Effects of antidiabetic drugs on mortality risks in individuals with type 2 diabetes: A prospective cohort study of UK Biobank participants

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Abstract

Objective: To investigate the mortality risk linked to prescription of different anti-diabetic medication classes.
Design: Prospective population-based study.
Setting: UK Biobank.
Participants: 410 389 of the 502 536 participants in UK Biobank with covariate data, clinical and prescription records were included in the analyses, 43 610 of which had been diagnosed type 2 diabetes (T2D). A nearest neighbour covariate matching (NNCM) algorithm based on covariates with relevant effects on survival was applied to match cohorts of anti-diabetic medication class users to minimally differing control cohorts, either with a T2D diagnosis or without. Kaplan Meier estimates and Cox proportional models were used to evaluate survival differences and hazard ratio between drug classes and controls.
Main outcome measures: All-cause mortality and causes of death.
Results : 13667 (3.3%) individuals died during a median of 12.2 years of follow-up. After applying NNCM, participants with T2D on metformin (average hazard ratio 0.39, 95% confidence interval 0.31 to 0.49) or SGLT2I (average hazard ratio 0.58, 95% confidence interval 0.36 to 0.93) have an increased survival probability compared to matched individuals with T2D. When compared to matched individuals without T2D, the survival probability of individuals with T2D increases only if prescribed SGLT2I (average hazard ratio 0.31, 95% confidence interval 0.19 to 0.51). NNCM-based analysis of matched individuals with T2D on both SGLT2I and metformin versus metformin only reveals increased survival in the presence of SGLT2I (average hazard ratio 0.29, 95% confidence interval 0.09 to 0.91), also when compared to matched identical individuals without T2D (average hazard ratio 0.05, 95% confidence interval 0.01 to 0.19). All the other anti-diabetic drugs analyzed are either detrimental in prolonging lifespan (insulin, thiazolidinediones, and sulfonylureas), or have no effect (DPP4 inhibitors and GLP1 receptor agonists).
Conclusion: The use of the current first-line anti-diabetic treatment, metformin, or sodium-glucose cotransporter 2 inhibitors (SGLT2I) increases the survival probability compared to matched individuals with diabetes using other anti-diabetic drugs. Only individuals on SGLT2I experience increased survival when compared to individuals without T2D.

Introduction

Several classes of drugs are routinely prescribed for type 2 diabetes mellitus (T2D) management, including the first-line treatment metformin, but also long-/intermediate- and short-acting insulins, sulfonylureas, as well as the more recent dipeptidyl peptidase 4 inhibitors (DPP4I), glucagon-like peptide 1 receptor agonists (GLP1RA), and sodium-glucose cotransporter 2 inhibitors (SGLT2I)[1 2]. These appear to differently affect long-term outcomes, amelioration of T2D-associated comorbidities, and potentially mortality risks[3-6].

The first and largest multicenter randomised clinical trial (RCT) of long-term outcomes of anti-diabetic drugs, the *UK Prospective Diabetes Study* (UKPDS) observed 5,102 individuals with type-2 diabetes (herein referred to as T2Ds) for a median of 10 years in a prospective manner. While all the available anti-diabetic treatments at the time (namely metformin, sulfonylureas, and different insulins) were more effective than diet to achieve glycemic control, only obese users of metformin showed a decrease in all-cause mortality[7]. Additional classes of anti-diabetic medications targeting other molecular pathways have since been developed and clinically tested[8]. Several randomised intervention studies have compared the effectiveness of the long-acting insulin glargine, sulfonylureas, GLPRA, SGLT2I and DPP4I in regards to the respective abilities to lower glycated hemoglobin (HbA1c), either in the unstratified diabetic population, or in subgroup of diabetic individuals [9-11]. Findings from other RCTs suggest that DPP4I, GLP1RA, and SGLT2I may have the potential to reduce mortality of T2Ds[4]. Nevertheless, such trials have a limited follow-up time, include a lower number of participants, exclude participants with pre-existing malignancies, and cannot compare outcomes with matched individuals without T2D, especially regarding mortalities and causes of death. Since there is still limited consensus on the most effective targeted second- or third-line treatment for T2D without comorbidities, the choice of add-on glucose lowering therapies is widely based on costs and side effect profiles, rather than efficacy or long-term outcomes [9]. Assessing changes in healthspan and lifespan driven by anti-

diabetic medications will guide patients and practitioners to more informed choices on second-line anti-diabetic medications, therefore this research endeavour is of utmost clinical importance. We here aim at investigating the effects of the current anti-diabetic drugs on all-cause mortality and causes of death in a large real-world cohort observed for a median of 12.02 years, by comparing T2Ds with different drug regimens, but also in comparison to individuals without T2D.

Results

Type 2 diabetes mortality and causes of death

We obtained data from the National Health Services (NHS) on clinical records and prescription details for 410,389 UK Biobank participants (**Fig 1a**), and followed the outcomes from the date of recruitment until the present (median of 12.01 years). Out of 410,389 UK Biobank participants, clinical records of 43,610 individuals reported a diagnosis of T2D (**Table 1**).

As expected [3] [12], individuals with T2D (green) had a lower survival probability than individuals without T2D (black) (**Fig 1b**). Deaths caused by many comorbidities, including neoplasms (2.23% of the individuals with T2D within the study succumb due to neoplasms vs 1.63% in non-diabetic control individuals - herein referred to as nonT2Ds), cardiovascular diseases (1.57% vs 0.57%) and COVID-19 (0.52% vs 0.13%) were more frequently observed in T2Ds than in nonT2Ds (**Fig S1a** and **b**, and **Supplementary Table 1**), also confirming previous findings regarding an increase in mortality from COVID-19 in T2Ds within the UK Biobank cohort[13] [14].

Specific anti-diabetic medication classes and all-cause mortality

Analysis of medications prescribed reveals that most T2Ds take only one drug class (33.74%), followed by individuals not prescribed any anti-diabetic drugs (31.02%) (**Fig S2a**). The remaining T2Ds are prescribed up to six drug classes (**Fig S2a**). There were similar percentages of deaths among the individuals with T2D of all drug regimens, at around 5% (**Fig S2b**). The most prescribed drug class is metformin (57.45% of T2Ds prescribed), followed by sulfonylureas (16.47%), long/intermediate-acting insulins (14.40%), DPP4I (13.66%), SGLT2I (8.49%), short-acting insulins (6.45%), GLP1RA (4.20%), thiazolidinediones (1.75%), meglitinides (0.12%) and acarbose (0.03%) (**Fig S2c**). Users of SGLT2I or GLP1RA had by far the lowest percentage of deaths during the study (1.51% and 2.95%) (**Fig S2d**).

By contrast, sulfonylureas, long/intermediate- or short-acting insulin users had the highest percentage of deaths (7.61%, 10.55%, and 9.10%) (**Fig S2d**). The most frequently prescribed compound was metformin (**Fig S2e**), which was also the drug class most commonly prescribed as a unique anti-diabetic therapy (**Fig S2f**) reflecting its role as a first-line treatment for T2D. Given the limited number of individuals using meglitinides and acarbose, these were not further analysed for considerations of insufficient statistical power.

Application of a Cox multivariate proportional hazard model considering baseline characteristics, lifestyle, and comorbidities, as well as anti-diabetes medication use revealed that metformin (HR 0.74, CI 0.67-0.83), DPP4I (HR 0.63, CI 0.53-0.75), SGLT2I (HR 0.40, CI 0.29-0.56), and GLP1RA (HR 0.55, CI 0.39-0.79) were linked to an increased survival probability (**Fig 1c**). When comparing Kaplan-Meier estimates of participants diagnosed with T2Ds only, drug users (blue) prescribed metformin, DPP4I, or SGLT2I had an increased survival probability compared to T2Ds not prescribed the individual drug (red) (**Fig S3**). Of note, and unlike for Cox analyses, Kaplan-Meier estimates do not correct for co-use of other anti-diabetic drugs.

When performing Kaplan-Meier estimates to compare survival probability of T2Ds using the respective compound (blue) to no-T2Ds (black), only SGLT2I users showed improved survival compared nonT2Ds (log-rank P value 0.003) (**Fig S3**). All other compounds, including metformin (log-rank P value < 0.001), DPP4I (log-rank P value 0.007), and GLP1RA (log-rank P value 0.16) failed to promote survival compared to non-T2D participants not prescribed any of these drugs (**Fig S3**). Of note, nonT2Ds in this analysis have not been matched to T2Ds for comorbidities or other confounders, nor do Kaplan-Meier estimates correct for co-use of additional anti-diabetic drugs within the T2D cohort.

Differences in anti-diabetic drug class use and age at first drug use require nearest neighbour covariate matching (NNCM)

Clinical availability of anti-diabetic drug classes differs considerably. Accordingly, our analysis revealed that DPP4I, SGLT2I, and GLP1RA have been used for a shorter period of time (median of 3.26, 2.57, and 2.35 years, respectively) than metformin (median of 8.87 years), sulfonylureas (median of 8.19 years), short-acting insulins (median of 11.72 years), long/intermediate-acting insulins (median of 8.14 years), or thiazolidinediones (median of 9.08 years) (**Fig S4a**). Also, individuals who are first-time users of these newer drugs are on average of higher age (median of 68.66 years for DPP4I, 64.34 for GLP1RA, and 64.47 for SGLT2I) than patients prescribed metformin (61.13), sulfonylureas (62.49), short-acting (57.39), long/intermediate-acting insulins (61.51), or thiazolidinediones (62.97) (**Fig S4b**). These findings could, at least in part, explain the survival differences depicted in **Fig 1** and **Fig S3** [15,16]. Therefore, measures to minimise such indication bias, as well as an immortal time bias appear mandatory, which were obtained by applying nearest neighbour covariate matching (or NNCM), a statistical learning method (see **Methods** and **Supplementary Information** for details).

SGLT2I and metformin extend lifespan in individuals with type 2 diabetes

After application of NNCM (**Fig S5a-b**), exposure to drugs was comparable among cohorts (**Fig S6**), and Kaplan-Meier estimates of survival of T2Ds using the drug of interest show that only users of metformin or SGLT2I had reduced all-cause mortality, when compared to matched T2D users of other drugs (**Fig 2a**). Drug use- and confounder-corrected Cox proportional multivariate hazard analysis corroborates the findings: metformin (HR 0.40, 95% CI 0.32 to 0.50) and SGLT2I (HR 0.47, 95% CI 0.29 to 0.74) improved the survival of its users of (**Fig 2b**). Confirming the Kaplan-Meier estimates (**Fig 2a**), users of sulfonylureas (HR 1.28, 95% CI 1.06-1.55), long/intermediate insulins (HR 1.72, 95% CI 1.36-2.17) and short-acting insulins (HR 1.72, 95% CI 1.16-2.55) had increased mortalities (**Fig 2b**).

Metformin users compared to T2D matched controls were protected from deaths caused by neoplasms (1.61% vs 3.73% deaths during the study) and cardiovascular disease (1.08% vs 2.81%), while SGLT2I users had fewer deaths by neoplasms (0.71% vs 1.75%) (**Fig S7**). Both sulfonylureas as well as long/intermediate-acting insulins increased the risk to die from neoplasms and from diseases of the circulatory system. Short-acting insulins did increase the risk to die from cardiovascular diseases but not from neoplasms (**Fig S7** and **Supplementary Table 2**).

SGLT2I reduce mortality risk compared to matched individuals without type 2 diabetes

To assess the absolute effect of individual anti-diabetic drugs on all-cause mortality, we matched T2Ds to control nonT2Ds by applying NNCM (**Fig S5c-d**).

In this analysis, only SGLT2I users had a survival advantage compared to matched nonT2Ds, while users of metformin had lower life expectancy than undiagnosed matched controls (**Fig 3a**). Of note, both latter findings are already anticipated in the analyses of the unmatched cohorts (**Fig S3**). Resembling the previous analyses (**Fig S3, Fig 2a**), sulfonylureas, long/intermediate-acting insulins, and short-acting insulin users had a survival disadvantage compared to matched non-T2D-diagnosed individuals (**Fig 3a**).

Cox proportional multivariate hazard analysis (**Fig 3b**) corroborates the positive effect of SGLT2I (HR 0.31, 95% CI 0.19 to 0.51) and DPP4I on survival (HR 0.63, 95% CI 0.49 to 0.79). However, DPP4I failed to reduce mortality in Kaplan-Meier estimates (**Fig 3a**) By contrast, metformin did not improve survival of its users compared to matched nonT2Ds (HR 0.94, 95% CI 0.84 to 1.07) (**Fig 3b**). Also, users of SGLT2I (0.61% vs 1.57%) and DDP4I (1.52% vs 2.59%) had significantly fewer deaths from neoplasms (**Fig S8**), whereas metformin did not exert such reduction. Causes of death for the other drugs are available in **Fig S8** and **Supplementary Table 3**.

Effects of SGLT2I in combination with metformin compared to metformin alone or to individuals without type 2 diabetes

Hence, when compared to nonT2Ds after NCCM, SGLT2I seems to be the most effective drug class to treat T2Ds, followed by DPP4I. However, a significant portion of T2Ds using one of these latter compounds also takes metformin (n=1131 for DPP4I & metformin, n=578 for SGLT2I & metformin), and up to 4 additional other antidiabetic drugs (**Fig S2a, c, e**). While corrected for different/combined drug use in the Cox analysis (**Fig 3b**), we nevertheless aimed to quantify the relative effects of such combined therapies. Again, by applying NNCM, we first matched T2Ds using metformin together with either DPP4I or SGLT2I, with T2Ds using metformin only. We next matched the exact same T2Ds using metformin plus either DPP4I or SGLT2I with nonT2Ds. Lastly, we used the exact same matched nonT2Ds to compare them with the exact same T2Ds using metformin only as above.

For DPP4I combined with metformin, no differences were observed in regards to survival by both Kaplan-Meier and Cox analyses (**Fig 4a**). By contrast, comparison of diabetic SGLT2/metformin users with NNC-matched individuals with T2Ds prescribed metformin only revealed a survival advantage, both by Kaplan-Meier (P = 2.31e-02) as well as Cox analyses (HR

0.29, 95% CI 0.09 to 0.91, P=0.03), for the *combined* use. Comparing the same SGLT2/metformin users with NNC-matched nonT2D individuals, a strong advantage for SGLT2I/metformin usage was observed for T2Ds (KM P = 2.32e-04; Cox HR 0.058, 95% CI 0.02 to 0.19). Of note, when comparing the matched metformin-only T2D with the *same* matched nonT2Ds as above, the effect was absent by Kaplan-Meier estimates (P = 1.09e-01), or markedly reduced for the Cox analysis (HR 0.42, 95% CI 0.21 to 0.87) (**Fig 4b**).

Also taking the findings depicted in **Fig 3** into account, these findings independently indicate that SGLT2I, when added to a first-line metformin treatment, extend survival beyond the life expectancy of non-diabetic control individuals, and notably better than metformin does either alone, or with any other antidiabetic co-medication but SGLT2I.

Discussion

Statement of principal findings

Multiple therapeutic options are available for type 2 diabetes. In the current study, the current first line-treatment, the biguanide metformin, was found capable of reducing the mortality of T2Ds when compared to other T2Ds not prescribed metformin (**Fig S3**, **Fig 1c**, **Fig 2a**, **Fig 2b**). However, and unlike SGLT2I, metformin was unable to reinstate normal (i.e. non-diabetic) life expectancy in T2Ds, as identified by higher mortality rates of T2Ds on metformin compared to nonT2Ds (**Fig S3, Fig 3b**) in the current study. Moreover, our findings not only identify a reduction in overall mortality risk of T2Ds following SGLT2I prescription compared to T2Ds on drugs other than SGLT2I, but also a reduction of mortality risk compared to nonT2Ds. The analyses also indicate a reduction in cancer-related deaths in SGLT2I users (**Fig S7**, **Fig S8**).

