04 October 2024

Study report

Title: Association between exposure to liraglutide versus active comparators and risk of acute hepatic injury

Version 1.2

Administrative details of the data analysis	
Substance(s)	Liraglutide
Condition/ADR(s)	Drug-induced liver injury
Short title of topic	Liraglutide and acute hepatic injury
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Reviewer	Daniel Morales, and Valentijn De Jong

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1. Brief description of the study (for publication in HMA-EMA Catalogue of RWD studies)

A cohort study which investigated a potentially increased risk of any liver disease (broad definition) and acute hepatic injury (narrow definition) among patients who initiated treatment with liraglutide.

2. Rationale and background

Drug-induced liver injury (DILI) is an uncommon but challenging clinical problem with respect to both diagnosis and management. (Hoofnagle & Bjornsson, 2019; Kullak-Ublick et al., 2017) Its incidence is estimated to be 14 to 19 cases per 100,000 person-years, with jaundice accompanying 30% of cases. (Hoofnagle & Bjornsson, 2019) It is the most frequent cause of acute liver failure in Western countries, accounting for more than half of cases. (Hoofnagle & Bjornsson, 2019; Stravitz & Lee, 2019)

There are many agents that can cause liver injury. Among the 971 prescription drugs described in LiverTox, the National Institutes of Health–sponsored website on hepatotoxicity, 447 (46%) have been implicated in causing liver injury in at least one published case report. (Hoofnagle & Bjornsson, 2019) More recently, there have been case reports of DILI after exposure to liraglutide. This substance is a glucagon-like peptide-1 (GLP-1) receptor agonists which are known as incretin mimetics because they act by increasing insulin release from the pancreas in response to food. Liraglutide is indicated for the treatment of adults, adolescents and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise. It is used as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, or in addition to other medicinal products for the treatment of diabetes.[1] It is also authorized for weight management in adult patients with an initial body mass index (BMI) of ≥ 30 kg/m^2 (obese), or ≥27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or T2DM), hypertension, dyslipidaemia or obstructive sleep apnoea.[2] Of 12 case reports of safety concerns regarding DILI following exposure to liraglutide, 11 cases recovered after liraglutide was withdrawn, including 2 cases where concomitant medication was simultaneously withdrawn, and three cases had normal liver enzyme levels before start of liraglutide treatment. In 10 cases, the symptoms appeared approximately after 10 days to six months of liraglutide initiation. According to the literature, time to onset of DILI differs significantly between drugs; although most DILI cases occur within 3 months of exposure to a drug, there are drugs that typically cause liver injury 3 to 12 months after starting (e.g., isoniazid, flutamide) and others for which the liver injury arises or becomes clinically evident after years of use (e.g., minocycline, amiodarone, nitrofurantoin).(British Society of Gastroenterology, 2022; European Association for the Study of the Liver, 2019; Hosack et al., 2023; National Institute of Diabetes and Digestive and Kidney Diseases, 2019)

The diagnosis of DILI is particularly challenging since it is based largely on exclusion of other causes.(Hoofnagle & Bjornsson, 2019) The main diagnostic elements include the timing of the onset of injury after the implicated agent has been started (latency), resolution after the agent is stopped (dechallenge), recurrence on re-exposure (rechallenge), knowledge of the agent's potential for hepatotoxicity (likelihood), and clinical features (phenotype).(Hoofnagle & Bjornsson, 2019) With few exceptions, there are no specific diagnostic markers for drug-induced liver injury, and special tests (liver biopsy, imaging, and testing for serologic markers) are helpful mostly in ruling out other causes of liver injury. Therefore, the identification of potential DILI events through diagnosis and procedural codes using electronic healthcare databases is difficult and Real-World Data (RWD) studies frequently

[1] Victoza | European Medicines Agency (europa.eu).
[2] Saxenda | European Medicines Agency (europa.eu).

use a sensitive case definition (i.e., broad outcome definition) in the hope of capturing most of true cases.

To support the evaluation of the safety concerns regarding liraglutide, a study was proposed to assess whether there is an association between liraglutide use and increased risk of acute hepatic injury when compared to patients who are prescribed an alternative treatment (e.g., substances in the sodium-glucose cotransporter-2 [SGLT-2] inhibitor or dipeptidyl peptidase 4 [DPP-4] inhibitor classes). However, given the challenges in the identification of DILI events through diagnosis and procedural codes, this study encompassed the measurement of three outcomes: two predefined phenotypes (developed by OHDSI[3] community) for acute hepatic injury and, a broader outcome definition which included any condition related to liver disease.

3. Research question and objectives

The main objective of this study was to assess whether there is an association between use of liraglutide and increased risk of:

- Any liver disease
- Acute liver injury
- Acute hepatic injury with no chronic hepatic failure

when compared to alternative treatments (i.e., empagliflozin [SGLT-2 inhibitor], dapagliflozin [SGLT-2 inhibitor], and sitagliptin [DPP-4 inhibitor]).

4. Methods

Box 1. Summary of study methods	
Recruitment period	From date of first recording of liraglutide in databases to the most recent available data, i.e., from August 1st, 2009, to June 30th, 2023, in IQVIA™ Medical Research Data (IMRD) UK and from July 14th, 2009, to June 30th, 2023, in IQVIA™ DA Germany. Of note, only the periods when both target and comparator treatments where available in the databases were included.
Eligibility criteria	• Eligibility criteria was applied at cohort entry (i.e., **index-date**, which is defined as date of initiation of treatment) *Inclusion criteria:* • Patients with at least one year of recorded medical history prior index-date. • Patients who initiated treatment (new users) with either liraglutide, empagliflozin, dapagliflozin, or sitagliptin. *Exclusion criteria:*

[3] OHDSI – Observational Health Data Sciences and Informatics. The Observational Health Data Sciences and Informatics program is a multi-stakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics.

Box 1. Summary of study methods	
	• Those with recorded history of the outcome prior index-date (Excluded conditions are specific to each outcome, see more details in Section 5.3).
Treatment protocols	Initiate any of the following substances at **index-date** (as monotherapy). *Target arms (exposure of interest):* • liraglutide (target arm [Cohort 1], class: GLP-1 receptor agonist) *Comparator arms:* • empagliflozin (comparator arm [Cohort 2], class: SGLT-2 inhibitor) • dapagliflozin (comparator arm [Cohort 3], class: SGLT-2 inhibitor) • sitagliptin (comparator arm [Cohort 4], class: DPP-4 inhibitor)
Assignment procedures	We assumed treatments are randomly assigned conditional on the propensity score (PS) [see Section 5.6, Potential confounding factors]
Index-date (cohort entry, beginning of follow-up)	The index-date was the date of the initiation of treatment defined as a prescription date for liraglutide, empagliflozin, dapagliflozin or sitagliptin.
Outcome	First ever recorded occurrence of any of the conditions (incident event) included in the definition for each outcome: "Diseases of liver" (comparison 1), acute hepatic injury (comparison 2), acute hepatic injury with no chronic hepatic failure (comparison 3) [See section 5.6, Outcomes, and Annex II]
Follow-up	Patients were followed-up from index-date up to maximum of 90 days. Thus, patients were followed-up from index-date to the earliest of: date of first occurrence of outcome, loss to follow-up, death, end of follow-up (90 days) or end of the study period [See Section 5.5, Follow-up period]
Causal contrast of interest	Intention to treat effect, i.e., patients were followed up irrespective of treatment switching or discontinuation.

Statistical methods	• Propensity score matching (PSM) was used to adjust for observed confounders measured at or before cohort entry.
	• Hazard ratios (HRs) were estimated using a Cox proportional hazards model.
	• Sensitivity analyses included:
	  ○ Using different follow-up periods: 180 and 365 days.
	  ○ Restricting study population to patients with type 2 diabetes mellitus (T2DM) who had been treated with metformin before index-date, which is considered first-line anti-diabetic treatment.
	
	[See Section 5.7. Statistical analyses]

4.1. Study design

New user active comparative cohort study design.

4.2. Data sources

This study was conducted using routinely collected data from two European countries. The selection of databases for this study was performed based on the ability to identify patients with diagnosis codes for clinical conditions classified as diseases of liver as well as treatments of interest.

The following database were used: IQVIA™ Medical Research Data (IMRD) UK, and IQVIA™ DA Germany. A brief description of these databases is provided in Annex 1.

4.3. Setting and study population

The following eligibility criteria was considered:

Inclusion criteria	Exclusion criteria
Patients registered with a GP-practice covered by IMRD (UK) and patients visiting general and specialist practices for IQVIA™ DA Germany database.	Patients with a recorded outcome **prior to index-date** were excluded from the analysis, i.e.,: • For "Diseases of liver" (broad definition), patients with any of the conditions included in this definition (Annex II, Table A1) were excluded. • For "Acute liver injury", patients with any of the conditions included in this definition (Annex II, Table A2) were excluded. • For "Acute liver injury with no chronic hepatic failure", patients with any of the conditions included in this definition (Annex II, Table A2 and A3) were excluded.
Patients with at least one year of recorded medical history prior to index-date, i.e., patients were require to have been observed at least once at minimum 365 days prior to entering the cohort (observation time).	For "Acute liver injury" and for "Acute liver injury with no chronic hepatic failure" outcomes, patients with specific hepatic-related conditions recorded prior index-date were excluded. See list of these specific conditions in Annex II, Table A2 and A3.
Patients who initiated treatment (new users) with liraglutide, empagliflozin, dapagliflozin or sitagliptin.	---

4.4. Study period

The study period covered from first time liraglutide was recorded in selected databases to the most recent available data, i.e., from August 1st, 2009, to June 30th 2023 in the IMRD UK, and from July 14th, 2009, to June 30th 2023 in the IQVIA™ DA Germany databases.

Of note, only the periods when both target and comparator treatments where available in the databases were included in the analyses.

4.5. Study follow-up

Patients were followed from index-date (date of treatment initiation in the database, see definition below) **up to maximum of 90 days**. Thus, patients were followed-up from index-date to the earliest of: date of first occurrence of outcome, loss to follow-up (e.g., transfer out date from the general practice in IMRD or date of last patient visit in IQVIA™ DA Germany, or date of last data collection from the practice), date of death, or end of the study period.

4.6. Variables

Exposure: Exposures of interest consisted of liraglutide class: (GLP-1 receptor agonist) [**target group**], and empagliflozin (SGLT-2 inhibitor), dapagliflozin (SGLT-2 inhibitor), and sitagliptin (DPP-4 inhibitor) [**comparator groups**]. Of note, the selection of comparators groups was based on the indication for these products[1-2,4-6], the absence of known risk for hepatic injury[4-6], the use of these medicines in previous comparative effectiveness studies (Bajaj et al., 2018; Fadini et al., 2019; Grabarczyk & Wissman, 2020; Htoo et al., 2022; Lee et al., 2014; Li et al., 2014; Nyeland et al., 2015; Reifsnider et al., 2022; Thomsen et al., 2021) and the frequency of prescribing of these medicines in the databases (Annex 2, A2.1 Exposures). Liraglutide[1,2], empagliflozin[4], dapagliflozin[5] and sitagliptin[6] are indicated for patients with insufficiently controlled T2DM as an adjunct to diet and exercise. They are indicated as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, and they are also recommended in addition to other medicinal products for the treatment of diabetes. In addition, hepatic injury or DILI are not specifically listed as an adverse reaction in the Summary of Product Characteristics (SmPC) for empagliflozin[4], dapagliflozin[5] or sitagliptin[6].

New users of liraglutide and comparator groups (empagliflozin, dapagliflozin, or sitagliptin) were identified based on the date of first prescription in the database. This date coincided with the start of patient's follow-up in the study, which we referred to as **index-date**.

Exposures were identified through OMOP CDM concept IDs of prescriptions recorded in the electronic health record. A detailed list of codes is provided in Annex 2.

Outcomes: The following outcome phenotypes were used:

Phenotype	Definition
1) Any liver disease (broad definition)	The earliest occurrence of any of the eligible conditions defining "Diseases of liver" outlined in Table A1 (See Annex 2: A2.2.1). This phenotype represents the incident (first ever) event and people with a history of Diseases of liver prior to index date are excluded. SNOMED diagnosis codes were used to identify conditions included in the "Diseases of Liver" phenotype.
2) Acute hepatic injury*	The earliest occurrence of any of the eligible conditions defining "Acute hepatic injury" outlined in Table A2 (See Annex 2: A2.2.2). This phenotype represents the incident (first ever) event and people with a history of Acute hepatic injury prior to index date are excluded. SNOMED diagnosis

[4] Jardiance, INN-Empagliflozin (europa.eu); label (fda.gov).

[5] Forxiga, INN-dapagliflozin (europa.eu); label (fda.gov).

[6] Januvia, INN-sitagliptin (europa.eu); 021995s050lbl.pdf (fda.gov)

Phenotype	Definition
	codes were used to identify conditions included in the "Acute hepatic injury" phenotype.
3) Acute hepatic injury with no chronic hepatic failure*	The earliest occurrence of any of the eligible conditions defining "Acute hepatic injury with no chronic hepatic failure" outlined in Table A2 (See Annex 2: A2.2.2) and excluding cases with previous chronic liver conditions outlined in Table A3 (See Annex 2: A2.2.3). This phenotype represents the incident (first ever) event, and people with history of chronic hepatic failure prior to index date were excluded. SNOMED diagnosis codes were used to identify conditions included in the "Acute hepatic injury with no chronic hepatic failure" phenotype.

* Phenotype developed by OHDSI (Observational Health Data Sciences and Informatics) community.

Potential confounding factors:

We generated a propensity score (PS) to control for measured confounders. A data-driven approach was used for the selection of these covariates which included generic characteristics (i.e., characteristics that are not selected based on the specific exposures and outcomes in the study). (Tian, Schuemie, and Suchard 2018) These characteristics included demographics, as well as all diagnoses, drug exposures, and measurement, observed up to 365 days prior to and on the day of treatment initiation. (Schuemie M. et al.) Calendar year was also considered in the models. These models typically involve more than thousands of covariates that are automatically constructed based on conditions, procedures and drugs in the records of the subjects. Covariates that occurred in fewer than 0.1% of the combined target and comparator cohorts in a pairwise comparison were excluded prior to model fitting. (Schuemie M. et al., 2021; Suchard et al., 2013)

4.7. Statistical analysis

4.7.1. Brief summary of the analysis method (for publication)

In the main analysis, the estimated treatment effect was the comparison between the risk of any liver disease, and acute hepatic injury, over 90-, 180-, 365-day follow-up, among patients who initiated liraglutide and patients who initiated empagliflozin, dapagliflozin, or sitagliptin, at baseline, regardless of subsequent changes in treatment or treatment discontinuation (intention-to-treat analysis).

4.7.2. Descriptive analysis

Descriptive analyses were performed to describe the study cohorts at baseline in terms of demographic characteristics, baseline comorbidities and medication history of concomitant treatments.

4.7.3. Main statistical analysis

Propensity score matching (PSM)

Propensity score (PS) matching (PSM) was used to adjust for differences between the treatment groups. Thus, after selecting a suitable comparator(s), patients were matched based on their PS using a one-to-one-matching. To estimate the PSM, we used large-scale regularized logistic regression (Schuemie M. et al., 2021; Schuemie M. et al., 2024; Suchard et al., 2013) implemented in the CohortMethod 5.2.1 R package, to select covariates which were measured within 365 days prior to index date and estimated the probability of treatment allocation. Thus, based on the available data, the method indicated which characteristics were predictive of the treatment assignment and were included in the model. (Schuemie M. et al., 2021)

The distributions of predefined (see the CohortMethod R package) baseline covariates before and after matching were compared between the two treatment arms by calculating and plotting standardized mean differences (SMD), to evaluate appropriate covariate balance (i.e., to evaluate whether the use of the PS makes the two treatment cohorts comparable).(Schuemie M. et al., 2024) The complete list of covariates is available upon request.

Intention-to-treat (ITT) analysis

For the main analysis, we applied an intention-to-treat (ITT) approach. Patients were classified according to treatment initiated at baseline and any event occurring during follow-up were attributed to baseline treatment regardless treatment discontinuation. Patients were followed up from the date of study treatment initiation (index date) up to maximum of **90 days**. Patients were censored at the earliest of: date of first occurrence of outcome, loss to follow-up (e.g., transfer out date from the general practice in IMRD or date of last patient visit in IQVIA™ DA Germany, or date of last data collection from the practice), date of death, end of follow-up (defined as 90 days from index-date), or end of the study period.

Cox proportional hazards model

Hazard ratios of the outcomes (i.e., any liver disease, acute hepatic injury, acute hepatic injury with no chronic hepatic failure) associated with treatment of interest (liraglutide) *versus* comparator (empagliflozin, dapagliflozin, or sitagliptin) were estimated using the Cox proportional hazards model.

4.7.4. Sensitivity analyses

The following sensitivity analyses were performed to test the validity of the underlying assumptions and the robustness of the study findings:

- Using different follow-up periods: A longer follow-up period of **180 days** and **365 days** (instead of 90 days), respectively, were also assessed.
- Restricting the study population to T2DM patients: To increase comparability between treatment cohorts (e.g., patients with same indication and similar disease stage), the study population was restricted to T2DM patients who had been treated with metformin before the index-date, which is considered the first-line anti-diabetic treatment.

4.7.5. Sample size

The sample size was driven by the availability of individuals with exposures and outcomes within each database and no *a priori* sample size requirement was stipulated.

Analyses were performed using R software and OMOP analytics suite "HADES".

4.8. Quality control

The study was conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance were adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents underwent at least one round a review by an experienced reviewer, and the results from the statistical analysis were also reviewed..

The quality control of the data is the responsibility of the data holder.

4.9. Deviation from the protocol

Follow-up period: In the protocol, a 90-day follow-up period was established as the main analysis. However, given the scarcity of acute hepatic live injury events, results for the 365-day follow-up are presented first in this report, then those for the 180-day follow-up and finally those for the 90-day follow-up.

IMRD UK database: Results based on the IMRD UK database are not reported because of concerns with regards to generalizability of these results. Only 358 to 694 patients per treatment arm were PS matched, which represents approximately 6-11% of new liraglutide users in the original cohort and 15-19% in the eligible cohort.

5. Results

5.1. Any liver disease

5.1.1. Liraglutide vs empagliflozin

Details of the patient cohort attrition for liraglutide vs empagliflozin (including all indications) in the IQVIA™ DA Germany database are shown in Figure 1.

Overall, 14,668 and 62,621 patients who were prescribed liraglutide or empagliflozin for the first time were identified. The number of eligible patients during the study period was 6,606 liraglutide and 45,047 empagliflozin initiators after restricting to time periods in which both treatments were available in the database, and excluding patients who were prescribed with both treatments (at the same day or different days) and those who did not meet the inclusion criteria.

Figure S1 illustrates the standardized differences for covariates comparing liraglutide vs empagliflozin cohorts before and after PS matching. Additionally, Table 1 shows the distributions of predefined baseline characteristics for both cohorts before and after PS matching. Before PS matching, there were baseline imbalances (SMD>0.1) in the following characteristics: Patients initiating liraglutide were

more likely to be younger, female, obese, and more likely to have a recorded prescription of medicines used in diabetes when compared to those initiating empagliflozin. In addition, liraglutide initiators were less likely to have a recorded diagnosis of atrial fibrillation, coronary arteriosclerosis, heart disease, and heart failure, and lower prevalence of use of agents acting on the renin-angiotensin system, anti-inflammatory and antirheumatic products, antithrombotic agents, beta blocking agents, calcium channel blockers, diuretics, substances for acid related disorders and lipid modifying agents.

5,176 patients per treatment arm were PS matched (35% of new liraglutide users in the original cohort and 78% in the eligible cohort, Figure 1).

After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance with an SMD of <0.1 (Figure S1, and Table 1).

Incidence rates (IR) of any liver disease in matched cohorts: The incidence per 1,000 person-years of any liver disease (Table 2) in empagliflozin and liraglutide initiators was: 35.24 and 31.09 followed-up for a maximum of 365 days; 46.10 and 41.87 followed-up for a maximum of 180 days; and 61.31 and 53.01 followed-up for a maximum of 90 days. When restricting the study population to patients with a recorded diagnosis of T2DM, IRs were similar or slightly greater than the IRs for empagliflozin and liraglutide initiators in the study population that included all indications. However, the uncertainty around these estimates reflected by the 95% confidence intervals suggests that the results were also compatible with a minor decrease of the IRs.

Hazard ratios (HR) for incident liver disease in matched cohorts: The HRs for incident liver disease among liraglutide compared to empagliflozin initiators by follow-up period are presented in Table 2. The point estimates are mostly below 1.00. However, the associated uncertainty reflected by the 95% confidence intervals indicates we do not have evidence to conclude a reduced risk of any liver disease in liraglutide initiators compared to empagliflozin initiators. Similar but slightly less precise estimates were obtained when restricting the study population to patients with recorded diagnosis of T2DM, which may be related to the lower number of events and available follow-up time.

5.1.2. Liraglutide vs dapagliflozin

Figure S2 illustrates patient attrition cohort for liraglutide and dapagliflozin treatment arms (including all indications) in IQVIA™ DA Germany. 5,684 patients per treatment arm were PS matched (39% of new liraglutide users in the original cohort and 78% in the eligible cohort).

Figure S3 and Table S1 shows SMD for covariates and predefined baseline characteristics before and after PS matching, respectively. After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance with an SMD of <0.1.

Table 3 shows IRs per 1,000 person years and HRs of any liver disease in dapagliflozin and liraglutide initiators. Results were consistent with those for liraglutide vs empagliflozin when the study population included either all indications or only patients with T2DM.

5.1.3. Liraglutide vs sitagliptin

Figure S4 illustrates patient attrition cohort for liraglutide and sitagliptin treatment arms (including all indications) in IQVIA™ DA Germany. 6,668 patients per treatment arm were PS matched (45% of new liraglutide users in the original cohort and 80% in the eligible cohort).

Figure S5 and Table S2 shows standardised mean differences for covariates and predefined baseline characteristics before and after PS matching, respectively. After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance with an SMD of <0.1.

Table 4 shows IRs per 1,000 person years and HRs of any liver disease in sitagliptin and liraglutide initiators. Results were consistent with those for liraglutide vs empagliflozin when the study population included either all indications or only patients with T2DM.

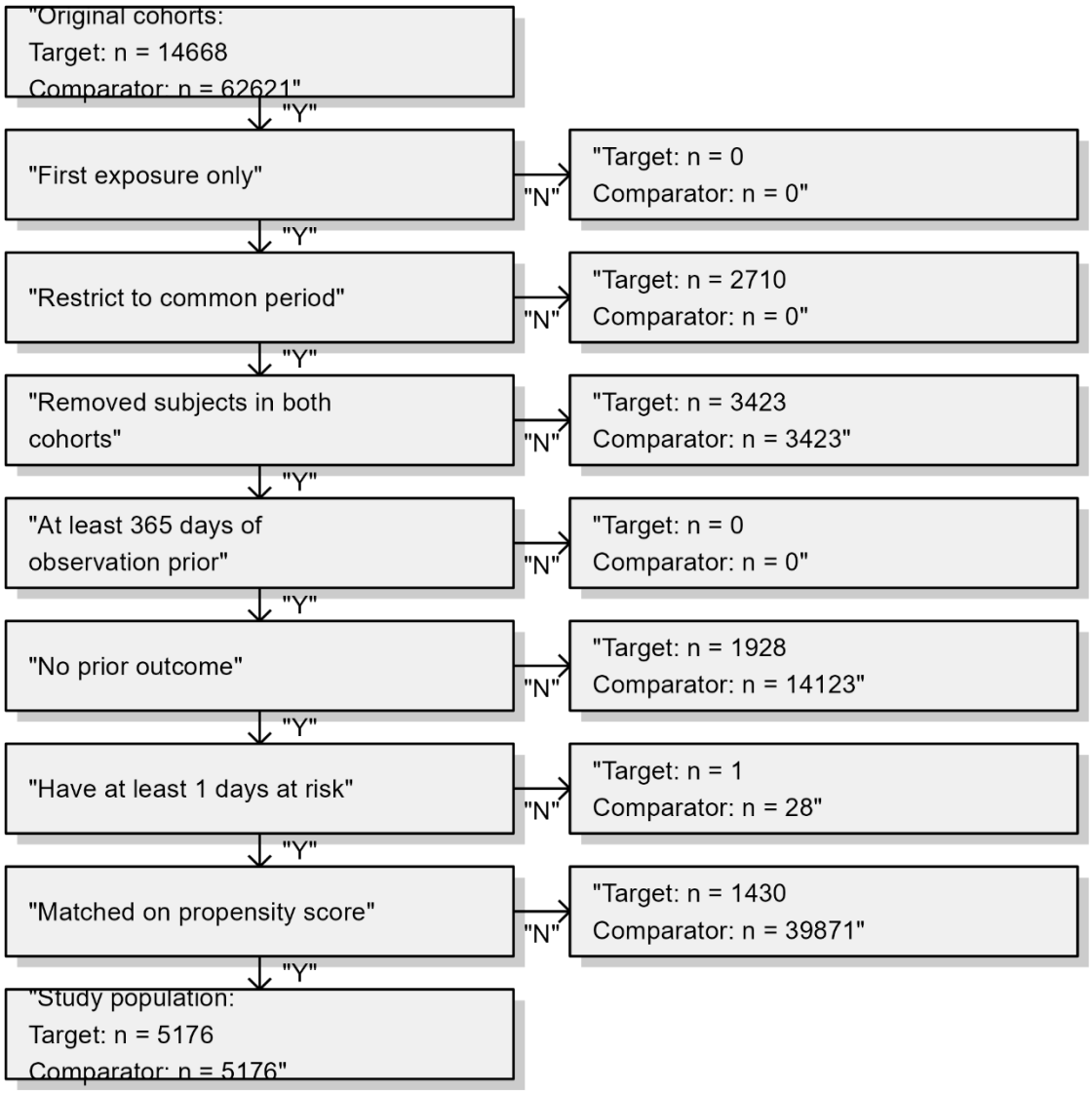

Figure 1. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **empagliflozin** during the study period in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

348 Table 1. Predefined[1] baseline characteristics before and after PS matching in the study population
349 including all indications, in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Covariates	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
5 - 9	--	0.0	--	--	--	--
10 - 14	0.0	0.0	0.02	0.0	--	--
15 - 19	0.2	0.0	0.06	0.1	0.1	-0.01
20 - 24	0.4	0.1	0.07	0.3	0.3	-0.01
25 - 29	0.7	0.2	0.10	0.7	0.9	-0.01
30 - 34	1.8	0.4	0.17	1.8	1.9	-0.01
35 - 39	3.2	1.0	0.18	3.1	3.3	-0.01
40 - 44	5.0	1.9	0.20	4.4	4.3	0.00
45 - 49	7.9	3.7	0.20	7.3	7.5	-0.01
50 - 54	12.9	7.2	0.21	12.2	12.2	0.00
55 - 59	16.1	11.5	0.14	15.0	15.8	-0.02
60 - 64	15.9	14.2	0.05	14.7	14.7	0.00
65 - 69	14.1	15.1	-0.03	14.5	14.6	0.00
70 - 74	10.8	14.1	-0.10	11.4	11.1	0.01
75 - 79	6.8	12.2	-0.17	8.4	7.5	0.03
80 - 84	3.4	11.1	-0.26	4.8	4.6	0.01
85 - 89	0.7	5.5	-0.23	1.1	1.0	0.02
90 - 94	0.1	1.3	-0.12	0.2	0.1	0.01
95 - 99	--	0.2	--	--	0.0	--
Gender: female	49.2	37.3	0.24	49.9	50.3	-0.01
Medical history: General						
Acute respiratory disease	12.2	12.5	-0.01	10.5	10.1	0.01
Attention deficit hyperactivity disorder	0.0	0.1	-0.01	0.0	--	--
Chronic liver disease	0.5	0.6	-0.01	0.0	0.0	-0.01
Chronic obstructive lung disease	4.5	6.0	-0.07	3.8	3.9	0.00
Crohn's disease	0.1	0.2	-0.02	0.2	0.1	0.02
Dementia	0.7	1.6	-0.07	0.7	0.7	0.00
Depressive disorder	8.5	7.3	0.05	6.5	6.4	0.00
Diabetes mellitus	44.3	42.4	0.04	36.3	36.1	0.00
Gastroesophageal reflux disease	1.3	1.9	-0.04	1.2	1.0	0.02
Gastrointestinal hemorrhage	0.4	0.7	-0.04	0.2	0.2	0.01
Human immunodeficiency virus infection	0.1	0.0	0.02	0.0	0.0	0.00
Hyperlipidemia	18.0	21.0	-0.07	12.2	11.8	0.01
Hypertensive disorder	32.1	36.5	-0.09	24.9	24.3	0.01
Lesion of liver	0.7	0.7	0.00	0.0	0.1	-0.01
Obesity	19.9	10.1	0.30	14.3	14.7	-0.01
Osteoarthritis	7.7	9.2	-0.05	6.1	6.0	0.00
Pneumonia	1.1	2.0	-0.06	1.0	0.8	0.03
Psoriasis	1.2	1.1	0.01	0.8	0.8	0.01
Renal impairment	8.7	8.6	0.00	5.9	5.7	0.01
Rheumatoid arthritis	1.0	1.1	-0.01	0.7	0.8	-0.01
Schizophrenia	0.1	0.2	-0.01	0.1	0.2	-0.01
Ulcerative colitis	0.2	0.2	-0.01	0.1	0.2	-0.02
Urinary tract infectious disease	2.9	3.6	-0.04	2.9	2.9	0.00
Viral hepatitis C	0.1	0.1	-0.01	--	0.0	--

Medical history: Cardiovascular disease						
Atrial fibrillation	2.1	5.4	-0.16	1.6	1.3	0.03
Cerebrovascular disease	3.1	5.1	-0.09	2.4	2.4	0.00
Coronary arteriosclerosis	3.8	10.0	-0.22	3.6	3.1	0.03
Heart disease	18.9	39.1	-0.42	15.8	14.4	0.04
Heart failure	5.6	16.4	-0.31	4.4	3.7	0.04
Ischemic heart disease	8.8	16.9	-0.22	6.9	6.7	0.01
Peripheral vascular disease	9.1	8.6	0.02	6.7	7.1	-0.01
Pulmonary embolism	0.6	0.9	-0.03	0.5	0.5	0.00
Venous thrombosis	1.2	1.3	-0.01	0.9	0.7	0.02
Medical history: Neoplasms						
Malignant lymphoma	0.3	0.4	-0.01	0.3	0.2	0.01
Malignant neoplasm of anorectum	0.0	0.2	-0.03	0.1	0.1	0.01
Malignant neoplastic disease	3.6	5.1	-0.07	2.8	2.5	0.02
Malignant tumor of breast	0.6	0.6	0.00	0.5	0.7	-0.03
Malignant tumor of colon	0.3	0.4	-0.01	0.1	0.2	-0.01
Malignant tumor of lung	0.1	0.1	-0.01	0.0	0.0	0.00
Malignant tumor of urinary bladder	0.1	0.2	-0.03	0.1	0.0	0.02
Primary malignant neoplasm of prostate	0.5	0.8	-0.04	0.3	0.3	0.00
Medication use						
Agents acting on the renin-angiotensin system	43.5	62.9	-0.39	40.3	38.3	0.04
Antibacterials for systemic use	18.6	19.0	-0.01	16.6	16.6	0.00
Antidepressants	8.7	9.1	-0.01	8.0	7.5	0.02
Antiepileptics	5.1	5.7	-0.03	5.2	5.3	0.00
Antiinflammatory and antirheumatic products	27.2	36.7	-0.20	25.2	24.0	0.03
Antineoplastic agents	0.8	1.1	-0.03	0.8	0.8	0.00
Antipsoriatics	0.4	0.4	0.01	0.4	0.2	0.03
Antithrombotic agents	19.4	41.0	-0.45	19.1	17.2	0.05
Beta blocking agents	28.4	47.8	-0.39	26.8	24.7	0.05
Calcium channel blockers	20.7	28.7	-0.18	19.3	18.3	0.03
Diuretics	31.5	47.7	-0.33	29.0	27.8	0.03
Drugs for acid related disorders	22.9	33.4	-0.23	22.0	21.3	0.02
Drugs for obstructive airway diseases	12.6	15.7	-0.09	11.8	11.7	0.00
Drugs used in diabetes	82.9	71.2	0.26	77.0	78.1	-0.03
Immunosuppressants	0.6	0.7	-0.01	0.5	0.5	0.00
Lipid modifying agents	32.0	48.8	-0.34	29.6	27.8	0.04
Opioids	9.1	11.0	-0.06	8.7	8.6	0.00
Psycholeptics	5.7	8.1	-0.09	5.7	5.4	0.01
Psychostimulants, agents used for adhd and nootropics	0.3	0.2	0.01	0.2	0.2	0.00

SMD: Standardized mean differences. **Target: Liraglutide. Comparator: Empagliflozin**.

(1) Covariates presented here are default groupings from the CohortMethod 5.2.1 package, which were measured within 365 days prior to index-date. The table does not accurately reflect the presence of chronic diseases in the patients, since chronic diseases that were recorded more than 365 days prior to the index-date and not repeated within 365 days prior to the index-date were not considered. Of note, only a small number of the baseline covariates used to fit the propensity score model is presented here. The complete list of covariates is available upon request.

Table 2. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **any liver disease** by treatment arm (**liraglutide vs empagliflozin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365-day follow-up														
Empagliflozin	4597.69	162	**35.24**	30.02	40.67	**1.00**	[Reference]	2059.64	82	**39.81**	31.56	48.55	**1.00**	[Reference]
Liraglutide	4534.54	141	**31.09**	26.02	36.39	**0.88**	0.70 1.10	2040.91	62	**30.38**	23.03	38.22	**0.76**	0.54 1.05
180-day follow-up														
Empagliflozin	2407.65	111	**46.10**	37.80	54.83	**1.00**	[Reference]	1067.41	58	**54.34**	41.22	68.39	**1.00**	[Reference]
Liraglutide	2388.55	100	**41.87**	33.91	50.24	**0.90**	0.69 1.19	1059.39	51	**48.14**	35.87	61.36	**0.88**	0.60 1.29
90-day follow-up														
Empagliflozin	1255.93	77	**61.31**	47.77	75.64	**1.00**	[Reference]	549.69	34	**61.85**	41.84	83.68	**1.00**	[Reference]
Liraglutide	1245.10	66	**53.01**	40.96	65.86	**0.86**	0.62 1.19	545.99	36	**65.94**	45.79	87.91	**1.06**	0.66 1.70

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

Table 3. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **any liver disease** by treatment arm (**liraglutide vs dapagliflozin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365day follow-up														
Dapagliflozin	5148.66	176	**34.18**	29.13	39.23	**1.00**	[Reference]	2336.80	72	**30.81**	23.96	38.09	**1.00**	[Reference]
Liraglutide	5013.65	172	**34.31**	29.32	39.49	**1.00**	0.81 1.23	2312.03	70	**30.28**	23.36	37.63	**0.98**	0.71 1.36
180-day follow-up														
Dapagliflozin	2673.31	112	**41.90**	34.41	49.75	**1.00**	[Reference]	1197.66	41	**34.23**	24.21	45.09	**1.00**	[Reference]
Liraglutide	2633.97	116	**44.04**	36.07	52.39	**1.05**	0.81 1.36	1192.97	51	**42.75**	31.85	54.49	**1.25**	0.83 1.89
90-day follow-up														
Dapagliflozin	1384.78	78	**56.33**	44.1	69.3	**1.00**	[Reference]	614.54	27	**43.94**	27.66	61.83	**1.00**	[Reference]
Liraglutide	1370.95	74	**53.98**	42.3	66.4	**0.95**	0.69 1.31	613.31	32	**52.18**	34.24	71.74	**1.19**	0.71 1.99

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

Table 4. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **any liver disease** by treatment arm (**liraglutide vs sitagliptin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365-day follow-up														
Sitagliptin	5989.41	207	**34.56**	29.89	39.40	**1.00**	[Reference]	2985.90	99	**33.16**	26.79	39.85	**1.00**	[Reference]
Liraglutide	6050.07	207	**34.21**	29.59	39.01	**0.99**	0.82 1.20	3014.09	114	**37.82**	31.19	44.79	**1.14**	0.87 1.50
180-day follow-up														
Sitagliptin	3122.72	144	**46.11**	38.75	53.80	**1.00**	[Reference]	1532.95	70	**45.66**	35.23	56.75	**1.00**	[Reference]
Liraglutide	3139.73	142	**45.23**	37.90	52.87	**0.98**	0.78 1.24	1545.09	79	**51.13**	40.13	62.78	**1.12**	0.81 1.55
90-day follow-up														
Sitagliptin	1626.35	102	**62.72**	51.00	75.01	**1.00**	[Reference]	788.70	49	**62.13**	45.64	79.88	**1.00**	[Reference]
Liraglutide	1622.22	91	**56.10**	45.00	67.81	**0.89**	0.67 1.18	790.44	48	**60.73**	44.28	78.44	**0.98**	0.66 1.46

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

5.2. Acute hepatic injury

5.2.1. Liraglutide vs empagliflozin

Details of the patient cohort attrition for liraglutide vs empagliflozin (including all indications) in the IQVIA™ DA Germany database are shown in Figure 2.

The number of eligible patients during the study period was 8,410 liraglutide and 58,011 empagliflozin initiators after restricting to time periods in which both treatments were available in the database, and excluding patients who were prescribed with both treatments (at the same day or different days) and those who did not meet the inclusion criteria.

Figure S6 illustrates the standardized differences for covariates comparing liraglutide vs empagliflozin cohorts before and after PS matching. Additionally, Table 5 shows the distribution of predefined baseline characteristics for both cohorts before and after PS matching. Before PS matching, there were baseline imbalances (SMD>0.1) in the following characteristics: Patients initiating liraglutide were more likely to be younger, female, obese, and more likely to have a recorded prescription of medicines used in diabetes when compared to those initiating empagliflozin. In addition, liraglutide initiators were less likely to have a recorded diagnosis of atrial fibrillation, coronary arteriosclerosis, heart disease, and heart failure, and lower prevalence of use of agents acting on the renin-angiotensin system, anti-inflammatory and antirheumatic products, antithrombotic agents, beta blocking agents, calcium channel blockers, diuretics, substances for acid related disorders and lipid modifying agents.

6,836 patients per treatment arm were PS matched (47% of new liraglutide users in the initial cohort and 81% in the eligible cohort, Figure 2).

After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance with an SMD of <0.1 (Figure S6, and Table 5).

