

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

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Figure S1. Cohort definition

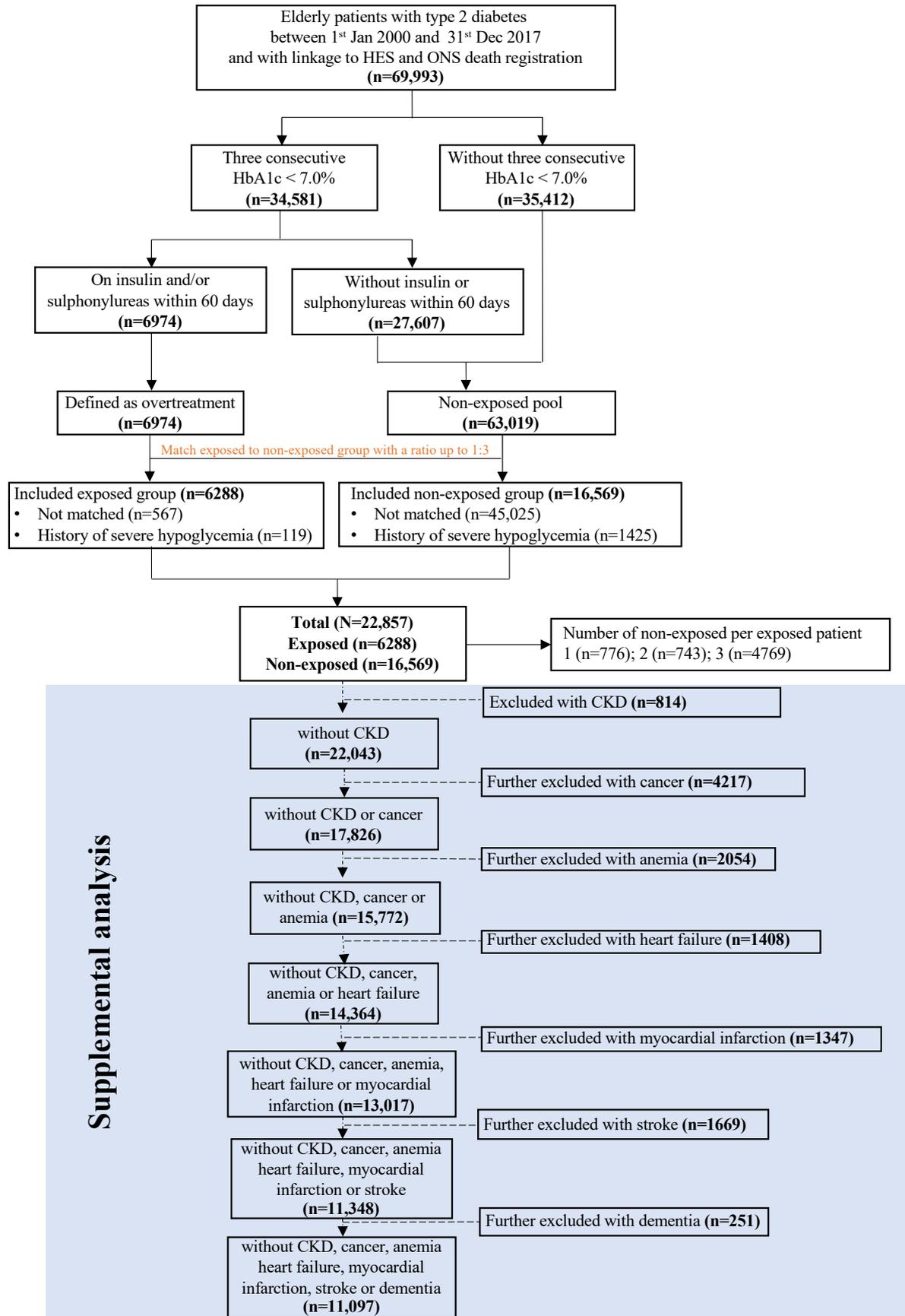


Table S1. Missing data

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/1.73m²) 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