SGLT2I were linked to increased survival probability in both Kaplan-Meier (**Fig 3a**) and Cox (**Fig 3b**) analyses; also, DPP4I were linked to increased survival in the Cox (**Fig 3b**) analysis only, however showed no mortality advantage in the Kaplan-Meier analysis (**Fig 3a**). Hence, when compared to nonT2Ds, SGLT2I seems to be the most effective drug class to treat T2Ds, followed by DPP4I. However, a significant portion of T2Ds using one of these latter compounds also take metformin (n=578 for SGLT2I & metformin, n=1131 for DPP4I & metformin). Therefore, we have performed subgroup analyses to directly compare the effect of users of metformin and SGLT2I or DPP4I against metformin alone. While adding DPP4I to metformin had no effect on survival (**Fig 4a**), the use of SGLT2I in combination with metformin was able to prolong lifespan in T2D patients compared to the ones using metformin alone, and SGLT2I and metformin users had a considerable survival advantage compared to noT2D or to metformin only users compared to noT2D (**Fig 4b**).

Earlier anti-diabetic drug classes (namely sulfonylureas, insulins, and thiazolidinediones) had either a pronounced negative impact on mortality risks, or showed no difference in survival, in accordance with what has been observed in previous studies [5 17].

Strengths and weaknesses of the study

This study uses data from the UK Biobank, a prospective study, and an innovative statistical learning algorithm, namely NNCM with priority matching of lifespan-modulating covariates, to compare longevity of real-world users of commonly prescribed anti-diabetic drug classes. Due to the inclusion of health records and outcomes, it provides the means to compare the mortality rates of a large number of T2D patients prescribed different medication classes, over a long observation time, and also against individuals without T2D.

For reasons of statistical power, we here report survival analyses among classes of anti-diabetic medications, rather than of individual compounds, under the implicit assumption that compounds

within each anti-diabetic drug class have similar mechanisms of action, and therefore comparable effects on longevity. However, differences in bioavailability, target affinity and off-target effects of individual compounds in the same drug class might influence long-term outcomes, and the effect of each drug may be lost or overstated when analysed in combination with other medications in the same drug class.

Although our analysis includes up to 15 years of observations for some individuals, the exposure time of the most recently introduced medications (namely SGLT2I, GLR1RA, and DPP4I) is considerably shorter than for other medications. However, this difference is also being corrected for in the NNCM (**Fig S5**), and should hence not affect the differences in mortality of the two drug classes where effects superior to metformin are being detectable already (SGLT2I and possibly DPP4I). However, a longer follow-up time in the UK Biobank will increase the power of this analysis and might reveal statistically significant effects also of the only more recent anti-diabetic medication without relevant impact on survival probability in the current analysis, namely GLP1RA (**Figs. 2a** and **b, 3a** and **b**).

Another potential limitation concerns both the Cox covariate corrections as well as the NNCM strategy, which are both based on characteristics quantified at UK Biobank recruitment and do not fully consider clinical events, nor changes in physical and lifestyle characteristics throughout the observation period. Therefore, treatment-independent changes in baseline characteristics but also other unmeasured confounders, which might affect treatment choice or contribute to all-cause mortality, cannot and hence are not accounted for in neither covariate correction nor NNCM. As commonly applied elsewhere, we have assumed that the distribution of unmeasured confounders is equal in controls and treated individuals throughout time, similarly to what is customary in RCTs, where these limitations likewise apply.

Strengths and weaknesses in relation to other studies, discussing important differences in results

The mortality-reducing capability of metformin observed in the current study is supported by long-standing evidence from the UKPDStudy indicating that metformin reduces mortality in obese T2Ds [7]. T2Ds prescribed metformin had similar survival to matched nonT2Ds not prescribed anti-diabetic medications, following covariate corrected Cox analysis (**Fig 3b**). These data reassuringly support the previous findings that metformin does not harm, and show that this compound indeed restores life expectancy to the extent of non-T2D-diagnosed individuals. Hence, the use of metformin as the first-line monotherapy for T2D is justified due to its proven limited side effects, weight neutrality, and low costs [8].

SGLT2I have been clinically available for a shorter time, compared to other anti-diabetic drug classes (in this study, median prescription length: 2.57 years, longest prescription: 7.83 years, patient-years: 12096). SGLT2I have been evaluated in several RCTs, including the EMPA-REG OUTCOME study [18], where empagliflozin was applied in addition to standard treatment (most frequently metformin) to T2Ds with pre-existing cardiovascular disease, to observe a lower rate of death from any cause in the empagliflozin group. Subsequent RCTs also testing other gliflozins on different subgroups of T2Ds very consistently confirmed and extended such findings on reduction in all cause-mortality of T2Ds following application of SGLT2I, all in the presence of metformin [4 19-21].

Moreover, we cannot exclude the possibility that SGLT2I or DPP4I, while showing advantageous effects over metformin in the current and previous analyses [4 19 20], may opposingly exert negative impact on long-term survival probability after extended use [22 23].

Meaning of the study: possible explanations and implications for clinicians and policymakers

The key results of this study encourage clinicians to consider both metformin and SGLT2I as independent or combined first-line treatment(s) in the management of T2D.

Moreover, the study prompts to investigate the health benefits of SGLT2I also in light of its previously unknown anti-cancer effects. One recent RCT has tested metformin, DPP4I, and SGLT2I separately in drug-naïve T2Ds, to find that all three drugs lowered HbA1c levels, with metformin being most effective in regards to the latter, but only the SGLT2I dapagliflozin in the absence of metformin lowers insulin levels and body mass, which could explain its ability to reduce cancer-related deaths [24].

Unanswered questions and future research

The mechanisms behind SGLT2I's ability to extend lifespan are not limited to their glucose-lowering abilities or improvement of cardiovascular outcomes, and remain to be further explored. The reduction of mortality via SGLT2I application cannot be fully explained by the limited improvement of cardiovascular risk factors [21], despite the fact that the key SGLT2I trials lasted up to 4.2 years (DECLARE-TIMI 58: 218 weeks; EMPA-REG OUTCOME: 161 weeks; CREDENCE: 136 weeks; CANVAS: 126 weeks). Insofar it is interesting that our current findings not only identify a reduction in overall mortality risk of T2Ds following SGLT2I, but also indicate a reduction in cancer-related deaths when compared to T2Ds on drugs other than SGLT2I (**Fig S7**) as well as nonT2Ds (**Fig S8**). These findings might hint at an additional advantage of SGLT2I use also for the improvement of survival in oncological patients with or even without T2D, since most RCTs on SGLT2I have excluded individuals with pre-existing cancer diagnoses from participation, but this hypothesis needs to be tested formally with an *ad hoc* RCT.

Also, these findings suggest to use specific anti-diabetic compounds as a preventative strategy to promote healthspan not only in T2Ds, but also in middle-aged to elderly nonT2Ds. This has

302 been previously hypothesized for metformin [25] as well as for SGLT2I [26], while controlled
303 interventional data are pending.

304

305 **Methods**

306 ***Datasets***

307 The UK Biobank is a prospective study that recruited 502,611 participants aged between
308 38 and 73 years from 22 sites across the UK with baseline measures collected between 2006 and
309 2010 [27]. Data have since been linked to hospital, prescription and mortality records [28]. We used
310 the British National Formulary codes 6.1.1.X (insulins) and 6.1.2.X (antidiabetic drugs) to select
311 anti-diabetic drugs from prescription records, and classified these according to ATC classification
312 (A10B).

313 More details can be found in **Supplementary Information** (refers also to subsequent
314 **Methods** sections)**.**

315 ***Criteria for Inclusion and Exclusion of Participants***

316 Only participants with clinical data and prescription data were included in the study.
317 Individuals that died of accidental causes or self-inflicted deaths (ICD10 codes starting with O, Q,
318 S, T, V, W, Y, X) were excluded from the analysis (**Fig 1a**). Characteristics of all individuals
319 included into the analyses can be found in **Table 1**. T2Ds had at least one ICD10 diagnosis
320 starting with E11; nonT2Ds were selected by the absence of such diagnoses, and also by the
321 absence of type 1 diabetes (ICD10 code E10).

322 ***Observation Time, Length of Exposure, and End Points***

The individuals were followed from recruitment (2006-2010) until censoring time (March 20th, 2021), for a median of 12.02 years. The primary endpoint was death from any cause, except self-inflicted death and death by accidents. No secondary endpoints were considered.

Nearest Neighbour Covariate Matching (NNCM) Strategy

T2D-diagnosed subjects prescribed the drug of interest were individually matched either with T2D subjects not prescribed that drug (T2Ds with drug vs. T2Ds without drug), or with nonT2Ds (T2Ds with drug vs nonT2Ds without drug). In the latter case, T2D diagnosis by definition was used as a sorting variable.

Each individual of the T2D with drug cohort was paired to the most similar individual of the T2D without drug or non-T2D-diagnosed cohort with an unsupervised nearest neighbours algorithm matching on covariate distances (**Fig S5** and **Supplementary Information**) [29-31].

A Cox proportional hazard multivariate model was used to determine within each cohort comparison the covariates contributing mostly to the observed mortality (having log(HR) > 0.05 or log(HR) < -0.05), hereafter referred to as priority-matched covariates (**Fig S5**), which were given a greater matching weight by the algorithm.

Survival analyses: General Remarks

Censoring time was independent of the event time for all individuals, and there were no known dependent competing risks, therefore survival analysis was carried out with Kaplan-Meier survival estimates and Cox proportional hazard models. Age at recruitment, sex, genetic principal components 1-20 (as proxy for population ethnic diversity), lifestyle factors (BMI, smoking, alcohol intake, physical exercise, Townsend deprivation index, sleep duration), comorbidities

(fractured/broken bones, cancer, cardiovascular disease, blood clots, deep vein thrombosis [DVT], bronchitis, emphysema, other serious medical condition), and use of diabetic drugs, were exogenous variables for Cox proportional hazard model. Of note, Cox analysis, by definition, included correction for antidiabetic drugs used by T2Ds. Detailed survival analyses for the observational cohort and NNCM can be found in **Supplementary Information**.

Cause of Death Analysis

Primary causes of death in ICD-10 notation were available from death records of the UK Biobank (data field 40001) and annotated into main disease chapters according to ICD-10 (version 2019, icd.who.int/browse10/2019/en). Deviations from the proportion of expected versus observed deaths of a certain cause within the case-control cohorts were calculated with a chi-squared test.

Code Availability

All the Analyses, Figures and Tables were created with Python3.7 and supporting libraries. Custom code for the analyses will be made available upon publication at *https://github.com/araldi/Anti-diabetics-and-survival-in-UKBB*.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Footnotes

Contributors

EA and MR designed the study. EA conducted the statistical analysis. EA and MR wrote the first draft. EA, CRJ, and MR critically revised the manuscript. MR is the guarantor of the manuscript and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethics approval

UK Biobank has obtained ethics approval from the North West Multi-Centre Research Ethics Committee (approval number: 11/NW/0382) and has obtained informed consent from all participants.

Transparency statement

The manuscript's guarantor (MR) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish government, and Northwest Regional Development Agency; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

No additional data available.

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Legends to Figures

Fig 1: Cohort structure and unmatched survival probabilities depending on diagnosis of type 2 diabetes and anti-diabetic drug classes used

a, Flowchart for inclusion/exclusion criteria in the UK Biobank cohort. Type 2 diabetes (T2D) diagnoses and anti-diabetic medication prescriptions were retrieved from general practice (GP) clinical records and primary care datasets in National Health Service (NHS) records. T2D diagnoses have ICD10 code starting with E11. Anti-diabetic medications were selected from brand name and compounds classified in British National Formulary as anti-diabetic, class 6.1.1 (insulins) and class 6.1.2 (anti-diabetic drugs). **b,** Kaplan-Meier curve of survival probability of individuals diagnosed with T2D (T2Ds) or not T2D-diagnosed controls (nonT2Ds). P value obtained from log-rank test. **c,** Forest plot of Cox proportional hazard multivariable modelling on overall survival. Shown are the natural logarithm of the hazard ratio (HR) and bars represent 95% confidence interval of anti-diabetic drug classes used.

Fig 2: Survival probabilities and causes of death of individuals with type 2 diabetes using a specific drug class compared to NNC-matched individuals with type 2 diabetes using any other drug class

a, Kaplan-Meier curves of survival probabilities of individuals diagnosed with T2D and either using specific anti-diabetic drug classes (cyan) or matched individuals not prescribed the specific drug class (pink), P values shown are calculated with log-rank test. **b,** Forest plot of Cox proportional hazard multivariable modelling on overall survival in individuals diagnosed with T2D and prescribed the specific drug class, and matched individuals diagnosed with T2D but not

prescribed the specific drug class. Shown is the hazard ratio (HR) and bars represent 95% confidence intervals of each anti-diabetic drug class.

Fig 3: Survival probabilities and causes of death of individuals with type 2 diabetes using a specific drug class compared to NNC-matched individuals without diagnosis of type 2 diabetes

a, Kaplan-Meier curves of survival probabilities of individuals diagnosed with T2D using specific anti-diabetic drug classes (cyan) or matched individuals not diagnosed with T2D (black). P values shown are calculated with log-rank test. **b,** Forest plot of Cox proportional hazard multivariable modelling on overall survival in individuals diagnosed with T2D and prescribed the specific drug class, and matched individuals not diagnosed with T2D. Shown is the hazard ratio (HR) and bars represent 95% confidence interval of each anti-diabetic drug class.

Fig 4: Subgroup analysis of DPP4I or SGLT2I combined with metformin with either metformin alone or matched nonT2Ds

a, Kaplan-Meier survival probability (left) and Cox proportional hazard multivariable modelling (right) of the reference group of individuals diagnosed with T2D using DPP4I and metformin (gold), NNC-matched individuals using metformin only (purple), and NNC-matched individuals without T2D diagnoses (black). Shown for Cox proportional hazard model is the hazard ratio (HR) and bars represent 95% confidence interval of each anti-diabetic drug class. **b,** Kaplan-Meier survival probability (left) and Cox proportional hazard multivariable modelling (right) of the reference group of individuals diagnosed with T2D using SGLT2I and metformin (gold), NNC-matched individuals using metformin only (purple), and NNC-matched individuals without T2D diagnoses (black). Shown for Cox proportional hazard model is the hazard ratio (HR) and bars represent 95% confidence interval of each anti-diabetic drug class.

Supplementary Figures

Supplementary Fig 1. a, Causes of death divided by ICD10 chapters for deceased individuals in the UK Biobank with (T2Ds) or without (Not T2Ds) T2D diagnoses. Deaths by accident or self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from analysis. P values obtained by chi-squared contingency test. **b,** Most frequent causes of death in the whole dataset divided by ICD10 subchapters for deceased individuals in the UK Biobank with (T2Ds) or without (Not T2Ds) T2D diagnoses. Deaths by accident or self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from analysis. P values obtained by chi-squared contingency test.

Supplementary Fig 2. a-b, Percentage (and number) of individuals diagnosed with T2D and using a combinations of anti-diabetic drug classes (a) and percentage (and number) of deaths within each drug regimen (b).
c-d, Percentage (and number) of individuals diagnosed with T2D and using a specific anti-diabetic drug class (c) and percentage (and number) of deaths within users of a specific compound class (d).
e, Number of T2D-diagnosed individuals in the UK Biobank using anti-diabetic compounds. Prescriptions for brand name compounds are included in the counts of the corresponding generic compound.
f-g, Percentage (and number) of users of anti-diabetic drug classes used as the only anti-diabetic medications in UK Biobank individuals (f) and corresponding death rates (and number of deaths) (g).
h, Individuals using anti-diabetic drugs and not diagnosed with type 2 diabetes (ICD10 code E11). These individuals were excluded from all the analyses.

