



## **Study Report**

**P3-C3-005**

# **DARWIN EU® - Incidence rates of venous thromboembolic events in patients with selected cancers**

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Version 4.0

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Public

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|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study title</b>                      | DARWIN EU® - Incidence rates of venous thromboembolic events in patients with selected cancers                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Study report version</b>             | V4.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <b>Active substance</b>                 | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <b>Research question and objectives</b> | <p>This study aimed to estimate incidence rates of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolisms [PE], venous thromboembolism [VTE] (composite of DVT and PE), pelvic venous thrombosis [PVT], splanchnic vein thrombosis [SVT], including hepatic and extra-hepatic vein thrombosis, retinal vein thrombosis [RVT], including retinal central vein thrombosis, and disseminated intravascular coagulation [DIC]) in adult patients (aged 18 and above) who were newly diagnosed with selected cancers (bone, brain, breast, colorectal, corpus uteri, kidney, leukaemia and lymphoma, liver, lung, melanoma, oesophageal, ovary, pancreas, prostate, stomach) during the period 2016–2022, and to describe their characteristics at the time of cancer diagnosis.</p> <p>The specific objectives of the study were:</p> <ol style="list-style-type: none"> <li>1. To estimate the incidence rates of thromboembolic events in patients newly diagnosed with each type of selected cancers stratified by country/data source, age group, sex, study period (2016–2019 and 2020–2022), and cancer stage one and two years after cancer diagnosis.</li> <li>2. To characterise cancer patients in terms of demographic characteristics, comorbidities, and concomitant medication before and at the time of diagnosis, as well as medications and procedures received in the first 90 days after cancer diagnosis.</li> </ol> |
| <b>Countries of study</b>               | Belgium, Denmark, Estonia, Finland, Germany, The Netherlands, Spain, United Kingdom                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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## 1. TITLE

DARWIN EU® - Incidence rates of venous thromboembolic events in patients with selected cancers

## 2. DESCRIPTION OF STUDY TEAM

| Study team roles                       | Names                                                                                             | Organisations                                    |
|----------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Principal Investigator                 | Anton Barchuk,<br>Talita Duarte-Salles                                                            | Erasmus MC                                       |
| Data Scientist                         | Cesar Barboza<br>Ioanna Nika**<br>Ger Inberg<br>Maarten van Kessel<br>Adam Black<br>Ross Williams | Erasmus MC                                       |
| Epidemiologist                         | Berta Raventós<br>Julieta Politi<br>Melissa Leung**                                               | Erasmus MC                                       |
| Clinical Domain Expert                 | Anton Barchuk                                                                                     | Erasmus MC                                       |
| Study Manager                          | Natasha Yefimenko                                                                                 | Erasmus MC                                       |
| Data Partner                           | Name                                                                                              | Organisation                                     |
| IQVIA LPD Belgium and IQVIA DA Germany | Gargi Jadhav<br>Isabella Kacmarczyk<br>Akram Mendez<br>Hanne van Ballegooijen<br>Dina Vojinovic   | IQVIA                                            |
| DK-DHR                                 | Claus Møldrup<br>Elvira Bräuner<br>Susanne Bruun                                                  | Danish Medicines Agency                          |
| EBB                                    | Marek Oja<br>Raivo Kolde                                                                          | Estonian Biobank, Estonia                        |
| FinOMOP-THL                            | Anna Hammis<br>Gustav Klingstedt                                                                  | Finnish Care Register for Health Care, Finland   |
| IPCI                                   | Katia Verhamme                                                                                    | Integrated Primary Care Information, Netherlands |
| SIDIAP                                 | Anna Palomar-Cros<br>Irene López-Sánchez<br>Agustina Giuliodori                                   | IDIAPJGol                                        |
| CPRD GOLD and UKBB                     | Antonella Delmestri                                                                               | University of Oxford                             |

\*Data partners do not have an investigator role. Data partners execute code at their data source, review and approve their results.

\*\*Added to the study team on the 26<sup>th</sup> of August 2025.

### 3. ABSTRACT

#### Title

DARWIN EU® - Incidence rates of venous thromboembolic events in patients with selected cancers

#### Rationale and background

Cancer patients have an increased risk of developing venous thromboembolism (VTE) compared to individuals without underlying malignancies, which is also recognised as one of the major causes of death in cancer patients. Cancer-associated venous thrombosis is relatively common: from 20% to 30% of all primary venous thromboembolic events are cancer-associated. The reported incidence varies across different populations and cancer types and can also be attributed to variations in patient characteristics, clinical management options, and the cancer stage at diagnosis. The incidence of VTE was found to be higher in cases of renal cell, ovarian, pancreatic, stomach, and lung cancers, as well as acute myelogenous leukaemia and non-Hodgkin lymphoma during the four months immediately preceding the cancer diagnosis. When investigating a potential safety signal associated with oncological treatments, the availability of recent and reliable information on the background rates of VTE in cancer patients is crucial.

#### Research question and objectives

##### Research questions

What were the incidence rates of venous thromboembolic events in adult patients who were newly diagnosed with selected cancers during the period 2016–2022?

##### Objectives

This study aimed to estimate incidence rates of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolisms [PE], venous thromboembolism [VTE] (composite of DVT and PE), pelvic venous thrombosis [PVT], splanchnic vein thrombosis [SVT], including hepatic and extra-hepatic vein thrombosis, retinal vein thrombosis [RVT], including retinal central vein thrombosis, and disseminated intravascular coagulation [DIC]) in adult patients (aged 18 and above) who were newly diagnosed with selected cancers (bone, brain, breast, colorectal, corpus uteri, kidney, leukaemia and lymphoma, liver, lung, melanoma, oesophageal, ovary, pancreas, prostate, stomach) during the period 2016–2022, and to describe their characteristics at the time of cancer diagnosis.

The specific objectives of the study were:

1. To estimate the incidence rates of thromboembolic events in patients newly diagnosed with each type of selected cancers stratified by country/data source, age group, sex, study period (2016–2019 and 2020–2022), and cancer stage one and two years after cancer diagnosis.
2. To characterise cancer patients in terms of demographic characteristics and comorbidities before and at the time of diagnosis, as well as medications and procedures received in the first 90 days after cancer diagnosis.

#### Methods

##### Study design

Population-based cohort study.

##### Population

The study population included all individuals aged 18 years and above with a primary diagnosis of one of the selected cancers (bone, brain, breast, colorectal, corpus uteri, kidney, leukaemia and lymphoma, liver, lung, melanoma, oesophageal, ovary, pancreas, prostate, stomach). The study period was from 01/01/2016

to 31/12/2022, which was at least one year prior to the last date of data availability in all data sources, to ensure sufficient time to capture potential outcomes of interest. Only patients with a first and single cancer diagnosis (excluding non-melanoma skin cancer) were included. Cancer cases and thromboembolic events were identified based on appropriate computable phenotyping algorithms. Conditions in the OMOP CDM used the Systematised Nomenclature of Medicine (SNOMED) as the standard vocabulary for diagnosis codes. The International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) was also considered for cancer diagnoses.

### Variables

Outcomes included thromboembolic events, specifically DVT, PE, VTE, PVT, SVT, RVT, and DIC. The outcomes were calculated in patients with selected cancer types and stratified by the American Joint Committee on Cancer and the International Union Against Cancer (AJCC/UICC) stage categories, age (18–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85 and above), sex, and study subperiod (2016–2019 and 2020–2022).

### Data sources

1. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
2. Danish Data Health Registries (DK-DHR), Denmark
3. Estonian Biobank (EBB), Estonia
4. Finnish Care Register for Health Care (FinOMOP-THL), Finland
5. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
6. Integrated Primary Care Information (IPCI), Netherlands
7. The Information System for the Development of Research in Primary Care (SIDAP), Spain
8. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
9. UK Biobank (UKBB), United Kingdom

### Study size

No sample size was calculated, as this was a descriptive study.

### Statistical analysis

Analyses were conducted separately for each data source and carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data.

The incidence rates (IRs) and 95% confidence intervals (95% CI) of thromboembolic events (Objective 1) were estimated over one and two years after the selected cancer diagnosis. Each cancer type and outcome was assessed separately.

A random-effects meta-analysis was applied to the overall crude incidence rates of thromboembolic events for selected cancer types to obtain summary estimates, with 95% CIs calculated using the Knapp-Hartung method.

Patient-level characterisation was conducted. Age and sex were described at the time of diagnosis. Comorbidities (Objective 2) were described at any time up to 181 days prior to the diagnosis date, 180 days up to one day prior to the diagnosis date, and at the diagnosis date. Medications were assessed at the diagnosis date and 90 days after the diagnosis date; procedures were described 90 days after the diagnosis date. AJCC/UICC stages were described within 30 days after the diagnosis date.

For all analyses, absolute and relative frequencies were reported. A minimum cell count of 5 was used when reporting results, with any smaller counts reported as "<5" and zero counts as "0". Overall analyses

were conducted separately for each data source. Stratification by age category, sex, study year, and cancer stage were performed when possible (i.e., when the minimum cell count was reached and data were available).

## Results

Our study included 975,962 cancer patients across nine data sources. The largest patient groups were breast cancer (173,017) and prostate cancer (154,254), followed by colorectal (116,633) and haematological malignancies (116,070). Altogether, 47,076 thromboembolic events were recorded within one year after cancer diagnosis, and 58,979 thromboembolic events after two years.

The highest IRs of thromboembolic events were consistently observed in pancreatic, oesophageal, liver, stomach, lung, brain, and ovarian cancers, whereas melanoma, breast, and prostate cancer patients showed the lowest rates.

Among outcomes, in the meta-analyses, VTE was the most common event across all selected cancers, except for liver cancer, with combined IRs (95% CI) ranging from 597 (491–726) per 100,000 PY in melanoma to 11,607 (7,574–17,787) in pancreatic cancer. PE was generally the second most frequent event across all selected cancer types, ranging from 389 (297–511) in melanoma to 8,671 (5,578–13,479) in pancreatic cancer, followed by DVT. Other outcomes (SVT, RVT, PVT) were rare across most cancers, except for SVT being the most common thromboembolic outcome in liver cancer with combined IR 7,448 [1,858–13,039] per 100,000 PY. IRs after two years of follow-up showed the same pattern as after one year, with lower absolute values.

Comorbidity patterns varied by cancer type: in the time window from 180 days to 1 day prior to diagnosis date, chronic obstructive pulmonary disease and pneumonia were prominent in lung cancer (7.7% in CPRD GOLD–24.5% in DK-DHR and 2.8% in CPRD GOLD–24.1% in DK-DHR, respectively), chronic liver disease and viral hepatitis in liver cancer (<5 counts in IQVIA LPD Belgium–23.1% in DK-DHR and 0% in IQVIA LPD Belgium–9.3% in EBB, respectively), obesity in corpus uteri (<5 counts in IQVIA LPD Belgium–11.1% in DK-DHR) and kidney cancers (0% in IQVIA LPD Belgium–6.2% in EBB), and gastrointestinal haemorrhage in stomach (<5 counts in IQVIA LPD Belgium–8.8% in FinOMOP-THL) and colorectal cancers (<5 counts in IQVIA LPD Belgium–11.5% in SIDIAP). Prevalent across most cancers were hypertension (highest in kidney cancer: 1.3% in CPRD GOLD–36.4% in IQVIA LPD Belgium), diabetes (highest in liver cancer: 1.8% in CPRD GOLD–27.5% in DK-DHR), and hyperlipidaemia (highest in pancreatic cancer: 0.3% in CPRD GOLD–28.6% in DK-DHR).

Medication use also varied by cancer type. In general, in the time window from 1 to 90 days after diagnosis date, opioid use was high in pancreatic (1.4% in UKBB–73.7% in FinOMOP-THL), stomach (1.2% in UKBB–53.8% in FinOMOP-THL), liver (<5 counts in UKBB–62.6% in FinOMOP-THL), and oesophageal cancers (0.9% in UKBB–60.5% in FinOMOP-THL), while antiepileptics were frequent in brain cancer (1.2% in UKBB–56.0% in SIDIAP), and antithrombotics in ovarian (0.6% in UKBB–80.2% in FinOMOP-THL) and haematological cancers (0.5% in UKBB–38.5% in DK-DHR). Radiotherapy was most frequent in brain cancer (0% in DK-DHR, FinOMOP-THL, IPCI, IQVIA DA Germany, IQVIA LPD Belgium, and SIDIAP–43.9% in EBB), whereas surgical procedures were most common in corpus uteri cancer (<5 counts in IQVIA DA Germany and IQVIA LPD Belgium–91.9% in EBB) and melanoma (<5 counts in IQVIA DA Germany and IQVIA LPD Belgium–95.5% in DK-DHR). Bone marrow transplantation was recorded in fewer than 1% of patients.

## Discussion

In this large multinational cohort study, which incorporated data from nine data sources across eight countries, we estimated the incidence of seven types of thromboembolic events among patients with selected cancers up to one and two years after cancer diagnosis. PE and DVT (and their combination) were the most frequently observed thromboembolic events. High incidence rates of thromboembolic events were seen in patients with gastrointestinal cancers, particularly pancreatic (the highest rates observed),

oesophageal, and stomach, but also in patients with lung, brain, ovarian cancer, while the lowest were observed in patient with melanoma, prostate, and breast cancer, highlighting differences in patient profiles. Finally, the characterisation of cancer patients provided insights into prevalent comorbidities and concomitant medication use across cancer types, suggesting differences in cancer patient profiles.

## 4. LIST OF ABBREVIATIONS

| Acronym/term | Description                                                                   |
|--------------|-------------------------------------------------------------------------------|
| ADHD         | Attention deficit hyperactivity disorder                                      |
| AJCC/UICC    | American Joint Committee on Cancer and the International Union Against Cancer |
| ATC          | Anatomical Therapeutic Chemical                                               |
| CDM          | Common Data Model                                                             |
| CI           | Confidence interval                                                           |
| CPRD         | Clinical Practice Research Datalink                                           |
| DARWIN EU®   | Data Analysis and Real World Interrogation Network                            |
| DK-DHR       | Danish Data Health Registries                                                 |
| DOI          | Declaration Of Interests                                                      |
| DQD          | Data Quality Dashboard                                                        |
| DRE          | Digital Research Environment                                                  |
| DVT          | Deep Venous Thrombosis                                                        |
| DIC          | Disseminated Intravascular Coagulation                                        |
| EHR          | Electronic Health Record                                                      |
| EMA          | European Medicines Agency                                                     |
| EBB          | Estonian Biobank                                                              |
| EGCUT        | Estonian Genome Center at the University of Tartu                             |
| ENCePP       | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance    |
| GP           | General Practitioner                                                          |
| HIV          | Human Immunodeficiency Virus                                                  |
| ICD-O-3      | International Classification of Diseases for Oncology, 3rd Edition            |
| ICD-10       | International Classification of Diseases, 10th revision                       |
| ICPC-1       | International Classification of Primary Care                                  |
| IPCI         | Integrated Primary Care Information Project                                   |
| IR           | Incidence rate                                                                |
| LPD          | Longitudinal Patient Database                                                 |
| OHDSI        | Observational Health Data Sciences and Informatics                            |
| OMOP         | Observational Medical Outcomes Partnership                                    |
| PE           | Pulmonary Embolism                                                            |
| PVT          | Pelvic Venous Thrombosis                                                      |
| PY           | Person-years                                                                  |
| RVT          | Retinal vein thrombosis                                                       |
| SIDIAP       | The Information System for the Development of Research in Primary Care        |
| SNOMED       | Systematized Nomenclature of Medicine                                         |
| SVT          | Splanchnic Vein Thrombosis                                                    |

|      |                        |
|------|------------------------|
| UKBB | UK Biobank             |
| VTE  | Venous Thromboembolism |

## 5. AMENDMENTS AND UPDATES

None.

## 6. MILESTONES

| Study deliverables                          | Timelines (planned) | Timelines (actual) |
|---------------------------------------------|---------------------|--------------------|
| Draft Study Protocol                        | December 2024       | December 2024      |
| Final Study Protocol                        | January 2025        | January 2025       |
| Creation of Analytical code and Phenotyping | February 2025       | February 2025      |
| Execution of Analytical Code on the data    | March-April 2025    | March-July 2025    |
| Draft Study Report                          | May 2025            | August 2025        |
| Final Study Report                          | June 2025           | September 2025     |

## 7. RATIONALE AND BACKGROUND

Cancer patients have an increased risk of developing venous thromboembolism (VTE) compared to individuals without underlying malignancies (1). VTE is also recognised as one of the major causes of death in cancer patients (2). Cancer-associated venous thrombosis is relatively common: from 20% to 30% of all primary venous thromboembolic events are cancer-associated (3). The reported incidence varies across different populations and cancer types and can also be attributed to variations in patient characteristics, clinical management options, and the cancer stage at diagnosis (3).

The association between cancer and thromboembolic events was assessed in various studies. In a large cohort of cancer patients, the incidence of thromboembolic events was found to be higher in cases of renal cell, ovarian, pancreatic, stomach, and lung cancers, as well as acute myelogenous leukaemia and non-Hodgkin lymphoma during the four months immediately preceding the cancer diagnosis (4). The prevalence of thromboembolic events at the time of diagnosis was highest for pancreatic cancer and lowest for breast cancer in a registry-based study (5). The risk of thromboembolic events was increased for all cancer types in another study conducted in the United States (6).

The incidence of thromboembolic events increased during the first few months of chemotherapy in a cohort of cancer patients followed for up to 12 months, with higher odds observed in pancreatic, gastric, and lung cancers (7). Certain cancer medications have also been associated with higher risks of thromboembolic events (7,8). Additionally, major surgery is known to be associated with thromboembolic events, with an increased risk that persists for 90 to 120 days post-surgery (9). A high rate of recurrent thromboembolic events is observed over time following the discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis (10).

When a potential safety signal of this nature, such as VTE associated with a cancer therapy, emerges in cancer populations, it can be challenging to assess the potential contribution of the therapy to the event without recent and reliable information on the background rates. This study addressed this knowledge gap by generating background incidence rates of thromboembolic events among patients with selected cancer types.

By providing this essential information, the study aims to improve the understanding of the risk profile for VTE in these populations and enabling a clearer understanding of the therapy's potential impact on VTE risk in this population.

## 8. RESEARCH QUESTION AND OBJECTIVES

This study aimed to estimate incidence rates of the following venous thromboembolic events:

- Deep vein thrombosis (DVT)
- Pulmonary embolisms (PE)
- Venous thromboembolism (VTE, composite of DVT and PE)
- Pelvic venous thrombosis (PVT)
- Splanchnic vein thrombosis (SVT), including hepatic and extra-hepatic vein thrombosis
- Retinal vein thrombosis (RVT), including retinal central vein thrombosis
- Disseminated intravascular coagulation (DIC)

in adult patients (aged 18 and above) newly diagnosed in 2016–2022 with the following selected cancers:

- Bone
- Brain
- Breast
- Colorectal
- Corpus uteri
- Kidney
- Leukaemia and Lymphoma
- Liver
- Lung
- Melanoma
- Oesophageal
- Ovary
- Pancreas
- Prostate
- Stomach

and to describe their characteristics at the time of cancer diagnosis.

The specific objectives of the study were:

1. To estimate the incidence rates of thromboembolic events in patients newly diagnosed with each type of selected cancers stratified by country/data source, age group, sex, study period (2016–2019 and 2020–2022), and cancer stage one and two years after cancer diagnosis.
2. To characterise cancer patients in terms of demographic characteristics and comorbidities before and at the time of diagnosis, as well as medications at the time of diagnosis, and medications and procedures received in the first 90 days after cancer diagnosis.

A description of the proposed objectives is presented in **Table 1**.

**Table 1. Primary and secondary research questions and objectives.**

A. Primary research question and objective.

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Objective:</b>                                                    | To estimate the incidence rates of thromboembolic events in patients newly diagnosed with each type of selected cancers stratified by country/data source, age group, sex, study period (2016–2019 and 2020–2022), and cancer stage one and two years after cancer diagnosis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Hypothesis:</b>                                                   | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Population (<i>mention key inclusion-exclusion criteria</i>):</b> | <p>The study population included all individuals aged 18 years and above with a primary diagnosis of selected cancers in the study period from 01/01/2016 to 31/12/2022.</p> <p>Selected cancer types include:</p> <ul style="list-style-type: none"> <li>• Malignant neoplasms of bone and articular cartilage (bone cancer)</li> <li>• Malignant neoplasm of meninges, brain and spinal cord, cranial nerves, and other parts of central nervous system (brain cancer)</li> <li>• Malignant neoplasm of breast (breast cancer)</li> <li>• Malignant neoplasm of colon, rectosigmoid junction, rectum, anus, and anal canal (colorectal cancer)</li> <li>• Malignant neoplasm of corpus uteri (corpus uteri cancer including corpus uteri cancer)</li> <li>• Malignant neoplasm of kidney, except renal pelvis (kidney cancer)</li> <li>• Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic, and related tissue (lymphoma and leukaemia)</li> <li>• Malignant neoplasm of liver and intrahepatic bile ducts (liver cancer)</li> <li>• Malignant neoplasm of trachea, bronchus, and lung (lung cancer)</li> <li>• Malignant melanoma of skin (skin melanoma)</li> <li>• Malignant neoplasm of oesophagus (specified in the protocol as oesophageal cancer)</li> <li>• Malignant neoplasm of ovary (ovarian cancer)</li> <li>• Malignant neoplasm of pancreas (pancreatic cancer)</li> <li>• Malignant neoplasm of prostate (prostate cancer)</li> <li>• Malignant neoplasm of stomach (stomach cancer)</li> </ul> <p>Only patients with the first and single cancer diagnosis (except non-melanoma skin cancer) were included. Additional eligibility of a minimum of 1 year of potential follow-up time was imposed to ensure sufficient time to capture potential outcomes of interest.</p> |
| <b>Exposure:</b>                                                     | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Comparator:</b>                                                   | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Outcome:</b>                                                      | <p>Venous thromboembolic events:</p> <ul style="list-style-type: none"> <li>• Deep vein thrombosis (DVT)</li> <li>• Pulmonary embolisms (PE)</li> <li>• Venous thromboembolism (VTE, composite of DVT and PE)</li> <li>• Pelvic venous thrombosis (PVT)</li> <li>• Splanchnic vein thrombosis (SVT), including hepatic and extra-hepatic vein thrombosis</li> <li>• Retinal vein thrombosis (RVT), including retinal central vein thrombosis</li> <li>• Disseminated intravascular coagulation (DIC)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|                                               |                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Time (when follow up begins and ends):</b> | For each outcome, study participants were followed up from the date of the selected cancer diagnosis (index date) until the earliest of the following events: occurrence of the outcome, end of follow up (1 year for the main analysis or 2 years), loss to follow-up, end of data availability, or date of death. |
| <b>Setting:</b>                               | Routinely collected data from 10 data sources in 8 European countries.                                                                                                                                                                                                                                              |
| <b>Main measures:</b>                         | Proportions and incidence rates.                                                                                                                                                                                                                                                                                    |

## B. Secondary research question and objective.

|                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Objective:</b>                                             | To characterise cancer patients in terms of demographic characteristics and comorbidities before and at the time of diagnosis, as well as medications and procedures received in the first 90 days after cancer diagnosis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Hypothesis:</b>                                            | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Population (mention key inclusion-exclusion criteria):</b> | <p>The study population included all individuals aged 18 years and above with a primary diagnosis of selected cancers in the study period from 01/01/2016 to 31/12/2022. Selected cancer types include:</p> <ul style="list-style-type: none"> <li>• Malignant neoplasms of bone and articular cartilage (bone cancer)</li> <li>• Malignant neoplasm of meninges, brain and spinal cord, cranial nerves, and other parts of central nervous system (brain cancer)</li> <li>• Malignant neoplasm of breast (breast cancer)</li> <li>• Malignant neoplasm of colon, rectosigmoid junction, rectum, anus, and anal canal (colorectal cancer)</li> <li>• Malignant neoplasm of corpus uteri (corpus uteri cancer including corpus uteri cancer)</li> <li>• Malignant neoplasm of kidney, except renal pelvis (kidney cancer)</li> <li>• Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic, and related tissue (lymphoma and leukaemia)</li> <li>• Malignant neoplasm of liver and intrahepatic bile ducts (liver cancer)</li> <li>• Malignant neoplasm of trachea, bronchus, and lung (lung cancer)</li> <li>• Malignant melanoma of skin (skin melanoma)</li> <li>• Malignant neoplasm of oesophagus (specified in the protocol as oesophageal cancer)</li> <li>• Malignant neoplasm of ovary (ovarian cancer)</li> <li>• Malignant neoplasm of pancreas (pancreatic cancer)</li> <li>• Malignant neoplasm of prostate (prostate cancer)</li> <li>• Malignant neoplasm of stomach (stomach cancer)</li> </ul> <p>Only patients with the first and single cancer diagnosis (except non-melanoma skin cancer) were included. Additional eligibility of a minimum of 1 year of potential follow-up time was imposed to ensure sufficient time to capture potential outcomes of interest.</p> |
| <b>Exposure:</b>                                              | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Comparator:</b>                                            | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Outcome:</b>                                               | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Time (when follow up begins and ends):</b>                 | Medical history (comorbidities) at the diagnosis date, 180 to 1 day prior to the diagnosis date and anytime to 181 days prior to diagnosis; medication and procedures from the diagnosis date to 90 days after diagnosis date.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Setting:</b>                                               | Routinely collected data from 10 data sources in 8 European countries.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Main measures:</b>                                         | Proportions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

## 9. RESEARCH METHODS

### 9.1. Study design

A cohort study was conducted using routinely collected health data from 9 data sources across 8 European countries. We conducted population-level descriptive epidemiology and patient-level characterisation studies, as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses ([Table 2](#)). A retrospective cohort study of all newly diagnosed adult patients with selected cancers was conducted to address Objective 1 (incidence of thromboembolic events).

Table 2. Description of study types and related study designs.

| Study type                                | Study design            |
|-------------------------------------------|-------------------------|
| Population-level descriptive epidemiology | Population-level cohort |
| Patient-level characterisation            | Cohort analysis         |

Figure 1 describes study design and relevant assessment windows.

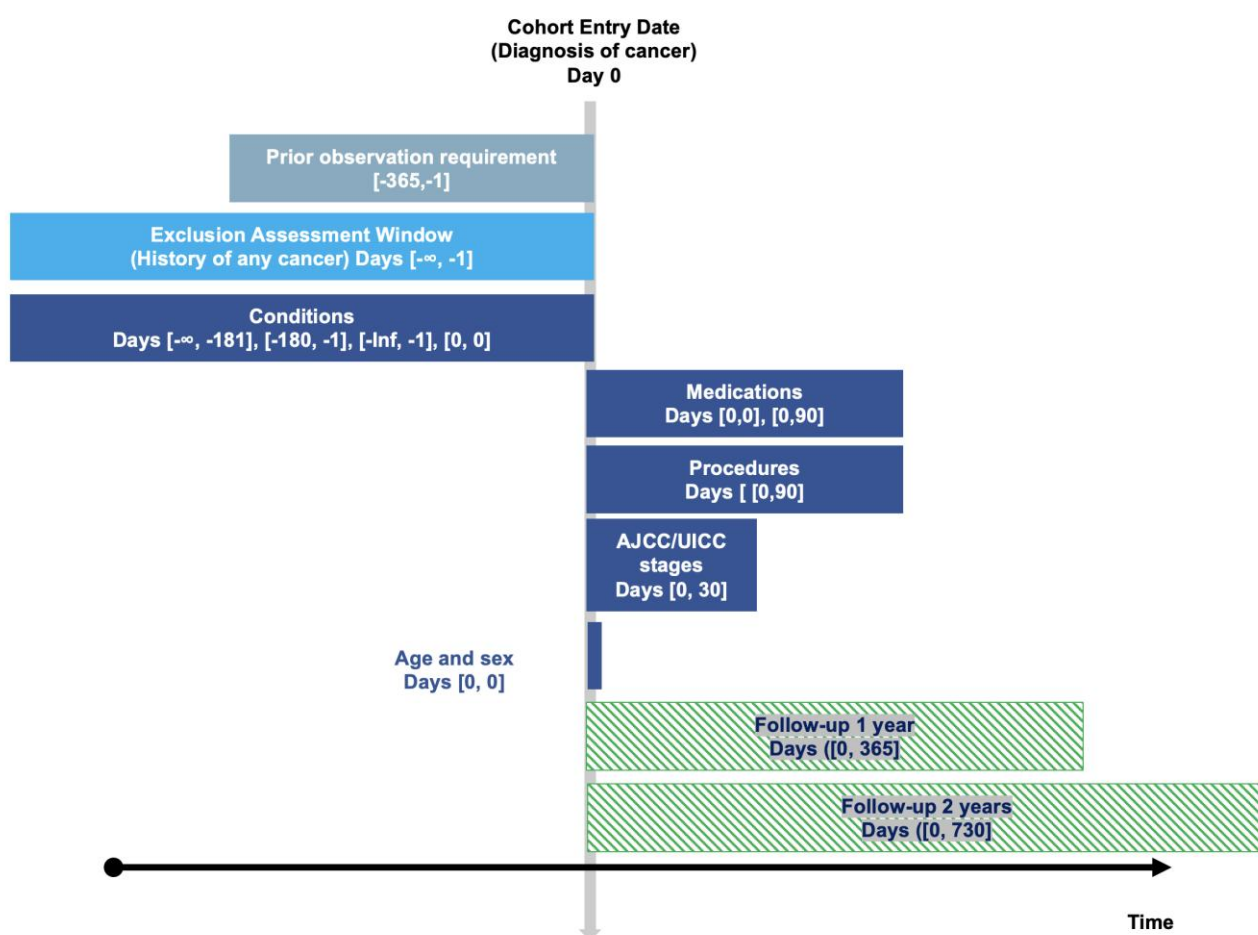


Figure 1. Graphical depiction of the study design.

## 9.2. Study setting and data sources

This study used routinely collected health data from 9 data sources from 8 European countries. All data sources have been previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

### Data sources

The following data sources were included in the study:

1. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
2. Danish Data Health Registries (DK-DHR), Denmark
3. Estonian Biobank (EBB), Estonia
4. Finnish Care Register for Health Care (FinOMOP-THL), Finland
5. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
6. Integrated Primary Care Information (IPCI), Netherlands
7. The Information System for the Development of Research in Primary Care (SIDIAP), Spain
8. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
9. UK Biobank (UKBB), United Kingdom

Information on data sources is available in [Table 3](#). Detailed description of data sources is available in [Annex I](#).

### Data source justification and key characteristics

The selected data sources met the criteria required to capture outcomes of interest and relevant data, enabling a patient-level characterisation of newly diagnosed cancer patients across different European settings and regions. The main criterion was a meaningful number of person counts for the population of interest (cancer patients) and outcomes (thromboembolic events) assessed at the feasibility stage for all data sources included in the study. Data sources were also selected based on European representativeness. Not all data sources had records of all outcomes of interest.