Incidence rates (IR) of acute hepatic injury in matched cohorts: The incidence per 1,000 person years of acute hepatic injury (Table 6) in empagliflozin and liraglutide initiators was: 1.47 and 1.49 followed-up for a maximum of 365 days; 0.93 and 1.26 followed-up for a maximum of 180 days; and 1.20 and 0.61 followed-up for a maximum of 90 days. Similar but less precise IRs in empagliflozin and liraglutide initiators were observed when restricting the study population to patients with a recorded diagnosis of T2DM.

Of note, these IRs were substantially lower than those for any liver disease due to the scarce number of recorded events.

Hazard ratios (HR) of acute hepatic injury in matched cohorts: The HRs for incident acute hepatic injury among liraglutide compared to empagliflozin initiators by follow-up period are shown in Table 6. The high uncertainty reflected by the wide 95% confidence intervals precludes a meaningful interpretation of the HRs. The lack of precision of these estimates was due to the scarcity of events and limited follow-up time (person-years).

Overall, much less precise estimates were obtained when restricting the study population to patients with recorded diagnosis of T2DM, which was related to the lower number of events and available follow-up time (person-years).

5.2.2. Liraglutide vs dapagliflozin

Figure S7 illustrates the patient attrition cohort for liraglutide and dapagliflozin treatment arms (including all indications) in IQVIA™ DA Germany. 7,339 patients per treatment arm were PS matched (50% of new liraglutide users in the original cohort and 77% in the eligible cohort).

Figure S8 shows SMD for covariates before and after PS matching. After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance with an SMD of <0.1.

Table 7 shows IRs per 1,000 person years and HRs of acute hepatic injury in dapagliflozin and liraglutide initiators. Results were consistent with those for liraglutide vs empagliflozin when the study population included either all indications or only patients with T2DM.

5.2.3. Liraglutide vs sitagliptin

Figure S9 illustrates patient attrition cohort for liraglutide and sitagliptin treatment arms (including all indications) in IQVIA™ DA Germany. 8,490 patients per treatment arm were PS matched (58% of new liraglutide users in the original cohort and 79% in the eligible cohort).

Figure S10 shows standardised mean differences for covariates and predefined baseline characteristics before and after PS matching. After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance with an SMD of <0.1.

Table 8 shows IRs per 1,000 person years and HRs of acute hepatic injury in sitagliptin and liraglutide initiators. Results were consistent with those for liraglutide vs empagliflozin when the study population included either all indications or only patients with T2DM.

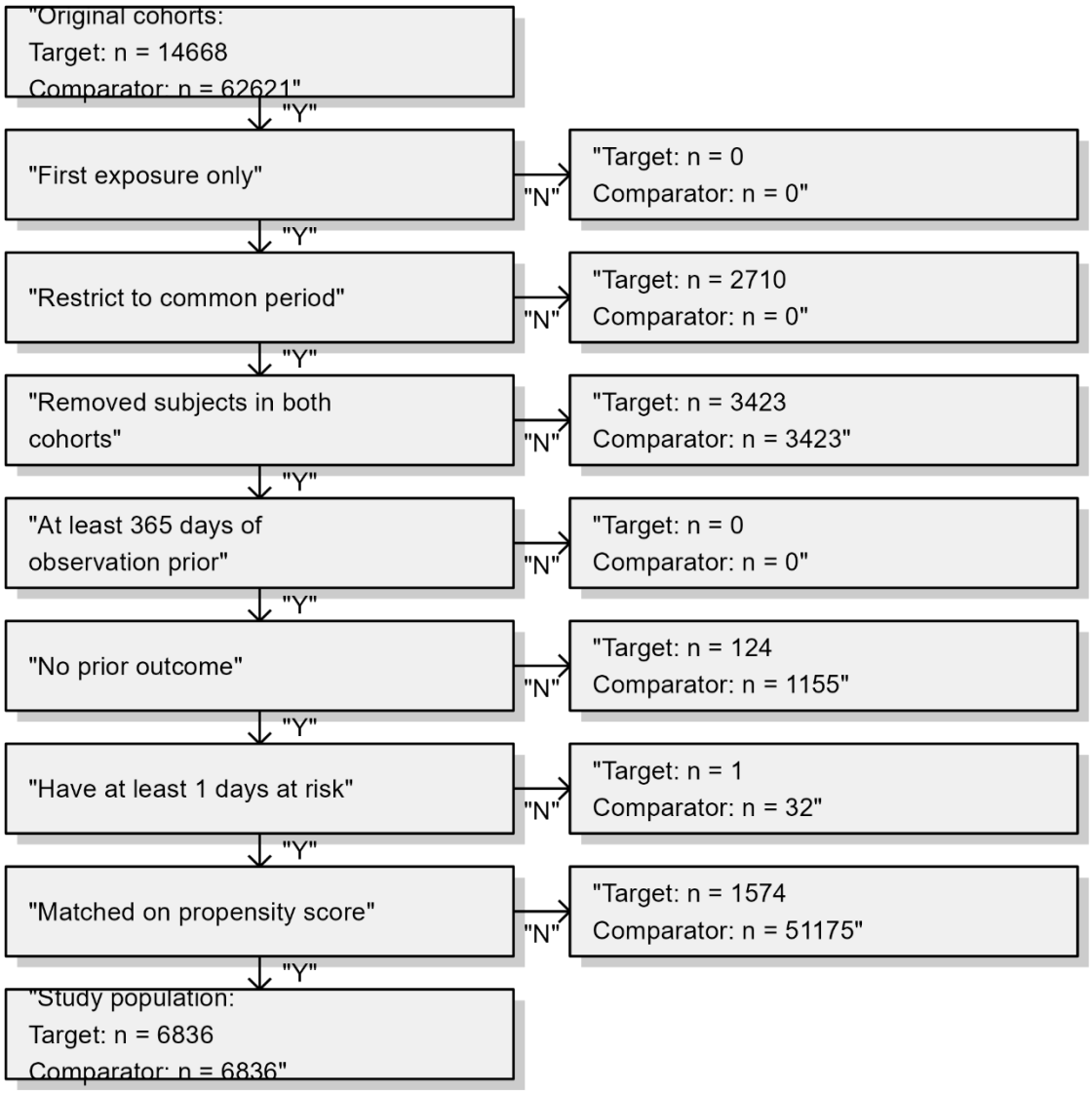

Figure 2. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **empagliflozin** during the study period in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

436 Table 5. Predefined[(1)] baseline characteristics before and after PS matching in the study population
437 including all indications, in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
5 - 9		0.0				
10 - 14	0.0	0.0	0.02	0.0	0.0	0.01
15 - 19	0.2	0.0	0.06	0.2	0.2	0.00
20 - 24	0.4	0.1	0.07	0.3	0.3	0.00
25 - 29	0.7	0.2	0.10	0.8	0.8	0.00
30 - 34	1.8	0.4	0.17	1.6	1.5	0.01
35 - 39	3.2	1.0	0.18	2.9	3.2	-0.01
40 - 44	5.0	1.9	0.20	4.0	4.0	0.00
45 - 49	7.9	3.7	0.20	7.3	7.5	-0.01
50 - 54	12.9	7.2	0.21	12.0	12.0	0.00
55 - 59	16.1	11.5	0.14	15.1	16.0	-0.02
60 - 64	15.9	14.2	0.05	15.5	15.6	0.00
65 - 69	14.1	15.1	-0.03	14.8	14.7	0.00
70 - 74	10.8	14.1	-0.10	11.3	11.0	0.01
75 - 79	6.8	12.2	-0.17	8.2	7.9	0.01
80 - 84	3.4	11.1	-0.26	4.7	4.3	0.02
85 - 89	0.7	5.5	-0.23	1.1	0.8	0.03
90 - 94	0.1	1.3	-0.12	0.2	0.2	0.00
95 - 99		0.2			0.0	
Gender: female	49.2	37.3	0.24	49.4	50.9	-0.03
Medical history: General						
Acute respiratory disease	12.2	12.5	-0.01	11.4	11.4	0.00
Attention deficit hyperactivity disorder	0.0	0.1	-0.01	0.0	0.0	0.00
Chronic liver disease	0.5	0.6	-0.01	0.3	0.4	-0.01
Chronic obstructive lung disease	4.5	6.0	-0.07	4.2	4.5	-0.02
Crohn's disease	0.1	0.2	-0.02	0.1	0.1	0.01
Dementia	0.7	1.6	-0.07	0.7	0.7	0.01
Depressive disorder	8.5	7.3	0.05	7.4	7.7	-0.01
Diabetes mellitus	44.3	42.4	0.04	38.5	38.5	0.00
Gastroesophageal reflux disease	1.3	1.9	-0.04	1.2	1.2	0.00
Gastrointestinal hemorrhage	0.4	0.7	-0.04	0.3	0.4	-0.01
Human immunodeficiency virus infection	0.1	0.0	0.02	0.0	0.0	0.02
Hyperlipidemia	18.0	21.0	-0.07	14.6	14.6	0.00
Hypertensive disorder	32.1	36.5	-0.09	27.4	27.2	0.00
Lesion of liver	0.7	0.7	0.00	0.5	0.7	-0.02
Obesity	19.9	10.1	0.30	16.1	17.3	-0.03
Osteoarthritis	7.7	9.2	-0.05	6.9	6.8	0.01
Pneumonia	1.1	2.0	-0.06	1.1	1.2	0.00
Psoriasis	1.2	1.1	0.01	1.0	0.9	0.00
Renal impairment	8.7	8.6	0.00	7.6	7.5	0.00
Rheumatoid arthritis	1.0	1.1	-0.01	0.9	0.7	0.01
Schizophrenia	0.1	0.2	-0.01	0.1	0.2	-0.01
Ulcerative colitis	0.2	0.2	-0.01	0.2	0.1	0.03
Urinary tract infectious disease	2.9	3.6	-0.04	3.0	3.3	-0.02
Viral hepatitis C	0.1	0.1	-0.01	0.1	0.1	0.02
Medical history: Cardiovascular disease						
Atrial fibrillation	2.1	5.4	-0.16	1.9	1.6	0.02
Cerebrovascular disease	3.1	5.1	-0.09	2.9	2.9	0.00
Coronary arteriosclerosis	3.8	10.0	-0.22	3.6	3.2	0.02
Heart disease	18.9	39.1	-0.42	17.2	16.1	0.03
Heart failure	5.6	16.4	-0.31	5.1	4.5	0.03

Ischemic heart disease	8.8	16.9	-0.22	7.7	7.6	0.00
Peripheral vascular disease	9.1	8.6	0.02	7.7	7.7	0.00
Pulmonary embolism	0.6	0.9	-0.03	0.5	0.5	0.00
Venous thrombosis	1.2	1.3	-0.01	1.0	1.1	-0.01
Medical history: Neoplasms						
Malignant lymphoma	0.3	0.4	-0.01	0.3	0.3	0.00
Malignant neoplasm of anorectum	0.0	0.2	-0.03	0.1	0.1	-0.02
Malignant neoplastic disease	3.6	5.1	-0.07	3.3	3.5	-0.01
Malignant tumor of breast	0.6	0.6	0.00	0.5	0.5	0.01
Malignant tumor of colon	0.3	0.4	-0.01	0.2	0.2	0.01
Malignant tumor of lung	0.1	0.1	-0.01	0.1	0.1	0.00
Malignant tumor of urinary bladder	0.1	0.2	-0.03	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.5	0.8	-0.04	0.4	0.4	-0.01
Medication use						
Agents acting on the renin-angiotensin system	43.5	62.9	-0.39	42.6	41.4	0.02
Antibacterials for systemic use	18.6	19.0	-0.01	17.6	17.3	0.01
Antidepressants	8.7	9.1	-0.01	8.3	8.4	-0.01
Antiepileptics	5.1	5.7	-0.03	5.4	5.4	0.00
Antiinflammatory and antirheumatic products	27.2	36.7	-0.20	25.7	24.6	0.02
Antineoplastic agents	0.8	1.1	-0.03	0.9	0.8	0.01
Antipsoriatics	0.4	0.4	0.01	0.4	0.4	0.00
Antithrombotic agents	19.4	41.0	-0.45	19.2	17.7	0.04
Beta blocking agents	28.4	47.8	-0.39	28.3	27.5	0.02
Calcium channel blockers	20.7	28.7	-0.18	21.0	20.5	0.01
Diuretics	31.5	47.7	-0.33	30.7	29.9	0.02
Drugs for acid related disorders	22.9	33.4	-0.23	23.5	22.4	0.03
Drugs for obstructive airway diseases	12.6	15.7	-0.09	12.6	12.1	0.01
Drugs used in diabetes	82.9	71.2	0.26	78.0	79.5	-0.04
Immunosuppressants	0.6	0.7	-0.01	0.6	0.4	0.03
Lipid modifying agents	32.0	48.8	-0.34	30.9	30.3	0.01
Opioids	9.1	11.0	-0.06	9.2	9.3	0.00
Psycholeptics	5.7	8.1	-0.09	5.9	5.9	0.00
Psychostimulants, agents used for adhd and nootropics	0.3	0.2	0.01	0.1	0.2	-0.01

SMD: Standardized mean differences. **Target: Liraglutide. Comparator: Empagliflozin.**

(1) Covariates presented here are default groupings from the CohortMethod 5.2.1 package, which were measured within 365 days prior to index-date. The table does not accurately reflect the presence of chronic diseases in the patients, since chronic diseases that were recorded more than 365 days prior to the index-date and not repeated within 365 days prior to the index-date were not considered. Of note, only a small number of the baseline covariates used to fit the propensity score model is presented here. The complete list of covariates is available upon request.

Table 6. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **acute hepatic injury** by treatment arm (**liraglutide vs empagliflozin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365-day follow-up														
Empagliflozin	6141.07	9	**1.47**	0.65	2.44	**1.00**	[Reference]	2910.78	8	**2.75**	1.03	4.81	**1.00**	[Reference]
Liraglutide	6056.89	9	**1.49**	0.66	2.48	**1.01**	0.40 2.60	2910.35	<5	(*)	(*)	(*)	**0.50**	0.13 1.59
180-day follow-up														
Empagliflozin	3209.05	<5	(*)	(*)	(*)	**1.00**	[Reference]	1505.16	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	3176.76	<5	(*)	(*)	(*)	**1.34**	0.30 6.82	1504.45	<5	(*)	(*)	(*)	**3.00**	0.38 60.55
90-day follow-up														
Empagliflozin	1666.02	<5	(*)	(*)	(*)	**1.00**	[Reference]	773.75	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	1650.44	<5	(*)	(*)	(*)	**0.50**	0.02 5.25	773.65	<5	(*)	(*)	(*)	**1.00**	0.04 25.28

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

(*) Cell suppression was applied to protect patient's privacy. A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as "<5".

Table 7. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **acute hepatic injury** by treatment arm (**liraglutide vs dapagliflozin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365 days														
Dapagliflozin	6660.11	15	**2.25**	1.20	3.45	**1.00**	[Reference]	3215.17	8	**2.49**	0.93	4.35	**1.00**	[Reference]
Liraglutide	6534.25	11	**1.68**	0.77	2.75	**0.75**	0.33 1.61	3190.13	7	**2.19**	0.63	4.08	**0.88**	0.31 2.45
180 days														
Dapagliflozin	3453.93	8	**2.32**	0.87	4.05	**1.00**	[Reference]	1647.18	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	3418.94	9	**2.63**	1.17	4.39	**1.14**	0.43 3.03	1643.57	7	**4.26**	1.22	7.91	**1.76**	0.53 6.70
90 days														
Dapagliflozin	1789.13	<5	(*)	(*)	(*)	**1.00**	[Reference]	845.30	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	1774.45	5	**2.82**	0.56	5.64	**1.26**	0.33 5.09	842.90	<5	(*)	(*)	(*)	**4.02**	0.59 78.53

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

(*) Cell suppression was applied to protect patient's privacy. A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as "<5".

Table 8. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **acute hepatic injury** by treatment arm (**liraglutide vs sitagliptin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365 days														
Sitagliptin	7710.90	25	**3.24**	2.07	4.54	**1.00**	[Reference]	4031.54	5	**1.24**	0.25	2.48	**1.00**	[Reference]
Liraglutide	7760.48	10	**1.29**	0.52	2.19	**0.40**	0.18 0.80	4060.01	9	**2.22**	0.99	3.69	**1.79**	0.62 5.83
180 days														
Sitagliptin	4007.91	11	**2.74**	1.25	4.49	**1.00**	[Reference]	2064.85	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	4016.81	7	**1.74**	0.50	3.24	**0.63**	0.23 1.61	2075.84	8	**3.85**	1.45	6.74	**2.66**	0.77 12.12
90 days														
Sitagliptin	2080.46	5	**2.40**	0.48	4.81	**1.00**	[Reference]	1060.15	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	2071.77	<5	(*)	(*)	(*)	**0.80**	0.20 3.04	1060.08	<5	(*)	(*)	(*)	**1.33**	0.29 6.77

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

(*) Cell suppression was applied to protect patient's privacy. A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as "<5".

N.B.: When restricting to a smaller population (i.e., T2DM patients), different patients may be matched, thus, patients who were not matched in the full population (e.g., population that includes all indications) could suddenly be matched in the restricted one. Whether this occurs depends on the order of matching in the algorithm for the cohort generation. Therefore, it is possible to observe for example seven events in the population that includes all indications and eight events in the T2DM population

5.3. Acute hepatic injury with no chronic hepatic failure

5.3.1. Liraglutide vs empagliflozin

Details of the patient cohort attrition for liraglutide vs empagliflozin (including all indications) in the IQVIA™ DA Germany database are shown in Figure 3.

The number of eligible patients during the study period was 8,433 liraglutide and 58,219 empagliflozin initiators after restricting to time periods in which both treatments were available in the database, and excluding patients who were prescribed with both treatments (at the same day or different days) and those who did not meet the inclusion criteria.

Figure S11 illustrates the standardized differences for covariates comparing liraglutide vs empagliflozin cohorts before and after PS matching. Additionally, Table 9 shows the distribution of predefined baseline characteristics for both cohorts before and after PS matching. Before PS matching, there were baseline imbalances (SMD>0.1) in the following characteristics: Patients initiating liraglutide were more likely to be younger, female, obese, and more likely to have a recorded prescription of medicines used in diabetes when compared to those initiating empagliflozin. In addition, liraglutide initiators were less likely to have a recorded diagnosis of atrial fibrillation, coronary arteriosclerosis, heart disease, and heart failure, and lower prevalence of use of agents acting on the renin-angiotensin system, anti-inflammatory and antirheumatic products, antithrombotic agents, beta blocking agents, calcium channel blockers, diuretics, substances for acid related disorders and lipid modifying agents.

6,856 patients per treatment arm were PS matched (47% of new liraglutide users in the initial cohort and 81% in the eligible cohort, Figure 2). All predefined covariates were balanced with an SMD of <0.1 after PS matching.

After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance (Figure S11, and Table 9).

Incidence rates (IR) of acute hepatic injury with no chronic hepatic failure in matched cohorts: The incidence per 1,000 person years of acute hepatic injury with no hepatic failure (Table 10) in empagliflozin and liraglutide initiators was: 0.65 and 1.15 in patients followed-up for a maximum of 365 days; 0.93 and 0.63 in patients followed-up for a maximum of 180 days; and 1.80 and 0.60 in patients followed-up for a maximum of 90 days. Similar but less precise IRs were found in empagliflozin and liraglutide initiators when restricting the study population to patients with a recorded diagnosis of T2DM (Table 10).

Of note, these IRs were substantially lower than those for any liver disease due to the scarce number of recorded events and the very limited follow-up time (person-years).

Hazard ratios (HR) of acute hepatic injury with no chronic hepatic failure in matched cohorts: The HRs for incident acute hepatic injury with no chronic hepatic failure among liraglutide compared to empagliflozin initiators by follow-up period are shown in Table 10. The high uncertainty reflected by the wide 95% confidence intervals precludes a meaningful interpretation of the HRs. The lack of precision of these estimates was due to the scanty number of events and limited follow-up time (person-years).

Overall, much less precise estimates were obtained when restricting the study population to patients with recorded diagnosis of T2DM, which was related to the scarcity of events and very limited follow-up time (person-years).

5.3.2. Liraglutide vs dapagliflozin

Figure S12 illustrates patient attrition cohort for liraglutide and dapagliflozin treatment arms (including all indications) in IQVIA™ DA Germany. 7,353 patients per treatment arm were PS matched (50% of new liraglutide users in the original cohort and 77% in the eligible cohort).

Figure S13 shows SMD for covariates before and after PS matching. After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance with an SMD of <0.1.

Table 11 shows IRs per 1,000 person years and HRs of acute hepatic injury with no chronic hepatic failure in dapagliflozin and liraglutide initiators. Results were consistent with those for liraglutide vs empagliflozin when the study population included either all indications or only patients with T2DM.

5.3.3. Liraglutide vs sitagliptin

Figure S14 illustrates the patient attrition cohort for the liraglutide and sitagliptin treatment arms (including all indications) in IQVIA™ DA Germany. 8,506 patients per treatment arm were PS matched (58% of new liraglutide users in the original cohort and 79% in the eligible cohort).

Figure S15 shows SMD for covariates before and after PS matching. After PS matching, the distribution of the predefined characteristics achieved an appropriate covariate balance with an SMD of <0.1.

Table 12 shows IRs per 1,000 person years and HRs of acute hepatic injury with no chronic hepatic failure in sitagliptin and liraglutide initiators. Results were consistent with those for liraglutide vs empagliflozin when the study population included either all indications or only patients with T2DM.

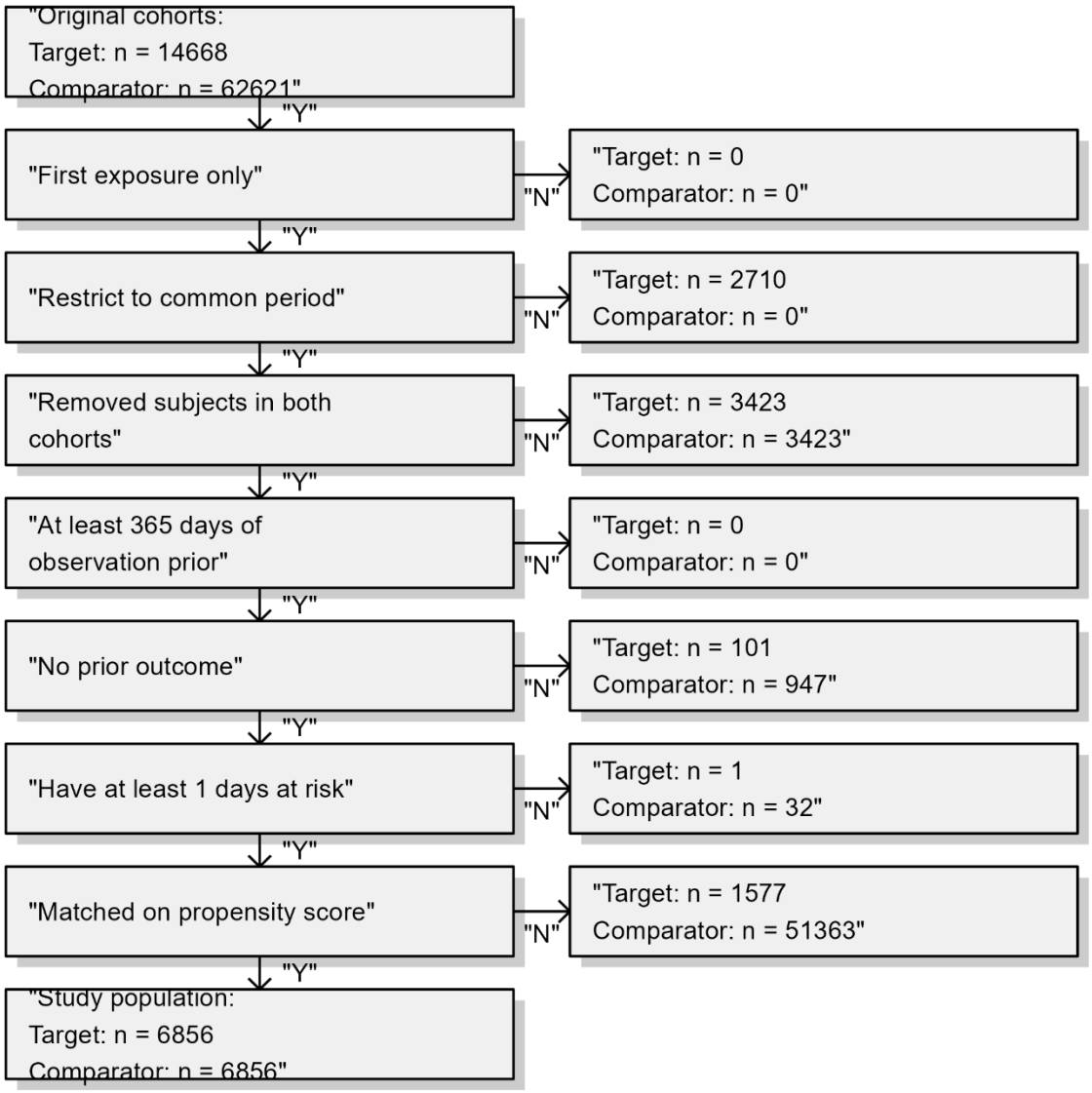

Figure 3. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **empagliflozin** during the study period in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

532 Table 9. Predefined[(1)] baseline characteristics before and after PS matching in the study population
533 including all indications, in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
5 - 9	--	0.0	--	--	0.0	--
10 - 14	0.0	0.0	0.02	0.0		
15 - 19	0.2	0.0	0.06	0.1	0.2	0.00
20 - 24	0.4	0.1	0.07	0.3	0.3	0.00
25 - 29	0.7	0.2	0.10	0.8	0.8	0.00
30 - 34	1.8	0.4	0.17	1.6	1.6	0.00
35 - 39	3.2	1.0	0.18	2.9	3.0	-0.01
40 - 44	5.0	1.9	0.20	4.2	4.3	-0.01
45 - 49	7.9	3.7	0.20	7.3	7.5	-0.01
50 - 54	12.9	7.2	0.21	11.8	12.1	-0.01
55 - 59	16.1	11.5	0.14	15.0	15.4	-0.01
60 - 64	15.9	14.2	0.05	15.4	15.8	-0.01
65 - 69	14.1	15.1	-0.03	14.9	15.0	0.00
70 - 74	10.8	14.1	-0.10	11.4	10.8	0.02
75 - 79	6.8	12.2	-0.17	8.3	8.0	0.01
80 - 84	3.4	11.1	-0.26	4.8	4.2	0.03
85 - 89	0.7	5.5	-0.23	1.1	0.9	0.02
90 - 94	0.1	1.3	-0.12	0.1	0.1	0.02
95 - 99		0.2				
Gender: female	49.2	37.3	0.24	49.9	50.2	-0.01
Medical history: General						
Acute respiratory disease	12.2	12.5	-0.01	11.4	11.0	0.01
Attention deficit hyperactivity disorder	0.0	0.1	-0.01	0.0	0.0	0.00
Chronic liver disease	0.5	0.6	-0.01	0.5	0.5	-0.01
Chronic obstructive lung disease	4.5	6.0	-0.07	4.3	4.1	0.01
Crohn's disease	0.1	0.2	-0.02	0.1	0.1	0.01
Dementia	0.7	1.6	-0.07	0.7	0.7	0.00
Depressive disorder	8.5	7.3	0.05	7.3	7.1	0.01
Diabetes mellitus	44.3	42.4	0.04	38.3	37.8	0.01
Gastroesophageal reflux disease	1.3	1.9	-0.04	1.3	1.2	0.01
Gastrointestinal hemorrhage	0.4	0.7	-0.04	0.3	0.4	0.00
Human immunodeficiency virus infection	0.1	0.0	0.02	0.0		
Hyperlipidemia	18.0	21.0	-0.07	14.6	14.3	0.01
Hypertensive disorder	32.1	36.5	-0.09	27.5	26.2	0.03
Lesion of liver	0.7	0.7	0.00	0.6	0.6	0.01
Obesity	19.9	10.1	0.30	16.1	16.9	-0.02
Osteoarthritis	7.7	9.2	-0.05	7.0	6.7	0.01
Pneumonia	1.1	2.0	-0.06	1.2	1.1	0.01
Psoriasis	1.2	1.1	0.01	0.9	1.0	-0.01
Renal impairment	8.7	8.6	0.00	7.7	7.4	0.01
Rheumatoid arthritis	1.0	1.1	-0.01	0.9	0.9	0.00
Schizophrenia	0.1	0.2	-0.01	0.1	0.2	-0.01
Ulcerative colitis	0.2	0.2	-0.01	0.2	0.1	0.00
Urinary tract infectious disease	2.9	3.6	-0.04	3.1	3.0	0.01
Viral hepatitis C	0.1	0.1	-0.01	0.1	0.1	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	2.1	5.4	-0.16	1.9	1.9	0.00
Cerebrovascular disease	3.1	5.1	-0.09	2.9	2.9	-0.01
Coronary arteriosclerosis	3.8	10.0	-0.22	3.5	3.2	0.02
Heart disease	18.9	39.1	-0.42	17.3	16.1	0.03
Heart failure	5.6	16.4	-0.31	5.2	4.4	0.03

Ischemic heart disease	8.8	16.9	-0.22	7.8	7.4	0.02
Peripheral vascular disease	9.1	8.6	0.02	7.7	8.0	-0.01
Pulmonary embolism	0.6	0.9	-0.03	0.6	0.6	0.00
Venous thrombosis	1.2	1.3	-0.01	1.0	0.7	0.03
Medical history: Neoplasms						
Malignant lymphoma	0.3	0.4	-0.01	0.3	0.3	-0.01
Malignant neoplasm of anorectum	0.0	0.2	-0.03	0.1	0.1	-0.01
Malignant neoplastic disease	3.6	5.1	-0.07	3.4	3.3	0.00
Malignant tumor of breast	0.6	0.6	0.00	0.5	0.5	0.01
Malignant tumor of colon	0.3	0.4	-0.01	0.2	0.2	-0.01
Malignant tumor of lung	0.1	0.1	-0.01	0.1	0.0	0.01
Malignant tumor of urinary bladder	0.1	0.2	-0.03	0.1	0.1	0.01
Primary malignant neoplasm of prostate	0.5	0.8	-0.04	0.4	0.4	0.00
Medication use						
Agents acting on the renin-angiotensin system	43.5	62.9	-0.39	42.7	40.2	0.05
Antibacterials for systemic use	18.6	19.0	-0.01	17.6	17.3	0.01
Antidepressants	8.7	9.1	-0.01	8.3	7.9	0.01
Antiepileptics	5.1	5.7	-0.03	5.4	5.4	0.00
Antiinflammatory and antirheumatic products	27.2	36.7	-0.20	25.6	25.3	0.01
Antineoplastic agents	0.8	1.1	-0.03	0.9	0.9	0.00
Antipsoriatics	0.4	0.4	0.01	0.4	0.4	0.00
Antithrombotic agents	19.4	41.0	-0.45	19.3	18.0	0.03
Beta blocking agents	28.4	47.8	-0.39	28.5	26.5	0.04
Calcium channel blockers	20.7	28.7	-0.18	20.8	20.4	0.01
Diuretics	31.5	47.7	-0.33	31.0	28.9	0.05
Drugs for acid related disorders	22.9	33.4	-0.23	23.6	22.1	0.04
Drugs for obstructive airway diseases	12.6	15.7	-0.09	12.5	11.9	0.02
Drugs used in diabetes	82.9	71.2	0.26	77.7	80.1	-0.06
Immunosuppressants	0.6	0.7	-0.01	0.6	0.5	0.01
Lipid modifying agents	32.0	48.8	-0.34	30.8	29.8	0.02
Opioids	9.1	11.0	-0.06	9.3	9.3	0.00
Psycholeptics	5.7	8.1	-0.09	5.9	5.7	0.01
Psychostimulants, agents used for adhd and nootropics	0.3	0.2	0.01	0.2	0.2	0.01

SMD: Standardized mean differences. **Target: Liraglutide. Comparator: Empagliflozin.**

(1) Covariates presented here are default groupings from the CohortMethod 5.2.1 package, which were measured within 365 days prior to index-date. The table does not accurately reflect the presence of chronic diseases in the patients, since chronic diseases that were recorded more than 365 days prior to the index-date and not repeated within 365 days prior to the index-date were not considered. Of note, only a small number of the baseline covariates used to fit the propensity score model is presented here. The complete list of covariates is available upon request.

Table 10. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **acute hepatic injury with no chronic hepatic failure** by treatment arm (**liraglutide vs empagliflozin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365 days														
Empagliflozin	6148.54	<5	(*)	(*)	(*)	**1.00**	[Reference]	2931.92	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	6067.65	7	**1.15**	0.33	2.14	**1.77**	0.54 6.77	2931.92	<5	(*)	(*)	(*)	**1.00**	0.19 5.42
180 days														
Empagliflozin	3210.24	<5	(*)	(*)	(*)	**1.00**	[Reference]	1515.87	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	3182,01	<5	(*)	(*)	(*)	**0.67**	0.09 4.05	1512.95	<5	(*)	(*)	(*)	**2.01**	0.19 43.13
90 days														
Empagliflozin	1669.30	<5	(*)	(*)	(*)	**1.00**	[Reference]	779.57	0	**0.00**	NA	NA	**1.00**	[Reference]
Liraglutide	1653.88	<5	(*)	(*)	(*)	**0.34**	0.02 2.63	778.18	<5	(*)	(*)	(*)	NA	NA NA

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

(*) Cell suppression was applied to protect patient's privacy. A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as "<5".

Table 11. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **acute hepatic injury with no chronic hepatic failure** by treatment arm (**liraglutide vs dapagliflozin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365 days														
Dapagliflozin	6724.45	8	**1.19**	0.45	2.08	**1.00**	[Reference]	3232.12	5	**1.55**	0.31	3.09	**1.00**	[Reference]
Liraglutide	6544.61	7	**1.07**	0.31	1.99	**0.89**	0.31 2.49	3210.20	5	**1.56**	0.31	3.12	**1.01**	0.28 3.61
180 days														
Dapagliflozin	3479.04	<5	(*)	(*)	(*)	**1.00**	[Reference]	1657.17	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	3424.56	6	**1.75**	0.58	3.21	**1.52**	0.43 5.94	1653.91	5	**3.02**	0.60	6.05	**2.51**	0.54 17.50
90 days														
Dapagliflozin	1797.52	<5	(*)	(*)	(*)	**1.00**	[Reference]	852.24	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	1777.77	<5	(*)	(*)	(*)	**1.35**	0.30 6.83	848.51	<5	(*)	(*)	(*)	4.02	0.60 78.67

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

(*) Cell suppression was applied to protect patient's privacy. A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as "<5".

Table 12. Matched incidence rates (IR) per 1000 person-years and hazard ratios (HR) of **acute hepatic injury with no chronic hepatic failure** by treatment arm (**liraglutide vs sitagliptin**) and follow-up period in the IQVIA™ DA Germany database

	All indications							Type 2 Diabetes mellitus						
Treatment arm	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**	**Follow-up (person-years)**	**n events**	**IR**	**95% CI**		**HR**	**95% CI**
365 days														
Sitagliptin	7692.87	8	**1.04**	0.39	1.82	**1.00**	[Reference]	4034.29	5	**1.24**	0.25	2.48	**1.00**	[Reference]
Liraglutide	7768.11	10	**1.29**	0.51	2.19	**1.24**	0.49 3.25	4068.82	8	**1.97**	0.74	3.44	**1.59**	0.53 5.26
180 days														
Sitagliptin	4001.28	6	**1.50**	0.50	2.75	**1.00**	[Reference]	2067.71	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	4019.60	7	**1.74**	0.50	3.23	**1.16**	0.39 3.61	2082.23	6	**2.88**	0.96	5.28	**1.49**	0.43 5.83
90 days														
Sitagliptin	2078.37	<5	(*)	(*)	(*)	**1.00**	[Reference]	1062.61	<5	(*)	(*)	(*)	**1.00**	[Reference]
Liraglutide	2072.56	<5	(*)	(*)	(*)	**1.00**	0.24 4.24	1064.34	<5	(*)	(*)	(*)	**2.00**	0.39 14.40

IR: incidence rate; HR: Hazard ratio; 95% CI: 95% confidence interval.

(*) Cell suppression was applied to protect patient's privacy. A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as "<5".

6. Discussion

In this comparative cohort study using the IQVIA™ DA Germany database, the IRs for any liver disease among liraglutide initiators varied from 53 to 56 per 1,000 person-years in patients followed-up for a maximum of 90 days and from 31 to 34 in patients followed-up for a maximum of 365 days. In general, similar or slightly greater IRs were observed when restricting the study population to patients with T2DM. However, the associated 95% CIs were compatible with similar, higher and lower incidence in the T2DM population. The IRs for any liver disease among initiators of comparator treatments varied from 56 (dapagliflozin) to 63 (sitagliptin) per 1,000 person-years in patients followed-up for a maximum of 90 days and from 34 (dapagliflozin) to 35 (empagliflozin, sitagliptin) in patients followed-up for a maximum of 365 days. In general, similar or lower IRs were observed when restricting the study population to patients with T2DM. However, the associated uncertainty (i.e., 95% CIs) were compatible with similar, higher and lower incidence in the T2DM population.

The IRs for acute hepatic injury and acute hepatic injury with no chronic hepatic failure were substantially lower than those for any liver disease given the scarce number of recorded events and the limited available follow-up.

The HRs of any liver disease for liraglutide initiators compared to active comparators varied from 0.86 to 1.05 in the study population that included all indications. The associated uncertainty of these estimates reflected by the 95% confidence intervals was compatible with similar, higher and lower risk of any liver disease in liraglutide initiators in comparison to empagliflozin, dapagliflozin or sitagliptin initiators.

There was substantial uncertainty around the HRs of acute hepatic injury and acute hepatic injury with no chronic hepatic failure for liraglutide initiators compared to active comparators due to the scarcity of events and limited available follow-up, preventing us from making any meaningful interpretation about the association between liraglutide initiation and risk of acute hepatic injury. Limitations in sample size and precision given the scarcity of these events mean it is not possible to confirm or exclude an association based upon the available data.

6.1. Limitations

Patient's medical history, as captured by GP practices included in the study, may be incomplete, particularly in the IQVIA™ DA Germany database. In Germany, there is no mandatory GP system and patients have free doctor choice. A specialist can be consulted without referral from the GP. As a result, data are collected from visits to various medical practices which are not linked by a unique patient identifier. Therefore, the entire medical history of patients might be fragmented. Thus, limitations of this study include the potential for missing data if exposure, outcomes, or covariates were not recorded or captured in an individual's electronic health record.