582 **Supplementary Fig 3.** Kaplan-Meier curves of survival probability of T2Ds either using a
583 specific anti-diabetic drug class (blue) or not using this drug class (red), and nonT2Ds (black). P
584 values shown are for each comparison calculated with log-rank test.
585
586 **Supplementary Fig 4. a,** Age at first use of anti-diabetic compounds classes. Mean is
587 represented by black dashed line, standard deviation by grey dashed line. Each bar represents
588 an interval of 5 years. Data obtained from NHS prescription data was cross-referenced with UK
589 Biobank recruitment data.
590 **b,** Length of use of anti-diabetic compounds classes at the event (death or censoring). Mean is
591 represented by black dashed line, standard deviation by grey dashed line. Each bar represents
592 an interval of 2 years. Data obtained from NHS prescription data cross-referenced with UK
593 Biobank recruitment data.
594
595 **Supplementary Fig 5. a,** Cox proportional hazard multivariate modelling of survival in T2D-
596 diagnosed individuals. Vertical fine dashed lines represent respectively log(HR) of -0.05 and of
597 0.05. Orange-coloured variables are responsible for a significant absolute change in log(HR)
598 greater than 0.05, therefore identified as priority-matched covariates for this cohort. **b,** Strategy
599 to match T2D-diagnosed individuals prescribed the drug of interest with control T2D-diagnosed
600 individuals prescribed other drugs. The priority-matched covariates were identified from Panel
601 A.
602 **c,** Cox proportional hazard multivariate modelling of survival in non T2D-diagnosed individuals
603 and T2D-diagnosed individuals. Vertical fine dashed lines represent respectively log(HR) of -
604 0.05 and of 0.05. Blue-coloured variables are responsible for a significant change in log(HR)
605 greater than 0.05, therefore identified as priority-matched covariates for this cohort. **d,** Strategy
606 to match T2D-diagnosed individuals prescribed the drug of interest with control not T2D-

607 diagnosed individuals.The priority-matched covariates were identified from Panel C. **e-f,**
608 Formulae of distance matrices for continuous (e) or binary (f) priority-matched covariates.
609
610 **Supplementary Fig 6:** Accuracy of Nearest Neighbour Covariate Matching (NNCM) of T2D-
611 diagnosed individuals treated with the drug of interest matched with control T2D-diagnosed
612 individuals using other drugs or none. Matched variables: age at recruitment [years], and age at
613 first drug use [years]. Other characteristics calculated from matched variables: Length of drug
614 use [years] and years between recruitment and first drug use.
615
616 **Supplementary Fig 7. a,** Causes of death divided by ICD10 chapters for T2D-diagnosed
617 individuals prescribed metformin, DPP4I, SGLT2I (all blue) and matched T2D-diagnosed
618 individuals prescribed other drugs (red). Data are represented as proportion of deaths within
619 each cohort. Deaths by accident or self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were
620 excluded from analysis. P values obtained by chi-squared contingency test.
621 **b,** Causes of death divided by ICD10 chapters for T2D-diagnosed individuals prescribed
622 sulfonylureas, long/intermediate-acting insulins, GLP1R agonists, short-acting insulins,
623 thiazolidinediones (all blue) and matched T2D-diagnosed individuals prescribed other drugs
624 (red). Data are represented as proportion of deaths within each cohort. Deaths by accident or
625 self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from analysis. P values
626 obtained by chi-squared contingency test.
627 **c,** Most frequent causes of death by ICD10 subchapters for T2D-diagnosed individuals
628 prescribed metformin, DPP4I, SGLT2I (all blue) and matched T2D-diagnosed individuals
629 prescribed other drugs (red). Data are represented as proportion of deaths within each cohort.
630 Deaths by accident or self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from
631 analysis. P values obtained by chi-squared contingency test.

d, Most frequent causes of death by ICD10 subchapters for T2D-diagnosed individuals prescribed sulfonylureas, long/intermediate-acting insulins, GLP1R agonists, short-acting insulins, thiazolidinediones (all blue) and matched T2D-diagnosed individuals prescribed other drugs (red). Data are represented as proportion of deaths within each cohort. Deaths by accident or self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from analysis. P values obtained by chi-squared contingency test.

Supplementary Fig 8. a, Causes of death divided by ICD10 chapters for T2D-diagnosed individuals prescribed metformin, DPP4I, SGLT2I (all blue) and for matched not T2D-diagnosed individuals (black). Data are represented as proportion of deaths within each cohort. Deaths by accident or self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from analysis. P values obtained by chi-squared contingency test.

b, Causes of death divided by ICD10 chapters for T2D-diagnosed individuals prescribed sulfonylureas, long/intermediate-acting insulins, GLP1R agonists, short-acting insulins, thiazolidinediones (all blue) and for matched not T2D-diagnosed individuals (black). Data are represented as proportion of deaths within each cohort. Deaths by accident or self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from analysis. P values obtained by chi-squared contingency test.

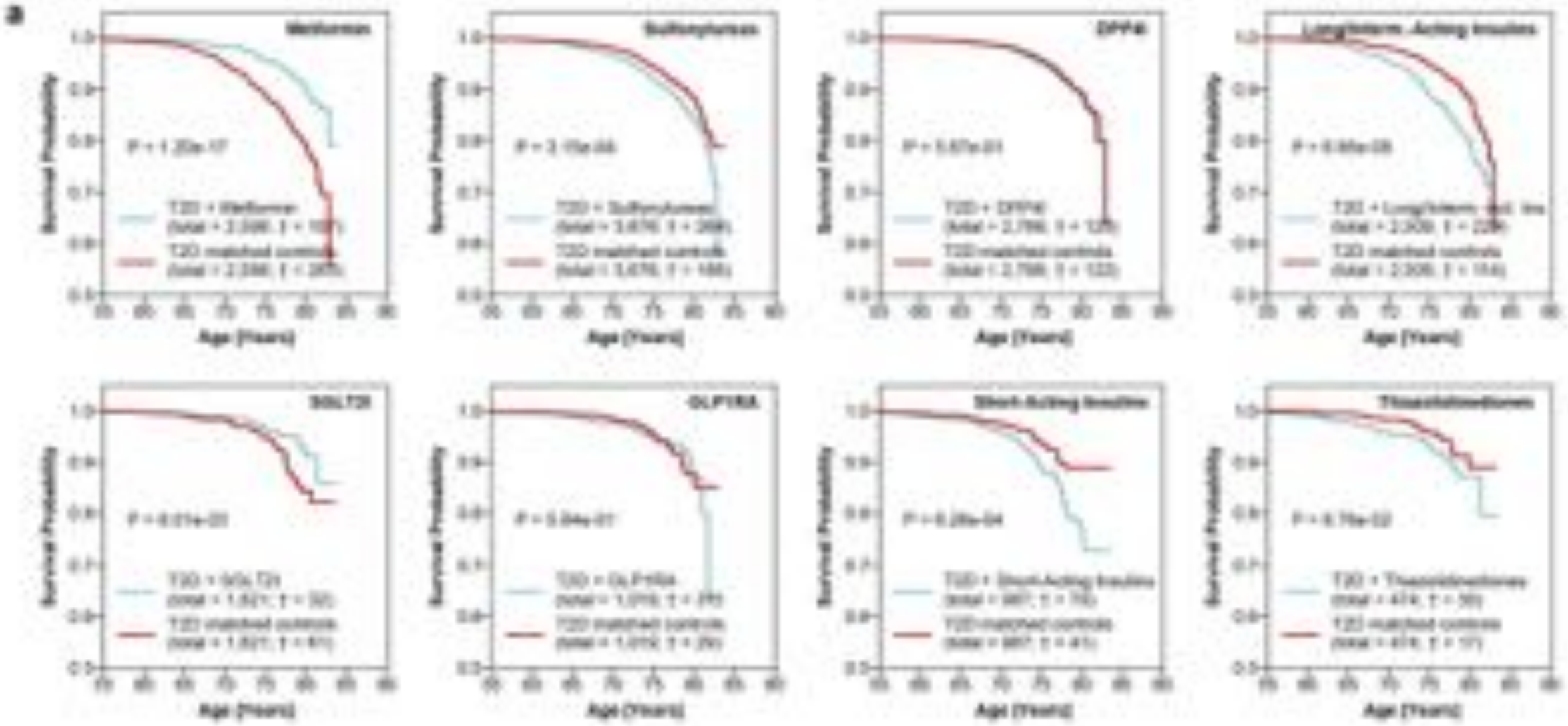
c, Most frequent causes of death by ICD10 subchapters for T2D-diagnosed individuals prescribed metformin, DPP4I, SGLT2I (all blue) and for matched not T2D-diagnosed individuals (black). Data are represented as proportion of deaths within each cohort. Deaths by accident or self-inflicted (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from analysis. P values obtained by chi-squared contingency test.

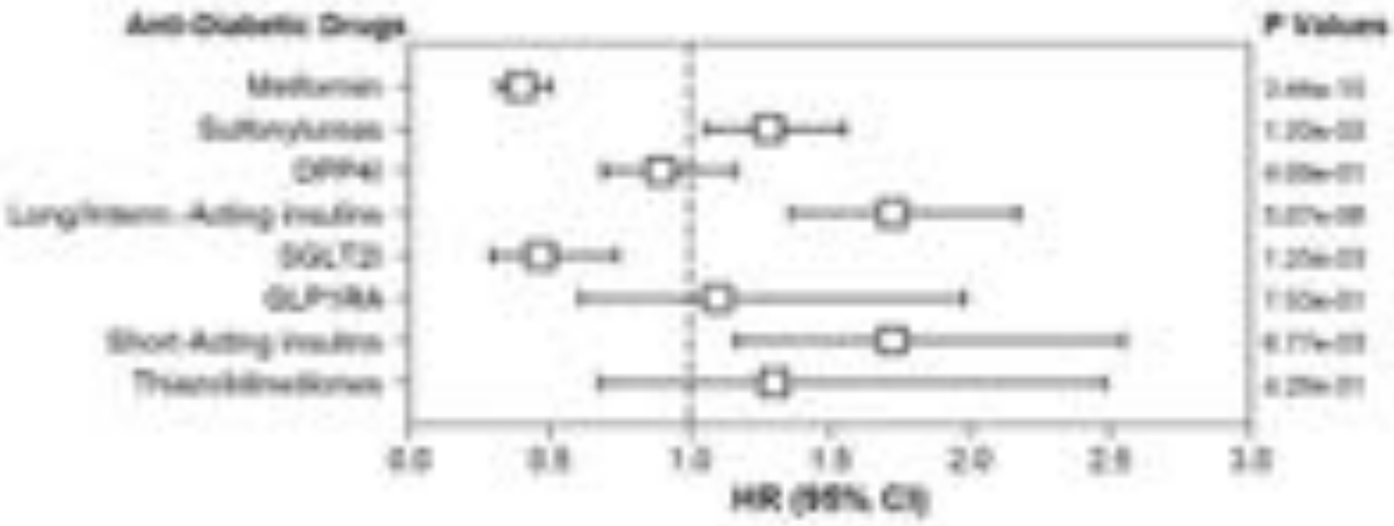
d, Most frequent causes of death by ICD10 subchapters for T2D-diagnosed individuals prescribed sulfonylureas, long/intermediate-acting insulins, GLP1R agonists, short-acting insulins, thiazolidinediones (all blue) and matched not T2D-diagnosed individuals (black). Data

658 are represented as proportion of deaths within each cohort. Deaths by accident or self-inflicted
659 (ICD10 codes O, Q, S, T, V, W, X, Y) were excluded from analysis. P values obtained by chi-
660 squared contingency test.

Figure 1

Figure 2





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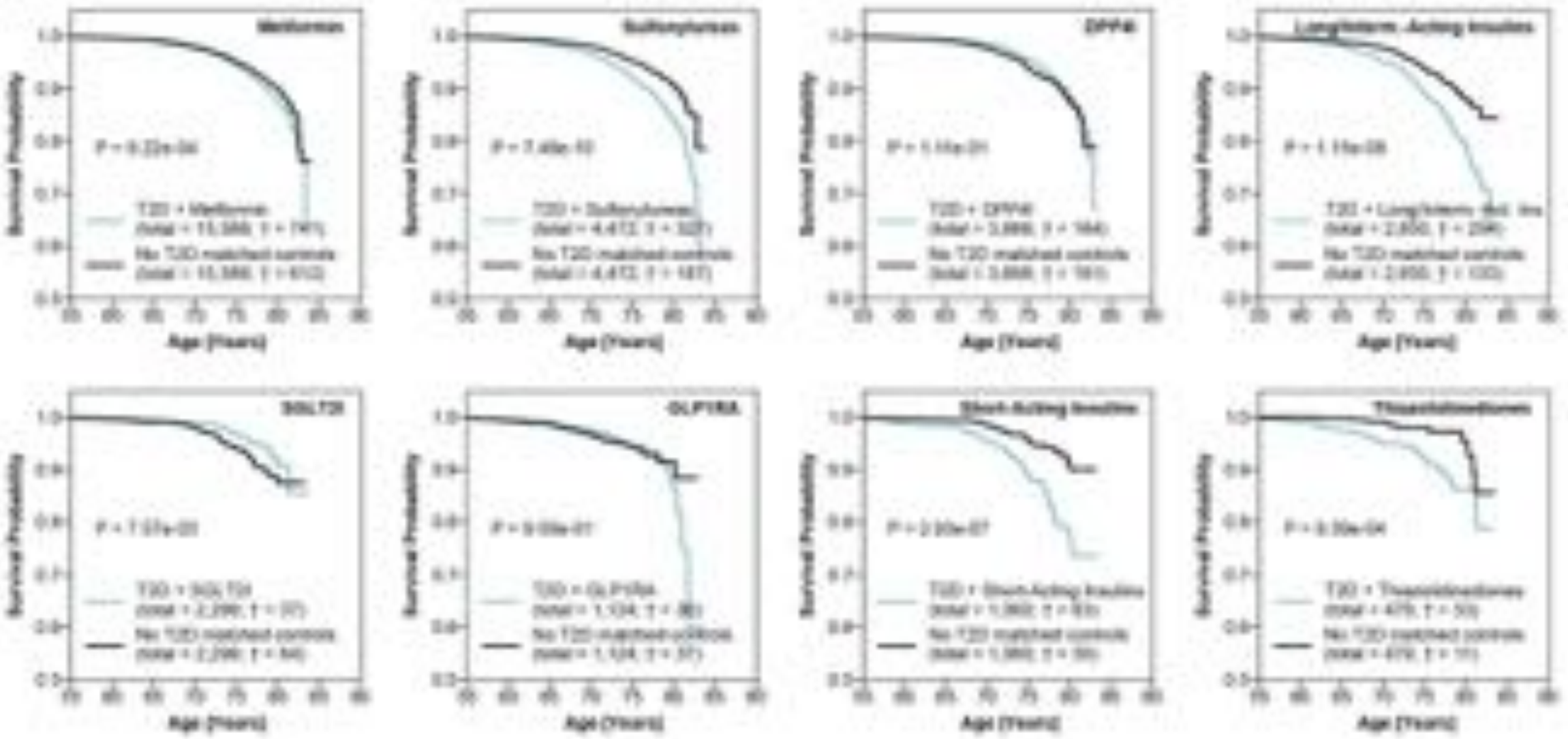


