

EMA-led RWE generation

Studying GLP1-RA safety

Frailty and polypharmacy in cancer

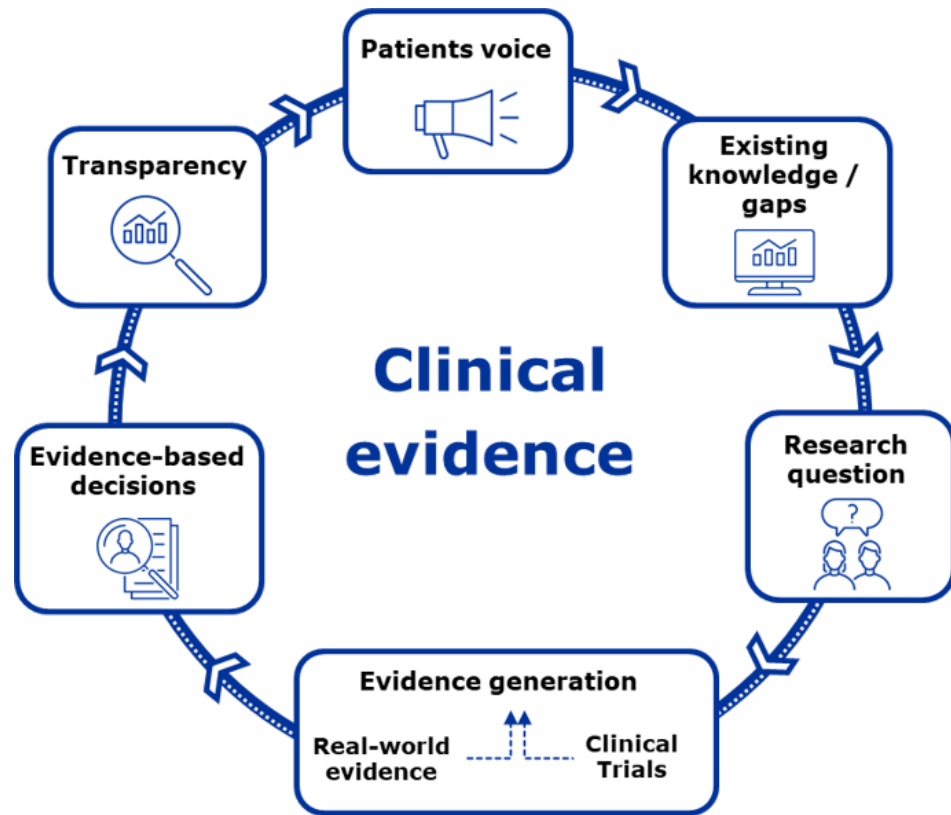
Presented by Daniel Morales – November 2025
PCWP/HCPWP meeting

Data Analytics and Methods Taskforce



Generating clinical evidence

Shared vision towards 2030



- **Patient** voice guides every step of the way
- Evidence generation is **planned** and guided by purpose, data, knowledge and expertise
- Research question **drives** evidence choice and embraces spectrum of data and methods
- Clinical trials remain core but should be **better, faster** and **optimised**
- Real world evidence is **enabled**, and its value is **established**
- High **transparency** level underpins societal trust

Clinical evidence 2025

Real world evidence

Enable the use and establish the value of RWE

- Enable data access (including via EHDS)
- Build processes
- Set standards
- Validate methods
- Train/share knowledge and manage change
- Establish value across various use cases
- Internationalise (build on ISPE-ISPOR, ICMRA, ICH)





RWD and RWE play a crucial role in bridging the gap between clinical research and practice

&

In the EU, generation of RWE for regulatory purpose already occurs



3 main pathways to use RWD for generating RWE



Studies using in-house databases

- **Primary and secondary care** health records from **Germany and UK**, and claims data from Europe (incl. Switzerland and United Kingdom), Australia, Canada, Japan and USA



Studies procured through EMA FWCs

- Framework contract (FWC) since September 2021: services of **8 research organisations** and academic institutions
- Access to **wide network of data**: 59 data sources in 21 EU countries
- Ability to leverage external **scientific expertise**



DARWIN EU®*

- EMA's federated network of data and services
- Covers 180 million patient records
- Built on the OMOP common data model

GLP-1 receptor agonists and suicidal ideation in patients with Type 2 diabetes mellitus (T2DM)

GLP-1 receptor agonists and suicidal ideation in T2DM

Background of signal


- Signal raised in PRAC following post marketing cases July 2023
- Literature articles on GLP1-RA showed either no change in the risk of depression/self-harm or a lower risk of depression/suicidality with the use of GLP1-RA.
- *Luppino et al 2010 and Tareen et al 2017:*

