note, however, that in our cohort 90% of the exposed subjects were on a sulphonylurea; therefore, our findings should be interpreted in relation to this characteristic of the exposed cohort. In our comprehensive analyses using alternative definitions of overtreatment, we also investigated the different prognostic relevance of glucose levels and glucose-lowering medications: when overtreatment is considered in the perspective of the long-term risk of severe hypoglycemia and death, sulphonylurea and insulin treatment are more relevant predictors than glucose levels.

Driven by the results of large-scale RCTs showing a neutral or increased risk of death in subjects with type 2 diabetes randomized to intensive compared to standard glucose control,(3-5; 25) there has been an emerging interest in the potential harms associated with glucose overtreatment, particularly among older, frail, multi-morbid patients.(26) This is also reflected in the changes in clinical recommendations on the diabetes management, which currently suggest relaxed HbA_{1c} goals in older patients with type 2 diabetes and other coexisting comorbidities.(27) Notwithstanding, in recent years a high prevalence of diabetes overtreatment, with varied definitions, has been reported in different countries.(10; 12; 15; 16; 28) While a HbA_{1c} <7% (53 mmol/mol) is widely accepted as a threshold of potential

overtreatment among older adults,(14; 28) most studies also considered the high risk for hypoglycemia as one of the key criteria, including insulin and/or sulphonylurea use,(10; 11; 13; 15; 16) ≥3 oral glucose-lowering medications,(13; 16) and/or coexisting comorbidities.(12; 16) In our study, to define potential overtreatment we initially considered subjects with type 2 diabetes aged 70 years or older and included the HbA_{1c} criterion (three consecutive values of HbA_{1c} <7% [53 mmol/mol]) alongside the medication criterion (concurrent use of glucose-lowering agents associated with a higher risk of hypoglycemia – insulin and/or sulphonylurea): in this cohort, these criteria resulted in 90% of exposed participants being on sulphonylurea. However, in view of the different definitions reported in the literature and a lack, to date, of a consensus, we also investigated associations using other possible definitions; these analyses allowed us to assess the combined and disjointed impact of the two criteria on the risk of severe hypoglycemia and mortality. We conducted extensive adjustment for other glucose-lowering medications, pre-existing comorbidities and other potential confounders, and estimated both relative and absolute risks, as a "statistically significant" increase in the relative risk may translate into a modest absolute risk difference; the combined information of these two metrics give more insights into the individual and public health relevance of HbA_{1c} levels, glucose-lowering treatments, and age (a component of any definition of overtreatment).

There is a growing consensus on the increased risk of hypoglycemia and its associated complications in elderly patients with type 2 diabetes under intensive glycemic control, possibly related to their slower counter-regulatory response to hypoglycemia.(27) A previous meta-analysis of five RCTs has shown that intensive glycemic control was associated with an approximately 2-fold increased risk of severe hypoglycemia;(25) this estimate is in line with our findings. Of note, we included subjects aged ≥70 years with a median diabetes duration of 4 years and a HbA_{1c} <7% (53 mmol/mol) in the exposed group; in contrast, in these RCTs the mean/median age and diabetes duration were 52 to 66 years and 8 to 11 years, respectively,

while the HbA_{1c} targets in the intensive treatment arms were <6.5% (48 mmol/mol) or <6.0% (42 mmol/mol).(25) However, our analysis using the 6.5% (48 mmol/mol) threshold showed results virtually identical to those of the main analysis, with a possible slightly higher risk of severe hypoglycemia in subjects with a longer diabetes duration. Moreover, a *post-hoc* analysis of the ACCORD trial in older (≥65 years) participants indicated that the proportion of subjects reporting a severe hypoglycemia was three times higher in the intensive compared to standard therapy arm,(29) consistent with our relative hazard estimate. Although the relative risk of severe hypoglycemia in our study was similar to the effect size reported in the ACCORD trial and the meta-analysis of intensive glycemic control, the absolute rates of severe hypoglycemia in our real-world study were lower compared to those reported in these trials, except when compared to the ADVANCE trial. In our study, rates of hospitalization for severe hypoglycemia were 17.5 and 9.2 per 1000 person-years among exposed and non-exposed subjects, respectively; rates in the intensive and standard arms were 7 and 4 per 1000 person-years in the ADVANCE (hypoglycemia requiring assistance from a third party),(5) 30 and 10 in the VADT (hypoglycemia resulting in complete loss of consciousness),(4) and 44.5 and 13.6 in the ACCORD subgroup of older participants (hypoglycemia requiring medical assistance).(29; 30)

Meta-analyses of RCTs have concluded that intensive glucose reduction may reduce CVD events compared to standard therapy while does not result in a reduction of all-cause or CVD-related mortality.(31; 32) In the ACCORD trial, in particular, a 22% higher mortality rate was observed in subjects randomized to intensive compared to standard glycemic control,(3) while we found no clear evidence of increased risks of mortality. In contrast with the uncertainty around intensive glucose control and cause-specific mortality, there is more robust and consistent evidence of a substantial excess risk of death (particularly non-CVD-related) in subjects with a previous sever episode of hypoglycemia.(33) A pathway whereby

overtreatment leads to an increased risk of severe hypoglycemia that, in turn, would increase the risk of death, has been postulated.(34) Although not the primary aim of our study, we did not find evidence of a mediating role of severe hypoglycemia in the association between overtreatment and mortality. The significantly greater risk of severe hypoglycemia compared to that of death in exposed subjects in our study would rather imply a different prognostic relevance of the factors considered in our models for these two outcomes; at the same time, our findings would suggest that other factors might be more relevant for the risk of death in patients who experienced a severe hypoglycemic episode.

Our extensive supplemental analyses suggested that treatment with insulin or sulphonylurea, rather than the low HbA_{1c} levels alone, is the key prognostic factor for hospitalization for severe hypoglycemia and mortality. In subjects with three consecutive HbA_{1c} <7% (53 mmol/mol), use of insulin and/or sulphonylurea was associated with a higher risk of severe hypoglycemia and mortality than use of any other glucose-lowering medications. Furthermore, among all subjects on insulin and/or sulphonylurea at baseline, those with three consecutive HbA_{1c} <7% (53 mmol/mol) had a lower risk of all outcomes. Interestingly, these two observations very closely mirror an observational study in subjects with type 2 diabetes aged over 75 years, where HbA_{1c} levels between 6.5% and 6.9% (48-52 mmol/mol) alone were not associated with a higher risk of death; contrariwise, when considered jointly with insulin or sulphonylurea therapy, the risk of death was more than doubled.(35) Moreover, in people with low HbA_{1c} levels, for SGLT-2i, DPP-4i, or GLP-1RA – which did not increase the risk of hypoglycemia in RCTs, there was no evidence of an association with hospitalization for severe hypoglycemia or cause-specific mortality compared to no treatment. Overall, our results contribute to the current evidence and debate over HbA_{1c}, glucose-lowering medications, and age as distinct yet complementary prognostic factors on the risk of severe hypoglycemia and mortality and give

insights into the definition of "diabetes overtreatment", from both an epidemiological and clinical perspective.

To our knowledge, this is the first study investigating the relative and absolute magnitude of the association between potential diabetes overtreatment and severe hypoglycemia hospitalization as well as cause-specific mortality. Our findings have important clinical implications. Currently, no clinical parameters are available to suggest when well-controlled glucose levels are indicative of an overtreatment and a possible "deintensification" of glucose treatments should be considered:(36) in this respect, the findings of a heterogeneous prognostic roles of HbA_{1c}, sulphonylurea, and insulin therapy may help clarify the evidence. Although during the study period new glucose-lowering agents have been made available and changes in the recommendations about glucose-lowering strategies occurred (particularly following the results of the ACCORD trial), we observed similar associations for all three outcomes over time, translating in very similar absolute risk estimates in hospitalization for severe hypoglycemia and small differences in cause-specific mortality. Some limitations of this study should also be considered. Our analyses are based on a large, UK electronic health record database: the generalizability of these findings should therefore be considered within the context of the healthcare systems where data have been collected and the potential misclassification bias in clinical coding, which cannot be completely ruled out as data were not collected for research purpose. Moreover, information collected in these databases are not as granular as that available in cohort studies or RCTs, where data are prospectively collected in line with a specific research plan. As such, we did not include other factors, i.e. neuropathies or the hemoglobin glycation index (the difference between the observed and the fasting plasma glucose predicted HbA_{1c}), which may act as confounders, mediators, or effect modifiers. In ACCORD and previous cohort studies, the risk of severe hypoglycemia and death has indeed been associated with the presence of neuropathy (peripheral and autonomic) and the

hemoglobin glycation index.(30; 37-39) We used consecutive HbA_{1c} measures to define overtreatment, which may lead to misclassification bias. However, in addition to age, gender and type 2 diabetes diagnosis year, we also matched by the number of HbA_{1c} measurements and the duration between being at risk of overtreatment and index date to minimize such bias. To account for confounding by indication, we have adjusted models for several potential confounders and assessed the robustness of our results using the inverse probability of treatment weighting; nevertheless, residual confounding may still be present and causality cannot be definitively established given the observational nature of the study.

In conclusion, a potential overtreatment of hyperglycemia, defined by consistently low HbA_{1c} measures and concurrent use of insulin and/or sulphonylurea, is common in elderly patients with type 2 diabetes and associated with a substantially higher risk of hospitalization for severe hypoglycemia while there is no clear of evidence of increased risks of mortality. Given the much greater number of exposed participants on sulphonylurea than insulin in our cohort, the results should be interpreted in this context and other investigations with larger samples are needed to disentangle the potential distinct effects of these two medications. In view of the increasing prevalence of multi-morbid, older patients with type 2 diabetes,(40) and the prognostic role of insulin and sulphonylurea, further research is warranted to explore the net clinical benefit of deintensification by replacing these treatments with other glucose-lowering medications in these patients.

Contribution
SL: study design, data extraction and preparation, statistical analysis, first draft; FZ: study design, statistical analysis, critical revision; CL: study design and critical revision; SS, MJD, KK: critical revision. All authors have approved the final manuscript; SL takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Conflict of interest
SL, FZ, and CL have no conflict of interests to declare.
SIS has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Sanofi-Aventis, Novo Nordisk, Janssen, Merck Sharp & Dohme, AstraZeneca, Lilly and Boehringer Ingelheim.

MJD acted as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen; as an advisory board member for Servier; and as a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International. MJD has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, and Janssen.

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Data sharing
Data access is through permission from Clinical Practice Research Datalink only; please send any enquiries to enquiries@cprd.com.

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Figures legend

Figure 1. Absolute risk and risk difference of hospitalization for severe hypoglycemia and mortality

Legend: Absolute risks in hospitalization for severe hypoglycemia (top 3 panels) and CVD- and non-CVD-related mortality (bottom 3 panels) over 10 years of follow-up at different ages, in subjects exposed (overtreatment, red) and non-exposed (green); the difference (exposed vs. non-exposed) is shown in blue. Estimates were multivariable adjusted and accounted for all-cause deaths as competing risk for severe hypoglycemia, and for non-CVD-related deaths for CVD-related mortality. In the bottom 3 panels, solid lines represent the risk of non-CVD-related death; dash lines the risk of CVD-related death; and the area the overall risk of death (non-CVD-related plus CVD-related death). Please note the different y-axis scale.

Figure 2. 5-year and 10-year risk difference in hospitalization for severe hypoglycemia and mortality

Legend: 5-year and 10-year differences (exposed vs. non-exposed to overtreatment) in hospitalization for severe hypoglycemia (green), CVD-related mortality (orange) and non-CVD-related mortality (blue) across ages are estimated in the multivariable-adjusted model with multiple imputation.

Table 1. Characteristics of subjects at index date by exposure

	Non-exposed (n=16,569)	Exposed (n=6288)	p-value
Age, years	76.6 (73.1-81.3)	76.8 (73.1-81.5)	0.370
⩽75	6531 (39.4%)	2449 (38.9%)	0.230
75-80	4901 (29.6%)	1820 (28.9%)	
80-85	3276 (19.8%)	1255 (20.0%)	
>85	1861 (11.2%)	764 (12.2%)	
Age at type 2 diabetes diagnosis, years	72.4 (68.3-77.1)	72.3 (68.1-77.3)	0.720
Gender			0.940
Male	8881 (53.6%)	3374 (53.7%)	
Female	7688 (46.4%)	2914 (46.3%)	
Ethnicity			0.470
White	14,878 (93.5%)	5678 (93.2%)	
Non-White	1034 (6.5%)	412 (6.8%)	
Townsend score, quintile			0.033
1 – most affluent	3597 (21.7%)	1304 (20.8%)	
2	4017 (24.3%)	1525 (24.3%)	
3	3587 (21.7%)	1294 (20.6%)	
4	3380 (20.4%)	1377 (21.9%)	
5 – most deprived	1975 (11.9%)	784 (12.5%)	
Diabetes durations, years	4.1 (2.2-6.9)	4.2 (2.2-7.1)	0.026
HbA_{1c} measurements from being at risk of overtreatment	5 (3-9)	5 (3-9)	<0.001
Time from being at risk of overtreatment, years	2.7 (1.7-4.7)	2.7 (1.6-4.9)	0.820
HbA_{1c}			
%	6.8 (6.3-7.5)	6.4 (6.0-6.7)	<0.001
mmol/mol	51 (45-59)	46 (42-50)	
BMI, kg/m^2	28.3 (25.3-31.8)	28.2 (25.1-32.0)	0.190
eGFR, $ml/min/1.73m^2$	62 (50-76)	58 (44-73)	<0.001
Blood pressure, mmHg			
Diastolic	74 (68-80)	72 (67-80)	<0.001
Systolic	137 (128-144)	137 (127-145)	0.690
Cholesterol, mmol/l			
Total	4.1 (3.6-4.8)	3.9 (3.4-4.6)	<0.001
HDL	1.3 (1.0-1.5)	1.2 (1.0-1.5)	<0.001
LDL	2.1 (1.6-2.7)	2.0 (1.6-2.6)	<0.001
Smoking status			0.590
Current smoker	1314 (7.9%)	488 (7.8%)	
Ex-smoker	7325 (44.3%)	2829 (45.0%)	
Non-smoker	7897 (47.8%)	2963 (47.2%)	
Alcohol consumption			0.001
Non-drinker	4084 (25.3%)	1675 (27.4%)	
Ex-drinker	892 (5.5%)	370 (6.0%)	
Drinker, <14 units /week	5402 (33.4%)	2016 (33.0%)	
Drinker, >14 units /week	1106 (6.8%)	367 (6.0%)	
Drinker, unknown units	4689 (29.0%)	1688 (27.6%)	
Glucose–lowering medications			<0.001
None	7483 (45.2%)	0 (0.0%)	
1	6344 (38.3%)	2992 (47.6%)	
2	2265 (13.7%)	2922 (46.5%)	
3	453 (2.7%)	361 (5.7%)	
4	23 (0.1%)	13 (0.2%)	
5	1 (0.0%)	0 (0.0%)	
Glinide	42 (0.3%)	12 (0.2%)	0.380

Metformin	7288 (44.0%)	2917 (46.4%)	0.001
DPP-4 inhibitor	506 (3.1%)	204 (3.2%)	0.460
GLP-1 receptor agonist	60 (0.4%)	21 (0.3%)	0.750
SGLT-2 inhibitor	23 (0.1%)	5 (0.1%)	0.250
Thiazolidinedione	694 (4.2%)	402 (6.4%)	<0.001
Mixed oral medication	158 (1.0%)	62 (1.0%)	0.820
Other diabetes medications	26 (0.2%)	7 (0.1%)	0.420
Use of sulphonylurea and insulin*			<0.001
Sulphonylurea and insulin	172 (5.1%)	53 (0.8%)	
Sulphonylurea only	2526 (75.2%)	5659 (90.0%)	
Insulin only	663 (19.7%)	576 (9.2%)	
Type of insulin*			
Basal	398 (2.4%)	217 (3.5%)	<0.001
Intermediate	431 (2.6%)	399 (6.3%)	<0.001
Prandial	148 (0.9%)	77 (1.2%)	0.023
Combination	139 (0.8%)	64 (1.0%)	0.200
Cardiovascular medications			
ACE inhibitor	6710 (40.5%)	2910 (46.3%)	<0.001
ARB	2633 (15.9%)	1226 (19.5%)	<0.001
Statin	10,617 (64.1%)	4422 (70.3%)	<0.001
Number of morbidities‡			<0.001
0	6367 (38.4%)	2262 (36.0%)	
1	5599 (33.8%)	2073 (33.0%)	
2	2873 (17.3%)	1159 (18.4%)	
3	1142 (6.9%)	501 (8.0%)	
4	424 (2.6%)	213 (3.4%)	
5	131 (0.8%)	62 (1.0%)	
6	23 (0.1%)	16 (0.3%)	
7	9 (0.1%)	2 (0.0%)	
8	1 (0.0%)	0 (0.0%)	
Myocardial Infarction	2007 (12.1%)	832 (13.2%)	0.022
Cancer	3189 (19.2%)	1244 (19.8%)	0.360
Heart failure	1765 (10.7%)	774 (12.3%)	<0.001
Peripheral arterial disease	906 (5.5%)	377 (6.0%)	0.120
Stroke	2433 (14.7%)	1002 (15.9%)	0.018
Dementia	553 (3.3%)	208 (3.3%)	0.910
Depression	3688 (22.3%)	1350 (21.5%)	0.200
Non-traumatic lower limb amputation	139 (0.8%)	80 (1.3%)	0.003
Chronic kidney disease	514 (3.1%)	300 (4.8%)	<0.001
Anemia	2137 (12.9%)	999 (15.9%)	<0.001

Data are shown as median (IQR) for continuous variables and number (%) for categorical variables; *p-values* obtained with Wilcoxon Rank-Sum test for continuous and Pearson's chi-square test for categorical variables.