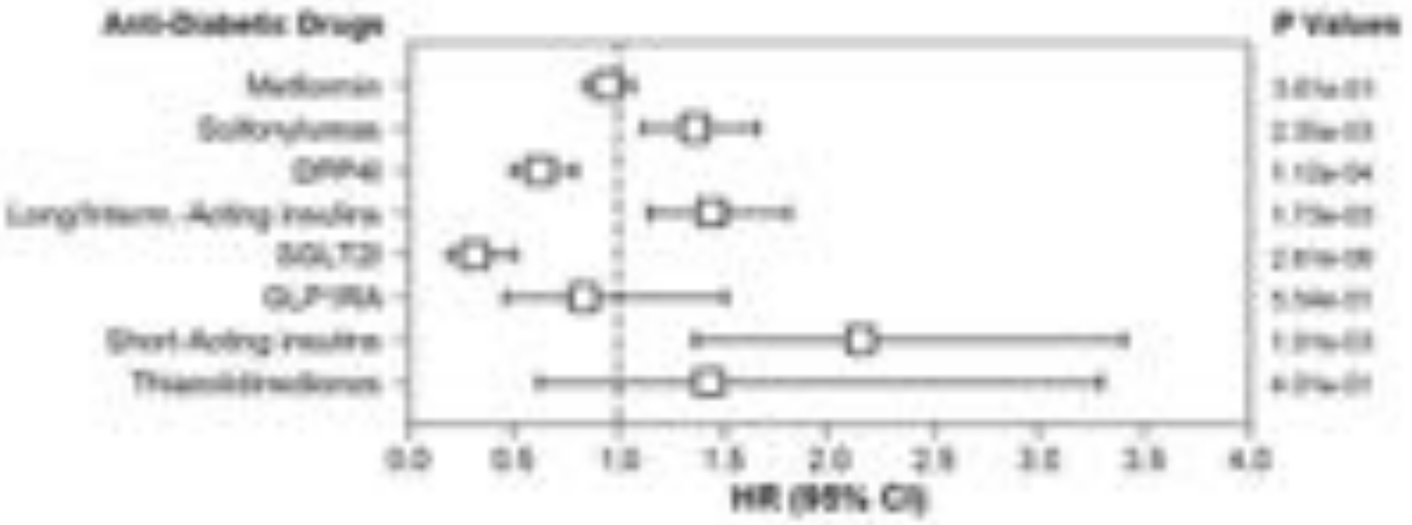
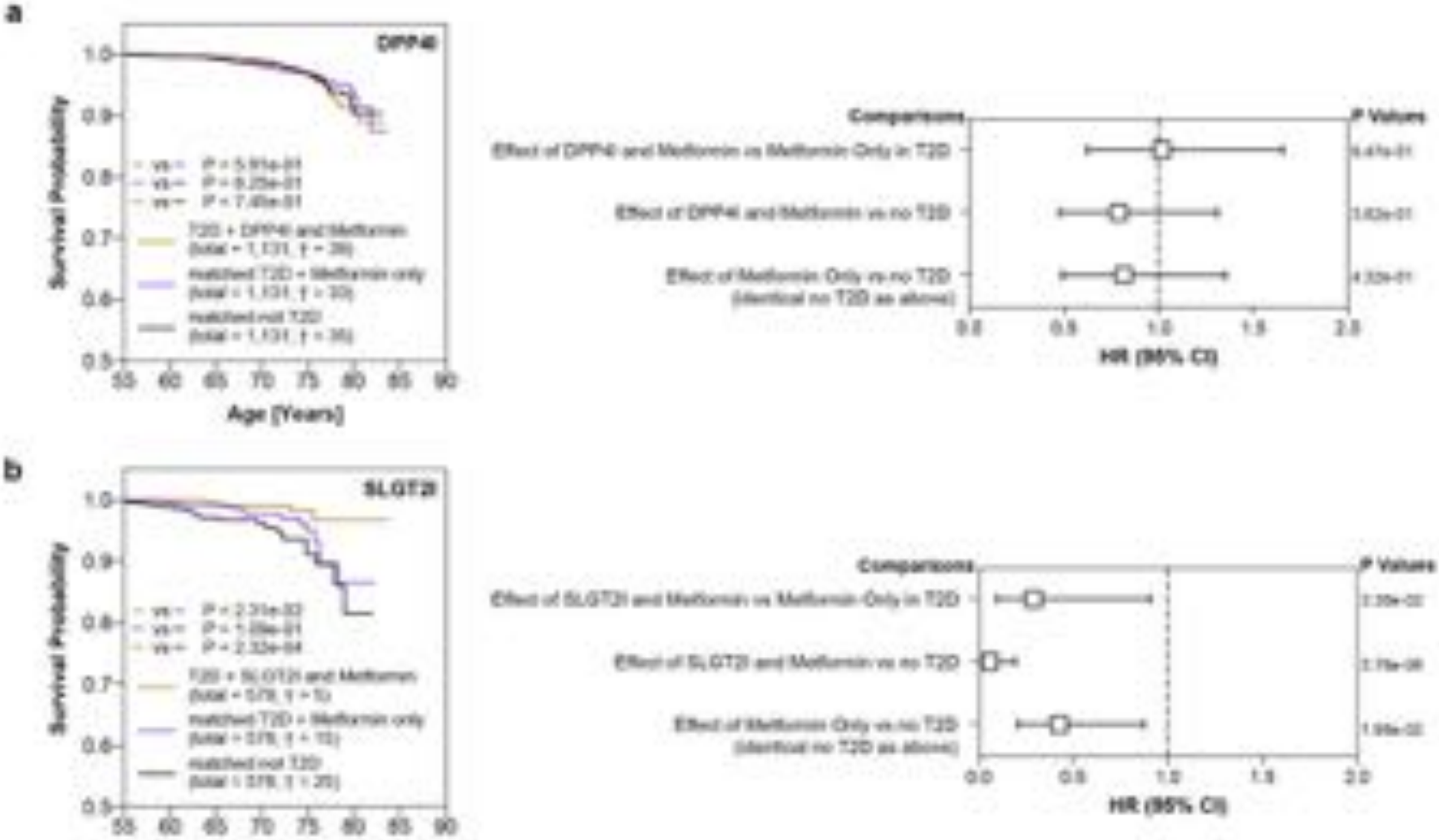


Figure 4



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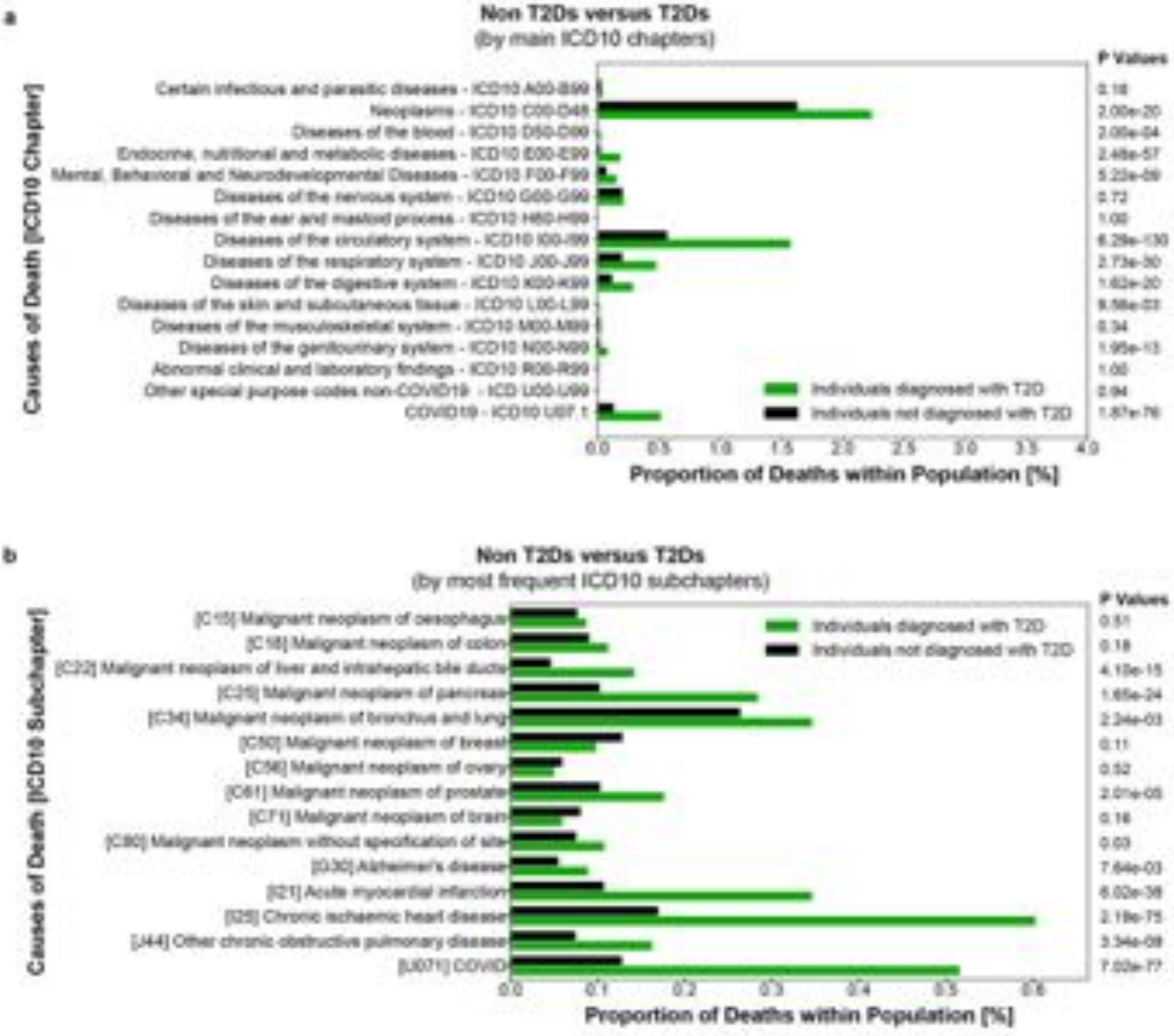
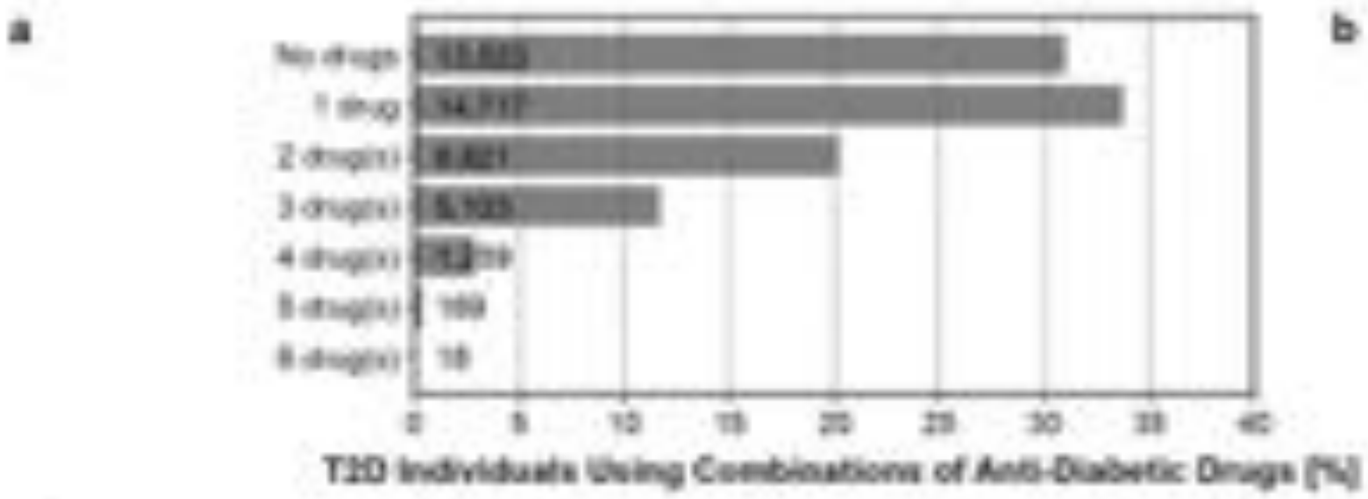
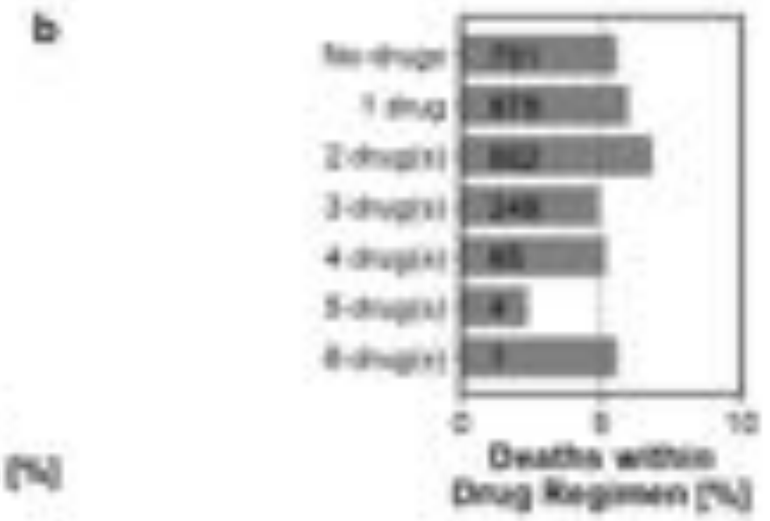
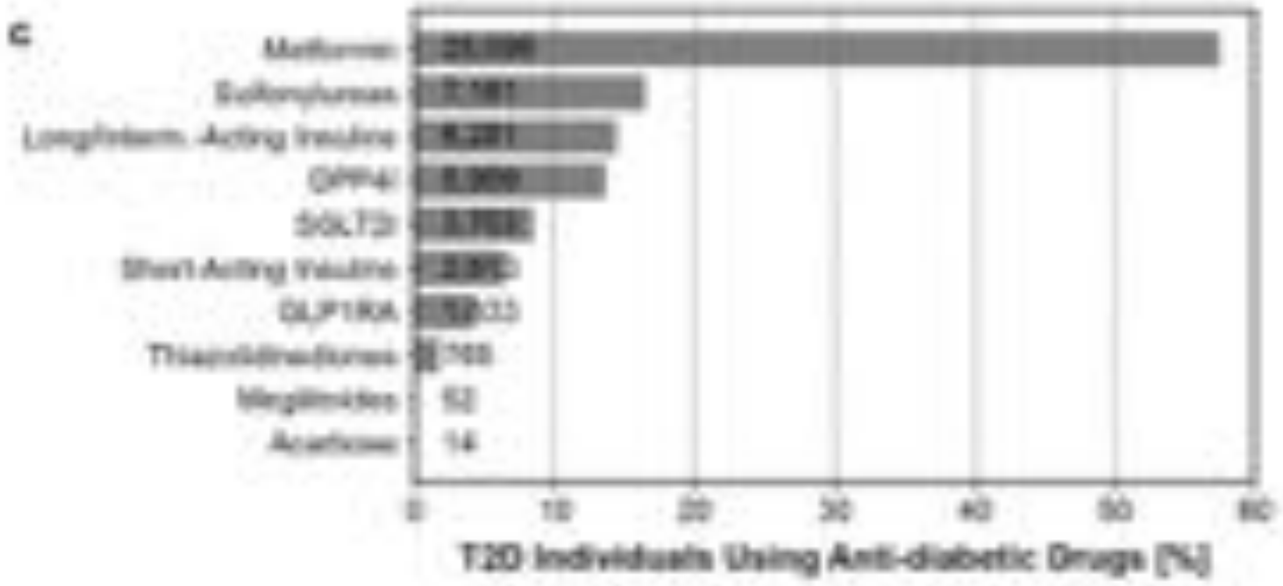
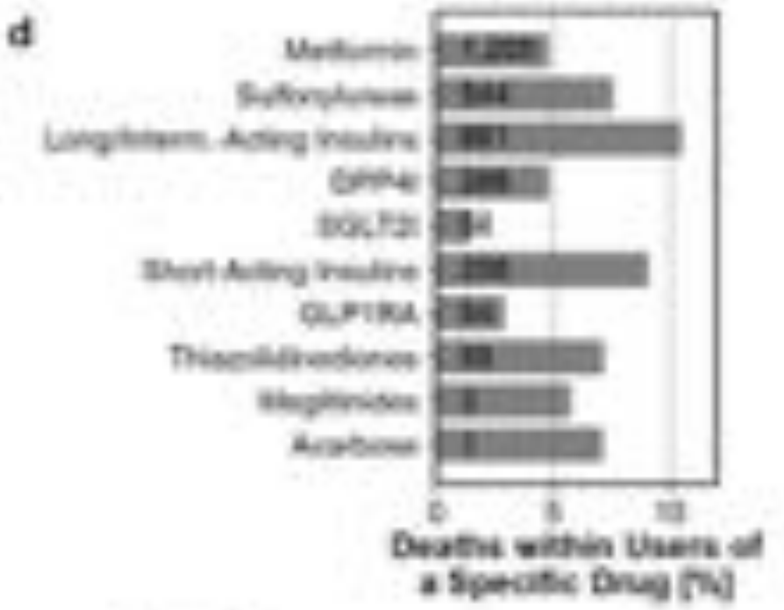