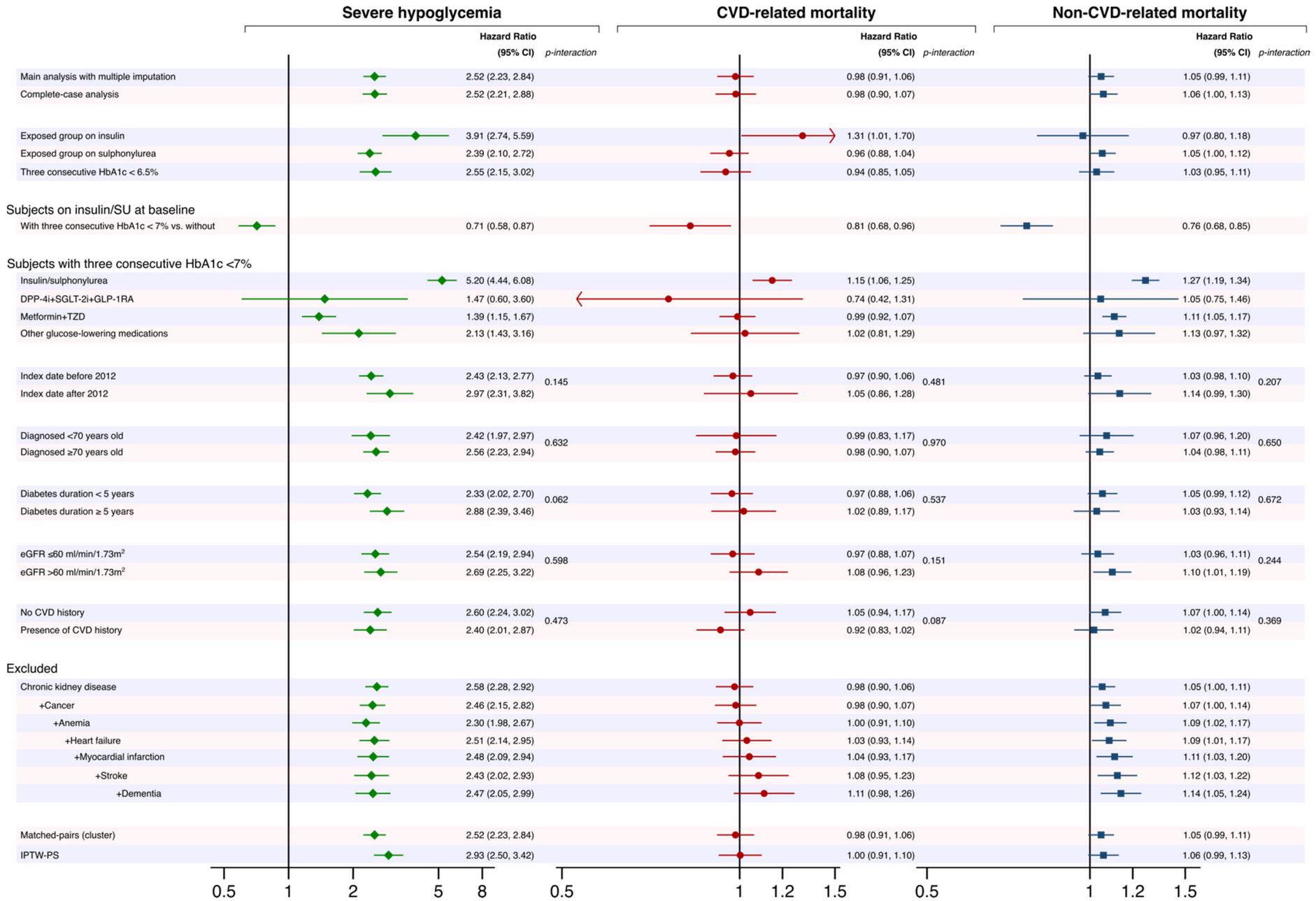
To account for the potential impact of matching, we conducted a supplemental analysis considering matched-pairs as clusters: the results of this analysis were identical to the estimates obtained in the main analysis without robust clustered standard errors (**Figure S2**).

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 HbA_{1c} 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/1.73m²: interaction analysis between exposure and eGFR (CKD-EPI);