Exposure misclassification may exist because only prescribing records were used as data on the actual uptake of these medicines by patients is not available. Information on medication used during hospitalisation, or actual duration of treatments are not captured in the included databases. Moreover, whether patients collected their prescriptions or consumed the prescribed medication is unknown. Analyses did not control for non-adherence to the study treatments, and the extent to which person-time exposure misclassification (e.g., when an initiator discontinues the use of target or comparator treatment) occurs on the ITT analysis was not estimated. However, it is worth noting that this would bias the estimates only if a large proportion of study participants change the baseline treatment early during the follow-up period.

In addition, as only primary care databases with no linkage to hospital diagnoses were used, this could lead to underestimation of the outcomes. Also, it may be possible that outcomes were recorded using terms that were not included in our case definitions, e.g., an acute hepatic outcome was not recorded as acute or was recorded as a nonspecific hepatic outcome. Furthermore, the date of recording an outcome might have been incorrect, if for example, a patient was hospitalised for the outcome, and only later when the patient is followed up in primary care the diagnosis was recorded in the GP records. It should be noted that it was not possible to confirm the outcome recording based on diagnosis codes with laboratory tests for liver function (ALT, AST and bilirubin) given the large number of missing data for these liver function tests in the selected databases.

To our knowledge, there is no data describing the accuracy of coding for acute hepatic injury and, more broadly, diseases of liver in IQVIA™ DA Germany databases. Therefore, we cannot exclude the possibility of outcome misclassification as the case definition was based on SNOMED codes without clinical validation or complementary clinical information based on hospital records. This measurement error would be applied the same way in each comparison group and, if such a bias is present, it would likely be non-differential between target and comparator groups, thus underestimating the actual risk and attenuating the estimated hazard ratio towards 1.

Finally, although more than 1,000 covariates were adjusted for, we cannot rule out the possibility of residual confounding as not all relevant potential confounders are captured in the selected databases (e.g., duration and severity of comorbidities, lifestyle factors or BMI,). Though, comorbidities for which treatments were recorded were corrected for, as the treatment would be included in the PS. In addition, we only measured comorbidities diagnosed/recorded within 365 days prior to index-date. Chronic diseases recorded >365 days prior to index-date were not considered in the PS. Mismeasured confounders would only partially adjust for confounding bias.

7. Conclusion

In our study, the incidence rate of any liver disease was similar for patients initiating liraglutide and patients initiating empagliflozin, dapagliflozin or sitagliptin, when accounting for measured confounders. The statistical uncertainty was limited, meaning that although the results are also compatible with minor differences of the incidence rate of any liver disease, they were incompatible with large differences. However, the results for acute hepatic injury were inconclusive due to limitations in sample size and limitation in patient linkage, which requires further research.

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Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS® Disease Analyzer Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

Annex 2 - Codelists

A2.1 Exposures

OMOP concept name	OMOP concept ID
Liraglutide (including combinations)	40170911
Empagliflozin (including combinations)	45774751
Dapagliflozin (including combinations)	44785829
Sitagliptin (including combinations)	1580747

Frequency of (number and percentage) of patients who received a first ever prescription for any SGLT-2 or any DPP-4 inhibitors in IMRD UK:

Substance	No. of patients first ever prescribed with any of the substances	% of patients ever prescribed with any of the substances
SGLT-2 inhibitors		
Dapagliflozin	10527	50.48
Empagliflozin	7410	35.53
Canagliflozin	2412	11.57
Metformin/Empagliflozin	232	1.11
Metformin/Dapagliflozin	160	0.77
Ertugliflozin	68	0.33
Metformin/Canagliflozin	23	0.11
Saxagliptin/Dapagliflozin	14	0.07
Linagliptin/Empagliflozin	9	0.04
Total	20855	100
DPP-4 inhibitors		
Sitagliptin	29471	54.61
Linagliptin	14074	26.08
Alogliptin	7115	13.18
Saxagliptin	2294	4.25
Vildagliptin	1017	1.88
Total	53971	100

A2.2 Outcomes

A2.2.1 Diseases of liver

The full list of SNOMED concept IDs (codes) defining Diseases of liver is contained in ATLAS: Home (ohdsi.org) (This webpage requires log in details).

Condition occurrences refer to concept IDs recorded in the persons record at a certain point in time. Concept IDs are organised into hierarchies and may be higher-level concept IDs or lower-level concept IDs commonly referred to as descendants.

The Diseases of liver phenotype is defined by the included concept IDs (and their descendants) outlined in Table A1.

The outcome phenotype is therefore the earliest occurrence of anyone of the eligible concept IDs (codes). When used in the comparative cohort analysis this phenotype represents **the incident (first ever) event and people with a history of Diseases of liver prior to index date are excluded**.

Table A1. Concept Set Definitions for the OHDSI Diseases of liver phenotype

Concept ID	Concept Name	Domain
194984	Disease of liver	Condition
4004305	Congenital floating liver	Condition
4194229	Congenital hepatic fibrosis	Condition
4251025	Congenital hepatomegaly	Condition
4221807	Congenital hyperplasia of intrahepatic bile duct	Condition
4050373	Congenital liver grooves	Condition
4247475	Congenital malposition of liver	Condition
4246947	Congenital microhepatia	Condition
606361	Congenital paucity of intrahepatic bile ducts	Condition
4078519	Congenital syphilitic hepatomegaly	Condition
4048592	Congenital viral hepatitis	Condition
36676512	Contiguous ABCD1 DXS1357E deletion syndrome	Condition
4096646	Contusion of liver	Condition
4156416	Copper storage associated hepatitis	Condition
4026135	Coxsackie virus hepatitis	Condition
4229773	Crigler-Najjar syndrome, type I	Condition
4152631	Crush injury of liver	Condition
4163687	Cruveilhier-Baumgarten syndrome	Condition
4232955	Cryptogenic cirrhosis	Condition
4139254	Cystic dilation of intrahepatic duct	Condition
36527583	Cystic hypersecretory carcinoma of intrahepatic bile duct	Condition
36550444	Cystic hypersecretory carcinoma of liver	Condition
4342780	Cyst of intrahepatic bile ducts	Condition
4092685	Cytomegalovirus hepatitis	Condition
37396401	Decompensated cirrhosis of liver	Condition
4098766	Deficiency of coagulation factor due to liver disease	Condition
4096025	Delayed rupture of liver	Condition
4079875	Delta-4-3-oxosteroid-5-beta-reductase deficiency	Condition
36536093	Desmoplastic small round cell tumor of intrahepatic bile duct	Condition
36536485	Desmoplastic small round cell tumor of liver	Condition
4012013	Diffuse hepatic necrosis	Condition
36529112	Diffuse large B-cell lymphoma, NOS, of intrahepatic bile duct	Condition
44503128	Diffuse large B-cell lymphoma, NOS, of liver	Condition
4055210	Diffuse nodular cirrhosis	Condition
3188271	Dilated intrahepatic bile duct	Condition
194984	Disease of liver	Condition
42537673	Disorder of liver co-occurrent and due to disorder of urea cycle	Condition
42538550	Disorder of liver due to disorder of amino acid metabolism	Condition
42537674	Disorder of liver due to disorder of mineral metabolism	Condition

Concept ID	Concept Name	Domain
4222609	Drug-induced cholestatic hepatitis	Condition
4342774	Drug-induced chronic hepatitis	Condition
4143008	Drug-induced cirrhosis of liver	Condition
4144765	Drug-induced disorder of liver	Condition
4231815	Drug-induced hepatic necrosis	Condition
4340942	Drug-induced hepatitis	Condition
4327030	Drug-induced intrahepatic cholestasis	Condition
4195953	Dubin-Johnson syndrome	Condition
4159158	Early cirrhosis	Condition
195749	Echinococcosis of liver	Condition
200656	Echinococcus granulosus infection of liver	Condition
193142	Echinococcus multilocularis infection of liver	Condition
4109794	Ectopic liver	Condition
42512502	Embryonal rhabdomyosarcoma, NOS, of liver	Condition
36531590	Embryonal sarcoma of intrahepatic bile duct	Condition
37396736	Embryonal sarcoma of liver	Condition
4145425	Empyema with hepatopleural fistula	Condition
36542170	Encapsulated papillary carcinoma of intrahepatic bile duct	Condition
36531263	Encapsulated papillary carcinoma of liver	Condition
36548797	Encapsulated papillary carcinoma with invasion of intrahepatic bile duct	Condition
36567135	Encapsulated papillary carcinoma with invasion of liver	Condition
45769564	End stage liver disease	Condition
4340382	Enflurane hepatitis	Condition
37017265	Enlargement of liver co-occurrent with human immunodeficiency virus infection	Condition
36561278	Epithelioid hemangioendothelioma, NOS, of intrahepatic bile duct	Condition
3655297	Epithelioid hemangioendothelioma of liver	Condition
3173052	Epithelioid hemangioendothelioma of liver	Condition
36532785	Epithelioid leiomyosarcoma of intrahepatic bile duct	Condition
36556246	Epithelioid leiomyosarcoma of liver	Condition
42511777	Epithelioid mesothelioma, malignant of liver	Condition
36557688	Epithelioid sarcoma, NOS, of intrahepatic bile duct	Condition
36538965	Epithelioid sarcoma, NOS, of liver	Condition
36559373	Epithelioma, malignant of intrahepatic bile duct	Condition
36545311	Epithelioma, malignant of liver	Condition
4119142	Epstein-Barr virus hepatitis	Condition
4246878	Erythropoietic coproporphyria	Condition
1553251	Ewing sarcoma of liver	Condition
1340280	Exacerbation of chronic active hepatitis	Condition
1340309	Exacerbation of disease of liver	Condition
1340354	Exacerbation of hepatic porphyria	Condition
1340355	Exacerbation of hepatocellular liver damage	Condition
1340378	Exacerbation of inflammatory disease of liver	Condition
1340389	Exacerbation of liver damage	Condition
1340484	Exacerbation of toxic liver disease	Condition
1340487	Exacerbation of type B viral hepatitis	Condition
1340499	Exacerbation of viral hepatitis C	Condition

Concept ID	Concept Name	Domain
1340500	Exacerbation of viral hepatitis, type A	Condition
3655408	Failed attempted termination of pregnancy complicated by acute necrosis of liver	Condition
4265212	Familial arthrogryposis-cholestatic hepatorenal syndrome	Condition
37109612	Familial hypercholanemia	Condition
4244271	Familial porphyria cutanea tarda	Condition
4058680	Fatty portal cirrhosis	Condition
36676856	Ferro-cerebro-cutaneous syndrome	Condition
37163225	Fever-associated acute infantile liver failure syndrome	Condition
36527682	Fibroblastic reticular cell tumor of intrahepatic bile duct	Condition
36522357	Fibroblastic reticular cell tumor of liver	Condition
4099699	Fibrolamellar hepatocellular carcinoma	Condition
42537672	Fibropolycystic disease of liver	Condition
36715922	Fibrosis of liver caused by alcohol	Condition
4221650	Floating liver	Condition
4294539	Florid cirrhosis	Condition
4207818	Focal hepatic necrosis	Condition
4133325	Focal nodular hyperplasia of liver	Condition
4109621	Focal nodular hypoplasia of liver	Condition
36519770	Follicular dendritic cell sarcoma of intrahepatic bile duct	Condition
36529127	Follicular dendritic cell sarcoma of liver	Condition
36529343	Follicular lymphoma, grade 1 of intrahepatic bile duct	Condition
36521269	Follicular lymphoma, grade 1 of liver	Condition
36540760	Follicular lymphoma, grade 2 of intrahepatic bile duct	Condition
36519541	Follicular lymphoma, grade 2 of liver	Condition
36554537	Follicular lymphoma, grade 3 of intrahepatic bile duct	Condition
36560121	Follicular lymphoma, grade 3 of liver	Condition
36560509	Follicular lymphoma, NOS, of intrahepatic bile duct	Condition
36543157	Follicular lymphoma, NOS, of liver	Condition
3655916	Fontan-associated liver disease	Condition
37164407	FTH1-related iron overload	Condition
4340389	Fulminant hepatic failure	Condition
4143845	Fulminant hepatitis	Condition
3180733	Fulminant liver failure secondary to parvovirus found in explanted liver	Condition
37160801	Fungal infection of liver	Condition
44503572	Ganglioneuroblastoma of liver	Condition
36543963	Giant cell and spindle cell carcinoma of intrahepatic bile duct	Condition
36542264	Giant cell and spindle cell carcinoma of liver	Condition
36565258	Giant cell carcinoma of intrahepatic bile duct	Condition
36562650	Giant cell carcinoma of liver	Condition
36556387	Giant cell sarcoma of intrahepatic bile duct	Condition
36533134	Giant cell sarcoma of liver	Condition
36538946	Glandular intraepithelial neoplasia, high grade of liver	Condition
36540479	Glassy cell carcinoma of intrahepatic bile duct	Condition
36526026	Glassy cell carcinoma of liver	Condition
4203601	Glissonian cirrhosis	Condition

Concept ID	Concept Name	Domain
4107542	Glucose-6-phosphate transport defect	Condition
4189519	Glycogenosis with glucoaminophosphaturia	Condition
4342778	Glycogen phosphorylase kinase deficiency	Condition
4182338	Glycogen phosphorylase kinase deficiency, autosomal recessive	Condition
37311725	Glycogen storage disease due to muscle phosphorylase kinase deficiency	Condition
4246087	Glycogen storage disease, hepatic form	Condition
4219504	Glycogen storage disease, type I	Condition
40480645	Glycogen storage disease type Ia	Condition
4284550	Glycogen storage disease type III	Condition
4009322	Glycogen storage disease, type IV	Condition
3655320	Glycogen storage disease type IXB	Condition
4163346	Glycogen storage disease, type VI	Condition
4213784	Glycogen storage disease type VIII	Condition
4291946	Glycogen storage disease type X	Condition
4031791	Glycogen synthase deficiency	Condition
4342771	Gonococcal hepatitis	Condition
3655102	Graft versus host disease of liver	Condition
3173966	Graft versus host disease of liver	Condition
4313846	Granulomatous hepatitis	Condition
37162089	Growth delay, intellectual disability, hepatopathy syndrome	Condition
36676898	Growth retardation, mild developmental delay, chronic hepatitis syndrome	Condition
4340381	Halothane hepatitis	Condition
36543050	Hemangioendothelioma, malignant of intrahepatic bile duct	Condition
44500382	Hemangioendothelioma, malignant of liver	Condition
4179531	Hemangioendothelioma of liver	Condition
4247079	Hemangioma of liver	Condition
36541745	Hemangiosarcoma of intrahepatic bile duct	Condition
443624	Hematoma and contusion of liver	Condition
193627	Injury of hepatic vein	Condition
193355	Injury of liver	Condition
36716541	Injury of liver due to birth trauma	Condition
201161	Injury of liver with open wound into abdominal cavity	Condition
193630	Injury of liver without open wound into abdominal cavity	Condition
37017028	Injury to liver during surgery	Condition
36538339	Interdigitating dendritic cell sarcoma of intrahepatic bile duct	Condition
36552348	Interdigitating dendritic cell sarcoma of liver	Condition
36567720	Intraductal carcinoma, noninfiltrating, NOS, of intrahepatic bile duct	Condition
36549713	Intraductal carcinoma, noninfiltrating, NOS, of liver	Condition
36518884	Intraductal micropapillary carcinoma of intrahepatic bile duct	Condition
36539365	Intraductal micropapillary carcinoma of liver	Condition
36553572	Intraductal papillary adenocarcinoma with invasion of intrahepatic bile duct	Condition
36543183	Intraductal papillary adenocarcinoma with invasion of liver	Condition
37162562	Intraductal papillary neoplasia with high grade intraepithelial neoplasia of liver	Condition
4001664	Intrahepatic bile duct carcinoma	Condition
4109620	Intrahepatic biliary atresia	Condition
4173349	Intrahepatic biliary hypoplasia	Condition

Concept ID	Concept Name	Domain
37162886	Intrahepatic cholangitis due to intrahepatic cholelithiasis	Condition
4096023	Intrahepatic hematoma	Condition
36530005	Intravascular large B-cell lymphoma of intrahepatic bile duct	Condition
36518931	Intravascular large B-cell lymphoma of liver	Condition
36715926	Ischemia reperfusion injury of liver	Condition
4340384	Ischemic hepatitis	Condition
37396394	Isolated polycystic liver disease	Condition
3183833	Isoniazid induced hepatotoxicity	Condition
36716035	Joubert syndrome with congenital hepatic fibrosis	Condition
4144116	Juvenile portal cirrhosis	Condition
36521057	Kaposi sarcoma of intrahepatic bile duct	Condition
36539048	Kaposi sarcoma of liver	Condition
36540282	Kupffer cell sarcoma of liver	Condition
195392	Laceration of liver	Condition
44782863	Laceration of liver with open wound into abdominal cavity	Condition
4340392	Laennec's cirrhosis, non-alcoholic	Condition
36534034	Langerhans cell histiocytosis, disseminated of intrahepatic bile duct	Condition
36523572	Langerhans cell histiocytosis, disseminated of liver	Condition
36558987	Langerhans cell sarcoma of intrahepatic bile duct	Condition
36556190	Langerhans cell sarcoma of liver	Condition
36540794	Large cell carcinoma, NOS, of intrahepatic bile duct	Condition
36538413	Large cell carcinoma, NOS, of liver	Condition
36558322	Large cell carcinoma with rhabdoid phenotype of intrahepatic bile duct	Condition
36519969	Large cell carcinoma with rhabdoid phenotype of liver	Condition
36565096	Large cell neuroendocrine carcinoma of intrahepatic bile duct	Condition
36537431	Large cell neuroendocrine carcinoma of liver	Condition
197676	Large liver	Condition
4049419	Latent cirrhosis	Condition
40488781	Leakage of bile from gallbladder bed	Condition
36552897	Leiomyosarcoma, NOS, of intrahepatic bile duct	Condition
36540847	Leiomyosarcoma, NOS, of liver	Condition
4104000	Lesion of liver	Condition
3199188	Lipitor hepatotoxicity	Observation
4026132	Liver abscess and sequelae of chronic liver disease	Condition
4055214	Liver abscess due to cholangitis	Condition
4055216	Liver abscess due to direct extension	Condition
4026133	Liver abscess due to portal pyemia	Condition
4058690	Liver abscess via hepatic artery	Condition
4055215	Liver abscess via umbilicus	Condition
37164288	Liver adenomatosis	Condition
4178553	Liver calculus	Condition
36559584	Liver cell adenoma of intrahepatic bile duct	Condition
36532550	Liver cell adenoma of liver	Condition
4001171	Liver cell carcinoma	Condition
605193	Liver cirrhosis due to classical cystic fibrosis	Condition
3185452	Liver cirrhosis secondary to nonalcoholic steatohepatitis	Condition

Concept ID	Concept Name	Domain
4225905	Liver cyst	Condition
4352876	Liver damage	Condition
3190339	Liver disease complicating cystic fibrosis	Condition
42536741	Liver disease co-occurrent and due to mitochondrial disorder	Condition
4141669	Liver disease due to cystic fibrosis	Condition
37162164	Liver disease due to peroxisomal disease	Condition
3189753	Liver disease due to TPN dependence	Condition
4341650	Liver disorder due to infection	Condition
45757190	Liver disorder in mother complicating childbirth	Condition
194699	Liver disorder in pregnancy	Condition
4109793	Liver hamartoma	Condition
4096644	Liver hematoma	Condition
4002479	Liver hyperplasia	Condition
40487085	Liver in central position	Condition
40491010	Liver in left sided position	Condition
442538	Liver moderate laceration with open wound into cavity	Condition
4277921	Liver regeneration	Condition
4047865	Liver rupture due to birth trauma	Condition
4047863	Liver subcapsular hematoma due to birth trauma	Condition
4340951	Liver transplant disorder	Condition
4341658	Liver transplant failure	Condition
4308395	Liver transplant failure and rejection	Condition
4341657	Liver transplant rejection	Condition
4200888	Local recurrence of malignant tumor of liver	Condition
4057084	Lupus hepatitis	Condition
37162573	Lymphangioma of liver	Condition
4154553	Lymphocytic portal hepatitis	Condition
36548976	Lymphoepithelial carcinoma of liver	Condition
3655641	Lymphogenic liver abscess	Condition
600665	Lymphoma of liver	Condition
36561660	Lymphoplasmacytic lymphoma of intrahepatic bile duct	Condition
36529169	Lymphoplasmacytic lymphoma of liver	Condition
4184779	Macronodular cirrhosis	Condition
201715	Major laceration of liver with open wound into abdominal cavity	Condition
443870	Major laceration of liver without open wound into abdominal cavity	Condition
4307072	Malarial hepatitis	Condition
42512422	Malignant fibrous histiocytoma of liver	Condition
36529303	Malignant histiocytosis of intrahepatic bile duct	Condition
36555089	Malignant histiocytosis of liver	Condition
36552291	Malignant lymphoma, large B-cell, diffuse, immunoblastic, NOS, of intrahepatic bile duct	Condition
36554702	Malignant lymphoma, large B-cell, diffuse, immunoblastic, NOS, of liver	Condition
36523558	Malignant lymphoma, mixed small and large cell, diffuse of intrahepatic bile duct	Condition
36562623	Malignant lymphoma, mixed small and large cell, diffuse of liver	Condition
36563309	Malignant lymphoma, non-Hodgkin, NOS, of intrahepatic bile duct	Condition

Concept ID	Concept Name	Domain
36532983	Malignant lymphoma, non-Hodgkin, NOS, of liver	Condition
36535744	Malignant lymphoma, NOS, of intrahepatic bile duct	Condition
44501293	Malignant lymphoma, NOS, of liver	Condition
36555001	Malignant mastocytosis of intrahepatic bile duct	Condition
36539632	Malignant mastocytosis of liver	Condition
4089662	Malignant neoplasm of interlobular bile ducts	Condition
4089663	Malignant neoplasm of intrahepatic canaliculi	Condition
4094865	Malignant neoplasm of intrahepatic gall duct	Condition
4246127	Malignant neoplasm of liver	Condition
36564783	Malignant tumor, clear cell type of intrahepatic bile duct	Condition
36564105	Malignant tumor, clear cell type of liver	Condition
36554159	Malignant tumor, giant cell type of intrahepatic bile duct	Condition
36564022	Malignant tumor, giant cell type of liver	Condition
36534058	Malignant tumor, small cell type of intrahepatic bile duct	Condition
36549955	Malignant tumor, small cell type of liver	Condition
36526296	Malignant tumor, spindle cell type of intrahepatic bile duct	Condition
36521364	Malignant tumor, spindle cell type of liver	Condition
36567784	Mantle cell lymphoma of intrahepatic bile duct	Condition
36567370	Mantle cell lymphoma of liver	Condition
36530569	Marginal zone B-cell lymphoma, NOS, of intrahepatic bile duct	Condition
36556854	Marginal zone B-cell lymphoma, NOS, of liver	Condition
36532480	Mast cell sarcoma of intrahepatic bile duct	Condition
36531172	Mast cell sarcoma of liver	Condition
36558555	Mature T-cell lymphoma, NOS, of intrahepatic bile duct	Condition
36555854	Mature T-cell lymphoma, NOS, of liver	Condition
4216214	Mauriac's syndrome	Condition
37395823	Mesenchymal hamartoma of liver	Condition
37311916	Mesothelial carcinoma of liver	Condition
4342777	Metabolic and genetic disorder affecting the liver	Condition
36542920	Microcystic adenoma of intrahepatic bile duct	Condition
36536326	Microcystic adenoma of liver	Condition
4311802	Microhepatia	Condition
4071022	Micronodular cirrhosis	Condition
4246999	Midzonal hepatic necrosis	Condition
444286	Minor laceration of liver with open wound into abdominal cavity	Condition
442773	Minor laceration of liver without open wound into abdominal cavity	Condition
4224597	Miscarriage with acute necrosis of liver	Condition
37204828	Mitochondrial DNA depletion syndrome, hepatocerebral form due to DGUOK deficiency	Condition
37204237	Mitochondrial DNA depletion syndrome hepatocerebrorenal form	Condition
4050640	Mixed micro and macronodular cirrhosis	Condition
42512261	Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) of liver	Condition
194199	Moderate laceration of liver with open wound into abdominal cavity	Condition
197416	Moderate laceration of liver without open wound into abdominal cavity	Condition
36548441	Mucinous adenocarcinoma of intrahepatic bile duct	Condition
44502340	Mucinous adenocarcinoma of liver	Condition

Concept ID	Concept Name	Domain
36553837	Mucinous cystadenoma, NOS, of intrahepatic bile duct	Condition
36543683	Mucinous cystadenoma, NOS, of liver	Condition
36517375	Mucinous cystic neoplasm with high grade dysplasia of intrahepatic bile duct	Condition
36560799	Mucinous cystic neoplasm with high grade dysplasia of liver	Condition
36544042	Scirrhous adenocarcinoma of liver	Condition
4046123	Secondary biliary cirrhosis	Condition
4215747	Secondary syphilis of liver	Condition
40487629	Separate hepatic venous and inferior caval venous connections to heart	Condition
4046017	Septal fibrosis of liver	Condition
36542243	Sezary syndrome of intrahepatic bile duct	Condition
36536579	Sezary syndrome of liver	Condition
35621839	Sickle cell hepatopathy	Condition
44502631	Signet ring cell carcinoma of intrahepatic bile duct	Condition
44501249	Small cell carcinoma, NOS, of liver	Condition
36552130	Small cell sarcoma of intrahepatic bile duct	Condition
36544214	Small cell sarcoma of liver	Condition
36545054	Solitary fibrous tumor/Hemangiopericytoma, grade 1 of intrahepatic bile duct	Condition
36542680	Solitary fibrous tumor/Hemangiopericytoma, grade 1 of liver	Condition
44500887	Solitary fibrous tumor, malignant of liver	Condition
40490872	Solitary necrotic nodule of liver	Condition
4119466	Space occupying lesion of liver	Condition
36546290	Spindle cell carcinoma, NOS, of intrahepatic bile duct	Condition
36517780	Spindle cell carcinoma, NOS, of liver	Condition
36534094	Spindle cell sarcoma of intrahepatic bile duct	Condition
44498970	Spindle cell sarcoma of liver	Condition
4231820	Spontaneous subcapsular liver hematoma	Condition
4270879	Sporadic porphyria cutanea tarda	Condition
36560819	Squamous cell carcinoma, NOS, of liver	Condition
36674831	Squamous cell carcinoma of liver and intrahepatic biliary tract	Condition
36686081	Stage 3 hepatic fibrosis	Condition
40482277	Steatohepatitis	Condition
4059290	Steatosis of liver	Condition
37017281	Steatosis of liver caused by retroviral protease inhibitor	Condition
4244063	Stellate laceration of liver with open wound into abdominal cavity	Condition
4167999	Stellate laceration of liver without open wound into abdominal cavity	Condition
37109745	Steroid dehydrogenase deficiency and dental anomaly syndrome	Condition
4059281	Subacute hepatic failure	Condition
36716709	Subacute hepatic failure caused by hepatitis virus	Condition
4059280	Subacute hepatic necrosis	Condition
4219115	Subacute noninfective hepatitis	Condition
4009167	Subcapsular hemorrhage of liver	Condition
4096645	Subcapsular liver hematoma	Condition
4342773	Subfulminant hepatic failure	Condition
37160993	Submassive hepatic necrosis	Condition
36518171	Superficial spreading adenocarcinoma of intrahepatic bile duct	Condition
36562678	Superficial spreading adenocarcinoma of liver	Condition

Concept ID	Concept Name	Domain
4319181	Supernumerary liver lobe	Condition
4345477	Symmer's pipe-stem fibrosis	Condition
36539369	Synovial sarcoma, NOS, of intrahepatic bile duct	Condition
36525733	Synovial sarcoma, NOS, of liver	Condition
4340395	Synthetic defect of bile acids	Condition
194861	Syphilis of liver	Condition
4053079	Syphilitic cirrhosis	Condition
4058682	Syphilitic portal cirrhosis	Condition
36520983	Systemic EBV positive T-cell lymphoproliferative disease of childhood of intrahepatic bile duct	Condition
36562636	Systemic EBV positive T-cell lymphoproliferative disease of childhood of liver	Condition
36547643	T-cell/histiocyte rich large B-cell lymphoma of intrahepatic bile duct	Condition
36522311	T-cell/histiocyte rich large B-cell lymphoma of liver	Condition
36545635	T-cell large granular lymphocytic leukemia of intrahepatic bile duct	Condition
36567772	T-cell large granular lymphocytic leukemia of liver	Condition
3190596	Tegretol hepatotoxicity	Condition
36562236	Teratoma, NOS, of intrahepatic bile duct	Condition
36529949	Teratoma, NOS, of liver	Condition
4102941	Torsion of liver lobe	Condition
4046016	Toxic cirrhosis	Condition
4055223	Toxic hepatitis	Condition
763865	Toxic hepatitis due to carbamazepine	Condition
4055224	Toxic liver disease	Condition
4052963	Toxic noninfectious hepatitis	Condition
4059287	Toxic portal cirrhosis	Condition
36518115	Trabecular adenocarcinoma of intrahepatic bile duct	Condition
44502616	Trabecular adenocarcinoma of liver	Condition
4096647	Transection of liver	Condition
36676683	Transient infantile hypertriglyceridemia and hepatosteatosis	Condition
1553602	Transitional cell carcinoma, NOS, of liver	Condition
4301613	Traumatic hemorrhage of liver	Condition
42537215	Traumatic rupture of liver	Condition
4108897	Trilobular liver	Condition
4091181	Tuberculosis of liver	Condition
36568388	Tumor cells, malignant of intrahepatic bile duct	Condition
36568033	Tumor cells, malignant of liver	Condition
4281232	Type B viral hepatitis	Condition
36674832	Undifferentiated carcinoma of liver and intrahepatic biliary tract	Condition
36532038	Undifferentiated sarcoma of intrahepatic bile duct	Condition
36533856	Undifferentiated sarcoma of liver	Condition
4055209	Unilobular portal cirrhosis	Condition
4238505	Variegate porphyria	Condition
4341654	Vascular disorder of liver	Condition
4277276	Veno-occlusive disease of the liver	Condition
4291005	Viral hepatitis	Condition
196625	Viral hepatitis A without hepatic coma	Condition

Concept ID	Concept Name	Domain
4313600	Viral hepatitis A without hepatic coma, without hepatitis delta	Condition
198683	Viral hepatitis B without hepatic coma	Condition
197494	Viral hepatitis C	Condition
37151819	Viral hepatitis C in mother during pregnancy	Condition
4063037	Viral hepatitis complicating pregnancy, childbirth and the puerperium	Condition
45768827	Viral hepatitis D	Condition
45769824	Viral hepatitis E	Condition
45757141	Viral hepatitis in mother complicating childbirth	Condition
45757142	Viral hepatitis in mother complicating pregnancy	Condition
4223947	Viral hepatitis, type A	Condition
4287644	Viral hepatitis, type G	Condition
193693	Viral hepatitis without hepatic coma	Condition
4098598	Westphal-Strumpell syndrome	Condition
4229262	Wilson's disease	Condition
36566973	Yolk sac tumor, NOS, of intrahepatic bile duct	Condition
36564402	Yolk sac tumor, NOS, of liver	Condition
4195620	Zieve's syndrome	Condition
4150383	Benign recurrent intrahepatic cholestasis	Condition
37397033	Bile acid CoA ligase deficiency and defective amidation	Condition
36403030	Bile duct adenocarcinoma in situ (C22.1, C24.0) of intrahepatic bile duct	Condition
36560428	Bile duct adenoma of intrahepatic bile duct	Condition
37162582	Bile duct adenoma of intrahepatic bile duct	Condition
36557612	Bile duct adenoma of liver	Condition
36534861	Bile duct cystadenocarcinoma of intrahepatic bile duct	Condition
36558079	Bile duct cystadenocarcinoma of liver	Condition
192675	Biliary cirrhosis	Condition
4059289	Biliary cirrhosis of children	Condition
3654612	Biliary intraepithelial neoplasia grade 3 of liver	Condition
4093474	Blastomycosis liver	Condition
36553955	B lymphoblastic leukemia/lymphoma, NOS, of intrahepatic bile duct	Condition
36542339	B lymphoblastic leukemia/lymphoma, NOS, of liver	Condition
36520675	B lymphoblastic leukemia/lymphoma with hyperdiploidy of intrahepatic bile duct	Condition
36567051	B lymphoblastic leukemia/lymphoma with hyperdiploidy of liver	Condition
36525166	B lymphoblastic leukemia/lymphoma with hypodiploidy (Hypodiploid ALL) of intrahepatic bile duct	Condition
36561935	B lymphoblastic leukemia/lymphoma with hypodiploidy (Hypodiploid ALL) of liver	Condition
36543893	B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1) of intrahepatic bile duct	Condition
36547421	B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1) of liver	Condition
36550037	B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1) of intrahepatic bile duct	Condition
36535793	B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1) of liver	Condition

Concept ID	Concept Name	Domain
36560680	B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); IL3-IGH of intrahepatic bile duct	Condition
36529602	B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); IL3-IGH of liver	Condition
36534985	B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1 of intrahepatic bile duct	Condition
36562821	B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1 of liver	Condition
36517998	B lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged of intrahepatic bile duct	Condition
36535313	B lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged of liver	Condition
37397143	Boichis syndrome	Condition
196715	Budd-Chiari syndrome	Condition
36521797	Burkitt lymphoma, NOS, of intrahepatic bile duct	Condition
36559150	Burkitt lymphoma, NOS, of liver	Condition
37160510	Calculus of intrahepatic bile duct	Condition
4058681	Capsular portal cirrhosis	Condition
4095558	Capsular tear of liver	Condition
36563877	Carcinoma, anaplastic, NOS, of intrahepatic bile duct	Condition
36534359	Carcinoma, anaplastic, NOS, of liver	Condition
1553303	Carcinoma, diffuse type of intrahepatic bile duct	Condition
4241788	Carcinoma in situ of intrahepatic bile ducts	Condition
4243887	Carcinoma in situ of liver	Condition
44503830	Carcinoma, NOS, of liver	Condition
44503831	Carcinomatosis of liver	Condition
36528550	Carcinoma, undifferentiated, NOS, of liver	Condition
36554076	Carcinoma with osteoclast-like giant cells of intrahepatic bile duct	Condition
36560567	Carcinoma with osteoclast-like giant cells of liver	Condition
36559208	Carcinosarcoma, embryonal of intrahepatic bile duct	Condition
36560422	Carcinosarcoma, embryonal of liver	Condition
36524302	Carcinosarcoma, NOS, of intrahepatic bile duct	Condition
44501155	Carcinosarcoma, NOS, of liver	Condition
4252074	Cardiac cirrhosis	Condition
4178542	Cardiac glycogen phosphorylase kinase deficiency	Condition
4141628	Cardiac portal cirrhosis	Condition
37397179	Caroli disease	Condition
37165048	Caroli syndrome	Condition
36519316	Cavernous hemangioma of intrahepatic bile duct	Condition
36554604	Cavernous hemangioma of liver	Condition
3654619	Cavernous hemangioma of liver	Condition
4058696	Central hemorrhagic necrosis of liver	Condition
4030392	Centrilobular hepatic necrosis	Condition
37166753	Cholangiocarcinoma of intrahepatic biliary tract	Condition
4157032	Cholangiohepatitis	Condition
4049282	Cholangiolitic cirrhosis	Condition
4261812	Cholangiolitis	Condition
4268608	Cholestanol storage disease	Condition

Concept ID	Concept Name	Domain
4102952	Cholestasis-edema syndrome, Norwegian type	Condition
4203366	Cholestasis in newborn	Condition
4159743	Cholestasis of parenteral nutrition	Condition
4340944	Cholestasis of pregnancy	Condition
45757110	Cholestasis of pregnancy complicating childbirth	Condition
36715140	Cholestasis with pigmentary retinopathy and cleft palate syndrome	Condition
4318541	Cholestatic hepatitis	Condition
37110503	Chorea co-occurrent and due to Wilson disease	Condition
44502053	Choriocarcinoma, NOS, of liver	Condition
4026125	Chronic active hepatitis	Condition
45769525	Chronic active hepatitis C	Condition
4173584	Chronic active type B viral hepatitis	Condition
4283078	Chronic active viral hepatitis	Condition
4009793	Chronic aggressive type B viral hepatitis	Condition
4232466	Chronic aggressive viral hepatitis	Condition
4146181	Chronic alcoholic hepatitis	Condition
37017009	Chronic alcoholic liver disease	Condition
36687200	Chronic autoimmune hepatitis	Condition
4340390	Chronic hepatic failure	Condition
37162893	Chronic hepatic failure due to portosystemic shunt	Condition
200763	Chronic hepatitis	Condition
3654685	Chronic hepatitis B co-occurrent with hepatitis C and hepatitis D	Condition
37175349	Chronic hepatitis B during pregnancy	Condition
198964	Chronic hepatitis C	Condition
35625141	Chronic hepatitis C caused by Hepatitis C virus genotype 1	Condition
35625296	Chronic hepatitis C caused by Hepatitis C virus genotype 1a	Condition
35625295	Chronic hepatitis C caused by Hepatitis C virus genotype 1b	Condition
35625139	Chronic hepatitis C caused by Hepatitis C virus genotype 2	Condition
35625040	Chronic hepatitis C caused by Hepatitis C virus genotype 3	Condition
35625140	Chronic hepatitis C caused by Hepatitis C virus genotype 4	Condition
35624867	Chronic hepatitis C caused by hepatitis C virus genotype 5	Condition
35624866	Chronic hepatitis C caused by hepatitis C virus genotype 6	Condition
3654682	Chronic hepatitis C co-occurrent with human immunodeficiency virus infection	Condition
45766656	Chronic hepatitis C with stage 2 fibrosis	Condition
45757726	Chronic hepatitis C with stage 3 fibrosis	Condition
42872885	Chronic hepatitis E	Condition
4212540	Chronic liver disease	Condition
4238978	Chronic lobular hepatitis	Condition
4322067	Chronic lymphocytic cholangitis-cholangiohepatitis	Condition
3655440	Chronic necrosis of liver	Condition
201613	Chronic nonalcoholic liver disease	Condition
200451	Chronic passive congestion of liver	Condition
199867	Chronic persistent hepatitis	Condition
4296554	Chronic persistent type B viral hepatitis	Condition
4247138	Chronic persistent viral hepatitis	Condition
4198610	Chronic rejection of liver transplant	Condition