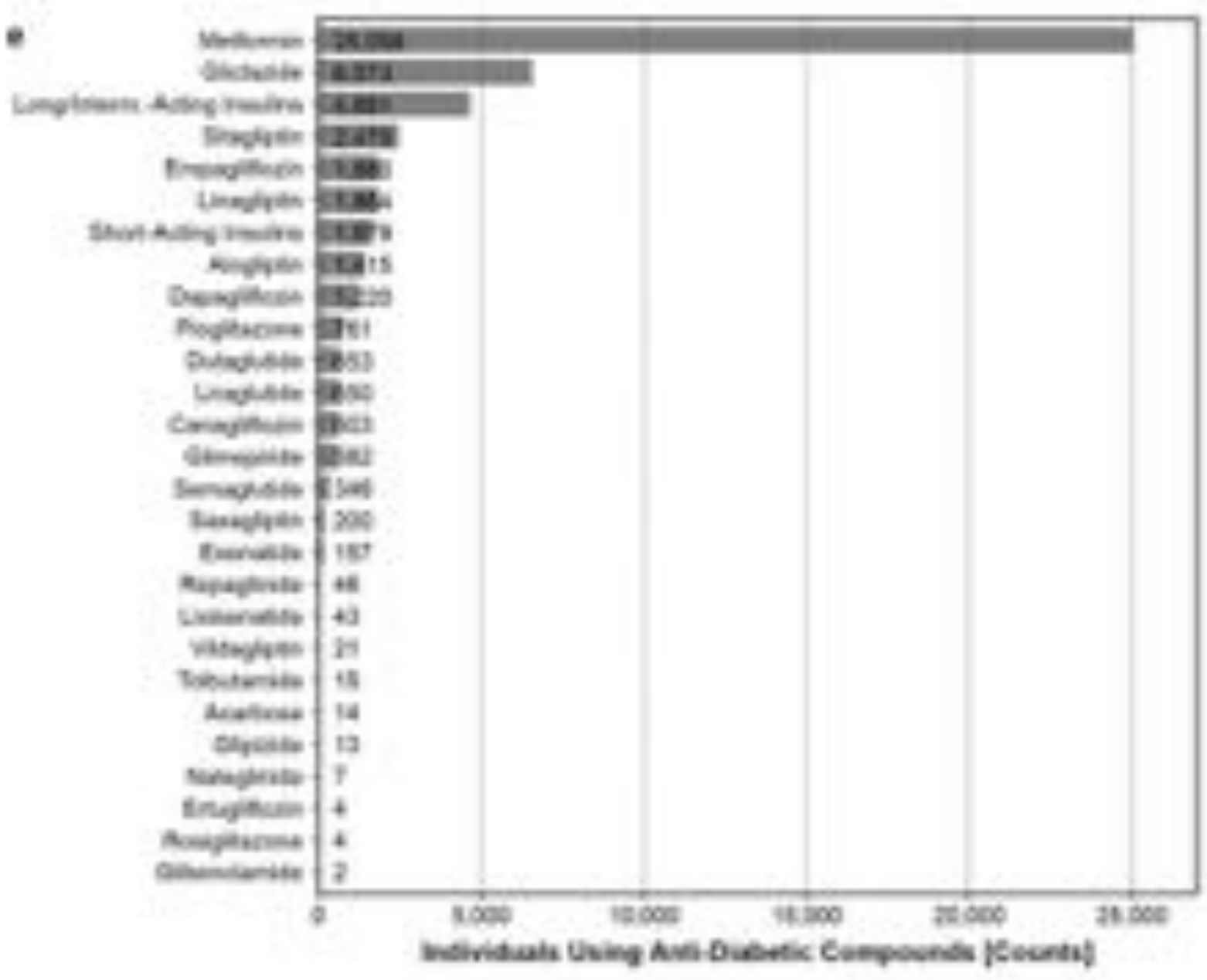
Figure S2

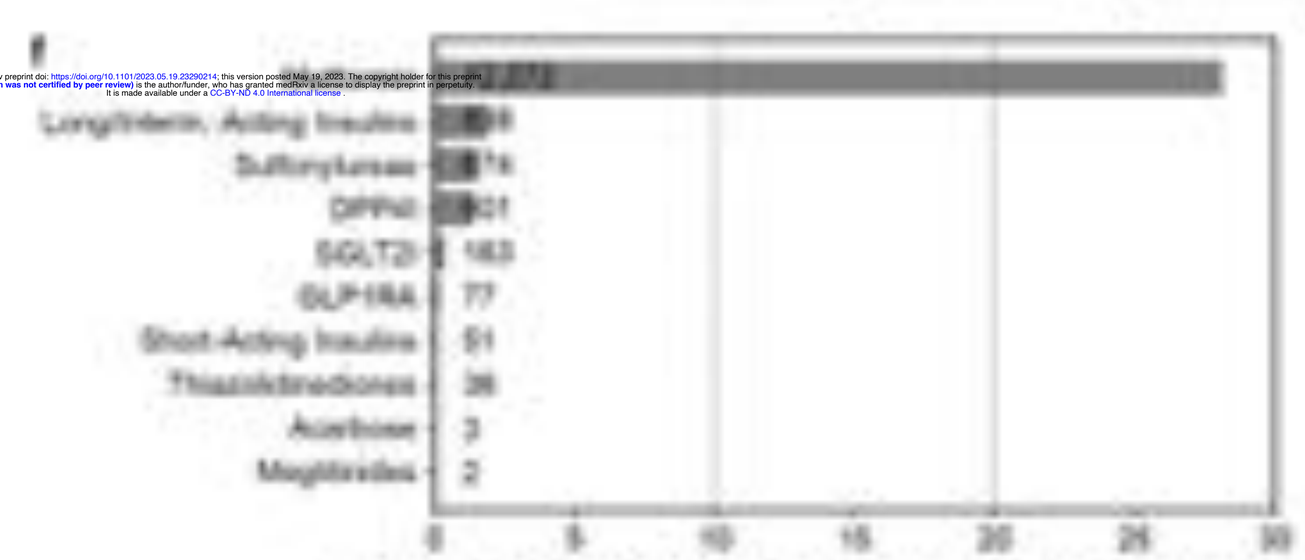












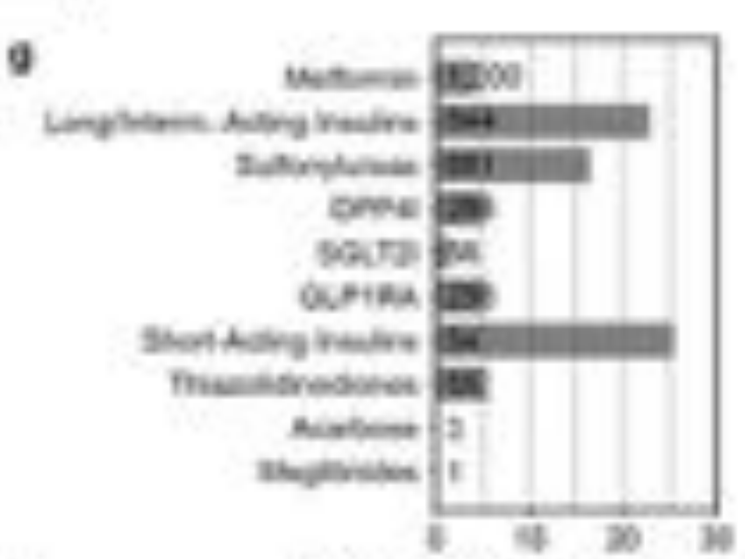


Figure S2 (continued)

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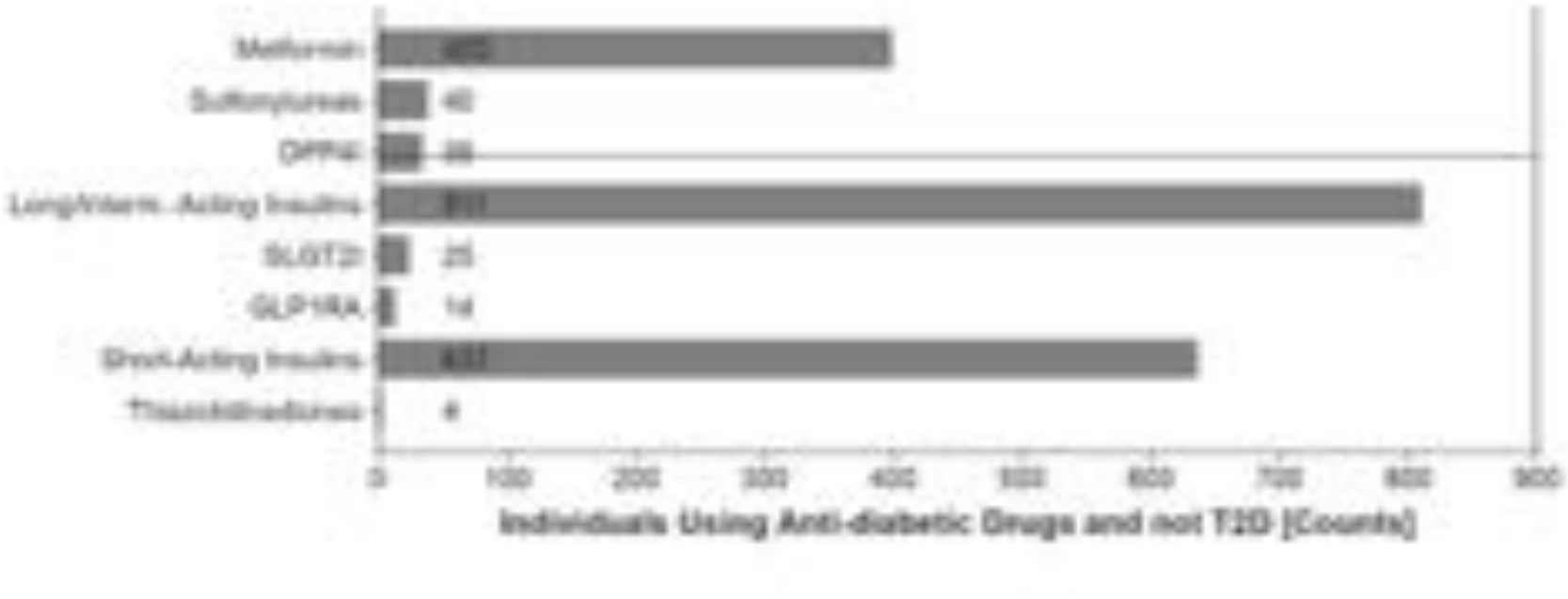

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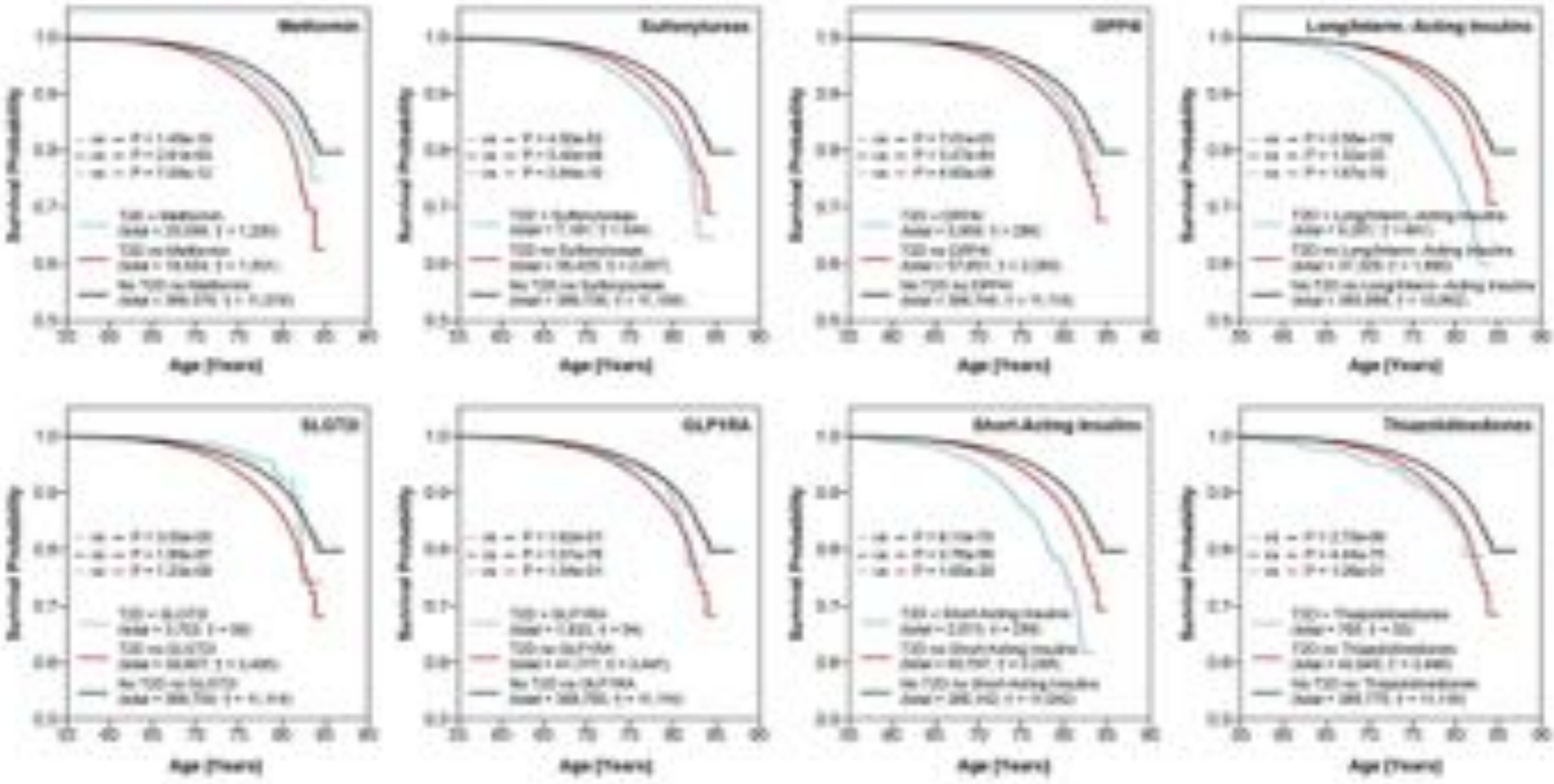