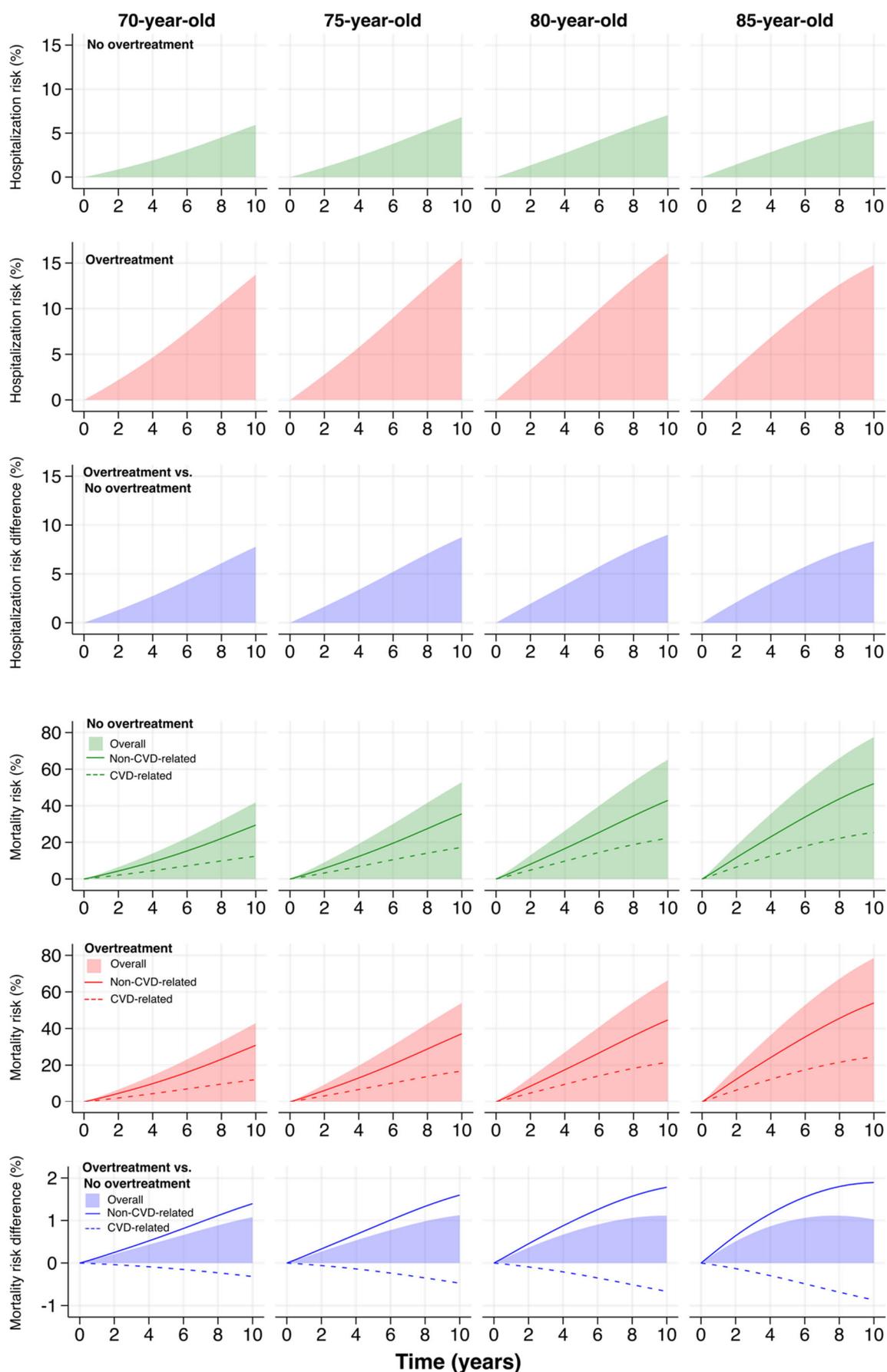
No CVD history/presence of CVD history: interaction analysis between exposure and CVD (history of heart failure, myocardial infarction, stroke, or peripheral vascular disease);

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);