- Obesity
- Diabetes mellitus type II } ↑ depression

- Potential association with the underlying condition

- Previous mental health diagnosis in patients with:

- T2D
- obesity
- obesity and T2D } ↑ suicide ideation and suicide attempt

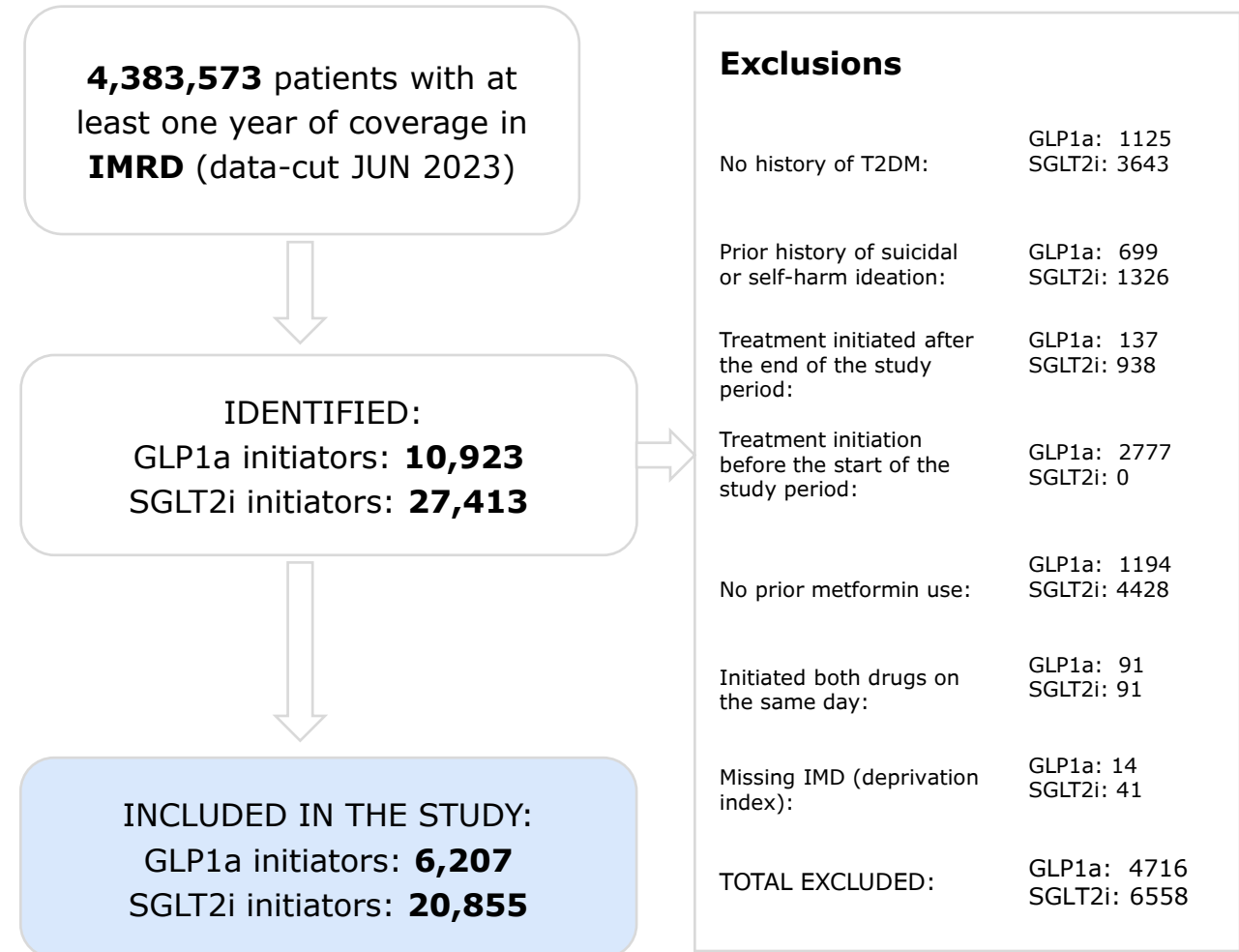
- Without prior mental health diagnosis =  suicide ideation and suicide attempt

The underlying mental health status of the population complicates the assessment of association with depression/suicide/self-injury