Additional criteria reflect other data quality domains assessed at the DARWIN EU® data partners onboarding stage. With every new release of the data partners OMOP CDM, the DARWIN EU® coordination centre also receives new results of the *CdmOnboarding*, *DashboardExport*, and *DataQualityDashboard* packages and assesses the quality of the data. No open quality issues related to the study population and outcomes were present for any of the data sources selected for the study.

Relevance was also assessed based on the previous research related to the study population of the outcome. Previously, IPCI, EBB, SIDIAP, CPRD GOLD, IQVIA DA Germany, UKBB, and EBB were used in studies with thromboembolic events as an outcome. (Ali et al., 2020, Mercadé-Besora et al., 2024, Li et al., 2022, Voss et al, 2023). CPRD GOLD, FinOMOP-THL, UKBB, SIDIAP, IPCI, and UKBB were used in studies repeated on cancer patients (Hagberg et al., 2023; Corby et al., 2024, Leinonen et al., 2017, Smith et al., 2024; Recalde et al, 2019; van Soest 2008; Chen et al., 2024).

In addition to that, DK-DHR is a nationwide fully representative data source that includes information from The National Patient Registry and The National Cancer Register.

Table 1. Description of the selected data sources.

| Country* | Name of Data source** | Justification for Inclusion                                                                                                                                                              | Health Care setting                     | Type of Data                      | Number of active subjects | Data lock for the last update |
|----------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------|---------------------------|-------------------------------|
| BE       | IQVIA LPD Belgium     | Covers primary care setting with information on cancer diagnoses and medical history.                                                                                                    | Primary care                            | EHRs                              | 1.1 M                     | 25/03/2024                    |
| DK       | DK-DHR                | National health data database which includes information on cancer diagnoses, staging, and medical history                                                                               | All settings                            | EHRs, registries, claims          | 8.5 M                     | 15/05/2024                    |
| EE       | EBB                   | Contains health insurance claims, digital prescriptions, discharge information, and causes of death through linkage with the national death register. Data is linked to cancer registry. | Primary care, hospital care (IP and OP) | EHRs, claims, registries, biobank | 0.2 M                     | 20/03/2023                    |
| FI       | FinOMOP-THL           | Nation-wide hospital registry data with high-quality information on cancer diagnoses and mortality.                                                                                      | Hospital care (IP and OP)               | EHRs, registries                  | 7.1 M                     | 24/06/2024                    |
| DE       | IQVIA DA Germany      | Covers primary care setting with information on cancer diagnoses and medical history.                                                                                                    | Primary care                            | EHRs                              | 43.1 M                    | 25/03/2024                    |
| NL       | IPCI                  | Covers primary care setting, data on cancer diagnoses previously validated, information available on comorbidities, medications, and date of death.                                      | Primary care                            | EHRs                              | 2.9 M                     | 29/08/2024                    |
| ES       | SIDIAP                | Covers primary care setting with information on                                                                                                                                          | Primary care                            | EHRs                              | 8.6 M                     | 01/06/2023                    |

| Country* | Name of Data source** | Justification for Inclusion                                                                                                   | Health Care setting                     | Type of Data              | Number of active subjects | Data lock for the last update |
|----------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------------------|---------------------------|-------------------------------|
|          |                       | cancer diagnoses and medical history.                                                                                         |                                         |                           |                           |                               |
| GB       | CPRD GOLD             | Covers primary care setting, data on cancer diagnoses, comorbidities, medications, and date of death.                         | Primary care, hospital care (OP)        | EHRs                      | 17.5 M                    | 15/04/2024                    |
| GB       | UKBB                  | Genetic data on biobank participants linked to EHRs from primary care, hospitalisations, cancer registrations, and mortality. | Primary care, hospital care (IP and OP) | EHRs, registries, biobank | 0.5 M                     | 16/02/2024                    |

EHR=electronic health record, IP=inpatient, OP=outpatient

\*Countries: BE=Belgium, DE=Germany, DK=Denmark, EE=Estonia, ES=Spain, FI=Finland, GB=United Kingdom of Great Britain and Northern Ireland, NL=The Netherlands

\*\*Data sources: IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank

### 9.3. Study period

The study period was from 01/01/2016 to 31/12/2022, ensuring that the end of available data in each source comes later (see [Table 3](#) Data lock for the last update column for more details).

### 9.4. Follow-up

Study participants were followed up from the date of cancer diagnosis (index date, [Table 4](#)) until the first occurrence of any of the following events: occurrence of the outcome, loss to follow-up, end of follow-up (one or two years), end of data availability, or date of death.

Table 4. Operational definition of time 0 (diagnosis/index date) and other primary time anchors.

| Study population name(s) | Time Anchor Description  | Number of entries | Type of entry | Washout window | Care Setting | Code Type       | Diagnosis position | Incident with respect to...                          |
|--------------------------|--------------------------|-------------------|---------------|----------------|--------------|-----------------|--------------------|------------------------------------------------------|
| Cancer patients          | Date of cancer diagnosis | Single entry      | Incident      | [any time, -1] | IP, OP, OT   | SNOMED, ICD-O-3 | Any                | Any cancer diagnosis except non-melanoma skin cancer |

ICD-O-3=International Classification of Diseases for Oncology, 3<sup>rd</sup> Edition, IP=inpatient, N/A=not applicable, OP=outpatient, OT=other, SNOMED=Systematized Nomenclature of Medicine.

## 9.5. Study population with inclusion and exclusion criteria

The study population consisted of all individuals aged 18 years and above with a primary diagnosis of the selected cancers during the study period. Cancer types included bone, brain, breast, colorectal, corpus uteri, kidney, leukaemia and lymphoma, liver, lung, melanoma, oesophageal, ovary, pancreas, prostate, and stomach. Only patients with a first and single cancer diagnosis (excluding non-melanoma skin cancer) were included. Patients with a prior cancer diagnosis (excluding non-melanoma skin cancer) were excluded to ensure that the outcomes were related to a single primary cancer type of interest and to avoid possible misclassification of second primary cancers and metastatic disease from previously diagnosed cancers.

Cancer cases and thromboembolic events were identified in the domain Conditions in the OMOP CDM and followed the Systematised Nomenclature of Medicine (SNOMED) as the standard vocabulary for diagnosis codes. For cancer diagnoses, the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) was also used. An additional eligibility criterion of a minimum of one year of potential follow-up time was imposed to ensure sufficient time to capture potential outcomes of interest. For instance, in a data source with data available through 31/12/2023, cancer cases diagnosed from 01/01/2016 up to 01/01/2022 were included. A prior history requirement of one year of observation before the diagnosis date was also imposed. This was particularly relevant for primary care data sources, where at least one year of observation prior to a cancer diagnosis was necessary to identify prevalent cases.

**Supplementary material** provides a code list for each cancer type. The operational definitions of the inclusion and exclusion criteria are presented in **Table 5** and **Table 6**, respectively.

Table 5. Operational definitions of inclusion criteria.

| Criterion                                      | Details                                                                                                                            | Order of application | Assessment window | Care Settings | Code Type       | Applied to study populations: |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------------|-------------------|---------------|-----------------|-------------------------------|
| Patients newly diagnosed with selected cancers | Primary selected cancer                                                                                                            | After                | -                 | IP, OP, OT    | SNOMED, ICD-O-3 | Cancer patients               |
| Age                                            | Participants aged 18 or above                                                                                                      | After                | At diagnosis date | IP, OP, OT    | N/A             | Cancer patients               |
| Minimum prior observation period of 365 days   | Only participants with a minimum observation period of 365 days prior to diagnosis date                                            | Before               | 365 days          | OP, OT        | N/A             | Cancer patients               |
| Minimum potential follow-up time               | Only participants with a cancer diagnosis occurring one year prior to end of data availability in the data source will be included | After                | [0, 365]          | IP, OP, OT    | N/A             | Cancer patients               |

IP=inpatient, N/A=not applicable, OP=outpatient, OT=other.

Table 6. Operational definitions of exclusion criteria.

| Criterion                   | Details                                                                                                             | Order of application | Assessment window                  | Care Settings | Code Type       | Diagnosis position | Applied to study populations: |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------|------------------------------------|---------------|-----------------|--------------------|-------------------------------|
| History of cancer diagnosis | Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior the diagnosis date | After                | Any time prior to cancer diagnosis | OP, IP, OT    | SNOMED, ICD-O-3 | Any                | Cancer patients               |
| Multiple primary tumours    | Participants with two diagnoses of cancer (any, excluding non-melanoma skin cancer) at the diagnosis date           | After                | At diagnosis date                  | OP, IP, OT    | SNOMED, ICD-O-3 | Any                | Cancer patients               |

IP=inpatient, N/A=not applicable, OP=outpatient, OT=other.

## 9.6. Variables

### 9.6.1. Exposures

None.

### 9.6.2. Outcomes

Conditions of interest included the following thromboembolic events:

- Deep vein thrombosis (DVT)
- Pulmonary embolisms (PE)
- Venous thromboembolism (VTE, composite of DVT and PE)
- Pelvic venous thrombosis (PVT)
- Splanchnic vein thrombosis (SVT), including hepatic and extra-hepatic vein thrombosis
- Retinal vein thrombosis (RVT), including retinal central vein thrombosis
- Disseminated intravascular coagulation (DIC)

The operational definition of the outcomes is presented in [Table 7](#).

A list of concepts based on SNOMED codes and aligned with previous studies that used OMOP CDM and VTE as an outcome (Burn et al., 2022) is provided in [Annex II](#).

**Table 7. Operational definitions of outcome.**

| Outcome name | Details               | Primary outcome | Type of outcome | Washout window | Care Settings | Code Type | Diagnosis Position | Applied to study populations |
|--------------|-----------------------|-----------------|-----------------|----------------|---------------|-----------|--------------------|------------------------------|
| DVT          | See Annex II Table S1 | Yes             | Binary          | [-365,-1]      | IP, OP, OT    | SNOMED    | Any                | Cancer patients              |
| PE           | See Annex II Table S2 | Yes             | Binary          | [-365,-1]      | IP, OP, OT    | SNOMED    | Any                | Cancer patients              |
| VTE          | See Annex II Table S3 | Yes             | Binary          | [-365,-1]      | IP, OP, OT    | SNOMED    | Any                | Cancer patients              |
| PVT          | See Annex II Table S4 | Yes             | Binary          | [-365,-1]      | IP, OP, OT    | SNOMED    | Any                | Cancer patients              |
| SVT          | See Annex II Table S5 | Yes             | Binary          | [-365,-1]      | IP, OP, OT    | SNOMED    | Any                | Cancer patients              |
| RVT          | See Annex II Table S6 | Yes             | Binary          | [-365,-1]      | IP, OP, OT    | SNOMED    | Any                | Cancer patients              |
| DIC          | See Annex II Table S7 | Yes             | Binary          | [-365,-1]      | IP, OP, OT    | SNOMED    | Any                | Cancer patients              |

DIC=disseminated intravascular coagulation, DVT=deep vein thrombosis, IP=inpatient, N/A=not applicable, OP=outpatient, OT=other, PE=pulmonary embolisms, PVT=pelvic venous thrombosis, RVT=retinal vein thrombosis, SVT=splanchnic vein thrombosis, VTE=venous thromboembolism.

### 9.6.3. Other covariates

The age at the cancer diagnosis date was described using the following age groups: 18–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85 and above. The sex (male/female) of study participants was also identified at cancer diagnosis date.

Comorbidities were described at any time up to 181 days prior to the cancer diagnosis, 180 days up to one day prior to the diagnosis date, and at the diagnosis date. Medications were assessed at the cancer diagnosis date and 90 days after the cancer diagnosis date; procedures were described 90 days after the diagnosis date. AJCC/UICC stages were described within 30 days after the date of diagnosis.

Comorbidities, medications, and procedures were selected based on definitions previously used in other DARWIN EU® studies. These included:

- Medical history: asthma, chronic obstructive lung disease, chronic liver disease, Crohn's disease, diabetes mellitus, gastroesophageal reflux disease, gastrointestinal bleeding, human immunodeficiency virus (HIV), COVID-19, hyperlipidaemia, hypertension, obesity, osteoarthritis, pneumonia, psoriasis, renal impairment, ulcerative colitis, viral hepatitis, visual system disorders; and neurological/psychiatric conditions such as schizophrenia, dementia, Parkinson's disease, depressive disorder, anxiety, and attention deficit hyperactivity disorder (ADHD). Thromboembolic event outcomes of interest mentioned above were also included. Any history of cancer (except non-melanoma skin cancer) was reported for quality assessment purposes and was expected to be zero prior to the diagnosis date in the study population.
- Medication use: agents acting on the renin-angiotensin system, antibacterials for systemic use, antidepressants, antiepileptics, anti-inflammatory and antirheumatic products, antineoplastic agents, anti-psoriatics, antithrombotic agents, beta blocking agents, calcium channel blockers, diuretics, drugs for acid-related disorders, drugs for obstructive airway diseases, drugs used in diabetes, immunosuppressants, lipid-modifying agents, opioids, psycholeptics, psychostimulants and agents used for ADHD and nootropics, as well as contraceptives.
- Procedures: surgical interventions, radiotherapy, and stem cell or bone marrow transplants.

The AJCC/UICC stages (Stages I–IV), assigned within 30 days after cancer diagnosis, were also described and used for stratification in Objective 1. Large-scale characterisation of conditions, medications, and procedures was also conducted. Top ten conditions were reported in the large-scale characterisation.

The list of concepts used to describe comorbidities, procedures, medications, and stages are provided in [Annex II](#). The operational definition of the covariates was described in [Table 8](#).

Table 8. Operational definitions of covariates.

| Characteristic  | Details                                                                            | Type of variable | Assessment window                | Care Settings | Code Type       | Applied to study populations |
|-----------------|------------------------------------------------------------------------------------|------------------|----------------------------------|---------------|-----------------|------------------------------|
| Comorbidities   | Large-scale patient-level characterisation with regard to underlying comorbidities | Binary           | [anytime; -181], [-180-1], [0,0] | IP, OP, OT    | SNOMED          | Cancer patients              |
| Medication use  | Large-scale patient-level characterisation with regard to use of concomitant drugs | Binary           | [0;0], [0,90]                    | IP, OP, OT    | RxNorm          | Cancer patients              |
| Procedures      | Large-scale patient-level characterisation with regard to procedures               | Binary           | [1,90]                           | IP, OP, OT    | SNOMED          | Cancer patients              |
| Sex             | Sex at birth                                                                       | Binary           | [0,0]                            | IP, OP, OT    | N/A             | Cancer patients              |
| Age             | Age at the time of cancer diagnosis                                                | Categorical      | [0,0]                            | IP, OP, OT    | N/A             | Cancer patients              |
| AJCC/UICC Stage | Stage at the time of diagnosis                                                     | Categorical      | [0,30]                           | IP, OP, OT    | Cancer Modifier | Cancer patients              |

AJCC/UICC=American Joint Committee on Cancer and the International Union Against Cancer, IP=inpatient, N/A=not applicable, OP=outpatient, OT=other.

## 9.7. Study size

No sample size was calculated, as this is a descriptive study.

## 9.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (see [Annex III](#)), the final study code package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the aggregated results.

The study results of all data sources were checked after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

Cell suppression was applied as required by data sources to protect people's privacy. Cell counts <5 were reported as "<5", except for zero counts, which were reported.

## 9.9. Statistical methods

### Data analyses

This study involved the analysis described in **Table 9**.

**Table 9. Description of study types and types of analysis.**

| Study type                                | Type of analyses                                                                                                                                                                                                           |
|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patient-level characterisation            | <ul style="list-style-type: none"> <li>- Large-scale characterisation</li> <li>- Patient-level characteristics</li> <li>- Prognosis/progression to a pre-specified outcome</li> <li>- Standard care description</li> </ul> |
| Population-level descriptive epidemiology | <ul style="list-style-type: none"> <li>- Incidence rates of the condition of interest</li> <li>- Prevalence rates of the condition of interest</li> </ul>                                                                  |

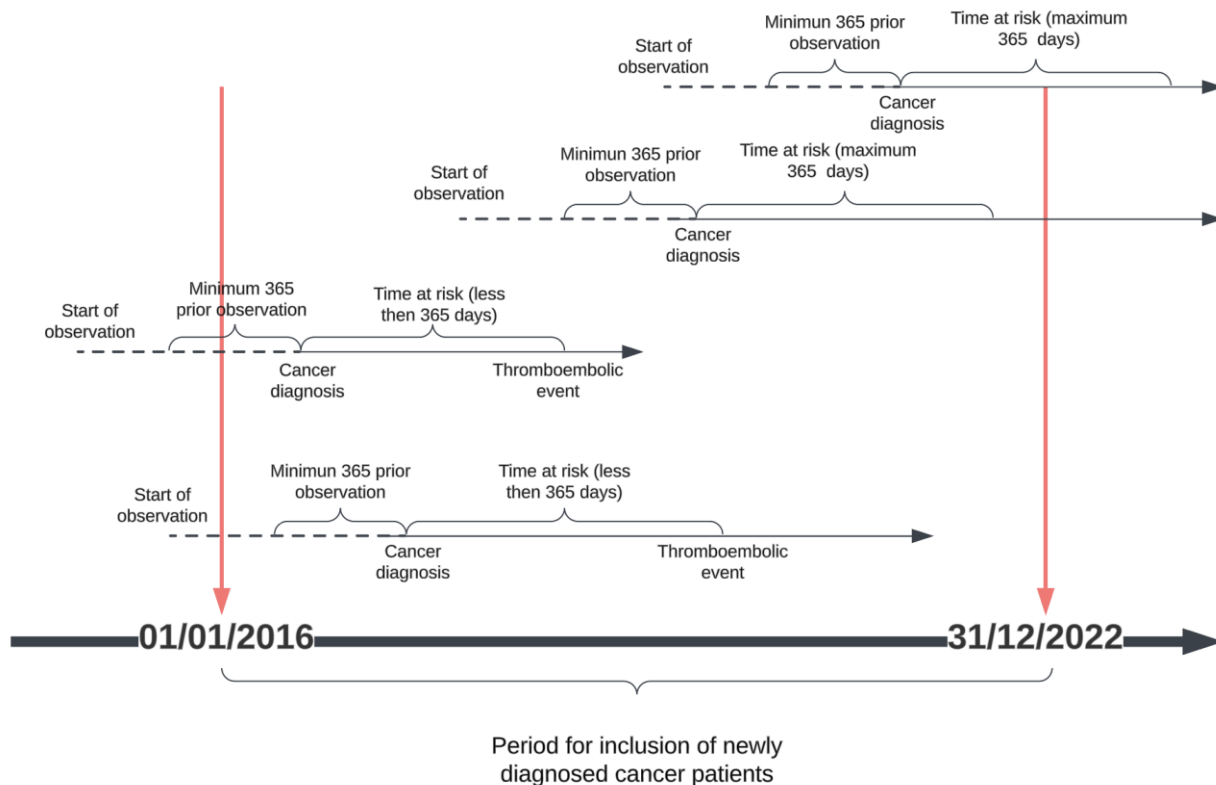
The incidence rates of thromboembolic events (Objective 1) were estimated over one and two years after the selected cancer diagnosis. The denominator of the incidence rate included the person-time contributed by cancer patients from the date of diagnosis until the event or the end of the respective follow-up period (one or two years). The numerator included the number of cases with the outcomes of interest that occurred during the same follow-up period (see **Figure 2**). Incidence rates were presented as cases per 100,000 person-time with 95% confidence intervals (95% CIs) derived using the exact method. Each cancer type and outcome was assessed separately.

Patient-level characterisation (Objective 2) was conducted as follows: age and sex were described at the time of diagnosis; comorbidities were described at any time up to 181 days prior to the cancer diagnosis, 180 days up to one day prior to the diagnosis date, and at the diagnosis date; medications were assessed at the diagnosis date and 90 days after the diagnosis date; procedures were described 90 days after the diagnosis date.

Large-scale characterisation of conditions, medications, and procedures was also conducted along the characterisation based on pre-specified phenotypes.

For all analyses, absolute frequencies and proportions were reported. A minimum cell count of 5 was used when reporting results, with any smaller counts reported as "<5" and zero counts as "0". Overall analyses were conducted separately for each data source.

Further stratification by age category (18–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85 and above), sex, study subperiod, and cancer stage (AJCC/UICC stages were described within 30 days after the date of diagnosis) was conducted when possible (i.e., when the minimum cell count was reached and data were available).



**Figure 2. Incidence rates within one year after diagnosis derivation.**

(The numerator is the number of the outcomes of interest (thromboembolic events), and the denominator is the time at risk up to 365 days.)

### Missing data

Subjects who were lost to follow-up before the end of the follow-up period (one or two years, respectively) without experiencing the outcome of interest were non-administratively censored and contributed to the denominator of the incidence rate with their observed time-at-risk. The implicit assumption made in calculating the incidence rate was that censoring occurred at random.

### R packages

The following R packages were used:

1. *CohortDiagnostics* (<https://github.com/OHDSI/CohortDiagnostics/>) to evaluate the phenotype algorithms developed for the study.
2. *IncidencePrevalence* (<https://github.com/darwin-eu/IncidencePrevalence>) to estimate incidence rates by dividing the number of events by the person-time. Incidence rates were calculated using the function *estimateIncidence()* with the denominator person-time specified by *generateDenominatorCohortSet()*.
3. *PatientProfiles* (<https://github.com/darwin-eu-dev/PatientProfiles>) and *CohortCharacteristics* (<https://github.com/darwin-eu-dev/CohortCharacteristics>) to summarise characteristics of cohorts of patients with cancer.
4. *meta* (<https://github.com/guido-s/meta>) to perform meta-analysis (see below).

## 9.10. Evidence synthesis

Results for all objectives are presented separately for each data source. A random-effects meta-analysis was applied to the overall crude incidence rates of thromboembolic events for selected cancer types to obtain summary estimates (using the Restricted Maximum Likelihood method), with 95% CI calculated using the Knapp-Hartung method.

## 9.11. Deviations from the protocol

FinOMOP-HUS did not participate in the study due to difficulties in obtain governmental approval in time.

# 10. RESULTS

All results are available in a web application (“Shiny App”) at: [EUPAS1000000440](https://eupas1000000440.shinyapps.io/).

## 10.1. Participants

Attrition of study participants across all data sources and cancer types is presented in **Table 10**. After excluding patients with prior history of cancer, counts per cancer type included: cancers of bone (n=3,328), brain (n=16,019), breast (n=191,151), colorectal (n=128,431), corpus uteri (n=25,296), oesophageal (n=15,547), kidney (n=32,881), liver (n=18,767), lung (n=105,527), leukaemia and lymphoma (n=126,499), melanoma (n=73,649), ovarian (n=16,794), pancreatic (n=32,647), prostate (n=169,739), and stomach cancer (n=19,687). Overall, we included 975,962 patients with cancer across nine data sources.

**Table 10. Attrition of study participants.**

|                     |                             | IQVIA<br>LPD | DK-<br>DHR | EBB   | FinOMOP-<br>THL | IQVIA<br>DA | IPCI  | SIDIAP | CPRD<br>GOLD | UKBB  |
|---------------------|-----------------------------|--------------|------------|-------|-----------------|-------------|-------|--------|--------------|-------|
| Bone cancer         | Qualifying initial records  | 21           | 586        | 50    | 960             | 1,291       | 0     | 1,796  | 470          | 122   |
|                     | No prior history of cancer* | 18           | 322        | 31    | 594             | 965         | 0     | 1,071  | 290          | 37    |
| Brain cancer        | Qualifying initial records  | 140          | 4,650      | 175   | 4,073           | 3,920       | 491   | 4,985  | 1,155        | 664   |
|                     | No prior history of cancer* | 128          | 3,510      | 132   | 3,318           | 3,240       | 297   | 3,955  | 932          | 507   |
| Breast cancer       | Qualifying initial records  | 1,905        | 35,560     | 1,384 | 40,996          | 60,761      | 7,131 | 34,324 | 18,963       | 5,808 |
|                     | No prior history of cancer* | 1,853        | 31,873     | 1,243 | 38,047          | 56,337      | 6,553 | 31,931 | 18,134       | 5,180 |
| Colorectal cancer   | Qualifying initial records  | 409          | 35,264     | 950   | 27,788          | 29,207      | 6,527 | 35,059 | 13,393       | 4,871 |
|                     | No prior history of cancer* | 382          | 29,279     | 762   | 23,146          | 24,061      | 5,400 | 29,755 | 11,798       | 3,848 |
| Corpus uteri cancer | Qualifying initial records  | 68           | 6,020      | 324   | 7,323           | 6,392       | 777   | 5,969  | 2,713        | 1,143 |
|                     | No prior history of cancer* | 60           | 4,910      | 260   | 6,121           | 5,113       | 622   | 4,858  | 2,453        | 899   |
| Oesophageal cancer  | Qualifying initial records  | 57           | 4,879      | 49    | 3,313           | 4,056       | 1,123 | 2,650  | 3,715        | 1,080 |
|                     | No prior history of cancer* | 53           | 3,168      | 35    | 2,487           | 3,121       | 837   | 1,860  | 3,223        | 763   |

|                              |                                | IQVIA<br>LPD | DK-<br>DHR | EBB   | FinOMOP-<br>THL | IQVIA<br>DA | IPCI  | SIDIAP | CPRD<br>GOLD | UKBB  |
|------------------------------|--------------------------------|--------------|------------|-------|-----------------|-------------|-------|--------|--------------|-------|
| Kidney<br>cancer             | Qualifying initial<br>records  | 40           | 8,594      | 381   | 8,293           | 11,714      | 1,412 | 9,849  | 1,283        | 1,380 |
|                              | No prior history of<br>cancer* | 33           | 6,498      | 289   | 6,394           | 9,149       | 1,068 | 7,404  | 1,096        | 950   |
| Liver cancer                 | Qualifying initial<br>records  | 37           | 4,775      | 121   | 5,563           | 4,282       | 832   | 7,622  | 1,538        | 753   |
|                              | No prior history of<br>cancer* | 35           | 3,338      | 75    | 4,177           | 3,214       | 557   | 5,618  | 1,297        | 456   |
| Lung cancer                  | Qualifying initial<br>records  | 540          | 37,091     | 505   | 21,507          | 25,951      | 7,232 | 27,635 | 14,037       | 3,765 |
|                              | No prior history of<br>cancer* | 486          | 27,757     | 332   | 16,828          | 20,343      | 5,288 | 20,068 | 11,844       | 2,581 |
| Lymphoma<br>and<br>Leukaemia | Qualifying initial<br>records  | 865          | 30,833     | 1,083 | 24,930          | 39,020      | 3,739 | 33,585 | 11,523       | 3,959 |
|                              | No prior history of<br>cancer* | 815          | 25,172     | 884   | 20,690          | 33,640      | 3,009 | 28,831 | 10,429       | 3,029 |
| Melanoma                     | Qualifying initial<br>records  | 138          | 20,197     | 632   | 10,571          | 32,386      | 3,658 | 9,181  | 5,855        | 2,401 |
|                              | No prior history of<br>cancer* | 130          | 17,145     | 526   | 8,820           | 28,972      | 3,096 | 7,928  | 5,235        | 1,797 |
| Ovarian<br>cancer            | Qualifying initial<br>records  | 61           | 4,171      | 279   | 4,134           | 5,784       | 628   | 4,161  | 1,997        | 880   |
|                              | No prior history of<br>cancer* | 54           | 2,842      | 217   | 3,085           | 4,603       | 473   | 3,244  | 1,704        | 572   |
| Pancreatic<br>cancer         | Qualifying initial<br>records  | 136          | 9,014      | 266   | 10,210          | 8,220       | 1,697 | 8,830  | 2,718        | 1,343 |
|                              | No prior history of<br>cancer* | 123          | 6,587      | 193   | 8,139           | 6,387       | 1,252 | 6,705  | 2,354        | 907   |
| Prostate<br>cancer           | Qualifying initial<br>records  | 952          | 33,709     | 1,256 | 40,495          | 57,911      | 5,125 | 26,690 | 16,562       | 8,241 |
|                              | No prior history of<br>cancer* | 920          | 29,476     | 1,067 | 36,620          | 51,871      | 4,527 | 22,704 | 15,485       | 7,069 |
| Stomach<br>cancer            | Qualifying initial<br>records  | 46           | 6,434      | 293   | 4,137           | 6,240       | 922   | 6,882  | 1,279        | 851   |
|                              | No prior history of<br>cancer* | 42           | 4,137      | 191   | 3,300           | 4,737       | 678   | 5,059  | 1,055        | 488   |

\*Counts shown after excluding patients with no prior history of cancer. IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.

## 10.2. Main results

### 10.2.1. Incidence rates of thromboembolic events (objective 1)

The incidence rates (IRs) and 95% CI of thromboembolic events per 100,000 person-years (PY) in patients newly diagnosed with selected cancers are reported by the data source and cancer type for the entire study period (2016–2022), with follow-up of one ([Tables 11–25](#)) and two years ([Annex V](#)) after cancer diagnosis.

Estimates obtained in the meta-analysis of IRs, along with the IRs estimates by data source, are also presented in [Figures 3–9](#). Selected results stratified by sex are presented [Figures 10–13](#). Results stratified by sub-period and age are available in the “Shiny app” ([EUPAS1000000440](#))

#### **Distribution of events**

DVT was not present in IQVIA LPD Belgium. PVT and SVT had limited counts in EBB, IQVIA LPD Belgium, IQVIA DA Germany, and IPCI. RVT was only not present in CPRD GOLD and SIDIAP.

Across all data sources and cancers, 47,076 thromboembolic events were included in the calculation of the IRs one year after cancer diagnosis: 21,153 (44.9%) VTE events; 15,441 (32.7%) PE events; 7,736 (16.4%) DVT events; 1,895 (4.0%) SVT events; 502 (1.1%) RVT events; 349 (0.7%) PVT events; and 199 (0.4%) DIC events. 58,979 thromboembolic events were included in the calculation of the IRs two years after cancer diagnosis. The distribution of thromboembolic outcomes two years after cancer diagnosis was similar to one year after.

#### **Incidence rates of thromboembolic events**

In general, the highest IRs of thromboembolic events observed across all selected cancers were VTE ([Tables 11–25](#)), except for liver cancer ([Table 18](#)), where the outcome with the highest IR per 100,000 PY was SVT in four data sources (DK-DHR, EBB, IQVIA DA Germany, and SIDIAP).

Across all selected cancers (except liver cancer), VTE IR [95% CI] per 100,000 PY was highest in pancreatic cancer (<5 events (IQVIA LPD Belgium) – 26,311 [21,797–31,485] (UKBB) - [Table 23](#)) and lowest in melanoma (0 (EBB and IQVIA LPD Belgium) – 803 [622–1,020] (FinOMOP-THL) - [Table 21](#)). In liver cancer, the second-highest IR [95% CI] per 100,000 PY was also VTE (0 (IQVIA LPD Belgium) – 11,803 [3,832–27,543] (EBB) - [Table 18](#)).