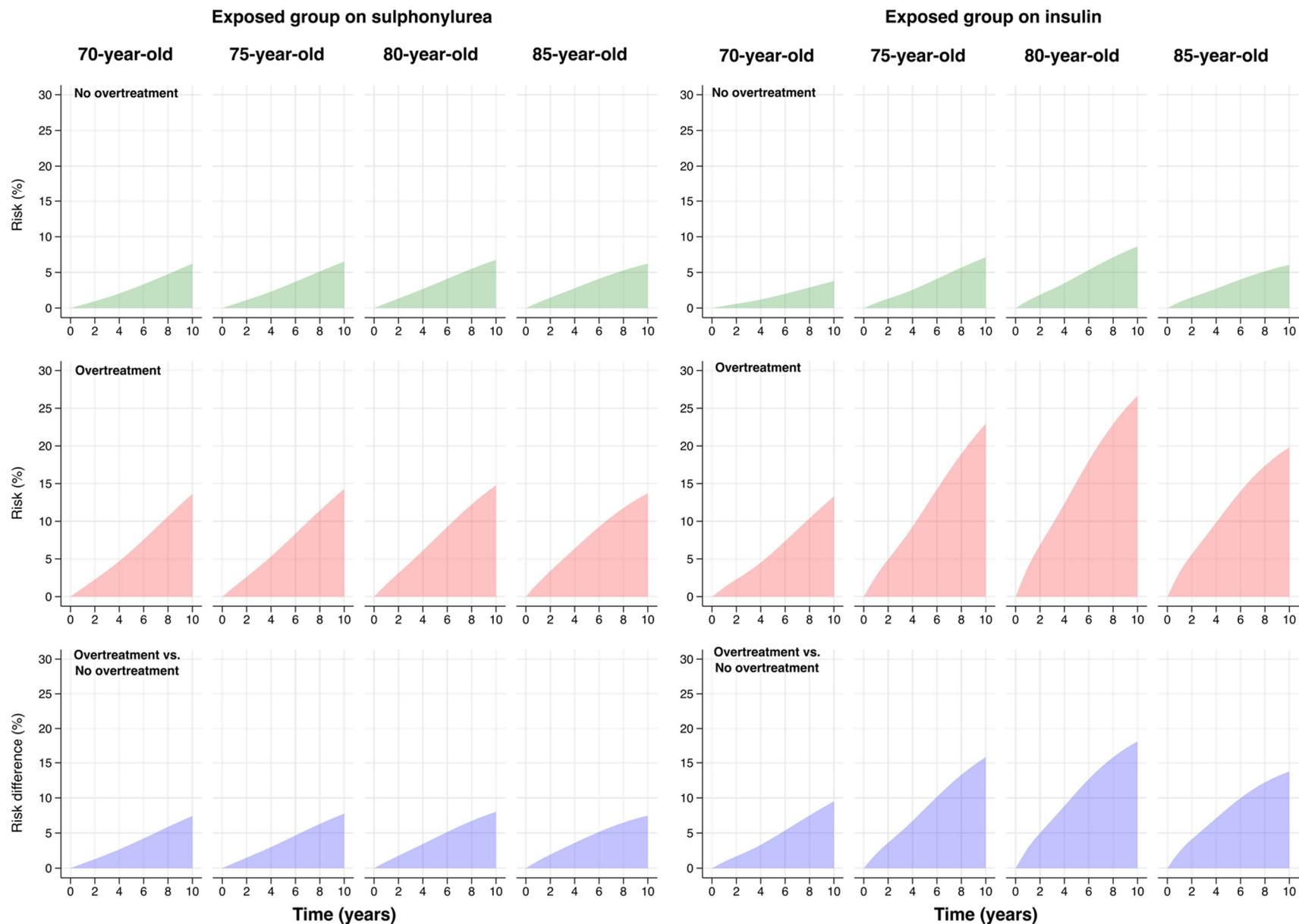
IPTW-PS: Hazard ratios exposed vs non-exposed with inverse probability of treatment weighting using propensity score.

Figure S3. Complete-case analysis results



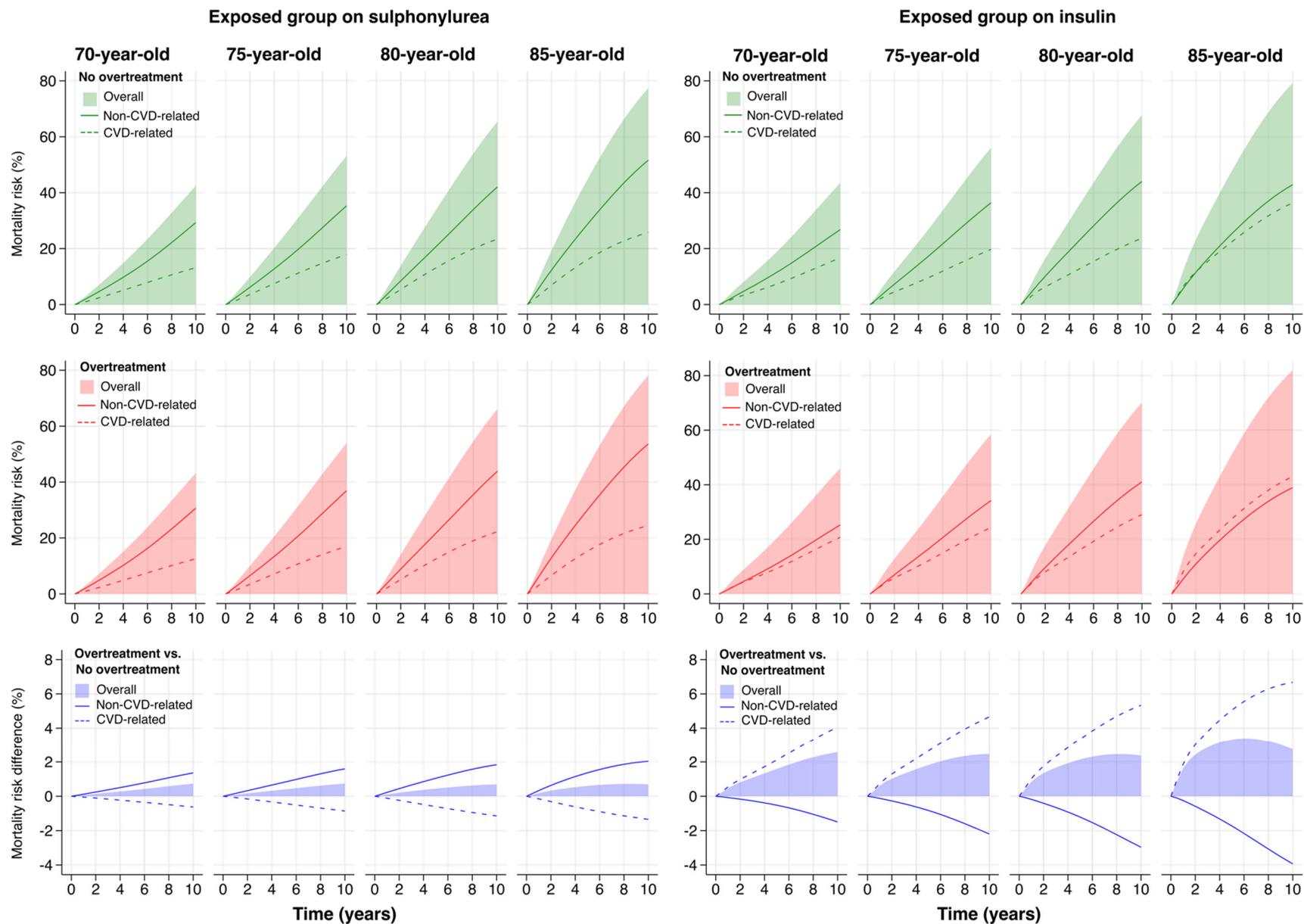
Absolute risks of hospitalization for severe hypoglycemia, CVD- and non-CVD-related mortality over 10 years of follow-up for different ages, in subjects exposed (overtreatment, red) and non-exposed (green); the risk difference (exposed vs. non-exposed) is shown in blue. Estimates are multivariable adjusted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