Concept ID	Concept Name	Domain
194574	Chronic type B viral hepatitis	Condition
4012113	Chronic viral hepatitis	Condition
192240	Chronic viral hepatitis B with hepatitis D	Condition
439674	Chronic viral hepatitis B without delta-agent	Condition
763021	Chronic viral hepatitis C with hepatic coma	Condition
42536529	Chronic viral hepatitis D	Condition
44805713	Cirrhosis associated with cystic fibrosis	Condition
194692	Cirrhosis - non-alcoholic	Condition
4064161	Cirrhosis of liver	Condition
37111265	Cirrhosis of liver caused by amiodarone	Condition
37117933	Cirrhosis of liver caused by methotrexate	Condition
37111266	Cirrhosis of liver caused by methyldopa	Condition
3656096	Cirrhosis of liver due to and following cardiac procedure	Condition
43531723	Cirrhosis of liver due to chronic hepatitis C	Condition
45772057	Cirrhosis of liver due to hepatitis B	Condition
42539566	Cirrhosis of liver with primary sclerosing cholangitis	Condition
4153294	Cirrhosis secondary to cholestasis	Condition
37110890	Cirrhotic cardiomyopathy	Condition
36530478	Clear cell adenocarcinoma, NOS, of intrahepatic bile duct	Condition
44500029	Clear cell adenocarcinoma, NOS, of liver	Condition
4292401	Clonorchiasis with biliary cirrhosis	Condition
4082062	Coccidiomycosis liver	Condition
4166154	Combined hepatocellular carcinoma and cholangiocarcinoma	Condition
36545431	Combined hepatocellular carcinoma and cholangiocarcinoma of intrahepatic bile duct	Condition
36560388	Comedocarcinoma, noninfiltrating of intrahepatic bile duct	Condition
36563831	Comedocarcinoma, noninfiltrating of liver	Condition
36553312	Comedocarcinoma, NOS, of intrahepatic bile duct	Condition
36529288	Comedocarcinoma, NOS, of liver	Condition
45771255	Compensated liver disease	Condition
4097699	Compensatory lobar hyperplasia of liver	Condition
200616	Complication of transplanted liver	Condition
36527551	Composite Hodgkin and non-Hodgkin lymphoma of intrahepatic bile duct	Condition
36521120	Composite Hodgkin and non-Hodgkin lymphoma of liver	Condition
4242051	Congenital abnormal fusion of liver lobes	Condition
40486609	Congenital abnormality of hepatic vein	Condition
4245796	Congenital abnormal shape of liver	Condition
4272088	Congenital absence of liver	Condition
4028974	Congenital absence of lobe of liver	Condition
444421	Congenital anomaly of liver	Condition
4005461	Congenital atrophy of left lobe of liver	Condition
36714289	Congenital bile acid synthesis defect type 3	Condition
37166820	Congenital cataract, severe neonatal hepatopathy, global developmental delay syndrome	Condition
44810466	Congenital cholestatic syndrome	Condition
197654	Congenital cystic disease of liver	Condition

Concept ID	Concept Name	Domain
4009157	Congenital dilatation of lobar intrahepatic bile duct	Condition
764977	Congenital dilatation of lobar intrahepatic bile duct with obstruction	Condition
4194969	Congenital duplication of liver	Condition
197134	Hematoma AND contusion of liver with open wound into abdominal cavity	Condition
4043254	Hemorrhage of liver	Condition
4087431	Hepatic actinomycosis	Condition
4316352	Hepatic amyloidosis	Condition
4175588	Hepatic and muscle glycogen phosphorylase kinase deficiency	Condition
4342883	Hepatic ascites	Condition
46273476	Hepatic ascites co-occurrent with chronic active hepatitis due to toxic liver disease	Condition
46269835	Hepatic ascites due to chronic alcoholic hepatitis	Condition
761941	Hepatic candidiasis	Condition
4243356	Hepatic coccidiosis	Condition
4296301	Hepatic congestion	Condition
4090101	Hepatic cryptococcosis	Condition
40492942	Hepatic cystadenoma	Condition
4245954	Hepatic duct dysplasia	Condition
4245975	Hepatic failure	Condition
4309163	Hepatic failure as a complication of care	Condition
4331292	Hepatic failure due to a procedure	Condition
606766	Hepatic failure following surgical procedure	Condition
4267417	Hepatic fibrosis	Condition
37162895	Hepatic fibrosis due to non-alcoholic fatty liver disease	Condition
36674996	Hepatic fibrosis, renal cyst, intellectual disability syndrome	Condition
4340948	Hepatic fibrosis with hepatic sclerosis	Condition
4175589	Hepatic glycogen phosphorylase kinase deficiency	Condition
37110707	Hepatic glycogen synthase deficiency	Condition
37017895	Hepatic granuloma	Condition
4026139	Hepatic granulomas in berylliosis	Condition
4058697	Hepatic granulomas in sarcoidosis	Condition
194417	Hepatic infarction	Condition
4337543	Hepatic necrosis	Condition
4207656	Hepatic porphyria	Condition
4345824	Hepatic schistosomal granuloma	Condition
4236011	Hepatic schistosomiasis	Condition
4340394	Hepatic sclerosis	Condition
4301208	Hepatic vein thrombosis	Condition
40487988	Hepatic vein to coronary sinus	Condition
40492965	Hepatic vein to left atrium and right atrium	Condition
40492963	Hepatic vein to left sided atrium	Condition
40492964	Hepatic vein to right sided atrium	Condition
37110194	Hepatic veno-occlusive disease with immunodeficiency syndrome	Condition
40483136	Hepatitis B and hepatitis C	Condition
40482214	Hepatitis B associated with Human immunodeficiency virus infection	Condition
37164421	Hepatitis B reinfection following liver transplantation	Condition

Concept ID	Concept Name	Domain
4059294	Hepatitis caused by adenovirus	Condition
36715820	Hepatitis caused by sexually transmissible virus	Condition
37163864	Hepatitis caused by Toxoplasma gondii	Condition
44809233	Hepatitis C genotype 1	Condition
44809234	Hepatitis C genotype 2	Condition
44809236	Hepatitis C genotype 3	Condition
44809237	Hepatitis C genotype 4	Condition
44809238	Hepatitis C genotype 5	Condition
44809239	Hepatitis C genotype 6	Condition
3189876	Hepatitis C without hepatic coma	Condition
197493	Hepatitis D superinfection of hepatitis B carrier	Condition
443632	Hepatitis due to acquired toxoplasmosis	Condition
194087	Hepatitis due to infection	Condition
4263363	Hepatitis in coxsackie viral disease	Condition
4055221	Hepatitis in late syphilis	Condition
442066	Hepatitis in secondary syphilis	Condition
4055219	Hepatitis in yellow fever	Condition
763020	Hepatitis with hepatic coma	Condition
4001172	Hepatoblastoma	Condition
36538197	Hepatoblastoma, NOS, of intrahepatic bile duct	Condition
603121	Hepatocellular adenoma	Condition
36566482	Hepatocellular carcinoma, clear cell type of intrahepatic bile duct	Condition
44502698	Hepatocellular carcinoma, clear cell type of liver	Condition
36542147	Hepatocellular carcinoma, fibrolamellar of intrahepatic bile duct	Condition
44501488	Hepatocellular carcinoma, NOS, of intrahepatic bile duct	Condition
36525074	Hepatocellular carcinoma, pleomorphic type of intrahepatic bile duct	Condition
36558585	Hepatocellular carcinoma, pleomorphic type of liver	Condition
36538815	Hepatocellular carcinoma, scirrhous of intrahepatic bile duct	Condition
44502018	Hepatocellular carcinoma, scirrhous of liver	Condition
36533174	Hepatocellular carcinoma, spindle cell variant of intrahepatic bile duct	Condition
44502019	Hepatocellular carcinoma, spindle cell variant of liver	Condition
4245953	Hepatocellular dysplasia	Condition
4282941	Hepatocellular jaundice	Condition
4303098	Hepatocellular liver damage	Condition
35622780	Hepatoencephalopathy due to combined oxidative phosphorylation defect type 1	Condition
761747	Hepatomegaly due to mononucleosis caused by cytomegalovirus	Condition
4222224	Hepatomegaly with AIDS (acquired immunodeficiency syndrome)	Condition
4278462	Hepatomphalocele	Condition
4174671	Hepatoptosis	Condition
3184471	Hepatopulmonary shunting	Condition
4159144	Hepatopulmonary syndrome	Condition
196455	Hepatorenal syndrome	Condition
4308408	Hepatorenal syndrome as a complication of care	Condition
4149888	Hepatorenal syndrome due to a procedure	Condition
4119093	Hepatorenal syndrome following delivery	Condition

Concept ID	Concept Name	Domain
37168714	Hepatorenal syndrome with acute kidney injury	Condition
4345823	Hepatosplenic schistosomiasis	Condition
3655317	Hepatosplenic schistosomiasis caused by Schistosoma haematobium	Condition
37160802	Hepatosplenic schistosomiasis caused by Schistosoma japonicum	Condition
36563470	Hepatosplenic T-cell lymphoma of intrahepatic bile duct	Condition
36537433	Hepatosplenic T-cell lymphoma of liver	Condition
4279681	Hepatosplenomegaly	Condition
4251631	Hereditary coproporphyria	Condition
45757252	Herpes simplex hepatitis	Condition
36530547	HHV8 positive diffuse large B-cell lymphoma of intrahepatic bile duct	Condition
36566463	HHV8 positive diffuse large B-cell lymphoma of liver	Condition
36534778	Histiocytic sarcoma of intrahepatic bile duct	Condition
36530148	Histiocytic sarcoma of liver	Condition
4090095	Histoplasmosis liver	Condition
36527838	Hodgkin granuloma of intrahepatic bile duct	Condition
36567505	Hodgkin granuloma of liver	Condition
36553300	Hodgkin lymphoma, lymphocyte depletion, diffuse fibrosis of intrahepatic bile duct	Condition
36554548	Hodgkin lymphoma, lymphocyte depletion, diffuse fibrosis of liver	Condition
36532456	Hodgkin lymphoma, lymphocyte depletion, NOS, of intrahepatic bile duct	Condition
36530242	Hodgkin lymphoma, lymphocyte depletion, NOS, of liver	Condition
36542215	Hodgkin lymphoma, lymphocyte depletion, reticular of intrahepatic bile duct	Condition
36559578	Hodgkin lymphoma, lymphocyte depletion, reticular of liver	Condition
36552881	Hodgkin lymphoma, lymphocyte-rich of intrahepatic bile duct	Condition
36565589	Hodgkin lymphoma, lymphocyte-rich of liver	Condition
36540253	Hodgkin lymphoma, mixed cellularity, NOS, of intrahepatic bile duct	Condition
36556417	Hodgkin lymphoma, mixed cellularity, NOS, of liver	Condition
36541090	Hodgkin lymphoma, nodular lymphocyte predominant of intrahepatic bile duct	Condition
36520031	Hodgkin lymphoma, nodular lymphocyte predominant of liver	Condition
36540871	Hodgkin lymphoma, nodular sclerosis, cellular phase of intrahepatic bile duct	Condition
36561018	Hodgkin lymphoma, nodular sclerosis, cellular phase of liver	Condition
36523009	Hodgkin lymphoma, nodular sclerosis, grade 1 of intrahepatic bile duct	Condition
36561445	Hodgkin lymphoma, nodular sclerosis, grade 1 of liver	Condition
36564844	Hodgkin lymphoma, nodular sclerosis, grade 2 of intrahepatic bile duct	Condition
36548056	Hodgkin lymphoma, nodular sclerosis, grade 2 of liver	Condition
36564642	Hodgkin lymphoma, nodular sclerosis, NOS, of intrahepatic bile duct	Condition
36552168	Hodgkin lymphoma, nodular sclerosis, NOS, of liver	Condition
36560219	Hodgkin lymphoma, NOS, of intrahepatic bile duct	Condition
36544940	Hodgkin lymphoma, NOS, of liver	Condition
36559844	Hodgkin sarcoma of intrahepatic bile duct	Condition
36539771	Hodgkin sarcoma of liver	Condition
4029123	Homozygous hereditary coproporphyria	Condition
4006312	Homozygous porphyria cutanea tarda	Condition
4029884	Homozygous variegate porphyria	Condition
4208985	Hunter's syndrome, mild form	Condition
4247774	Hunter's syndrome, severe form	Condition

Concept ID	Concept Name	Domain
4323557	Hydrohepatosis	Condition
4161644	Hyperacute rejection of liver transplant	Condition
4340950	Hyperbilirubinemia - conjugated - type III	Condition
36675115	Hyperbiliverdinemia	Condition
36674388	Hypercholesterolemia due to cholesterol 7alpha-hydroxylase deficiency	Condition
42536533	Hypersensitivity disease of liver caused by drug	Condition
4340946	Hypoxia-associated cirrhosis	Condition
37396157	Idiopathic copper associated cirrhosis of liver	Condition
37164806	Idiopathic ductopenia	Condition
36716883	Idiopathic granulomatous hepatitis	Condition
4079849	Idiopathic hepatitis in infancy	Condition
37164807	Idiopathic peliosis hepatis	Condition
4268006	Indian childhood cirrhosis	Condition
43530913	Induced termination of pregnancy complicated by acute necrosis of liver	Condition
45766163	Infantile hemangioma of liver	Condition
4234839	Infection by Opisthorchis viverrini	Condition
3655321	Infection of liver and spleen caused by Schistosoma mansoni	Condition
3655669	Infection of liver caused by parasite	Condition
37163850	Infection of liver transplant	Condition
4340393	Infectious cirrhosis	Condition
4008083	Infectious neonatal hepatitis	Condition
36567076	Infiltrating duct carcinoma, NOS, of intrahepatic bile duct	Condition
36551545	Infiltrating duct carcinoma, NOS, of liver	Condition
194990	Inflammatory disease of liver	Condition
37399368	Inflammatory pseudotumor of liver	Condition
37162712	Mucinous cystic neoplasm with high-grade intraepithelial neoplasia of liver	Condition
36566791	Mucin-producing adenocarcinoma of intrahepatic bile duct	Condition
36554673	Mucin-producing adenocarcinoma of liver	Condition
4323827	Mucopolysaccharidosis, MPS-II	Condition
4148254	Multilobular portal cirrhosis	Condition
192824	Mumps hepatitis	Condition
36676640	Muscular hypertrophy, hepatomegaly, polyhydramnios syndrome	Condition
36557842	Myeloid or lymphoid neoplasm with FGFR1 abnormalities of intrahepatic bile duct	Condition
36560134	Myeloid or lymphoid neoplasm with FGFR1 abnormalities of liver	Condition
36547434	Myeloid or lymphoid neoplasm with PDGFRA rearrangement of intrahepatic bile duct	Condition
36537306	Myeloid or lymphoid neoplasm with PDGFRA rearrangement of liver	Condition
44499619	Myeloid sarcoma of liver	Condition
36527087	Myeloproliferative neoplasm, unclassifiable of intrahepatic bile duct	Condition
36537048	Myeloproliferative neoplasm, unclassifiable of liver	Condition
36528061	Myoepithelial carcinoma of intrahepatic bile duct	Condition
36556399	Myoepithelial carcinoma of liver	Condition
36535696	Myosarcoma of intrahepatic bile duct	Condition
36534043	Myosarcoma of liver	Condition
36541502	Myxoid leiomyosarcoma of intrahepatic bile duct	Condition

Concept ID	Concept Name	Domain
36543069	Myxoid leiomyosarcoma of liver	Condition
37205068	Navajo neurohepatopathy	Condition
4239091	Necrosis of liver of pregnancy	Condition
42536722	Neonatal hemorrhage of liver	Condition
4320490	Neonatal hepatitis	Condition
4318835	Neonatal hepatocellular damage	Condition
4214373	Neonatal hepatosplenomegaly	Condition
37399026	Neonatal intrahepatic cholestasis due to citrin deficiency	Condition
4130519	Neoplasm of intrahepatic bile ducts	Condition
4130518	Neoplasm of liver	Condition
4317541	Neoplasm of uncertain behavior of intrahepatic bile ducts	Condition
4313636	Neoplasm of uncertain behavior of liver	Condition
36518547	Neuroendocrine carcinoma, NOS, of intrahepatic bile duct	Condition
42512137	Neuroendocrine tumor, NOS, of intrahepatic bile duct	Condition
44500135	Neuroendocrine tumor, NOS, of liver	Condition
36555158	NK/T-cell lymphoma, nasal and nasal type of intrahepatic bile duct	Condition
36527055	NK/T-cell lymphoma, nasal and nasal type of liver	Condition
4001168	Nodular hyperplasia of liver	Condition
37018557	Nodular regenerative hyperplasia of liver	Condition
37017427	Nodular regenerative hyperplasia of liver caused by antiretroviral drug	Condition
4322895	Nodule of liver	Condition
4026131	Non-alcoholic fatty liver	Condition
37164766	Non-alcoholic fatty liver disease	Condition
36716710	Non-alcoholic fatty liver disease without non-alcoholic steatohepatitis	Condition
37169717	Nonalcoholic fatty liver during pregnancy	Condition
40484532	Nonalcoholic steatohepatitis	Condition
36557286	Noninfiltrating intraductal papillary adenocarcinoma of intrahepatic bile duct	Condition
36538737	Noninfiltrating intraductal papillary adenocarcinoma of liver	Condition
42512523	Non-small cell carcinoma of intrahepatic bile duct	Condition
4340941	Nonspecific reactive hepatitis	Condition
44783142	North American Indian childhood cirrhosis	Condition
36674397	NPHP3-related Meckel-like syndrome	Condition
4048057	Nutritional cirrhosis	Condition
4003673	Obstructive biliary cirrhosis	Condition
37017654	Occult chronic type B viral hepatitis	Condition
444117	Opisthorchiasis	Condition
37161129	Opisthorchis felineus infection	Condition
42512425	Osteosarcoma, NOS, of liver	Condition
44502704	Papillary adenocarcinoma, NOS, of liver	Condition
44498958	Papillary cystadenocarcinoma, NOS, of liver	Condition
4140536	Parasitic cirrhosis	Condition
4009165	Parenchymatous degeneration of liver	Condition
4173182	Parenteral nutrition-related hepatitis	Condition
42537675	Partial nodular transformation of liver	Condition
37163155	Pediatric hepatocellular carcinoma	Condition
4240725	Peliosis hepatis	Condition

Concept ID	Concept Name	Domain
4342775	Pericellular fibrosis of congenital syphilis	Condition
44502225	Perihilar cholangiocarcinoma of intrahepatic bile duct	Condition
4171096	Perinatal hepatitis	Condition
37172861	Perinatal hepatitis B	Condition
37172860	Perinatal hepatitis C	Condition
4173181	Perinatal hepatocellular damage	Condition
4203168	Peripheral hepatic necrosis	Condition
3655942	Periportal fibrosis	Condition
602626	Phlebosclerosis of intrahepatic vein	Condition
4059285	Pigmentary portal cirrhosis	Condition
4300060	Pigment cirrhosis	Condition
4055211	Pipestem portal cirrhosis	Condition
36548643	Plasmablastic lymphoma of intrahepatic bile duct	Condition
36525154	Plasmablastic lymphoma of liver	Condition
36562547	Plasmacytoma, extramedullary of intrahepatic bile duct	Condition
44502851	Plasmacytoma, extramedullary of liver	Condition
36520572	Plasmacytoma, NOS, of intrahepatic bile duct	Condition
36537152	Plasmacytoma, NOS, of liver	Condition
36518028	Pleomorphic carcinoma of intrahepatic bile duct	Condition
36530153	Pleomorphic carcinoma of liver	Condition
36541454	Polygonal cell carcinoma of intrahepatic bile duct	Condition
36530664	Polygonal cell carcinoma of liver	Condition
4264925	Porphyria cutanea tarda	Condition
4304584	Portal cirrhosis	Condition
4058685	Portal fibrosis without cirrhosis	Condition
192670	Portal pyemia	Condition
4066291	Portal triaditis	Condition
4098583	Posthepatitic cirrhosis	Condition
4313567	Postnecrotic cirrhosis	Condition
4103088	Posttransfusion viral hepatitis	Condition
1553325	Post-transplant lymphoproliferative disorder, NOS, of intrahepatic bile duct	Condition
1553301	Post-transplant lymphoproliferative disorder, NOS, of liver	Condition
3183806	Postviral gastroparesis	Condition
36564208	Precursor cell lymphoblastic lymphoma, NOS, of intrahepatic bile duct	Condition
36554099	Precursor cell lymphoblastic lymphoma, NOS, of liver	Condition
36534498	Precursor T-cell lymphoblastic leukemia of intrahepatic bile duct	Condition
36567111	Precursor T-cell lymphoblastic leukemia of liver	Condition
602006	Primary adenocarcinoma of intrahepatic bile duct	Condition
4135822	Primary biliary cholangitis	Condition
37164403	Primary biliary cholangitis and/or primary sclerosing cholangitis and autoimmune hepatitis overlap syndrome	Condition
4094864	Primary carcinoma of liver	Condition
37162578	Primary carcinosarcoma of liver	Condition
36715927	Primary cholangiocarcinoma of intrahepatic biliary tract	Condition
37162060	Primary combined hepatocellular carcinoma and cholangiocarcinoma	Condition
37162572	Primary cystadenocarcinoma of intrahepatic bile duct	Condition

Concept ID	Concept Name	Domain
37162601	Primary embryonal carcinoma of liver	Condition
37167574	Primary embryonal sarcoma of liver	Condition
37166672	Primary epithelioid hemangioendothelioma of liver	Condition
37162058	Primary fibrolamellar hepatocellular carcinoma	Condition
37399544	Primary hepatic neuroendocrine carcinoma	Condition
37167661	Primary hepatoblastoma of liver	Condition
37166184	Primary intrahepatic bile duct carcinoma	Condition
37164805	Primary intrahepatic lithiasis	Condition
37162059	Primary liver cell carcinoma	Condition
40490929	Primary malignant neoplasm of intrahepatic bile duct	Condition
201519	Primary malignant neoplasm of liver	Condition
37167595	Primary squamous cell carcinoma of liver and intrahepatic biliary tract	Condition
37162732	Primary teratocarcinoma of liver	Condition
37167535	Primary undifferentiated carcinoma of liver and intrahepatic biliary tract	Condition
607683	Progressive familial intrahepatic cholestasis type 1	Condition
607718	Progressive familial intrahepatic cholestasis type 2	Condition
37162165	Progressive familial intrahepatic cholestasis type 3	Condition
4253211	Progressive intrahepatic cholestasis	Condition
36544032	Pseudosarcomatous carcinoma of intrahepatic bile duct	Condition
44502321	Pseudosarcomatous carcinoma of liver	Condition
37109889	Pulmonary fibrosis, hepatic hyperplasia, bone marrow hypoplasia syndrome	Condition
4173094	Pyogenic hepatic abscess	Condition
4260073	Q fever hepatitis	Condition
4201597	Radiation hepatitis	Condition
40488872	Reactivation of hepatitis B viral hepatitis	Condition
45773146	Reactivation of hepatitis C viral hepatitis	Condition
4026126	Recurrent hepatitis	Condition
37162668	Recurrent hepatitis C virus induced liver disease following liver transplant	Condition
4316361	Red blood cell sequestration in liver	Condition
4183882	Relapsing type A viral hepatitis	Condition
4238508	Relapsing viral hepatitis	Condition
35622407	Renal hepatic pancreatic dysplasia	Condition
37109995	Retinohepatoendocrinologic syndrome	Condition
37399445	Reynolds syndrome	Condition
36525687	Rhabdoid tumor, NOS, of intrahepatic bile duct	Condition
44500894	Rhabdoid tumor, NOS, of liver	Condition
36522045	Rhabdomyosarcoma, NOS, of intrahepatic bile duct	Condition
44501537	Rhabdomyosarcoma, NOS, of liver	Condition
4033143	Riedel's lobe of liver	Condition
4139925	Rotor syndrome	Condition
4340943	Rupture of liver	Condition
3654951	Rupture of liver due to Echinococcus granulosus infection	Condition
36550905	Sarcoma, NOS, of intrahepatic bile duct	Condition
4115271	Sarcoma of liver	Condition
4096793	Sawdust liver	Condition
4346170	Schistosomal hepatomegaly	Condition

Concept ID	Concept Name	Domain
36559206	Scirrhous adenocarcinoma of intrahepatic bile duct	Condition
4031812	3-Beta-hydroxy-delta-5-C27-steroid dehydrogenase deficiency	Condition
4100865	Abnormal connection of hepatic vein to atrium	Condition
40488972	Abnormality of hepatic vein	Condition
4108896	Abnormal liver lobulation	Condition
201901	Abscess of liver	Condition
4332942	Accelerated rejection of liver transplant	Condition
4216564	Accessory liver	Condition
44499564	Acinar cell carcinoma of intrahepatic bile duct	Condition
42512483	Acinar cell carcinoma of liver	Condition
196438	Acquired arteriovenous fistula of liver	Condition
606453	Acquired paucity of intrahepatic bile ducts	Condition
607765	Acquired porphyria cutanea tarda	Condition
201343	Acute alcoholic liver disease	Condition
201065	Acute and subacute liver necrosis	Condition
4157033	Acute cholangiohepatitis	Condition
37396531	Acute fatty liver of pregnancy	Condition
4048523	Acute focal hepatitis	Condition
4078071	Acute fulminating type A viral hepatitis	Condition
4027854	Acute fulminating type B viral hepatitis	Condition
4260842	Acute fulminating viral hepatitis	Condition
4026032	Acute hepatic failure	Condition
36716708	Acute hepatic failure caused by hepatitis virus	Condition
4184847	Acute hepatic failure due to drugs	Condition
4243475	Acute hepatitis	Condition
439673	Acute hepatitis B with delta-agent (coinfection) without hepatic coma	Condition
4341652	Acute hepatitis B with hepatitis D	Condition
192242	Acute hepatitis C	Condition
197490	Acute hepatitis E	Condition
4055207	Acute hepatitis - non-infective	Condition
37162423	Acute infantile liver failure, cerebellar ataxia, peripheral sensory motor neuropathy syndrome	Condition
36715006	Acute infantile liver failure due to synthesis defect of mitochondrial deoxyribonucleic acid encoded protein	Condition
36676901	Acute infantile liver failure with multisystemic involvement syndrome	Condition
36676304	Acute infectious hepatitis	Condition
45768686	Acute multi-acinar necrosis of liver	Condition
4058676	Acute necrosis of liver	Condition
37167450	Acute necrosis of liver following ectopic pregnancy	Condition
37167419	Acute necrosis of liver following molar pregnancy	Condition
37017151	Acute on chronic alcoholic liver disease	Condition
37162877	Acute passive congestion of liver	Condition
4250743	Acute red atrophy of liver	Condition
4331678	Acute rejection of liver transplant	Condition
4169242	Acute toxic hepatitis	Condition
4098652	Acute type A viral hepatitis	Condition

Concept ID	Concept Name	Domain
197795	Acute type B viral hepatitis	Condition
4211974	Acute viral hepatitis	Condition
36542389	Adenocarcinoma in situ, NOS, of intrahepatic bile duct	Condition
36545521	Adenocarcinoma in situ, NOS, of liver	Condition
44499881	Adenocarcinoma, NOS, of intrahepatic bile duct	Condition
44501569	Adenocarcinoma, NOS, of liver	Condition
4252535	Adenocarcinoma of liver	Condition
37204022	Adenocarcinoma of liver and intrahepatic biliary tract	Condition
36517577	Adenocarcinoma with mixed subtypes of intrahepatic bile duct	Condition
36564124	Adenocarcinoma with mixed subtypes of liver	Condition
4310731	Adenoma of liver	Condition
42511687	Adenosquamous carcinoma of intrahepatic bile duct	Condition
36521399	Adenosquamous carcinoma of liver	Condition
37162686	Adult hepatocellular carcinoma	Condition
4048083	Advanced cirrhosis	Condition
604694	Agenesis of liver	Condition
196463	Alcoholic cirrhosis	Condition
193256	Alcoholic fatty liver	Condition
4340385	Alcoholic fibrosis and sclerosis of liver	Condition
4340386	Alcoholic hepatic failure	Condition
4340383	Alcoholic hepatitis	Condition
201612	Alcoholic liver damage	Condition
37164788	Alcoholic steatohepatitis	Condition
36550032	ALK positive large B-cell lymphoma of intrahepatic bile duct	Condition
36559574	ALK positive large B-cell lymphoma of liver	Condition
4139051	Allergic hepatitis	Condition
192275	Alpha-1-antitrypsin deficiency	Condition
4097874	Alpha-1-antitrypsin hepatitis	Condition
45763922	Alpha-methylacyl-CoA racemase deficiency disorder	Condition
4319160	Amebic hepatitis	Condition
194560	Amebic liver abscess	Condition
36553287	Anaplastic large cell lymphoma, T-cell and Null-cell type of intrahepatic bile duct	Condition
44501121	Anaplastic large cell lymphoma, T-cell and Null-cell type of liver	Condition
36524532	Angioimmunoblastic T-cell lymphoma of intrahepatic bile duct	Condition
36524484	Angioimmunoblastic T-cell lymphoma of liver	Condition
36520704	Angiomyolipoma of intrahepatic bile duct	Condition
37162622	Angiomyolipoma of liver	Condition
36547848	Angiomyolipoma of liver	Condition
36545229	Angiomyosarcoma of intrahepatic bile duct	Condition
36526204	Angiomyosarcoma of liver	Condition
4003021	Angiosarcoma of liver	Condition
4193635	Anicteric type A viral hepatitis	Condition
4203326	Anicteric type B viral hepatitis	Condition
4168151	Anicteric viral hepatitis	Condition
4138237	Anomalous pulmonary venous drainage to hepatic veins	Condition

Concept ID	Concept Name	Domain
4341656	Antichymotrypsin deficiency-alpha-1	Condition
4136964	Arteriohepatic dysplasia	Condition
4224145	Arteriovenous malformation of liver	Condition
37395593	Arthritis due to viral infection and co-occurrent with hepatitis	Condition
4231698	Atrophy of liver	Condition
37162862	Autoantibody negative autoimmune hepatitis	Condition
200762	Autoimmune hepatitis	Condition
36715923	Autoimmune hepatitis type 1	Condition
36717496	Autoimmune hepatitis type 2	Condition
36715924	Autoimmune hepatitis type 3	Condition
4340391	Autoimmune liver disease	Condition
619148	Autosomal dominant polycystic liver disease	Condition
4104791	Avulsion of liver	Condition
37399734	Bacterial hepatitis	Condition
3655650	Bacterial liver abscess	Condition
4055212	Bacterial portal cirrhosis	Condition
36556320	Basal cell adenocarcinoma of intrahepatic bile duct	Condition
36554731	Basal cell adenocarcinoma of liver	Condition
36520139	B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma of intrahepatic bile duct	Condition
36523019	B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma of liver	Condition
602031	Benign carcinoid tumor of liver	Condition
3654614	Benign intrahepatic cholestasis type 1	Condition
37162154	Benign intrahepatic cholestasis type 2	Condition
4240010	Benign neoplasm of intrahepatic bile ducts	Condition
4243427	Benign neoplasm of liver	Condition

A2.2.2 Acute Hepatic Injury

The full list of SNOMED concept IDs (codes) defining Acute Hepatic Injury is contained in ATLAS: Home (ohdsi.org) (This webpage requires log in details).

The following explains the logic used to define the phenotype of Acute Hepatic Injury and how it is used in the study.

Condition occurrences refer to concept IDs recorded in the persons record at a certain point in time. Concept IDs are organised into hierarchies and may be higher-level concept IDs or lower-level concept IDs commonly referred to as descendants.

The Acute Hepatic Injury phenotype is defined by the included concept IDs and their descendants outlined in Table A2. Some of the descendent concept IDs are considered unrelated or non-specific for acute hepatic injury and have been excluded. If a lower-level concept ID is excluded so too are its descendants unless they are forced back into the list of included concept IDs.

The outcome phenotype is therefore the earliest occurrence of anyone of the eligible concept IDs (codes). When used in the comparative cohort analysis this phenotype represents **the incident (first ever) event, and people with a history of Acute Hepatic Injury prior to index date are excluded**.

760 Table A2. Concept Set Definitions for the OHDSI Acute Hepatic Injury outcome

Concept ID	Concept Name	Domain	Vocabulary	Descendants
Included higher-level concept IDs				
4144765	Drug-induced disorder of liver	Condition	SNOMED	YES
4245975	Hepatic failure	Condition	SNOMED	YES
194990	Inflammatory disease of liver	Condition	SNOMED	YES
193355	Injury of liver	Condition	SNOMED	YES
4048523	Acute focal hepatitis	Condition	SNOMED	YES
4352876	Liver damage	Condition	SNOMED	YES
4055224	Toxic liver disease	Condition	SNOMED	YES
Excluded lower-level concept IDs				
201612	Alcoholic liver damage	Condition	SNOMED	YES
3190596	Tegretol hepatotoxicity	Condition	Nebraska Lexicon	YES
3183833	Isoniazid induced hepatotoxicity	Condition	Nebraska Lexicon	YES
3199188	Lipitor hepatotoxicity	Observation	Nebraska Lexicon	YES
37017281	Steatosis of liver caused by retroviral protease inhibitor	Condition	SNOMED	YES
37017427	Nodular regenerative hyperplasia of liver caused by antiretroviral drug	Condition	SNOMED	YES
37166820	Congenital cataract, severe neonatal hepatopathy, global developmental delay syndrome	Condition	SNOMED	YES
3180733	Fulminant liver failure secondary to parvovirus found in explanted liver	Condition	Nebraska Lexicon	YES
45769564	End stage liver disease	Condition	SNOMED	YES
4340386	Alcoholic hepatic failure	Condition	SNOMED	YES
4340390	Chronic hepatic failure	Condition	SNOMED	YES
37395593	Arthritis due to viral infection and co-occurrent with hepatitis	Condition	SNOMED	YES
37399368	Inflammatory pseudotumor of liver	Condition	SNOMED	YES
194087	Hepatitis due to infection	Condition	SNOMED	YES
4201597	Radiation hepatitis	Condition	SNOMED	YES
4026139	Hepatic granulomas in berylliosis	Condition	SNOMED	YES
37164788	Alcoholic steatohepatitis	Condition	SNOMED	YES
763865	Toxic hepatitis due to carbamazepine	Condition	SNOMED	YES
4340382	Enflurane hepatitis	Condition	SNOMED	YES
4340383	Alcoholic hepatitis	Condition	SNOMED	YES
4340381	Halothane hepatitis	Condition	SNOMED	YES
4342774	Drug-induced chronic hepatitis	Condition	SNOMED	YES
4301613	Traumatic hemorrhage of liver	Condition	SNOMED	YES
193627	Injury of hepatic vein	Condition	SNOMED	YES
1340389	Exacerbation of liver damage	Condition	OMOP Extension	YES
36716541	Injury of liver due to birth trauma	Condition	SNOMED	YES
37017028	Injury to liver during surgery	Condition	SNOMED	YES
4152631	Crush injury of liver	Condition	SNOMED	YES
4340943	Rupture of liver	Condition	SNOMED	YES
4096646	Contusion of liver	Condition	SNOMED	YES
4096647	Transection of liver	Condition	SNOMED	YES
195392	Laceration of liver	Condition	SNOMED	YES
201161	Injury of liver with open wound into abdominal cavity	Condition	SNOMED	YES
193630	Injury of liver without open wound into abdominal cavity	Condition	SNOMED	YES
4104791	Avulsion of liver	Condition	SNOMED	YES

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A2.2.3. Acute Hepatic Injury with no chronic hepatic failure

The full list of SNOMED concept IDs (codes) defining Acute Hepatic Injury with no chronic hepatic failure is contained in ATLAS: Home (ohdsi.org) (This webpage requires log in details).

The following explains the logic used to define the phenotype of Acute Hepatic Injury with no chronic hepatic failure and how it is used in the study.

Condition occurrences refer to concept IDs recorded in the persons record at a certain point in time. Concept IDs are organised into hierarchies and may be higher-level concept IDs or lower-level concept IDs commonly referred to as descendants.

The Acute Hepatic Injury with no chronic hepatic failure phenotype is defined by:

- The included concept IDs (and their descendants) outlined in Table A2 (above). Some of the descendent concept IDs are considered unrelated or non-specific for acute hepatic injury with no chronic hepatic failure and have been excluded. If a lower-level concept ID is excluded so too are its descendants unless they are forced back into the list of included concept IDs.
- The concept IDs outline in Table A3 (below) corresponding to chronic conditions which are considered to identify "no previous chronic liver disease".

I.e., only patients who fulfil the criteria of **acute hepatic injury** (as defined in Table A2 above) **AND "no previous chronic liver disease"** are included in this phenotype.

The outcome phenotype is therefore the earliest occurrence of anyone of the eligible concept IDs (codes). When used in the comparative cohort analysis this phenotype represents **the incident (first ever) event and people with a history of Acute Hepatic Injury with no chronic hepatic failure prior to index date are excluded**.