Across all selected cancers (except liver cancer), the outcome with the second-highest IR [95% CI] per 100,000 PY was PE. When cancer types were compared, PE IRs were lowest in melanoma (0 (EBB and IQVIA LPD Belgium) – 654 [492–851] (FinOMOP-THL) - [Table 21](#)) and highest in pancreatic cancer (<5 events (IQVIA LPD Belgium) – 20,555 [16,630–25,128] (UKBB) - [Table 23](#)). In liver cancer, PE was the outcome with the third-highest IR [95% CI] per 100,000 PY (0 (IQVIA LPD Belgium) – 8,062 [5,111–12,097] (UKBB) - [Table 18](#)).

Across all selected cancers (except liver cancer), the outcome with the third-highest IR [95% CI] per 100,000 PY was DVT: lowest in melanoma (0 (EBB and IQVIA LPD Belgium) – 427 [292–602] (SIDIAP) - [Table 21](#)) and highest in pancreatic cancer (0 (IQVIA LPD Belgium) – 7,437 [5,209–10,295] (UKBB) - [Table 23](#)).

Except for liver cancer, IR of SVT, PVT, RVT, and DIC in general were much lower or could not be identified. In bone, brain, corpus uteri, melanoma, and prostate cancer, the outcome with the lowest IR [95%CI] per 100,000 PY was SVT (bone, brain, and corpus uteri cancer and melanoma: 0 or <5 events across all data sources – prostate cancer: 0 (EBB, IPCI, and IQVIA LPD Belgium) – 42 [19 - 80] (SIDIAP)). The outcome with the lowest IR [95%CI] per 100,000 PY was PVT in lymphoma and leukaemia (0 (IPCI, IQVIA DA Germany, IQVIA LPD Belgium, and UKBB) – 114 [76–163] (SIDIAP) - [Table 20](#)). ). The outcome with the lowest IR [95%CI] per 100,000 PY was DIC in colorectal cancer (0 (IPCI, IQVIA DA Germany, and IQVIA LPD Belgium) – 211 [152–284] (FinOMOP-THL) - [Table 14](#)), lung cancer (0 (DK-DHR, EBB, IPCI, IQVIA DA Germany, IQVIA LPD Belgium, and UKBB) – 176 [104–279] (FinOMOP-THL) - [Table 19](#)), and breast cancer. Across all other cancers, the outcome with the lowest IR [95%CI] per 100,000 PY was RVT (oesophageal, liver, ovarian, and

stomach cancer: 0 or <5 events across all data sources – pancreatic cancer: 0 (CPRD GOLD, EBB, IPCI, IQVIA LPD Belgium, and UKBB) – 123 [40–286] (SIDIAP) - [Table 23](#)).

The IRs of thromboembolic events two years after cancer diagnosis were similar to those one year after ([Tables 26–40](#)). The three outcomes with the highest IRs were also VTE, PE, and DVT. However, the absolute IRs were lower two years after cancer diagnosis than one year.

For example, the outcome with the highest IR [95% CI] per 100,000 PY in liver was SVT (0 (IPCI and IQVIA LPD Belgium) – 12,650 [11,737–13,614] (SIDIAP) - [Table 33](#)). It was between 0 (IPCI and IQVIA LPD Belgium) – 18,052 [95% CI: 16,673–19,513] (SIDIAP) ([Table 18](#)) calculated for one year of follow-up.

**Table 11. Incidence rates [95% confidence interval] of thromboembolic events in bone cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                                               | IQVIA LPD | DK-DHR             | EBB | IQVIA DA           | IPCI | SIDIAP               | UKBB | CPRD GOLD            | FinOMOP-THL          |
|-----------------------------------------------|-----------|--------------------|-----|--------------------|------|----------------------|------|----------------------|----------------------|
| Deep vein thrombosis (DVT)                    | 0         | NC                 | 0   | NC                 |      | 2,237 [1,385, 3,420] | 0    | 3,188 [1,282, 6,568] | 1,371 [551, 2,825]   |
| Disseminated intravascular coagulation (DIC)  | 0         | 0                  | 0   | 0                  |      | NC                   | 0    | 0                    | 0                    |
| PE and DVT combined (VTE)                     | 0         | 2,207 [810, 4,803] | 0   | 1,076 [465, 2,120] |      | 3,107 [2,081, 4,462] | 0    | 4,680 [2,244, 8,607] | 5,486 [3,615, 7,982] |
| Pelvic vein thrombosis (PVT)                  | 0         | 0                  | 0   | 0                  |      | NC                   | 0    | 0                    | NC                   |
| Pulmonary embolism (PE)                       | 0         | 1,834 [596, 4,280] | 0   | 662 [215, 1,544]   |      | 1,372 [731, 2,347]   | 0    | NC                   | 4,590 [2,909, 6,887] |
| Retinal vein thrombosis (RVT)                 | 0         | 0                  | 0   | 0                  |      | NC                   | 0    | 0                    | 0                    |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0         | 0                  | 0   | 0                  |      | NC                   | 0    | 0                    | 0                    |

IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank

Table 12. Incidence rates [95% confidence interval] of thromboembolic events in brain cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).

|                                               | IQVIA<br>LPD | DK-DHR                  | EBB                      | IQVIA<br>DA             | IPCI                     | SIDIAP                  | UKBB                      | CPRD<br>GOLD             | FinOMOP-<br>THL          |
|-----------------------------------------------|--------------|-------------------------|--------------------------|-------------------------|--------------------------|-------------------------|---------------------------|--------------------------|--------------------------|
| Deep vein thrombosis (DVT)                    | 0            | 1,111<br>[738, 1,605]   | NC                       | 1,257<br>[842, 1,805]   | 2,371<br>[770, 5,533]    | 4,238<br>[3,505, 5,079] | 3,051<br>[1,463, 5,611]   | 4,087<br>[2,561, 6,188]  | 3,551<br>[2,829, 4,402]  |
| Disseminated intravascular coagulation (DIC)  | 0            | NC                      | 0                        | 0                       | 0                        | NC                      | 0                         | 0                        | 0                        |
| PE and DVT combined (VTE)                     | NC           | 4,761<br>[3,938, 5,706] | 8,538<br>[3,686, 16,824] | 2,600<br>[1,979, 3,354] | 7,802<br>[4,460, 12,670] | 7,426<br>[6,435, 8,527] | 10,159<br>[6,949, 14,341] | 9,911<br>[7,402, 12,997] | 9,451<br>[8,224, 10,809] |
| Pelvic vein thrombosis (PVT)                  | 0            | 0                       | 0                        | 0                       | 0                        | 213 [78, 463]           | 0                         | NC                       | 377 [173, 716]           |
| Pulmonary embolism (PE)                       | NC           | 4,067<br>[3,312, 4,941] | 7,313<br>[2,940, 15,067] | 1,518<br>[1,057, 2,111] | 5,271<br>[2,631, 9,431]  | 4,528<br>[3,769, 5,395] | 8,753<br>[5,817, 12,651]  | 5,911<br>[4,043, 8,344]  | 6,293<br>[5,310, 7,404]  |
| Retinal vein thrombosis (RVT)                 | 0            | NC                      | 0                        | 0                       | 0                        | NC                      | NC                        | NC                       | NC                       |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0            | 0                       | 0                        | NC                      | 0                        | 0                       | 0                         | 0                        | 0                        |

IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank

Table 13. Incidence rates [95% confidence interval] of thromboembolic events in breast cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).

|                                              | IQVIA<br>LPD      | DK-<br>DHR        | EBB                   | IQVIA DA                | IPCI                  | SIDIAP                  | UKBB                  | CPRD<br>GOLD            | FinOMOP-<br>THL         |
|----------------------------------------------|-------------------|-------------------|-----------------------|-------------------------|-----------------------|-------------------------|-----------------------|-------------------------|-------------------------|
| Deep vein thrombosis (DVT)                   | 0                 | 239<br>[188, 300] | 454<br>[147, 1,059]   | 472 [412, 540]          | 616<br>[436, 846]     | 760 [665, 865]          | 432<br>[271, 654]     | 1,034<br>[885, 1,200]   | 486 [418, 563]          |
| Disseminated intravascular coagulation (DIC) | 0                 | NC                | 0                     | NC                      | 0                     | 20 [7, 43]              | 0                     | 0                       | NC                      |
| PE and DVT combined (VTE)                    | 524<br>[239, 994] | 845<br>[745, 955] | 1,283<br>[701, 2,152] | 1,106<br>[1,011, 1,207] | 1,178<br>[922, 1,484] | 1,342<br>[1,215, 1,479] | 1,155<br>[877, 1,493] | 1,916<br>[1,710, 2,139] | 1,482<br>[1,359, 1,613] |
| Pelvic vein thrombosis (PVT)                 | 0                 | NC                | NC                    | 0                       | 0                     | 62 [37, 97]             | 0                     | 36 [13, 77]             | 76 [50, 109]            |
| Pulmonary embolism (PE)                      | 524<br>[239, 994] | 660<br>[573, 758] | 809<br>[370, 1,535]   | 740 [663, 823]          | 615<br>[435, 845]     | 736 [642, 839]          | 807<br>[579, 1,095]   | 945 [803, 1,104]        | 1,062 [959, 1,173]      |
| Retinal vein thrombosis (RVT)                | 0                 | 55 [32, 88]       | NC                    | 28 [15, 48]             | 0                     | 23 [9, 47]              | NC                    | 71 [37, 124]            | 76 [50, 109]            |

|                                               | IQVIA LPD | DK-DHR     | EBB | IQVIA DA | IPCI | SIDIAP      | UKBB | CPRD GOLD | FinOMOP-THL |
|-----------------------------------------------|-----------|------------|-----|----------|------|-------------|------|-----------|-------------|
| Splanchnic extrahepatic vein thrombosis (SVT) | NC        | 19 [7, 42] | NC  | NC       | 0    | 39 [20, 68] | 0    | NC        | 13 [4, 31]  |

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EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank

**Table 14. Incidence rates [95% confidence interval] of thromboembolic events in colorectal cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                                               | IQVIA LPD          | DK-DHR               | EBB                  | IQVIA DA             | IPCI                 | SIDIAP               | UKBB                 | CPRD GOLD            | FinOMOP-THL          |
|-----------------------------------------------|--------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| Deep vein thrombosis (DVT)                    | 0                  | 732 [631, 844]       | 916 [336, 1,994]     | 970 [834, 1,123]     | 640 [432, 914]       | 1,722 [1,565, 1,891] | 1,700 [1,294, 2,193] | 2,258 [1,967, 2,580] | 1,089 [950, 1,242]   |
| Disseminated intravascular coagulation (DIC)  | 0                  | NC                   | 0                    | 0                    | 0                    | 138 [96, 191]        | NC                   | NC                   | NC                   |
| PE and DVT combined (VTE)                     | 1,852 [680, 4,032] | 3,042 [2,829, 3,266] | 3,469 [2,174, 5,253] | 2,529 [2,303, 2,771] | 2,481 [2,047, 2,981] | 3,400 [3,176, 3,635] | 5,240 [4,497, 6,072] | 5,569 [5,099, 6,071] | 4,539 [4,245, 4,848] |
| Pelvic vein thrombosis (PVT)                  | 0                  | NC                   | NC                   | 0                    | 0                    | 73 [44, 114]         | NC                   | 61 [22, 133]         | 211 [152, 284]       |
| Pulmonary embolism (PE)                       | 1,852 [680, 4,032] | 2,445 [2,256, 2,646] | 2,786 [1,651, 4,403] | 1,724 [1,540, 1,924] | 1,826 [1,459, 2,258] | 2,179 [2,002, 2,367] | 4,084 [3,435, 4,819] | 3,540 [3,172, 3,939] | 3,711 [3,447, 3,989] |
| Retinal vein thrombosis (RVT)                 | NC                 | 74 [44, 115]         | 0                    | 32 [12, 69]          | 0                    | 38 [18, 71]          | 199 [80, 410]        | 102 [49, 188]        | 133 [88, 193]        |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0                  | 162 [116, 218]       | NC                   | 85 [48, 137]         | 0                    | 349 [281, 428]       | 170 [62, 370]        | 275 [181, 400]       | 176 [123, 243]       |

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EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank

**Table 15. Incidence rates [95% confidence interval] of thromboembolic events in corpus uteri cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                                              | IQVIA LPD | DK-DHR           | EBB                | IQVIA DA         | IPCI | SIDIAP               | UKBB | CPRD GOLD          | FinOMOP-THL      |
|----------------------------------------------|-----------|------------------|--------------------|------------------|------|----------------------|------|--------------------|------------------|
| Deep vein thrombosis (DVT)                   | 0         | 735 [509, 1,028] | 2,221 [721, 5,183] | 956 [683, 1,302] | NC   | 2,084 [1,680, 2,556] | NC   | 1,254 [827, 1,825] | 919 [686, 1,205] |
| Disseminated intravascular coagulation (DIC) | 0         | 0                | 0                  | 0                | 0    | NC                   | 0    | 0                  | 0                |

|                                               | IQVIA<br>LPD | DK-DHR                     | EBB                        | IQVIA<br>DA                | IPCI                       | SIDIAP                     | UKBB                       | CPRD<br>GOLD               | FinOMOP-<br>THL            |
|-----------------------------------------------|--------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| PE and DVT combined (VTE)                     | NC           | 2,484<br>[2,045,<br>2,989] | 3,126<br>[1,257,<br>6,441] | 1,773<br>[1,390,<br>2,229] | 2,137<br>[1,104,<br>3,734] | 3,415<br>[2,889,<br>4,010] | 2,476<br>[1,533,<br>3,785] | 2,951<br>[2,262,<br>3,783] | 3,033<br>[2,590,<br>3,529] |
| Pelvic vein thrombosis (PVT)                  | 0            | NC                         | NC                         | 0                          | 0                          | NC                         | 0                          | 0                          | 192 [96,<br>344]           |
| Pulmonary embolism (PE)                       | NC           | 1,757<br>[1,393,<br>2,187] | NC                         | 1,052<br>[765,<br>1,413]   | 1,405<br>[607,<br>2,769]   | 2,032<br>[1,634,<br>2,497] | 2,465<br>[1,526,<br>3,768] | 1,901<br>[1,364,<br>2,579] | 2,297<br>[1,916,<br>2,731] |
| Retinal vein thrombosis (RVT)                 | 0            | NC                         | NC                         | NC                         | 0                          | NC                         | 0                          | NC                         | 105 [39,<br>229]           |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0            | NC                         | 0                          | NC                         | 0                          | NC                         | 0                          | 0                          | NC                         |

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**Table 16. Incidence rates [95% confidence interval] of thromboembolic events in oesophageal cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                                               | IQVIA<br>LPD | DK-DHR                     | EBB | IQVIA DA                   | IPCI                       | SIDIAP                     | UKBB                        | CPRD<br>GOLD                 | FinOMOP-<br>THL            |
|-----------------------------------------------|--------------|----------------------------|-----|----------------------------|----------------------------|----------------------------|-----------------------------|------------------------------|----------------------------|
| Deep vein thrombosis (DVT)                    | 0            | 612 [326,<br>1,047]        | NC  | 798 [465,<br>1,277]        | 814 [264,<br>1,899]        | 3,677<br>[2,701,<br>4,889] | 2,235<br>[1,190,<br>3,822]  | 3,821<br>[3,016,<br>4,776]   | 1,236 [755,<br>1,909]      |
| Disseminated intravascular coagulation (DIC)  | 0            | 0                          | 0   | 0                          | 0                          | NC                         | 0                           | 0                            | NC                         |
| PE and DVT combined (VTE)                     | 0            | 4,561<br>[3,686,<br>5,581] | NC  | 2,823<br>[2,149,<br>3,641] | 4,340<br>[2,835,<br>6,359] | 6,512<br>[5,179,<br>8,083] | 9,764<br>[7,335,<br>12,740] | 10,089<br>[8,723,<br>11,609] | 6,635<br>[5,421,<br>8,039] |
| Pelvic vein thrombosis (PVT)                  | 0            | 0                          | 0   | 0                          | 0                          | 0                          | 0                           | NC                           | 0                          |
| Pulmonary embolism (PE)                       | 0            | 4,081<br>[3,259,<br>5,046] | NC  | 2,126<br>[1,551,<br>2,844] | 3,629<br>[2,274,<br>5,494] | 3,971<br>[2,957,<br>5,221] | 7,973<br>[5,816,<br>10,669] | 6,357<br>[5,300,<br>7,564]   | 5,358<br>[4,280,<br>6,625] |
| Retinal vein thrombosis (RVT)                 | 0            | NC                         | 0   | 0                          | 0                          | 0                          | 0                           | 0                            | NC                         |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0            | NC                         | 0   | 0                          | 0                          | 765 [367,<br>1,406]        | NC                          | NC                           | NC                         |

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Table 17. Incidence rates [95% confidence interval] of thromboembolic events in kidney cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).

|                                               | IQVIA<br>LPD | DK-DHR                  | EBB                     | IQVIA<br>DA             | IPCI                    | SIDIAP                  | UKBB                    | CPRD<br>GOLD            | FinOMOP-<br>THL         |
|-----------------------------------------------|--------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Deep vein thrombosis (DVT)                    | 0            | 839<br>[619, 1,113]     | NC                      | 625<br>[458, 834]       | NC                      | 3,663<br>[3,210, 4,163] | 4,224<br>[2,943, 5,875] | 1,669<br>[934, 2,753]   | 773 [560, 1,042]        |
| Disseminated intravascular coagulation (DIC)  | 0            | 0                       | 0                       | 0                       | 0                       | 91 [33, 197]            | 0                       | 0                       | NC                      |
| PE and DVT combined (VTE)                     | 0            | 2,332<br>[1,948, 2,769] | 3,262<br>[1,408, 6,427] | 2,000<br>[1,687, 2,355] | 1,989<br>[1,179, 3,144] | 4,781<br>[4,258, 5,351] | 6,921<br>[5,228, 8,988] | 5,224<br>[3,810, 6,990] | 3,128<br>[2,673, 3,639] |
| Pelvic vein thrombosis (PVT)                  | 0            | 0                       | NC                      | 0                       | 0                       | 107 [43, 220]           | 0                       | NC                      | 214 [111, 374]          |
| Pulmonary embolism (PE)                       | 0            | 1,645<br>[1,328, 2,015] | 2,000<br>[649, 4,668]   | 1,520<br>[1,250, 1,831] | 1,636<br>[916, 2,698]   | 2,109<br>[1,771, 2,493] | 3,449<br>[2,310, 4,954] | 3,610<br>[2,469, 5,096] | 2,597<br>[2,186, 3,062] |
| Retinal vein thrombosis (RVT)                 | 0            | 87 [28, 203]            | 0                       | NC                      | 0                       | NC                      | NC                      | NC                      | NC                      |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0            | NC                      | 0                       | NC                      | 0                       | 363<br>[233, 541]       | NC                      | 0                       | NC                      |

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Table 18. Incidence rates [95% confidence interval] of thromboembolic events in liver cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).

|                                              | IQVIA<br>LPD | DK-DHR                  | EBB                       | IQVIA<br>DA             | IPCI                    | SIDIAP                  | UKBB                     | CPRD<br>GOLD            | FinOMOP-<br>THL         |
|----------------------------------------------|--------------|-------------------------|---------------------------|-------------------------|-------------------------|-------------------------|--------------------------|-------------------------|-------------------------|
| Deep vein thrombosis (DVT)                   | 0            | 1,493<br>[992, 2,158]   | NC                        | 1,016<br>[629, 1,554]   | 3,263<br>[1,629, 5,838] | 2,558<br>[2,072, 3,124] | 3,426<br>[1,643, 6,301]  | 1,309<br>[628, 2,408]   | 1,383 [940, 1,963]      |
| Disseminated intravascular coagulation (DIC) | 0            | NC                      | 0                         | NC                      | 0                       | 312 [161, 546]          | 0                        | 0                       | 0                       |
| PE and DVT combined (VTE)                    | 0            | 4,587<br>[3,654, 5,687] | 11,803<br>[3,832, 27,544] | 2,911<br>[2,216, 3,755] | 6,422<br>[3,975, 9,816] | 4,551<br>[3,890, 5,291] | 9,291<br>[6,069, 13,613] | 5,109<br>[3,616, 7,013] | 6,419<br>[5,400, 7,575] |
| Pelvic vein thrombosis (PVT)                 | 0            | 0                       | 0                         | 0                       | 0                       | 0                       | 0                        | 0                       | NC                      |
| Pulmonary embolism (PE)                      | 0            | 3,206<br>[2,440, 4,135] | NC                        | 1,937<br>[1,384, 2,638] | 3,596<br>[1,858, 6,282] | 2,851<br>[2,339, 3,442] | 8,062<br>[5,111, 12,097] | 3,686<br>[2,449, 5,327] | 5,538<br>[4,603, 6,608] |
| Retinal vein thrombosis (RVT)                | 0            | NC                      | 0                         | 0                       | 0                       | NC                      | 0                        | NC                      | NC                      |

|                                               | IQVIA<br>LPD | DK-DHR                  | EBB                       | IQVIA<br>DA             | IPCI | SIDIAP                     | UKBB                     | CPRD<br>GOLD            | FinOMOP-<br>THL         |
|-----------------------------------------------|--------------|-------------------------|---------------------------|-------------------------|------|----------------------------|--------------------------|-------------------------|-------------------------|
| Splanchnic extrahepatic vein thrombosis (SVT) | 0            | 4,926<br>[3,966, 6,048] | 15,696<br>[6,311, 32,340] | 3,203<br>[2,477, 4,075] | 0    | 18,051<br>[16,673, 19,513] | 7,614<br>[4,772, 11,527] | 3,659<br>[2,432, 5,289] | 3,293<br>[2,585, 4,134] |

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**Table 19. Incidence rates [95% confidence interval] of thromboembolic events in lung cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                                               | IQVIA<br>LPD          | DK-DHR                  | EBB                      | IQVIA<br>DA             | IPCI                    | SIDIAP                    | UKBB                     | CPRD<br>GOLD            | FinOMOP-<br>THL         |
|-----------------------------------------------|-----------------------|-------------------------|--------------------------|-------------------------|-------------------------|---------------------------|--------------------------|-------------------------|-------------------------|
| Deep vein thrombosis (DVT)                    | 0                     | 877<br>[747, 1,024]     | NC                       | 954<br>[797, 1,133]     | 1,094<br>[781, 1,490]   | 4,064<br>[3,729, 4,421]   | 2,196<br>[1,569, 2,991]  | 1,953<br>[1,638, 2,310] | 1,460<br>[1,233, 1,715] |
| Disseminated intravascular coagulation (DIC)  | 0                     | 27 [9, 63]              | 0                        | 0                       | 0                       | 87 [45, 153]              | 0                        | NC                      | NC                      |
| PE and DVT combined (VTE)                     | 1,868<br>[751, 3,850] | 5,665<br>[5,319, 6,028] | 7,813<br>[4,631, 12,348] | 3,358<br>[3,053, 3,686] | 4,024<br>[3,392, 4,741] | 10,208<br>[9,663, 10,775] | 9,972<br>[8,542, 11,574] | 7,477<br>[6,836, 8,162] | 8,455<br>[7,883, 9,058] |
| Pelvic vein thrombosis (PVT)                  | 0                     | 0                       | 0                        | 0                       | 0                       | 51 [21, 105]              | 0                        | NC                      | 176 [104, 279]          |
| Pulmonary embolism (PE)                       | 1,868<br>[751, 3,850] | 4,930<br>[4,609, 5,268] | 6,412<br>[3,589, 10,576] | 2,643<br>[2,376, 2,933] | 3,008<br>[2,470, 3,629] | 7,589<br>[7,125, 8,075]   | 8,512<br>[7,209, 9,984]  | 5,623<br>[5,075, 6,213] | 7,325<br>[6,797, 7,883] |
| Retinal vein thrombosis (RVT)                 | 0                     | 71 [38, 121]            | 0                        | 50 [20, 104]            | 0                       | 58 [25, 115]              | NC                       | 71 [23, 165]            | 167 [98, 268]           |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0                     | NC                      | 0                        | NC                      | 0                       | 204 [136, 295]            | 0                        | NC                      | 127 [68, 217]           |

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**Table 20. Incidence rates [95% confidence interval] of thromboembolic events in leukaemia and lymphoma after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                                              | IQVIA<br>LPD | DK-DHR            | EBB                   | IQVIA<br>DA       | IPCI                  | SIDIAP                  | UKBB                | CPRD<br>GOLD            | FinOMOP-<br>THL |
|----------------------------------------------|--------------|-------------------|-----------------------|-------------------|-----------------------|-------------------------|---------------------|-------------------------|-----------------|
| Deep vein thrombosis (DVT)                   | 0            | 481<br>[396, 580] | 1,313<br>[630, 2,415] | 624<br>[533, 726] | 1,166<br>[787, 1,664] | 1,452<br>[1,307, 1,610] | 888<br>[569, 1,322] | 1,297<br>[1,071, 1,557] | 529 [430, 644]  |
| Disseminated intravascular coagulation (DIC) | NC           | 52 [27, 90]       | NC                    | NC                | 0                     | 254 [196, 323]          | 216 [79, 471]       | NC                      | 26 [9, 61]      |

|                                               | IQVIA<br>LPD        | DK-DHR                  | EBB                     | IQVIA<br>DA             | IPCI                    | SIDIAP                  | UKBB                    | CPRD<br>GOLD            | FinOMOP-<br>THL         |
|-----------------------------------------------|---------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| PE and DVT combined (VTE)                     | 688<br>[224, 1,607] | 1,718<br>[1,550, 1,899] | 1,997<br>[1,117, 3,293] | 1,291<br>[1,158, 1,436] | 2,650<br>[2,054, 3,366] | 2,418<br>[2,229, 2,620] | 2,465<br>[1,902, 3,141] | 2,391<br>[2,077, 2,739] | 1,683<br>[1,501, 1,882] |
| Pelvic vein thrombosis (PVT)                  | 0                   | NC                      | NC                      | 0                       | 0                       | 114 [76, 163]           | 0                       | 55 [18, 128]            | 111 [69, 170]           |
| Pulmonary embolism (PE)                       | 688<br>[224, 1,607] | 1,316<br>[1,171, 1,474] | 1,167<br>[534, 2,216]   | 794<br>[692, 908]       | 1,477<br>[1,045, 2,027] | 1,291<br>[1,155, 1,439] | 1,856<br>[1,378, 2,447] | 1,204<br>[988, 1,454]   | 1,228<br>[1,074, 1,399] |
| Retinal vein thrombosis (RVT)                 | NC                  | 148<br>[102, 207]       | 0                       | 84 [53, 126]            | 0                       | 43 [21, 77]             | NC                      | 143 [76, 244]           | 201 [143, 277]          |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0                   | 69 [40, 112]            | NC                      | 69 [42, 108]            | 0                       | 211 [158, 275]          | NC                      | 55 [18, 127]            | 84 [48, 137]            |

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**Table 21. Incidence rates [95% confidence interval] of thromboembolic events in melanoma after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                                               | IQVIA<br>LPD | DK-DHR            | EBB | IQVIA<br>DA       | IPCI              | SIDIAP         | UKBB             | CPRD<br>GOLD      | FinOMOP-<br>THL  |
|-----------------------------------------------|--------------|-------------------|-----|-------------------|-------------------|----------------|------------------|-------------------|------------------|
| Deep vein thrombosis (DVT)                    | 0            | 192<br>[131, 270] | 0   | 231<br>[172, 303] | 239 [96, 492]     | 427 [292, 602] | NC               | 207 [99, 381]     | 177 [99, 293]    |
| Disseminated intravascular coagulation (DIC)  | 0            | NC                | 0   | 0                 | 0                 | NC             | 0                | 0                 | NC               |
| PE and DVT combined (VTE)                     | 0            | 630<br>[515, 764] | 0   | 437<br>[354, 534] | 515<br>[288, 850] | 723 [544, 944] | 626 [312, 1,119] | 524<br>[339, 773] | 803 [622, 1,020] |
| Pelvic vein thrombosis (PVT)                  | 0            | NC                | NC  | 0                 | 0                 | NC             | 0                | 0                 | NC               |
| Pulmonary embolism (PE)                       | 0            | 457<br>[360, 572] | 0   | 262<br>[199, 339] | 272<br>[117, 535] | 385 [258, 554] | 452 [195, 891]   | 331<br>[189, 537] | 654 [492, 851]   |
| Retinal vein thrombosis (RVT)                 | 0            | 54 [25, 102]      | NC  | 36 [16, 71]       | 0                 | NC             | 0                | NC                | NC               |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0            | 0                 | 0   | NC                | 0                 | NC             | 0                | NC                | NC               |

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Table 22. Incidence rates [95% confidence interval] of thromboembolic events in ovarian cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).

|                                               | IQVIA<br>LPD | DK-DHR                  | EBB                     | IQVIA<br>DA             | IPCI                    | SIDIAP                  | UKBB                      | CPRD<br>GOLD             | FinOMOP-<br>THL         |
|-----------------------------------------------|--------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|---------------------------|--------------------------|-------------------------|
| Deep vein thrombosis (DVT)                    | 0            | 1,233<br>[832, 1,760]   | NC                      | 1,242<br>[899, 1,673]   | 1,532<br>[562, 3,333]   | 2,783<br>[2,197, 3,479] | 3,719<br>[2,239, 5,808]   | 3,197<br>[2,314, 4,307]  | 1,380 [967, 1,911]      |
| Disseminated intravascular coagulation (DIC)  | 0            | 0                       | 0                       | 0                       | 0                       | 0                       | 0                         | 0                        | 0                       |
| PE and DVT combined (VTE)                     | 0            | 6,145<br>[5,176, 7,243] | 4,302<br>[1,857, 8,477] | 3,856<br>[3,222, 4,579] | 5,254<br>[3,209, 8,114] | 6,515<br>[5,586, 7,555] | 10,757<br>[8,034, 14,107] | 9,483<br>[7,862, 11,339] | 6,977<br>[5,973, 8,101] |
| Pelvic vein thrombosis (PVT)                  | 0            | 0                       | NC                      | 0                       | 0                       | NC                      | 0                         | 0                        | 606 [346, 984]          |
| Pulmonary embolism (PE)                       | 0            | 5,264<br>[4,375, 6,281] | 3,739<br>[1,503, 7,705] | 2,945<br>[2,399, 3,579] | 3,608<br>[1,973, 6,054] | 4,591<br>[3,825, 5,466] | 7,896<br>[5,615, 10,794]  | 6,527<br>[5,221, 8,061]  | 5,828<br>[4,921, 6,854] |
| Retinal vein thrombosis (RVT)                 | 0            | NC                      | 0                       | 0                       | 0                       | NC                      | 0                         | NC                       | NC                      |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0            | NC                      | 0                       | 0                       | 0                       | 352<br>[169, 648]       | NC                        | NC                       | NC                      |

IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank

Table 23. Incidence rates [95% confidence interval] of thromboembolic events in pancreatic cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).

|                                              | IQVIA<br>LPD | DK-DHR                     | EBB                       | IQVIA<br>DA             | IPCI                     | SIDIAP                     | UKBB                       | CPRD<br>GOLD               | FinOMOP-<br>THL            |
|----------------------------------------------|--------------|----------------------------|---------------------------|-------------------------|--------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| Deep vein thrombosis (DVT)                   | 0            | 2,503<br>[2,002, 3,092]    | NC                        | 1,462<br>[1,110, 1,890] | 3,286<br>[2,083, 4,931]  | 5,221<br>[4,536, 5,981]    | 7,437<br>[5,209, 10,295]   | 7,237<br>[5,702, 9,058]    | 3,052<br>[2,548, 3,627]    |
| Disseminated intravascular coagulation (DIC) | 0            | NC                         | 0                         | 0                       | 0                        | 244 [117, 449]             | NC                         | 0                          | 0                          |
| PE and DVT combined (VTE)                    | NC           | 11,279<br>[10,158, 12,488] | 11,429<br>[6,085, 19,544] | 4,543<br>[3,895, 5,268] | 8,497<br>[6,452, 10,984] | 11,380<br>[10,345, 12,491] | 26,311<br>[21,796, 31,485] | 16,244<br>[13,853, 18,929] | 13,482<br>[12,373, 14,664] |
| Pelvic vein thrombosis (PVT)                 | 0            | NC                         | 0                         | 0                       | 0                        | NC                         | 0                          | 0                          | 559 [358, 832]             |
| Pulmonary embolism (PE)                      | NC           | 9,013<br>[8,023, 10,090]   | 10,187<br>[5,264, 17,795] | 3,476<br>[2,918, 4,109] | 5,416<br>[3,833, 7,434]  | 8,264<br>[7,394, 9,209]    | 20,555<br>[16,630, 25,128] | 9,746<br>[7,947, 11,831]   | 11,285<br>[10,280, 12,361] |
| Retinal vein thrombosis (RVT)                | 0            | NC                         | 0                         | NC                      | 0                        | 123 [40, 286]              | 0                          | 0                          | NC                         |

|                                                       | IQVIA<br>LPD | DK-DHR                   | EBB                         | IQVIA<br>DA          | IPCI | SIDIAP                     | UKBB                       | CPRD<br>GOLD               | FinOMOP-<br>THL            |
|-------------------------------------------------------|--------------|--------------------------|-----------------------------|----------------------|------|----------------------------|----------------------------|----------------------------|----------------------------|
| Splanctic<br>extrahepatic<br>vein thrombosis<br>(SVT) | 0            | 1,293<br>[943,<br>1,730] | 7,671<br>[3,508,<br>14,563] | 689<br>[458,<br>996] | 0    | 6,400<br>[5,640,<br>7,234] | 5,937<br>[3,976,<br>8,526] | 1,928<br>[1,194,<br>2,948] | 1,679<br>[1,314,<br>2,115] |

IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank

**Table 24. Incidence rates [95% confidence interval] of thromboembolic events in prostate cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                                                    | IQVIA<br>LPD | DK-DHR                   | EBB                      | IQVIA<br>DA            | IPCI                     | SIDIAP                   | UKBB                   | CPRD<br>GOLD             | FinOMOP-<br>THL   |
|----------------------------------------------------|--------------|--------------------------|--------------------------|------------------------|--------------------------|--------------------------|------------------------|--------------------------|-------------------|
| Deep vein<br>thrombosis (DVT)                      | 0            | 373<br>[305,<br>451]     | 639<br>[235,<br>1,392]   | 416<br>[358,<br>481]   | 592<br>[383,<br>874]     | 660 [555,<br>779]        | 276<br>[166,<br>431]   | 478<br>[371,<br>606]     | 334 [277,<br>400] |
| Disseminated<br>intravascular<br>coagulation (DIC) | 0            | 0                        | 0                        | 0                      | 0                        | 61 [32,<br>104]          | 0                      | NC                       | NC                |
| PE and DVT<br>combined (VTE)                       | NC           | 1,019<br>[904,<br>1,144] | 1,081<br>[519,<br>1,989] | 974<br>[884,<br>1,072] | 1,271<br>[952,<br>1,662] | 1,085<br>[949,<br>1,236] | 779<br>[584,<br>1,019] | 1,062<br>[898,<br>1,246] | 851 [757,<br>954] |
| Pelvic vein<br>thrombosis (PVT)                    | 0            | NC                       | 642<br>[236,<br>1,397]   | 0                      | 0                        | 47 [23,<br>86]           | 0                      | NC                       | 104 [73,<br>143]  |
| Pulmonary<br>embolism (PE)                         | NC           | 719<br>[623,<br>825]     | 636<br>[233,<br>1,384]   | 633<br>[561,<br>712]   | 711<br>[479,<br>1,014]   | 620 [518,<br>735]        | 538<br>[378,<br>741]   | 629<br>[506,<br>773]     | 600 [522,<br>687] |
| Retinal vein<br>thrombosis (RVT)                   | NC           | 116 [80,<br>163]         | 0                        | 34 [19,<br>56]         | 0                        | 75 [43,<br>122]          | NC                     | 160<br>[101,<br>240]     | 161 [122,<br>209] |
| Splanctic<br>extrahepatic vein<br>thrombosis (SVT) | 0            | NC                       | 0                        | 13 [5,<br>29]          | 0                        | 42 [19,<br>80]           | NC                     | NC                       | NC                |

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**Table 25. Incidence rates [95% confidence interval] of thromboembolic events in stomach cancer after 1 year of follow-up, by database, per 100,000 person-years (2016–2022).**

|                               | IQVIA<br>LPD | DK-DHR                 | EBB | IQVIA<br>DA            | IPCI                     | SIDIAP                     | UKBB                     | CPRD<br>GOLD               | FinOMOP-<br>THL       |
|-------------------------------|--------------|------------------------|-----|------------------------|--------------------------|----------------------------|--------------------------|----------------------------|-----------------------|
| Deep vein<br>thrombosis (DVT) | 0            | 934<br>[621,<br>1,350] | NC  | 929<br>[631,<br>1,319] | 1,484<br>[597,<br>3,058] | 3,836<br>[3,221,<br>4,535] | 2,265<br>[978,<br>4,463] | 3,359<br>[2,105,<br>5,085] | 1,213 [799,<br>1,764] |

|                                               | IQVIA<br>LPD | DK-DHR                  | EBB                      | IQVIA<br>DA             | IPCI                    | SIDIAP                  | UKBB                      | CPRD<br>GOLD             | FinOMOP-<br>THL         |
|-----------------------------------------------|--------------|-------------------------|--------------------------|-------------------------|-------------------------|-------------------------|---------------------------|--------------------------|-------------------------|
| Disseminated intravascular coagulation (DIC)  | 0            | NC                      | 0                        | 0                       | 0                       | 299<br>[149, 535]       | 0                         | 0                        | 0                       |
| PE and DVT combined (VTE)                     | NC           | 5,660<br>[4,827, 6,596] | 7,554<br>[3,771, 13,516] | 2,647<br>[2,117, 3,269] | 3,896<br>[2,309, 6,157] | 7,805<br>[6,906, 8,788] | 11,422<br>[8,122, 15,614] | 8,340<br>[6,248, 10,909] | 7,272<br>[6,175, 8,507] |
| Pelvic vein thrombosis (PVT)                  | 0            | 0                       | NC                       | 0                       | 0                       | 273<br>[131, 501]       | 0                         | 0                        | NC                      |
| Pulmonary embolism (PE)                       | NC           | 4,882<br>[4,115, 5,751] | 5,988<br>[2,738, 11,367] | 1,973<br>[1,522, 2,514] | 2,539<br>[1,312, 4,435] | 5,256<br>[4,532, 6,064] | 9,836<br>[6,812, 13,744]  | 5,219<br>[3,614, 7,293]  | 6,262<br>[5,254, 7,407] |
| Retinal vein thrombosis (RVT)                 | 0            | NC                      | 0                        | NC                      | 0                       | NC                      | NC                        | 0                        | NC                      |
| Splanchnic extrahepatic vein thrombosis (SVT) | 0            | NC                      | 0                        | NC                      | 0                       | 1,556<br>[1,178, 2,015] | NC                        | NC                       | 222 [72, 517]           |

IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank

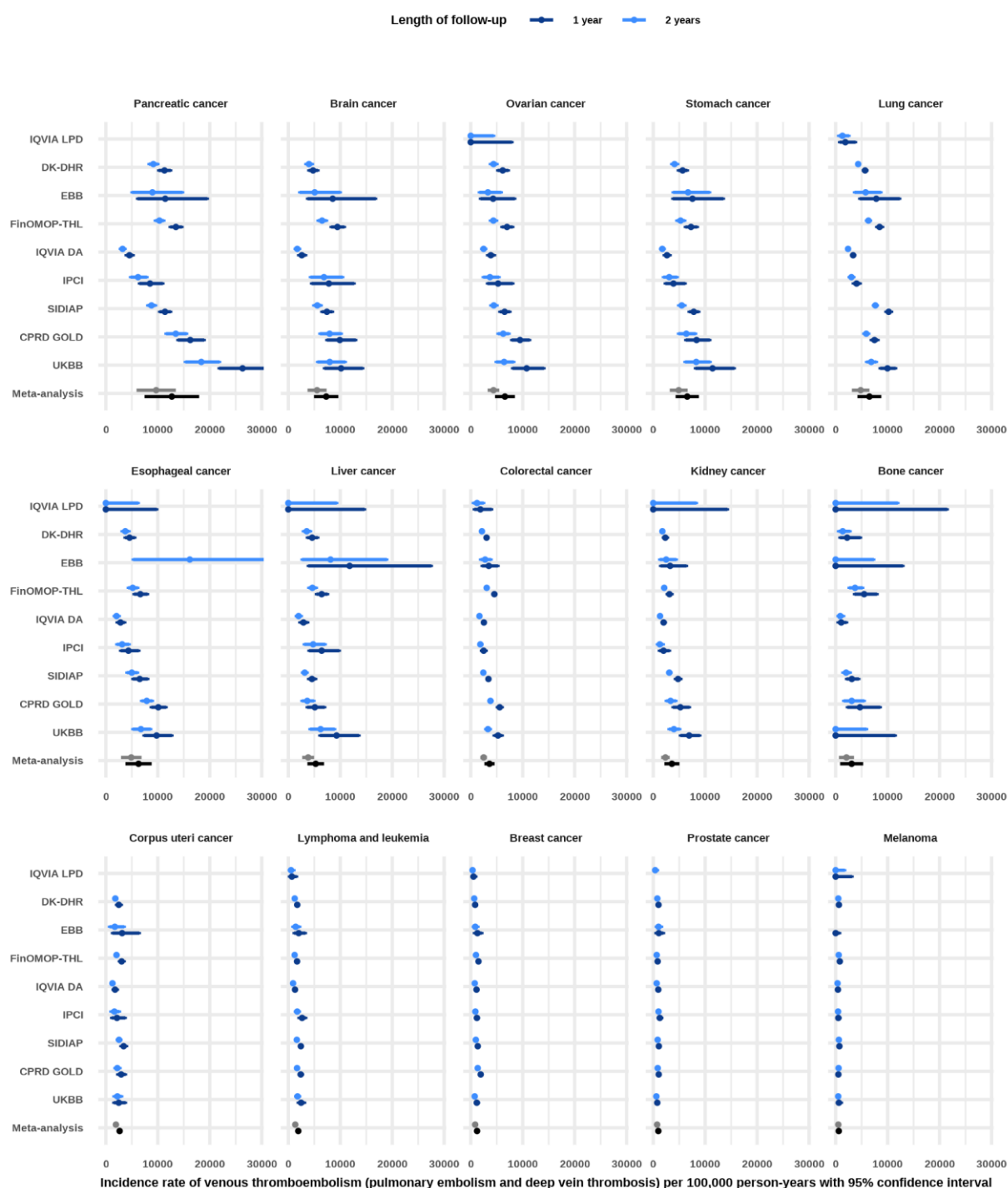
### Meta-analyses of incidence rates across data sources for each cancer type

In all cancers except for liver cancer, the outcome with the highest combined IR [95% CI] per 100,000 PY one year after cancer diagnosis was VTE: lowest in melanoma 602 [478–726] ( $I^2=66.8\%$ ) and highest in pancreatic cancer 12,697 [7,443–17,951] ( $I^2=98\%$ ) (**Figure 3**). In liver cancer, the outcome with the highest combined IR [95% CI] per 100,000 PY one year after cancer diagnosis was SVT: 7,448 [1,858–13,039] ( $I^2=98.4\%$ ).

In bone cancer, the outcome with the second-highest combined IR [95% CI] per 100,000 PY was DVT: 1,967 [181–3,753] ( $I^2=24.5\%$ ) (**Figure 4**). In liver cancer, the outcome with the second-highest combined IR [95% CI] per 100,000 PY was SVT: 7,448 [1,858–13,039] ( $I^2=98.4\%$ ) (**Figure 5**). Across all other cancers, the outcome with the second-highest combined IR [95% CI] per 100,000 PY was PE: lowest in melanoma (393 [267–519]) ( $I^2=74.9\%$ ) and highest in pancreatic cancer (9,502 [5,369–13,636]) ( $I^2=97.5\%$ ) (**Figure 6**).

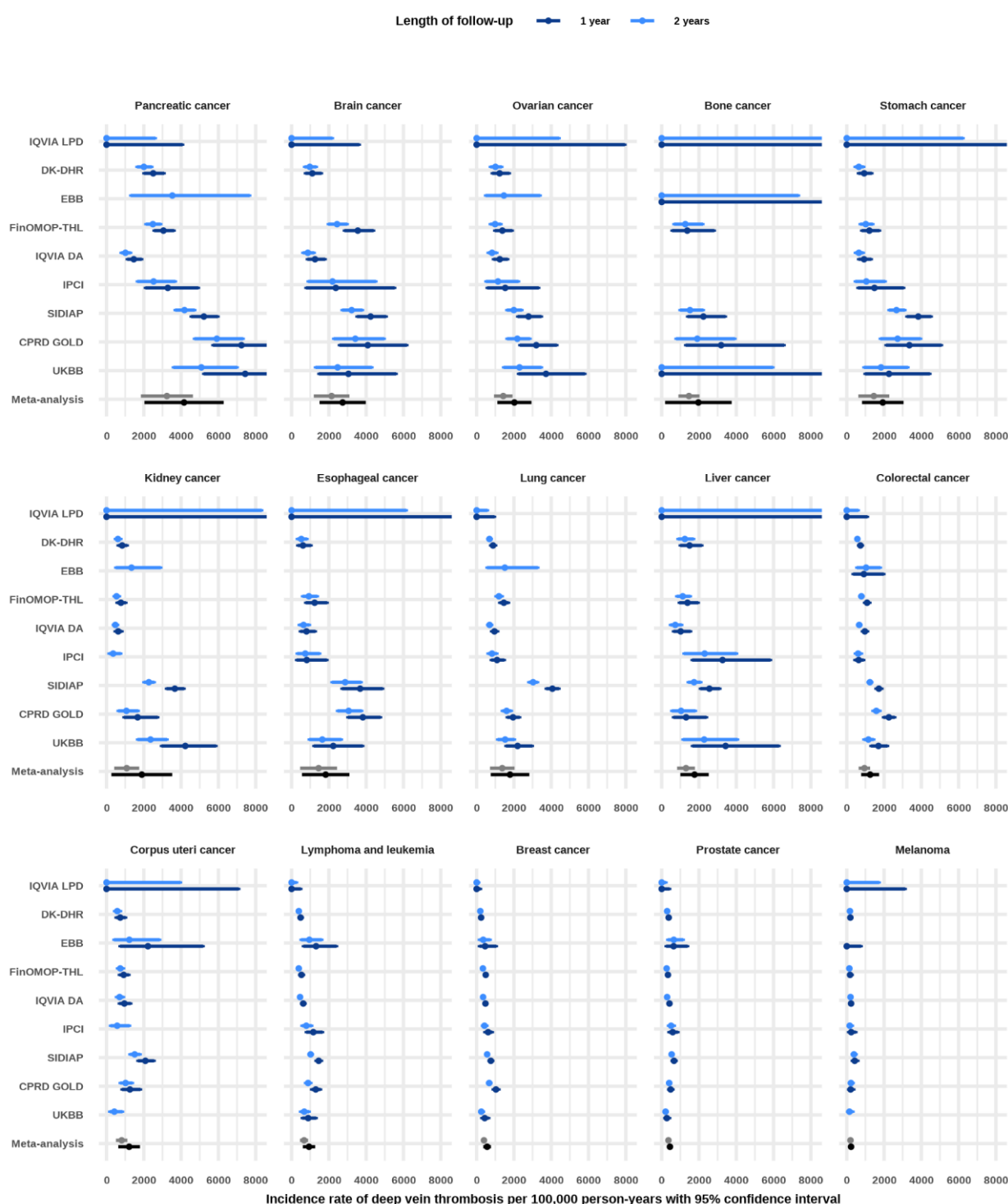
The outcome with the third-highest combined IR [95% CI] per 100,000 PY was PE in bone cancer: 1,941 [0–4,552] ( $I^2=82\%$ ) and liver cancer: 3,781 [2,152–5,410] ( $I^2=87.7\%$ ) (**Figure 6**). Across all other cancers, the outcome with the third-highest combined IR [95% CI] per 100,000 PY was DVT: lowest in melanoma (230 [147–314]) ( $I^2=46\%$ ) and highest in pancreatic cancer (4,159 [2,034–6,283]) ( $I^2=95.6\%$ ) (**Figure 4**).

The IRs of thromboembolic events two years after cancer diagnosis were similar to those one year after, but with lower absolute IRs (**Figures 3–9**). For example, the outcome with the highest combined IR [95% CI] per 100,000 PY across all cancers, except for liver cancer, was VTE: lowest in melanoma (512 [427–598]) ( $I^2=74.2\%$ ) and highest in pancreatic cancer (9,681 [5,901–13,462]) ( $I^2=98.5\%$ ) (**Figure 3**).



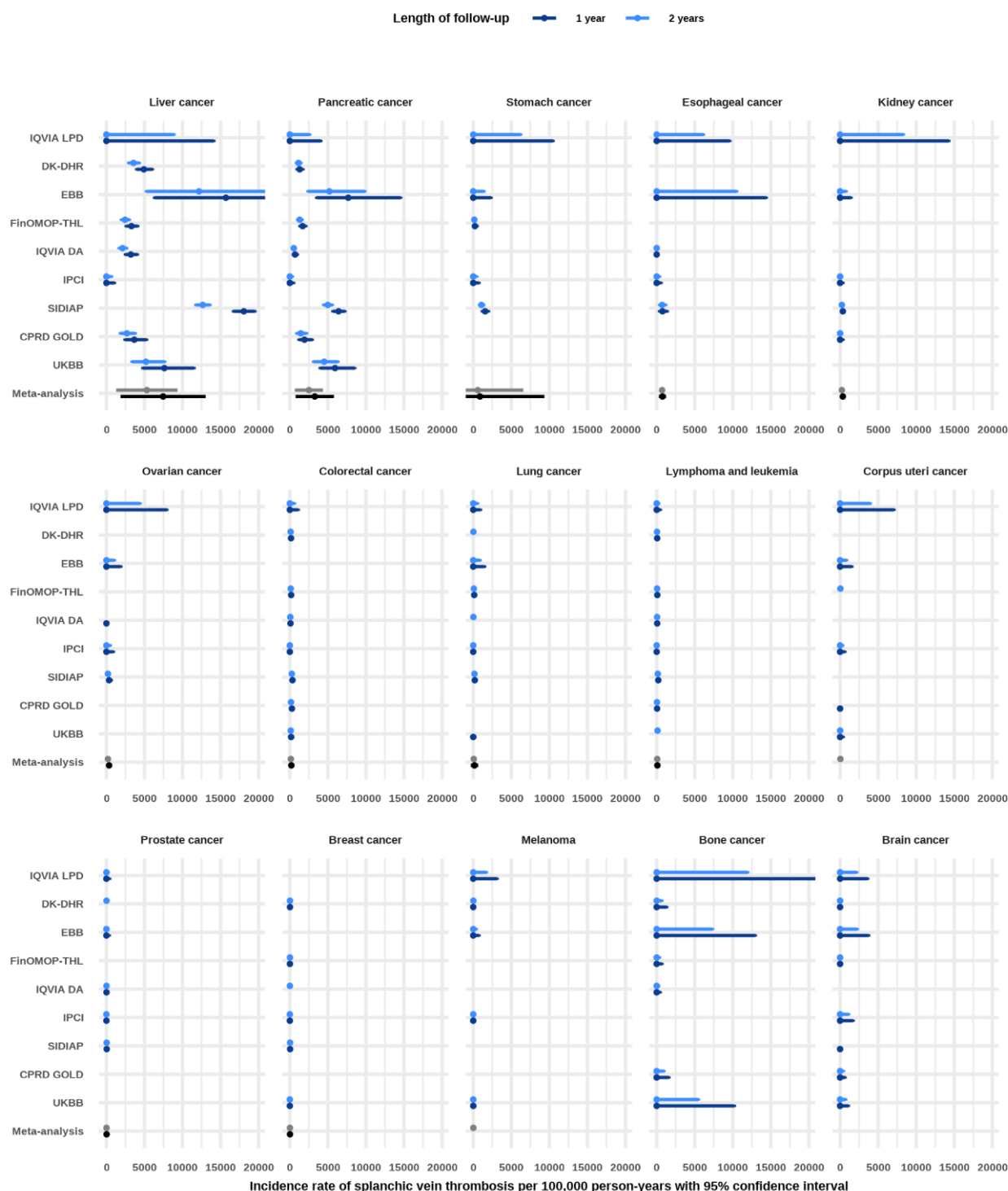
**Figure 3. Meta-analysis of IRs with 95% CI of venous thromboembolism (VTE - pulmonary embolism (PE) and deep vein thrombosis (DVT) combined) per 100,000 person-years in cancer patients one (365 days) and two years (730 days) years after diagnosis.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



**Figure 4. Meta-analysis of IRs with 95% CI of deep vein thrombosis (DVT) per 100,000 person-years in cancer one (365 days) and two years (730 days) years after diagnosis.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



**Figure 5. Meta-analysis of IRs with 95% CI of splanchnic vein thrombosis (SVT) per 100,000 person-years in cancer patients one (365 days) and two years (730 days) after diagnosis.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



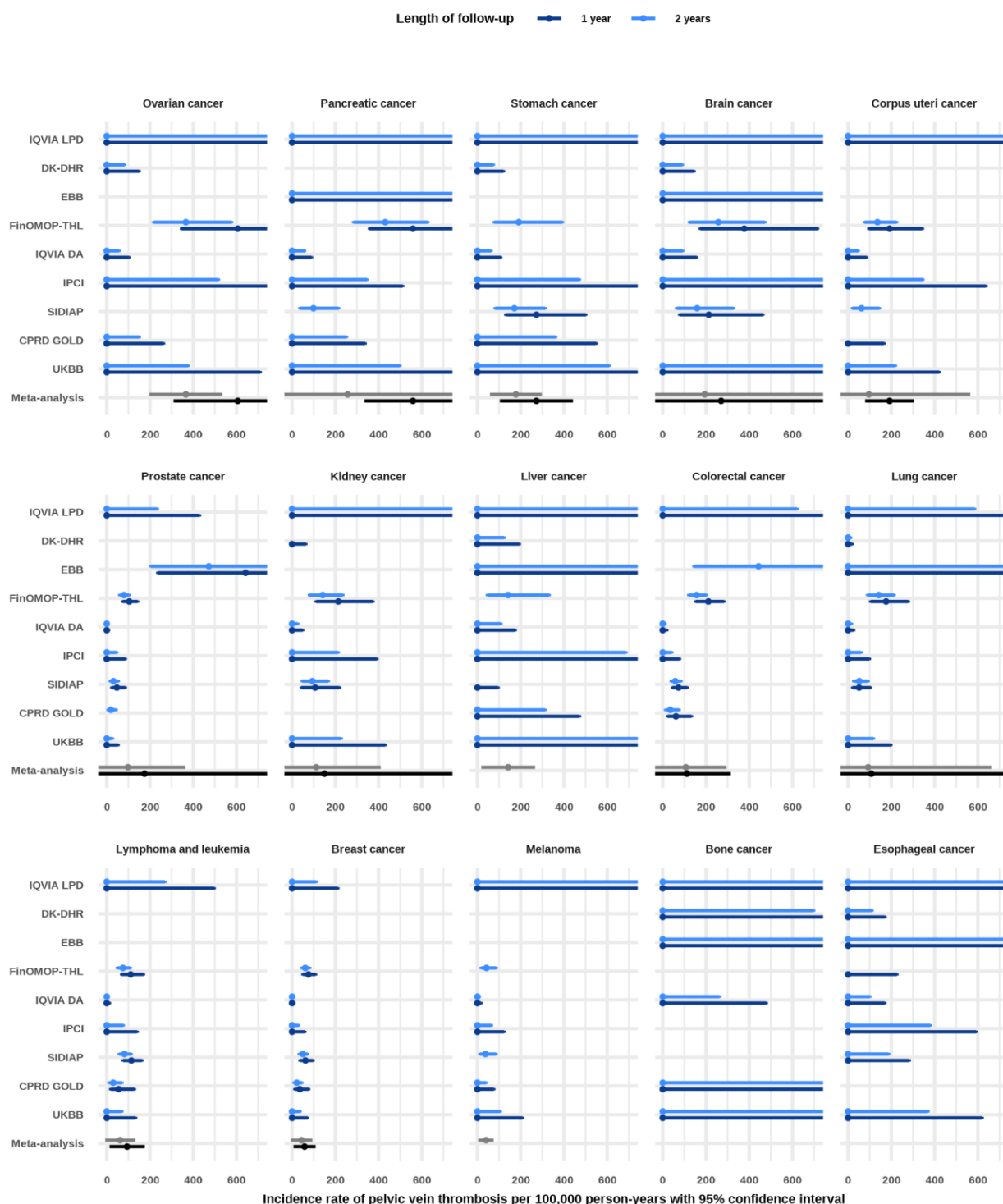
**Figure 6. Meta-analysis of IRs with 95% CI of pulmonary embolism (PE) per 100,000 person-years in cancer patients one (365 days) and two years (730 days) years after diagnosis after diagnosis.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



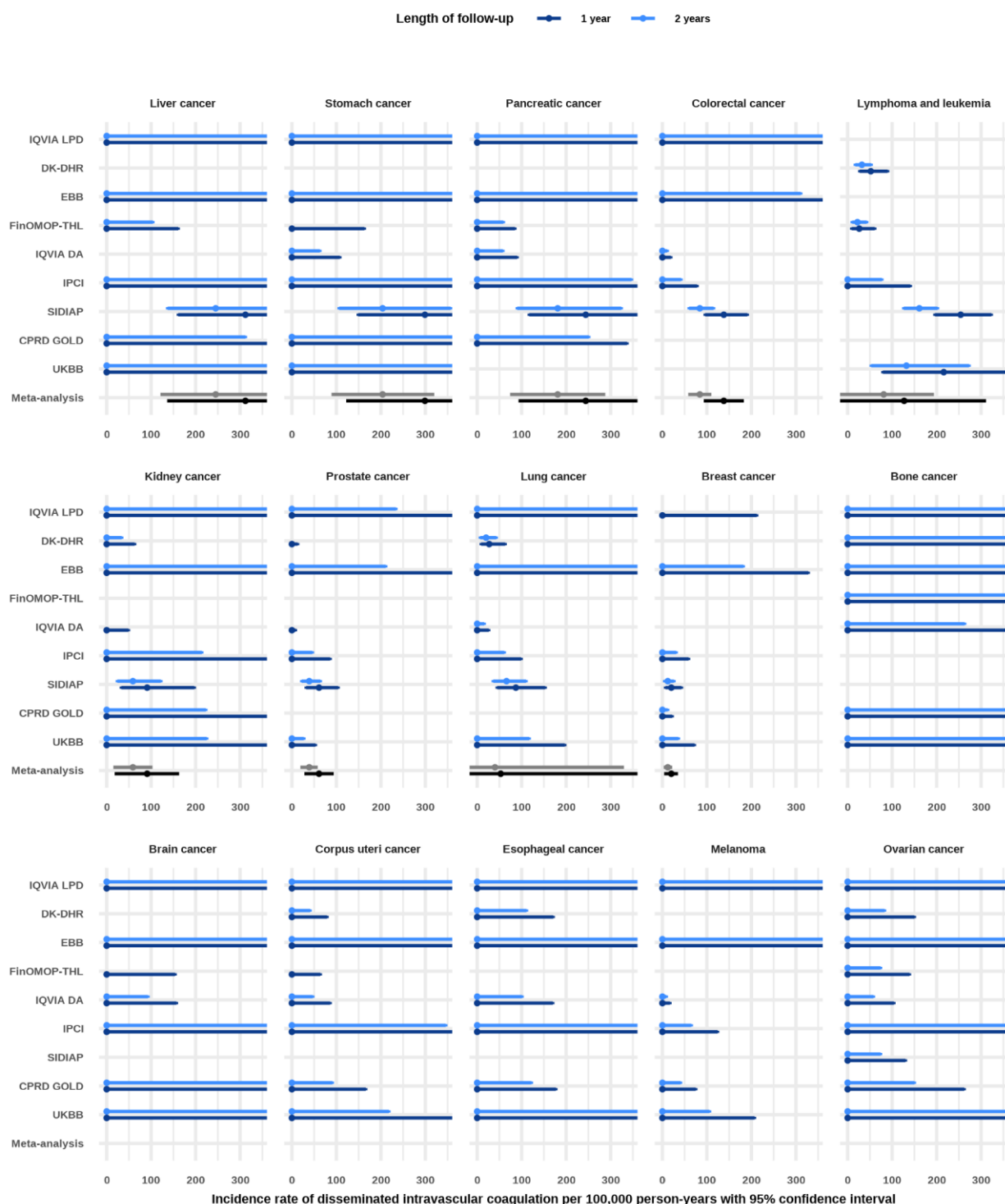
**Figure 7. Meta-analysis of IRs with 95% CI of retinal vein thrombosis (RVT) per 100,000 person-years in cancer patients one (365 days) and two years (730 days) years after diagnosis.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



**Figure 8. Meta-analysis of IRs with 95% CI of pelvic vein thrombosis (PVT) per 100,000 person-years in cancer patients one (365 days) and two years (730 days) years after diagnosis.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



**Figure 9. Meta-analysis of IRs with 95% CI of disseminated intravascular coagulation (DIC) per 100,000 person-years in cancer patients one and two years after diagnosis.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.