*Could be combined with other drugs;
‡Maximum number of conditions: 10;
eGFR: estimated glomerular filtration rate, calculated using the CKD-EPI equation; DPP-4: Dipeptidyl Peptidase 4; GLP-1: Glucagon-like peptide-1; SGLT-2: sodium-glucose transport protein 2; ARB: angiotensin II receptor blocker.

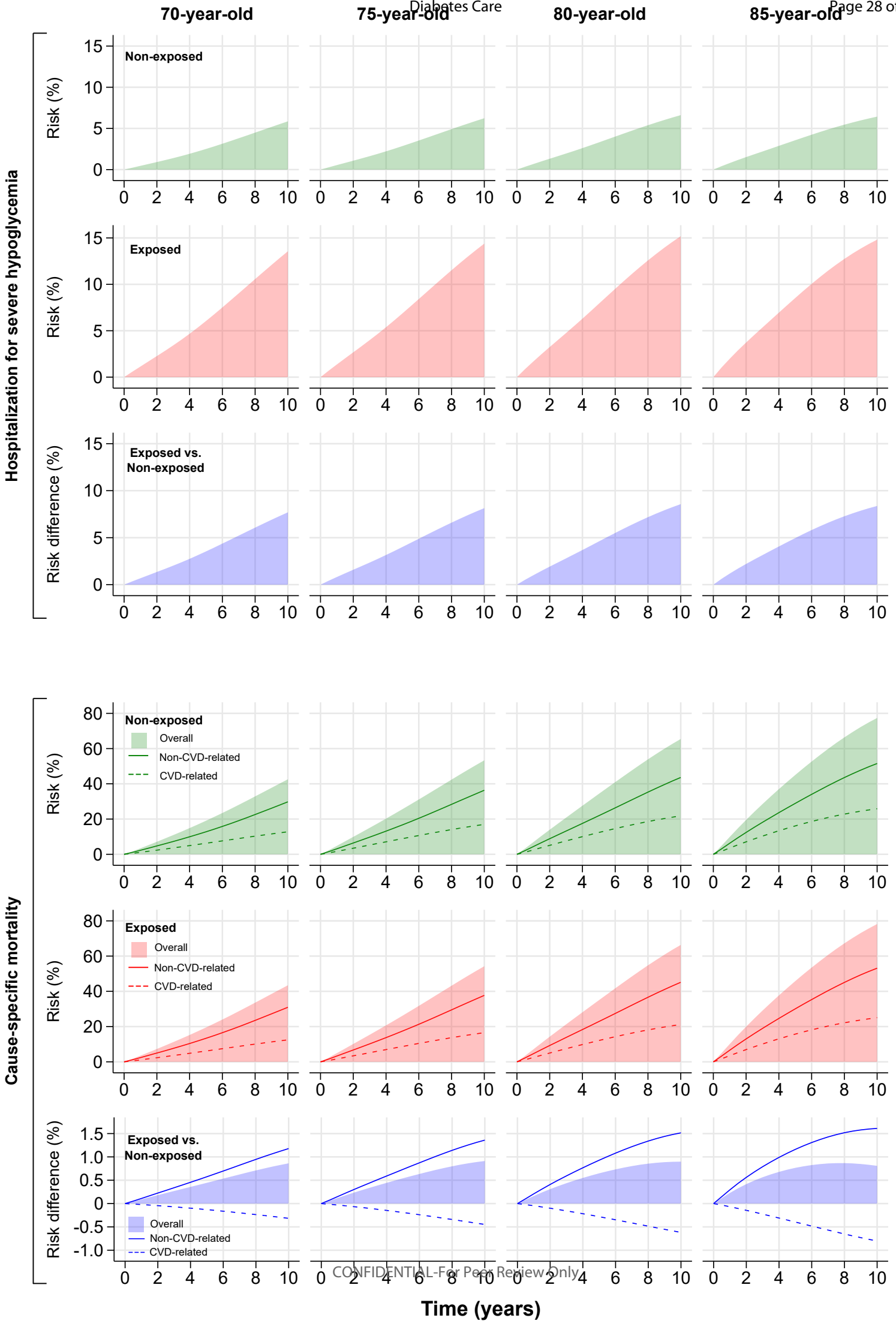
Table 2. Hazard ratios for hospitalization for severe hypoglycemia and cause-specific mortality

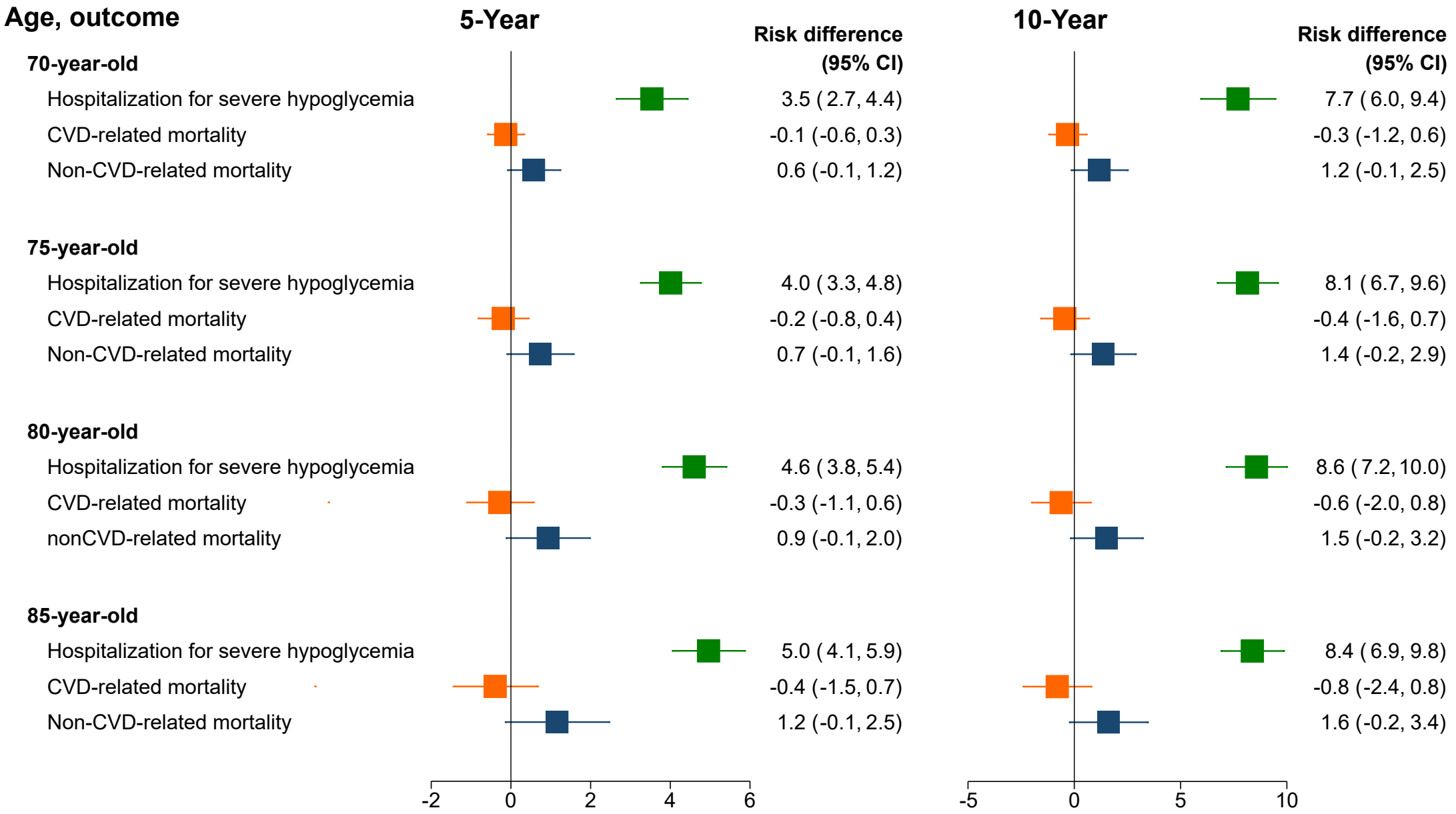
Outcome	Person-years	Events/Subjects	Hazard ratio (95% confidence interval)	
			Age-adjusted	Multivariable adjusted
Hospitalization for severe hypoglycemia	121,457	1392/22,857	1.90 (1.71, 2.11)	2.52 (2.23, 2.84)
Cardiovascular mortality	125,409	3670/22,857	1.02 (0.95, 1.10)	0.98 (0.91, 1.06)
Non-cardiovascular mortality	125,409	7208/22,857	1.05 (1.00, 1.10)	1.05 (0.99, 1.11)

Hazard ratios comparing exposed vs non-exposed to overtreatment.

Multivariable models adjusted for: age (restricted cubic spline with 4 knots), number of HbA_{1c} measurements from being at risk of overtreatment to index date, length of time frame from being at risk of overtreatment to index date, gender, ethnicity (White, non-White), deprivation (quintiles), diabetes durations, BMI, blood pressure (diastolic and systolic), alcohol (no drinker, ex-drinker, yes but unknown units, yes with ≤14 units/week, yes with >14 units/week), smoking (no smoker, ex-smoker, current smoker), HbA_{1c}, total, HDL, and LDL cholesterol, eGFR (CKD-EPI equation), glucose-lowering medication (glinide, metformin, dipeptidyl peptidase 4 inhibitor, glucagon-like peptide 1 receptor agonist, sodium-glucose cotransporter protein 2 inhibitor, thiazolidinedione, mixed oral glucose-lowering medication, and other glucose-lowering medications), ACE inhibitor, angiotensin II receptor blocker, statin, medical history of: heart failure, stroke, myocardial infarction, cancer, peripheral arterial disease, chronic kidney disease, non-traumatic lower limb amputation, depression, dementia, and anemia.

FIGURE 1




Age, outcome
5-Year
Risk difference (95% CI)
10-Year
Risk difference (95% CI)
70-year-old
Hospitalization for severe hypoglycemia
3.5 (2.7, 4.4)
7.7 (6.0, 9.4)
CVD-related mortality
-0.1 (-0.6, 0.3)
-0.3 (-1.2, 0.6)
Non-CVD-related mortality
0.6 (-0.1, 1.2)
1.2 (-0.1, 2.5)
75-year-old
Hospitalization for severe hypoglycemia
4.0 (3.3, 4.8)
8.1 (6.7, 9.6)
CVD-related mortality
-0.2 (-0.8, 0.4)
-0.4 (-1.6, 0.7)
Non-CVD-related mortality
0.7 (-0.1, 1.6)
1.4 (-0.2, 2.9)
80-year-old
Hospitalization for severe hypoglycemia
4.6 (3.8, 5.4)
8.6 (7.2, 10.0)
CVD-related mortality
-0.3 (-1.1, 0.6)
-0.6 (-2.0, 0.8)
nonCVD-related mortality
0.9 (-0.1, 2.0)
1.5 (-0.2, 3.2)
85-year-old
Hospitalization for severe hypoglycemia
5.0 (4.1, 5.9)
8.4 (6.9, 9.8)
CVD-related mortality
-0.4 (-1.5, 0.7)
-0.8 (-2.4, 0.8)
Non-CVD-related mortality
1.2 (-0.1, 2.5)
1.6 (-0.2, 3.4)
-2
0
2
4
6
-5
0
5
10

Supplemental material

Glucose control, sulphonylurea, and insulin treatment in elderly people with type 2 diabetes and risk of severe hypoglycemia and death: an observational study

Suping Ling, Francesco Zaccardi, Claire Lawson, Samuel I Seidu, Melanie J Davies, Kamlesh Khunti

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Figure S1. Cohort definition