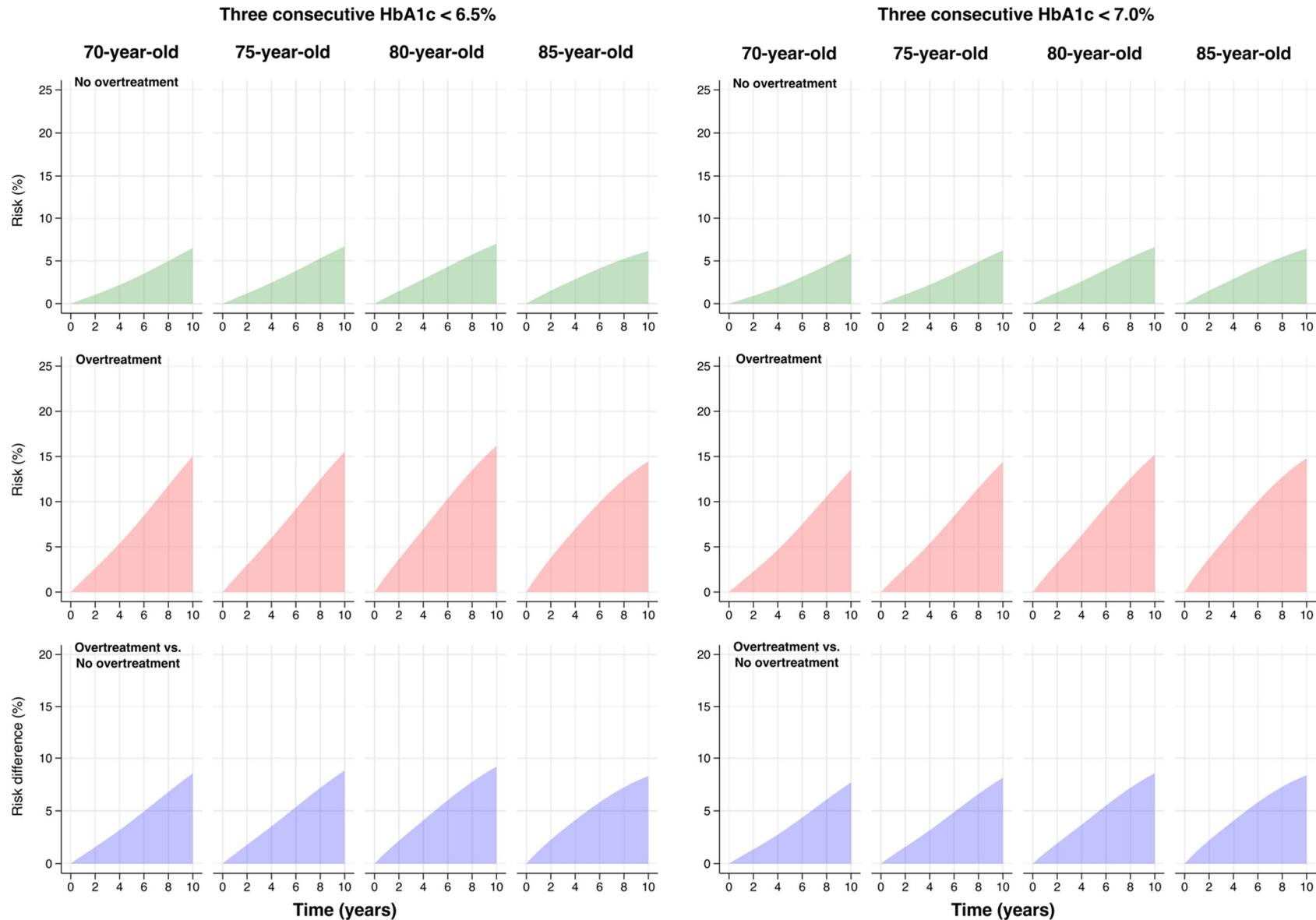
Absolute risks of hospitalization for severe hypoglycemia over 10 years of follow-up for different ages, in subjects with (red) and without (green) overtreatment; the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and accounted for all-cause 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