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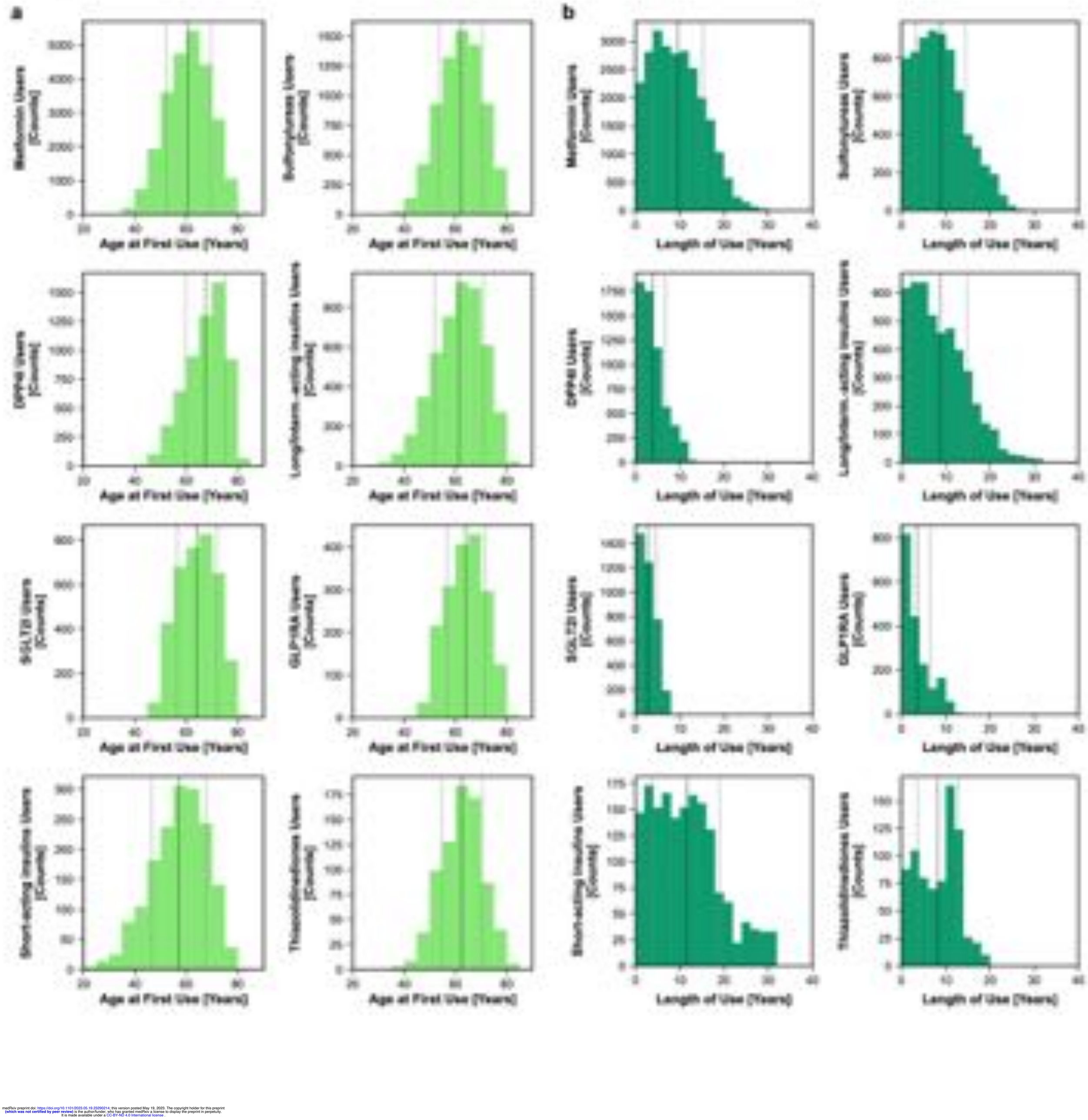
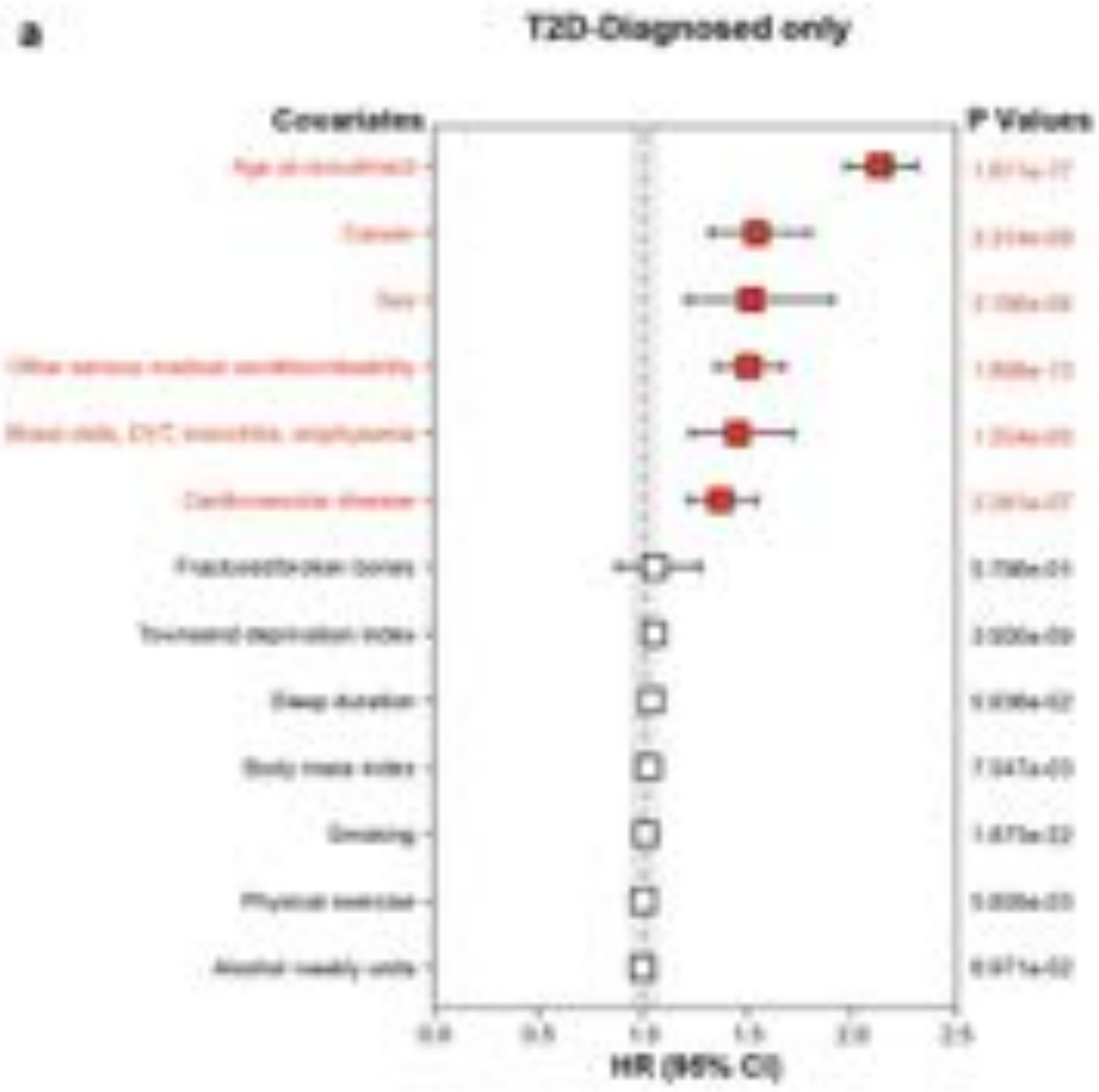
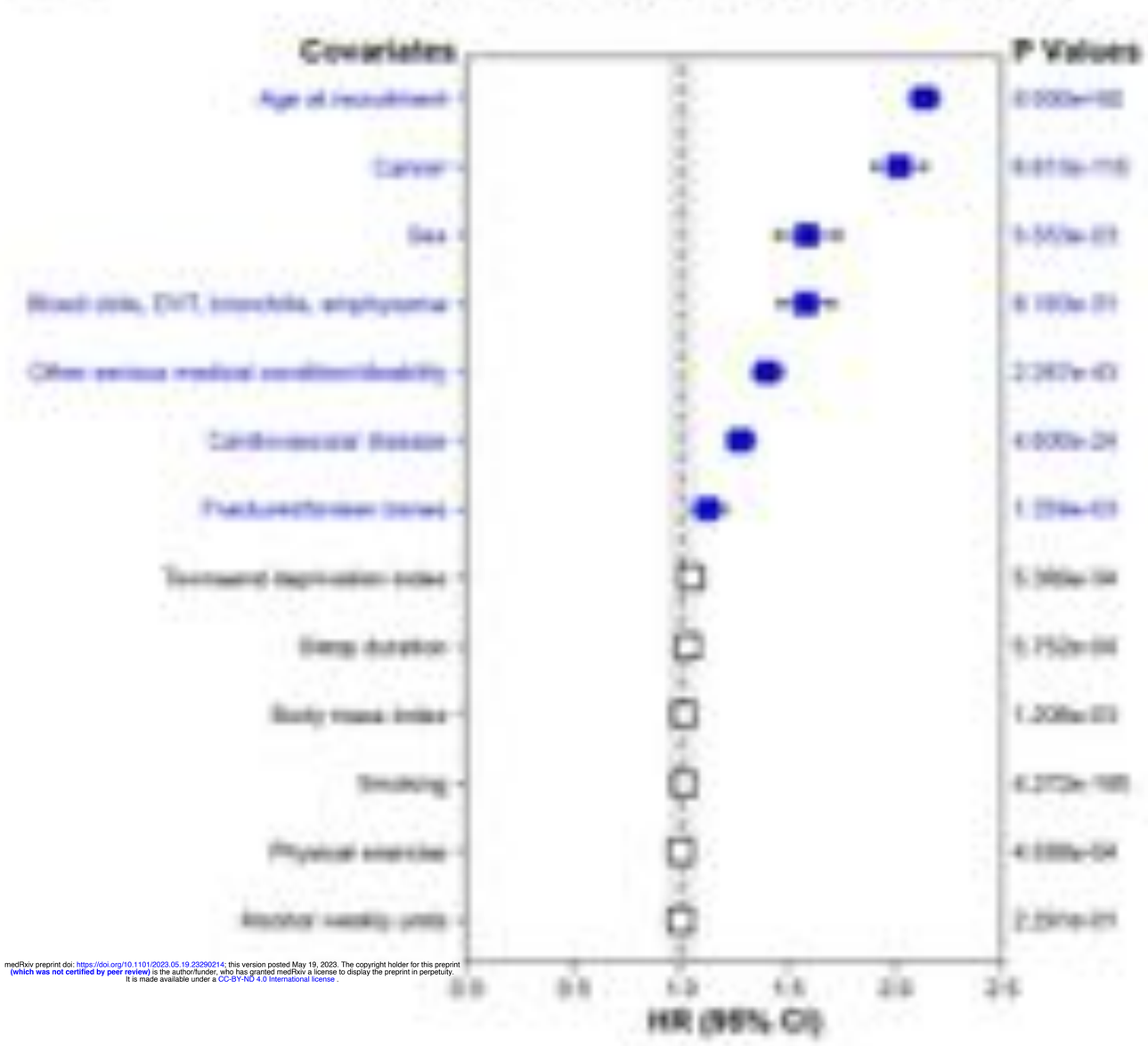


Figure S5





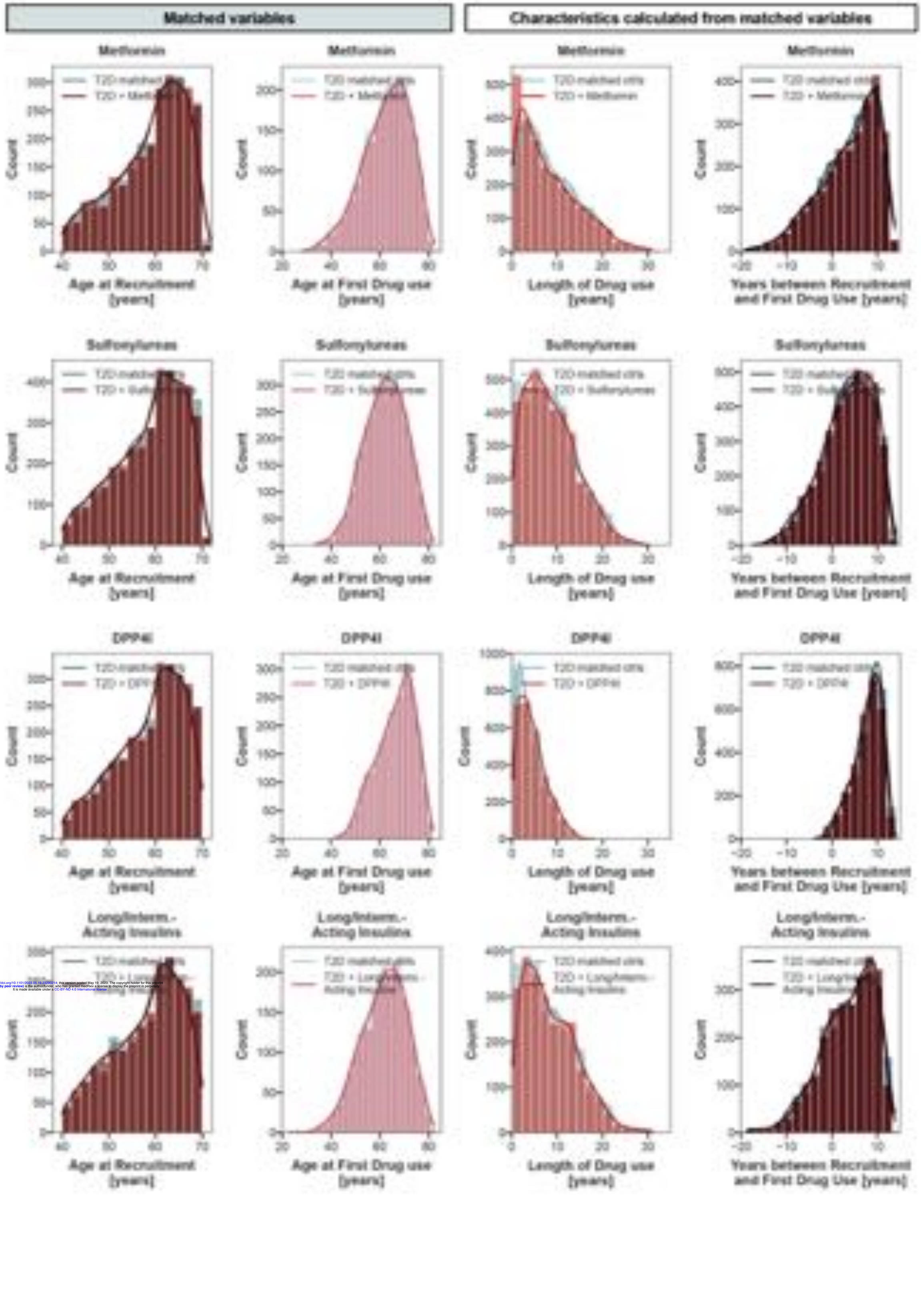
e **Distance Metrics for Priority-Matched Quantitative Covariates**
(e.g. Age at recruitment)