### **Incidence rates of thromboembolic events in selected cancers by sex**

Comparisons in the IRs between females and males one year after cancer diagnosis were not consistent between data sources, and low event counts in subgroups limited the comparison of IRs by sex—results are available in the “Shiny app” ([EUPAS1000000440](#)). Some differences in point estimates were observed across data sources between females and males, although the 95% CIs overlapped.

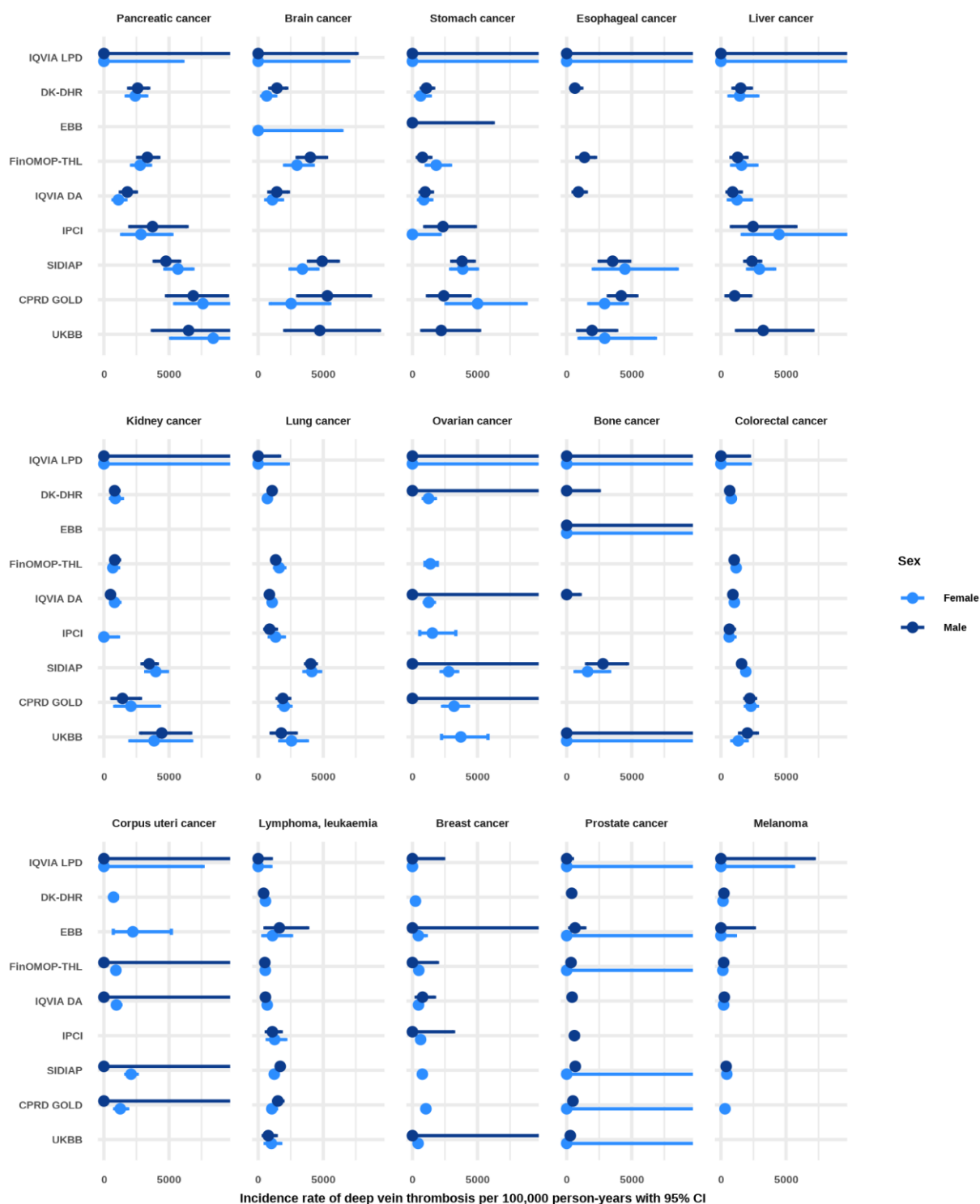
Point estimates of the IRs were lower among females than males for the following thromboembolic event outcomes [95% CI]:

- DVT in brain cancer (lowest: 657 [264–1,354] among females versus 1,443 [893–2,205] among males in DK-DHR; highest: 2,528 [928–5,503] among females versus 5,316 [3,039–8,633] among males in CPRD GOLD) (**Figure 10**);
- VTE in brain cancer (lowest: 2,218 [1,449–3,250] among females versus 3,009 [2,071–4,225] among males in IQVIA DA Germany; highest: 7,149 [3,569–12,792] among females versus 13,033 [8,067–19,922] among males in UKBB) and melanoma (lowest: 392 [288–522] among females versus 491 [363–650] among males in IQVIA DA Germany; highest: 585 [375–870] among females versus 1,015 [735–1,367] among males in FinOMOP-THL) (**Figure 11**);
- PE in melanoma (lowest: 232 [154–336] among females versus 298 [201–426] among males in IQVIA DA Germany; highest: 459 [276–716] among females versus 843 [590–1,167] among males in FinOMOP-THL) and brain cancer (lowest: 1,175 [642–1,971] among females versus 1,884 [1,166–2,880] among males in IQVIA DA Germany; highest: 7,690 [3,973–13,432] among females versus 9,767 [5,583–15,861] among males in UKBB) (**Figure 12**);
- and SVT in liver cancer (lowest: 1,491 [744–2,668] among females versus 4,158 [3,132–5,412] among males in IQVIA DA Germany; highest: 13,351 [11,280–15,692] among females versus 20,198 [18,443–22,074] among males in SIDIAP) and colorectal cancer (lowest: 115 [63–194] among females versus 202 [134–292] among males in DK-DHR; highest: 228 [148–337] among females versus 436 [337–554] among males in SIDIAP) (**Figure 13**).

Point estimates of the IRs were lower among females than males for the following outcomes [95% CI]:

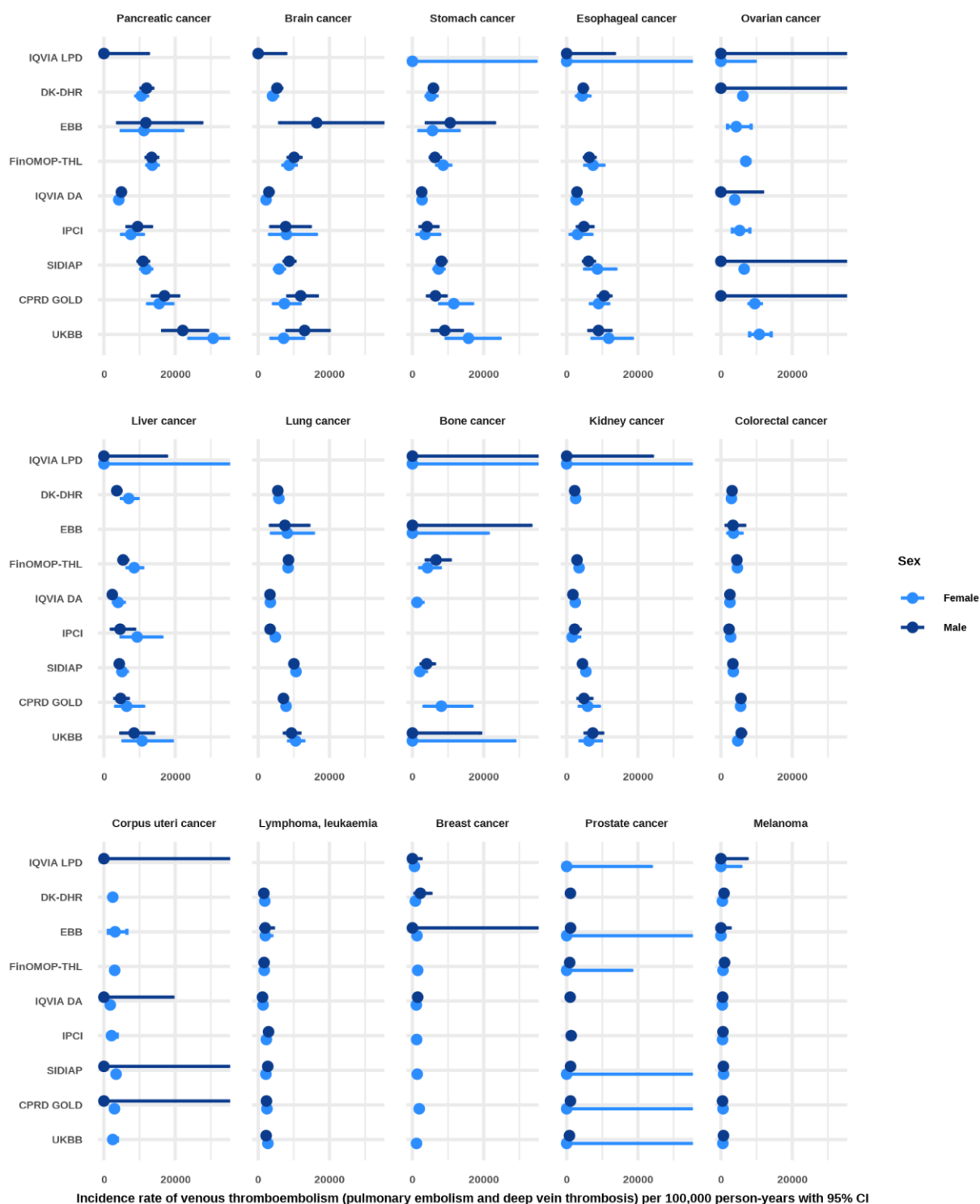
- DVT in liver cancer (lowest: 1,235 [565–2,344] among females versus 897 [464–1,567] among males in IQVIA DA Germany; highest: 4,460 [1,637–9,707] among females versus 2,468 [801–5,760] among males in IPCI) (**Figure 10**);
- VTE in liver cancer (lowest: 3,965 [2,635–5,731] among females versus 2,347 [1,595–3,331] among males in IQVIA DA Germany; highest: 10,716 [5,349–19,173] among females versus 8,465 [4,738–13,962] among males in UKBB) (**Figure 11**);
- and PE in stomach cancer (lowest: 1,983 [1,328–2,848] among females versus 1,965 [1,376–2,720] among males in IQVIA DA Germany; highest: 14,029 [8,172–22,461] among females versus 7,572 [4,411–12,124] among males in UKBB) and liver cancer (lowest: 2,772 [1,693–4,282] among females versus 1,489 [909–2,299] among males in IQVIA DA Germany; highest: 9,488 [4,550–17,449] among females versus 7,226 [3,848–12,357] among males in UKBB) (**Figure 12**).

Similar to the IRs stratified one year after cancer diagnosis, IRs two years after cancer diagnosis were lower among females than males of: DVT in brain cancer, VTE in brain cancer and melanoma, PE in melanoma and brain cancer, and SVT in liver cancer and colorectal cancer; and IRs were higher among females than males of: PE in stomach cancer and DVT, VTE, and PE in liver cancer.



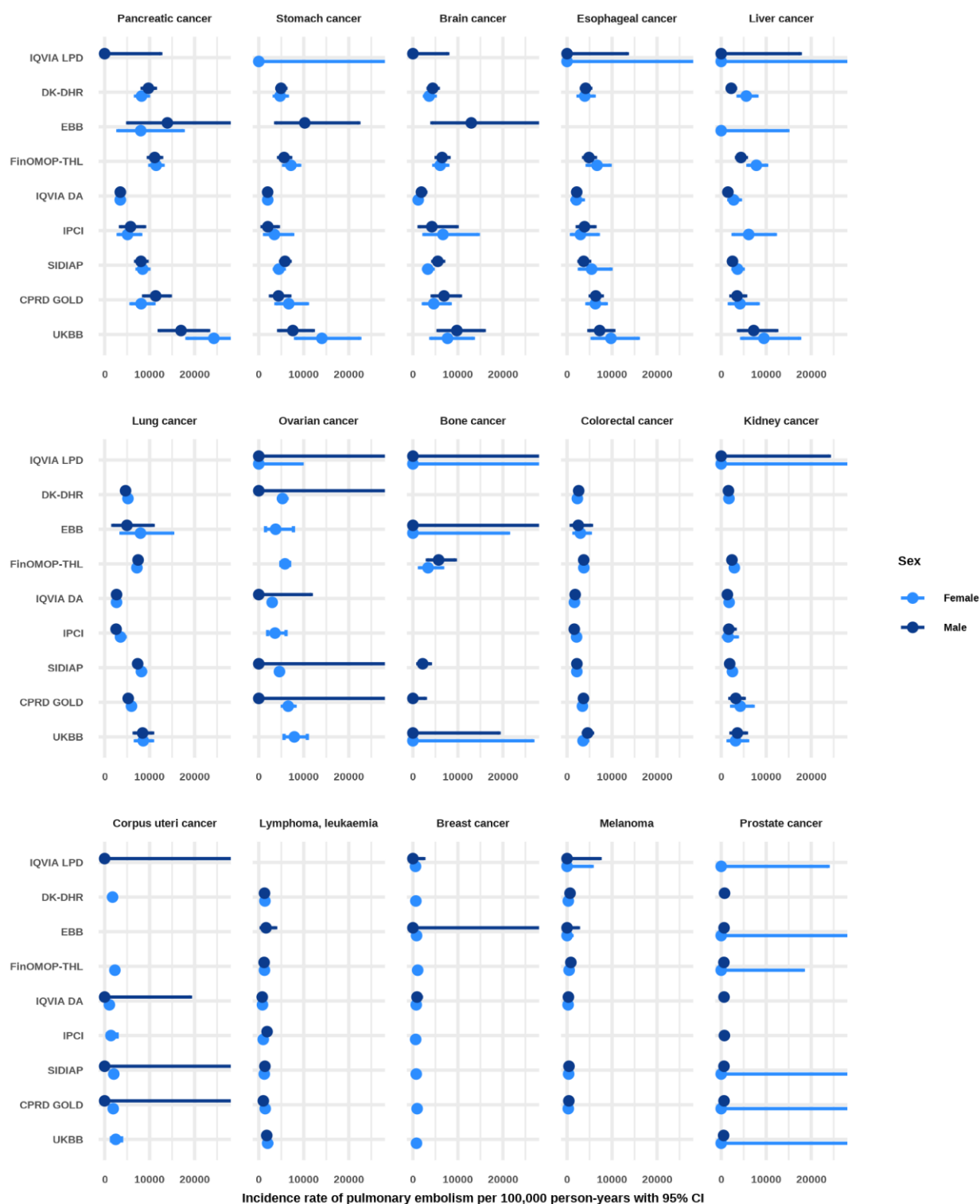
**Figure 10. IRs with 95% CI of deep vein thrombosis (DVT) per 100,000 person-years in cancer patients by sex**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



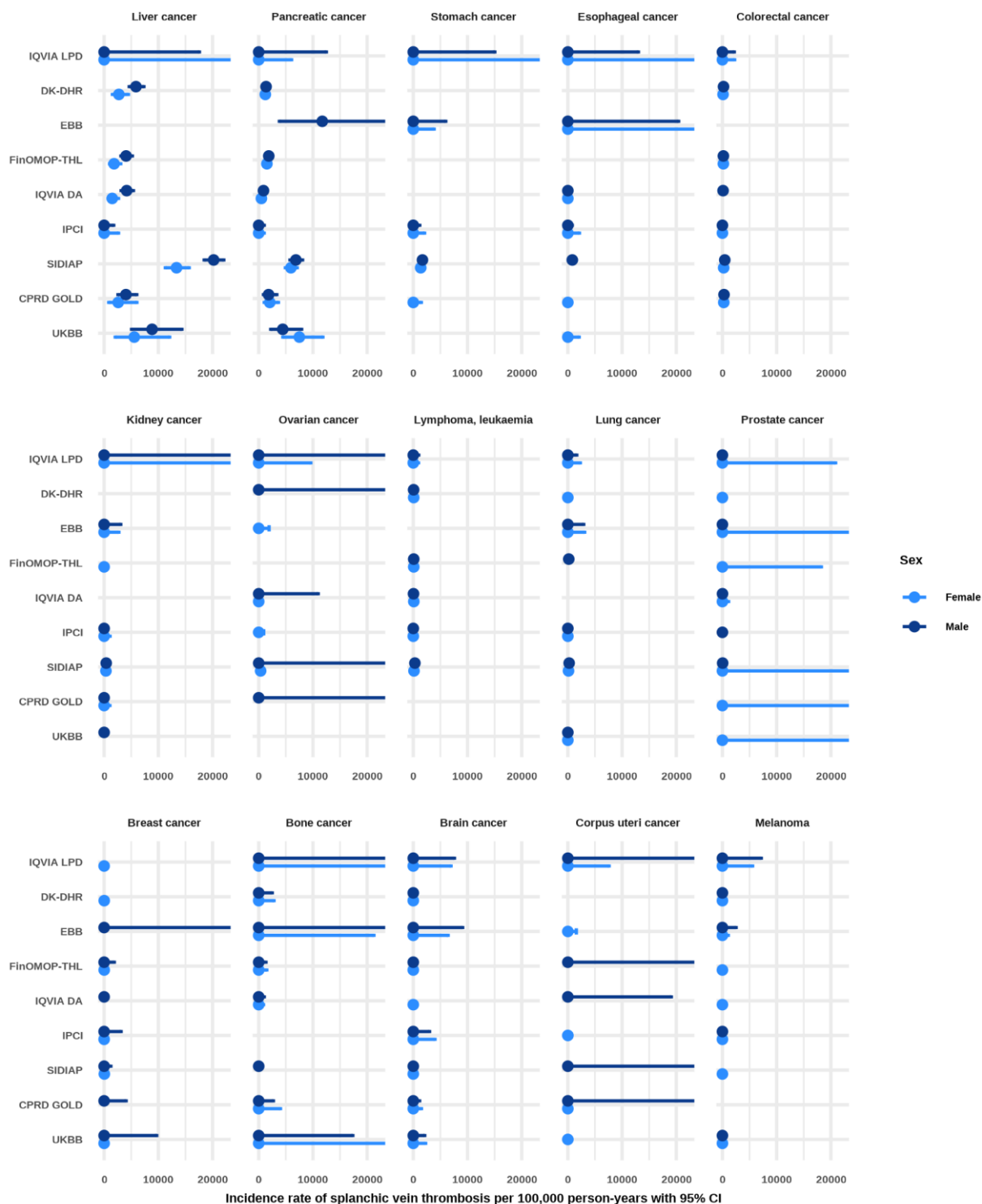
**Figure 11. IRs with 95% CI of venous thromboembolism (VTE – pulmonary embolism (PE) and deep vein thrombosis (DVT) combined) per 100,000 person-years in cancer patients by sex.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



**Figure 12. IRs with 95% CI of pulmonary embolism (PE) per 100,000 person-years in cancer patients by sex.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.



**Figure 13. IRs with 95% CI of splanchnic vein thrombosis (SVT) per 100,000 person-years in cancer patients by sex.**

(Cancer types are ordered by meta-analytical estimate of IRs, 95% CI is cut above maximum IR to improve visualisation and comparison. IRs for outcomes with less than 5 observations were not calculated and omitted from analysis). IQVIA LPD=IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium); DK-DHR=Danish Data Health Registries; EBB=Estonian Biobank; FinOMOP-THL=Finnish Care Register for Health Care; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=Integrated Primary Care Information; SIDIAP=The Information System for the Development of Research in Primary Care; CPRD GOLD=Clinical Practice Research Datalink GOLD; UKBB=UK BioBank.

### **Incidence rates by age group**

Results stratified by age are available in the “Shiny app” ([EUPAS1000000440](#)).

Trends in the IRs between age groups one year after cancer diagnosis were not consistent between data sources and low event counts in subgroups limited the comparison of IRs between age groups. However, an increasing trend of IRs with age was observed in ovarian cancer for VTE and PE:

- The IR of VTE increased with age in ovarian cancer in CPRD GOLD, DK-DHR, FinOMOP-THL, IQVIA DA Germany, SIDIAP, and UKBB. The IRs [95% CI] per 100,000 PY of VTE in ovarian cancer were lowest in IQVIA DA Germany (from 1,977 [987–3,537] in the age group 45 to 54 years to 6,583 [2,842–12,971] in the age group ≥85 years) and highest in UKBB (from 7,298 [3,337–13,854] in the age group 55 to 64 years to 16,275 [9,303–26,429] in the age group 75 to 84 years).
- The IR of PE increased with age in ovarian cancer in CPRD GOLD, DK-DHR, IQVIA DA Germany, SIDIAP, and UKBB, but not FinOMOP-THL. The IRs of PE in ovarian cancer were lowest in IQVIA DA Germany (from 1,780 [853–3,273] in the age group 45 to 54 years to 4,694 [1,723–10,218] in the age group ≥85 years) and highest in UKBB (from 4,780 [1,754–10,404] in the age group 55 to 64 years to 13,989 [7,648–23,471] in the age group 75 to 84 years).

Similar to the IRs stratified by age one year after cancer diagnosis, increases with age were observed in the IRs of VTE in ovarian cancer two years after cancer diagnosis. In line with the overall results, the absolute IRs two years after cancer diagnosis were lower than one year after across the subgroups.

### **Incidence rates by subperiod**

Results stratified by subperiod (2016–2019 and 2020–2022) are available in the “Shiny app” ([EUPAS1000000440](#)).

Comparisons in the IRs between 2016–2019 and 2020–2022 one year after cancer diagnosis were not consistent between data sources and low event counts in subgroups limited the comparison of IRs between 2016–2019 and 2020–2022. Some differences in point estimates were observed across data sources between 2016–2019 and 2020–2022, although the 95% CIs overlapped.

Point estimates of the IR were lower in 2016–2019 than 2020–2022 of the following outcomes [95% CI]:

- DVT in brain cancer (lowest: 936 [512–1,570] in 2016–2019 versus 1,366 [747–2,292] in 2020–2022 in DK-DHR; highest: 3,615 [1,925–6,181] in 2016–2019 versus 5,038 [2,304–9,564] in 2020–2022 in CPRD GOLD);
- PE in prostate cancer (lowest: 466 [355–599] in 2016–2019 versus 861 [672–1,086] in 2020–2022 in SIDIAP; highest: 588 [322–987] in 2016–2019 versus 869 [497–1,411] in 2020–2022 in IPCI), ovarian cancer (lowest: 2,704 [2,019–3,546] in 2016–2019 versus 3,253 [2,407–4,301] in 2020–2022 in IQVIA DA Germany; highest: 6,846 [4,290–10,365] in 2016–2019 versus 9,851 [5,738–15,772] in 2020–2022 in UKBB), and kidney cancer (lowest: 1,528 [1,169–1,963] in 2016–2019 versus 1,510 [1,121–1,991] in 2020–2022 in IQVIA DA Germany; highest: 2,403 [1,280–4,110] in 2016–2019 versus 5,337 [3,050–8,666] in 2020–2022 in UKBB);
- and SVT in pancreatic cancer (lowest: 596 [308–1,041] in 2016–2019 versus 780 [446–1,267] in 2020–2022 in IQVIA DA Germany; highest: 5,521 [4,589–6,588] in 2016–2019 versus 7,505 [6,284–8,894] in 2020–2022 in SIDIAP).

Point estimates of the IR of DVT in oesophageal cancer [95% CI] were higher in 2016–2019 than 2020–2022 (lowest: 1,007 [503–1,801] in 2016–2019 versus 578 [212–1,257] in 2020–2022 in IQVIA DA Germany; highest: 4,621 [3,518–5,961] in 2016–2019 versus 2,437 [1,445–3,852] in 2020–2022 in CPRD GOLD).

## **IRs by stage**

The subpopulation with cancer stage recorded was too small to allow for stratification by cancer stage: this was only available in EBB and for approximately half of the study population in this data source, limiting the ability to meaningfully estimate IRs.

### **10.2.2. Patient characterisation (objective 2)**

#### **Demographics (sex and age) at the time of cancer diagnosis**

Demographic characteristics of patients newly diagnosed with selected cancers are reported by data source for the entire study period (2016–2022) in [Annex V](#).

The percentage of females was highest in corpus uteri cancer (93.3% (IQVIA LPD Belgium) – 100% (DK-DHR, EBB, IPCI, and UKBB)), ovarian cancer (83.3% (IQVIA LPD Belgium) – 100% in EBB, IPCI, and UKBB, and breast cancer (91.3% (IQVIA LPD Belgium) – 99.6% (EBB)).

Apart from corpus uteri, ovarian, breast, and prostate cancer, the sex distribution was most skewed in oesophageal cancer (females: 17.8% (SIDAP) – 31.4% (EBB)), followed by liver cancer (females: 17.1% (IQVIA LPD Belgium) – 54.7% (EBB)) and kidney cancer (females: 32.5% (DK-DHR) – 53.3% (EBB)).

The proportions of females and males were more similar to each other in brain cancer (females: 42.4% (IPCI) – 57.6% (EBB)), colorectal cancer (females: 42.2% (SIDAP) – 62.5% (EBB)), lymphoma and leukaemia (females: 42.8% (IPCI) – 60.0% (EBB)), and pancreatic cancer (females: 47.7% (DK-DHR) – 63.4% (IQVIA LPD Belgium)). Only melanoma was recorded more frequently among females than males, in all data sources except for FinOMOP-THL (females: 48.7% (FinOMOP-THL) – 69.6% (EBB)).

The lowest median [interquartile range] ages were observed among people with melanoma (52 [40–66] (EBB) – 70 [63–75] (UKBB)), breast cancer (58 [49–67] (EBB) – 68 [61–73] (UKBB)), and brain cancer (56 [47–66] (EBB) – 70 [63–74] (UKBB)).

The highest median [interquartile range] ages were observed among people with pancreatic cancer (69 [59–77] (EBB) – 73 [65–80] (CPRD GOLD) and [67–76] (UKBB)), stomach cancer (66 [55–75] (EBB) – 75 [65–82] (CPRD GOLD)), and liver cancer (69 [59–75] (EBB) – 73 [68–76] (UKBB)).

#### **Comorbidities anytime up to 181 days prior to the date of diagnosis of cancer**

Comorbidities anytime up to 181 days prior to diagnosis date in patients newly diagnosed with selected cancers are reported by the data source for the entire study period (2016–2022) in [Annex V](#).

Across all cancers, visual system disorder was overall the most prevalent condition. Its prevalence ranged from 11% IQVIA LPD Belgium in brain cancer to – 88% in EBB in liver cancer. Essential hypertension was the third most prevalent condition in bone cancer (17% (DK-DHR) – 35% (EBB)), and the second most prevalent condition across all other cancers.

In bone cancer, the second most prevalent condition was osteoarthritis (14% (CPRD GOLD) – 55% (EBB)). Osteoarthritis was the third most prevalent condition in the other cancers except liver, lung, and prostate cancer. Its prevalence was lowest in melanoma (10% (IPCI) – 42% (EBB)) and highest in pancreatic cancer (15% (IPCI) – 64% (EBB)). In liver cancer, the third most prevalent condition was diabetes mellitus (24% (IPCI) – 44% (FinOMOP-THL)). Hyperlipidaemia was the third most prevalent condition in lung cancer (9% (IPCI) – 48% (DK-DHR)) and prostate cancer (9% (IPCI) – 40% (IQVIA LPD Belgium)).

Some conditions had a higher prevalence in a particular cancer than other cancers:

- obesity in kidney cancer (counts <5 (IQVIA LPD Belgium) – 28% (EBB)) and corpus uteri cancer (5% (IPCI) – 37% (EBB));

- Chronic obstructive lung disease (21% (FinOMOP-THL) – 29% (DK-DHR and IQVIA LPD Belgium)) in lung cancer;
- and chronic liver disease in liver cancer (7% (IPCI) – 33% (EBB)).

Across all data sources and cancers, 6 conditions were recorded among fewer than 2% of cases: ADHD, Crohn's disease, HIV, RVT, and SVT.

#### Comorbidities 180 days to 1 day prior to diagnosis date

Comorbidities 180 days up to 1 day prior to diagnosis date in patients newly diagnosed with selected cancers are reported by the data source for the entire study period (2016–2022) in [Annex V](#).

Essential hypertension was the second most prevalent condition in liver cancer (0.5% (CPRD GOLD) – 29.3% (EBB)) and lung cancer (0.6% (CPRD GOLD) – 30.9% (IQVIA LPD Belgium)), and the most prevalent condition in all other cancers. Its prevalence was lowest in bone cancer (counts <5 (CPRD GOLD, EBB, IQVIA LPD Belgium, and UKBB) – 12.1% (FinOMOP-THL) and highest in kidney cancer (1.3% (CPRD GOLD) – 36.4% (IQVIA LPD Belgium)). In liver cancer, the most prevalent condition was diabetes mellitus (1.8% (CPRD GOLD) – 27.5% (DK-DHR)). In lung cancer, the most prevalent condition was chronic obstructive lung disease (7.7% (CPRD GOLD) – 24.5% (DK-DHR)),

Besides essential hypertension, these conditions were among the four most prevalent in most cancers:

- visual system disorder (lowest prevalence in bone cancer (0% (IQVIA LPD Belgium)) – 22.6% (EBB) and highest in stomach cancer (2.3% (IQVIA DA Germany) – 20.4% (EBB));
- diabetes mellitus (lowest prevalence in bone cancer (counts <5 (CPRD GOLD, EBB, IQVIA LPD Belgium, and UKBB)) – 6.8% (DK-DHR) and highest in liver cancer (1.8% (CPRD GOLD) – 27.5% (DK-DHR));
- and hyperlipidaemia (lowest prevalence in bone cancer (counts <5 (CPRD GOLD, EBB, IQVIA LPD Belgium, and UKBB)) – 17.4% (DK-DHR) and highest in pancreatic cancer (0.3% (CPRD GOLD) – 28.6% (DK-DHR)).

Exceptions, with other conditions among the four most common, were:

- In bone cancer, the prevalence of osteoarthritis (counts <5 (CPRD GOLD, EBB, IQVIA LPD Belgium, and UKBB) – 11.6% (IQVIA DA Germany)) was among the four highest.
- In oesophageal cancer, the prevalence of gastroesophageal reflux disease (0.8% (IPCI) – 28.6% (EBB)) was among the four highest.
- In liver cancer, the prevalence of chronic liver disease (counts <5 (IQVIA LPD Belgium) – 23.1% (DK-DHR)) was among the four highest.
- In lung cancer, the prevalence of pneumonia (2.8% (CPRD GOLD) – 24.1% (DK-DHR)) was among the four highest.