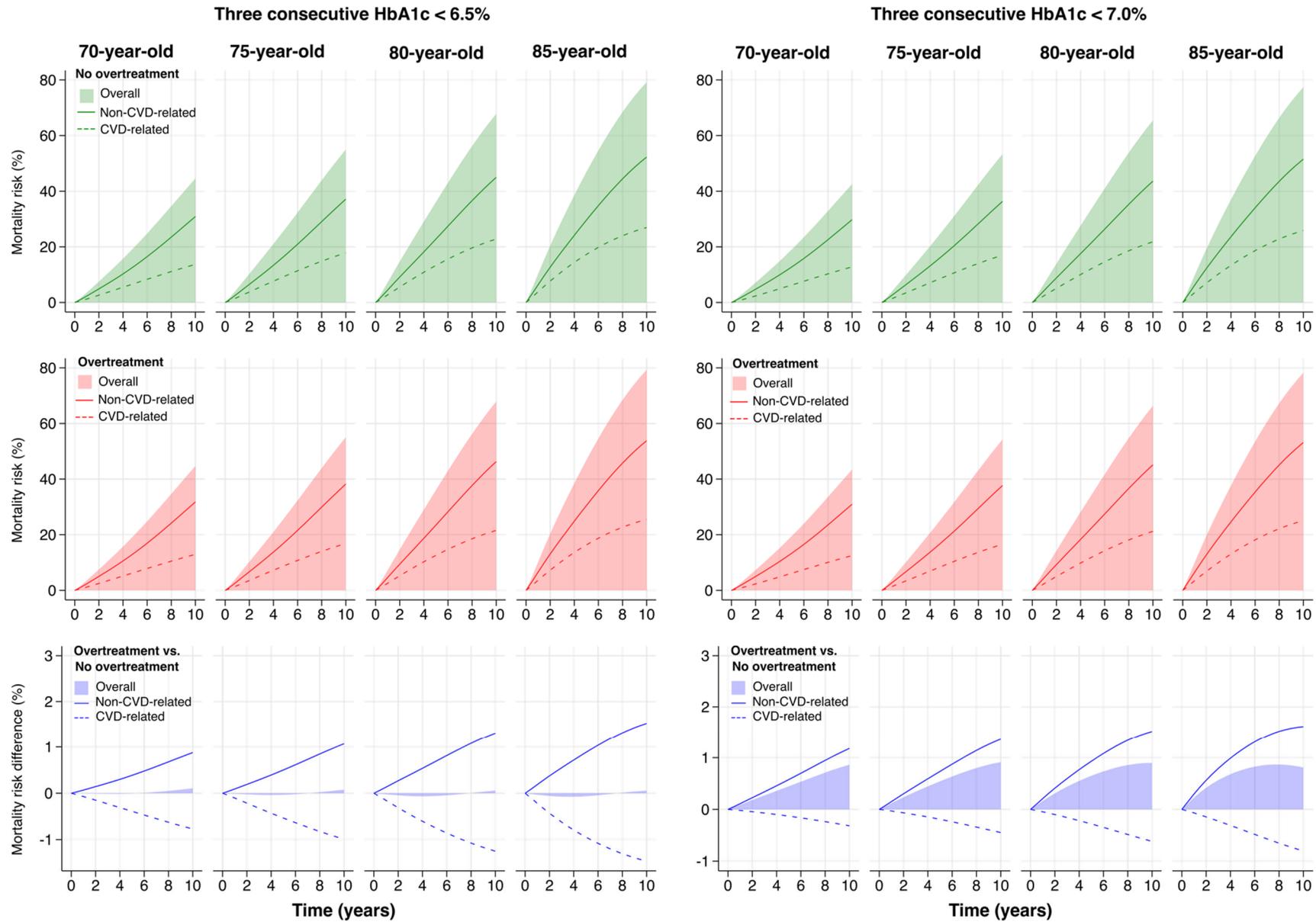
Absolute risks in CVD- and non-CVD-related mortality over 10 years of follow-up at different ages, in subjects with (red) and without (green) overtreatment; the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and, for CVD-related mortality, 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