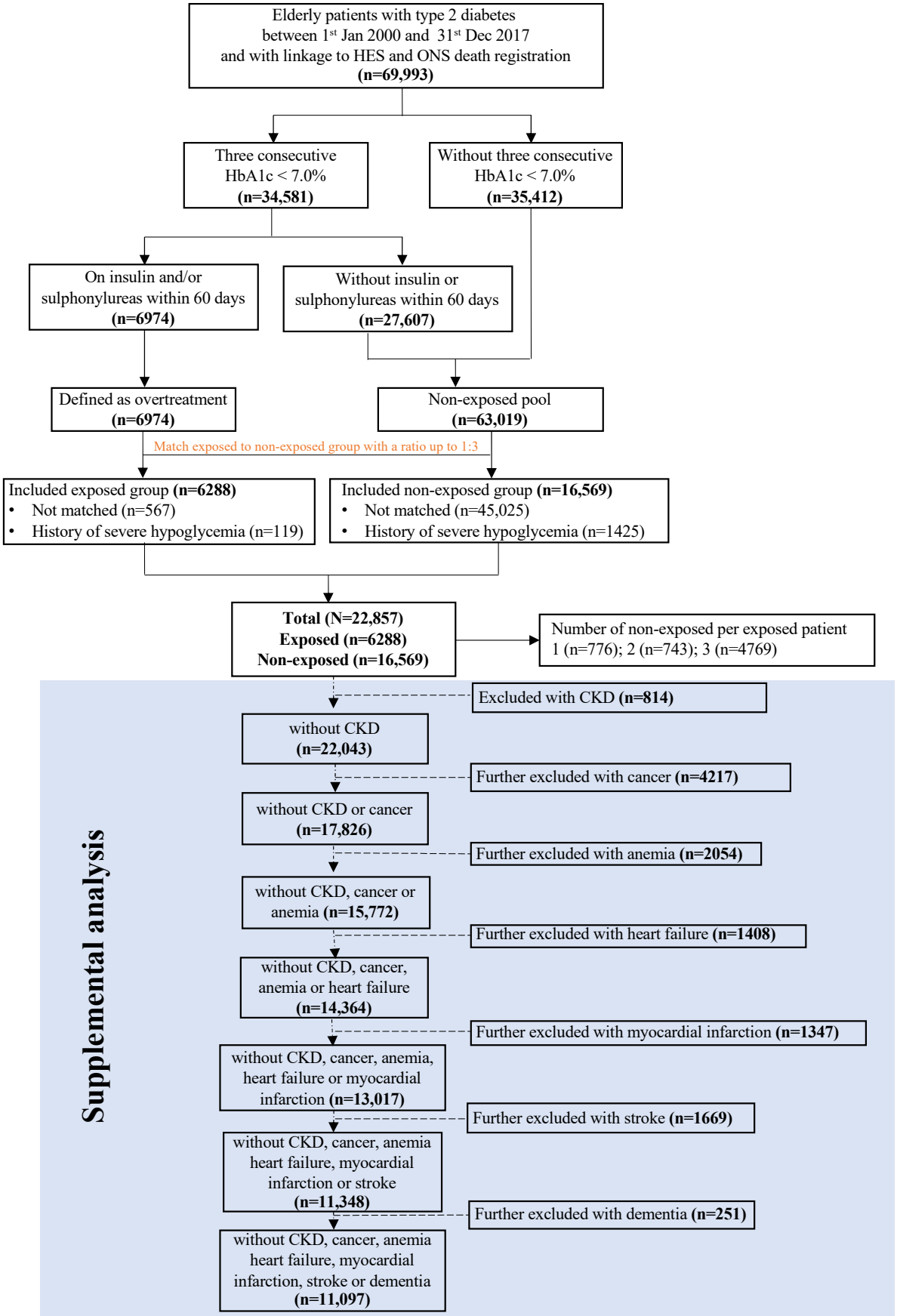


Table S1. Missing data

Table S1a. Subjects with implausible values

Variable	Implausible values	Number of subjects
Body Mass Index	<10 or >70 kg/m^2	41
Total Cholesterol	=0 or >10 mmol/l	3
Low-density lipoproteins	=0 or >10 mmol/l	5
High-Density lipoproteins	=0 or >10 mmol/l	0
Diastolic blood pressure	=0 mmHg	3
Systolic blood pressure	=0 mmHg	1
eGFR	>150 ml/min/1.73m^2	3

These implausible values have been coded as missing data and included in the Table S1b below. Total sample N=22,857.
eGFR: estimated Glomerular Filtration Rate

Table S1b. Missing data for each variable

Variable	Number of subjects with missing data	%
eGFR	13	0.06
+Townsend score	17	0.07
Total Cholesterol	18	0.08
Smoking status	41	0.18
Systolic blood pressure	66	0.29
Diastolic blood pressure	68	0.30
Body mass index	174	0.76
Alcohol consumption	568	2.49
Ethnicity	855	3.74
High-density lipoproteins	976	4.27
Low-density lipoproteins	2638	11.54

eGFR: estimated Glomerular Filtration Rate

Table S1c. Number of subjects and variables with missing data

Number of variables with missing data	Number of subjects	%
0	18,797	82.24
1	2809	12.29
2	1142	5.00
3	95	0.42
4	14	0.06
Total	22,857	100.00

Supplemental analyses

We conducted several supplemental analyses to assess the robustness of our results. To be consistent with the analytical framework of the main analysis, we performed multiple imputation in all supplemental analyses reported below, except for the complete-case analysis; estimates were combined using Rubin's rules across 10 imputed databases.

Complete case analysis

The results of the analyses using the complete-case database (N=18,797, 1167 hospitalizations for hypoglycemia; 2896 CVD deaths; 5760 non-CVD deaths) were virtually identical to the relative (**Figure S2**) and absolute (**Figure S3**) risk estimates obtained in the main, multiple imputed analysis.

Definition of the exposure (overtreatment)

In the main analysis, we defined the exposure (overtreatment) using two criteria: the HbA_{1c} criterion (three consecutive values of HbA_{1c} <7%) *and* the drug criterion (while on insulin and/or sulphonylurea within 60 days prior to the third HbA_{1c} measure date). As there is no consensus on the definition of overtreatment, we explored associations across different definitions. The results of these supplemental investigations may help disentangle the role of glucose-lowering medications and low HbA_{1c}.

First, we investigated the drug criterion. To determine the potential different impact of insulin vs sulphonylurea on the risk of outcomes, overtreatment was defined in subjects with three consecutive values of HbA_{1c} <7% (53 mmol/mol) and on: (1) Insulin only (HbA_{1c} criterion + insulin only); (2) Sulphonylurea only (HbA_{1c} criterion + sulphonylurea only). A third group (HbA_{1c} criterion + insulin + sulphonylurea) was not defined due to the very limited number of exposed subjects (n=53; **Table 1**). These two groups/definitions of overtreatment were then used to explore associations with the risk of hospitalization for severe hypoglycemia and cause-specific mortality. Compared to their matched non-exposed subjects, the first group (insulin only) had a higher risk of hospitalization for severe hypoglycemia (HR: 3.91; 95% CI: 2.74, 5.59), CVD-related mortality (1.31; 1.01, 1.70) but not non-CVD-related mortality (0.97; 0.80, 1.18); corresponding estimates for the second group (sulphonylurea only) were 2.39 (2.10,

2.72), 0.96 (0.88, 1.04) and 1.05 (1.00, 1.12) (**Figure S2**). While for insulin only the associations were stronger than those observed in the main analysis for severe hypoglycemia and CVD-related death, estimates for sulphonylurea only were virtually identical to those of the main analysis for all three outcomes. These differences of the relative hazards were mirrored by differences in the absolute risks, for both hospitalization for severe hypoglycemia (**Figure S4**) and cause-specific mortality (**Figure S5**). In addition, we have conducted a further supplemental analysis by excluding exposed subjects who were temporarily on insulin (i.e., who received insulin for less than 6 months by the index date or started insulin within 6 months before the index date): the results were largely consistent with those of the main analysis (severe hypoglycemia [HR: 2.51; 95% CI: 2.22, 2.83]; CVD-related mortality [0.98; 0.91, 1.06]; non-CVD-related mortality [1.05; 0.99, 1.04]).

Second, we explored the HbA_{1c} criterion. To determine the effect of different HbA_{1c} threshold, we re-defined the exposed group as three consecutive HbA_{1c} <6.5% (48 mmol/mol) while on insulin and/or sulphonylurea within 60 days prior to the third HbA_{1c} measure date. The results using this definition were largely in line with those of the main analysis, in terms of both relative (**Figure S2**) and absolute (**Figure S6 –** hospitalization; **Figure S7 –** cause-specific mortality) risk. Furthermore, to understand the risk of the three outcomes related to consistently low HbA_{1c} in a graded fashion, we have conducted further stratified analyses restricted to non-exposed subjects with 1 or 2 consecutive HbA_{1c} <7% before the index date; results are very similar to those of the main analysis. Compared to non-exposed subjects with two consecutive HbA_{1c} <7% before the index date, potential overtreatment with sulphonylurea and/or insulin was associated with an increased risk of severe hypoglycemia (HR: 3.42; 95% CI: 2.92, 4.00) and non-CVD-related mortality (1.08; 1.03, 1.16) but not CVD-related mortality (1.00; 0.92, 1.10). Compared to non-exposed subjects with one HbA_{1c} <7%, the HRs for the three outcomes were: severe hypoglycemia 2.92 (95% CI: 2.54, 3.34); non-CVD-related mortality 1.06 (95% CI: 1.00, 1.12); and CVD-related mortality 1.00 (95% CI: 0.92, 1.08).

Third, we restricted the population to subjects on insulin and/or sulphonylurea within 60 days prior to the index date and compared the risk of outcomes in subjects with three consecutive HbA_{1c} <7% compared to those without: the hazard ratio was 0.71 (95% CI: 0.58, 0.87) for hospitalization for severe hypoglycemia; 0.81 (0.68, 0.96) for CVD-related mortality; and 0.76 (0.68, 0.85) for non-CVD-related mortality (**Figure S2**).

Lastly, we used only the HbA_{1c} criterion to define overtreatment, i.e. subjects three HbA_{1c} <7%, regardless of medications at baseline. The glucose-lowering agents used in the 60 days prior to

the index date were then grouped in four categories: (1) insulin and/or sulphonylurea (with or without other medications); (2) newer agents: sodium-glucose cotransporter protein 2 inhibitor (SGLT-2i), dipeptidyl peptidase 4 inhibitor (DPP-4i), and glucagon-like peptide 1 receptor agonist (GLP-1RA) (with or without other medications, but without insulin or sulphonylurea); (3) metformin and/or thiazolidinedione (with or without other medications, but without insulin, sulphonylurea or newer agents); (4) and others (without insulin, sulphonylurea, newer agents, metformin, or thiazolidinedione). These four groups were compared to no medication (reference, HR=1). Use of insulin and/or sulphonylurea was associated with a higher risk of admission for severe hypoglycemia (HR: 5.20; 95% CI: 4.44, 6.08), CVD- (1.15; 1.06, 1.25), and non-CVD-related (1.27; 1.19, 1.34) mortality (**Figure S2**). Conversely, no associations were found with newer medications for all three outcomes; an increased risk with metformin and/or thiazolidinedione for hospitalization for severe hypoglycemia (HR: 1.39; 1.15, 1.67) and non-CVD mortality (HR: 1.11; 1.05, 1.17); and a higher risk for hospitalization for severe hypoglycemia (HR: 2.13; 1.43, 3.16) in other glucose-lowering medications group (**Figure S2**).

Overall, these results would suggest that the drug criterion may be more relevant than the HbA1c criterion in the definition of overtreatment, at least when overtreatment is considered from the prognostic perspective of long-term risk of severe hypoglycemia and death. Moreover, these supplemental results would indicate that the newer medications are associated with a lower risk of severe hypoglycemia compared to older ones, although the estimates are based on a smaller group of subjects (N=370).

Changes in clinical recommendations

As diabetes management guidelines changed during the 20-year period considered in our analysis, the understanding of diabetes treatment and the number of exposed subjects could have changed over time. We therefore conducted a stratified analysis based on the time subjects entered the cohort (index date): 01/Jan/2000 to 31/Dec/2011 vs 01/Jan/2012 to 31/Dec/2017. We considered 2012 as cut-off, allowing a 2-year lag time following the post-hoc analyses of the ACCORD study suggesting an increased risk of death associated with severe hypoglycemia.(1) We did not find evidence of heterogeneity of effects for all three outcomes across the two study periods (**Figure S2**), translating in very similar absolute risk estimates in hospitalization for severe hypoglycemia (**Figure S8**) and small differences in cause-specific mortality (**Figure S9**).

Age at diabetes diagnosis and diabetes duration

Age and diabetes duration are associated with a higher risk of hypoglycemia.(2; 3) We therefore explored interactions across diabetes duration (<5 vs ≥5 years) and age at T2D diagnosis (<70 vs ≥70 years old), showing consistent effect for all three outcomes (**Figure S2**).

Previous medical history

To assess whether the association differed by presence of previous complications, we performed interaction analyses across eGFR values (> 60 vs ≤ 60 ml/min/1.73m^2) and presence of CVD (heart failure, stroke, myocardial infarction, or peripheral arterial disease): results were consistent across these two effect modifiers, for all three outcomes (**Figure S2**). As renal impairment, anemia, or cancer may cause a low HbA_{1c};(4) history of heart failure, myocardial infarction, stroke may increase the risk of death;(5-7) and dementia may increase the risk of hypoglycemia,(8) to minimize the risk of reverse causality, we estimated associations following a progressive exclusion of subjects with these conditions at baseline. In these analyses, estimates were not materially changed following progressive exclusions, and were consistent with those of the main analysis (**Figure S2**).

Matching and adjustment

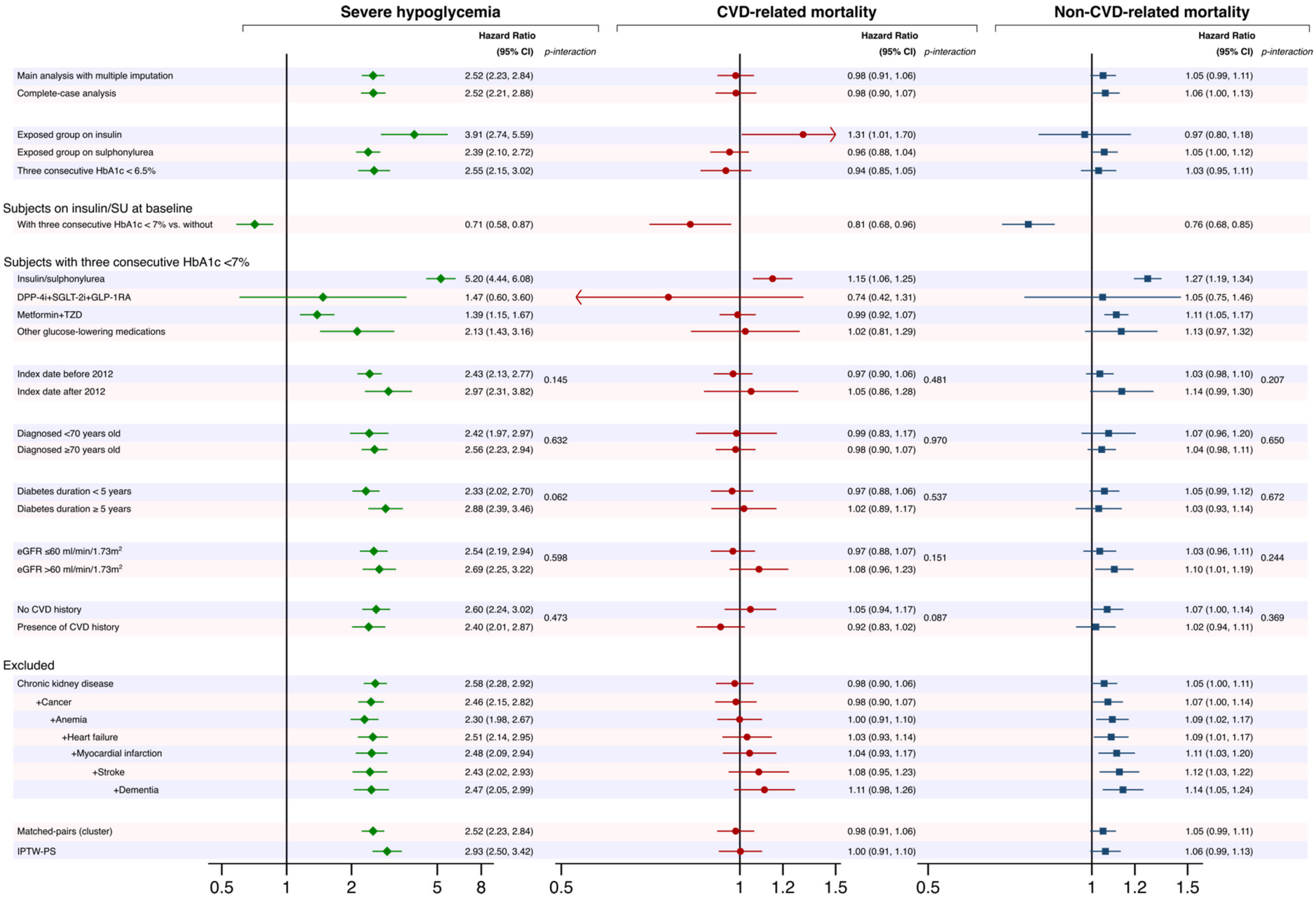
To account for the potential impact of matching, we conducted a supplemental analysis considering matched-pairs as clusters: the results of this analysis were identical to the estimates obtained in the main analysis without robust clustered standard errors (**Figure S2**).