Table A3. Concept Set Definitions for the OHDSI chronic liver disease

Concept Id	Concept Name	Domain
763021	Chronic viral hepatitis C with hepatic coma	Condition
42536529	Chronic viral hepatitis D	Condition
44805713	Cirrhosis associated with cystic fibrosis	Condition
194692	Cirrhosis - non-alcoholic	Condition
4064161	Cirrhosis of liver	Condition
37111265	Cirrhosis of liver caused by amiodarone	Condition
37117933	Cirrhosis of liver caused by methotrexate	Condition
37111266	Cirrhosis of liver caused by methyldopa	Condition
3656096	Cirrhosis of liver due to and following cardiac procedure	Condition
43531723	Cirrhosis of liver due to chronic hepatitis C	Condition
45772057	Cirrhosis of liver due to hepatitis B	Condition
42539566	Cirrhosis of liver with primary sclerosing cholangitis	Condition
4153294	Cirrhosis secondary to cholestasis	Condition
37110890	Cirrhotic cardiomyopathy	Condition
4292401	Clonorchiasis with biliary cirrhosis	Condition
4163687	Cruveilhier-Baumgarten syndrome	Condition
4232955	Cryptogenic cirrhosis	Condition
37396401	Decompensated cirrhosis of liver	Condition
4055210	Diffuse nodular cirrhosis	Condition
4212540	Chronic liver disease	Condition
37017151	Acute on chronic alcoholic liver disease	Condition
4048083	Advanced cirrhosis	Condition
196463	Alcoholic cirrhosis	Condition
37162862	Autoantibody negative autoimmune hepatitis	Condition

Concept Id	Concept Name	Domain
4055212	Bacterial portal cirrhosis	Condition
192675	Biliary cirrhosis	Condition
4059289	Biliary cirrhosis of children	Condition
4058681	Capsular portal cirrhosis	Condition
4252074	Cardiac cirrhosis	Condition
4141628	Cardiac portal cirrhosis	Condition
4049282	Cholangiolitic cirrhosis	Condition
4026125	Chronic active hepatitis	Condition
45769525	Chronic active hepatitis C	Condition
4173584	Chronic active type B viral hepatitis	Condition
4283078	Chronic active viral hepatitis	Condition
4009793	Chronic aggressive type B viral hepatitis	Condition
4232466	Chronic aggressive viral hepatitis	Condition
4146181	Chronic alcoholic hepatitis	Condition
37017009	Chronic alcoholic liver disease	Condition
36687200	Chronic autoimmune hepatitis	Condition
4340390	Chronic hepatic failure	Condition
37162893	Chronic hepatic failure due to portosystemic shunt	Condition
200763	Chronic hepatitis	Condition
3654685	Chronic hepatitis B co-occurrent with hepatitis C and hepatitis D	Condition
37175349	Chronic hepatitis B during pregnancy	Condition
198964	Chronic hepatitis C	Condition
35625141	Chronic hepatitis C caused by Hepatitis C virus genotype 1	Condition
35625296	Chronic hepatitis C caused by Hepatitis C virus genotype 1a	Condition
35625295	Chronic hepatitis C caused by Hepatitis C virus genotype 1b	Condition
35625139	Chronic hepatitis C caused by Hepatitis C virus genotype 2	Condition
35625040	Chronic hepatitis C caused by Hepatitis C virus genotype 3	Condition
35625140	Chronic hepatitis C caused by Hepatitis C virus genotype 4	Condition
35624867	Chronic hepatitis C caused by hepatitis C virus genotype 5	Condition
35624866	Chronic hepatitis C caused by hepatitis C virus genotype 6	Condition
3654682	Chronic hepatitis C co-occurrent with human immunodeficiency virus infection	Condition
45766656	Chronic hepatitis C with stage 2 fibrosis	Condition
42872885	Chronic hepatitis E	Condition
4212540	Chronic liver disease	Condition
4238978	Chronic lobular hepatitis	Condition
4322067	Chronic lymphocytic cholangitis-cholangiohepatitis	Condition
3655440	Chronic necrosis of liver	Condition
201613	Chronic nonalcoholic liver disease	Condition
200451	Chronic passive congestion of liver	Condition
199867	Chronic persistent hepatitis	Condition
4296554	Chronic persistent type B viral hepatitis	Condition
4247138	Chronic persistent viral hepatitis	Condition
4198610	Chronic rejection of liver transplant	Condition
194574	Chronic type B viral hepatitis	Condition

Concept Id	Concept Name	Domain
4012113	Chronic viral hepatitis	Condition
192240	Chronic viral hepatitis B with hepatitis D	Condition
439674	Chronic viral hepatitis B without delta-agent	Condition
4342774	Drug-induced chronic hepatitis	Condition
4143008	Drug-induced cirrhosis of liver	Condition
4159158	Early cirrhosis	Condition
1340280	Exacerbation of chronic active hepatitis	Condition
4058680	Fatty portal cirrhosis	Condition
4294539	Florid cirrhosis	Condition
4203601	Glissonian cirrhosis	Condition
36676898	Growth retardation, mild developmental delay, chronic hepatitis syndrome	Condition
46273476	Hepatic ascites co-occurrent with chronic active hepatitis due to toxic liver disease	Condition
4340946	Hypoxia-associated cirrhosis	Condition
37396157	Idiopathic copper associated cirrhosis of liver	Condition
37164806	Idiopathic ductopenia	Condition
4268006	Indian childhood cirrhosis	Condition
4340393	Infectious cirrhosis	Condition
4144116	Juvenile portal cirrhosis	Condition
4340392	Laennec's cirrhosis, non-alcoholic	Condition
4049419	Latent cirrhosis	Condition
605193	Liver cirrhosis due to classical cystic fibrosis	Condition
3185452	Liver cirrhosis secondary to nonalcoholic steatohepatitis	Condition
4184779	Macronodular cirrhosis	Condition
4071022	Micronodular cirrhosis	Condition
4050640	Mixed micro and macronodular cirrhosis	Condition
4148254	Multilobular portal cirrhosis	Condition
44783142	North American Indian childhood cirrhosis	Condition
4048057	Nutritional cirrhosis	Condition
4003673	Obstructive biliary cirrhosis	Condition
37017654	Occult chronic type B viral hepatitis	Condition
4140536	Parasitic cirrhosis	Condition
4059285	Pigmentary portal cirrhosis	Condition
4300060	Pigment cirrhosis	Condition
4304584	Portal cirrhosis	Condition
4098583	Posthepatitic cirrhosis	Condition
4313567	Postnecrotic cirrhosis	Condition
3183806	Postviral gastroparesis	Condition
4135822	Primary biliary cholangitis	Condition
607683	Progressive familial intrahepatic cholestasis type 1	Condition
607718	Progressive familial intrahepatic cholestasis type 2	Condition
37162165	Progressive familial intrahepatic cholestasis type 3	Condition
4253211	Progressive intrahepatic cholestasis	Condition
37109889	Pulmonary fibrosis, hepatic hyperplasia, bone marrow hypoplasia syndrome	Condition

Concept Id	Concept Name	Domain
4183882	Relapsing type A viral hepatitis	Condition
4238508	Relapsing viral hepatitis	Condition
37399445	Reynolds syndrome	Condition
4046123	Secondary biliary cirrhosis	Condition
4053079	Syphilitic cirrhosis	Condition
4058682	Syphilitic portal cirrhosis	Condition
4046016	Toxic cirrhosis	Condition
4059287	Toxic portal cirrhosis	Condition
4055209	Unilobular portal cirrhosis	Condition

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Annex III: Supplementary material

A3. 1 Main analysis: Including all indications for liraglutide

A3. 1. 1 Any liver disease

A3. 1. 1. 1 Liraglutide vs Empagliflozin

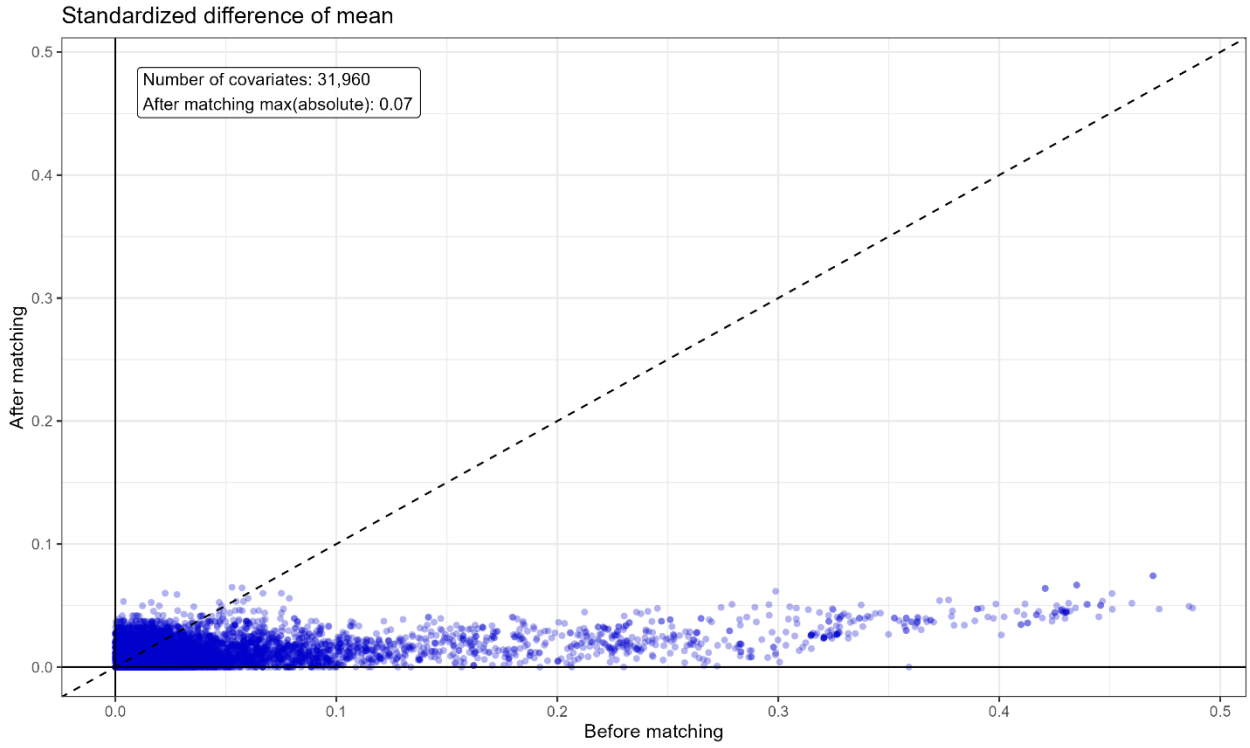

Figure S1. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs empagliflozin**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

803 **A3. 1. 1. 2 Liraglutide vs Dapagliflozin**

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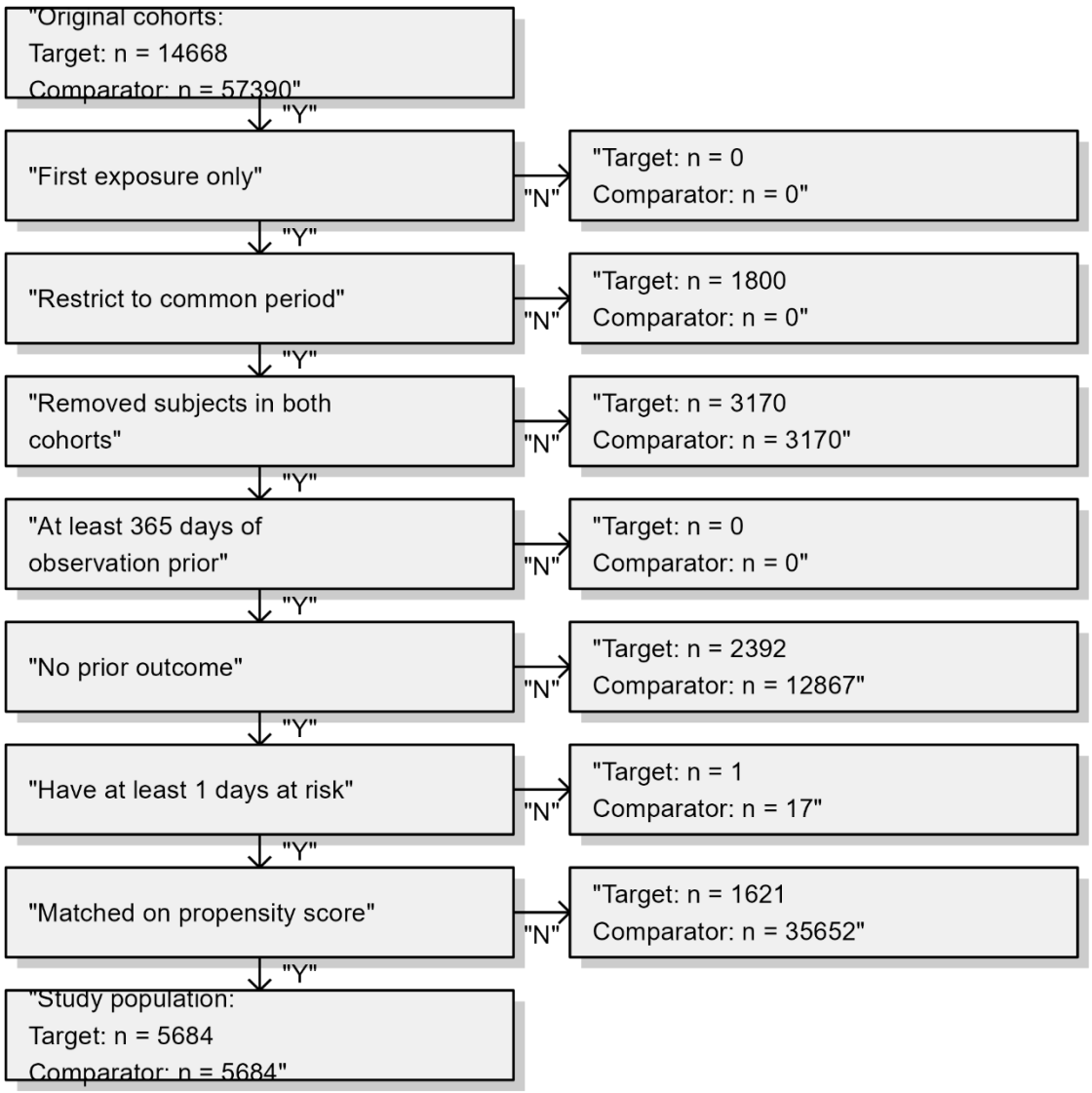


805

806 Figure S2. Patient cohort attrition. Target arm refers to patients who initiated treatment with
807 **liraglutide** and comparator arm refers to patients who initiated treatment with **dapagliflozin** in the
808 IQVIA™ DA Germany database.

809 N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure
810 per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these
811 two conditions appear as null in the respective boxes on the right.

812

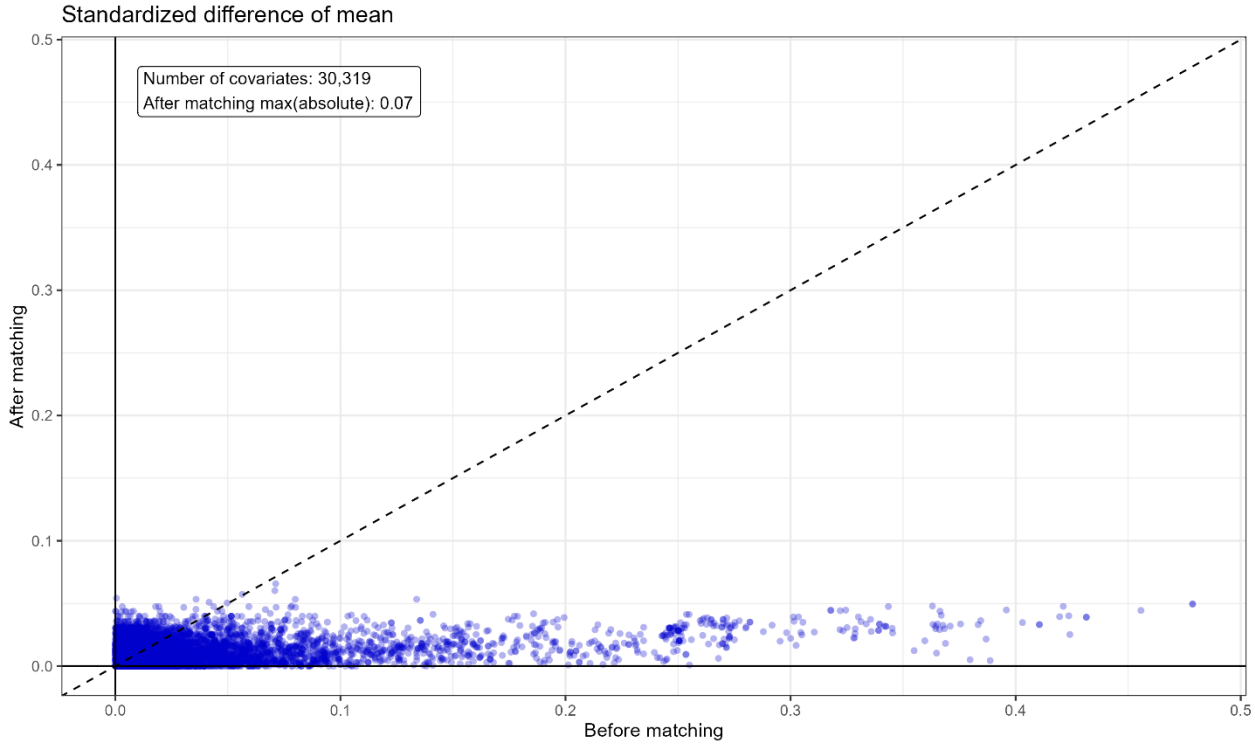


Figure S3. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs dapagliflozin**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

821 Table S1. Predefined[1] baseline characteristics before and after PS matching in the study population
822 including all indications, in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
10 - 14	0.0	0.0	0.02	0.0	--	--
15 - 19	0.2	0.0	0.04	0.2	0.2	-0.01
20 - 24	0.4	0.2	0.05	0.4	0.4	0.00
25 - 29	0.7	0.4	0.06	1.0	1.0	0.00
30 - 34	1.8	0.8	0.10	2.0	2.3	-0.02
35 - 39	3.2	1.5	0.13	2.9	3.3	-0.02
40 - 44	5.0	2.8	0.13	4.9	5.0	0.00
45 - 49	7.9	5.0	0.13	7.1	7.8	-0.03
50 - 54	12.9	9.0	0.13	12.2	12.5	-0.01
55 - 59	16.1	12.8	0.10	15.1	14.8	0.01
60 - 64	15.9	15.1	0.02	15.0	15.1	0.00
65 - 69	14.1	14.9	-0.02	13.7	13.5	0.01
70 - 74	10.8	12.8	-0.06	11.5	11.1	0.01
75 - 79	6.8	10.3	-0.12	8.1	7.8	0.01
80 - 84	3.4	9.1	-0.21	4.6	4.2	0.02
85 - 89	0.7	4.3	-0.19	1.1	0.9	0.02
90 - 94	0.1	1.0	-0.10	0.2	0.2	0.00
95 - 99	--	0.2	--	--	0.0	--
Gender: female	49.2	39.3	0.20	49.4	49.8	-0.01
Medical history: General						
Acute respiratory disease	12.2	13.0	-0.03	11.6	10.4	0.04
Attention deficit hyperactivity disorder	0.0	0.1	-0.01	0.0	--	--
Chronic liver disease	0.5	0.5	0.00	0.0	--	--
Chronic obstructive lung disease	4.5	5.1	-0.03	3.9	3.9	0.00
Crohn's disease	0.1	0.1	0.00	0.1	0.1	0.01
Dementia	0.7	1.3	-0.05	0.8	0.7	0.02
Depressive disorder	8.5	7.3	0.05	6.5	6.5	0.00
Diabetes mellitus	44.3	45.0	-0.01	38.9	38.8	0.00
Gastroesophageal reflux disease	1.3	1.9	-0.05	1.3	1.4	-0.01
Gastrointestinal hemorrhage	0.4	0.7	-0.04	0.2	0.2	0.00
Human immunodeficiency virus infection	0.1	0.0	0.01	0.0	0.1	-0.01
Hyperlipidemia	18.0	20.2	-0.05	12.7	12.7	0.00
Hypertensive disorder	32.1	35.9	-0.08	26.2	26.1	0.00
Lesion of liver	0.7	0.6	0.01	0.1	0.0	0.02
Obesity	19.9	10.0	0.30	14.9	15.8	-0.03
Osteoarthritis	7.7	8.9	-0.04	6.4	6.5	0.00
Pneumonia	1.1	1.6	-0.04	1.0	0.9	0.01
Psoriasis	1.2	1.1	0.01	0.8	0.7	0.01
Renal impairment	8.7	7.8	0.04	5.2	5.3	0.00
Rheumatoid arthritis	1.0	1.1	-0.01	0.7	0.7	0.00

Schizophrenia	0.1	0.1	-0.01	0.1	0.1	0.00
Ulcerative colitis	0.2	0.2	0.00	0.1	0.1	0.02
Urinary tract infectious disease	2.9	3.3	-0.02	3.0	3.0	0.00
Viral hepatitis C	0.1	0.1	0.00	--	--	--
Medical history: Cardiovascular disease						
Atrial fibrillation	2.1	4.1	-0.11	1.6	1.5	0.00
Cerebrovascular disease	3.1	3.9	-0.04	2.3	2.2	0.01
Coronary arteriosclerosis	3.8	6.6	-0.12	3.8	3.5	0.02
Heart disease	18.9	29.2	-0.23	16.5	15.8	0.02
Heart failure	5.6	12.4	-0.22	4.5	4.3	0.01
Ischemic heart disease	8.8	11.5	-0.09	7.6	7.6	0.00
Peripheral vascular disease	9.1	6.4	0.11	6.3	6.1	0.01
Pulmonary embolism	0.6	0.6	0.00	0.4	0.4	-0.01
Venous thrombosis	1.2	1.2	0.00	0.9	1.0	-0.01
Medical history: Neoplasms						
Malignant lymphoma	0.3	0.3	0.00	0.2	0.2	0.00
Malignant neoplasm of anorectum	0.0	0.1	-0.02	0.0	0.0	0.01
Malignant neoplastic disease	3.6	4.5	-0.04	2.6	2.3	0.01
Malignant tumor of breast	0.6	0.5	0.01	0.5	0.4	0.01
Malignant tumor of colon	0.3	0.3	-0.01	0.2	0.2	0.00
Malignant tumor of lung	0.1	0.1	0.00	0.0	--	--
Malignant tumor of urinary bladder	0.1	0.2	-0.02	0.1	0.1	0.01
Primary malignant neoplasm of prostate	0.5	0.7	-0.03	0.3	0.4	-0.01
Medication use						
Agents acting on the renin-angiotensin system	43.5	60.1	-0.34	41.4	40.0	0.03
Antibacterials for systemic use	18.6	18.9	-0.01	17.1	16.8	0.01
Antidepressants	8.7	8.7	0.00	7.8	7.7	0.00
Antiepileptics	5.1	5.0	0.00	5.2	5.3	-0.01
Antiinflammatory and antirheumatic products	27.2	33.8	-0.14	26.1	24.3	0.04
Antineoplastic agents	0.8	1.1	-0.02	0.8	0.5	0.03
Antipsoriatics	0.4	0.5	-0.01	0.4	0.4	0.00
Antithrombotic agents	19.4	31.9	-0.27	19.7	18.8	0.02
Beta blocking agents	28.4	42.2	-0.28	27.3	25.7	0.04
Calcium channel blockers	20.7	27.9	-0.16	19.6	19.3	0.01
Diuretics	31.5	43.8	-0.25	29.3	28.3	0.02
Drugs for acid related disorders	22.9	30.7	-0.17	22.3	21.5	0.02
Drugs for obstructive airway diseases	12.6	14.8	-0.06	12.3	11.8	0.02
Drugs used in diabetes	83.2	78.2	0.12	78.0	78.3	-0.01
Immunosuppressants	0.6	0.7	-0.01	0.5	0.5	-0.01
Lipid modifying agents	32.0	44.3	-0.25	30.0	28.6	0.03
Opioids	9.1	9.8	-0.02	8.7	8.2	0.02
Psycholeptics	5.7	7.3	-0.06	5.5	5.1	0.02
Psychostimulants, agents used for adhd and nootropics	0.3	0.2	0.01	0.3	0.2	0.01

SMD: Standardized mean differences. **Target: Liraglutide. Comparator: Dapagliflozin.**

(1) Covariates presented here are default groupings from the CohortMethod 5.2.1 package, which were measured within 365 days prior to index-date. The table does not accurately reflect the presence of chronic diseases in the patients, since chronic diseases that were recorded more than 365 days prior to the index-date and not repeated

within 365 days prior to the index-date were not considered. Of note, only a small number of the baseline covariates used to fit the propensity score model is presented here. The complete list of covariates is available upon request.

A3. 1. 1. 3 Liraglutide vs Sitagliptin

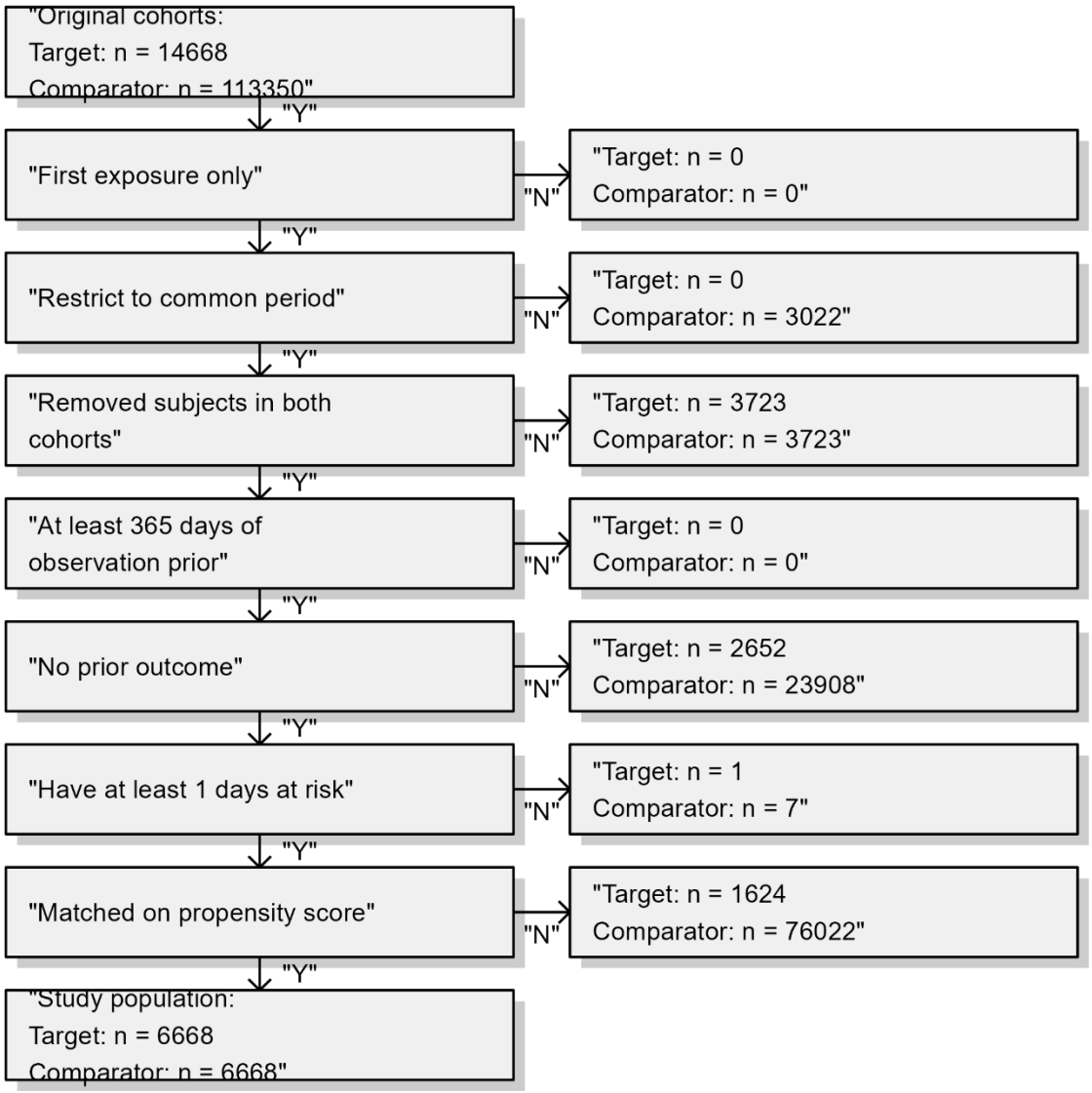
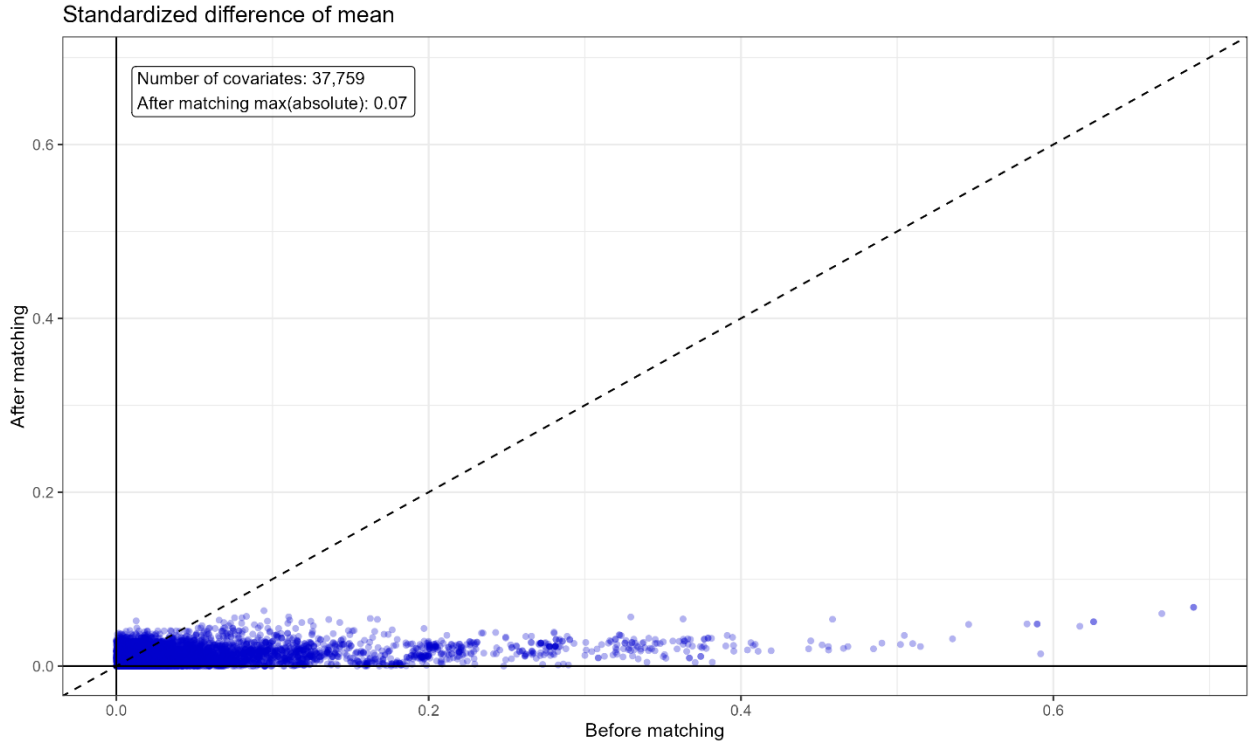


Figure S4. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **sitagliptin** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.



841

842 Figure S5. Scatter plot of the standardized difference in means (SMD) of each covariate before and
843 after PS matching comparing the following treatment cohorts: **liraglutide vs sitagliptin**, in the
844 IQVIA™ DA Germany database.

845 Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1.
846 However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS
847 matching.

848

849 Table S2. Predefined[1] baseline characteristics before and after PS matching in the study population
850 including all indications, in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
5 - 9		0.0				
10 - 14	0.0	0.0	0.02	0.0	0.0	0.02
15 - 19	0.2	0.0	0.06	0.2	0.1	0.02
20 - 24	0.4	0.1	0.08	0.4	0.3	0.02
25 - 29	0.7	0.2	0.09	1.0	0.8	0.02
30 - 34	1.8	0.5	0.16	1.6	1.7	-0.01
35 - 39	3.2	1.1	0.18	3.2	3.0	0.01
40 - 44	5.0	2.3	0.17	4.9	5.0	0.00
45 - 49	7.9	4.4	0.16	7.8	7.9	0.00
50 - 54	12.9	7.7	0.19	12.7	13.2	-0.02
55 - 59	16.1	11.1	0.15	15.3	15.5	-0.01
60 - 64	15.9	13.4	0.07	15.3	16.4	-0.03
65 - 69	14.1	14.0	0.00	14.1	14.2	0.00
70 - 74	10.8	13.8	-0.09	11.0	10.8	0.01
75 - 79	6.8	13.8	-0.21	7.7	7.3	0.02
80 - 84	3.4	10.9	-0.25	3.8	3.2	0.03
85 - 89	0.7	5.1	-0.21	0.7	0.4	0.04
90 - 94	0.1	1.3	-0.12	0.1	0.0	0.03
95 - 99		0.1			0.0	
Gender: female	49.2	44.2	0.10	49.0	49.1	0.00
Medical history: General						
Acute respiratory disease	12.2	13.7	-0.04	11.1	10.6	0.02
Attention deficit hyperactivity disorder	0.0	0.1	-0.03	0.0	0.0	-0.01
Chronic liver disease	0.5	0.5	-0.01	0.0	0.0	0.01
Chronic obstructive lung disease	4.5	5.5	-0.04	3.8	3.4	0.02
Crohn's disease	0.1	0.2	-0.01	0.1	0.0	0.01
Dementia	0.7	2.5	-0.12	0.6	0.6	0.00
Depressive disorder	8.5	8.1	0.02	6.5	6.2	0.01
Diabetes mellitus	44.3	54.1	-0.20	40.9	40.4	0.01
Gastroesophageal reflux disease	1.3	1.9	-0.05	1.2	0.9	0.02
Gastrointestinal hemorrhage	0.4	0.7	-0.04	0.2	0.2	0.00
Human immunodeficiency virus infection	0.1	0.0	0.01	0.0		
Hyperlipidemia	18.0	19.6	-0.04	12.9	12.2	0.02
Hypertensive disorder	32.1	39.1	-0.14	26.6	25.3	0.03
Lesion of liver	0.7	0.8	-0.01	0.1	0.1	0.00
Obesity	19.9	7.9	0.41	14.1	14.7	-0.02
Osteoarthritis	7.7	9.9	-0.08	6.3	5.9	0.02
Pneumonia	1.1	2.0	-0.06	0.9	0.8	0.01
Psoriasis	1.2	1.0	0.02	0.8	0.7	0.01
Renal impairment	8.7	7.2	0.06	4.9	4.7	0.01

Rheumatoid arthritis	1.0	1.2	-0.02	0.6	0.6	0.01
Schizophrenia	0.1	0.2	-0.02	0.1	0.1	-0.01
Ulcerative colitis	0.2	0.2	-0.01	0.1	0.2	-0.01
Urinary tract infectious disease	2.9	4.6	-0.08	2.8	2.5	0.02
Viral hepatitis C	0.1	0.1	0.00	0.0		
Medical history: Cardiovascular disease						
Atrial fibrillation	2.1	2.8	-0.04	1.5	1.2	0.02
Cerebrovascular disease	3.1	4.5	-0.07	2.1	2.1	0.00
Coronary arteriosclerosis	3.8	4.5	-0.03	3.4	2.9	0.03
Heart disease	18.9	24.6	-0.13	15.6	14.5	0.03
Heart failure	5.6	7.6	-0.08	4.0	4.1	0.00
Ischemic heart disease	8.8	10.7	-0.06	7.1	6.5	0.02
Peripheral vascular disease	9.1	6.4	0.11	6.6	6.1	0.02
Pulmonary embolism	0.6	0.6	0.00	0.4	0.4	0.00
Venous thrombosis	1.2	1.3	-0.01	0.8	0.7	0.00
Medical history: Neoplasms						
Malignant lymphoma	0.3	0.3	-0.01	0.2	0.1	0.01
Malignant neoplasm of anorectum	0.0	0.2	-0.04	0.0	0.0	-0.01
Malignant neoplastic disease	3.6	5.2	-0.07	2.5	2.4	0.01
Malignant tumor of breast	0.6	0.6	0.00	0.4	0.4	0.01
Malignant tumor of colon	0.3	0.4	-0.02	0.1	0.1	0.01
Malignant tumor of lung	0.1	0.2	-0.02	0.0	0.0	-0.01
Malignant tumor of urinary bladder	0.1	0.2	-0.03	0.1	0.1	0.01
Primary malignant neoplasm of prostate	0.5	0.7	-0.03	0.3	0.3	0.01
Medication use						
Agents acting on the renin-angiotensin system	43.5	59.8	-0.33	40.5	39.6	0.02
Antibacterials for systemic use	18.6	22.4	-0.09	16.9	16.4	0.01
Antidepressants	8.7	9.8	-0.04	7.7	7.7	0.00
Antiepileptics	5.1	5.6	-0.02	4.7	4.6	0.01
Antiinflammatory and antirheumatic products	27.2	37.5	-0.21	25.0	23.9	0.03
Antineoplastic agents	0.8	1.2	-0.03	0.7	0.7	-0.01
Antipsoriatics	0.4	0.5	-0.01	0.3	0.4	-0.02
Antithrombotic agents	19.4	31.7	-0.27	18.2	17.5	0.02
Beta blocking agents	28.4	42.7	-0.29	25.9	24.6	0.03
Calcium channel blockers	20.7	29.5	-0.20	18.7	18.2	0.01
Diuretics	31.5	44.9	-0.27	28.4	27.2	0.03
Drugs for acid related disorders	22.9	32.6	-0.21	20.1	18.9	0.03
Drugs for obstructive airway diseases	12.6	15.2	-0.07	11.4	10.3	0.04
Drugs used in diabetes	82.8	86.1	-0.09	77.9	78.1	0.00
Immunosuppressants	0.6	0.8	-0.02	0.4	0.4	0.00
Lipid modifying agents	32.0	40.6	-0.18	28.5	28.4	0.00
Opioids	9.1	11.9	-0.09	8.3	7.8	0.02
Psycholeptics	5.7	9.5	-0.13	5.4	5.2	0.01
Psychostimulants agents used for adhd and nootropics	0.3	0.3	0.00	0.2	0.2	0.02

851 SMD: Standardized mean differences. **Target: Liraglutide. Comparator: Sitagliptin.**

(1) Covariates presented here are default groupings from the CohortMethod 5.2.1 package, which were measured within 365 days prior to index-date. The table does not accurately reflect the presence of chronic diseases in the patients, since chronic diseases that were recorded more than 365 days prior to the index-date and not repeated within 365 days prior to the index-date were not considered. Of note, only a small number of the baseline covariates used to fit the propensity score model is presented here. The complete list of covariates is available upon request.