$$e^{\frac{(x_{control} - x_{case})^2}{0.1^2}} - 1$$

f **Distance Metrics for Priority-Matched Binary Covariates**
(e.g. Comorbidities at Recruitment)

$$e^{\sum_{i=1}^{n} |x_{i,control} - x_{i,case}|} - 1$$

Figure S6



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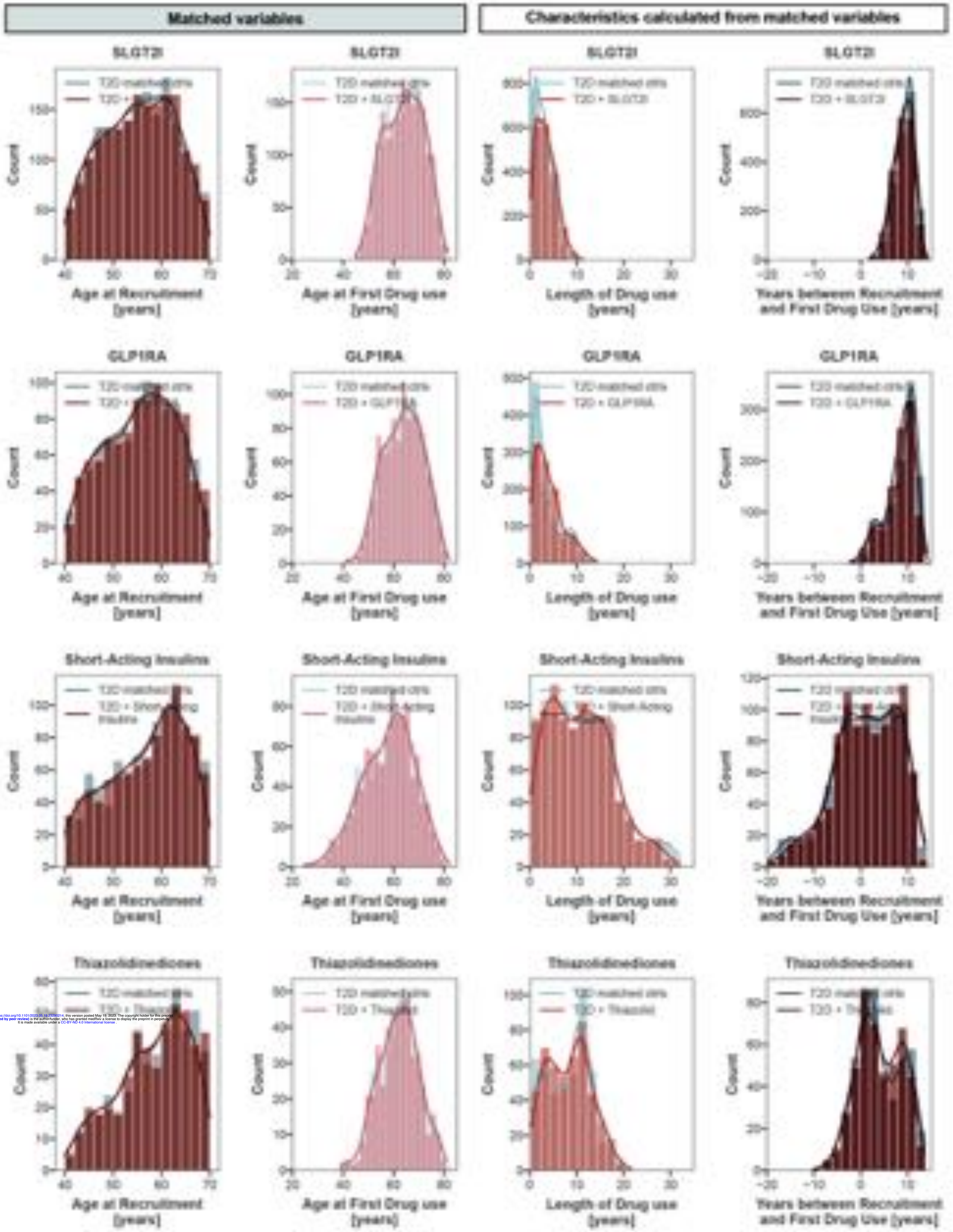

Figure S7

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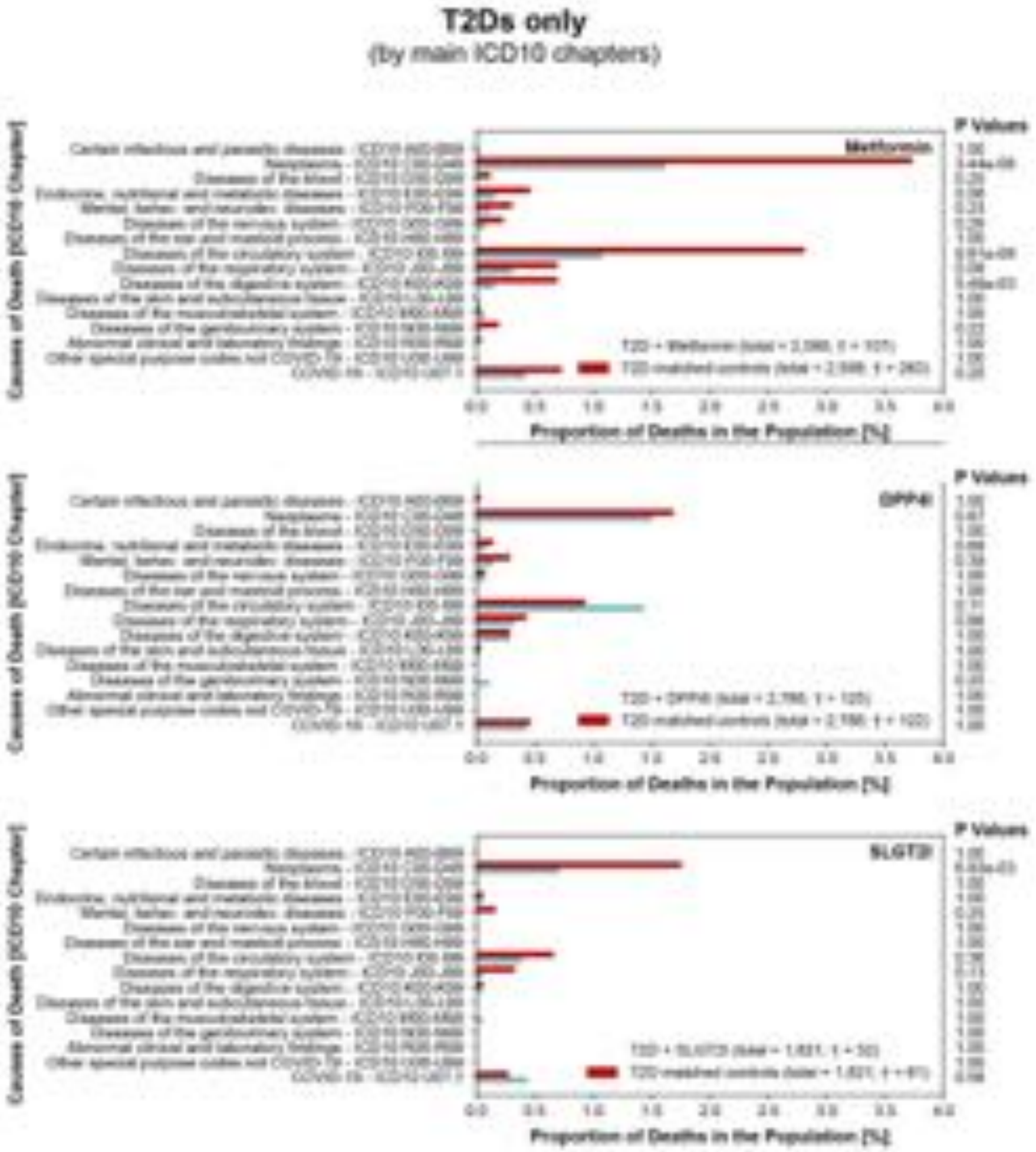

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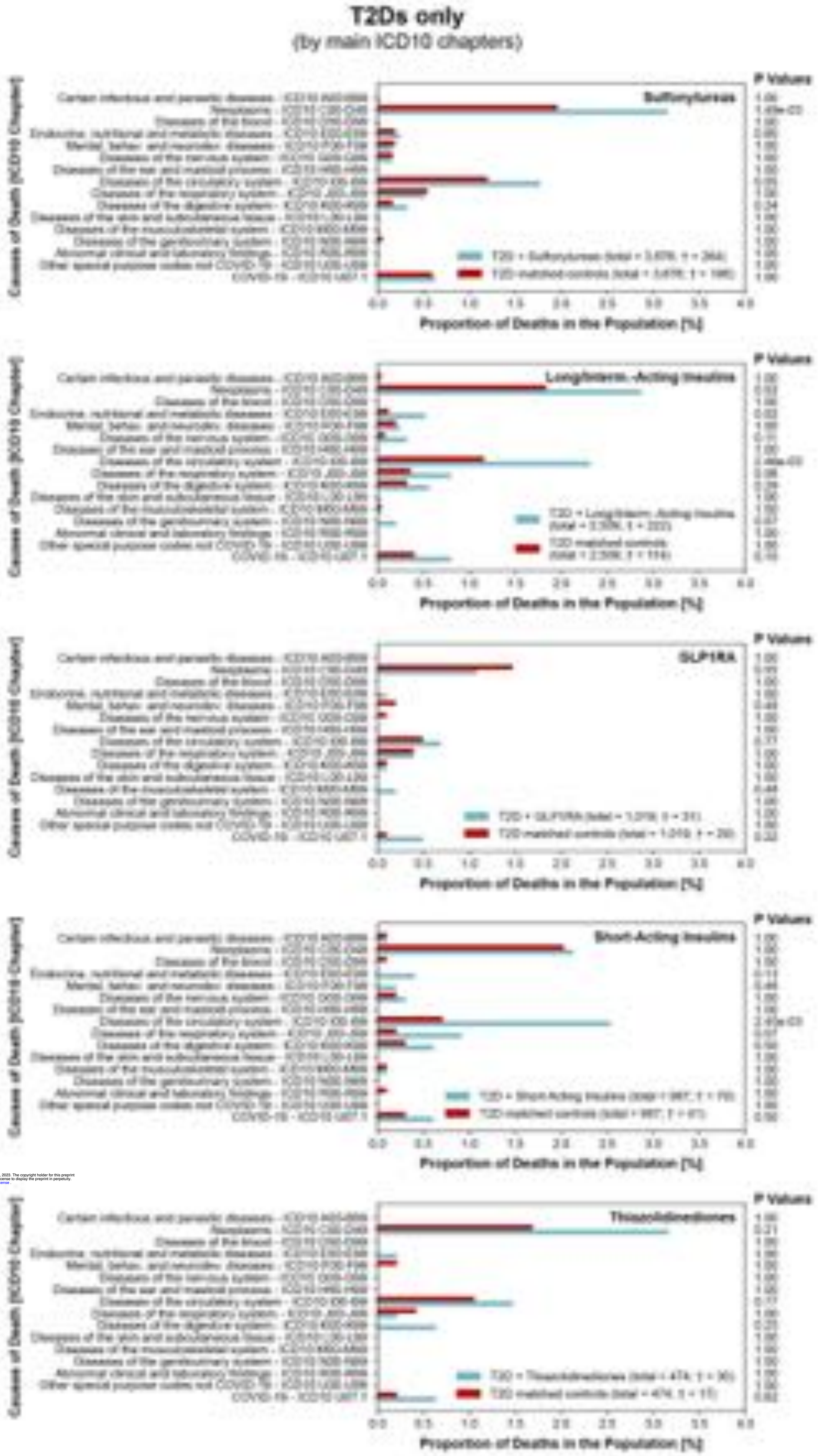

Figure S7 (continued)

c

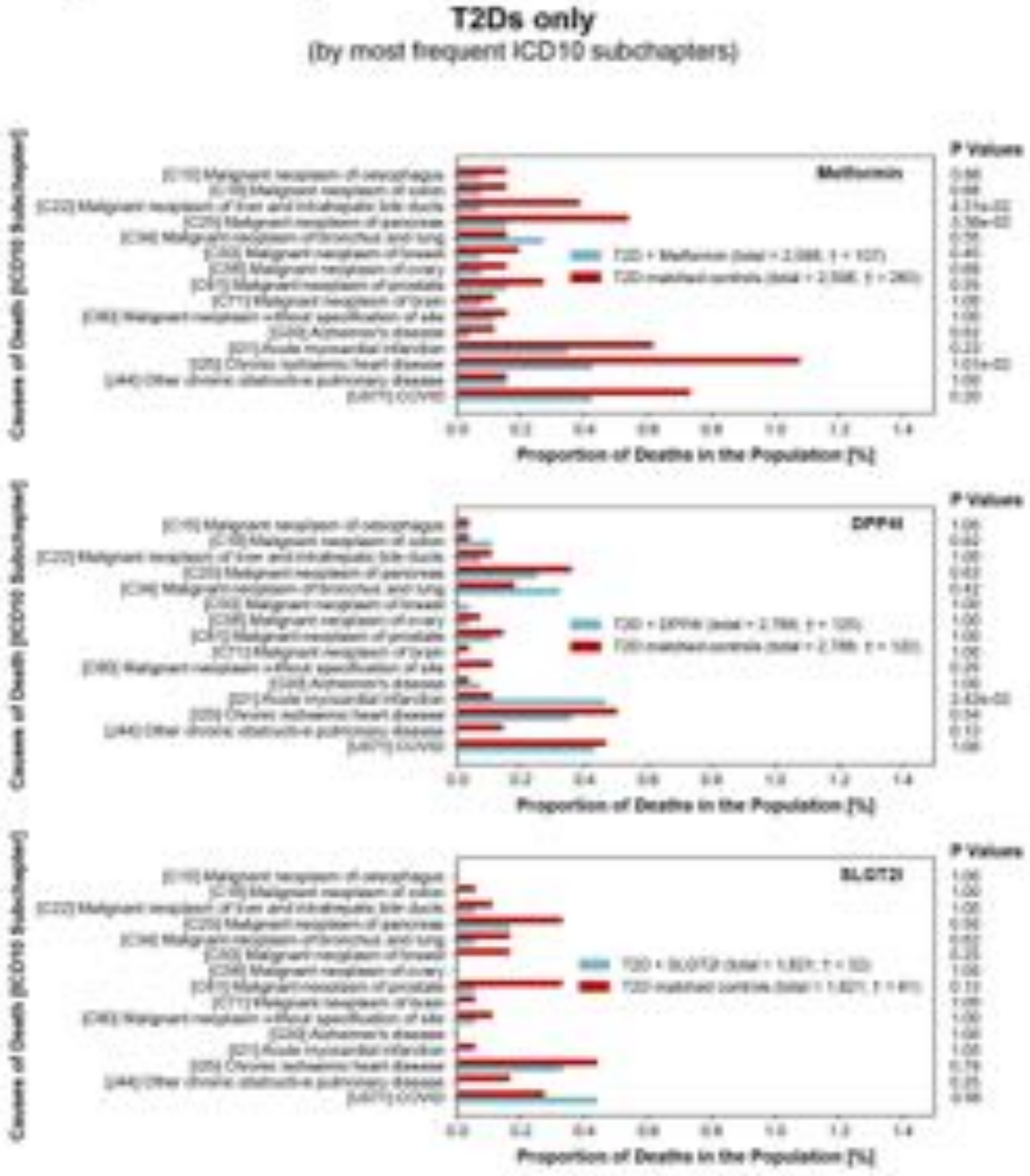

Figure S7 (continued)