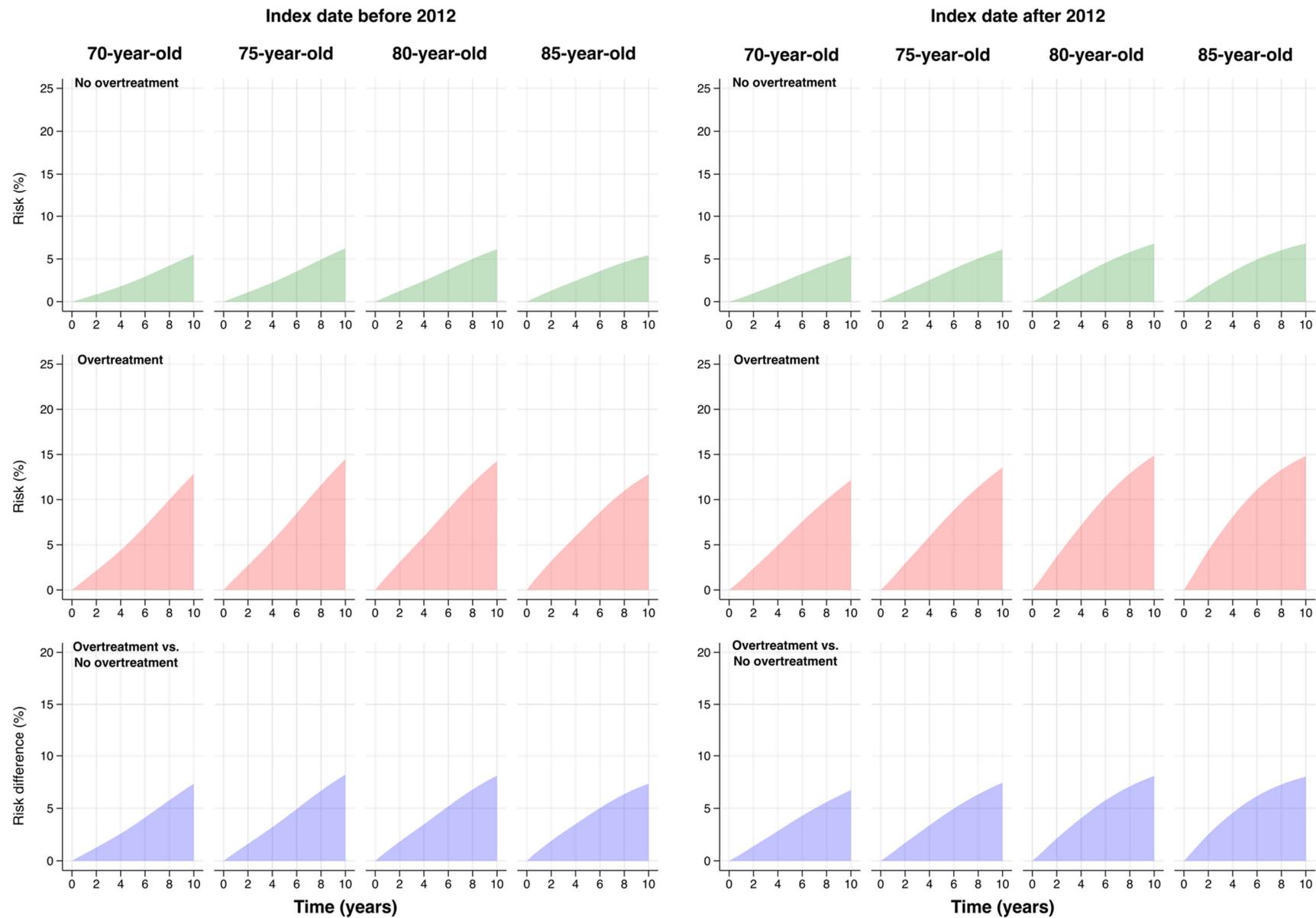
Absolute risks of hospitalization for severe hypoglycemia over 10 years of follow-up for different ages, in subjects with (red) and without (green) overtreatment; the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and accounted for all-cause 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 HbA_{1c} 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