In addition to the approach of matching and adjustment used in the main analysis, an alternative approach is the inverse probability of treatment weighting (IPTW) using propensity score (9). The probability of being exposed was estimated using a conditional logistic regression with all covariates considered in the main analysis (socio-demographics, lifestyle factors, laboratory tests, medication uses, and medical history). Then, IPTW Royston-Parmar-Lambert parametric survival models were used to estimate associations for all three outcomes. While the HR of the association between exposure and severe hypoglycemia was slightly higher than the estimate obtained in the main analysis [2.93 (95% CI: 2.50, 3.42) vs. 2.52 (2.23, 2.84)], HRs of cause-specific mortality were virtually identical to the main analysis estimates (**Figure S2**).

Mediation analysis: hypoglycemia and mortality

Hypoglycemia has been suggested as a possible mechanism linking intensive glucose control and risk of death in patients with T2D.(10-12) To assess the potential mediation role of hypoglycemia in the associations between the exposure and mortality, we conducted a mediation analysis using the "med4way" Stata command.(13) In this population, there was no evidence of severe hypoglycemia as a mediating factor between the exposure and CVD- and non-CVD-related mortality (**Table S2**).

Figure S2. Hazard ratios for severe hypoglycemia and CVD- and non-CVD-related mortality in supplemental analyses



Multivariable models adjusted, where applicable, for: age (restricted cubic spline with 4 knots), number of HbA_{1c} measurements from being at risk of overtreatment to index date, length of time frame from being at risk of overtreatment to index date, gender, ethnicity (White, non-White), deprivation (quintiles), diabetes durations, BMI, blood pressure (diastolic and systolic), alcohol (no drinker, ex-drinker, yes but unknown units, yes with ≤14 units/week, yes with >14 units/week), smoking (no smoker, ex-smoker, current smoker), HbA_{1c}, total cholesterol, HDL, LDL, eGFR (CKD-EPI equation), glucose-lowering medications (glinide, metformin, dipeptidyl peptidase 4 inhibitor [DPP-4i], glucagon-like peptide 1 receptor agonist [GLP-1RA], sodium-glucose cotransporter protein 2 inhibitor [SGLT-2i], thiazolidinedione [TZD], mixed oral glucose-lowering medication, and other glucose-lowering medications), ACE inhibitor, angiotensin II receptor blocker, statin, medical history of: heart failure, stroke, myocardial infarction, cancer, peripheral arterial disease, chronic kidney disease, non-traumatic lower limb amputation, depression, dementia, and anemia.

Main analysis with multiple imputation: hazard ratios comparing exposure (three consecutive values of HbA_{1c} <7% [53 mmol/mol] while on insulin and/or sulphonylurea within 60 days prior to the third HbA1c measurement date) vs. not exposed;

Complete-case analysis: hazard ratios comparing exposed vs. not exposed within complete cases;

Exposed group on insulin: stratified analysis within exposed group on insulin (drug criterion of overtreatment; details reported in the "Supplemental Analyses" paragraph) and their matched comparators;

Exposed group on sulphonylurea: stratified analysis within exposed group on sulphonylurea (drug criterion of overtreatment; details reported in the "Supplemental Analyses" paragraph) and their matched comparators;

Three consecutive HbA_{1c} <6.5%: exposure (overtreatment) defined by three consecutive HbA_{1c} <6.5% and on insulin and/or sulphonylurea within 60 days prior to the third HbA_{1c} measurement date (HbA_{1c} criterion of overtreatment; details reported in the "Supplemental Analyses" paragraph);

Subjects on insulin/SU at baseline: With three consecutive HbA_{1c} <7% vs. without: comparison between subjects with three consecutive HbA_{1c} <7% to those without, in subjects on insulin and/or sulphonylurea within 60 days prior to the index date.

Subjects with three consecutive HbA_{1c} <7%: supplemental analyses restricted to subjects with three HbA_{1c} <7%, regardless of medication uses at baseline. The glucose-lowering medications use in the 60 days prior to the index date were grouped in four categories: (1) insulin and/or sulphonylurea (with or without other medications); (2) newer agents: SGLT2i, DPP-4i and GLP-1RA (with or without other medications, but without insulin or sulphonylurea); (3) metformin and/or thiazolidinedione (with or without other medications, but without insulin, sulphonylurea or newer agents); (4) and others (without insulin, sulphonylurea, newer agents, metformin or thiazolidinedione); groups 1-4 were compared to no medication (reference, HR=1).

Index date before/after 2012: Interaction analysis between exposure and index date [before 31/12/2011 (inclusive) or after 01/01/2012 (inclusive)];

T2D diagnosed <70 years/≥70 years: interaction analysis between exposure and age;

Diabetes duration <5 years/≥5 years: interaction analysis between exposure and diabetes duration at baseline;

eGFR ≤60/>60 ml/min/1.73m^2: interaction analysis between exposure and eGFR (CKD-EPI);

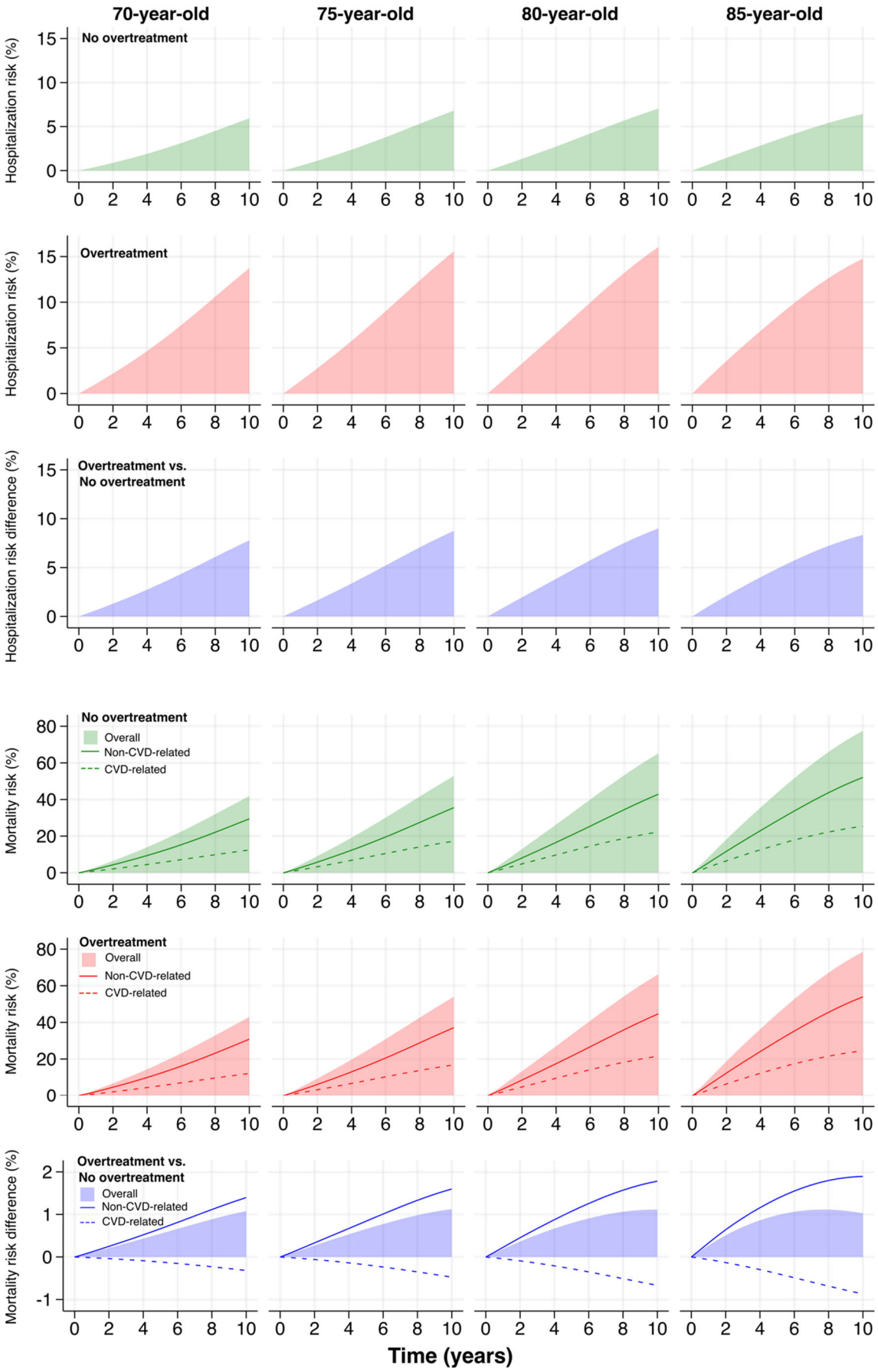
No CVD history/presence of CVD history: interaction analysis between exposure and CVD (history of heart failure, myocardial infarction, stroke, or peripheral vascular disease);

Excluded: Hazard ratios exposed vs non-exposed with progressive exclusion of subjects with history of CKD, cancer, anemia, heart failure, myocardial infarction, stroke and dementia (Figure S1);

Matched-pairs (cluster): Hazard ratios exposed vs non-exposed considering the non-exposed subjects matched to the same exposed subject as a cluster (robust standard errors);

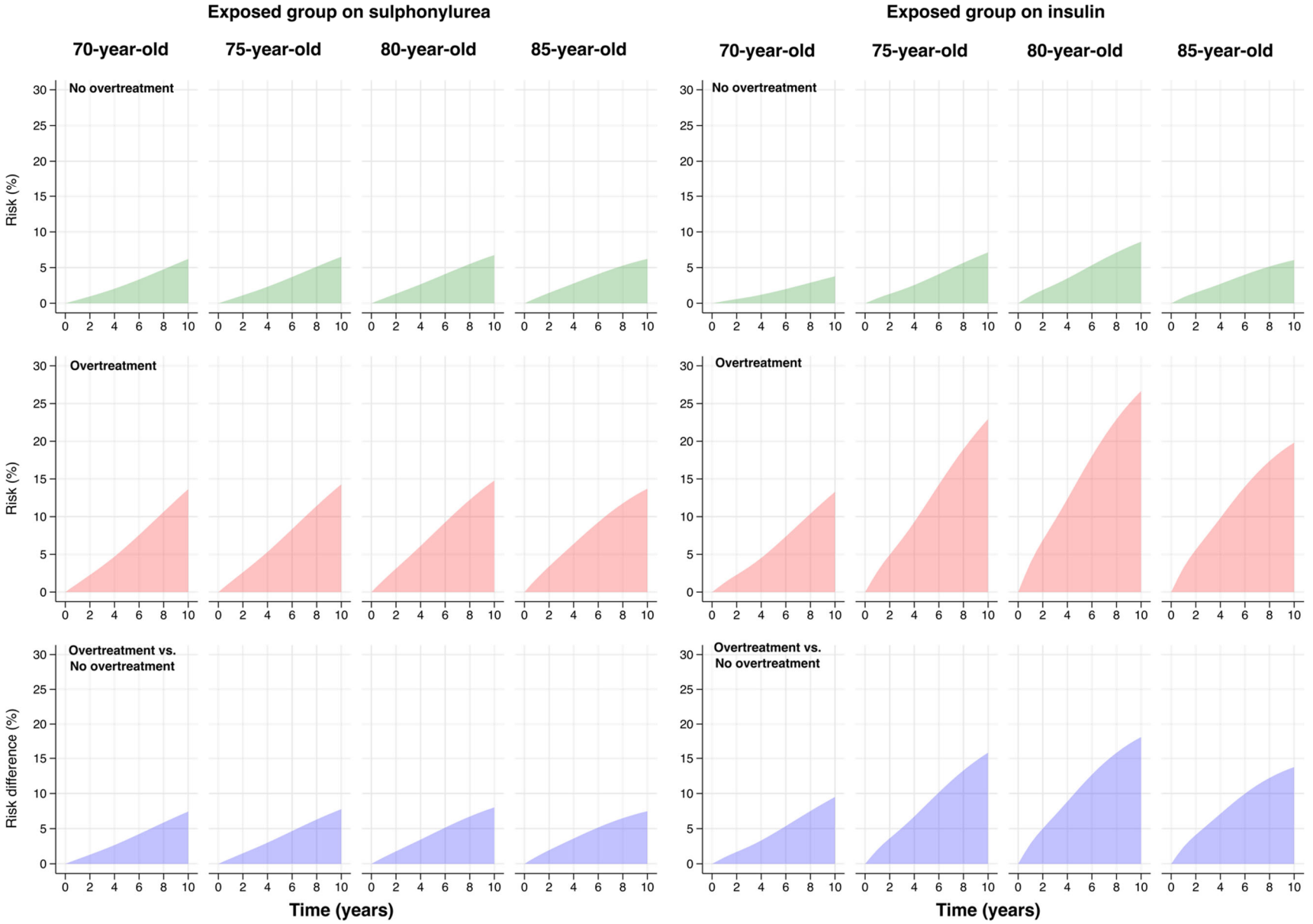
IPTW-PS: Hazard ratios exposed vs non-exposed with inverse probability of treatment weighting using propensity score.