A3. 1. 2 Acute hepatic injury

A3.1.2.1 Liraglutide vs Empagliflozin

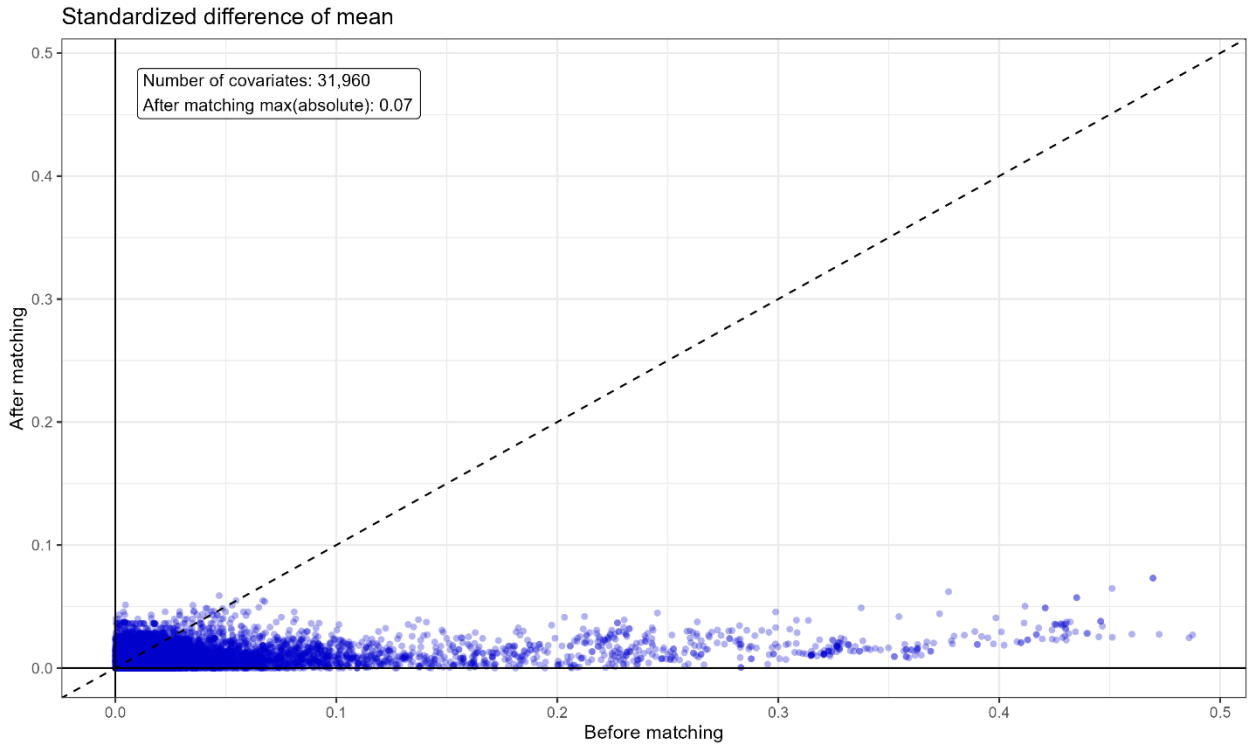


Figure S6. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs empagliflozin**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3.1.2.2 Liraglutide vs Dapagliflozin

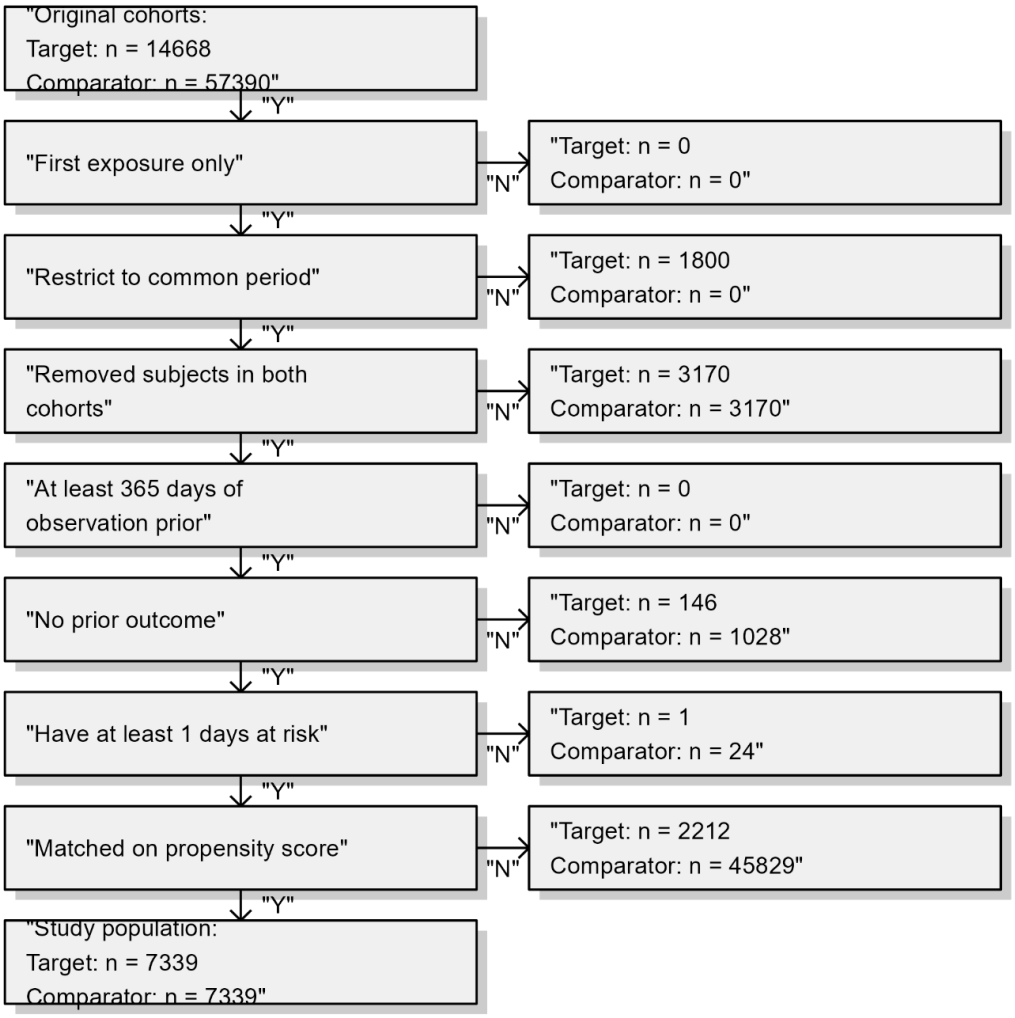


Figure S7. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **dapagliflozin** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

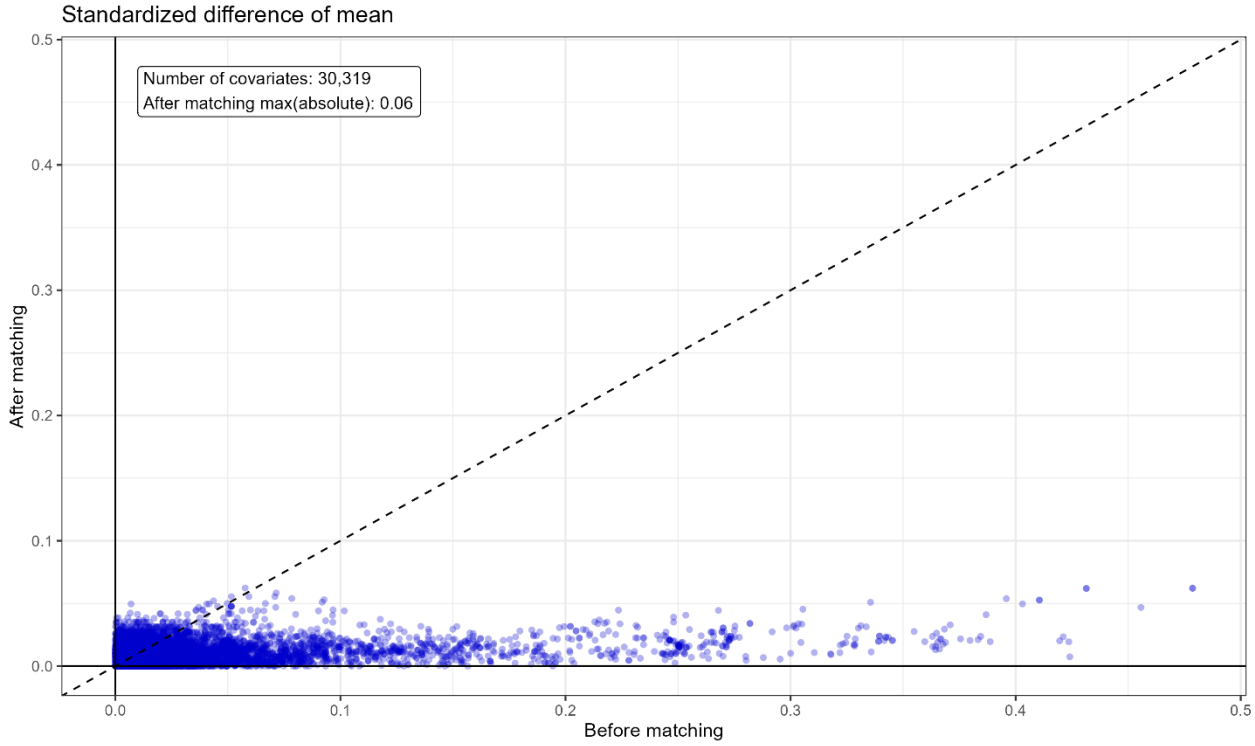


Figure S8. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs dapagliflozin**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3.1.2.3 Liraglutide vs Sitagliptin

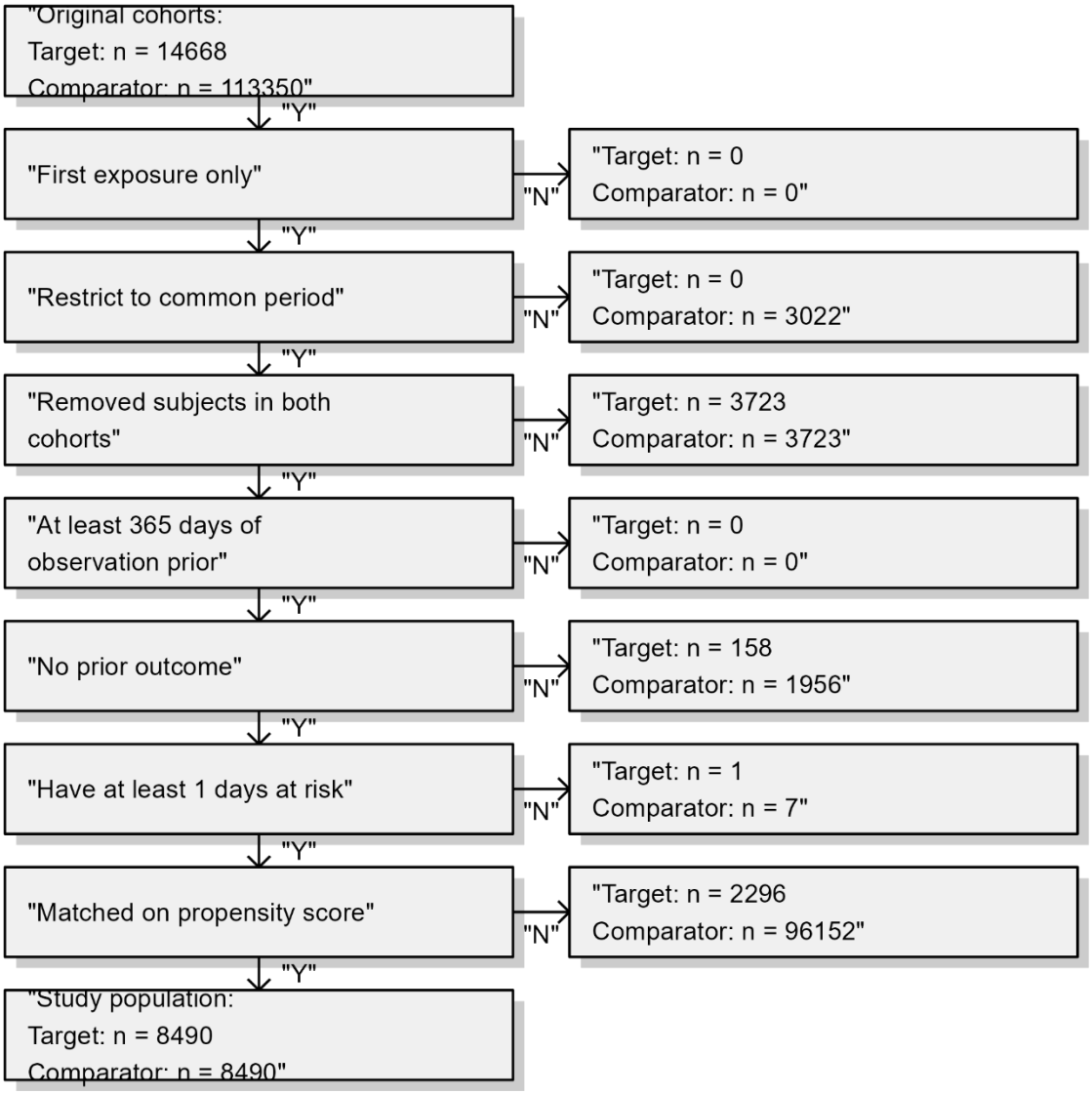


Figure S9. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **sitagliptin** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

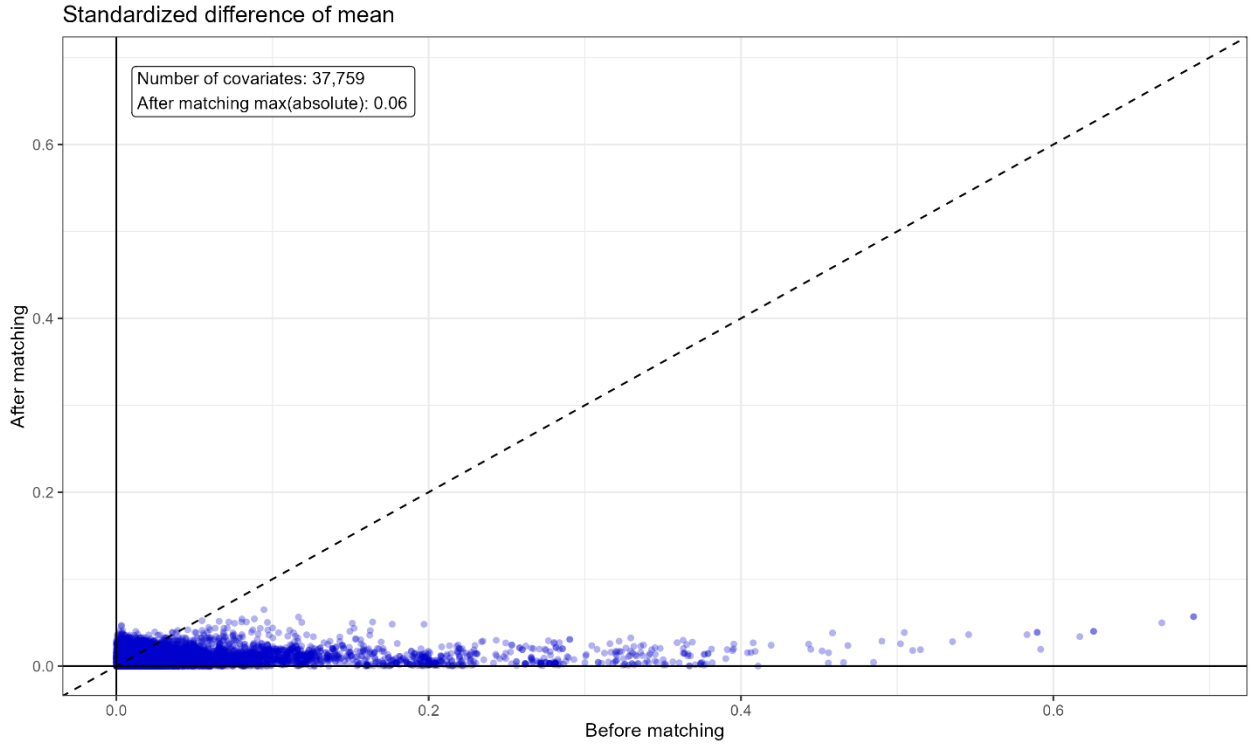


Figure S10. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs sitagliptin**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3. 1. 3 Acute hepatic injury with no chronic hepatic failure

A3.1.3.1 Liraglutide vs Empagliflozin

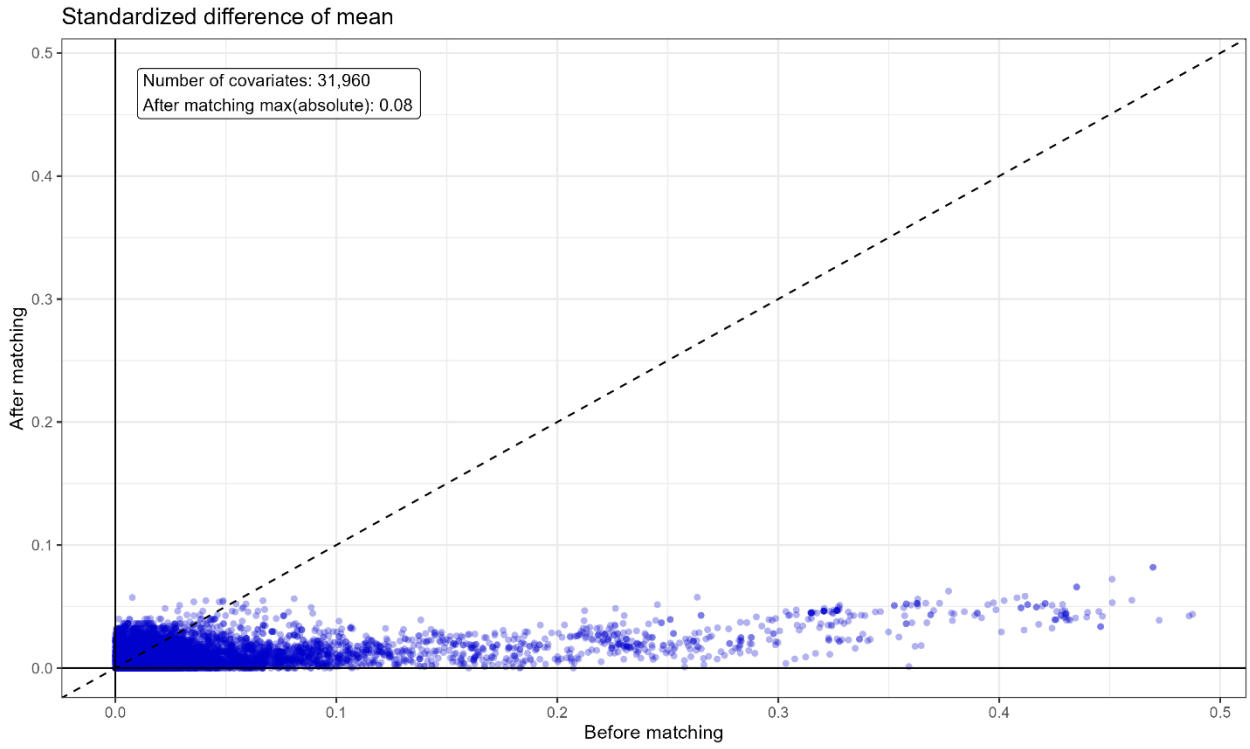


Figure S11. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs empagliflozin**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3.1.3.2 Liraglutide vs Dapagliflozin

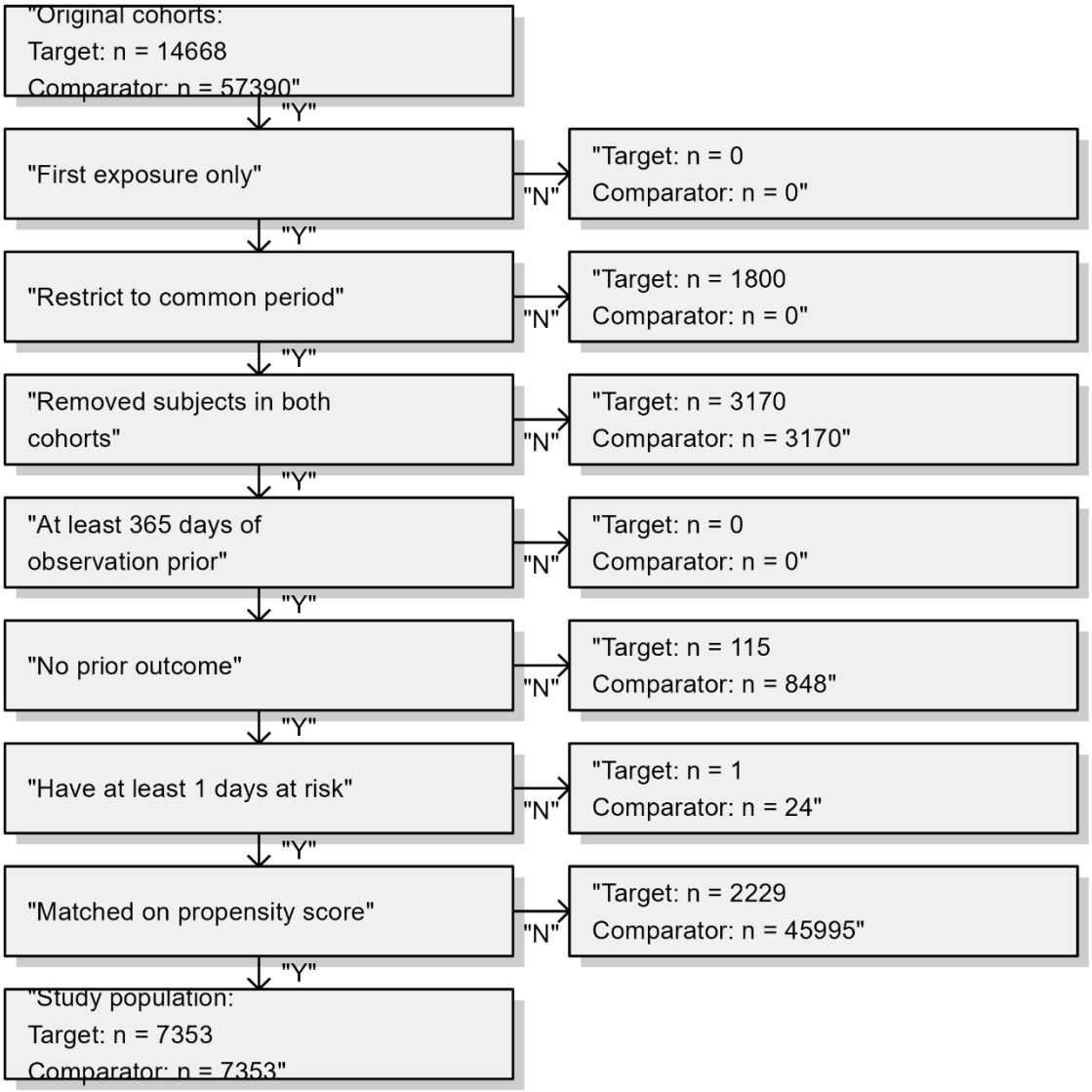


Figure S12. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **dapagliflozin** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

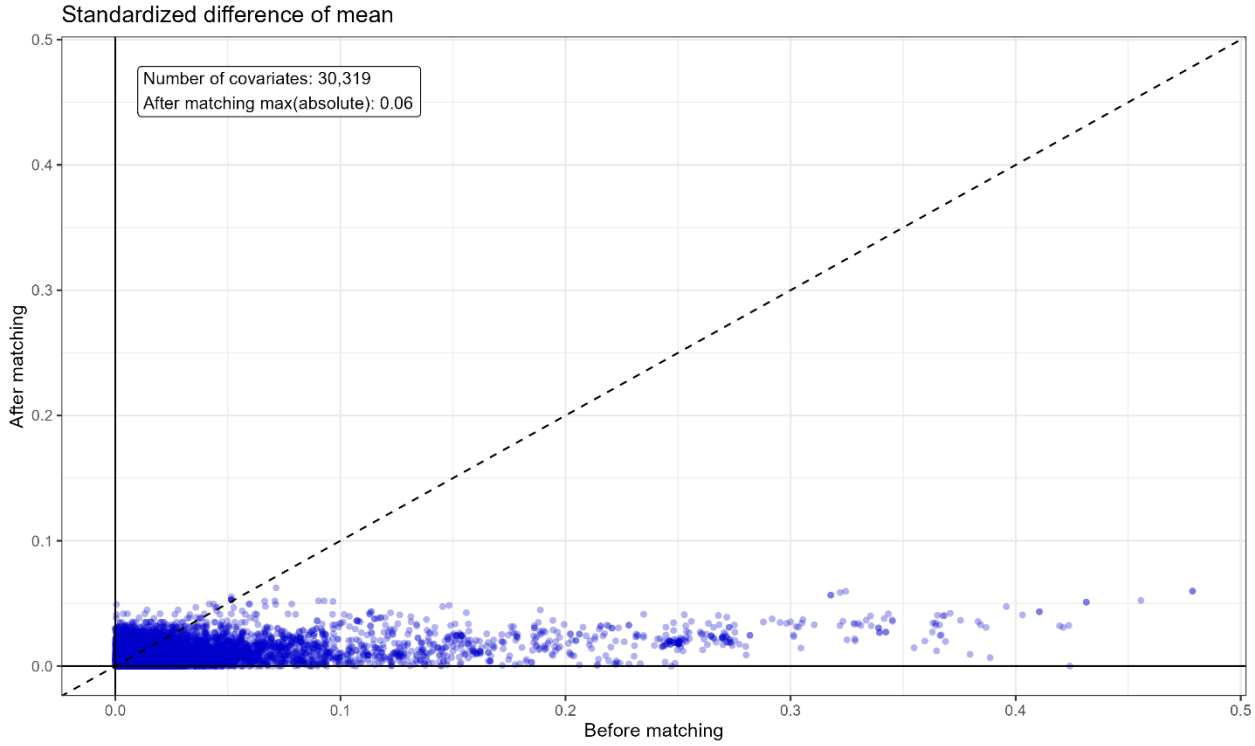
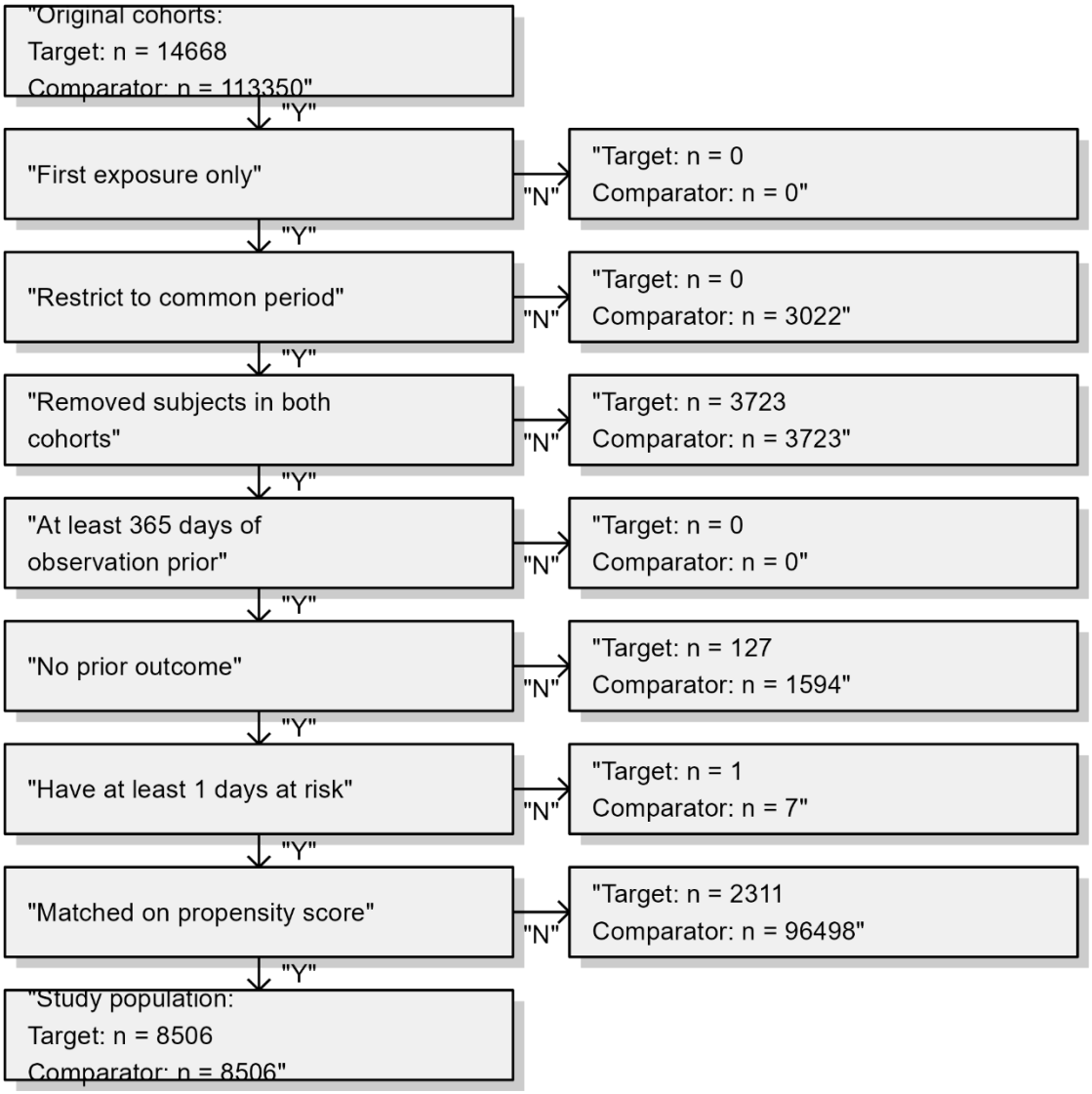


Figure S13. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs dapagliflozin**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

946 **A3.1.3.3 Liraglutide vs Sitagliptin**

947



948

949 Figure S14. Patient cohort attrition. Target arm refers to patients who initiated treatment with
950 **liraglutide** and comparator arm refers to patients who initiated treatment with **sitagliptin** in the
951 IQVIA™ DA Germany database.

952 N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure
953 per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these
954 two conditions appear as null in the respective boxes on the right.

955

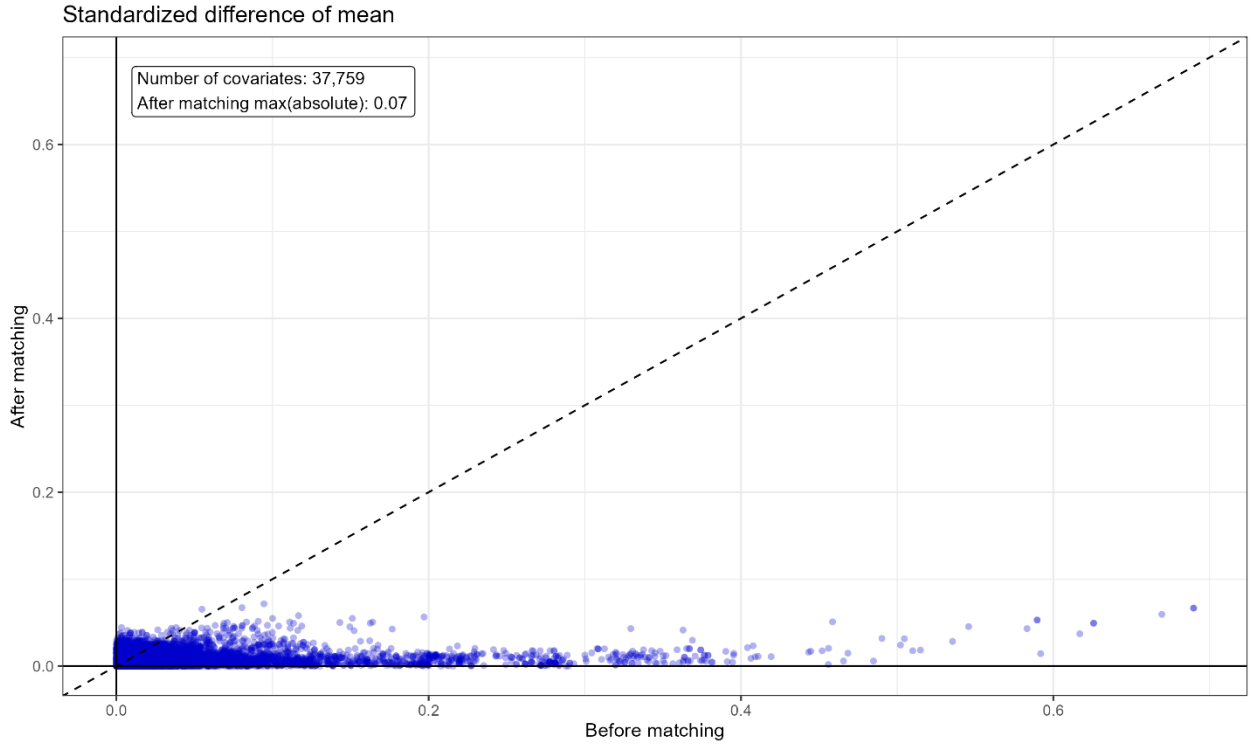


Figure S15. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs sitagliptin**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3. 2 Sensitivity analysis: Restricting to type 2 diabetes mellitus (T2DM) patients

A3. 2. 1 Any liver disease

A3. 2. 1. 1 Liraglutide vs Empagliflozin

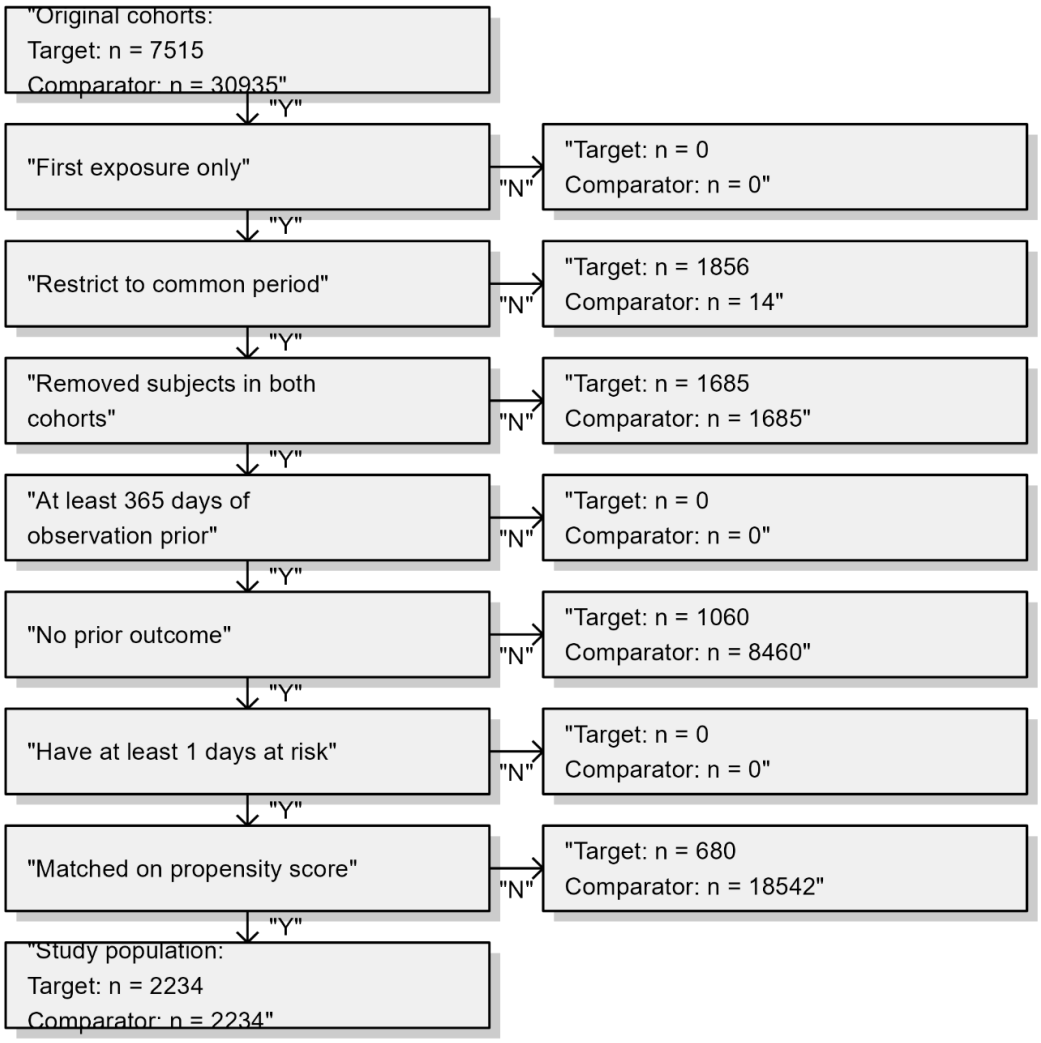


Figure S16. Patient cohort attrition. Target arm refers to T2DM patients who initiated treatment with **liraglutide,** and comparator arm refers to patients who initiated treatment with **empagliflozin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

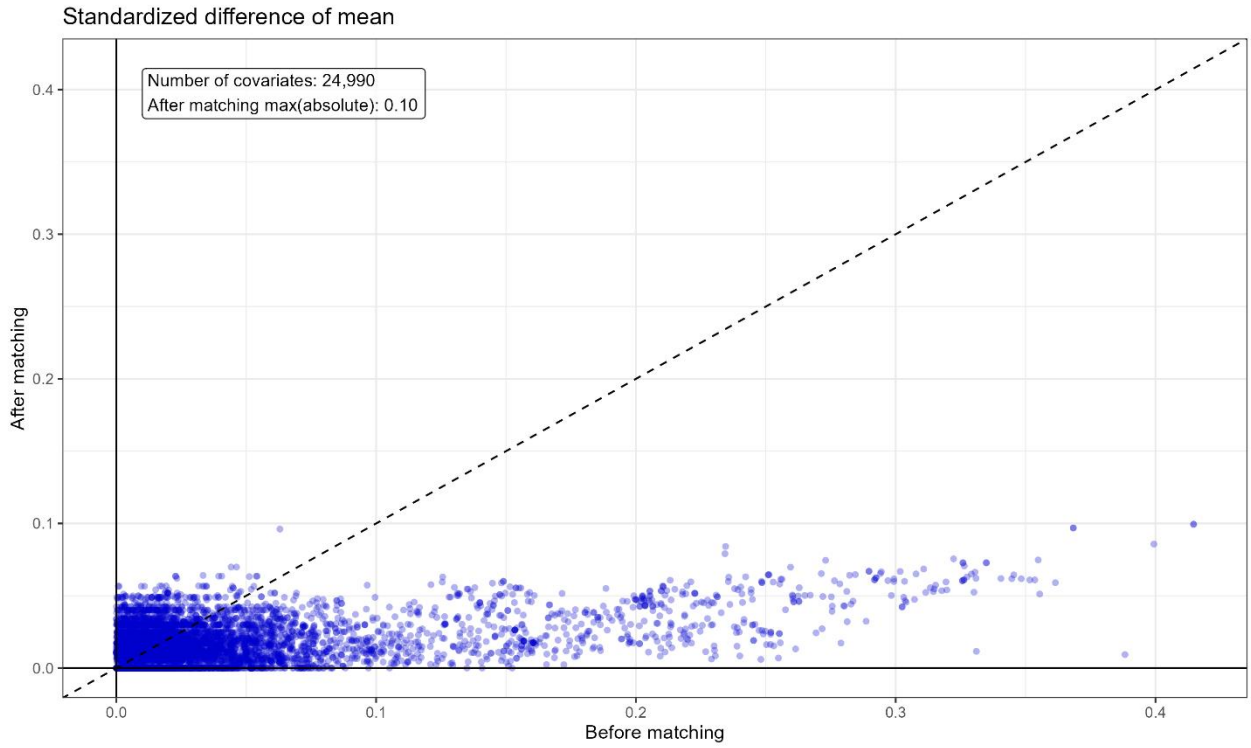


Figure S17. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs empagliflozin**, in **T2DM patients** in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