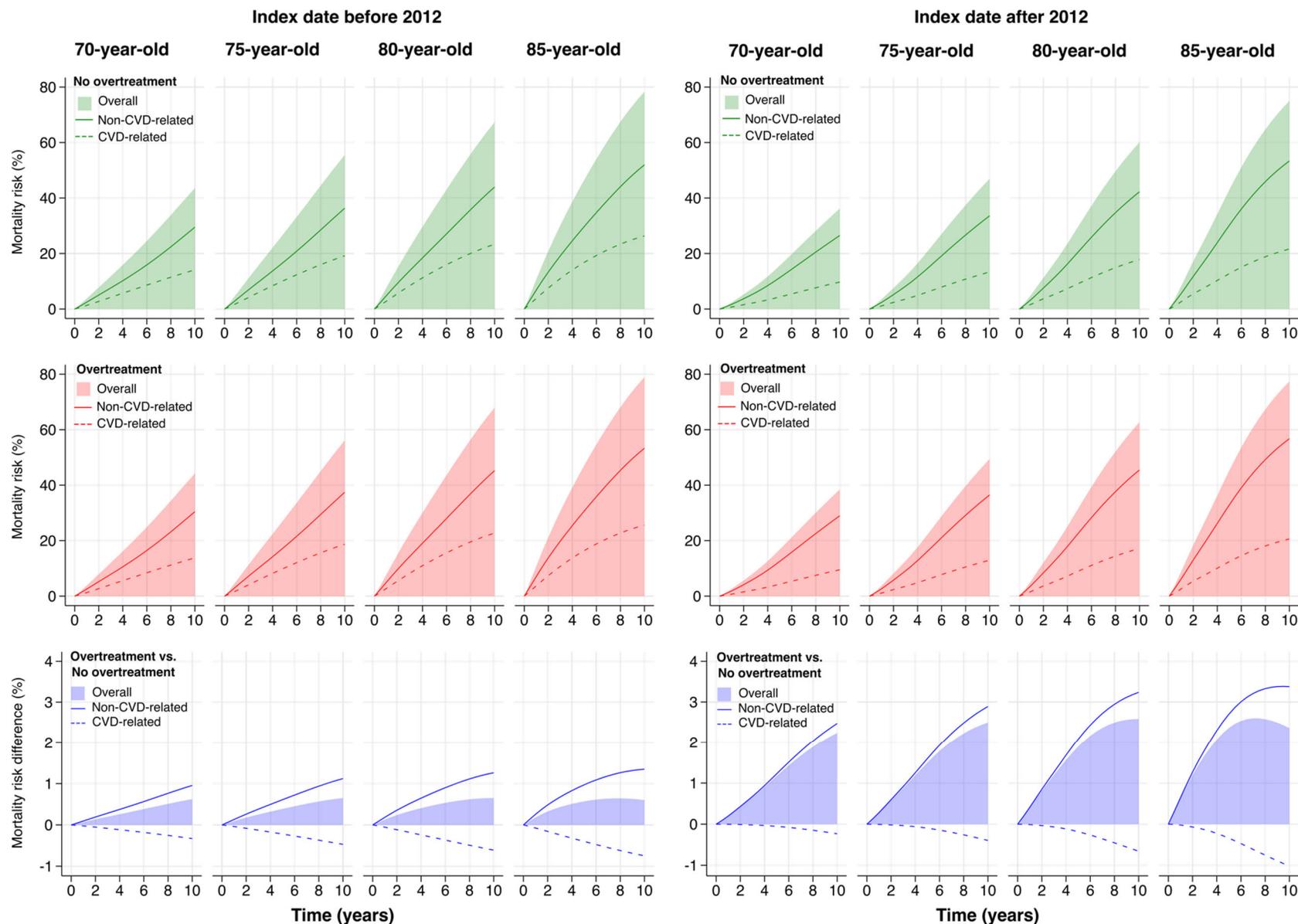
Absolute risks in CVD- and non-CVD-related mortality over 10 years of follow-up at different ages, in subjects with (red) and without (green) overtreatment; the risk difference (overtreatment vs. no overtreatment) is shown in blue. Estimates were multivariable adjusted and, for CVD-related mortality, 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 HbA_{1c} 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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