Figure S3. Complete-case analysis results



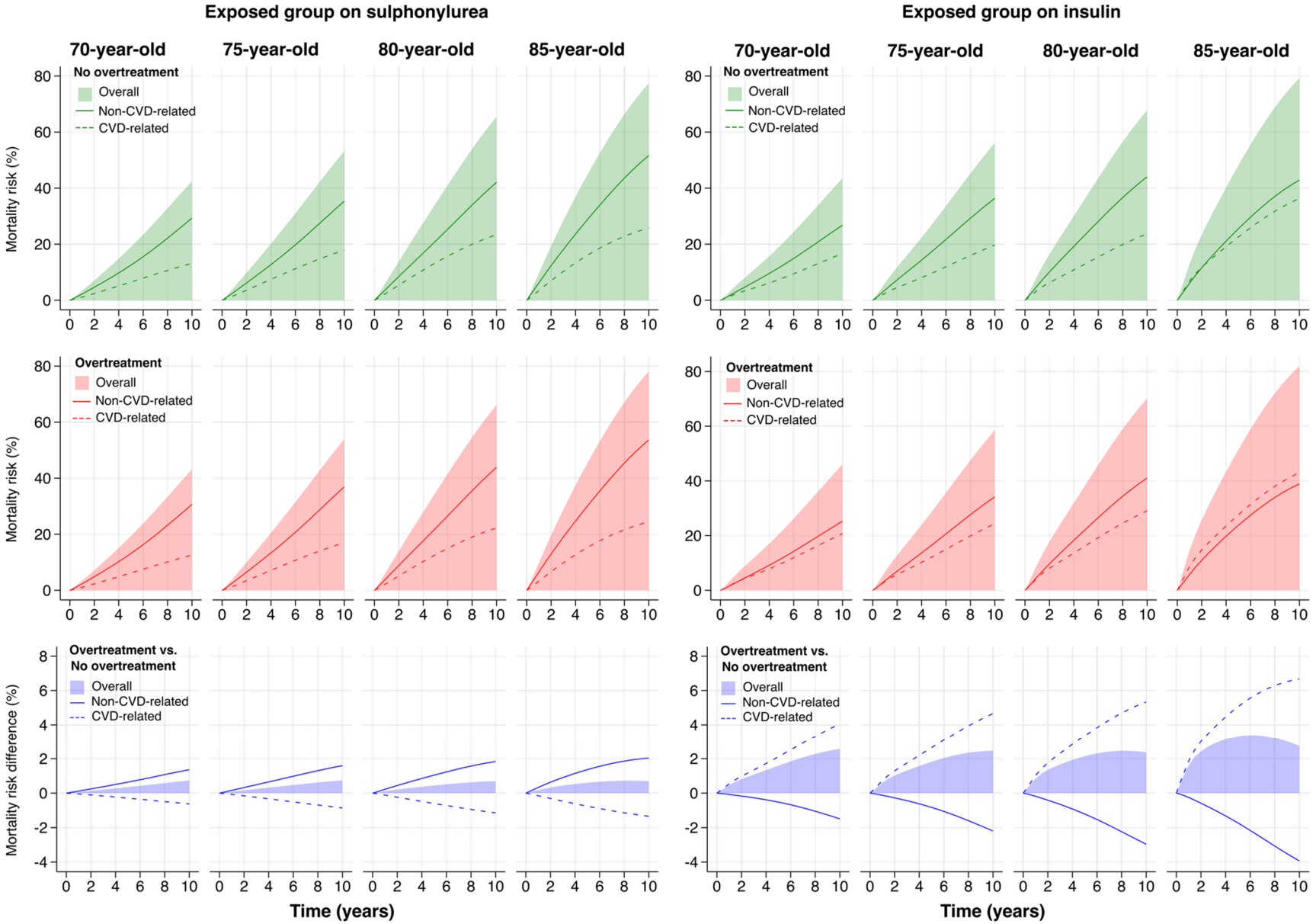
Absolute risks of hospitalization for severe hypoglycemia, CVD- and non-CVD-related mortality over 10 years of follow-up for different ages, in subjects exposed (overtreatment, red) and non-exposed (green); the risk difference (exposed vs. non-exposed) is shown in blue. Estimates are multivariable adjusted and account for all-cause death and non-CVD-related death as competing risk for severe hypoglycemia and CVD-related mortality, respectively.

Figure S4. Absolute risk and risk difference in hospitalization for severe hypoglycemia in subjects with overtreatment on sulphonylurea and insulin



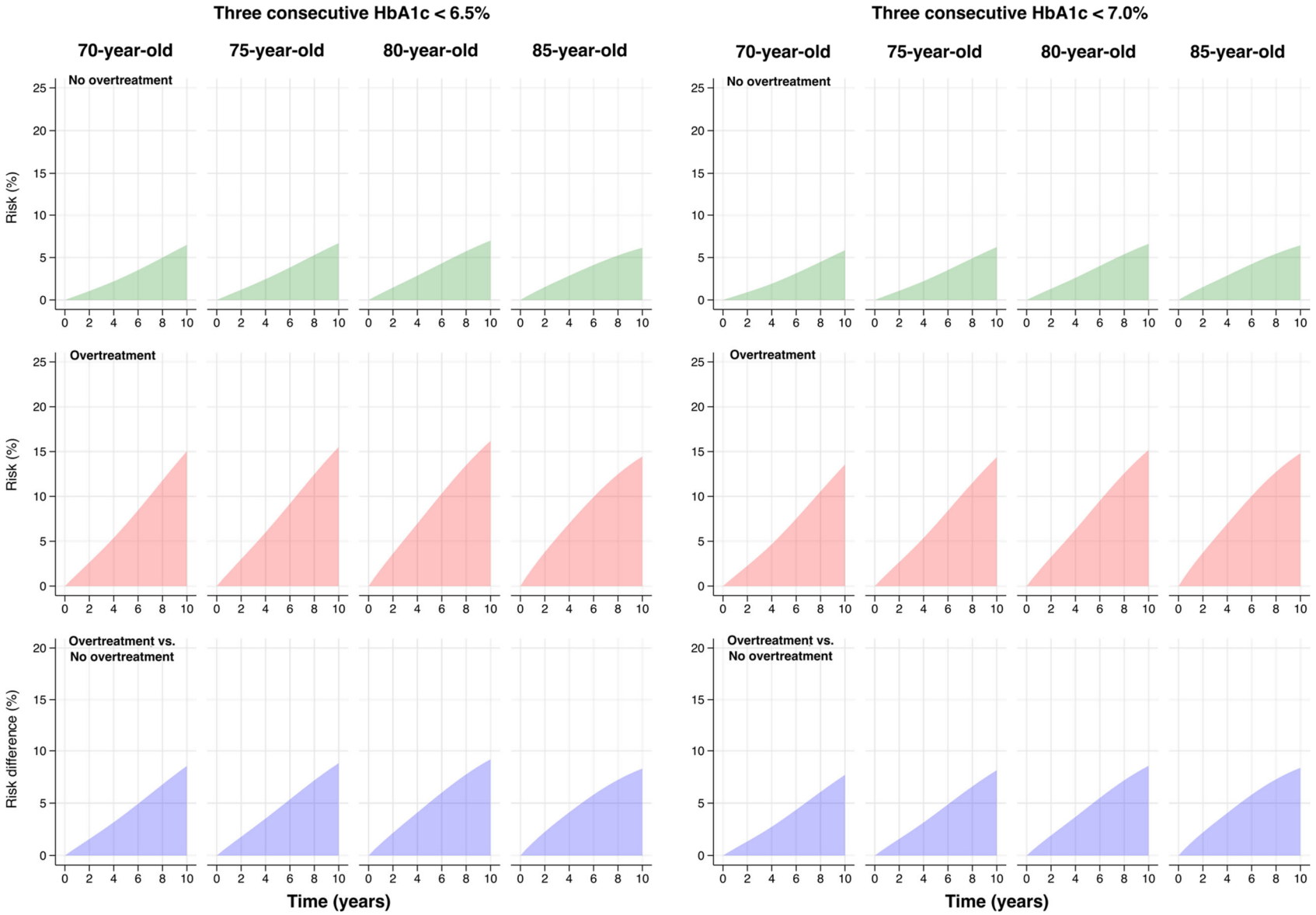
Absolute risks of hospitalization for severe hypoglycemia over 10 years of follow-up for different ages, in subjects with (red) and without (green) overtreatment; the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and accounted for all-cause deaths as competing risk. Details on the definition of the overtreatment are reported in the "Definition of the exposure" paragraph.

Figure S5. Absolute risk and risk differences in cause-specific death in subjects with overtreatment on sulphonylurea and insulin



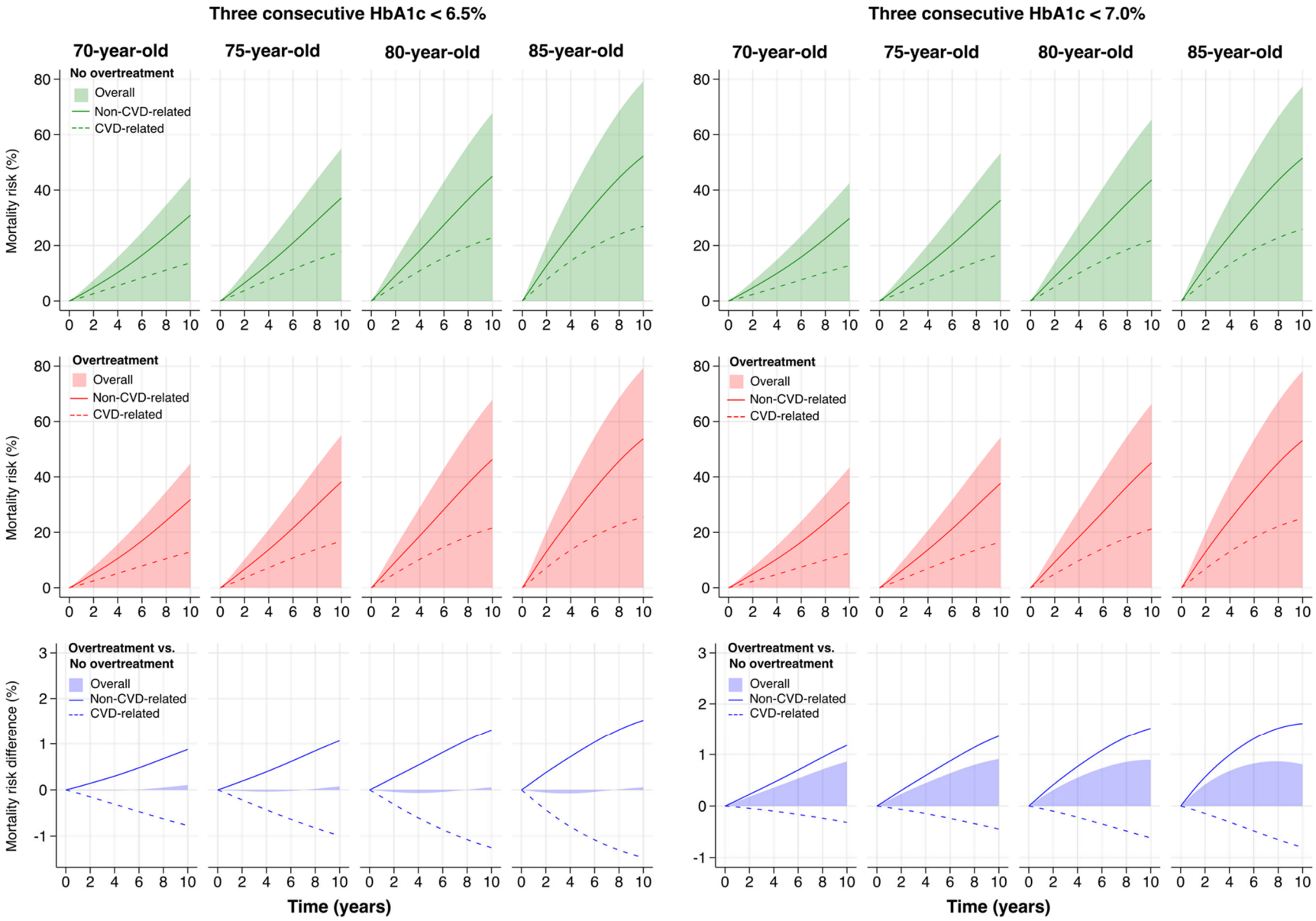
Absolute risks in CVD- and non-CVD-related mortality over 10 years of follow-up at different ages, in subjects with (red) and without (green) overtreatment; the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and, for CVD-related mortality, accounted for non-CVD-related deaths as competing risk. Details on the definition of the overtreatment are reported in the "Definition of the exposure" paragraph.

Figure S6. Absolute risk and risk difference in hospitalization for severe hypoglycemia in subjects with overtreatment defined by HbA_{1c} thresholds



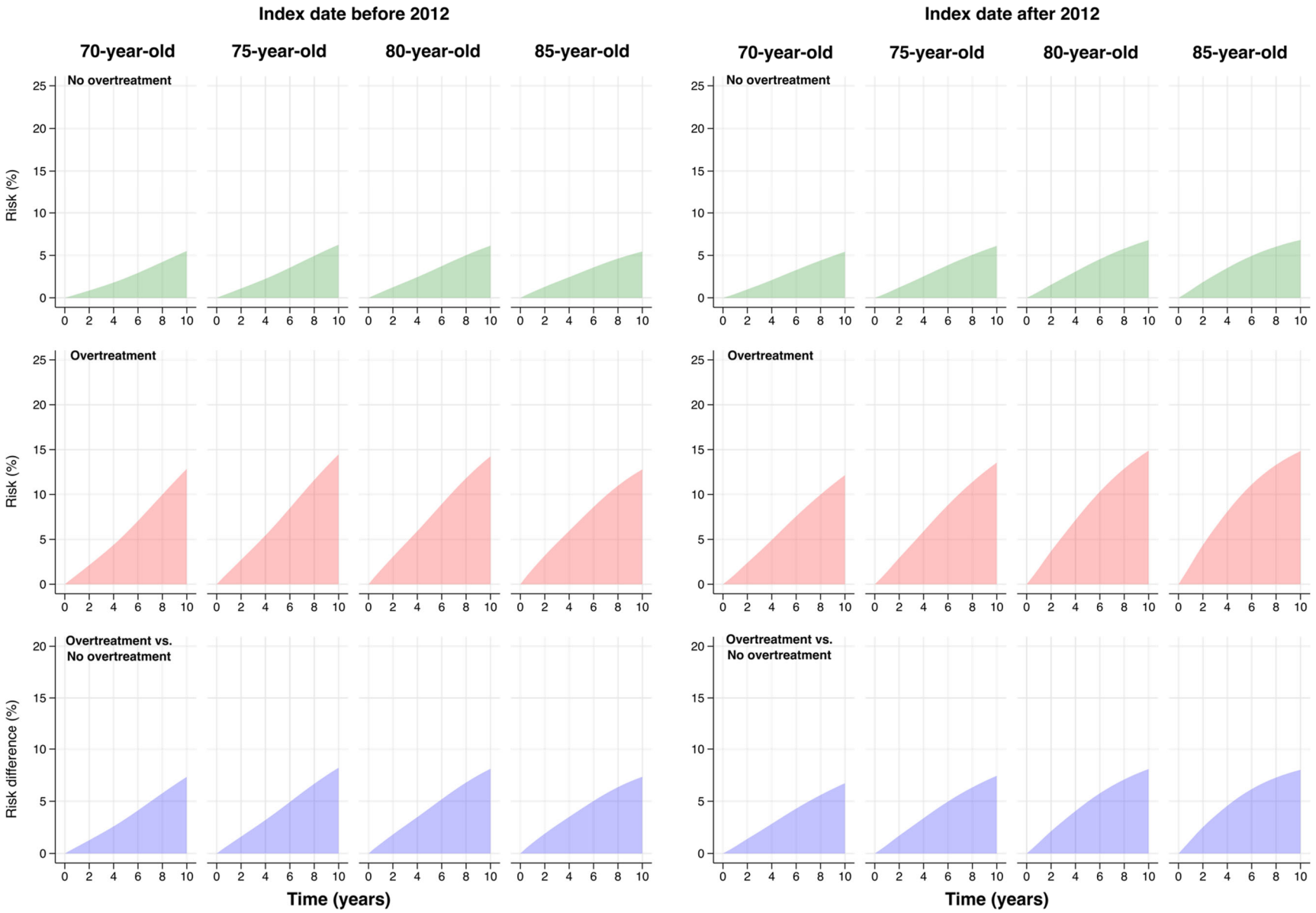
Absolute risks of hospitalization for severe hypoglycemia over 10 years of follow-up for different ages, in subjects with (red) and without (green) overtreatment; the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and accounted for all-cause deaths as competing risk. **Three consecutive HbA_{1c} <6.5%**: overtreatment defined by three consecutive HbA_{1c} <6.5% and on insulin and/or sulphonylurea within 60 days prior to the third HbA1c measurement date; **Three consecutive HbA_{1c} <7.0%:** outcome as defined in the main analysis.