d

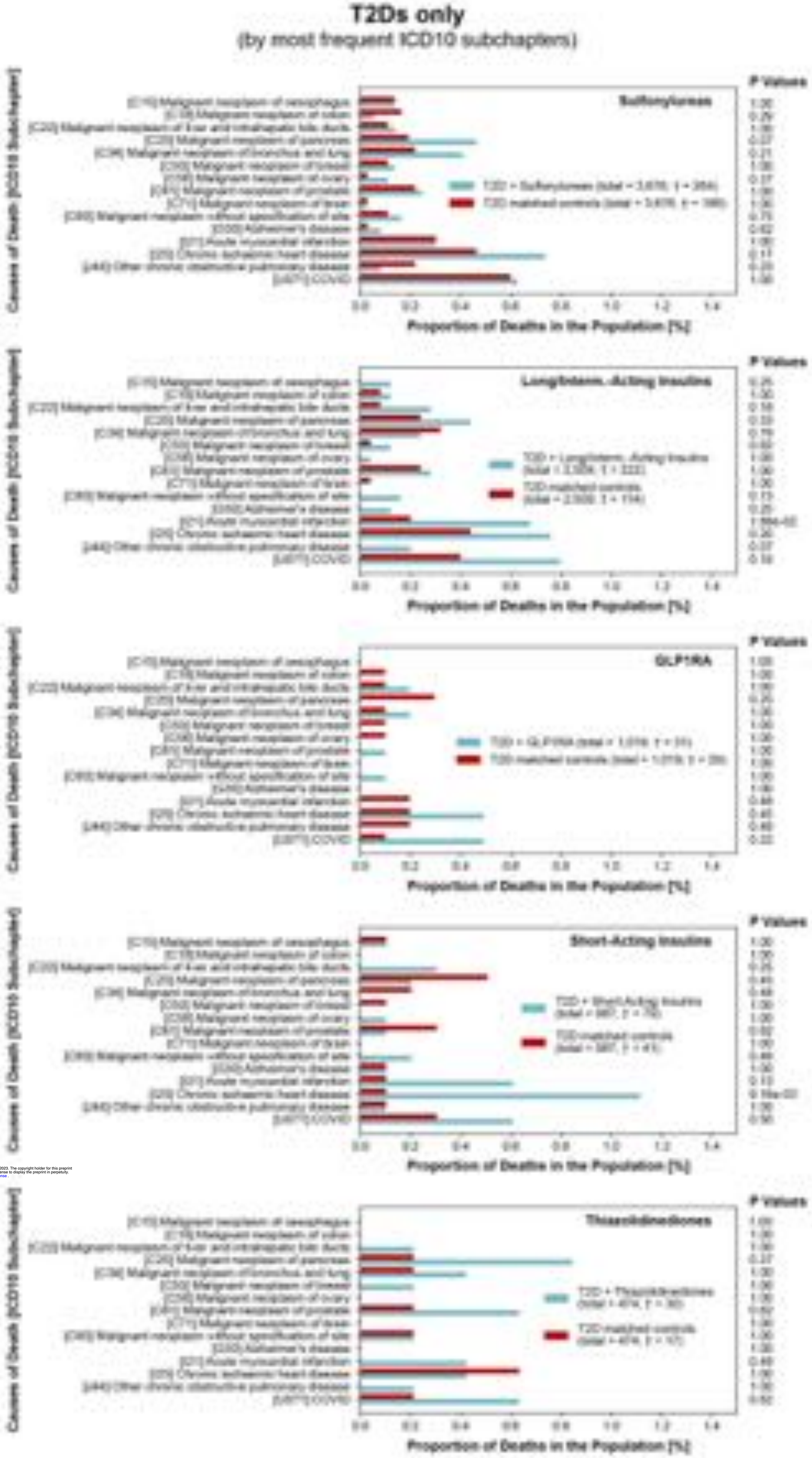

Figure S8

a

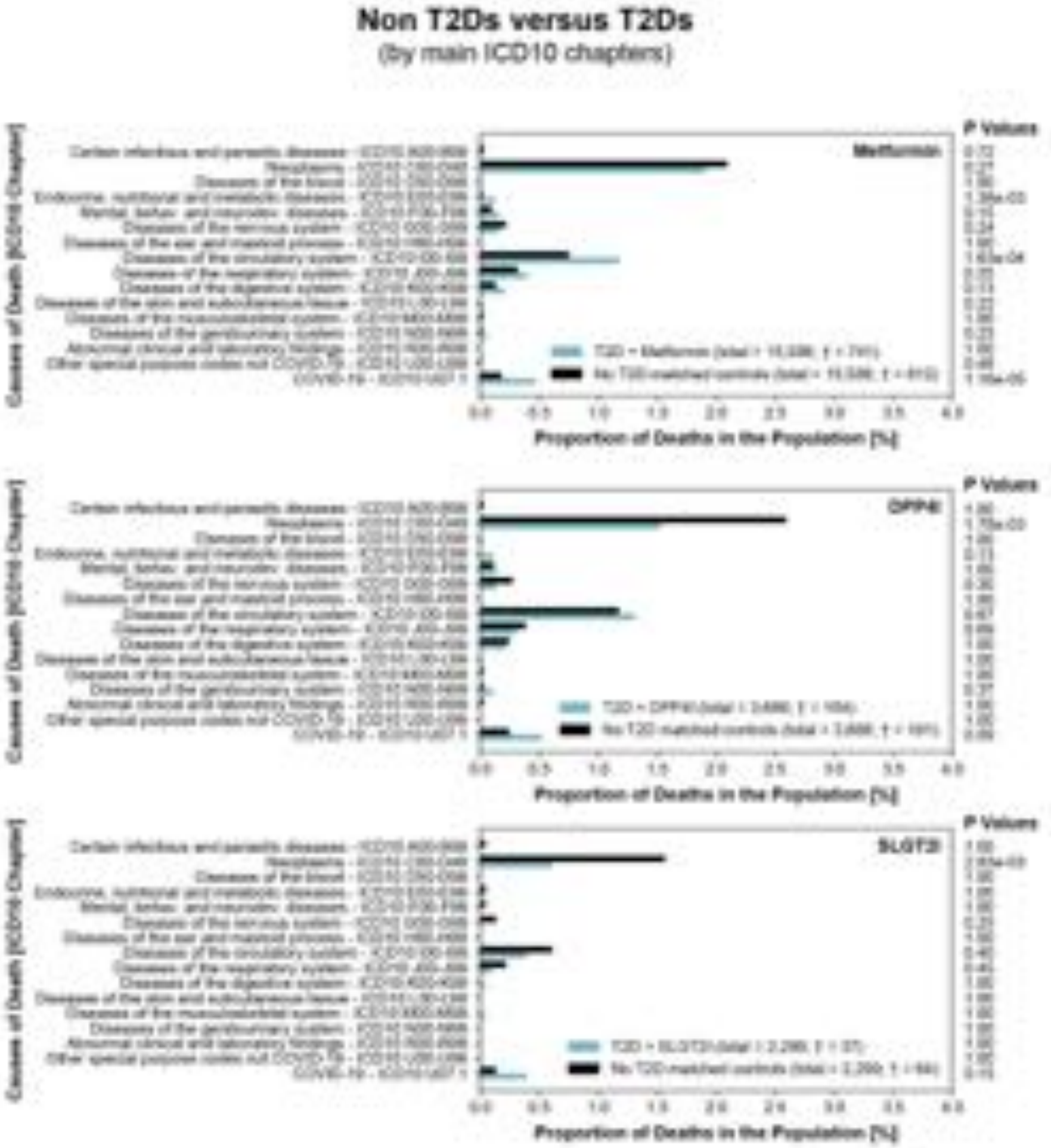

Figure S8 (continued)

b

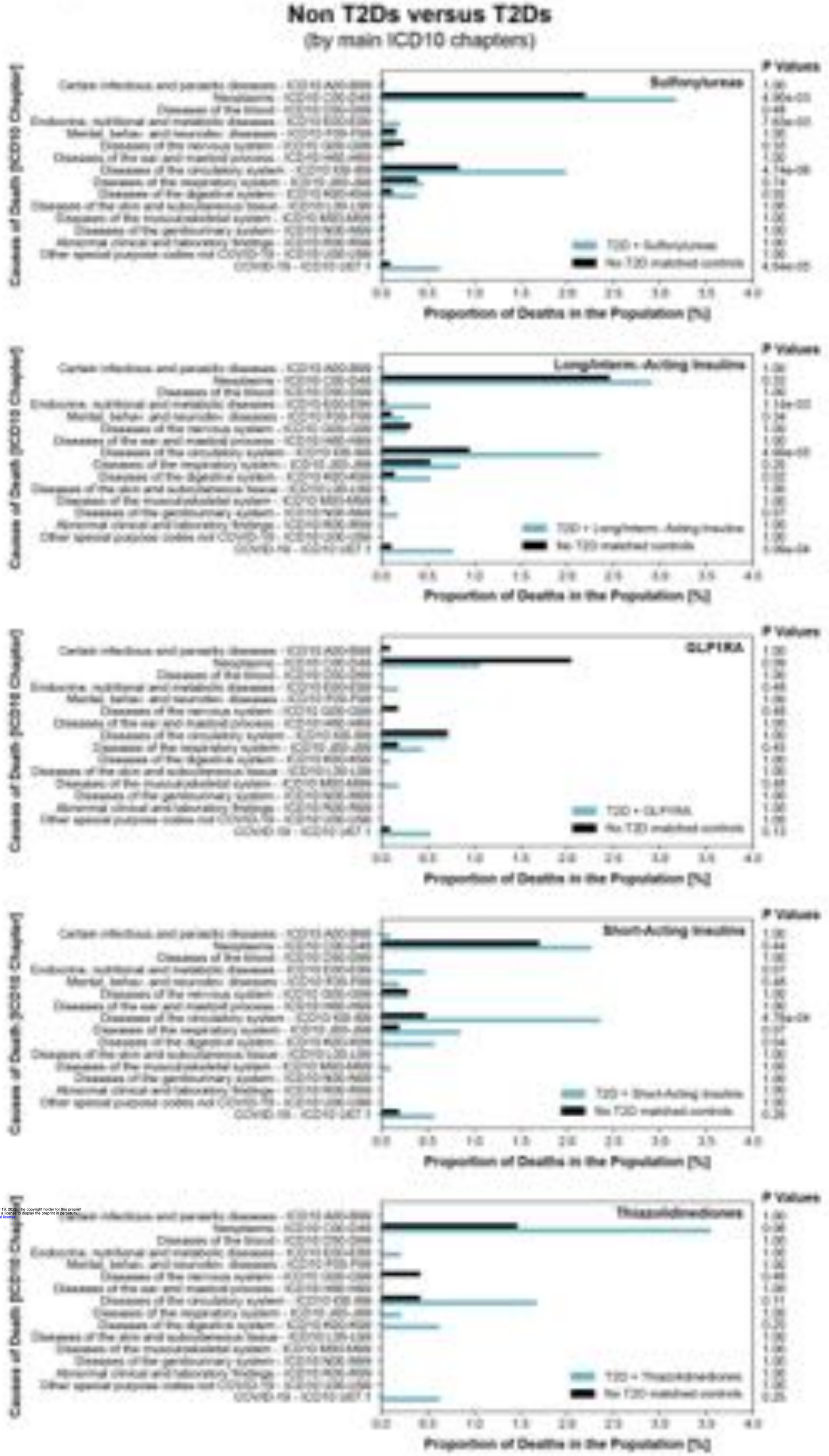

Figure S8 (continued)

c

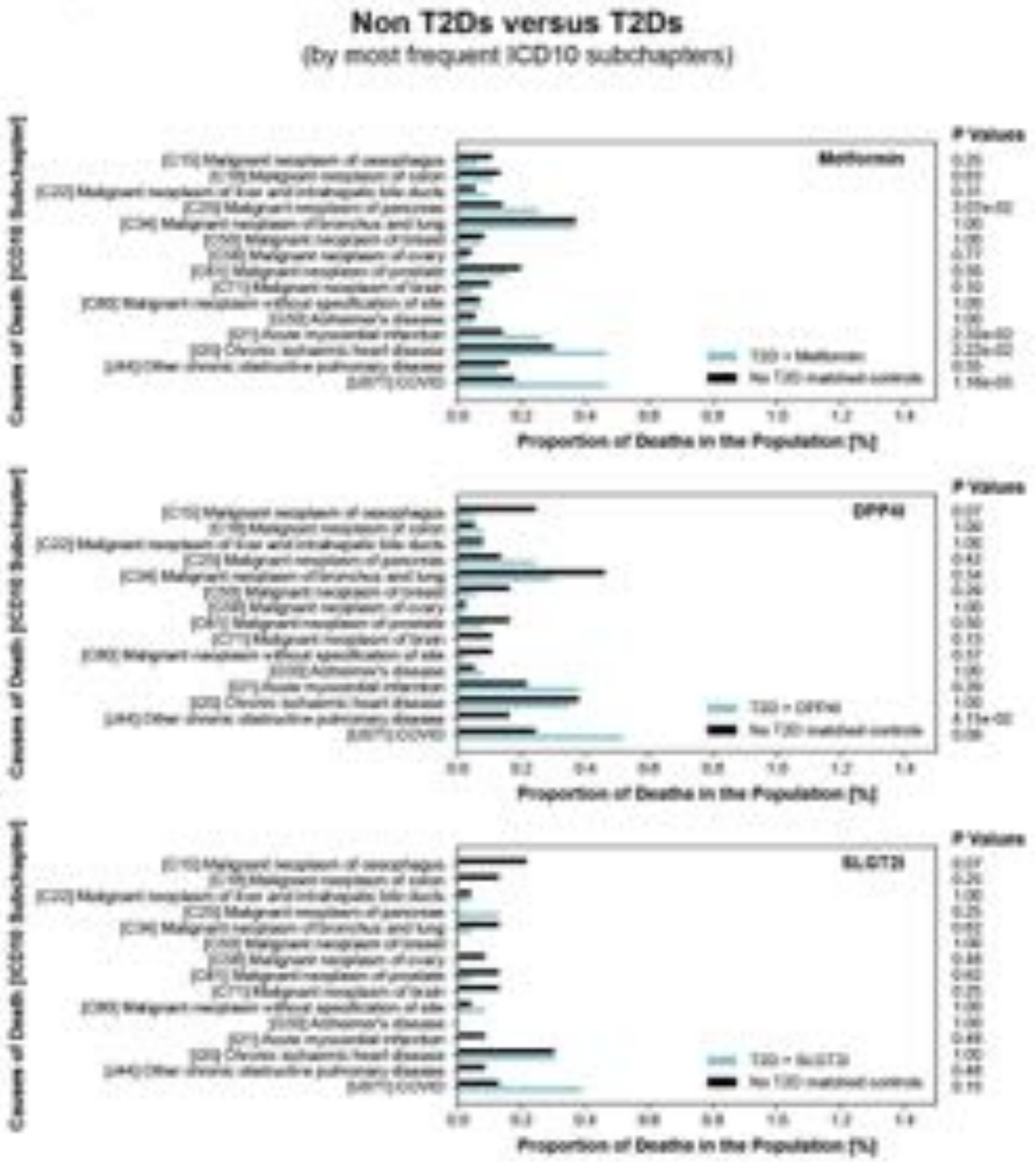

Figure S8 (continued)

d