Some conditions had a higher prevalence in a particular cancer than other cancers:

- Gastrointestinal haemorrhage in colorectal cancer (counts <5 (IQVIA LPD Belgium) – 11.5% (SIDIAP)) and stomach cancer (counts <5 (IQVIA LPD Belgium) – 8.8% (FinOMOP-THL));
- Obesity in corpus uteri cancer (counts <5 (IQVIA LPD Belgium) – 11.1% (DK-DHR));
- Renal impairment in kidney cancer (counts <5 (IQVIA LPD Belgium) – 7.2% (SIDIAP));
- Viral hepatitis in liver cancer (0% (IQVIA LPD Belgium) – 9.3% (EBB));
- Pneumonia in lymphoma and leukaemia (0.8% (CPRD GOLD) – 7.9% (DK-DHR)).

Across all data sources and cancers, 12 conditions were recorded among fewer than 2% of cases: SVT, DVT, PVT, ulcerative colitis, schizophrenia, Parkinson's disease, thromboembolic disorder, Crohn's disease, retinal vein thrombosis broad, HIV, ADHD, and RVT.

### Comorbidities at diagnosis date

Comorbidities at diagnosis date in patients newly diagnosed with selected cancers are reported by the data source for the entire study period (2016–2022) in Annex V. The ranking was similar to what was observed in other time windows.

Essential hypertension was the second most prevalent condition in lung cancer (0.1% (CPRD GOLD) – 28.3% (UKBB)), and the most prevalent condition in all other cancers. Its prevalence was lowest in melanoma (0% (CPRD GOLD)) – 15.4% (IQVIA LPD Belgium) and highest in liver cancer (0% (CPRD GOLD and EBB) – 31.4% (IQVIA LPD Belgium)). In lung cancer, the most prevalent condition was chronic obstructive lung disease (1.4% (CPRD GOLD) – 22.7% (UKBB)). Among the three most prevalent conditions in most cancers were hyperlipidaemia (lowest prevalence in melanoma (0% (CPRD GOLD, EBB, and IPCI)) – 7.7% (IQVIA LPD Belgium) and highest in stomach cancer (0% (CPRD GOLD and IPCI) – 23.8% (IQVIA LPD Belgium)) and diabetes mellitus (lowest prevalence in bone cancer (0% (CPRD GOLD, EBB, IQVIA LPD Belgium, and UKBB)) – 3.7% (SIDIAP) and highest in pancreatic cancer (0.4% (CPRD GOLD) – 17.2% (UKBB)).

Exceptions were:

- In bone cancer, the prevalence of osteoarthritis (0% (IQVIA LPD Belgium) – 8.8% (IQVIA DA Germany)) was among the three highest and higher than the prevalence of diabetes mellitus (0% (CPRD GOLD, EBB, and IQVIA LPD Belgium) – 3.7% (SIDIAP)).
- In corpus uteri cancer, the prevalence of obesity (0% (IPCI) – 14.4% (DK-DHR)) was among the three highest and higher than the prevalence of hyperlipidaemia (0% (EBB) – 10% (SIDIAP)).
- In oesophageal cancer, the prevalence of chronic obstructive lung disease (counts <5 (CPRD GOLD, EBB, IPCI, and IQVIA LPD Belgium) – 6.6% (UKBB)) was among the three highest and higher than the prevalence of hyperlipidaemia (0% (CPRD GOLD, EBB) – 10.9% (SIDIAP)).
- In kidney cancer, the prevalence of renal impairment (0% (IQVIA LPD Belgium) – 12.7% (UKBB)) was among the three highest and higher than the prevalence of diabetes mellitus (0% (CPRD GOLD) – 9% (UKBB)).
- In liver cancer, the prevalence of chronic liver disease (counts <5 (IQVIA LPD Belgium) – 27.5% (SIDIAP)) was among the three highest and higher than the prevalence of hyperlipidaemia (0% (CPRD GOLD) – 13.8% (SIDIAP)).
- In melanoma, the prevalence of visual system disorder (counts <5 (IQVIA LPD Belgium) – 7.4% (SIDIAP)) was among the three highest and higher than the prevalence of diabetes mellitus (counts <5 (CPRD GOLD and EBB) – 3.9% (IQVIA LPD Belgium)).

Some conditions had a higher prevalence in a particular cancer than other cancers:

- gastrointestinal haemorrhage in colorectal cancer (0% (IQVIA LPD Belgium) – 9.4% (SIDIAP)) and stomach cancer (counts <5 (IQVIA LPD Belgium) – 9.9% (SIDIAP));
- viral hepatitis (counts <5 (CPRD GOLD, EBB, IPCI, and IQVIA LPD Belgium) – 15.1% (SIDIAP)) and SVT (0% (IPCI and IQVIA LPD Belgium) – 8.1% (SIDIAP) in liver cancer;
- pneumonia in lung cancer (0.7% (CPRD GOLD) – 8.5% (SIDIAP));
- and pneumonia in lymphoma and leukaemia (0.4% (CPRD GOLD) – 4.3% (SIDIAP)).

Across all data sources and cancers, 11 conditions were recorded among fewer than 2% of cases: Parkinson's disease, psoriasis, thromboembolic disorder, HIV, schizophrenia, ulcerative colitis, Crohn's disease, ADHD, retinal vein thrombosis broad, pelvic vein thrombosis, and retinal vein thrombosis narrow.

### Medications at diagnosis date

Medications at diagnosis date in patients newly diagnosed with selected cancers are reported by the data source for the entire study period (2016–2022) in [Annex V](#). The prevalence of antineoplastic agents was lowest in bone cancer (counts <5 (CPRD GOLD, DK-DHR, EBB, FinOMOP-THL, IPCI, IQVIA LPD Belgium, and UKBB) – 1.3% (SIDIAP)) ([Table 101](#)) and highest in lymphoma and leukaemia (0% (UKBB) – 15.3% (IQVIA LPD Belgium)) ([Table 110](#)).

Across most cancers, the three medications with the highest prevalence were:

- agents acting on the renin angiotensin system (lowest prevalence in bone cancer (0% (UKBB)) – 27.1% (SIDIAP) and highest in liver cancer (0% (UKBB) – 41.8% (SIDIAP));
- drugs for acid-related disorders (lowest prevalence in melanoma (counts <5 (UKBB)) – 28.0% (SIDIAP) and highest in stomach cancer (counts <5 (UKBB) – 63.0% (SIDIAP));
- and lipid-modifying agents (lowest prevalence in bone cancer (0% (UKBB)) – 27.8% (IQVIA LPD Belgium) and highest in lung cancer (counts <5 (UKBB) – 39.8% (CPRD GOLD)).

Exceptions were:

- In brain cancer, the prevalence of antiepileptics (0% (UKBB) – 29.8% (SIDIAP)) was among the three highest and higher than the prevalence of lipid-modifying agents (0% (UKBB) – 26.1% (SIDIAP)).
- In liver cancer, the prevalence of diuretics (0% (UKBB) – 33% (DK-DHR)) was among the three highest and higher than the prevalence of lipid-modifying agents (0% (UKBB) – 33.1% (CPRD GOLD)).
- In lymphoma and leukaemia, the prevalence of antithrombotic agents (counts <5 (UKBB) – 28.3% (DK-DHR)) was among the three highest and higher than the prevalence of lipid-modifying agents (0.2% (UKBB) – 27.8% (CPRD GOLD)).
- In ovarian cancer, the prevalence of antithrombotic agents (0% (UKBB) – 46.3% (IQVIA LPD Belgium)) was among the three highest and higher than the prevalence of lipid-modifying agents (0% (UKBB) – 25.9% (IQVIA LPD Belgium)).
- In pancreatic cancer, the prevalence of opioids (counts <5 (UKBB) – 33.6% (FinOMOP-THL)) was among the three highest and higher than the prevalence of lipid-modifying agents (0% (UKBB) – 35.1% (SIDIAP)).

Some medications had a higher prevalence in a particular cancer than other cancers:

- anti-inflammatory and antirheumatic products (0% (UKBB) – 24.2% (FinOMOP-THL) and opioids (0% (EBB and UKBB) – 28.6% (CPRD GOLD)) in bone cancer;
- opioids in lung cancer (counts <5 (UKBB) – 27% (IQVIA LPD Belgium));
- antidepressants in breast cancer (counts <5 (UKBB) – 19.9% (SIDIAP));
- and drugs for obstructive airway diseases in lung cancer (0% (UKBB) – 39% (SIDIAP)).

Across all data sources and cancers, antipsoriatics and psychostimulants for ADHD were recorded among fewer than 2% of cases.

### Medications 1 to 90 days after diagnosis date

Medications 1 to 90 days after diagnosis date in patients newly diagnosed with selected cancers are reported by the data source for the entire study period (2016–2022) in [Annex V](#).

In kidney cancer, melanoma, and prostate cancer, the most prevalent medication was agents acting on the angiotensin renin system. In corpus uteri cancer and ovarian cancer, the most prevalent medication was antithrombotic agents. Across all other cancers, the most prevalent medication was drugs for acid-related disorders. The prevalence of antineoplastic agents was lowest in prostate cancer (counts <5 (UKBB) – 7.6% (DK-DHR)) and highest in brain cancer (counts <5 (CPRD GOLD, IQVIA LPD Belgium, and UKBB) – 43.4% (DK-DHR)).

Some medications had a higher prevalence in a particular cancer than other cancers:

- opioids in bone (0% (UKBB) – 57.4% (FinOMOP-THL)), oesophageal (0.9% (UKBB) – 60.5% (FinOMOP-THL)), liver (counts <5 (UKBB) – 62.6% (FinOMOP-THL)), lung (1.4% (UKBB) – 58.9% (CPRD GOLD)), pancreatic (1.4% (UKBB) – 73.7% (FinOMOP-THL)), and stomach cancer (1.2% (UKBB) – 53.8% (FinOMOP-THL))
- antiepileptics in brain cancer (1.2% (UKBB) – 56.0% (SIDIAP));
- diuretics in liver cancer (counts <5 (UKBB) – 48.3% (DK-DHR));
- and drugs for obstructive airway diseases in lung cancer (1.0% (UKBB) – 49.0% (SIDIAP)).

Across all data sources and cancers, psychostimulants for ADHD and antipsoriatics were recorded among fewer than 2% of cases.

### Medical procedures 1 to 90 days after diagnosis date

Medical procedures 1 to 90 days after diagnosis date in patients newly diagnosed with selected cancers are reported by the data source for the entire study period (2016–2022) in [Annex V](#).

The prevalence of surgical procedure was lowest in lymphoma and leukaemia (0% (IQVIA DA Germany)) – 42.3% (UKBB) and highest in corpus uteri cancer (counts <5 (IQVIA DA Germany and IQVIA LPD Belgium) – 91.9% (EBB)) and melanoma (counts <5 (IQVIA DA Germany and IQVIA LPD Belgium) – 95.5% (DK-DHR)).

The prevalence of radiotherapy was lowest in ovarian cancer (0% (DK-DHR, FinOMOP-THL, IPCI, IQVIA DA Germany, IQVIA LPD Belgium, SIDIAP)) – counts <5 (CPRD GOLD, EBB, UKBB)) and highest in brain cancer (0% (DK-DHR, FinOMOP-THL, IPCI, IQVIA DA Germany, IQVIA LPD Belgium, and SIDIAP) – 43.9% (EBB)).

Bone marrow transplantation in the first 90 days after diagnosis was recorded among fewer than 1% of cases of lymphoma and leukaemia.

### Large-scale characterisation

All common conditions, medications and procedures were assessed per cancer and per data source in the relevant time windows. Results of the large-scale characterisation are available in the Shiny app ([EUPAS1000000440](#)). In general, large-scale characterisation reflected the conditions, medication and procedures used which describes common comorbidities, symptoms and symptomatic treatment before the diagnosis and conditions, and diagnostic procedures related to diagnosis on date of cancer diagnosis.

## 11. DISCUSSION

### 11.1. Key results

Overall, our study included 975,962 cancer patients across nine data sources and eight countries in Europe. The most frequent cancers were breast (173,017) and prostate cancer (154,254), followed by colorectal cancer (116,633) and haematological malignancies (116,070).

Across all data sources and cancers, 47,076 thromboembolic events were included in the calculation of the IRs one year after cancer diagnosis.

Highest IRs for the most outcomes were observed in pancreatic cancer, oesophageal cancer, liver and stomach cancer, lung cancer, brain cancer and ovarian cancer, and lowest in melanoma, breast, and prostate cancer. Across all data sources, the outcome with the highest combined IR one year after cancer diagnosis was VTE. The combined IR [95% CI] per 100,000 PY of VTE ranged from 597 [491–726] ( $I^2=51.1\%$ ) in melanoma to 11,607 [7,574–17,787] ( $I^2=95.2\%$ ) in pancreatic cancer.

Across all cancers, except for bone and liver cancer, the outcome with the second-highest combined IR was PE. The IR [95% CI] per 100,000 PY of PE ranged from 389 [297–511] ( $I^2=71.1\%$ ) in melanoma to 8,671 [5,578–13,479] ( $I^2=96.9\%$ ) in pancreatic cancer. Across all cancers, except for bone and liver cancer, the outcome with the third-highest combined IR was DVT. The IR [95% CI] per 100,000 PY of DVT ranged from 239 [180–318] ( $I^2=51.1\%$ ) in melanoma to 3,592 [2,081–6,201] ( $I^2=95.2\%$ ) in pancreatic cancer. In all cancers except for brain, breast, prostate, bone, and pancreatic cancer, the outcome with the lowest combined IR was PVT. The IR [95% CI] per 100,000 PY of PVT ranged from 239 [180–318] ( $I^2=51.1\%$ ) in melanoma to 3,592 [2,081–6,201] ( $I^2=95.2\%$ ) in pancreatic cancer. The IRs of thromboembolic events two years after cancer diagnosis were similar to those one year after, but with lower absolute IRs.

Stratification of IRs by age group, sex, and study period was limited by the low event counts in some subgroups and comparisons were not consistent between all data sources. However, despite overlap in 95% CIs, some differences in point estimates between subgroups were observed across multiple data sources and after one, as well as two years of follow-up.

Firstly, stratified by age, the IRs of VTE in ovarian cancer increased with increasing age. Secondly, stratified by sex, IRs were lower among females than males for: DVT in brain cancer, VTE in brain cancer and melanoma, PE in melanoma and brain cancer, and SVT in liver cancer and colorectal cancer; and IRs were higher among females than males for: PE in stomach cancer and DVT, VTE, and PE in liver cancer. Thirdly, stratified by calendar period IRs were slightly lower in 2016–2019 than 2020–2022 for: DVT in brain cancer, PE in prostate cancer, and SVT in pancreatic cancer, while the IRs were higher of DVT in oesophageal cancer in 2016–2019 than 2020–2022.

Cancer patient's characteristics were also described. Across all data sources except for EBB, the proportion of females was smaller than males in oesophageal, liver, kidney, stomach, bone, and lung cancer. The proportions of females and males were more similar to each other in brain cancer, colorectal cancer, lymphoma and leukaemia, and pancreatic cancer. Melanoma was recorded more frequently among females than males, in all data sources, except for FinOMOP-THL (females: 48.7% (FinOMOP-THL) – 69.6% (EBB)).

The lowest median [interquartile range] ages were observed among people with melanoma (52 [40–66] (EBB) – 70 [63–75] (UKBB)), breast cancer (58 [49–67] (EBB) – 68 [61–73] (UKBB)), and brain cancer (56 [47–66] (EBB) – 70 [63–74] (UKBB)). The highest median [interquartile range] ages were observed among people with pancreatic cancer (69 [59–77] (EBB) – 73 [65–80] (CPRD GOLD) and [67–76] (UKBB)), stomach cancer (66 [55–75] (EBB) – 75 [65–82] (CPRD GOLD)), and liver cancer (69 [59–75] (EBB) – 73 [68–76] (UKBB)).

The most prevalent conditions across all cancers anytime up to 181 days prior to cancer diagnosis were visual system disorder, essential hypertension, and osteoarthritis. The following conditions stood out because of their relatively high prevalence in a particular cancer anytime up to 181 days prior to the cancer diagnosis: obesity in kidney cancer, chronic obstructive lung disease in lung cancer, and chronic liver disease in liver cancer.

The most prevalent conditions across most cancers 180 days up to 1 day prior to cancer diagnosis were essential hypertension, diabetes mellitus, visual system disorder, and hyperlipidaemia. The following conditions stood out because of their relatively high prevalence in a particular cancer 180 days up to 1 day prior to cancer diagnosis: chronic obstructive lung disease and pneumonia in lung cancer, osteoarthritis in bone cancer, gastroesophageal reflux disease in oesophageal cancer, chronic liver disease and viral hepatitis in liver cancer, gastrointestinal haemorrhage in colorectal cancer and stomach cancer, obesity in corpus uteri cancer, renal impairment in kidney cancer, and pneumonia in lymphoma and leukaemia.

The most prevalent medications across most cancers on the date of cancer diagnosis were agents acting on the renin angiotensin system, drugs for acid-related disorders, and lipid-modifying agents. The following medications stood out because of their relatively high prevalence in a particular cancer on the date of cancer diagnosis: antiepileptics in brain cancer, diuretics in liver cancer, antithrombotic agents in lymphoma and leukaemia, antithrombotic agents in ovarian cancer, opioids in pancreatic cancer, anti-inflammatory and antirheumatic products in bone cancer, opioids and drugs for obstructive airway diseases in lung cancer, and antidepressants in breast cancer.

The most prevalent medications 1 to 90 days after the cancer diagnosis varied between cancers: agents acting on the angiotensin renin system were the most prevalent in kidney cancer, melanoma, and prostate cancer; antithrombotic agents were the most prevalent in corpus uteri cancer and ovarian cancer; and drugs for acid-related disorders were the most prevalent across all other cancers.

The following medications stood out because of their relatively high prevalence in a particular cancer 1 to 90 days after cancer diagnosis: opioids in bone, oesophageal, liver, pancreatic, and stomach cancer; antiepileptics in brain cancer; diuretics in liver cancer; and drugs for obstructive airway diseases in lung cancer.

The prevalence of antineoplastic agents on the date of cancer diagnosis was lowest in bone cancer and highest in lymphoma and leukaemia. In the time period from 1 to 90 days after the cancer diagnosis, the prevalence was lowest in prostate cancer and highest in brain cancer.

The prevalence of surgical procedure 1 to 90 days after cancer diagnosis was lowest in lymphoma and leukaemia and highest in corpus uteri cancer and melanoma. The prevalence of radiotherapy 1 to 90 days after cancer diagnosis was lowest in ovarian cancer and highest in brain cancer. Across all data sources and cancers, bone marrow transplantation was recorded among fewer than 1% of cases.

## 11.2. Limitations of the research methods

The study was conducted using routinely collected health care data, and so data quality aspects must be considered. In particular, the identification of cancer patients and thromboembolic events may vary across data sources. While relatively few false positives are expected, false negatives may be more likely, especially for primary care data sources that lack patient-level linkage to secondary care data. We expect misclassification to be minimal in registry data sources (DK-DHR, EBB, FinOMOP-THL, and UKBB) and in the primary care data sources where cancer diagnoses have been previously validated (CPRD GOLD, SIDIAP). Underestimation of thromboembolic events is also possible, particularly for rare events with complex diagnoses, such as RVT and SVT.

Given the large number and diverse nature of participating data sources, it is important to note that differences in patient representations might have arisen from disparate coding practices and specifics of

data capture. The granularity or detail of concepts representing clinical facts can vary across source terminologies (e.g., ICD-10, Read codes), influencing how information is later transformed into standardised vocabularies(11). The preliminary code lists created to identify cancer patients include codes from standard vocabularies used in cancer registries, such as ICD-O-3 codes. However, most data sources had information on cancer diagnoses using SNOMED codes, which may not be granular enough to cover all the topology and histology details of cancer (12). ICD-O-3 codes were only available at DK-DHR, EBB, and UKBB.

In addition, for the calculation of incidence rates (Objective 1), we applied a one-year washout to exclude patients who experienced the thromboembolic events under study prior to index date. Given that acute thromboembolic events can be the first manifestation of an occult malignancy, patients with thromboembolic events who are subsequently diagnosed with cancer may have been missed.

Finally, as suggested by previous studies, consideration should be given to the sources of heterogeneity between data sources, especially in the presence of large variability in incidence rates of thromboembolic events between data sources, as well as between age groups and gender strata, which warrants the need for stratification and may limit the interpretation of the combined estimate (13).

### 11.3. Interpretation

Overall, our study included 975,962 cancer patients across nine data sources from eight countries in Europe. Notably, more than 250,000 patients were included in the IQVIA DA Germany data sources, followed by DK-DHR in Denmark (approximately 196,000), FinOMOP-THL in Finland (181,766), and SIDIAP in Spain (180,991). Other data sources contributed from 5,132 (EBB) to 87,329 (CPRD GOLD) cancer patients to our study. To date, this is one of the largest cohort studies to explore the incidence of venous thromboembolic events in cancer patients.

The distribution of cancer patients was in line with the burden of selected cancers in Europe. Out of all 975,962 included individuals with cancer, the majority had breast (173,017; 17.7%) and prostate cancer (154,254; 15.8%), followed by colorectal cancer (116,633; 12.0%) and haematological malignancies (116,070; 11.9%). Only 3,328 (0.3%) patients with bone cancer were included in our study; however, this cancer type was the only one that could not be identified in one of the data sources (IPCI), suggesting possible difficulties in identifying rare cancer types in primary healthcare (14).

Overall, at least 32,700 VTE were identified across all data sources and individuals with cancer of any type, more than 9,000 in SIDIAP, more than 7,000 in FinOMOP-THL, and more than 6,000 in DK-DHR. The absolute number of PE events was the highest among other thromboembolic events in the study, exceeding 18,900 cases, followed by DVT (more than 9,900) and SVT (2,288); however, the numbers of cases of RVT and PVT were much lower in our study. Previous research mainly focused on DVT and PE (defined as VTE) (15,16). However, we also included relatively rare thromboembolic events, such as RVT and PVT, which were still identified across several data sources, and incidence rates for these events could be obtained.

The highest incidence rates for PE, DVT and other thromboembolic events were observed in gastrointestinal cancers: pancreatic cancer, oesophageal, and stomach cancer; lung cancer, brain cancer, and ovarian cancer. These results align well with previous findings from large cohort studies. In the cohort of cancer patients in the Veterans Affairs Health Care System, the highest incidence rates were observed among patients with solid tumours: patients with pancreatic cancer, brain cancer, and gastric and oesophageal cancer (17,18). In contrast, patients with melanoma, prostate cancer, and thyroid cancer had the lowest incidence of VTE. In a recent meta-analysis, pancreatic cancer was associated with higher-than-average VTE risk. Other cancer types with high VTE risk were brain and ovarian cancers (19).

The reasons why certain cancer types have a higher risk of VTE incidence are multifactorial. In our study, we were unable to account for the stage of the cancer at diagnosis, which is considered a key predictor of a

higher incidence of VTE across different cancer types (17). While a similar AJCC/UICC classification is used across different malignancies, similar stage categories are not comparable between cancer types. The prognosis for early-stage pancreatic cancer is less favourable than for early-stage prostate or breast cancer. Therefore, the higher incidence rates of VTE are more common in cancers that have a less favourable prognosis.

Treatment is another critical factor that can affect the risk of VTE in cancer patients. Different treatment options of cancer patients, including surgery, chemotherapy, immunotherapy, and targeted therapy, carry additional risk of thromboembolic events (9,20). In our study, longer follow-up was associated with a lower incidence of VTE for all cancer types, suggesting a higher risk of these events in the first year compared to the second year after diagnosis. This is in line with previous findings and can partially be explained by the intensity of treatment in the first year after diagnosis (8,21). At the same time, the selection of patients with less advanced and lethal diseases by the second year after diagnosis can also contribute to this finding.

Despite the presence of various data sources that represent different settings, ranking in terms of incidence rates within different cancer types was similar, and meta-analyses of the results for each combination of cancer type and venous thromboembolic event likely reflect an average risk across cancer patients in Europe recorded in different data sources. Between-study heterogeneity was pronounced for all meta-analyses, which likely reflects the differences between data sources in terms of the included cancer patients and the ability to collect information on thromboembolic events. However, when we compared different cancer types, the results in the meta-analytical estimates were consistent with those in the individual data sources. For example, incidence rates of VTE were highest in pancreatic cancer compared to other cancers across all data sources.

The results of our study can be compared to those that used the same data sources we included. Previously, CPRD GOLD, IQVIA DA Germany, IPCI, and SIDIAP were used in the study to assess the risk of thromboembolic events in the general population (22). In this study, among other outcomes, the incidence of DVT, SVT, and PE was estimated among the general population between 2017 and 2019. The highest incidence rates of PE and DVT were observed in IPCI, and the lowest in IQVIA DA Germany. In our study, the lowest incidence rates among those data sourced were also observed in IQVIA DA Germany; however, higher rates were observed in CPRD GOLD. The CPRD GOLD data source was also used in studies to describe cancer incidence trends in the UK (23) and probably has more complete information on cancer patients (24) than other primary healthcare data sources.

In addition to estimating the incidence rates of thromboembolic events, we performed a characterisation of cancer patients in terms of demographics, comorbidities, and medications used. Compared to patients with haematological malignancies, patients with solid tumours were older. Sex distribution was in line with expectations, with oesophageal, stomach, bone, and kidney cancer being more common in men than in women (25). We observed the presence of female patients with prostate cancer in several data sources (e.g., DK-DHR 2.2% in 2016–2019 and 6.6% in 2020–2022). Previous observational research highlighted the presence of females in the data source of prostate cancer patients (26). A detailed examination of a sample of these clinical records in this study revealed some errors in the use of diagnostic codes (e.g., women with breast cancer that were erroneously introduced as prostate cancer patients). However, it is also important to acknowledge the presence of transgender females in the EHR. The risk of prostate cancer in transgender women could be the same as that in the male populations (27); however, participation of transgender persons in screening programmes is limited, suggesting advanced stage at cancer diagnosis and higher risk of worse outcomes (28).

In our study, we characterised cancer patients in terms of several pre-specified comorbidities before cancer diagnosis. Interpretation of the prevalence of these conditions should be careful, as they may represent different categories and may be linked to the following cancer diagnosis. Some conditions that were

prevalent across all cancer types likely reflected the prevalence of these conditions in the general population within similar demographic groups. For example, the most prevalent conditions in our study were visual system disorders, osteoarthritis, and essential hypertension. Still, some conditions had relatively high prevalence in some cancer types compared to other cancer types in our study. Comorbidities that were selected for characterisation could represent possible risk factors for the development of cancer but could also be markers or consequences of a malignant tumour that is likely to be present before the formal medical diagnosis. Some conditions captured in data sources may also represent primary non-cancer diagnoses based on non-specific symptoms that later will be considered as cancer.

For example, we observed a higher relative prevalence of obesity in corpus uteri cancer compared to other cancer types. Obesity is a well-established risk factor for the development of corpus uteri cancer. While globally around 3.6% of all cancers are attributed to high body mass index, corpus uteri cancer was associated with the highest population attributable fraction globally, i.e., 34% (29). We also observed that patients with lung cancer had a higher prevalence of chronic obstructive lung disease compared to other cancer types. Both chronic obstructive lung disease and lung cancer share a common cause: tobacco smoking, and lung cancer is one of the most common causes of death in patients with chronic obstructive lung disease (30). Pneumonia was much more common in lung cancer patients in our study, suggesting that a shared etiological factor can cause both, but also that lung cancer patients can be diagnosed at an advanced stage following pneumonia diagnosis, which can be a first manifestation of the malignant disease. Finally, chronic liver disease and hepatitis were more prevalent in liver cancer patients. Major risk factors for liver cancer include chronic infection with the hepatitis B virus and the hepatitis C virus (31).

Characterisation by medication used also revealed some groups of drugs that were more commonly used in specific cancer types. For example, in brain cancer, there was a higher prevalence of antiepileptics and, in pancreatic cancer, opioids. Both groups of drugs are likely to be used as part of symptomatic care. For example, pain is the primary symptom of pancreatic cancer (32). Opioids were also commonly used in cancer types that are more likely to be diagnosed at an advanced stage and thus require pain management: bone, oesophageal, liver, lung, pancreatic, and stomach cancer.

Antithrombotic agents were commonly used in patients with haematological malignancies and ovarian cancer patients, reflecting current guidelines on VTE prophylaxis in cancer patients. VTE prophylaxis currently is based on the Khorana score, (33) which lists both ovarian cancer and haematological malignancies at a higher risk of VTE.

Finally, we characterised the patient in terms of procedures in the first 90 days after cancer diagnosis, revealing that surgical procedures are more likely to be conducted in corpus uteri cancer and melanoma patients, while radiotherapy is common in brain cancer patients, which reflects current guidelines and initial treatment options in the first months after diagnosis. Surgical procedures were also more common in solid cancer types that are more likely to be diagnosed at an earlier stage.

#### 11.4. Generalisability

We utilised electronic healthcare data from nine data sources across eight European countries, thereby enhancing the generalizability of our findings to the broader European region.

These data sources included primary care records, national health registries, and claims data sources or a combination of those. The observed heterogeneity in our results suggests differences in follow-up duration, data collection practices, and cancer diagnostic and management practices. While these differences may limit comparability within Europe, they can further constrain generalisability to non-European settings, where healthcare systems, population characteristics, and data infrastructure may differ substantially.

## 12. CONCLUSION

In this large multinational cohort study, which incorporated data from nine data sources across eight countries in Europe, we estimated the incidence of thromboembolic events among patients with selected cancers. PE and VTE were the most frequently observed thromboembolic events. The highest incidence rates of thromboembolic events were seen in patients with lung, brain, ovarian, and gastrointestinal cancers, particularly pancreatic, oesophageal, and stomach cancers and lowest in melanoma, prostate, and breast cancer. Finally, the characterisation of cancer patients provided insights into prevalent comorbidities and concomitant medication use across cancer types, suggesting differences in cancer patient profiles.

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## 14. ANNEXES

### ANNEX I. Data sources description

#### IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium)

Belgium Longitudinal patient data (LPD) is collected from GP prescribing systems and contains patient records on all signs and symptoms, diagnoses, and prescribed medications. The information recorded allows patients and doctors to be monitored longitudinally. Data are recorded directly in real-time during patient consultations via a practice management software system. It is used in studies to provide various market insights such as treatment trends, patient pathway analysis, and treatment compliance. The panel of contributing physicians (a stable 300 GPs) is maintained as a representative sample of Belgium's primary care physician population according to three criteria known to influence prescribing: age, sex, and geographical distribution. Currently, the database covers 1.1 M cumulative patients from 2012 through to the present. The panel consists of a stable 300 GPs that are geographically well-spread. The total number of active GPs in Belgium is 15.602. The regional geographical spread of physicians in the LPD data is also representative of the distribution across the country: 57% GPs in the North (compared to 54% nationally), 31% in the South (33% nationally) and 12% in Brussels (13%). The data provider has more than 2.250 GPs under contract, so a replacement is easily found in case of a dropout. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is needed for drug utilisation studies.