Figure S7. Absolute risk and risk differences in cause-specific death in subjects with overtreatment defined by HbA_{1c} thresholds



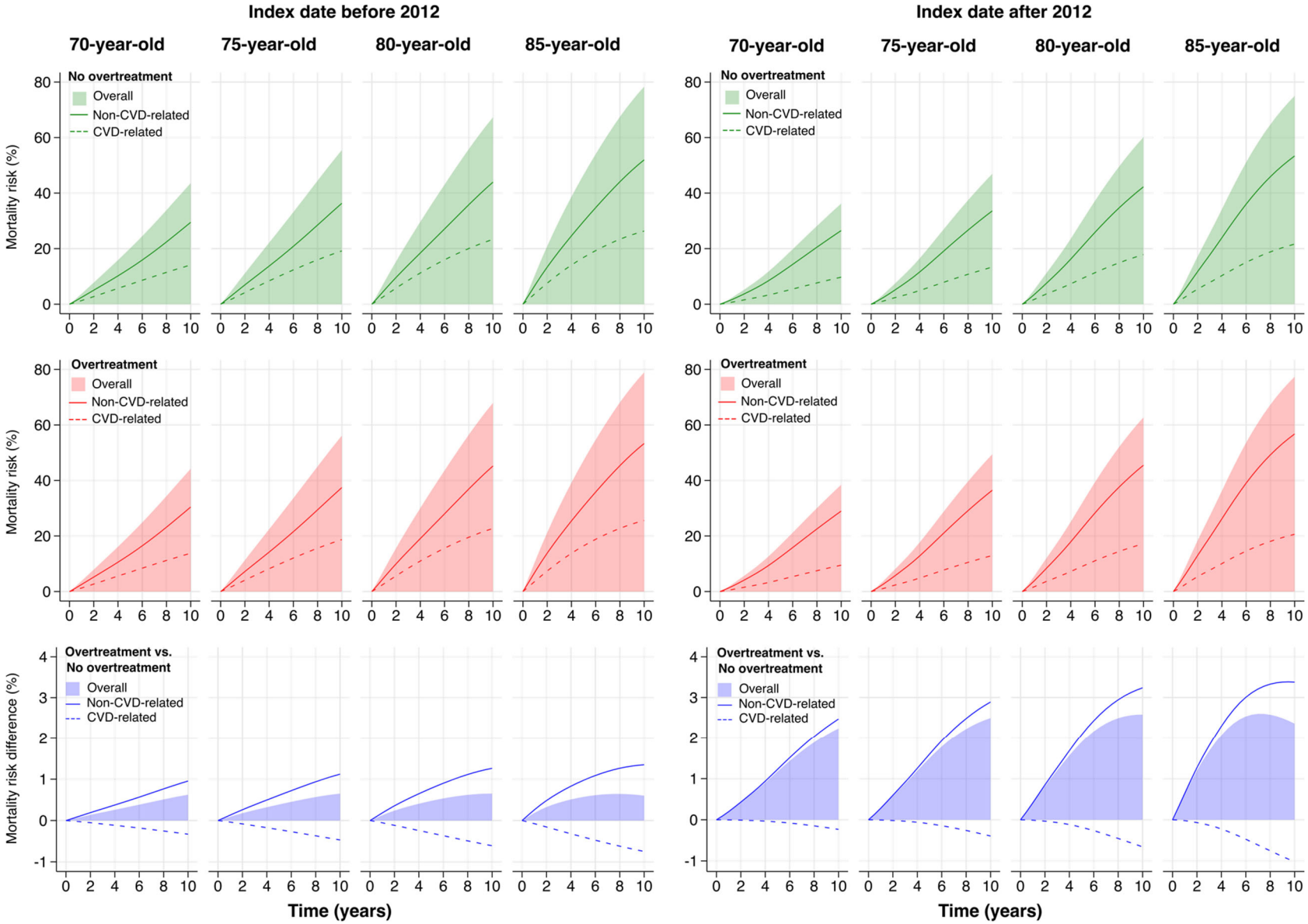
Absolute risks in CVD- and non-CVD-related mortality over 10 years of follow-up at different ages, in subjects with (red) and without (green) overtreatment; the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and, for CVD-related mortality, accounted for non-CVD-related deaths as competing risk. **Three consecutive HbA_{1c} <6.5%**: overtreatment defined by three consecutive HbA_{1c} <6.5% and on insulin and/or sulphonylurea within 60 days prior to the third HbA1c measurement date; **Three consecutive HbA_{1c} <7.0%:** outcome as defined in the main analysis.

Figure S8. Absolute risk and risk difference in hospitalization for severe hypoglycemia stratified by index date



Absolute risks of hospitalization for severe hypoglycemia over 10 years of follow-up for different ages, in subjects exposed (overtreatment, red) and non-exposed (green); the risk difference (exposed vs. non-exposed) is shown in blue. Estimates were multivariable adjusted and accounted for all-cause deaths as competing risk. **Before 2012:** the index date was before 31/12/2011 (inclusive); **After 2012:** the index date was after 01/01/2012 (inclusive).

Figure S9. Absolute risk and risk differences in cause-specific death stratified by index date



Absolute risks in CVD- and non-CVD-related mortality over 10 years of follow-up at different ages, in subjects exposed (overtreatment, red) and non-exposed (green); the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and, for CVD-related mortality, accounted for non-CVD-related deaths as competing risk. **Before 2012:** the index date was before 31/12/2011 (inclusive); **After 2012:** the index date was after 01/01/2012 (inclusive).

Table S2. Mediation effect of severe hypoglycemia on the association between exposure and mortality

Outcome	Total excess relative risk (95% CI)	Excess relative risk due to pure indirect effect (95% CI)	Proportion pure indirect effect, % (95% CI)	Overall proportion mediated, % (95% CI)
CVD-related mortality	0.96 (0.76, 1.23)	0.99 (0.95, 1.03)	28.6 (-49.4, 106.7)	-32.8 (-174.3, 108.8)
Non-CVD-related mortality	1.03 (0.95, 1.12)	1.01 (0.99, 1.03)	24.9 (-37.6, 154.4)	63.8 (-68.8, 196.4)

Total excess relative risk: total effect of exposure (overtreatment) on the outcomes (CVD-related mortality and non-CVD-related mortality).
Excess relative risk due to pure indirect effect: effect due to mediation (severe hypoglycemia) only.
Proportion pure indirect effect: proportion of effect due to mediation (severe hypoglycemia) only.
Overall proportion mediated: proportion of effect due to mediation and mediated interaction.

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 1 and 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Page 3 and 4
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Page 5 and 6

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page 5 and 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 6 and 7 Code list available online
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			

Bias	9	Describe any efforts to address potential sources of bias			Page 7 and 8
Study size	10	Explain how the study size was arrived at			Page 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Page 7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Page 7 and 8
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 5 and 20

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 5
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 5, 6 and 9 and supplemental material figure S1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Page 9, table 1 and supplemental material table S1
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure			Page 9 and 10, table 2

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Page 9 to 11, table 2, figure 1 and 2
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Page 11 to 13, supplemental material figure S2 to S9
Discussion					
Key results	18	Summarise key results with reference to study objectives			Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			Page 14 to 19

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			Page 18
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Page 20
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 20, and code lists are available online

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Glucose control, sulphonylurea, and insulin treatment in elderly people with type 2 diabetes and risk of severe hypoglycemia and death: an observational study

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Online-only Supplemental Material: supplemental analyses, Tables: 2, Figures: 9~~;~~ ~~and~~ R~~r~~eferences ~~for~~ of the supplemental material

RECORD checklist

Abstract

Objective: To estimate the relative and absolute risk of severe hypoglycemia and mortality associated with glucose control, sulphonylurea and insulin treatment in elderly people with type 2 diabetes.

Research Design and Methods: We identified elderly subjects (≥70 years) with type 2 diabetes between 2000 and 2017 in the UK CPRD primary care database with linkage to hospitalization and death data. Subjects with three consecutive HbA_{1c} <7% (53 mmol/mol) while on insulin and/or sulphonylurea within 60 days prior to the third HbA_{1c} (exposed) were matched to not exposed. Hazard ratios (HRs) and absolute risks were estimated for hospitalizations for severe hypoglycemia and cardiovascular and non-cardiovascular-related mortality.

Results: Among 22,857 included subjects (6288 [27.5%] exposed, of which 5659 [90.0%] on sulphonylurea), 10,878 (47.6%) deaths and 1392 (6.1%) severe hypoglycemic episodes occurred during the follow-up. Compared to non-exposed, the adjusted HR in exposed was 2.52 (95% CI: 2.23, 2.84) for severe hypoglycemia; 0.98 (0.91, 1.06) for cardiovascular mortality; and 1.05 (0.99, 1.11) for non-cardiovascular mortality. In a 70-, 75-, 80- and 85-year-old subject, the 10-year risk of severe hypoglycemia was 7.7%, 8.1%, 8.6%, and 8.4% higher than non-exposed while differences for non-cardiovascular mortality ranged from 1.2% (-0.1, 2.5) in a 70-year-old to 1.6% (-0.2, 3.4) in an 85-year-old subject. Sulphonylurea and ~~, particularly,~~ insulin were more relevant predictors of severe hypoglycemia and death than glucose levels.

Conclusions: ~~S~~Elderly subjects with type 2 diabetes and low HbA_{1c} on sulphonylurea or insulin treatment experienced a substantially higher risk of hospitalization for severe hypoglycemia but had no clear evidence of increased risks of mortality~~while on insulin or sulphonylurea~~

~~experienced a substantially higher risk of severe hypoglycemia and a possible, marginally higher risk of non-cardiovascular mortality~~.

Glucose control in people with type 2 diabetes plays an important role in reducing the risk of cardiovascular disease (CVD).(1) While there is robust epidemiological evidence of a progressive association between glucose levels and risk of long-term vascular complications,(2) intensive glucose control aiming at normal glucose levels has not been consistently associated with a reduced risk of cardiovascular events or mortality in randomized controlled trials (RCTs) of subjects with type 2 diabetes.(3-5) Conversely, intensive glucose control could increase the short- and long-term risk of hypoglycemia-related complications.(6) Combined with the emerging observational evidence showing a higher mortality in patients experiencing severe hypoglycemic episodes,(7; 8) the results of these RCTs raised a greater awareness on the risk associated with an excessive glucose control and contributed to the development of the clinical concept of "diabetes overtreatment", whereby an intense glucose control may result in more harms than benefits, particularly in elderly patients.(9)

A definition of "overtreatment" based on the combination of glucose (HbA_{1c}), treatment (medications associated with a higher risk of hypoglycemia), and ~~a~~ demographic (age, given the higher risk of hypoglycemia and hypoglycemia-associated complications in elderly patients) criteria has been adopted in many observational studies,(10) particularly those using electronic health records,(11; 12) although other definitions have been reported in the literature.(13) In particular, HbA_{1c} lower than 7% (53 mmol/mol) in subjects older than 65 years who are at risk of hypoglycemia while on insulin and/or sulfonylurea have been suggested as criteria to identify patients at risk of potential overtreatment.(11; 14) To date, the available epidemiological studies have mainly described the incidence and risk factors of overtreatment;(10-13; 15; 16) to what extent overtreatment is associated with the relative and absolute risk of severe hypoglycemia and cause-specific mortality remains, however, largely unknown. At the same time, there is limited evidence on the comparative relevance of the

defining elements of overtreatment on long-term outcomes, which may contribute to its heterogeneous definitions.

To help clarify the evidence, we used UK primary care data to investigate the presence and the magnitude of the association of potential overtreatment, and of its defining elements age, HbA_{1c}, and glucose-lowering agents, with the relative and absolute risk of hospitalization for severe hypoglycemia and CVD- and non-CVD-related mortality in elderly people with type 2 diabetes.

Methods

Data source

In conducting and reporting this study, we followed the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.(17) We used the Clinical Practice Research Datalink (CPRD) to identify a cohort of elderly subjects with type 2 diabetes in the UK. CPRD is a primary care database of anonymized electronic health records from general practices, with approximately 7% of the UK population of which is broadly representative in terms of age and sex, which has been validated and extensively used for epidemiological research during the last 30 years.(18; 19) CPRD routinely collects data on demographics, laboratory tests, diagnoses, referrals, prescriptions, and health-related behaviors.(18) We used Hospital Episodes Statistics (HES) Admitted Care to define the medical history of included subjects and the Office for National Statistics (ONS) Death Registration to obtain date and cause of death. The patient-level linkage is carried out by a trusted third party using a 8-stage stepwise deterministic methodology.(20) This study has been approved by the Independent Scientific Advisory Committee (ISAC; protocol number: 18_156R2). The code lists used in the study are available at https://github.com/supingling/overtreatment.

Population

We included all elderly subjects (≥70 years) with diagnosis code(s) of type 2 diabetes between Jan 1, 2000 and Dec 31, 2017 and randomly assigned a day and month of birth ~~for~~ to each subject as they are not available in CPRD due to the anonymization process. All subjects were considered at risk of being exposed to overtreatment since the 70th birthday, if diagnosed with

type 2 diabetes before 70 years old; or since the date of diagnosis, if it occurred after 70 years old. Subjects had also to be registered within an up-to-standard practice for a minimum of one year before the diagnosis of type 2 diabetes; those without linkage to HES or ONS death registration were not eligible for this study.

Exposure

In line with the available evidence from previous epidemiological studies using electronic health records and the clinical recommendations about the definition of "overtreatment",(11-14) we defined the exposure based on the glycemic control and the concurrent use of glucose-lowering agents associated with a higher risk of hypoglycemia.~~:~~ ~~t~~The exposed group included subjects with three consecutive values of HbA_{1c} <7% (53 mmol/mol) while on insulin and/or sulphonylurea within 60 days prior to the third HbA_{1c} measurement date; index date was identified as the first occurrence of these criteria. Up to 3 non-exposed subjects were matched to those exposed by year of birth ± 1 year, year of type 2 diabetes diagnosis, gender, number of HbA_{1c} measurements since being at risk of overtreatment until index date, and the length of the time frame from being at risk of overtreatment to index date ± 6 months. The non-exposed group included all subjects with type 2 diabetes aged ≥70 years between Jan 1, 2000 and Dec 31, 2017 who did not meet the criteria for the exposure. We further excluded subjects with history of severe hypoglycemia before ~~entering the study (~~index date~~)~~ in both the exposed and non-exposed group.

Outcomes

Outcomes included hospitalization for severe hypoglycemia and CVD- and non-CVD-related death. Severe hypoglycemia was defined as an admission to the hospital reporting the ICD-10

code of "E16.0", "E16.1" or "E16.2" in HES Admitted Care; date and the underlying cause of death, defined using ICD-10 codes, were ascertained via linkage to ONS Death Registration. For severe hypoglycemia, subjects were followed-up until the first hospitalization for severe hypoglycemia, death, or Dec 31, 2017 (HES linkage date), whichever occurred first; for mortality, they were followed-up until death or Feb 14, 2018 (ONS linkage date).

Covariates

Socio-demographic factors included: age at index date, gender, ethnicity (White, non-White, obtained from HES and CPRD), diabetes durations, and deprivation (Townsend score in 2001: quintile 1 - most affluent; quintile 5 - most deprived). BMI, alcohol consumption (no drinker, ex-drinker, yes but unknown units, yes with ≤14 units/week, yes with >14 units/week), smoking status (no smoker, ex-smoker, current smoker), HbA_{1c}, blood pressure, total, HDL, and LDL cholesterol, and estimated glomerular filtration rate (CKD-EPI equation) were identified in CPRD using the closest value to the index date. Glucose-lowering medications, ACE inhibitors, angiotensin II receptor blockers, and statins were identified through prescriptions in CPRD within 60 days prior to the index date. Heart failure, stroke, myocardial infarction, cancer, peripheral arterial disease, chronic kidney disease, non-traumatic lower limb amputation, dementia, anemia, and depression were assessed by the presence of at least one diagnosis (or procedure) code in CPRD or HES before the index date.