Table S3. Predefined[1] baseline characteristics before and after PS matching in **T2DM patients** in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
10 - 14		0.0				
15 - 19	0.1	0.0	0.04	0.1	0.1	0.00
20 - 24	0.3	0.1	0.06	0.3	0.3	0.01
25 - 29	0.6	0.2	0.08	0.5	0.7	-0.02
30 - 34	1.4	0.5	0.11	1.4	1.5	0.00
35 - 39	2.9	1.2	0.13	2.5	2.5	0.00
40 - 44	5.3	2.3	0.18	4.3	4.6	-0.02
45 - 49	8.1	4.7	0.15	7.7	7.6	0.01
50 - 54	14.5	9.2	0.17	13.1	14.4	-0.04
55 - 59	17.6	13.8	0.11	17.1	17.3	-0.01
60 - 64	17.0	16.5	0.01	16.5	16.4	0.00
65 - 69	14.3	16.0	-0.05	15.2	15.9	-0.02
70 - 74	9.6	13.9	-0.13	9.8	8.0	0.06
75 - 79	5.4	10.7	-0.18	7.3	6.8	0.02
80 - 84	2.5	7.4	-0.20	3.5	3.2	0.02
85 - 89	0.3	2.9	-0.17	0.5	0.6	-0.01
90 - 94	0.0	0.5	-0.07	0.1	0.0	0.02
95 - 99		0.0			0.1	
Gender: female	45.6	35.8	0.20	47.1	49.5	-0.05
Medical history: General						
Acute respiratory disease	14.1	14.9	-0.02	12.7	12.0	0.02
Attention deficit hyperactivity disorder	0.1	0.1	-0.01	0.0		
Chronic liver disease	0.5	0.6	-0.01		0.0	
Chronic obstructive lung disease	5.0	5.9	-0.04	4.7	4.2	0.02
Crohn's disease	0.1	0.1	0.00	0.3	0.2	0.01
Dementia	0.9	1.4	-0.05	0.9	0.9	0.01
Depressive disorder	9.9	8.4	0.05	7.7	8.4	-0.02
Gastroesophageal reflux disease	1.5	2.2	-0.05	1.5	1.3	0.02
Gastrointestinal hemorrhage	0.5	0.7	-0.03	0.2	0.3	-0.02
Human immunodeficiency virus infection	0.1	0.0	0.02	0.0		
Hyperlipidemia	22.9	24.7	-0.04	15.7	15.5	0.00
Hypertensive disorder	41.1	42.2	-0.02	32.6	31.9	0.02
Lesion of liver	0.7	0.7	0.00	0.0	0.0	0.00
Obesity	20.6	12.2	0.24	14.5	15.6	-0.03
Osteoarthritis	9.0	10.5	-0.05	7.3	7.1	0.01
Pneumonia	1.3	1.9	-0.05	1.0	0.7	0.03
Psoriasis	1.6	1.3	0.03	1.2	1.1	0.01
Renal impairment	8.6	7.7	0.03	5.2	5.0	0.01
Rheumatoid arthritis	1.0	1.1	-0.01	0.8	0.7	0.01
Schizophrenia	0.2	0.2	0.00	0.2		
Ulcerative colitis	0.2	0.2	-0.01	0.1	0.2	-0.01
Urinary tract infectious disease	3.3	3.9	-0.03	3.5	4.1	-0.03
Viral hepatitis C	0.1	0.1	-0.01			
Medical history: Cardiovascular disease						
Atrial fibrillation	2.3	3.4	-0.06	1.9	1.8	0.01
Cerebrovascular disease	3.8	4.9	-0.05	2.9	2.5	0.03
Coronary arteriosclerosis	4.0	8.7	-0.18	4.3	4.0	0.01
Heart disease	21.7	32.0	-0.22	18.8	17.8	0.03
Heart failure	6.5	9.7	-0.11	5.4	5.1	0.01
Ischemic heart disease	10.1	16.1	-0.17	8.7	7.7	0.04
Peripheral vascular disease	9.9	9.2	0.02	7.3	7.3	0.00

Pulmonary embolism	0.6	0.7	-0.01	0.5	0.4	0.01
Venous thrombosis	1.3	1.2	0.00	0.8	0.6	0.02
Medical history: Neoplasms						
Malignant lymphoma	0.3	0.3	0.00	0.2	0.2	0.01
Malignant neoplasm of anorectum	0.1	0.2	-0.03	0.0	0.1	-0.02
Malignant neoplastic disease	4.1	4.7	-0.03	3.1	2.7	0.02
Malignant tumor of breast	0.7	0.6	0.02	0.5	0.7	-0.02
Malignant tumor of colon	0.3	0.3	0.01	0.2	0.1	0.03
Malignant tumor of lung	0.1	0.1	0.00		0.0	
Malignant tumor of urinary bladder	0.1	0.2	-0.01	0.1	0.0	0.03
Primary malignant neoplasm of prostate	0.6	0.7	-0.02	0.3	0.2	0.01
Medication use						
Agents acting on the renin-angiotensin system	53.6	66.7	-0.27	51.1	47.9	0.07
Antibacterials for systemic use	21.0	21.0	0.00	18.7	18.9	-0.01
Antidepressants	9.7	9.6	0.00	9.2	9.3	0.00
Antiepileptics	5.3	5.8	-0.02	5.7	5.5	0.01
Antiinflammatory and antirheumatic products	32.0	42.2	-0.21	31.2	29.2	0.04
Antineoplastic agents	0.8	1.2	-0.04	0.9	0.8	0.01
Antipsoriatics	0.4	0.4	0.00	0.4	0.3	0.01
Antithrombotic agents	22.4	38.0	-0.33	24.1	21.1	0.07
Beta blocking agents	34.8	47.5	-0.26	33.4	32.3	0.02
Calcium channel blockers	25.1	33.5	-0.18	24.1	22.4	0.04
Diuretics	37.4	45.0	-0.15	35.3	34.0	0.03
Drugs for acid related disorders	26.2	35.4	-0.19	26.5	24.9	0.04
Drugs for obstructive airway diseases	14.2	16.2	-0.05	13.1	12.3	0.02
Drugs used in diabetes	100.0	100.0	0.00	100.0	100.0	0.00
Immunosuppressants	0.7	0.7	0.00	0.6	0.6	-0.01
Lipid modifying agents	38.9	53.5	-0.29	37.7	34.7	0.06
Opioids	10.2	11.1	-0.03	9.7	9.2	0.02
Psycholeptics	5.8	7.9	-0.08	5.7	4.9	0.03
Psychostimulants agents used for adhd and nootropics	0.2	0.2	0.00	0.1	0.2	-0.01

SMD: Standardized mean differences. **Target: Liraglutide. Comparator: Empagliflozin.**

(1) Covariates presented here are default groupings from the CohortMethod 5.2.1 package, which were measured within 365 days prior to index-date. The table does not accurately reflect the presence of chronic diseases in the patients, since chronic diseases that were recorded more than 365 days prior to the index-date and not repeated within 365 days prior to the index-date were not considered. Of note, only a small number of the baseline covariates used to fit the propensity score model is presented here. The complete list of covariates is available upon request.

A3. 2. 1. 2 Liraglutide vs Dapagliflozin

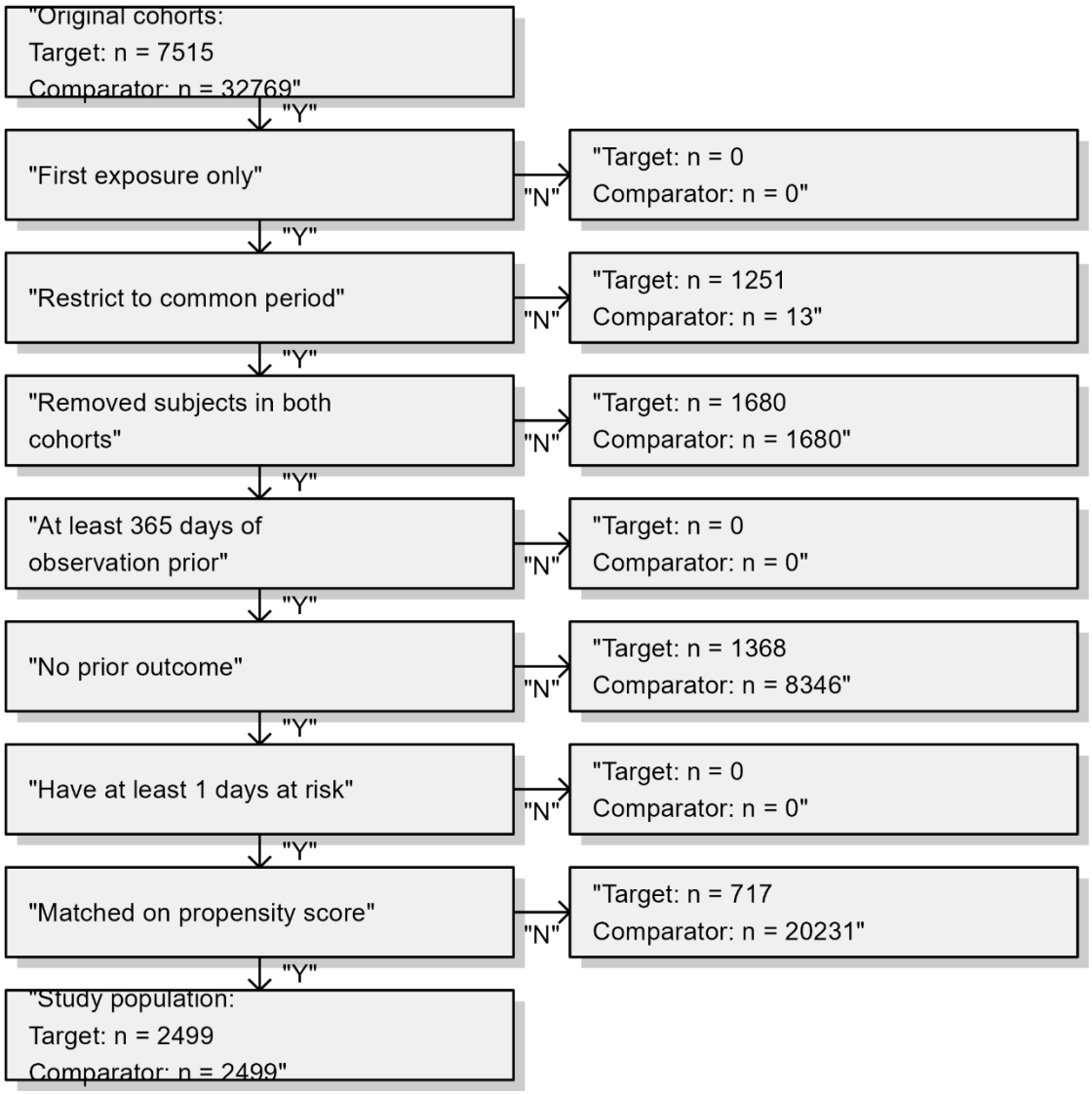


Figure S18. Patient cohort attrition. Target arm refers to T2DM patients who initiated treatment with **liraglutide,** and comparator arm refers to patients who initiated treatment with **dapagliflozin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

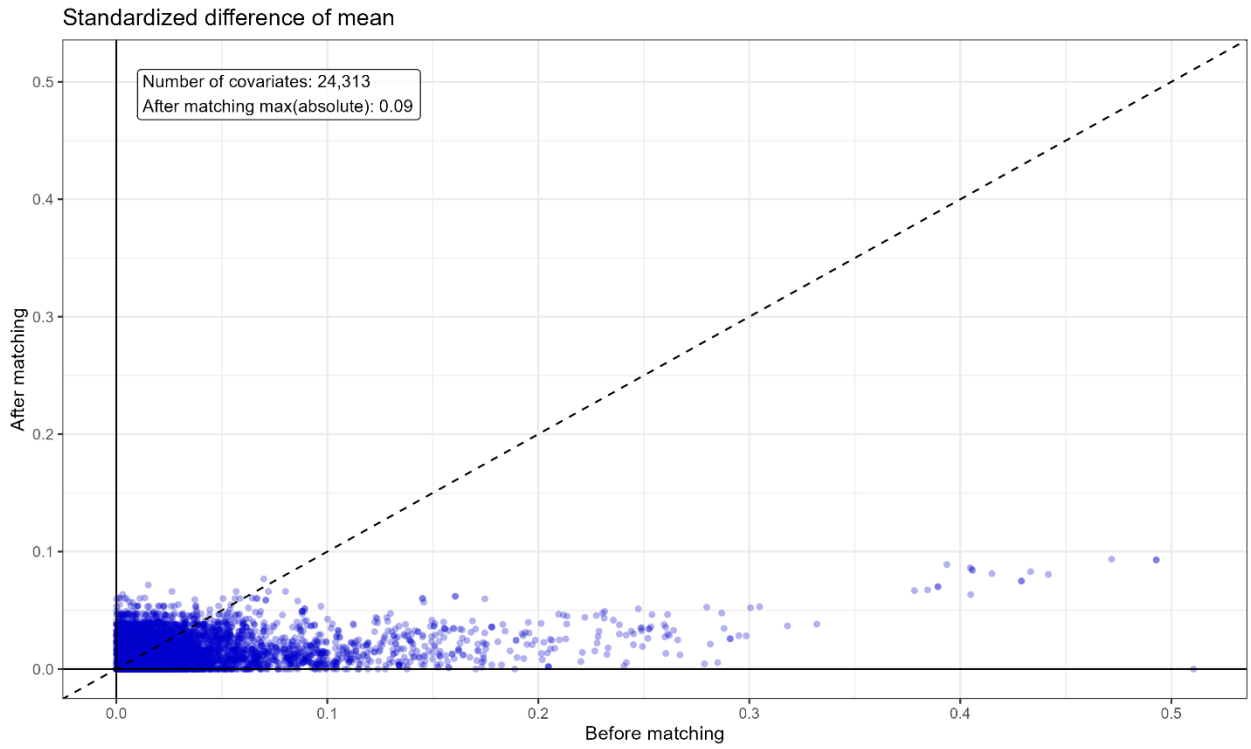


Figure S19. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs dapagliflozin**, **in T2DM patients**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

Table S4. Predefined[1] baseline characteristics before and after PS matching in **T2DM patients** in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
10 - 14		0.0				
15 - 19	0.1	0.0	0.05	0.2	0.2	0.00
20 - 24	0.3	0.1	0.06	0.3	0.2	0.02
25 - 29	0.6	0.3	0.05	0.6	0.4	0.03
30 - 34	1.4	0.8	0.06	1.6	1.6	0.00
35 - 39	2.9	1.7	0.09	2.8	3.0	-0.02
40 - 44	5.3	3.3	0.11	4.6	4.3	0.01
45 - 49	8.1	5.9	0.09	7.7	8.6	-0.03
50 - 54	14.5	10.7	0.12	13.7	14.2	-0.01
55 - 59	17.6	14.6	0.08	17.5	16.5	0.03
60 - 64	17.0	16.9	0.00	16.2	17.0	-0.02
65 - 69	14.3	15.8	-0.04	14.6	14.2	0.01
70 - 74	9.6	12.5	-0.09	9.9	9.2	0.02
75 - 79	5.4	8.9	-0.13	6.8	6.7	0.00
80 - 84	2.5	6.0	-0.16	3.0	3.2	-0.01
85 - 89	0.3	2.1	-0.13	0.4	0.6	-0.03
90 - 94	0.0	0.4	-0.06	0.1	0.1	0.00
95 - 99		0.0			0.0	
Gender: female	45.6	38.5	0.15	46.4	49.3	-0.06
Medical history: General						
Acute respiratory disease	14.1	15.1	-0.03	13.8	12.2	0.05
Attention deficit hyperactivity disorder	0.1	0.1	-0.01	0.0	0.0	0.00
Chronic liver disease	0.5	0.4	0.01			
Chronic obstructive lung disease	5.0	4.8	0.01	4.4	3.9	0.02
Crohn's disease	0.1	0.1	0.01	0.2	0.1	0.02
Dementia	0.9	1.2	-0.03	0.8	0.9	-0.01
Depressive disorder	9.9	8.0	0.07	7.6	8.5	-0.03
Gastroesophageal reflux disease	1.5	2.1	-0.04	1.5	1.8	-0.02
Gastrointestinal hemorrhage	0.5	0.7	-0.03	0.2	0.2	0.01
Human immunodeficiency virus infection	0.1	0.0	0.01	0.0		
Hyperlipidemia	22.9	22.2	0.02	16.1	15.7	0.01
Hypertensive disorder	41.1	39.9	0.02	32.9	32.9	0.00
Lesion of liver	0.7	0.5	0.03	0.1		
Obesity	20.6	11.0	0.29	14.5	16.2	-0.05
Osteoarthritis	9.0	9.5	-0.02	7.6	6.8	0.03
Pneumonia	1.3	1.4	-0.01	1.2	1.1	0.01
Psoriasis	1.6	1.1	0.04	1.2	0.9	0.03
Renal impairment	8.6	5.6	0.12	4.2	4.5	-0.02
Rheumatoid arthritis	1.0	1.1	-0.01	0.6	0.8	-0.02
Schizophrenia	0.2	0.2	0.00	0.2	0.2	-0.01
Ulcerative colitis	0.2	0.1	0.01	0.1	0.1	0.00
Urinary tract infectious disease	3.3	3.5	-0.01	3.3	3.3	0.00
Viral hepatitis C	0.1	0.1	-0.01			
Medical history: Cardiovascular disease						
Atrial fibrillation	2.3	2.4	-0.01	1.7	1.4	0.03
Cerebrovascular disease	3.8	3.6	0.01	2.4	2.5	0.00
Coronary arteriosclerosis	4.0	5.0	-0.05	4.0	4.3	-0.02
Heart disease	21.7	22.1	-0.01	17.8	18.6	-0.02
Heart failure	6.5	6.6	-0.01	4.2	4.9	-0.03
Ischemic heart disease	10.1	9.7	0.02	8.6	9.2	-0.02
Peripheral vascular disease	9.9	6.2	0.15	6.6	6.7	0.00

Pulmonary embolism	0.6	0.4	0.02	0.3	0.2	0.02
Venous thrombosis	1.3	1.1	0.02	1.0	0.9	0.00
Medical history: Neoplasms						
Malignant lymphoma	0.3	0.2	0.02	0.2	0.1	0.03
Malignant neoplasm of anorectum	0.1	0.1	-0.01	0.0	0.1	-0.02
Malignant neoplastic disease	4.1	4.0	0.01	2.7	2.3	0.03
Malignant tumor of breast	0.7	0.5	0.03	0.4	0.7	-0.03
Malignant tumor of colon	0.3	0.3	0.01	0.2	0.2	0.02
Malignant tumor of lung	0.1	0.1	0.01			
Malignant tumor of urinary bladder	0.1	0.1	-0.01	0.1	0.0	0.03
Primary malignant neoplasm of prostate	0.6	0.6	-0.01	0.3	0.2	0.03
Medication use						
Agents acting on the renin-angiotensin system	53.6	61.6	-0.16	51.2	50.5	0.02
Antibacterials for systemic use	21.0	20.6	0.01	19.0	17.7	0.03
Antidepressants	9.7	9.0	0.03	9.2	9.2	0.00
Antiepileptics	5.3	4.8	0.02	5.2	6.2	-0.04
Antiinflammatory and antirheumatic products	32.0	37.0	-0.10	30.7	30.5	0.00
Antineoplastic agents	0.8	1.1	-0.03	0.6	0.5	0.02
Antipsoriatics	0.4	0.4	0.01	0.3	0.2	0.02
Antithrombotic agents	22.4	27.5	-0.11	22.9	22.2	0.02
Beta blocking agents	34.8	40.2	-0.11	33.5	33.2	0.01
Calcium channel blockers	25.1	31.1	-0.13	24.4	23.1	0.03
Diuretics	37.4	40.6	-0.06	33.9	34.7	-0.02
Drugs for acid related disorders	26.2	31.1	-0.11	26.7	27.9	-0.03
Drugs for obstructive airway diseases	14.2	15.1	-0.02	13.7	12.5	0.04
Drugs used in diabetes	100.0	100.0	0.00	100.0	100.0	0.00
Immunosuppressants	0.7	0.7	0.00	0.5	0.4	0.01
Lipid modifying agents	38.9	46.0	-0.14	36.3	34.8	0.03
Opioids	10.2	9.8	0.01	9.6	9.2	0.01
Psycholeptics	5.8	6.8	-0.04	5.4	5.1	0.01
Psychostimulants agents used for adhd and nootropics	0.2	0.2	-0.01	0.1	0.2	-0.02

SMD: Standardized mean differences. **Target: Liraglutide. Comparator: Dapagliflozin.**

(1) Covariates presented here are default groupings from the CohortMethod 5.2.1 package, which were measured within 365 days prior to index-date. The table does not accurately reflect the presence of chronic diseases in the patients, since chronic diseases that were recorded more than 365 days prior to the index-date and not repeated within 365 days prior to the index-date were not considered. Of note, only a small number of the baseline covariates used to fit the propensity score model is presented here. The complete list of covariates is available upon request.

A3. 2. 1. 3 Liraglutide vs Sitagliptin

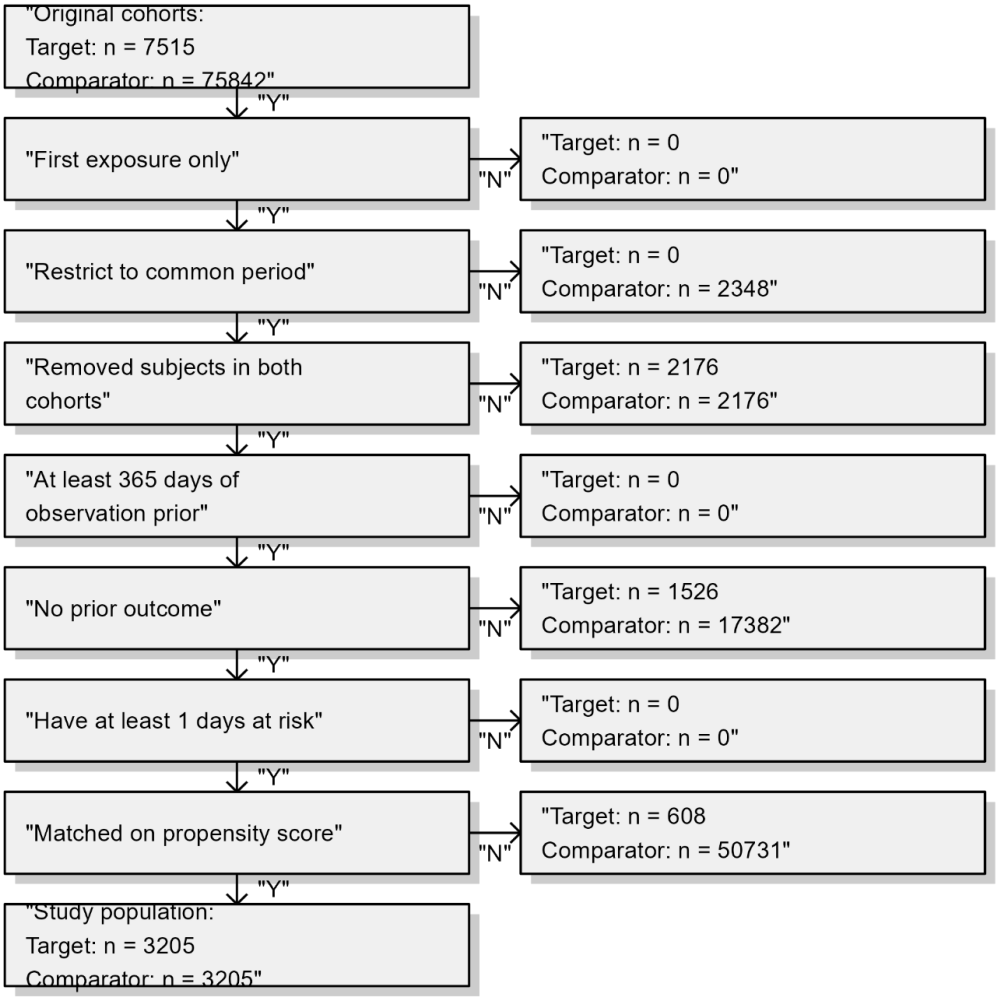


Figure S20. Patient cohort attrition. Target arm refers to T2DM patients who initiated treatment with **liraglutide,** and comparator arm refers to patients who initiated treatment with **sitagliptin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

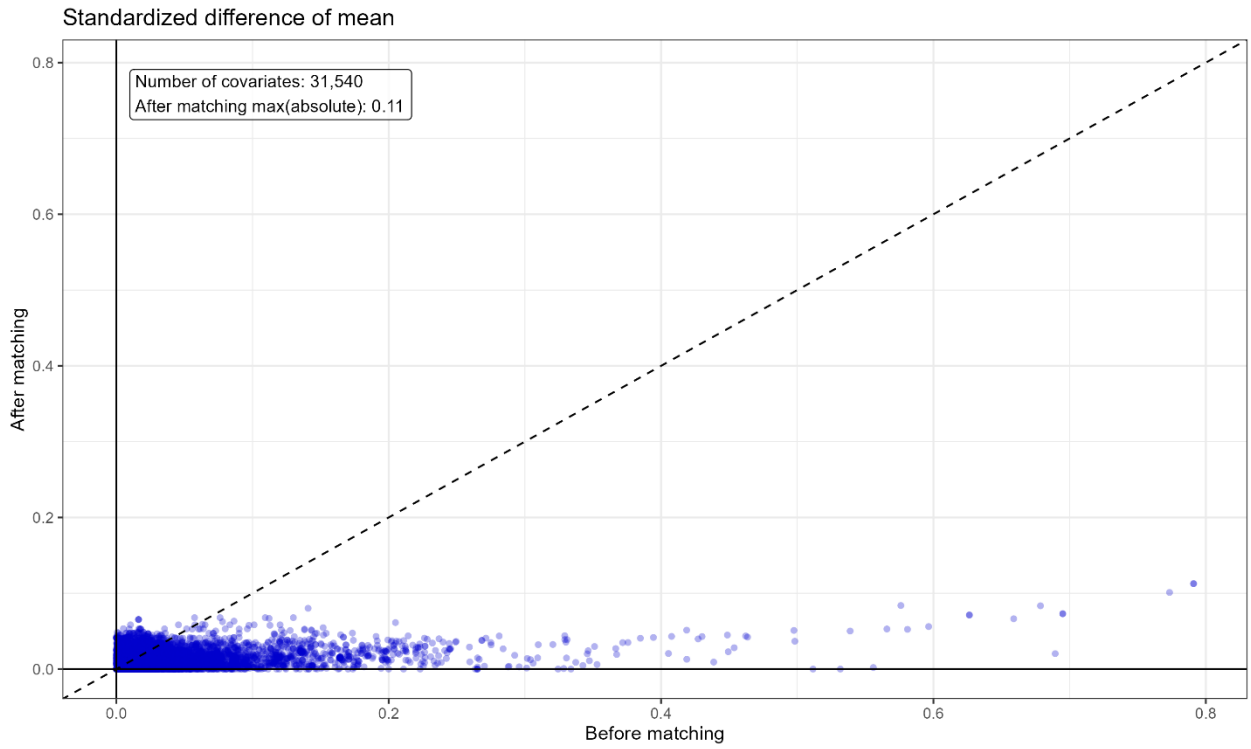


Figure S21. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs sitagliptin**, in **T2DM patients**, in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

Table S5. Predefined[1] baseline characteristics before and after PS matching in **T2DM patients** in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
5 - 9		0.0				
10 - 14		0.0			0.0	
15 - 19	0.1	0.0	0.06	0.2	0.2	0.00
20 - 24	0.3	0.1	0.08	0.3	0.3	0.01
25 - 29	0.6	0.2	0.07	0.6	0.7	0.00
30 - 34	1.4	0.5	0.11	1.4	1.5	-0.01
35 - 39	2.9	1.2	0.14	2.8	3.3	-0.03
40 - 44	5.3	2.7	0.16	5.4	6.2	-0.03
45 - 49	8.1	5.1	0.13	8.1	8.1	0.00
50 - 54	14.5	8.8	0.19	15.0	15.0	0.00
55 - 59	17.6	12.6	0.15	17.2	17.2	0.00
60 - 64	17.0	14.8	0.06	16.5	16.4	0.00
65 - 69	14.3	14.7	-0.01	13.9	13.1	0.03
70 - 74	9.6	13.8	-0.12	9.5	9.6	0.00
75 - 79	5.4	12.5	-0.22	5.9	5.3	0.03
80 - 84	2.5	8.6	-0.23	2.7	2.7	0.00
85 - 89	0.3	3.4	-0.18	0.4	0.3	0.01
90 - 94	0.0	0.8	-0.09	0.1	0.1	-0.01
95 - 99		0.0			0.1	
Gender: female	45.6	42.3	0.07	45.6	45.8	-0.01
Medical history: General						
Acute respiratory disease	14.1	15.2	-0.03	13.3	13.4	0.00
Attention deficit hyperactivity disorder	0.1	0.2	-0.03	0.0	0.0	0.00
Chronic liver disease	0.5	0.5	0.00	0.0		
Chronic obstructive lung disease	5.0	5.4	-0.01	4.2	4.6	-0.02
Crohn's disease	0.1	0.2	-0.01	0.1	0.1	0.01
Dementia	0.9	2.1	-0.09	0.7	0.9	-0.02
Depressive disorder	9.9	8.2	0.06	7.4	7.6	-0.01
Gastroesophageal reflux disease	1.5	2.1	-0.04	1.4	1.3	0.01
Gastrointestinal hemorrhage	0.5	0.7	-0.02	0.2	0.2	-0.01
Human immunodeficiency virus infection	0.1	0.0	0.01	0.0	0.0	0.00
Hyperlipidemia	22.9	22.0	0.02	16.9	16.5	0.01
Hypertensive disorder	41.1	42.9	-0.04	34.2	34.2	0.00
Lesion of liver	0.7	0.7	0.00	0.1	0.0	0.02
Obesity	20.6	8.5	0.41	14.7	16.3	-0.04
Osteoarthritis	9.0	10.6	-0.05	7.1	6.4	0.03
Pneumonia	1.3	1.9	-0.04	1.0	1.0	0.00
Psoriasis	1.6	1.1	0.05	1.0	0.8	0.02
Renal impairment	8.6	5.8	0.12	3.9	4.0	0.00
Rheumatoid arthritis	1.0	1.1	-0.01	0.6	0.5	0.01
Schizophrenia	0.2	0.2	-0.01	0.1	0.1	-0.01
Ulcerative colitis	0.2	0.2	-0.01	0.2	0.2	-0.01
Urinary tract infectious disease	3.3	4.6	-0.06	3.3	2.9	0.02
Viral hepatitis C	0.1	0.1	-0.01			
Medical history: Cardiovascular disease						
Atrial fibrillation	2.3	2.5	-0.01	1.7	1.8	-0.01
Cerebrovascular disease	3.8	4.3	-0.03	2.3	2.4	-0.01
Coronary arteriosclerosis	4.0	4.4	-0.02	3.3	3.2	0.01
Heart disease	21.7	24.2	-0.06	17.7	17.9	0.00
Heart failure	6.5	6.7	-0.01	4.9	4.6	0.01
Ischemic heart disease	10.1	10.9	-0.03	8.1	8.3	-0.01

Peripheral vascular disease	9.9	6.0	0.16	6.5	6.6	0.00
Pulmonary embolism	0.6	0.6	0.00	0.5	0.5	0.00
Venous thrombosis	1.3	1.3	0.00	0.7	0.6	0.02
Medical history: Neoplasms						
Malignant lymphoma	0.3	0.3	0.00	0.2	0.1	0.02
Malignant neoplasm of anorectum	0.1	0.2	-0.03		0.0	
Malignant neoplastic disease	4.1	4.9	-0.04	2.6	2.2	0.03
Malignant tumor of breast	0.7	0.6	0.02	0.4	0.5	0.00
Malignant tumor of colon	0.3	0.4	-0.01	0.2	0.2	-0.01
Malignant tumor of lung	0.1	0.1	-0.01			
Malignant tumor of urinary bladder	0.1	0.2	-0.02	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.6	0.7	-0.01	0.3	0.3	-0.01
Medication use						
Agents acting on the renin-angiotensin system	53.6	62.3	-0.18	51.0	49.7	0.03
Antibacterials for systemic use	21.0	23.5	-0.06	19.4	19.7	-0.01
Antidepressants	9.7	9.4	0.01	8.6	9.1	-0.02
Antiepileptics	5.3	5.1	0.01	4.9	4.9	0.00
Antiinflammatory and antirheumatic products	32.0	39.8	-0.16	29.5	28.6	0.02
Antineoplastic agents	0.8	1.2	-0.04	0.7	0.7	0.00
Antipsoriatics	0.4	0.4	0.01	0.3	0.3	0.01
Antithrombotic agents	22.4	30.1	-0.17	22.0	20.9	0.03
Beta blocking agents	34.8	42.9	-0.16	32.9	32.1	0.02
Calcium channel blockers	25.1	30.5	-0.12	23.1	23.4	-0.01
Diuretics	37.4	44.5	-0.14	34.5	34.3	0.00
Drugs for acid related disorders	26.2	32.1	-0.13	24.1	23.1	0.03
Drugs for obstructive airway diseases	14.2	15.4	-0.03	13.0	12.2	0.02
Drugs used in diabetes	100.0	100.0	0.00	100.0	100.0	0.00
Immunosuppressants	0.7	0.7	0.00	0.5	0.6	-0.01
Lipid modifying agents	38.9	42.1	-0.07	36.0	35.2	0.02
Opioids	10.2	11.3	-0.04	9.3	9.7	-0.01
Psycholeptics	5.8	8.6	-0.10	5.1	5.4	-0.02
Psychostimulants agents used for adhd and nootropics	0.2	0.2	-0.01	0.1	0.2	-0.01

SMD: Standardized mean differences. **Target: Liraglutide. Comparator: Sitagliptin.**

(1) Covariates presented here are default groupings from the CohortMethod 5.2.1 package, which were measured within 365 days prior to index-date. The table does not accurately reflect the presence of chronic diseases in the patients, since chronic diseases that were recorded more than 365 days prior to the index-date and not repeated within 365 days prior to the index-date were not considered. Of note, only a small number of the baseline covariates used to fit the propensity score model is presented here. The complete list of covariates is available upon request.