#### Danish Data Health Registries (DK-DHR)

Danish health data is collected, stored, and managed in national health registers at the Danish Health Data Authority. It covers the entire population of Denmark, which makes it possible to study the development of diseases and their treatment over time. Data on gender, age and geography in Danish health data is complete due to mandatory reporting on all patients from birth to death in all hospitals and medical clinics. Personal identification numbers link data across registers, so health data on all Danes are available throughout their lives, regardless of whether they have moved around the country. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. The legislation ensures a balance between personal data protection and use for research purposes. In the present database, we have access to the following registries for the entire Danish population of 5.9 million persons from 1.1.1995: The Central Person Registry (CPR), The National Patient Registry (LPR), The Register of Pharmaceutical Sales (LSR), The National Cancer Register (CAR), The Cause of Death registry (DAR), The Clinical Laboratory Information Register (LAB), COVID-19 test and vaccination Registries (SSI-OVD, SSI-DDV), The complete Vaccination registry (DDV\_all).

#### Estonian Biobank (EBB)

The EBB collects data in Estonia and is maintained at the Estonian Genome Center, University of Tartu. It is a nationwide database, and the network of recruitment offices for EBB covers all 15 counties of the country. The Estonian Genome Project Foundation initiated the Estonian Biobank Project in 1999, which was transformed into the Estonian Genome Center of the University of Tartu (EGCUT) in 2007. The data is available from 2004 onwards. The Estonian Biobank cohort is a volunteer-based sample of the Estonian resident adult population. EBB represents an Estonian population-based cohort size of 52,000 participants aged 18 years and older recruited at GP offices, private practices, and hospitals or in the recruitment offices of the Estonian Genome Center. The age, sex, and geographical distribution closely reflect those of the Estonian adult population and encompass nearly 5% of the population. Overall, the representation of men in the biobank is 3.4%, and women's is 5.5%. Older people tend to participate less frequently; however, all age groups are well represented. The database obtains data from the biobank records. All participants have undergone a standardised health assessment, including providing blood samples for purification of DNA, white blood cells, and plasma, and completed a questionnaire covering various health-related topics, such

as lifestyle, diet, and clinical diagnoses. Diseases and health problems are recorded as ICD-10 codes and prescribed medicine according to the ATC classification.

For all starting data collectors, the first ten questionnaires were monitored for completeness and illogical answers, and after that, 10% were selected randomly for monitoring; 21% were inspected and corrected when necessary. From the monitored questionnaires, 99% were classified as high quality, meaning all the fields were filled in, and the answers appeared logical. Follow-up data are available via linkage with national health-related registries and re-examination of participants. Furthermore, electronic health records are updated every half year for phenotypic outcome information. The EBB database is regularly linked with national registries, hospital databases, and the national health insurance fund database, which holds treatment and service bills. Vital status (death date and causes) is obtained from the Causes of Death Registry. Participation in the EBB cohort is voluntary; therefore, the biobank does not represent a classical random sample and could be subject to recruitment bias. Although recruitment was open to everyone, there is a disproportion of ethnic Estonians and ethnic Russians in the biobank, with Estonians being overrepresented and Russians underrepresented. Also, the limited depth of collected data can sometimes limit the number of projects in which the data can be used

#### Finnish Care Register for Health Care (FinOMOP-THL)

The Finnish Care Register for Health Care (fi: Hoitoilmoitusrekisteri) continues the former Hospital Discharge Register, which originally gathered data on hospital discharge. The Care Register has comprehensive data on services and service users nationwide, including Finnish public inpatient and outpatient primary and specialised care. Since 1998, the register has covered public outpatient and inpatient specialised care and private inpatient care (TerveysTHL). Since 2011, the register has covered public primary care (AvoTHL). Since 2020, the register has covered private outpatient care and occupational care. The CDM is currently produced from the data collection on inpatient and outpatient specialised care (TerveysTHL) and is limited to observation periods commencing after 01/01/2015. The Register of Primary Health Care Visits (AvoTHL) is currently outside the scope of the CDM and will be added to CDM during the remainder of 2023. The inclusion of data collected before 2015 is also being planned. The National Population Registry is also used as a source for the CDM database. The National Population Registry data forms the basis for forming the patient population. This ensures up-to-date location (municipality of residence) of patients and complete death occurrences (although not the cause of death). Using the complete population as a basis for the person table also facilitates calculations on a population level, e.g. incidence rates. The database has been used to assess the quality of cancer registry data in Finland.

#### IQVIA Disease Analyzer Germany (IQVIA DA Germany)

Germany DA is collected from extracts of patient management software used by GPs and specialists from ambulatory care settings. Patients visiting multiple providers are not cross-identified for data protection reasons and, therefore, recorded as separate in the system. Dates of service include from 1992 through the present. The first and last consultation dates define observation time. Germany has no mandatory GP system, and patients can choose specialists. Drugs are recorded as prescriptions of marketed products. No explicit registration or approval is needed for drug utilisation studies.

#### Integrated Primary Care Information (IPCI)

The database collects data in the Netherlands. It was started in 1992 by the Department of Medical Informatics of the Erasmus University Medical Center in Rotterdam, the Netherlands. The current database contains patient records from 2006 onwards when the size of the database started to increase significantly. IPCI is a nationwide Dutch database. However, it mainly covers the central part of the country, including the most densely populated and non-urban areas. The IPCI database contains data from records of general practitioners' (GPs) practices. It contains information on all patients registered with GPs responsible for non-emergency care and referrals. More than 99% of the Dutch population has health insurance, and

almost all citizens are registered with a general practitioner. Over 12 months, around 78% of the population has at least one contact with their GP. IPCI included around 350 GP practices out of around 5000 in the country (~ 7%). The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex.

IPCI obtains data from computer-based patient records. Patient-level data includes demographic information, complaints and symptoms, diagnoses, laboratory test results, lifestyle factors, and correspondence with secondary care, such as referral and discharge letters. Dutch GPs use the International Classification of Primary Care (ICPC-1) coding for complaints, symptoms, and diagnoses, an international standard developed and updated by the World Organization of Family Doctors (WONCA) International Classification Committee.

Extensive quality control steps are performed before each data release. These include comparing patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g., reliability of birth and mortality rates) and medical data (e.g., availability of durations of prescriptions, completeness of laboratory results, availability of hospital letters and prescriptions, the proportion of patients with blood pressure measurement, etc.).

IPCI is not linked with other databases. Vital status (death date and cause) is collected based on GP records. The main limitation is that IPCI is limited to GP records, and although it contains information on referrals and discharge letters, it may not capture specific hospital information.

#### The Information System for the Development of Research on Primary Care (SIDIAP)

The database collects data in Spain and is maintained by the SIDIAP team, supported by the Catalan Health Institute and the Institute for Primary Health Care Research Jordi Gol i Gurina. It contains patient records from 2005 onwards and is updated every six months. It is a regional database covering the region of Catalonia. SIDIAP collects data in the primary care setting. It contains data from the population registered in over 280 primary care practices throughout Catalonia. Approximately 80% of the population registered with primary care is covered by SIDIAP. The demographic composition within SIDIAP closely mirrors that of the broader Catalan population, encompassing a representative spectrum of geographic distribution, age, and sex proportions. SIDIAP obtains data from electronic health records. The dataset covers demographics, all-cause mortality, disease diagnoses, prescription and dispensation records of drugs, results of laboratory tests, socio-economic indicators, vaccination records, lifestyle information, parent-child linkage, and various clinical parameters. Diseases are classified under the International Classification of Diseases 10th revision (ICD-10). Quality checks have been implemented, including central identification of duplicate patient IDs and visual inspection for temporal patterns in the registry of a certain variable. Furthermore, the data undergoes assessment for availability (longitudinally and reliability), plausibility (range checks and unusual values), and visualisation tools. Specifically, for biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed. SIDIAP is linked with numerous other databases. It integrates data from external sources, including laboratory biomarker data, drug prescription and dispensation records, hospital discharge records, mental health centres, and other specific disease registries. Vital status (death date and cause) is collected through linkage with the civil registry. The main limitation is that SIDIAP covers only primary health care records. However, it is combined with data from various other sources through effective linkages. This study will be conducted using primary care data linked to hospital discharge data. The SIDIAP includes 76% of the cancer diagnoses in the cancer registries but includes a considerable number of cases that are not in the registries (39%) and can be used for studies related to cancer.

### Clinical Practice Research Datalink GOLD (Oxford) (CPRD GOLD)

The Clinical Practice Research Datalink (CPRD) collects data from three primary care electronic patient record (EPR) systems: Vision®, EMIS Web®, and TPP®. Vision® and EMIS Web® contribute to the observational databases CPRD GOLD, which includes practices across the UK, and CPRD Aurum, which hosts practices from England, respectively. Vision®, EMIS Web®, and TPP® underlie the CPRD Interventional Research services. 98% of the population in the United Kingdom (UK) is registered with a GP primarily responsible for non-emergency care and referrals to secondary care as needed. The CPRD GOLD January 2024 release has 364 currently contributing GP practices (7 in England, 110 in Wales, 207 in Scotland, and 40 in Northern Ireland). CPRD GOLD Jan-2024 contains 984 historical and current GP practices from the four UK constituent countries [median of 19.1 (13.4–21.9) years of GP contribution], with coverage of >21.3 million patients. Of these, nearly 3 million are alive and currently registered in a contributing GP practice. CPRD GOLD provides longitudinal information about patients' demographics, symptoms, conditions, referrals, vaccinations, prescriptions, measurements, and laboratory test results collected by participating GP practices, as part of their NHS care. While, in the raw data, clinical and prescribing information is coded by using Vision® bespoke coding systems (i.e., medcode and prodcode, respectively), CPRD provides dictionaries for their translation into standard coding systems.

### UK Biobank (UKBB)

UK Biobank is a powerful biomedical database that can be accessed globally to enable discoveries to improve public health. UK Biobank contains in-depth genetic, biomarker, imaging, and health information from over half a million volunteers living in the UK aged 40–69 years at the time of recruitment (2006–2010). UK Biobank has collected unprecedented biological and medical data for a large-scale, long-term prospective study. With their consent, they regularly provide blood, urine and saliva samples and detailed information about their lifestyle, which is then linked to their health-related records (e.g. primary care data, hospital data, cancer registry) to provide a deeper understanding of how individuals experience diseases. Since 2012, the UK Biobank database, the largest and richest of its kind, has been open to applications from researchers. The resource is available in anonymised format to scientists from the UK and worldwide, subject to verification that the research is health-related and in the public interest. Researchers are required to publish their results in an open-source publication site or an academic journal and return their findings to the UK Biobank. At the time of writing, nearly 3,600 research applications have been approved for using UK Biobank data, and 3,239 peer-reviewed articles based on them have been published.

## ANNEX II: List of Stand-Alone documents

Concepts to define cancer patients (populations of interest) are available in a stand-alone document (DARWIN\_EU\_P3\_C3\_005\_Cancer\_phenotypes.xlsx). **Tables S1 to S7** include concepts used to define outcomes (thromboembolic events), and **Tables S8 to S11** include concepts used to describe comorbidities, procedures, medications, and stages. All descendants of concepts to describe comorbidities, procedures, medications, and stages were also added to create respective concept sets.

**Table S1. List of concepts used to define deep vein thrombosis (DVT)**

| Concept ID | Concept Name                                                              | Domain    | Vocabulary |
|------------|---------------------------------------------------------------------------|-----------|------------|
| 762047     | Acute bilateral thrombosis of subclavian veins                            | Condition | SNOMED     |
| 762148     | Acute deep vein thrombosis of bilateral iliac veins                       | Condition | SNOMED     |
| 37169261   | Acute deep vein thrombosis of bilateral lower limbs following procedure   | Condition | SNOMED     |
| 37169249   | Acute deep vein thrombosis of bilateral upper limbs following procedure   | Condition | SNOMED     |
| 35616028   | Acute deep vein thrombosis of left iliac vein                             | Condition | SNOMED     |
| 35615035   | Acute deep vein thrombosis of left lower limb following procedure         | Condition | SNOMED     |
| 35615031   | Acute deep vein thrombosis of left upper limb following procedure         | Condition | SNOMED     |
| 43531681   | Acute deep vein thrombosis of lower limb                                  | Condition | SNOMED     |
| 35616027   | Acute deep vein thrombosis of right iliac vein                            | Condition | SNOMED     |
| 35615034   | Acute deep vein thrombosis of right lower limb following procedure        | Condition | SNOMED     |
| 35615030   | Acute deep vein thrombosis of right upper limb following procedure        | Condition | SNOMED     |
| 44782746   | Acute deep venous thrombosis                                              | Condition | SNOMED     |
| 44782751   | Acute deep venous thrombosis of axillary vein                             | Condition | SNOMED     |
| 762008     | Acute deep venous thrombosis of bilateral axillary veins                  | Condition | SNOMED     |
| 760875     | Acute deep venous thrombosis of bilateral calves                          | Condition | SNOMED     |
| 765155     | Acute deep venous thrombosis of bilateral iliofemoral veins               | Condition | SNOMED     |
| 762017     | Acute deep venous thrombosis of bilateral internal jugular veins          | Condition | SNOMED     |
| 762417     | Acute deep venous thrombosis of bilateral legs                            | Condition | SNOMED     |
| 761461     | Acute deep venous thrombosis of bilateral pelvic veins                    | Condition | SNOMED     |
| 762020     | Acute deep venous thrombosis of bilateral popliteal veins                 | Condition | SNOMED     |
| 765546     | Acute deep venous thrombosis of bilateral tibial veins                    | Condition | SNOMED     |
| 762004     | Acute deep venous thrombosis of both upper extremities                    | Condition | SNOMED     |
| 44782742   | Acute deep venous thrombosis of calf                                      | Condition | SNOMED     |
| 44782747   | Acute deep venous thrombosis of femoral vein                              | Condition | SNOMED     |
| 762015     | Acute deep venous thrombosis of iliofemoral vein of left leg              | Condition | SNOMED     |
| 765541     | Acute deep venous thrombosis of iliofemoral vein of right lower extremity | Condition | SNOMED     |
| 44782748   | Acute deep venous thrombosis of iliofemoral vein                          | Condition | SNOMED     |
| 44782752   | Acute deep venous thrombosis of internal jugular vein                     | Condition | SNOMED     |
| 762009     | Acute deep venous thrombosis of left axillary vein                        | Condition | SNOMED     |
| 760876     | Acute deep venous thrombosis of left calf                                 | Condition | SNOMED     |

|          |                                                                              |           |                  |
|----------|------------------------------------------------------------------------------|-----------|------------------|
| 765540   | Acute deep venous thrombosis of left femoral vein                            | Condition | SNOMED           |
| 765922   | Acute deep venous thrombosis of left internal jugular vein                   | Condition | SNOMED           |
| 762418   | Acute deep venous thrombosis of left lower extremity                         | Condition | SNOMED           |
| 761462   | Acute deep venous thrombosis of left pelvic vein                             | Condition | SNOMED           |
| 618482   | Acute deep venous thrombosis of left peroneal vein                           | Condition | SNOMED           |
| 765537   | Acute deep venous thrombosis of left upper extremity                         | Condition | SNOMED           |
| 44782767 | Acute deep venous thrombosis of lower extremity as complication of procedure | Condition | SNOMED           |
| 44782761 | Acute deep venous thrombosis of pelvic vein                                  | Condition | SNOMED           |
| 762022   | Acute deep venous thrombosis of popliteal vein of right leg                  | Condition | SNOMED           |
| 44782743 | Acute deep venous thrombosis of popliteal vein                               | Condition | SNOMED           |
| 762021   | Acute deep venous thrombosis of popliteal vein of left leg                   | Condition | SNOMED           |
| 762010   | Acute deep venous thrombosis of right axillary vein                          | Condition | SNOMED           |
| 760877   | Acute deep venous thrombosis of right calf                                   | Condition | SNOMED           |
| 762013   | Acute deep venous thrombosis of right femoral vein                           | Condition | SNOMED           |
| 762018   | Acute deep venous thrombosis of right internal jugular vein                  | Condition | SNOMED           |
| 762419   | Acute deep venous thrombosis of right lower extremity                        | Condition | SNOMED           |
| 765229   | Acute deep venous thrombosis of right pelvic vein                            | Condition | SNOMED           |
| 618681   | Acute deep venous thrombosis of right peroneal vein                          | Condition | SNOMED           |
| 762005   | Acute deep venous thrombosis of right upper extremity                        | Condition | SNOMED           |
| 44782745 | Acute deep venous thrombosis of thigh                                        | Condition | SNOMED           |
| 44782744 | Acute deep venous thrombosis of tibial vein                                  | Condition | SNOMED           |
| 762026   | Acute deep venous thrombosis of tibial vein of left leg                      | Condition | SNOMED           |
| 765156   | Acute deep venous thrombosis of tibial vein of right leg                     | Condition | SNOMED           |
| 44782421 | Acute deep venous thrombosis of upper extremity                              | Condition | SNOMED           |
| 44782766 | Acute deep venous thrombosis of upper extremity as complication of procedure | Condition | SNOMED           |
| 37171353 | Acute ischemia of colon due to thrombosis of mesenteric vein                 | Condition | SNOMED           |
| 37170675 | Acute ischemia of small intestine due to thrombosis of mesenteric vein       | Condition | SNOMED           |
| 762048   | Acute thrombosis of left subclavian vein                                     | Condition | SNOMED           |
| 45757410 | Acute thrombosis of mesenteric vein                                          | Condition | SNOMED           |
| 762049   | Acute thrombosis of right subclavian vein                                    | Condition | SNOMED           |
| 36712892 | Acute thrombosis of splenic vein                                             | Condition | SNOMED           |
| 44782762 | Acute thrombosis of subclavian vein                                          | Condition | SNOMED           |
| 4179911  | Axillary vein thrombosis                                                     | Condition | SNOMED           |
| 37109253 | Bilateral acute deep vein thrombosis of femoral veins                        | Condition | SNOMED           |
| 618678   | Bilateral acute deep venous thrombosis of peroneal veins                     | Condition | SNOMED           |
| 609003   | Bilateral deep femoral vein thrombophlebitis                                 | Condition | SNOMED           |
| 3179900  | Bilateral deep vein thromboses                                               | Condition | Nebraska Lexicon |
| 40478951 | Bilateral deep vein thrombosis of lower extremities                          | Condition | SNOMED           |

|          |                                                                     |           |                  |
|----------|---------------------------------------------------------------------|-----------|------------------|
| 609002   | Bilateral femoral vein thrombophlebitis                             | Condition | SNOMED           |
| 608965   | Bilateral iliac vein thrombophlebitis                               | Condition | SNOMED           |
| 1245776  | Bilateral popliteal vein thrombophlebitis                           | Condition | SNOMED           |
| 609006   | Bilateral tibial vein thrombophlebitis                              | Condition | SNOMED           |
| 4042396  | Deep thrombophlebitis                                               | Condition | SNOMED           |
| 4046884  | Deep vein thrombosis of leg related to air travel                   | Condition | SNOMED           |
| 3655221  | Deep vein thrombosis of lower extremity due to intravenous drug use | Condition | SNOMED           |
| 4133004  | Deep venous thrombosis                                              | Condition | SNOMED           |
| 761013   | Deep venous thrombosis of bilateral pelvic veins                    | Condition | SNOMED           |
| 37163011 | Deep venous thrombosis of calf                                      | Condition | SNOMED           |
| 45773536 | Deep venous thrombosis of femoropopliteal vein                      | Condition | SNOMED           |
| 763942   | Deep venous thrombosis of left lower extremity                      | Condition | SNOMED           |
| 1075379  | Deep venous thrombosis of left posterior tibial vein                | Condition | SNOMED           |
| 761980   | Deep venous thrombosis of left upper extremity                      | Condition | SNOMED           |
| 443537   | Deep venous thrombosis of lower extremity                           | Condition | SNOMED           |
| 4133975  | Deep venous thrombosis of pelvic vein                               | Condition | SNOMED           |
| 40480555 | Deep venous thrombosis of peroneal vein                             | Condition | SNOMED           |
| 1075377  | Deep venous thrombosis of posterior tibial vein                     | Condition | SNOMED           |
| 4322565  | Deep venous thrombosis of profunda femoris vein                     | Condition | SNOMED           |
| 763941   | Deep venous thrombosis of right lower extremity                     | Condition | SNOMED           |
| 1075378  | Deep venous thrombosis of right posterior tibial vein               | Condition | SNOMED           |
| 761928   | Deep venous thrombosis of right upper extremity                     | Condition | SNOMED           |
| 4207899  | Deep venous thrombosis of tibial vein                               | Condition | SNOMED           |
| 4028057  | Deep venous thrombosis of upper extremity                           | Condition | SNOMED           |
| 193512   | Embolism and thrombosis of the renal vein                           | Condition | SNOMED           |
| 435565   | Embolism and thrombosis of the vena cava                            | Condition | SNOMED           |
| 4258295  | Embolism from thrombosis of vein of distal lower extremity          | Condition | SNOMED           |
| 40481089 | Embolism from thrombosis of vein of lower extremity                 | Condition | SNOMED           |
| 40479840 | Embolism from thrombosis of vein of thigh                           | Condition | SNOMED           |
| 4119760  | Iliofemoral deep vein thrombosis                                    | Condition | SNOMED           |
| 4124856  | Inferior mesenteric vein thrombosis                                 | Condition | SNOMED           |
| 608964   | Left iliac vein thrombophlebitis                                    | Condition | SNOMED           |
| 602592   | Left peroneal vein thrombophlebitis                                 | Condition | SNOMED           |
| 600938   | Left subclavian vein thrombophlebitis                               | Condition | SNOMED           |
| 37164448 | Lemierre syndrome                                                   | Condition | SNOMED           |
| 4281689  | Phlegmasia alba dolens                                              | Condition | SNOMED           |
| 4284538  | Phlegmasia cerulea dolens                                           | Condition | SNOMED           |
| 3185768  | Popliteal vein thrombosis                                           | Condition | Nebraska Lexicon |

|          |                                                        |           |        |
|----------|--------------------------------------------------------|-----------|--------|
| 4309333  | Postoperative deep vein thrombosis                     | Condition | SNOMED |
| 1245858  | Postpartum acute deep vein thrombosis                  | Condition | SNOMED |
| 46285905 | Provoked deep vein thrombosis                          | Condition | SNOMED |
| 608963   | Right iliac vein thrombophlebitis                      | Condition | SNOMED |
| 602583   | Right peroneal vein thrombophlebitis                   | Condition | SNOMED |
| 600939   | Right subclavian vein thrombophlebitis                 | Condition | SNOMED |
| 4033521  | Splenic vein thrombosis                                | Condition | SNOMED |
| 4055089  | Superior mesenteric vein thrombosis                    | Condition | SNOMED |
| 4230403  | Thrombophlebitis of axillary vein                      | Condition | SNOMED |
| 4069561  | Thrombophlebitis of deep femoral vein                  | Condition | SNOMED |
| 761831   | Thrombophlebitis of deep vein of bilateral lower limbs | Condition | SNOMED |
| 761830   | Thrombophlebitis of deep vein of left lower limb       | Condition | SNOMED |
| 761808   | Thrombophlebitis of deep vein of left upper limb       | Condition | SNOMED |
| 761832   | Thrombophlebitis of deep vein of right lower limb      | Condition | SNOMED |
| 761809   | Thrombophlebitis of deep vein of right upper limb      | Condition | SNOMED |
| 4221821  | Thrombophlebitis of deep veins of lower extremity      | Condition | SNOMED |
| 440750   | Thrombophlebitis of deep veins of upper extremities    | Condition | SNOMED |
| 4203618  | Thrombophlebitis of femoropopliteal vein               | Condition | SNOMED |
| 4176614  | Thrombophlebitis of iliac vein                         | Condition | SNOMED |
| 764715   | Thrombophlebitis of internal jugular vein              | Condition | SNOMED |
| 608904   | Thrombophlebitis of left axillary vein                 | Condition | SNOMED |
| 761821   | Thrombophlebitis of left deep femoral vein             | Condition | SNOMED |
| 761819   | Thrombophlebitis of left femoral vein                  | Condition | SNOMED |
| 609000   | Thrombophlebitis of left popliteal vein                | Condition | SNOMED |
| 609005   | Thrombophlebitis of left tibial vein                   | Condition | SNOMED |
| 4318407  | Thrombophlebitis of mesenteric vein                    | Condition | SNOMED |
| 608903   | Thrombophlebitis of right axillary vein                | Condition | SNOMED |
| 761820   | Thrombophlebitis of right deep femoral vein            | Condition | SNOMED |
| 761818   | Thrombophlebitis of right femoral vein                 | Condition | SNOMED |
| 609001   | Thrombophlebitis of right popliteal vein               | Condition | SNOMED |
| 609004   | Thrombophlebitis of right tibial vein                  | Condition | SNOMED |
| 4205652  | Thrombophlebitis of subclavian vein                    | Condition | SNOMED |
| 4110339  | Thrombophlebitis of the anterior tibial vein           | Condition | SNOMED |
| 4111868  | Thrombophlebitis of the common iliac vein              | Condition | SNOMED |
| 4110343  | Thrombophlebitis of the external iliac vein            | Condition | SNOMED |
| 439314   | Thrombophlebitis of the femoral vein                   | Condition | SNOMED |
| 4109877  | Thrombophlebitis of the internal iliac vein            | Condition | SNOMED |
| 4112171  | Thrombophlebitis of the popliteal vein                 | Condition | SNOMED |

|          |                                                                |           |        |
|----------|----------------------------------------------------------------|-----------|--------|
| 4112172  | Thrombophlebitis of the posterior tibial vein                  | Condition | SNOMED |
| 4250765  | Thrombophlebitis of tibial vein                                | Condition | SNOMED |
| 42538533 | Thrombosis of iliac vein                                       | Condition | SNOMED |
| 44811347 | Thrombosis of internal jugular vein                            | Condition | SNOMED |
| 765049   | Thrombosis of left peroneal vein                               | Condition | SNOMED |
| 4317289  | Thrombosis of mesenteric vein                                  | Condition | SNOMED |
| 4203836  | Thrombosis of subclavian vein                                  | Condition | SNOMED |
| 4175649  | Thrombosis of the popliteal vein                               | Condition | SNOMED |
| 4153353  | Traumatic thrombosis of axillary vein                          | Condition | SNOMED |
| 46285904 | Unprovoked deep vein thrombosis                                | Condition | SNOMED |
| 37163265 | Venous thromboembolism due to thrombosis of vein of lower limb | Condition | SNOMED |

**Table S2. List of concepts used to define pulmonary embolism (PE).**

| Concept ID | Concept Name                                                        | Domain    | Vocabulary |
|------------|---------------------------------------------------------------------|-----------|------------|
| 608954     | Acute cor pulmonale due to septic pulmonary embolism                | Condition | SNOMED     |
| 4120091    | Acute massive pulmonary embolism                                    | Condition | SNOMED     |
| 45768439   | Acute pulmonary embolism                                            | Condition | SNOMED     |
| 45768888   | Acute pulmonary thromboembolism                                     | Condition | SNOMED     |
| 762808     | Infarction of lung due to embolus                                   | Condition | SNOMED     |
| 40480461   | Infarction of lung due to iatrogenic pulmonary embolism             | Condition | SNOMED     |
| 4108681    | Postoperative pulmonary embolus                                     | Condition | SNOMED     |
| 37160752   | Postoperative pulmonary thromboembolism                             | Condition | SNOMED     |
| 1244882    | Pulmonary artery embolism due to foreign body                       | Condition | SNOMED     |
| 440417     | Pulmonary embolism                                                  | Condition | SNOMED     |
| 37109911   | Pulmonary embolism due to and following acute myocardial infarction | Condition | SNOMED     |
| 37016922   | Pulmonary embolism on long-term anticoagulation therapy             | Condition | SNOMED     |
| 43530605   | Pulmonary embolism with pulmonary infarction                        | Condition | SNOMED     |
| 4253796    | Pulmonary microemboli                                               | Condition | SNOMED     |
| 4121618    | Pulmonary thromboembolism                                           | Condition | SNOMED     |
| 36713113   | Saddle embolus of pulmonary artery                                  | Condition | SNOMED     |
| 35615055   | Saddle embolus of pulmonary artery with acute cor pulmonale         | Condition | SNOMED     |
| 40479606   | Septic pulmonary embolism                                           | Condition | SNOMED     |
| 4119607    | Subacute massive pulmonary embolism                                 | Condition | SNOMED     |

Table S3. List of concepts used to define venous thromboembolism (VTE).