Statistical analysis

We reported the characteristics of included subjects stratified by exposure status as median and interquartile range (IQR) for continuous and number and percentage for categorical variables. We used the Royston-Parmar-Lambert parametric survival model, with time into the study (i.e.,

from ~~the~~ index date) as time scale;(21) the index date of the non-exposed subjects was the same calendar date of the matched exposed subjects. The advantage of this model over the Cox regression is the possibility to investigate relative (hazard ratio, HR) as well as absolute effects. Accounting for competing risk, we used standardized cause-specific cumulative incidence functions to quantify the 5-year and 10-year absolute risk in severe hypoglycemia, CVD- and non-CVD-related death in exposed and non-exposed subjects and their difference.(22; 23) To allow the effect of the exposure to change across age, we tested a non-linear interaction between a restricted cubic spline transformation of age and the exposure. We further adjusted for socio-demographic and lifestyle factors, laboratory tests, medications, and previous medical conditions. To account for missing data, we performed multiple imputation and combined estimates using Rubin's rules across 10 imputed datasets;(24) we also conducted a complete-case analysis. To assess the robustness of our results, and investigate the comparative role of glucose control and therapies on the risk of the three outcomes, we performed several supplemental analyses (details reported in the ~~s~~Supplemental ~~m~~Material).

All analyses were conducted using Stata/IC 16.0 and estimates are reported with 95% confidence interval (CI).

Results

Cohort characteristics

The details of cohort definition are shown in Figure S1. Overall, of 69,993 people with type 2 diabetes aged ≥70 years and with linkage to HES and ONS, 6974 were defined as exposed. After matching, 686 exposed and 46,450 non-exposed subjects were excluded due to no matching or ~~a~~ history of severe hypoglycemia, leaving 6288 (27.5%) and 16,569 subjects, respectively, for the analysis.

The pattern of missing data is reported in Table S1. The characteristics of included subjects at index date, stratified by exposure, are shown in Table 1. Compared to non-exposed, exposed subjects had lower HbA_{1c} (6.4% [46 mmol/l] and 6.8% [51 mmol/l]), eGFR, diastolic blood pressure and cholesterol; they were also more likely to be non-drinkers and on thiazolidinedione, ACE inhibitors, angiotensin II receptor blockers and statins. Among the exposed subjects, 90.0% were on a sulphonylurea compared to 75.2% in the non-exposed; corresponding proportions for insulin were 9.2% and 19.7%. Marginal differences were observed for pre-existing comorbidities, ranging from 0.8% for depression (21.5% in the exposed and 22.3% in the non-exposed) to 3.0% for anemia (15.9% and 12.9%, respectively). All other socio-demographic and clinical characteristics were balanced between the two groups.

Hospitalization for severe hypoglycemia

During 121,457 person-years of follow-up (median, 4.9 years), 1392 (6.1%) subjects were admitted to hospital for severe hypoglycemia; hospitalization rates were 17.5 (95% CI: 16.1, 18.9) and 9.2 (8.6, 9.8) per 1000 person-years in exposed and non-exposed subjects,

respectively. Adjusting only for age, the rate of hospitalization for severe hypoglycemia was higher in the exposed compared to non-exposed group (HR: 1.90; 95% CI: 1.71, 2.11). Upon further adjustment for other potential confounders, the HR increased to 2.52 (2.23, 2.84) (Table 2).

Figure 1 shows the absolute risk of severe hypoglycemia in exposed and non-exposed subjects ~~exposed and non-exposed to overtreatment~~. Regardless of age, the risk of severe hypoglycemia was always higher in the exposed than non-exposed subjects: in a 70-year-old subject, the risk progressively increased up to 6.0% at 5 years and 13.6% at 10 years; corresponding estimates in a 75-, 80- and 85-year-old subject were 6.8% and 14.4%; 7.9% and 15.2%; and 8.5% and 14.8%, respectively. In contrast, in a 70-year-old non-exposed subject, the risk similarly increased over time but to a smaller extent, resulting 2.5% at 5 years and 5.9% at 10 years; corresponding estimates in a 75-, 80- and 85-year-old subject were 2.9% and 6.2%; 3.3% and 6.6%; and 3.6% and 6.4%, respectively. These estimates translated in a 10-year absolute risk difference, comparing exposed to non-exposed, of 7.7% (95% CI: 6.0, 9.4) for a 70-year-old subject; 8.1% (6.7, 9.6) for a 75-year-old subject; 8.6% (7.2, 10.0) for an 80-year-old subject; and 8.4% (6.9, 9.8) for an 85-year-old subject, respectively (Figures 1-2).

Cardiovascular and non-cardiovascular-related mortality

During 125,409 person-years of follow-up (median, 5.2 years), 3670 (16.1%) CVD-related and 7208 (31.5%) non-CVD-related deaths occurred. The crude CVD-related mortality rates were 29.7 (95% CI: 28.0, 31.6) and 29.1 (28.0, 30.2) per 1000 person-years in exposed and non-exposed subjects, respectively; corresponding estimates for non-CVD-related death were 59.6 (57.1, 62.2) and 56.7 (55.1, 58.2). In multivariable models, ~~estimates indicated a possible marginally higher rate of non-CVD-related death (~~the adjusted HR was~~:~~ 1.05 (~~;~~ 95% CI: 0.99,

1.11) for non-CVD-related and 0.98 (0.91, 1.06) for CVD-related death comparing ~~in~~ exposed to non-exposed subjects ~~while there was no evidence of an association with CVD-related death (0.98; 0.91, 1.06)~~ (Table 2).

Figure 1 presents the absolute risk of CVD- and non-CVD-related death over 10 years in exposed and non-exposed subjects. In a 75-year-old non-exposed subject, the risk of CVD- and non-CVD-related death was 8.9% and 16.7% at 5 years and 17.0% and 36.3% at 10 years, respectively; in an 85-year-old subject, corresponding estimates were 16.1% and 28.9% at 5 years and 25.9% and 51.5% at 10 years. In contrast, in a 75-year-old exposed subject ~~exposed to overtreatment~~, the risk of CVD- and non-CVD-related death was 8.7% and 17.4% at 5 years and 16.6% and 37.7% at 10 years; in an 85-year-old subject, corresponding estimates were 15.7% and 30.1% at 5 years and 25.1% and 53.1% at 10 years. These estimates led to marginal absolute risk differences across ages and over time (Figure 1-2). The 10-year risk of non-CVD-related mortality, comparing subjects exposed to non-exposed, ranged from a minimum increase of 1.2% (-0.1, 2.5) in a 70-year-old subject to a maximum increase of 1.6% (-0.2, 3.4) in an 85-year-old subject (Figure 2). Differences in CVD-related death were smaller: for the same comparison at the same follow-up time, differences ranged from a minimum decrease of 0.3% to a maximum decrease of 0.8%.

Supplemental analyses

Results of the complete-case analysis, shown in Figure S2-S3, were consistent with those of the main analysis.

Supplemental analyses investigating the risk of hypoglycemia and cause-specific death for alternative definitions of the exposure are detailed in the Supplemental Material. When defining overtreatment as three consecutive values of HbA_{1c} <7% (53 mmol/mol) and insulin

only or sulphonylurea only (there were only 53 exposed subjects to both medications; Table 1), the estimates for three outcomes were virtually identical to those of the main analysis for the group of subjects on sulphonylurea only. In the group of subjects on insulin only, however, the HRs for hospitalization for severe hypoglycemia (3.91; 95% CI: 2.74 to 5.59) and CVD-related mortality (1.31; 1.01, 1.70) were higher compared to those obtained in the main analysis (Figure S2); these differences in the HRs were mirrored in the absolute risk estimates (Figure S4 and S5). Using three consecutive HbA_{1c} <6.5% (48 mmol/mol) while on insulin and/or sulphonylurea within 60 days prior to the index date did not result in different relative (Figure S2) or absolute (Figure S6 and S7) risks compared to the 7% (53 mmol/mol) threshold. Conversely, in subjects on insulin and/or sulphonylurea within 60 days prior to the index date, people with three consecutive HbA_{1c} <7% (53 mmol/mol) had a lower risk of hospitalization for severe hypoglycemia (HR: 0.71; 0.58, 0.87), CVD-related mortality (0.81; 0.68, 0.96), and non-CVD-related mortality (0.76; 0.68, 0.85) compared to those without (Figure S2). Lastly, when limiting the definition only to the HbA_{1c} criterion (~~,~~i.e. subjects with three HbA_{1c} <7% (53 mmol/mol) regardless of medications at baseline), compared to no treatment the use of insulin and/or sulphonylurea was associated with a higher risk of admission for severe hypoglycemia (HR: 5.20; 4.44, 6.08), CVD- related (1.15; 1.06, 1.25), and non-CVD-related (1.27; 1.19, 1.34) mortality, while no associations were found with the newer medications ~~(~~sodium-glucose cotransport protein 2 inhibitor (~~[~~SGLT-2i)~~]~~, d~~D~~ipeptidyl ~~P~~peptidase 4 inhibitor ~~[~~(DPP-4i)~~]~~, or ~~G~~glucagon-like peptide-1 receptor agonist [GLP-1RA]) for all three outcomes (Figure S2).

Stratified analyses by calendar time (to account for changes in clinical recommendations on the management of diabetes), age at diagnosis of type 2 diabetes, diabetes duration, renal function, or prevalent CVD; excluding subjects with previous comorbidities (to reduce the risk of reverse causation); or using alternative statistical methods (robust standard errors or inverse

probability of treatment weighting), yielded results consistent with those obtained in the main analysis (Figure S2, S8, and S9). There was no evidence of severe hypoglycemia as a mediating factor between ~~overtreatment~~ the exposure and CVD- or non-CVD-related mortality (Table S2).

Discussion

In this retrospective population-based study, we used data of primary care subjects with type 2 diabetes aged ≥70 years and low HbA_{1c} while on insulin and/or sulphonylurea to estimate the relative and absolute risk of hospitalization for severe hypoglycemia, CVD- and non-CVD-related mortality. ~~–~~These subjects, who have been considered as exposed to a potential overtreatment,(11; 14) had a 2.5-fold increased hazard of severe hypoglycemia, translating into a 7-9% higher absolute risk at 10 years, when compared to those not exposed. However, there was no clear evidence of increased risks of mortality associated with ~~T~~the combination of low HbA_{1c} and insulin and/or sulphonylurea ~~was potentially and marginally associated also with a higher risk of non-CVD-related mortality, being the absolute risk 1-2% higher at 10 years; conversely, no association was observed with CVD-related mortality~~. It is important to note, however, that in our cohort 90% of the exposed subjects were on a sulphonylurea; therefore, our ~~These~~ findings should be ~~-~~interpreted in relation to ~~the~~ this characteristic ~~characteristics o~~of the exposed cohort.~~, as 90% of the exposed subjects were on a sulphonylurea.~~ In our comprehensive analyses using alternative definitions of overtreatment, we also investigated the different prognostic relevance of glucose levels and glucose-lowering medications: when overtreatment is considered in the perspective of the long-term risk of severe hypoglycemia and death, sulphonylurea and~~, particularly,~~ insulin treatment ~~is~~ are ~~a~~ more relevant predictors than glucose levels.

Driven by the results of large-scale RCTs showing a neutral or increased risk of death in subjects with type 2 diabetes randomized to intensive compared to standard glucose control,(3-5; 25) there has been an emerging interest in the potential harms associated with glucose overtreatment, particularly among older, frail, multi-morbid patients.(26) This is also reflected in the changes in clinical recommendations on the diabetes management, which currently

suggest relaxed HbA_{1c} goals in older patients with type 2 diabetes and other coexisting comorbidities.(27) Notwithstanding, in recent years a high prevalence of diabetes overtreatment, with varied definitions, has been reported in different countries.(10; 12; 15; 16; 28) While a HbA_{1c} <7% (53 mmol/mol) is widely accepted as a threshold of potential overtreatment among older adults,(14; 28) most studies also considered the high risk for hypoglycemia as one of the key criteria, including insulin and/or sulphonylurea use,(10; 11; 13; 15; 16) ≥3 oral glucose-lowering medications,(13; 16) and/or coexisting comorbidities.(12; 16) In our study, to define potential overtreatment we initially considered subjects with type 2 diabetes aged 70 years or older and included the HbA_{1c} criterion (three consecutive values of HbA_{1c} <7% [53 mmol/mol]) alongside the medication criterion (concurrent use of glucose-lowering agents associated with a higher risk of hypoglycemia – insulin and/or sulphonylurea): in this cohort, these criteria resulted in 90% of exposed participants being on sulphonylurea. However, in view of the different definitions reported in the literature and a lack, to date, of a consensus, we also investigated associations using other possible definitions; these analyses allowed us to assess the combined and disjointed impact of the two criteria on the risk of severe hypoglycemia and mortality. We conducted extensive adjustment for other glucose-lowering medications, pre-existing comorbidities and other potential confounders, and estimated both relative and absolute risks, as a "statistically significant" increase in the relative risk may translate into a modest absolute risk difference; the combined information of these two metrics give more insights into the individual and public health relevance of HbA_{1c} levels, glucose-lowering treatments, and age (a component of any definition of overtreatment).

There is a growing consensus on the increased risk of hypoglycemia and its associated complications in elderly patients with type 2 diabetes under intensive glycemic control, ~~mainly~~ possibly related to~~due to~~ their slower counter-regulatory response to hypoglycemia.(27) A previous meta-analysis of five RCTs has shown that intensive glycemic control was associated

with an approximately 2-fold increased risk of severe hypoglycemia;(25) this estimate is in line with our findings. Of note, we included subjects aged ≥70 years with a median diabetes duration of 4 years and a HbA_{1c} <7% (53 mmol/mol) in ~~those~~ the exposed group; in contrast, in these RCTs the mean/median age and diabetes duration were 52 to 66 years and 8 to 11 years, respectively, while the HbA_{1c} targets in the intensive treatment arms were <6.5% (48 mmol/mol) or <6.0% (42 mmol/mol).(25) However, our analysis using the 6.5% (48 mmol/mol) threshold showed results virtually identical to those of the main analysis, with a possible slightly higher risk of severe hypoglycemia in subjects with a longer diabetes duration. Moreover, a *post-hoc* analysis of the ACCORD trial in older (≥65 years) participants indicated that the proportion of subjects reporting a severe hypoglycemia was three times higher in the intensive compared to standard therapy arm,(29) consistent with our relative hazard estimate. Although the relative risk of severe hypoglycemia in our study was similar to the effect size reported in the ACCORD trial and the meta-analysis of intensive glycemic control, the absolute rates of severe hypoglycemia in our real-world study were lower compared to those reported in these trials, except when compared to the ADVANCE trial. In our study, rates of hospitalization for severe hypoglycemia were 17.5 and 9.2 per 1000 person-years among exposed and non-exposed ~~people~~subjects ~~exposed and non-exposed to overtreatment~~, respectively; rates in the intensive and standard arms were 7 and 4 per 1000 person-years in the ADVANCE (hypoglycemia requiring assistance from a third party),(5) 30 and 10 in the VADT (hypoglycemia resulting in complete loss of consciousness),(4) and 44.5 and 13.6 in the ACCORD subgroup of older participants (hypoglycemia requiring medical assistance).(29; 30)

Meta-analyses of RCTs have concluded that intensive glucose reduction may reduce CVD events compared to standard therapy while does not result in a reduction of all-cause or CVD-related mortality.(31; 32) In the ACCORD trial, in particular, a 22% higher mortality rate was

observed in subjects randomized to intensive compared to standard glycemic control,(3) while we found no clear evidence of increased risks of mortality~~we observed a possible 5% increased hazard of non-CVD-related deaths in the subjects exposed to overtreatment and no evidence of an association with CVD-related mortality~~. In contrast with the uncertainty around intensive glucose control and cause-specific mortality, there is more robust and consistent evidence of a substantial excess risk of death (particularly non-CVD-related) in subjects with a previous sever episode of hypoglycemia.(33) A pathway whereby overtreatment leads to an increased risk of severe hypoglycemia that, in turn, would increase the risk of death, has been postulated.(34) Although not the primary aim of our study, we did not find evidence of a mediating role of severe hypoglycemia in the association between overtreatment and mortality. The significantly greater risk of severe hypoglycemia compared to that of death in exposed subjects in our study would rather imply a different prognostic relevance of the factors considered in our models for these two outcomes; at the same time, our findings would suggest that other factors might be more relevant for the risk of death in patients who experienced a severe hypoglycemic episode.