A3. 2. 2 Acute hepatic injury

A3. 2. 2. 1 Liraglutide vs Empagliflozin

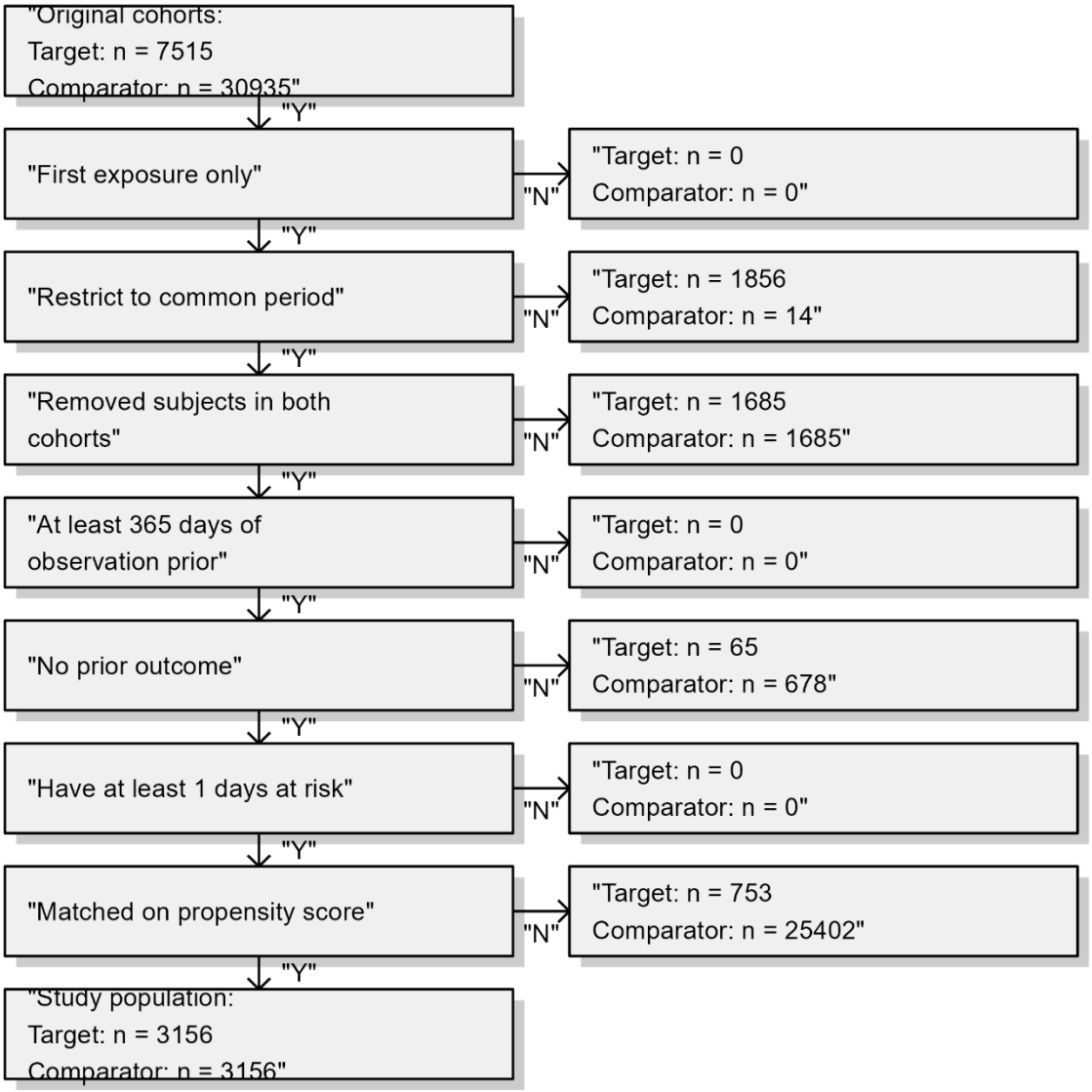


Figure S22. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **empagliflozin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

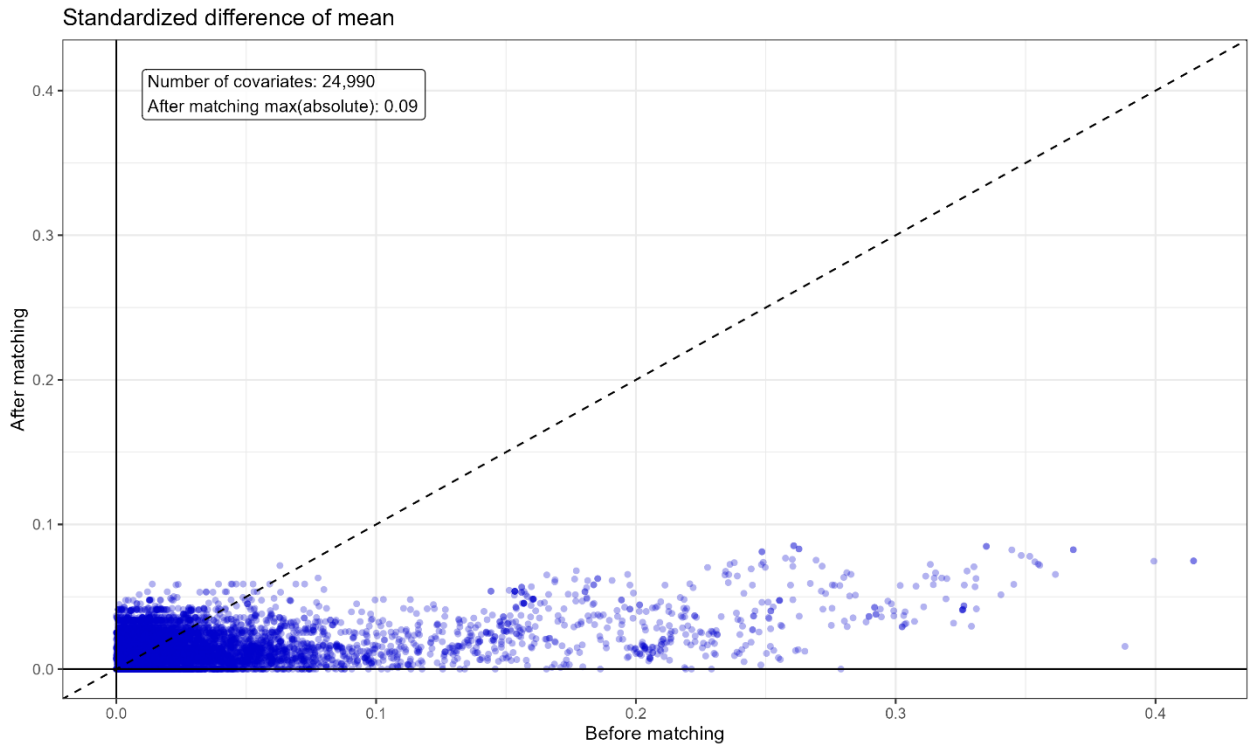


Figure S23. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs empagliflozin**, in **T2DM patients** in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3. 2. 2. 2 Liraglutide vs Dapagliflozin

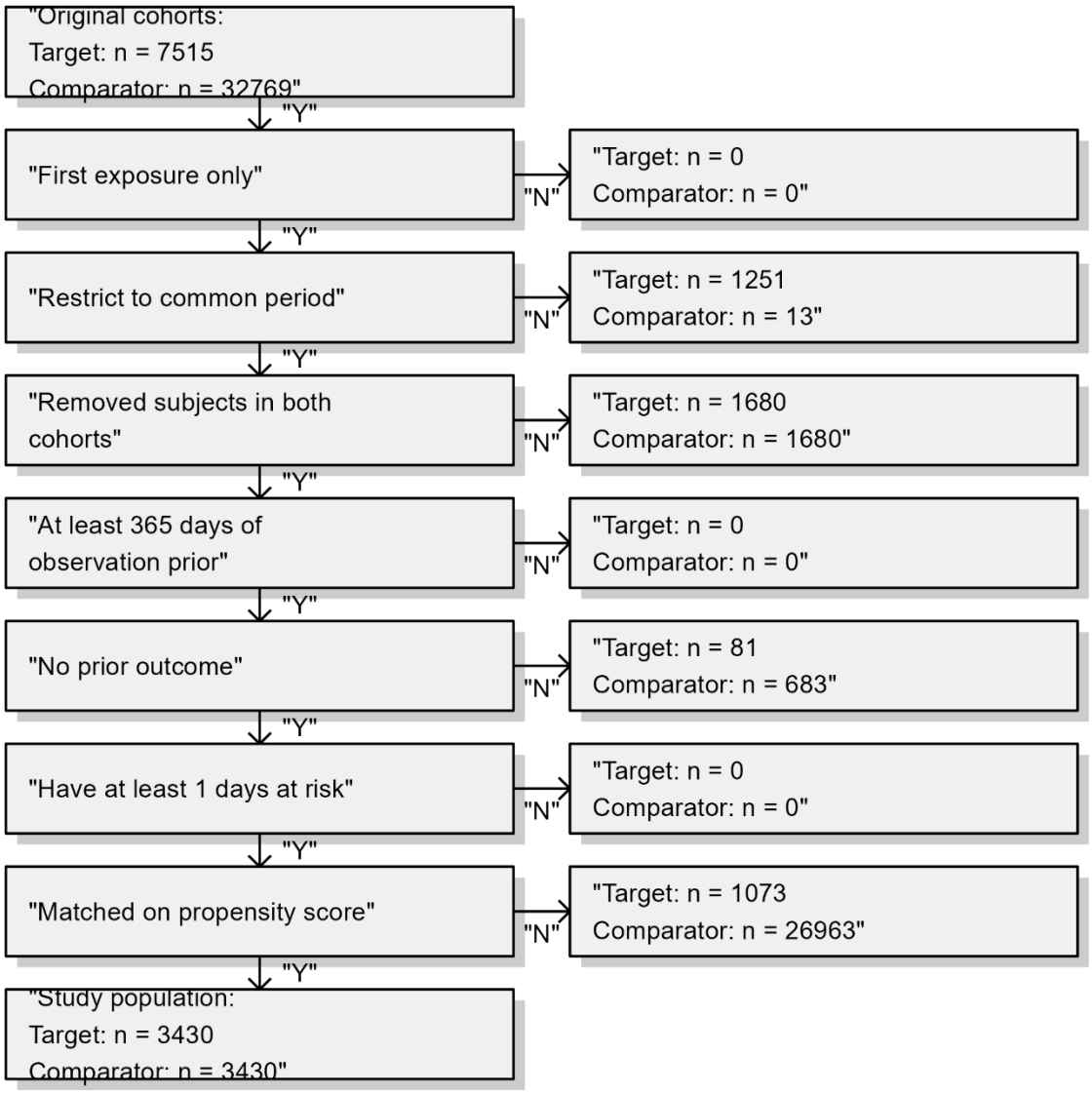


Figure S24. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **dapagliflozin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

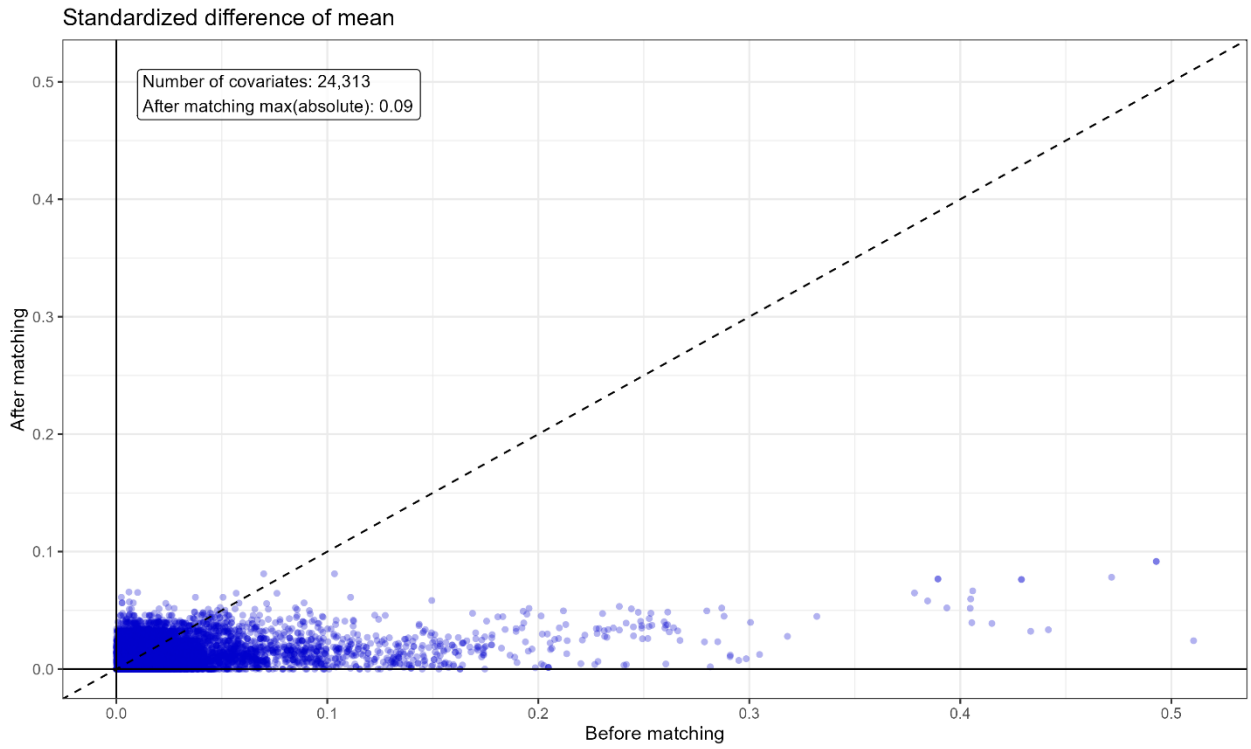


Figure S25. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs dapagliflozin**, in **T2DM patients** in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3. 2. 2. 3 Liraglutide vs Sitagliptin

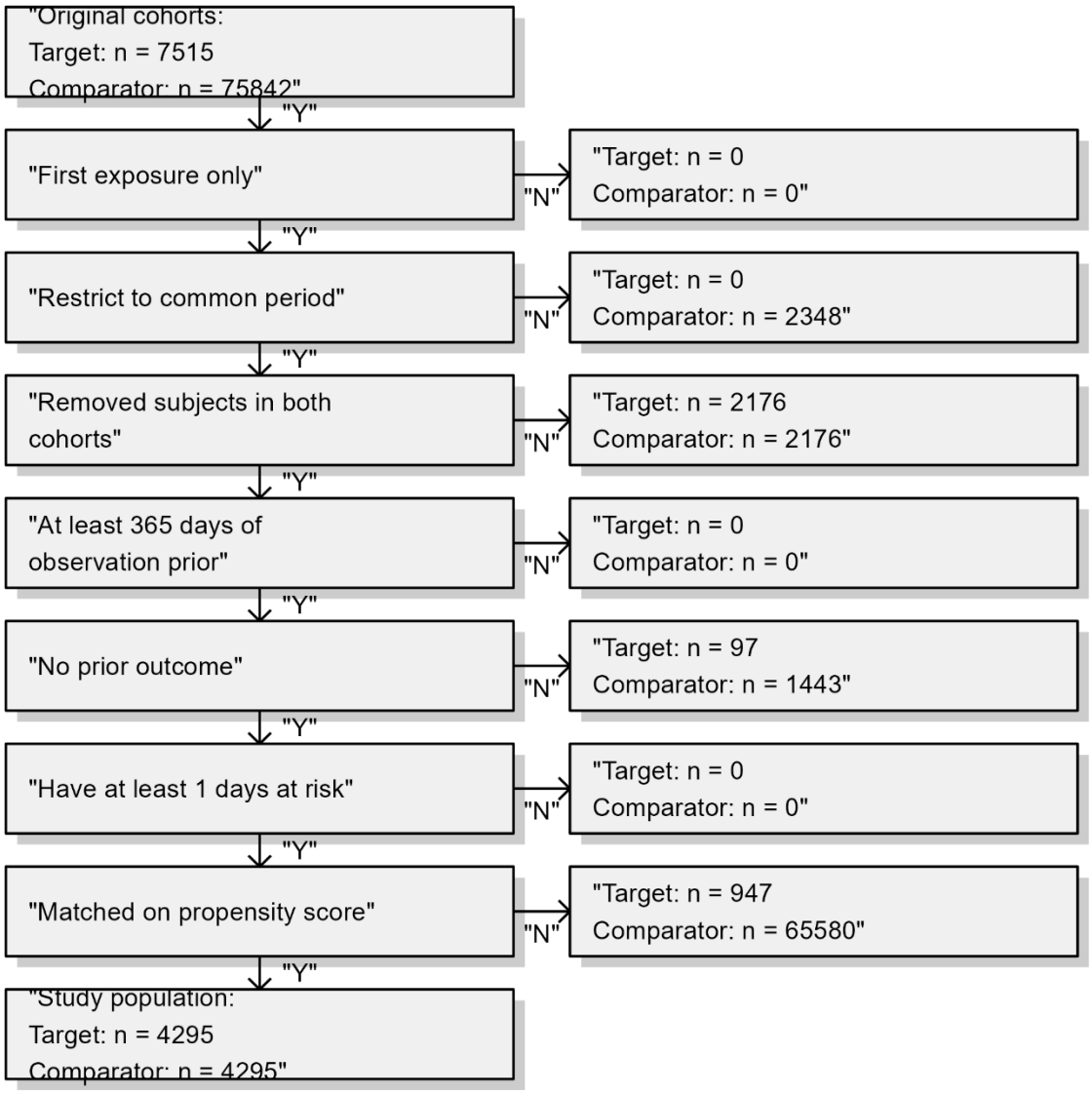


Figure S26. Patient cohort attrition. Target arm refers to patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **sitagliptin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

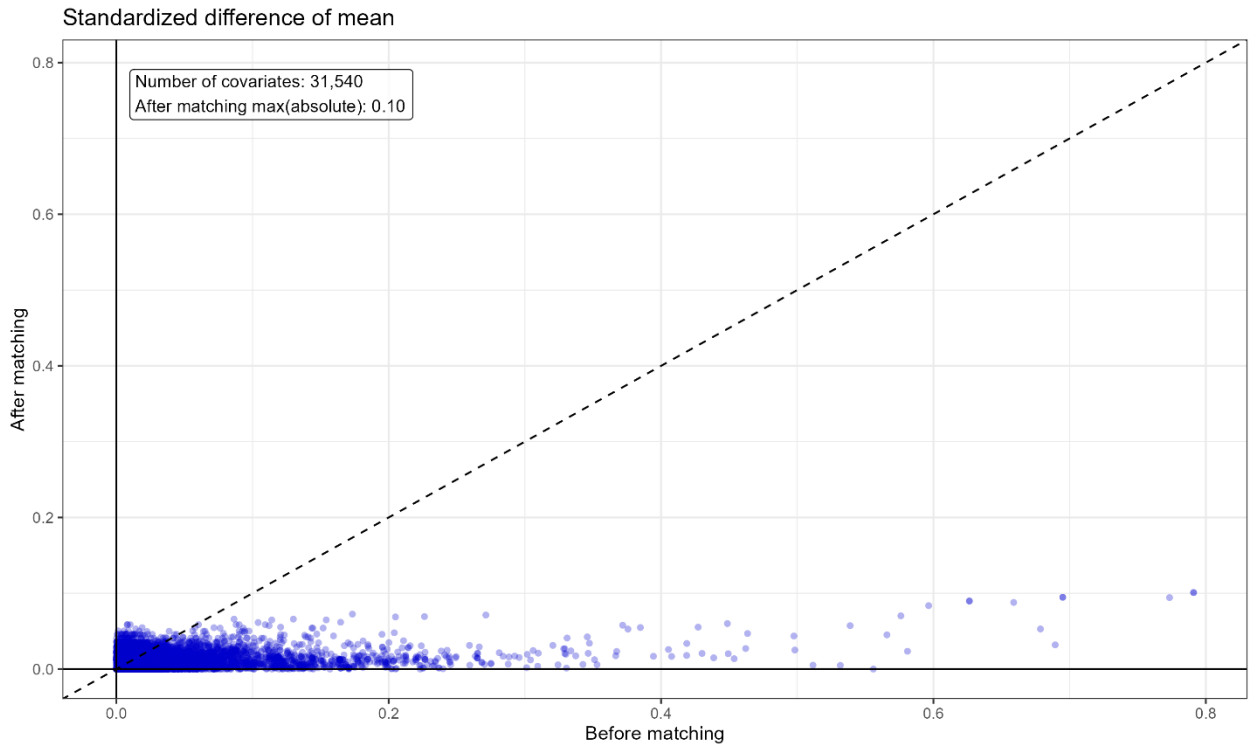


Figure S27. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs sitagliptin**, in **T2DM patients** in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3. 2. 3 Acute hepatic injury with no chronic hepatic failure

A3. 2. 3. 1 Liraglutide vs Empagliflozin

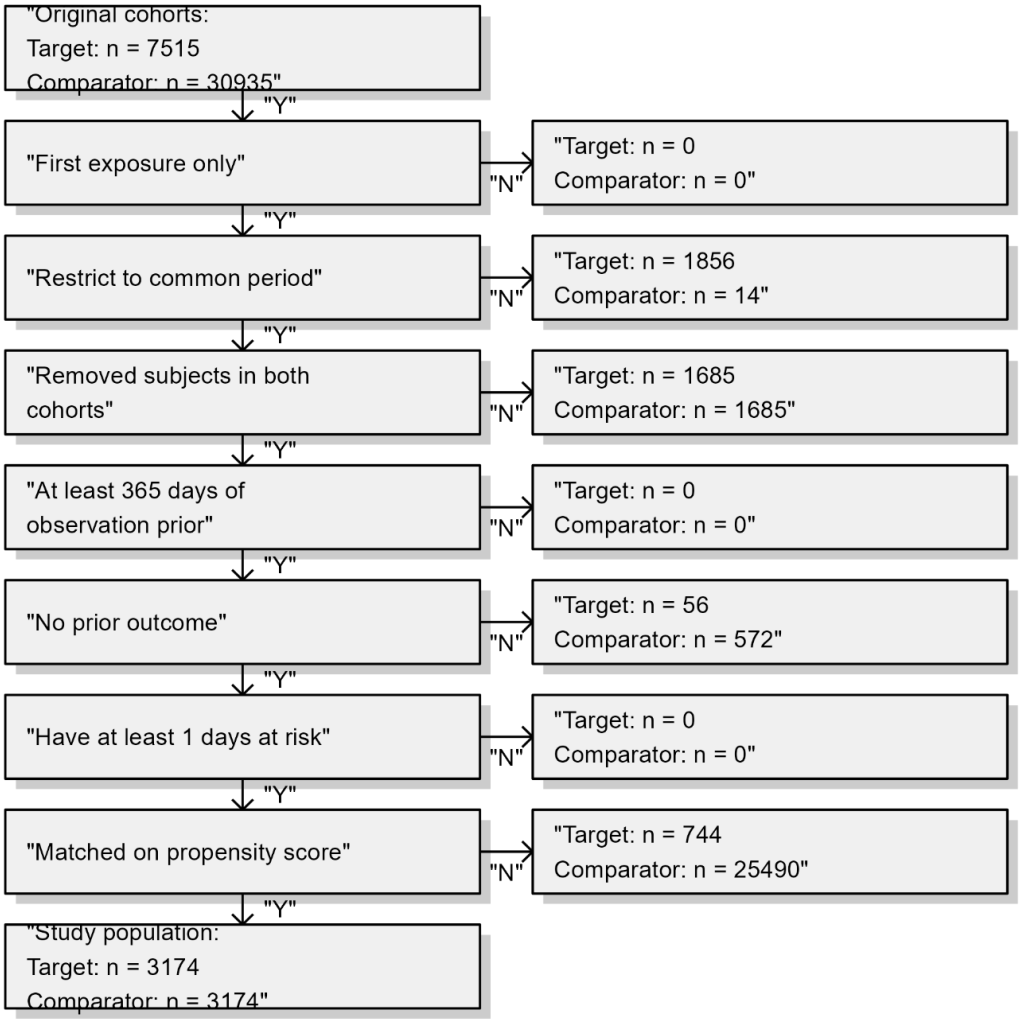


Figure S28. Patient cohort attrition. Target arm refers to **T2DM patients** who initiated treatment with **liraglutide,** and comparator arm refers to patients who initiated treatment with **empagliflozin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

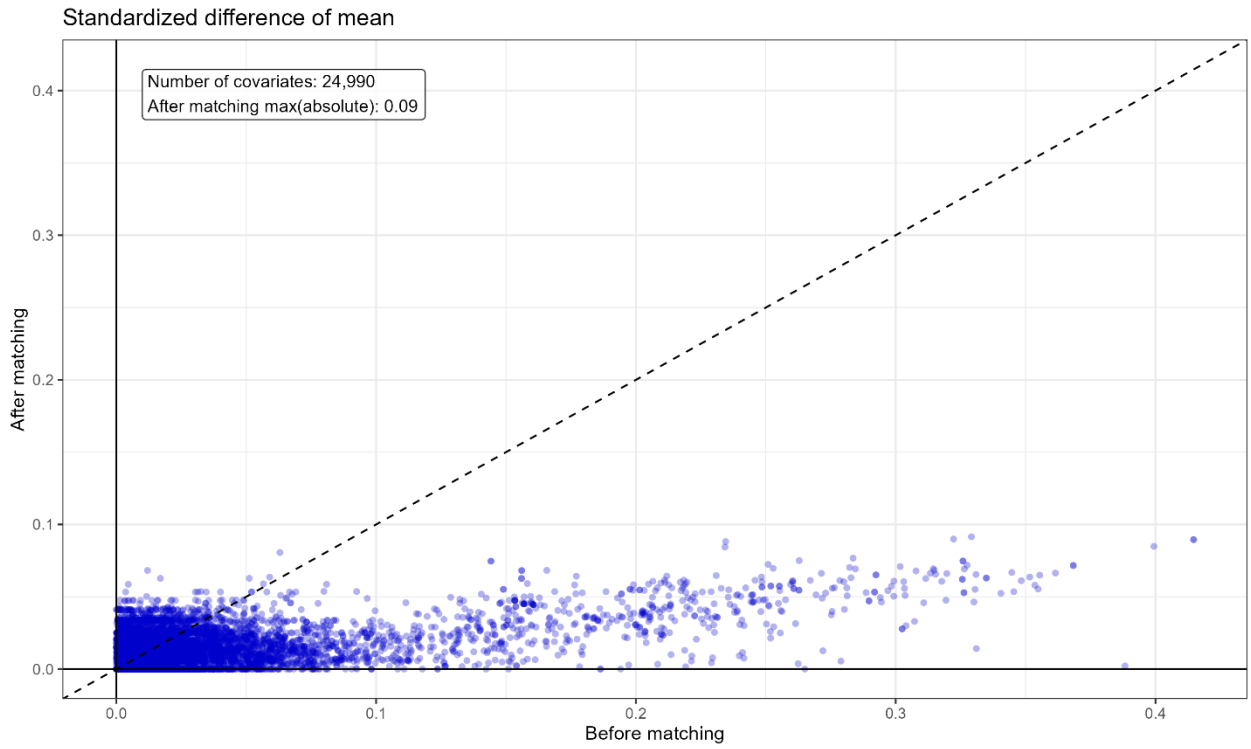


Figure S29. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs empagliflozin**, in **T2DM patients** in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3. 2. 3. 2 Liraglutide vs Dapagliflozin

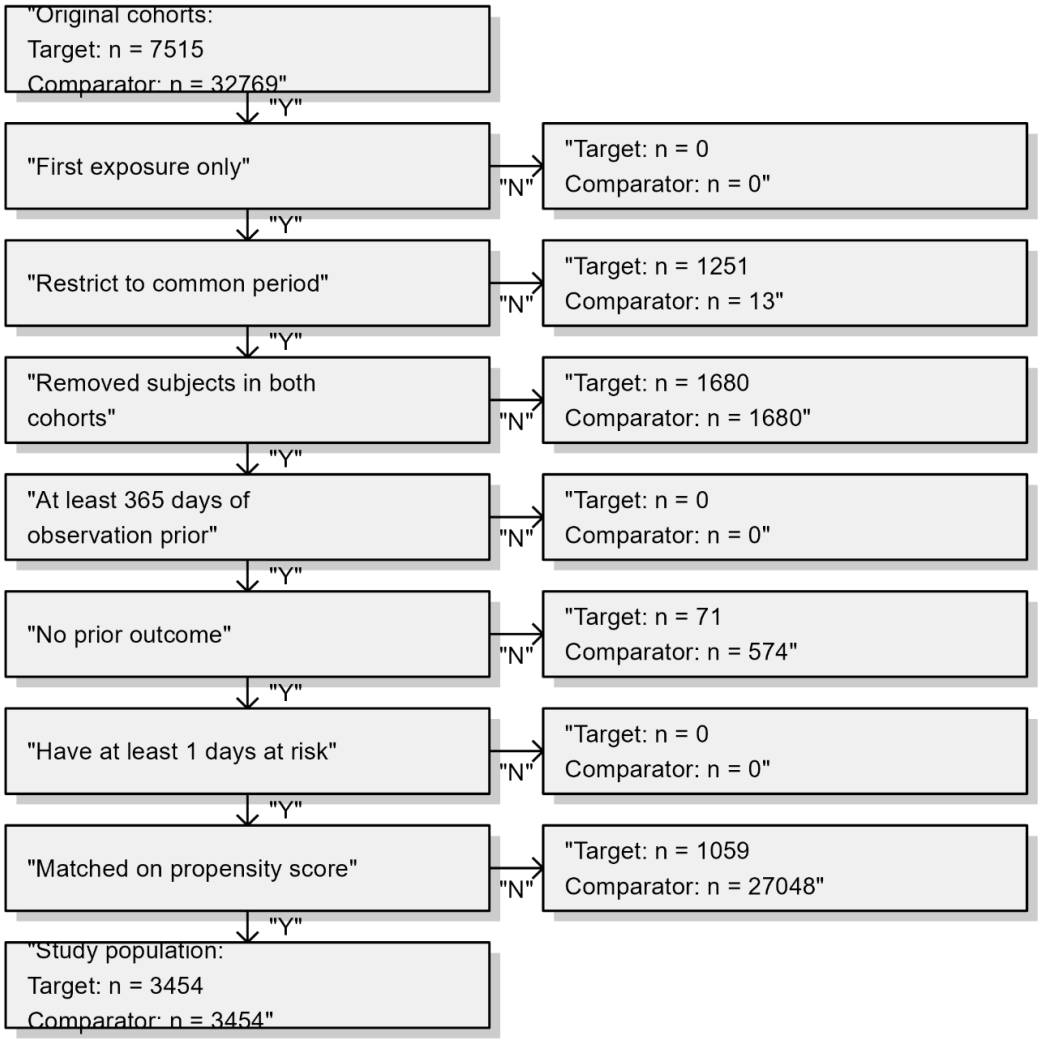


Figure S30. Patient cohort attrition. Target arm refers to T2DM patients who initiated treatment with **liraglutide**, and comparator arm refers to patients who initiated treatment with **dapagliflozin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

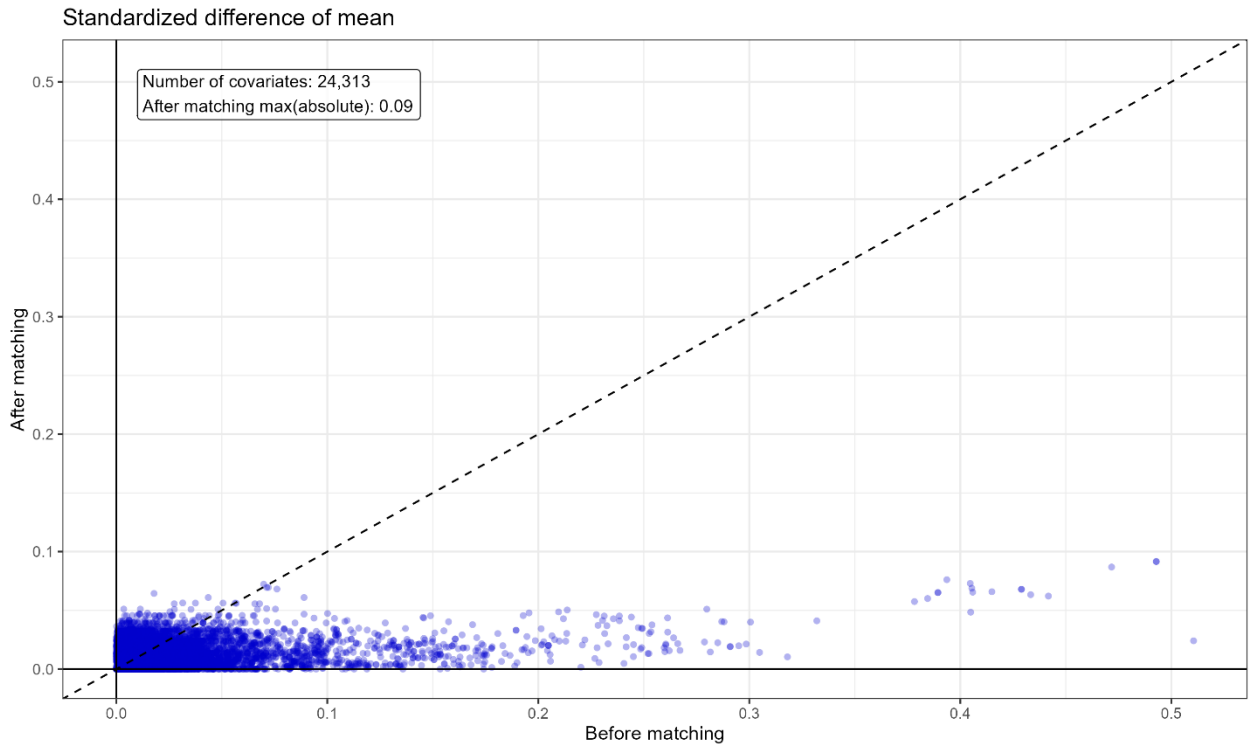


Figure S31. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs dapagliflozin**, in **T2DM patients** in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.

A3. 2. 3. 3 Liraglutide vs Sitagliptin

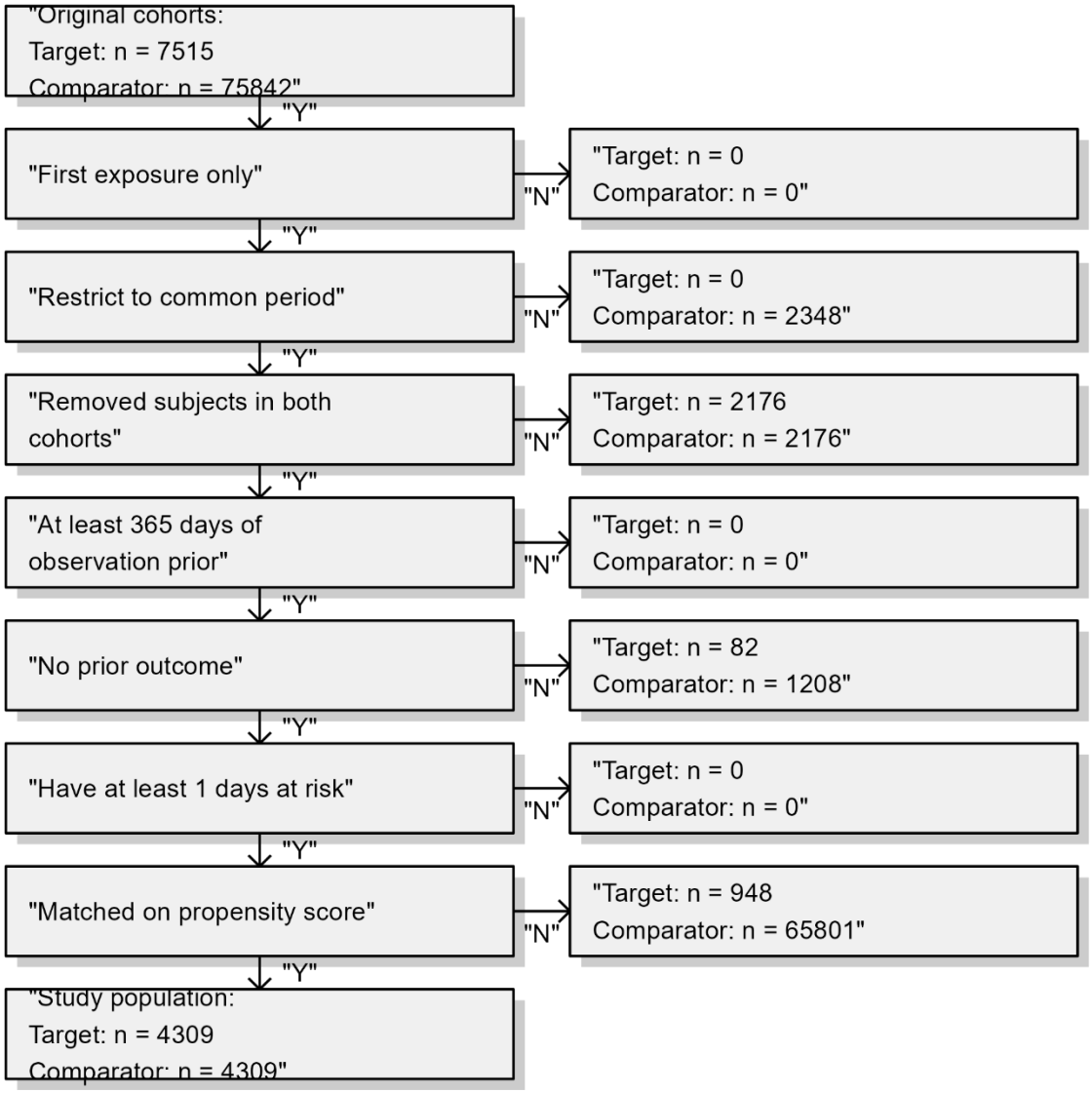


Figure S32. Patient cohort attrition. Target arm refers to T2DM patients who initiated treatment with **liraglutide** and comparator arm refers to patients who initiated treatment with **sitagliptin** in **T2DM patients** in the IQVIA™ DA Germany database.

N.B.: For this study, the original cohorts (box on the top) already met the eligibility requirements of first exposure per patient and a minimum observation time prior to index-date of 365 days. Therefore, exclusions based on these two conditions appear as null in the respective boxes on the right.

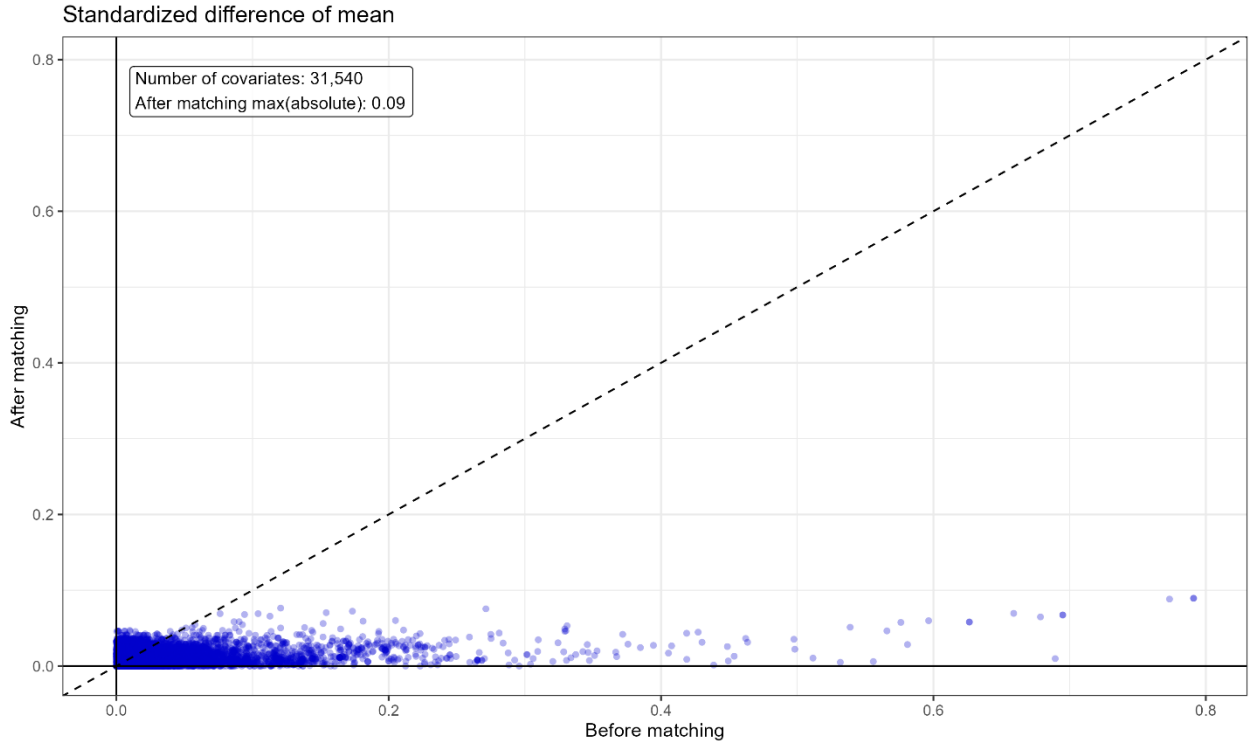


Figure S33. Scatter plot of the standardized difference in means (SMD) of each covariate before and after PS matching comparing the following treatment cohorts: **liraglutide vs sitagliptin**, in **T2DM patients** in the IQVIA™ DA Germany database.

Before PS matching, there were baseline imbalances in several covariates whose SMD was >0.1. However, all covariates achieved an appropriate covariate balance with a SMD of <0.1 after PS matching.