| Concept ID | Concept Name                                                              | Domain    | Vocabulary |
|------------|---------------------------------------------------------------------------|-----------|------------|
| 762047     | Acute bilateral thrombosis of subclavian veins                            | Condition | SNOMED     |
| 608954     | Acute cor pulmonale due to septic pulmonary embolism                      | Condition | SNOMED     |
| 762148     | Acute deep vein thrombosis of bilateral iliac veins                       | Condition | SNOMED     |
| 37169261   | Acute deep vein thrombosis of bilateral lower limbs following procedure   | Condition | SNOMED     |
| 37169249   | Acute deep vein thrombosis of bilateral upper limbs following procedure   | Condition | SNOMED     |
| 35616028   | Acute deep vein thrombosis of left iliac vein                             | Condition | SNOMED     |
| 35615035   | Acute deep vein thrombosis of left lower limb following procedure         | Condition | SNOMED     |
| 35615031   | Acute deep vein thrombosis of left upper limb following procedure         | Condition | SNOMED     |
| 43531681   | Acute deep vein thrombosis of lower limb                                  | Condition | SNOMED     |
| 35616027   | Acute deep vein thrombosis of right iliac vein                            | Condition | SNOMED     |
| 35615034   | Acute deep vein thrombosis of right lower limb following procedure        | Condition | SNOMED     |
| 35615030   | Acute deep vein thrombosis of right upper limb following procedure        | Condition | SNOMED     |
| 44782746   | Acute deep venous thrombosis                                              | Condition | SNOMED     |
| 44782751   | Acute deep venous thrombosis of axillary vein                             | Condition | SNOMED     |
| 762008     | Acute deep venous thrombosis of bilateral axillary veins                  | Condition | SNOMED     |
| 760875     | Acute deep venous thrombosis of bilateral calves                          | Condition | SNOMED     |
| 765155     | Acute deep venous thrombosis of bilateral iliofemoral veins               | Condition | SNOMED     |
| 762017     | Acute deep venous thrombosis of bilateral internal jugular veins          | Condition | SNOMED     |
| 762417     | Acute deep venous thrombosis of bilateral legs                            | Condition | SNOMED     |
| 761461     | Acute deep venous thrombosis of bilateral pelvic veins                    | Condition | SNOMED     |
| 762020     | Acute deep venous thrombosis of bilateral popliteal veins                 | Condition | SNOMED     |
| 765546     | Acute deep venous thrombosis of bilateral tibial veins                    | Condition | SNOMED     |
| 762004     | Acute deep venous thrombosis of both upper extremities                    | Condition | SNOMED     |
| 44782742   | Acute deep venous thrombosis of calf                                      | Condition | SNOMED     |
| 44782747   | Acute deep venous thrombosis of femoral vein                              | Condition | SNOMED     |
| 762015     | Acute deep venous thrombosis of iliofemoral vein of left leg              | Condition | SNOMED     |
| 765541     | Acute deep venous thrombosis of iliofemoral vein of right lower extremity | Condition | SNOMED     |
| 44782748   | Acute deep venous thrombosis of iliofemoral vein                          | Condition | SNOMED     |
| 44782752   | Acute deep venous thrombosis of internal jugular vein                     | Condition | SNOMED     |
| 762009     | Acute deep venous thrombosis of left axillary vein                        | Condition | SNOMED     |
| 760876     | Acute deep venous thrombosis of left calf                                 | Condition | SNOMED     |
| 765540     | Acute deep venous thrombosis of left femoral vein                         | Condition | SNOMED     |
| 765922     | Acute deep venous thrombosis of left internal jugular vein                | Condition | SNOMED     |
| 762418     | Acute deep venous thrombosis of left lower extremity                      | Condition | SNOMED     |
| 761462     | Acute deep venous thrombosis of left pelvic vein                          | Condition | SNOMED     |

|          |                                                                              |           |                     |
|----------|------------------------------------------------------------------------------|-----------|---------------------|
| 618482   | Acute deep venous thrombosis of left peroneal vein                           | Condition | SNOMED              |
| 765537   | Acute deep venous thrombosis of left upper extremity                         | Condition | SNOMED              |
| 44782767 | Acute deep venous thrombosis of lower extremity as complication of procedure | Condition | SNOMED              |
| 44782761 | Acute deep venous thrombosis of pelvic vein                                  | Condition | SNOMED              |
| 762022   | Acute deep venous thrombosis of politeal vein of right leg                   | Condition | SNOMED              |
| 44782743 | Acute deep venous thrombosis of popliteal vein                               | Condition | SNOMED              |
| 762021   | Acute deep venous thrombosis of popliteal vein of left leg                   | Condition | SNOMED              |
| 762010   | Acute deep venous thrombosis of right axillary vein                          | Condition | SNOMED              |
| 760877   | Acute deep venous thrombosis of right calf                                   | Condition | SNOMED              |
| 762013   | Acute deep venous thrombosis of right femoral vein                           | Condition | SNOMED              |
| 762018   | Acute deep venous thrombosis of right internal jugular vein                  | Condition | SNOMED              |
| 762419   | Acute deep venous thrombosis of right lower extremity                        | Condition | SNOMED              |
| 765229   | Acute deep venous thrombosis of right pelvic vein                            | Condition | SNOMED              |
| 618681   | Acute deep venous thrombosis of right peroneal vein                          | Condition | SNOMED              |
| 762005   | Acute deep venous thrombosis of right upper extremity                        | Condition | SNOMED              |
| 44782745 | Acute deep venous thrombosis of thigh                                        | Condition | SNOMED              |
| 44782744 | Acute deep venous thrombosis of tibial vein                                  | Condition | SNOMED              |
| 762026   | Acute deep venous thrombosis of tibial vein of left leg                      | Condition | SNOMED              |
| 765156   | Acute deep venous thrombosis of tibial vein of right leg                     | Condition | SNOMED              |
| 44782421 | Acute deep venous thrombosis of upper extremity                              | Condition | SNOMED              |
| 44782766 | Acute deep venous thrombosis of upper extremity as complication of procedure | Condition | SNOMED              |
| 37171353 | Acute ischemia of colon due to thrombosis of mesenteric vein                 | Condition | SNOMED              |
| 37170675 | Acute ischemia of small intestine due to thrombosis of mesenteric vein       | Condition | SNOMED              |
| 4120091  | Acute massive pulmonary embolism                                             | Condition | SNOMED              |
| 45768439 | Acute pulmonary embolism                                                     | Condition | SNOMED              |
| 45768888 | Acute pulmonary thromboembolism                                              | Condition | SNOMED              |
| 762048   | Acute thrombosis of left subclavian vein                                     | Condition | SNOMED              |
| 45757410 | Acute thrombosis of mesenteric vein                                          | Condition | SNOMED              |
| 762049   | Acute thrombosis of right subclavian vein                                    | Condition | SNOMED              |
| 36712892 | Acute thrombosis of splenic vein                                             | Condition | SNOMED              |
| 44782762 | Acute thrombosis of subclavian vein                                          | Condition | SNOMED              |
| 4179911  | Axillary vein thrombosis                                                     | Condition | SNOMED              |
| 37109253 | Bilateral acute deep vein thrombosis of femoral veins                        | Condition | SNOMED              |
| 618678   | Bilateral acute deep venous thrombosis of peroneal veins                     | Condition | SNOMED              |
| 609003   | Bilateral deep femoral vein thrombophlebitis                                 | Condition | SNOMED              |
| 3179900  | Bilateral deep vein thromboses                                               | Condition | Nebraska<br>Lexicon |
| 40478951 | Bilateral deep vein thrombosis of lower extremities                          | Condition | SNOMED              |

|          |                                                                     |           |        |
|----------|---------------------------------------------------------------------|-----------|--------|
| 609002   | Bilateral femoral vein thrombophlebitis                             | Condition | SNOMED |
| 608965   | Bilateral iliac vein thrombophlebitis                               | Condition | SNOMED |
| 1245776  | Bilateral popliteal vein thrombophlebitis                           | Condition | SNOMED |
| 609006   | Bilateral tibial vein thrombophlebitis                              | Condition | SNOMED |
| 44782732 | Chronic pulmonary embolism                                          | Condition | SNOMED |
| 45768887 | Chronic pulmonary thromboembolism                                   | Condition | SNOMED |
| 45771016 | Chronic pulmonary thromboembolism without pulmonary hypertension    | Condition | SNOMED |
| 4042396  | Deep thrombophlebitis                                               | Condition | SNOMED |
| 4046884  | Deep vein thrombosis of leg related to air travel                   | Condition | SNOMED |
| 3655221  | Deep vein thrombosis of lower extremity due to intravenous drug use | Condition | SNOMED |
| 4133004  | Deep venous thrombosis                                              | Condition | SNOMED |
| 761013   | Deep venous thrombosis of bilateral pelvic veins                    | Condition | SNOMED |
| 37163011 | Deep venous thrombosis of calf                                      | Condition | SNOMED |
| 45773536 | Deep venous thrombosis of femoropopliteal vein                      | Condition | SNOMED |
| 763942   | Deep venous thrombosis of left lower extremity                      | Condition | SNOMED |
| 1075379  | Deep venous thrombosis of left posterior tibial vein                | Condition | SNOMED |
| 761980   | Deep venous thrombosis of left upper extremity                      | Condition | SNOMED |
| 443537   | Deep venous thrombosis of lower extremity                           | Condition | SNOMED |
| 4133975  | Deep venous thrombosis of pelvic vein                               | Condition | SNOMED |
| 40480555 | Deep venous thrombosis of peroneal vein                             | Condition | SNOMED |
| 1075377  | Deep venous thrombosis of posterior tibial vein                     | Condition | SNOMED |
| 4322565  | Deep venous thrombosis of profunda femoris vein                     | Condition | SNOMED |
| 763941   | Deep venous thrombosis of right lower extremity                     | Condition | SNOMED |
| 1075378  | Deep venous thrombosis of right posterior tibial vein               | Condition | SNOMED |
| 761928   | Deep venous thrombosis of right upper extremity                     | Condition | SNOMED |
| 4207899  | Deep venous thrombosis of tibial vein                               | Condition | SNOMED |
| 4028057  | Deep venous thrombosis of upper extremity                           | Condition | SNOMED |
| 193512   | Embolism and thrombosis of the renal vein                           | Condition | SNOMED |
| 435565   | Embolism and thrombosis of the vena cava                            | Condition | SNOMED |
| 4258295  | Embolism from thrombosis of vein of distal lower extremity          | Condition | SNOMED |
| 40481089 | Embolism from thrombosis of vein of lower extremity                 | Condition | SNOMED |
| 40479840 | Embolism from thrombosis of vein of thigh                           | Condition | SNOMED |
| 4119760  | Iliofemoral deep vein thrombosis                                    | Condition | SNOMED |
| 43530934 | Induced termination of pregnancy complicated by pulmonary embolism  | Condition | SNOMED |
| 762808   | Infarction of lung due to embolus                                   | Condition | SNOMED |
| 40480461 | Infarction of lung due to iatrogenic pulmonary embolism             | Condition | SNOMED |
| 4124856  | Inferior mesenteric vein thrombosis                                 | Condition | SNOMED |
| 608964   | Left iliac vein thrombophlebitis                                    | Condition | SNOMED |

|          |                                                                     |           |                     |
|----------|---------------------------------------------------------------------|-----------|---------------------|
| 602592   | Left peroneal vein thrombophlebitis                                 | Condition | SNOMED              |
| 600938   | Left subclavian vein thrombophlebitis                               | Condition | SNOMED              |
| 37164448 | Lemierre syndrome                                                   | Condition | SNOMED              |
| 4281689  | Phlegmasia alba dolens                                              | Condition | SNOMED              |
| 4284538  | Phlegmasia cerulea dolens                                           | Condition | SNOMED              |
| 3185768  | Popliteal vein thrombosis                                           | Condition | Nebraska<br>Lexicon |
| 4309333  | Postoperative deep vein thrombosis                                  | Condition | SNOMED              |
| 4108681  | Postoperative pulmonary embolus                                     | Condition | SNOMED              |
| 37160752 | Postoperative pulmonary thromboembolism                             | Condition | SNOMED              |
| 1245858  | Postpartum acute deep vein thrombosis                               | Condition | SNOMED              |
| 46285905 | Provoked deep vein thrombosis                                       | Condition | SNOMED              |
| 1244882  | Pulmonary artery embolism due to foreign body                       | Condition | SNOMED              |
| 440417   | Pulmonary embolism                                                  | Condition | SNOMED              |
| 37109911 | Pulmonary embolism due to and following acute myocardial infarction | Condition | SNOMED              |
| 3655209  | Pulmonary embolism due to and following ectopic pregnancy           | Condition | SNOMED              |
| 3655210  | Pulmonary embolism due to and following molar pregnancy             | Condition | SNOMED              |
| 37016922 | Pulmonary embolism on long-term anticoagulation therapy             | Condition | SNOMED              |
| 43530605 | Pulmonary embolism with pulmonary infarction                        | Condition | SNOMED              |
| 4253796  | Pulmonary microemboli                                               | Condition | SNOMED              |
| 4121618  | Pulmonary thromboembolism                                           | Condition | SNOMED              |
| 4236271  | Recurrent pulmonary embolism                                        | Condition | SNOMED              |
| 608963   | Right iliac vein thrombophlebitis                                   | Condition | SNOMED              |
| 602583   | Right peroneal vein thrombophlebitis                                | Condition | SNOMED              |
| 600939   | Right subclavian vein thrombophlebitis                              | Condition | SNOMED              |
| 36713113 | Saddle embolus of pulmonary artery                                  | Condition | SNOMED              |
| 35615055 | Saddle embolus of pulmonary artery with acute cor pulmonale         | Condition | SNOMED              |
| 40479606 | Septic pulmonary embolism                                           | Condition | SNOMED              |
| 4033521  | Splenic vein thrombosis                                             | Condition | SNOMED              |
| 4119607  | Subacute massive pulmonary embolism                                 | Condition | SNOMED              |
| 4055089  | Superior mesenteric vein thrombosis                                 | Condition | SNOMED              |
| 4230403  | Thrombophlebitis of axillary vein                                   | Condition | SNOMED              |
| 4069561  | Thrombophlebitis of deep femoral vein                               | Condition | SNOMED              |
| 761831   | Thrombophlebitis of deep vein of bilateral lower limbs              | Condition | SNOMED              |
| 761830   | Thrombophlebitis of deep vein of left lower limb                    | Condition | SNOMED              |
| 761808   | Thrombophlebitis of deep vein of left upper limb                    | Condition | SNOMED              |
| 761832   | Thrombophlebitis of deep vein of right lower limb                   | Condition | SNOMED              |
| 761809   | Thrombophlebitis of deep vein of right upper limb                   | Condition | SNOMED              |

|          |                                                                |           |        |
|----------|----------------------------------------------------------------|-----------|--------|
| 4221821  | Thrombophlebitis of deep veins of lower extremity              | Condition | SNOMED |
| 440750   | Thrombophlebitis of deep veins of upper extremities            | Condition | SNOMED |
| 4203618  | Thrombophlebitis of femoropopliteal vein                       | Condition | SNOMED |
| 4176614  | Thrombophlebitis of iliac vein                                 | Condition | SNOMED |
| 764715   | Thrombophlebitis of internal jugular vein                      | Condition | SNOMED |
| 608904   | Thrombophlebitis of left axillary vein                         | Condition | SNOMED |
| 761821   | Thrombophlebitis of left deep femoral vein                     | Condition | SNOMED |
| 761819   | Thrombophlebitis of left femoral vein                          | Condition | SNOMED |
| 609000   | Thrombophlebitis of left popliteal vein                        | Condition | SNOMED |
| 609005   | Thrombophlebitis of left tibial vein                           | Condition | SNOMED |
| 4318407  | Thrombophlebitis of mesenteric vein                            | Condition | SNOMED |
| 608903   | Thrombophlebitis of right axillary vein                        | Condition | SNOMED |
| 761820   | Thrombophlebitis of right deep femoral vein                    | Condition | SNOMED |
| 761818   | Thrombophlebitis of right femoral vein                         | Condition | SNOMED |
| 609001   | Thrombophlebitis of right popliteal vein                       | Condition | SNOMED |
| 609004   | Thrombophlebitis of right tibial vein                          | Condition | SNOMED |
| 4205652  | Thrombophlebitis of subclavian vein                            | Condition | SNOMED |
| 4110339  | Thrombophlebitis of the anterior tibial vein                   | Condition | SNOMED |
| 4111868  | Thrombophlebitis of the common iliac vein                      | Condition | SNOMED |
| 4110343  | Thrombophlebitis of the external iliac vein                    | Condition | SNOMED |
| 439314   | Thrombophlebitis of the femoral vein                           | Condition | SNOMED |
| 4109877  | Thrombophlebitis of the internal iliac vein                    | Condition | SNOMED |
| 4112171  | Thrombophlebitis of the popliteal vein                         | Condition | SNOMED |
| 4112172  | Thrombophlebitis of the posterior tibial vein                  | Condition | SNOMED |
| 4250765  | Thrombophlebitis of tibial vein                                | Condition | SNOMED |
| 42538533 | Thrombosis of iliac vein                                       | Condition | SNOMED |
| 44811347 | Thrombosis of internal jugular vein                            | Condition | SNOMED |
| 765049   | Thrombosis of left peroneal vein                               | Condition | SNOMED |
| 4317289  | Thrombosis of mesenteric vein                                  | Condition | SNOMED |
| 4203836  | Thrombosis of subclavian vein                                  | Condition | SNOMED |
| 4175649  | Thrombosis of the popliteal vein                               | Condition | SNOMED |
| 4153353  | Traumatic thrombosis of axillary vein                          | Condition | SNOMED |
| 46285904 | Unprovoked deep vein thrombosis                                | Condition | SNOMED |
| 37163265 | Venous thromboembolism due to thrombosis of vein of lower limb | Condition | SNOMED |

Table S4. List of concepts used to define pelvic vein thrombosis (PVT) (concept sets included all descendants of listed concepts).

| Concept ID | Concept Name                                                              | Domain    | Vocabulary |
|------------|---------------------------------------------------------------------------|-----------|------------|
| 762148     | Acute deep vein thrombosis of bilateral iliac veins                       | Condition | SNOMED     |
| 35616028   | Acute deep vein thrombosis of left iliac vein                             | Condition | SNOMED     |
| 35616027   | Acute deep vein thrombosis of right iliac vein                            | Condition | SNOMED     |
| 765155     | Acute deep venous thrombosis of bilateral ileofemoral veins               | Condition | SNOMED     |
| 761461     | Acute deep venous thrombosis of bilateral pelvic veins                    | Condition | SNOMED     |
| 762015     | Acute deep venous thrombosis of ileofemoral vein of left leg              | Condition | SNOMED     |
| 765541     | Acute deep venous thrombosis of ileofemoral vein of right lower extremity | Condition | SNOMED     |
| 761462     | Acute deep venous thrombosis of left pelvic vein                          | Condition | SNOMED     |
| 44782761   | Acute deep venous thrombosis of pelvic vein                               | Condition | SNOMED     |
| 765229     | Acute deep venous thrombosis of right pelvic vein                         | Condition | SNOMED     |
| 608965     | Bilateral iliac vein thrombophlebitis                                     | Condition | SNOMED     |
| 765152     | Chronic deep vein thrombosis of bilateral iliac veins                     | Condition | SNOMED     |
| 35616026   | Chronic deep vein thrombosis of left iliac vein                           | Condition | SNOMED     |
| 761439     | Chronic deep vein thrombosis of left pelvic vein                          | Condition | SNOMED     |
| 46271548   | Chronic deep vein thrombosis of pelvic vein                               | Condition | SNOMED     |
| 35616025   | Chronic deep vein thrombosis of right iliac vein                          | Condition | SNOMED     |
| 761441     | Chronic deep vein thrombosis of right pelvic vein                         | Condition | SNOMED     |
| 765542     | Chronic deep venous thrombosis of bilateral ileofemoral veins             | Condition | SNOMED     |
| 761440     | Chronic deep venous thrombosis of bilateral pelvic veins                  | Condition | SNOMED     |
| 765543     | Chronic deep venous thrombosis of left ileofemoral vein                   | Condition | SNOMED     |
| 762016     | Chronic deep venous thrombosis of right ileofemoral vein                  | Condition | SNOMED     |
| 761013     | Deep venous thrombosis of bilateral pelvic veins                          | Condition | SNOMED     |
| 4133975    | Deep venous thrombosis of pelvic vein                                     | Condition | SNOMED     |
| 608964     | Left iliac vein thrombophlebitis                                          | Condition | SNOMED     |
| 4285751    | Pelvic thrombophlebitis in puerperium                                     | Condition | SNOMED     |
| 608963     | Right iliac vein thrombophlebitis                                         | Condition | SNOMED     |
| 4176614    | Thrombophlebitis of iliac vein                                            | Condition | SNOMED     |
| 4317290    | Thrombophlebitis of pelvic vein                                           | Condition | SNOMED     |
| 4111868    | Thrombophlebitis of the common iliac vein                                 | Condition | SNOMED     |
| 4110343    | Thrombophlebitis of the external iliac vein                               | Condition | SNOMED     |
| 4109877    | Thrombophlebitis of the internal iliac vein                               | Condition | SNOMED     |
| 42538533   | Thrombosis of iliac vein                                                  | Condition | SNOMED     |
| 4319327    | Thrombosis of pelvic vein                                                 | Condition | SNOMED     |

Table S5. List of concepts used to splanchnic vein thrombosis (SVT).

| Concept ID | Concept Name                                                           | Domain    | Vocabulary |
|------------|------------------------------------------------------------------------|-----------|------------|
| 37171353   | Acute ischemia of colon due to thrombosis of mesenteric vein           | Condition | SNOMED     |
| 37170675   | Acute ischemia of small intestine due to thrombosis of mesenteric vein | Condition | SNOMED     |
| 45757410   | Acute thrombosis of mesenteric vein                                    | Condition | SNOMED     |
| 36712892   | Acute thrombosis of splenic vein                                       | Condition | SNOMED     |
| 196715     | Budd-Chiari syndrome                                                   | Condition | SNOMED     |
| 4301208    | Hepatic vein thrombosis                                                | Condition | SNOMED     |
| 4124856    | Inferior mesenteric vein thrombosis                                    | Condition | SNOMED     |
| 4092406    | Portal thrombophlebitis                                                | Condition | SNOMED     |
| 199837     | Portal vein thrombosis                                                 | Condition | SNOMED     |
| 4033521    | Splenic vein thrombosis                                                | Condition | SNOMED     |
| 4055089    | Superior mesenteric vein thrombosis                                    | Condition | SNOMED     |
| 4318407    | Thrombophlebitis of mesenteric vein                                    | Condition | SNOMED     |
| 4317289    | Thrombosis of mesenteric vein                                          | Condition | SNOMED     |

Table S6. List of concepts used to define retinal vein thrombosis (RVT).

| Concept ID | Concept Name                                                      | Domain    | Vocabulary |
|------------|-------------------------------------------------------------------|-----------|------------|
| 437544     | Arterial retinal branch occlusion                                 | Condition | SNOMED     |
| 3657106    | Bilateral occlusion of branch retinal arteries                    | Condition | SNOMED     |
| 37310623   | Bilateral occlusion of central retinal arteries                   | Condition | SNOMED     |
| 37169454   | Bilateral vascular occlusion of retina of eyes                    | Condition | SNOMED     |
| 4336004    | Branch macular artery occlusion                                   | Condition | SNOMED     |
| 4339013    | Branch retinal vein occlusion with macular edema                  | Condition | SNOMED     |
| 4334248    | Branch retinal vein occlusion with neovascularization             | Condition | SNOMED     |
| 4199035    | Branch retinal vein occlusion with no neovascularization          | Condition | SNOMED     |
| 437540     | Central retinal artery occlusion                                  | Condition | SNOMED     |
| 313761     | Central retinal vein occlusion                                    | Condition | SNOMED     |
| 4208221    | Central retinal vein occlusion - ischemic                         | Condition | SNOMED     |
| 4208222    | Central retinal vein occlusion - non-ischemic                     | Condition | SNOMED     |
| 4339010    | Central retinal vein occlusion with macular edema                 | Condition | SNOMED     |
| 4334246    | Central retinal vein occlusion with neovascularization            | Condition | SNOMED     |
| 4338905    | Cilioretinal artery occlusion                                     | Condition | SNOMED     |
| 42535735   | Combined occlusion by thrombus of retinal artery and retinal vein | Condition | SNOMED     |
| 4102317    | Incipient occlusion of retinal vein                               | Condition | SNOMED     |
| 4083482    | Macular branch retinal vein occlusion                             | Condition | SNOMED     |
| 37206377   | Occlusion of branch of retinal vein of left eye                   | Condition | SNOMED     |

|          |                                                  |           |                  |
|----------|--------------------------------------------------|-----------|------------------|
| 37206378 | Occlusion of branch of retinal vein of right eye | Condition | SNOMED           |
| 37206381 | Occlusion of central retinal vein of left eye    | Condition | SNOMED           |
| 37206380 | Occlusion of central retinal vein of right eye   | Condition | SNOMED           |
| 36713329 | Occlusion of left branch retinal artery          | Condition | SNOMED           |
| 37207955 | Occlusion of left central retinal artery         | Condition | SNOMED           |
| 3657873  | Occlusion of left cilioretinal artery            | Condition | SNOMED           |
| 36713330 | Occlusion of right branch retinal artery         | Condition | SNOMED           |
| 37207895 | Occlusion of right central retinal artery        | Condition | SNOMED           |
| 3657872  | Occlusion of right cilioretinal artery           | Condition | SNOMED           |
| 4334245  | Retinal artery occlusion                         | Condition | SNOMED           |
| 4324290  | Retinal phlebitis                                | Condition | SNOMED           |
| 440392   | Retinal vascular occlusion                       | Condition | SNOMED           |
| 3183076  | Right branch retinal artery occlusion            | Condition | Nebraska Lexicon |
| 4216561  | Thrombophlebitis of retinal vein                 | Condition | SNOMED           |
| 4187790  | Thrombosis of retinal vein                       | Condition | SNOMED           |
| 3657847  | Vascular occlusion of retina of left eye         | Condition | SNOMED           |
| 3657848  | Vascular occlusion of retina of right eye        | Condition | SNOMED           |
| 312622   | Venous retinal branch occlusion                  | Condition | SNOMED           |

**Table S7. List of concepts used to define disseminated intravascular coagulation (DIC).**

| Concept ID | Concept Name                           | Domain    | Vocabulary |
|------------|----------------------------------------|-----------|------------|
| 37117819   | Acquired purpura fulminans             | Condition | SNOMED     |
| 436093     | Disseminated intravascular coagulation | Condition | SNOMED     |
| 4028488    | Purpura fulminans                      | Condition | SNOMED     |

**Table S8. List of concepts used to describe comorbidities (concept sets included all descendants of listed concepts).**

| Code     | Name                                     | Domain    | Vocabulary |
|----------|------------------------------------------|-----------|------------|
| 441542   | Anxiety                                  | Condition | SNOMED     |
| 317009   | Asthma                                   | Condition | SNOMED     |
| 438409   | Attention deficit hyperactivity disorder | Condition | SNOMED     |
| 46271022 | Chronic kidney disease                   | Condition | SNOMED     |
| 4212540  | Chronic liver disease                    | Condition | SNOMED     |
| 255573   | Chronic obstructive pulmonary disease    | Condition | SNOMED     |
| 37311061 | COVID-19                                 | Condition | SNOMED     |

|         |                                        |           |        |
|---------|----------------------------------------|-----------|--------|
| 201606  | Crohn's disease                        | Condition | SNOMED |
| 4182210 | Dementia                               | Condition | SNOMED |
| 440383  | Depressive disorder                    | Condition | SNOMED |
| 201820  | Diabetes mellitus                      | Condition | SNOMED |
| 320128  | Essential hypertension                 | Condition | SNOMED |
| 318800  | Gastroesophageal reflux disease        | Condition | SNOMED |
| 192671  | Gastrointestinal hemorrhage            | Condition | SNOMED |
| 439727  | Human immunodeficiency virus infection | Condition | SNOMED |
| 432867  | Hyperlipidemia                         | Condition | SNOMED |
| 4329847 | Myocardial infarction                  | Condition | SNOMED |
| 433736  | Obesity                                | Condition | SNOMED |
| 80180   | Osteoarthritis                         | Condition | SNOMED |
| 381270  | Parkinson's disease                    | Condition | SNOMED |
| 255848  | Pneumonia                              | Condition | SNOMED |
| 140168  | Psoriasis                              | Condition | SNOMED |
| 4030518 | Renal impairment                       | Condition | SNOMED |
| 435783  | Schizophrenia                          | Condition | SNOMED |
| 4159647 | Thromboembolic disorder                | Condition | SNOMED |
| 81893   | Ulcerative colitis                     | Condition | SNOMED |
| 4291005 | Viral hepatitis                        | Condition | SNOMED |
| 4134440 | Visual system disorder                 | Condition | SNOMED |

Table S9. List of concepts used to describe procedures (concept sets included all descendants of listed concepts).

| Code    | Name                                   | Domain    | Vocabulary |
|---------|----------------------------------------|-----------|------------|
| 4301351 | Surgical procedure                     | Procedure | SNOMED     |
| 4120445 | Hemopoietic stem cell transplant       | Procedure | SNOMED     |
| 4029715 | Radiation oncology AND/OR radiotherapy | Procedure | SNOMED     |

Table S10. List of concepts used to describe medications (concept sets included all descendants of listed concepts).

| Code     | Name                                                  | Domain | Vocabulary |
|----------|-------------------------------------------------------|--------|------------|
| 21601782 | Agents acting on the renin-angiotensin system         | Drug   | ATC        |
| 21602796 | Antibacterials for systemic use                       | Drug   | ATC        |
| 21604686 | Antidepressants                                       | Drug   | ATC        |
| 21604390 | Antiepileptics                                        | Drug   | ATC        |
| 21603932 | Antiinflammatory and antirheumatic products           | Drug   | ATC        |
| 21601387 | Antineoplastic agents                                 | Drug   | ATC        |
| 21602028 | Antipsoriatics                                        | Drug   | ATC        |
| 21600960 | Antithrombotic agents                                 | Drug   | ATC        |
| 21601664 | Beta blocking agents                                  | Drug   | ATC        |
| 21601744 | Calcium channel blockers                              | Drug   | ATC        |
| 21601461 | Diuretics                                             | Drug   | ATC        |
| 21600046 | Drugs for acid related disorders                      | Drug   | ATC        |
| 21603248 | Drugs for obstructive airway diseases                 | Drug   | ATC        |
| 21600712 | Drugs used in diabetes                                | Drug   | ATC        |
| 21602472 | Hormonal contraceptives for systemic use              | Drug   | ATC        |
| 21603890 | Immunosuppressants                                    | Drug   | ATC        |
| 21601853 | Lipid modifying agents                                | Drug   | ATC        |
| 21604254 | Opioids                                               | Drug   | ATC        |
| 21604489 | Psycholeptics                                         | Drug   | ATC        |
| 21604752 | Psychostimulants, agents used for adhd and nootropics | Drug   | ATC        |

Table S11. List of concepts used to describe AJCC/UICC stage categories (concept sets included all descendants of listed concepts).

| ID      | Name              | Domain      | Vocabulary      |
|---------|-------------------|-------------|-----------------|
| 1633306 | AJCC/UICC Stage 1 | Measurement | Cancer Modifier |
| 1634209 | AJCC/UICC Stage 2 | Measurement | Cancer Modifier |
| 1633650 | AJCC/UICC Stage 3 | Measurement | Cancer Modifier |
| 1633308 | AJCC/UICC Stage 4 | Measurement | Cancer Modifier |

## ANNEX III. Additional information

### DATA MANAGEMENT

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: <https://ohdsi.github.io/CommonDataModel> and in The Book of OHDSI: <http://book.ohdsi.org>

The analytic code for this study was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing patient-level data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

#### Data storage and protection

For this study, personal data from individuals in various EU member states were processed, using information collected from national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

### QUALITY CONTROL

#### General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI <http://book.ohdsi.org/DataQuality.html>). In particular, all data partners ran the OHDSI *DataQualityDashboard* tool (<https://github.com/OHDSI/DataQualityDashboard>). This tool provides numerous checks relating to the conformance, completeness, and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions. Completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

#### Study specific quality control

The SNOMED codes of the conditions and outcomes of interest were derived from ATLAS. The codes were then reviewed by two clinical epidemiologists to consider their relevance and accuracy. In addition, the *CohortDiagnostics* R package (<https://github.com/OHDSI/CohortDiagnostics>) was run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed for a consideration of the validity of the study cohort of patients with the selected conditions and outcomes in each of the databases and informed decisions around whether multiple definitions were required.

## ANNEX IV: Glossary

### Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

### Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

### Common Data Model (CDM)

A standardised data structure that enables data from multiple sources to be harmonised, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

### Complex Studies

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

### Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Center in Rotterdam, Netherlands .

### Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

### Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

### Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

### DARWIN EU®

The European Medicines Agency's (EMA) and European medicines regulators federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

### EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

### Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

### Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

### GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

### Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

### Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

### Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

### OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

### Patient-Level Data

Data related to individual patients, often de-identified, used for longitudinal or detailed analyses.

### OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

### Real-World Data (RWD)

Data relating to patient health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

### Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

### Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

### Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

### Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

### Very Complex Studies

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.