Our extensive supplemental analyses suggested that treatment with insulin or sulphonylurea, rather than the low HbA_{1c} levels alone, is the key prognostic factor for hospitalization for severe hypoglycemia and mortality. In subjects with three consecutive HbA_{1c} <7% (53 mmol/mol), use of insulin and/or sulphonylurea was associated with a higher risk of severe hypoglycemia and mortality than use of any other glucose-lowering medications. Furthermore, among all subjects on insulin and/or sulphonylurea at baseline, those with three consecutive HbA_{1c} <7% (53 mmol/mol) had a lower risk of all outcomes. Interestingly, these two observations very closely mirror an observational study in subjects with type 2 diabetes aged over 75 years, where HbA_{1c} levels between 6.5% and 6.9% (48-52 mmol/mol) alone were not associated with a higher risk of death; contrariwise, when considered jointly with insulin or sulphonylurea

therapy, the risk of death was more than doubled.(35) Moreover, in people with low HbA_{1c} levels, for SGLT-2i, DPP-4i, or GLP-1RA – which did not increase the risk of hypoglycemia in RCTs, there was no evidence of an association with hospitalization for severe hypoglycemia or cause-specific mortality compared to no treatment. Overall, our results contribute to the current evidence and debate over HbA_{1c}, glucose-lowering medications, and age as distinct yet complementary prognostic factors on the risk of severe hypoglycemia and mortality and give insights into the definition of "diabetes overtreatment", from both an epidemiological and clinical perspective.

To our knowledge, this is the first study investigating the relative and absolute magnitude of the association between potential diabetes overtreatment and severe hypoglycemia hospitalization as well as cause-specific mortality. Our findings have important clinical implications. Currently, no clinical parameters are available to suggest when well-controlled glucose levels are indicative of an overtreatment and a possible "deintensification" of glucose treatments should be considered:(36) in this respect, the findings of a heterogeneous prognostic roles of HbA_{1c}, sulphonylurea, and insulin therapy may help clarify the evidence. Although during the study period new glucose-lowering agents have been made available and changes in the recommendations about glucose-lowering strategies occurred (particularly following the results of the ACCORD trial), we observed similar associations for all three outcomes over time, translating in very similar absolute risk estimates in hospitalization for severe hypoglycemia and small differences in cause-specific mortality. Some limitations of this study should also be considered. Our analyses are based on a large, UK electronic health record database: the generalizability of these findings should therefore be considered within the context of the healthcare systems where data have been collected and the potential misclassification bias in clinical coding, which cannot be completely ruled out as data were not collected for research purpose. Moreover, information collected in these databases are not as

granular as that available in cohort studies or RCTs, where data are prospectively collected in line with a specific research plan. As such, we did not include other factors, i.e. neuropathies or the hemoglobin glycation index (the difference between the observed and the fasting plasma glucose predicted HbA_{1c}), which may act as confounders, mediators, or effect modifiers. In ACCORD and previous cohort studies, the risk of severe hypoglycemia and death has indeed been associated with the presence of neuropathy (peripheral and autonomic) and the hemoglobin glycation index.(30; 37-39) We used consecutive HbA_{1c} measures to define overtreatment, which may lead to misclassification bias. However, in addition to age, gender and type 2 diabetes diagnosis year, we also matched by the number of HbA_{1c} measurements and the duration between being at risk of overtreatment and index date to minimize such bias. To account for confounding by indication, we have adjusted models for several potential confounders and assessed the robustness of our results using the inverse probability of treatment weighting; nevertheless, residual confounding may still be present and causality cannot be definitively established given the observational nature of the study.

In conclusion, a potential overtreatment of hyperglycemia, defined by consistently low HbA_{1c} measures and concurrent use of insulin and/or sulphonylurea, is common in elderly patients with type 2 diabetes and ~~a potential overtreatment of hyperglycemia with insulin or sulphonylurea is common in elderly patients with type 2 diabetes and~~ associated with a substantially higher risk of hospitalization for severe hypoglycemia while there is no clear ~~and a possible, marginally higher risk~~ of evidence of increased risks of mortality~~non-CVD death; in contrast, there was no evidence of an increased risk in CVD death~~. Given the much greater number of exposed participants on sulphonylurea than insulin in our cohort, the results should be interpreted in this context and other investigations with larger samples are needed to disentangle the potential distinct effects of these two medications. In view of the increasing prevalence of multi-morbid, older patients with type 2 diabetes,(40) and the prognostic role of

insulin and sulphonylurea, further research is warranted to explore the net clinical benefit of deintensification by replacing these treatments with other glucose-lowering medications in these patients.

Contribution
SL: study design, data extraction and preparation, statistical analysis, first draft; FZ: study design, statistical analysis, critical revision; CL: study design and critical revision; SS, MJD, KK: critical revision. All authors have approved the final manuscript; SL takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Conflict of interest
SL, FZ, and CL have no conflict of interests to declare.
SIS has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Sanofi-Aventis, Novo Nordisk, Janssen, Merck Sharp & Dohme, AstraZeneca, Lilly and Boehringer Ingelheim.

MJD acted as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen; as an advisory board member for Servier; and as a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International. MJD has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, and Janssen.

KK reports personal fees from Amgen, Bayer, NAPP, Roche, Berlin-Chemie AG/Menarini Group, and Sanofi-Aventis; and grants and personal fees from Pfizer, Boehringer Ingelheim, AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, and Servier outside of the submitted work.

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Data sharing
Data access is through permission from Clinical Practice Research Datalink only; please send any enquiries to enquiries@cprd.com.

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Figures legend

Figure 1. Absolute risk and risk difference of hospitalization for severe hypoglycemia and mortality

Legend: Absolute risks in hospitalization for severe hypoglycemia (top 3 panels) and CVD- and non-CVD-related mortality (bottom 3 panels) over 10 years of follow-up at different ages, in subjects exposed (overtreatment, red) and non-exposed (green); the difference (exposed vs. non-exposed) is shown in blue. Estimates were multivariable adjusted and accounted for all-cause deaths as competing risk for severe hypoglycemia, and for non-CVD-related deaths for CVD-related mortality. In the bottom 3 panels, solid lines represent the risk of non-CVD-related death; dash lines the risk of CVD-related death; and the area the overall risk of death (non-CVD-related plus CVD-related death). Please note the different y-axis scale.

Figure 2. 5-year and 10-year risk difference in hospitalization for severe hypoglycemia and mortality

Legend: 5-year and 10-year differences (exposed vs. non-exposed to overtreatment) in hospitalization for severe hypoglycemia (green), CVD-related mortality (orange) and non-CVD-related mortality (blue) across ages are estimated in the multivariable-adjusted model with multiple imputation.

Table 1. Characteristics of subjects at index date by exposure

	Non-exposed (n=16,569)	Exposed (n=6288)	p-value
Age, years	76.6 (73.1-81.3)	76.8 (73.1-81.5)	0.370
⩽75	6531 (39.4%)	2449 (38.9%)	0.230
75-80	4901 (29.6%)	1820 (28.9%)	
80-85	3276 (19.8%)	1255 (20.0%)	
>85	1861 (11.2%)	764 (12.2%)	
Age at type 2 diabetes diagnosis, years	72.4 (68.3-77.1)	72.3 (68.1-77.3)	0.720
Gender			0.940
Male	8881 (53.6%)	3374 (53.7%)	
Female	7688 (46.4%)	2914 (46.3%)	
Ethnicity			0.470
White	14,878 (93.5%)	5678 (93.2%)	
Non-White	1034 (6.5%)	412 (6.8%)	
Townsend score, quintile			0.033
1 – most affluent	3597 (21.7%)	1304 (20.8%)	
2	4017 (24.3%)	1525 (24.3%)	
3	3587 (21.7%)	1294 (20.6%)	
4	3380 (20.4%)	1377 (21.9%)	
5 – most deprived	1975 (11.9%)	784 (12.5%)	
Diabetes durations, years	4.1 (2.2-6.9)	4.2 (2.2-7.1)	0.026
HbA_{1c} measurements from being at risk of overtreatment	5 (3-9)	5 (3-9)	<0.001
Time from being at risk of overtreatment, years	2.7 (1.7-4.7)	2.7 (1.6-4.9)	0.820
HbA_{1c}			
%	6.8 (6.3-7.5)	6.4 (6.0-6.7)	<0.001
mmol/mol	51 (45-59)	46 (42-50)	
BMI, kg/m^2	28.3 (25.3-31.8)	28.2 (25.1-32.0)	0.190
eGFR, $ml/min/1.73m^2$	62 (50-76)	58 (44-73)	<0.001
Blood pressure, mmHg			
Diastolic	74 (68-80)	72 (67-80)	<0.001
Systolic	137 (128-144)	137 (127-145)	0.690
Cholesterol, mmol/l			
Total	4.1 (3.6-4.8)	3.9 (3.4-4.6)	<0.001
HDL	1.3 (1.0-1.5)	1.2 (1.0-1.5)	<0.001
LDL	2.1 (1.6-2.7)	2.0 (1.6-2.6)	<0.001
Smoking status			0.590
Current smoker	1314 (7.9%)	488 (7.8%)	
Ex-smoker	7325 (44.3%)	2829 (45.0%)	
Non-smoker	7897 (47.8%)	2963 (47.2%)	
Alcohol consumption			0.001
Non-drinker	4084 (25.3%)	1675 (27.4%)	
Ex-drinker	892 (5.5%)	370 (6.0%)	
Drinker, <14 units /week	5402 (33.4%)	2016 (33.0%)	
Drinker, >14 units /week	1106 (6.8%)	367 (6.0%)	
Drinker, unknown units	4689 (29.0%)	1688 (27.6%)	
Glucose–lowering medications			<0.001
None	7483 (45.2%)	0 (0.0%)	
1	6344 (38.3%)	2992 (47.6%)	
2	2265 (13.7%)	2922 (46.5%)	
3	453 (2.7%)	361 (5.7%)	
4	23 (0.1%)	13 (0.2%)	
5	1 (0.0%)	0 (0.0%)	
Glinide	42 (0.3%)	12 (0.2%)	0.380

Metformin	7288 (44.0%)	2917 (46.4%)	0.001
DPP-4 inhibitor	506 (3.1%)	204 (3.2%)	0.460
GLP-1 receptor agonist	60 (0.4%)	21 (0.3%)	0.750
SGLT-2 inhibitor	23 (0.1%)	5 (0.1%)	0.250
Thiazolidinedione	694 (4.2%)	402 (6.4%)	<0.001
Mixed oral medication	158 (1.0%)	62 (1.0%)	0.820
Other diabetes medications	26 (0.2%)	7 (0.1%)	0.420
Use of sulphonylurea and insulin*			<0.001
Sulphonylurea and insulin	172 (5.1%)	53 (0.8%)	
Sulphonylurea only	2526 (75.2%)	5659 (90.0%)	
Insulin only	663 (19.7%)	576 (9.2%)	
Type of insulin*			
Basal	398 (2.4%)	217 (3.5%)	<0.001
Intermediate	431 (2.6%)	399 (6.3%)	<0.001
Prandial	148 (0.9%)	77 (1.2%)	0.023
Combination	139 (0.8%)	64 (1.0%)	0.200
Cardiovascular medications			
ACE inhibitor	6710 (40.5%)	2910 (46.3%)	<0.001
ARB	2633 (15.9%)	1226 (19.5%)	<0.001
Statin	10,617 (64.1%)	4422 (70.3%)	<0.001
Number of morbidities‡			<0.001
0	6367 (38.4%)	2262 (36.0%)	
1	5599 (33.8%)	2073 (33.0%)	
2	2873 (17.3%)	1159 (18.4%)	
3	1142 (6.9%)	501 (8.0%)	
4	424 (2.6%)	213 (3.4%)	
5	131 (0.8%)	62 (1.0%)	
6	23 (0.1%)	16 (0.3%)	
7	9 (0.1%)	2 (0.0%)	
8	1 (0.0%)	0 (0.0%)	
Myocardial Infarction	2007 (12.1%)	832 (13.2%)	0.022
Cancer	3189 (19.2%)	1244 (19.8%)	0.360
Heart failure	1765 (10.7%)	774 (12.3%)	<0.001
Peripheral arterial disease	906 (5.5%)	377 (6.0%)	0.120
Stroke	2433 (14.7%)	1002 (15.9%)	0.018
Dementia	553 (3.3%)	208 (3.3%)	0.910
Depression	3688 (22.3%)	1350 (21.5%)	0.200
Non-traumatic lower limb amputation	139 (0.8%)	80 (1.3%)	0.003
Chronic kidney disease	514 (3.1%)	300 (4.8%)	<0.001
Anemia	2137 (12.9%)	999 (15.9%)	<0.001

Data are shown as median (IQR) for continuous variables and number (%) for categorical variables; *p-values* obtained with Wilcoxon Rank-Sum test for continuous and Pearson's chi-square test for categorical variables.

*Could be combined with other drugs;
‡Maximum number of conditions: 10;
eGFR: estimated glomerular filtration rate, calculated using the CKD-EPI equation; DPP-4: Dipeptidyl Peptidase 4; GLP-1: Glucagon-like peptide-1; SGLT-2: sodium-glucose transport protein 2; ARB: angiotensin II receptor blocker.

Table 2. Hazard ratios for hospitalization for severe hypoglycemia and cause-specific mortality

Outcome	Person-years	Events/Subjects	Hazard ratio (95% confidence interval)	
			Age-adjusted	Multivariable adjusted
Hospitalization for severe hypoglycemia	121,457	1392/22,857	1.90 (1.71, 2.11)	2.52 (2.23, 2.84)
Cardiovascular mortality	125,409	3670/22,857	1.02 (0.95, 1.10)	0.98 (0.91, 1.06)
Non-cardiovascular mortality	125,409	7208/22,857	1.05 (1.00, 1.10)	1.05 (0.99, 1.11)

Hazard ratios comparing exposed vs non-exposed to overtreatment.

Multivariable models adjusted for: age (restricted cubic spline with 4 knots), number of HbA_{1c} measurements from being at risk of overtreatment to index date, length of time frame from being at risk of overtreatment to index date, gender, ethnicity (White, non-White), deprivation (quintiles), diabetes durations, BMI, blood pressure (diastolic and systolic), alcohol (no drinker, ex-drinker, yes but unknown units, yes with ≤14 units/week, yes with >14 units/week), smoking (no smoker, ex-smoker, current smoker), HbA_{1c}, total, HDL, and LDL cholesterol, eGFR (CKD-EPI equation), glucose-lowering medication (glinide, metformin, dipeptidyl peptidase 4 inhibitor, glucagon-like peptide 1 receptor agonist, sodium-glucose cotransporter protein 2 inhibitor, thiazolidinedione, mixed oral glucose-lowering medication, and other glucose-lowering medications), ACE inhibitor, angiotensin II receptor blocker, statin, medical history of: heart failure, stroke, myocardial infarction, cancer, peripheral arterial disease, chronic kidney disease, non-traumatic lower limb amputation, depression, dementia, and anemia.