GLP-1 receptor agonists and suicidal ideation in T2DM

Study design

Design:	Cohort , active comparator, new user in IMRD (UK)
Eligibility (at index date):	History of T2DM and metformin No history of suicidal/self-harm ideation
Treatment strategies:	Initiation of GLP1-RA Initiation of SGLT2i
Study period:	March 2013 – June 2023
Outcome:	Composite endpoint of suicide- and self-harm-related events



GLP-1 receptor agonists and suicidal ideation in T2DM

Drug Exposure

Substance		No. of individuals initiating each drug	% of individuals initiating each drug
GLP-1 receptor agonists			
Liraglutide		1922	30.97
Semaglutide	83.5%	1638	26.39
Dulaglutide		1619	26.08
SGLT-2 inhibitors			
Dapagliflozin		10527	50.48
Empagliflozin	97.6%	7410	35.53
Canagliflozin		2412	11.57

Composite outcome

Clinical terms included in outcome definition	N	Percent
Suicidal thoughts	85	28.3
PHQ9 score - thoughts of suicide or self-harm	77	25.7
Suicidal ideation	46	15.3
Intentional drug overdose	14	4.7
Thoughts of deliberate self-harm	12	4.0
Moderate suicide risk	9	3.0
Deliberate drug overdose / other poisoning	9	3.0
Suicidal	8	2.7
Suicide attempt	7	2.3
Intentionally harming self	6	2.0
At risk of DSH - deliberate self-harm	5	1.7
Other suicide-related codes	22	7.3
Total	300	100.0

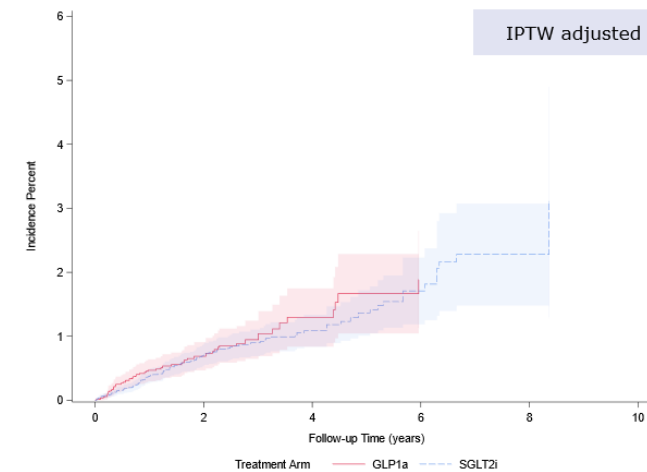
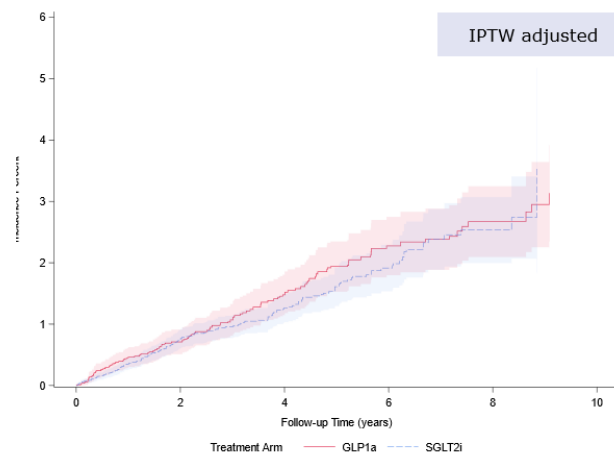
GLP-1 receptor agonists and suicidal ideation in T2DM

Intention-to-treat

On-treatment

Treatment arm	N	n events	Hazard ratios (95% CI)
<i>Unadjusted analysis</i>			
GLP-1 receptor agonist	6207	125.0	1.71 (1.35-2.16)
SGLT-2 inhibitors	20855	175.0	[Reference]
<i>IPTW adjusted analysis</i>			
GLP-1 receptor agonist	6103	81.8	1.10 (0.86-1.41)
SGLT-2 inhibitors	20923	200.0	[Reference]

Treatment arm	N	n events	Hazard ratios (95% CI)
<i>Unadjusted analysis</i>			
GLP-1 receptor agonist	6207	60.0	1.65 (1.20-2.26)
SGLT-2 inhibitors	20855	110.0	[Reference]
<i>IPTW adjusted analysis</i>			
GLP-1 receptor agonist	6103	41.1	1.11 (0.80-1.56)
SGLT-2 inhibitors	20923	120.4	[Reference]



GLP-1 receptor agonists and risk of suicide- and self-harm-related events among T2DM patients

The RWE study conducted by EMA , based on electronic health records, examined the risk of suicidal thoughts and thoughts of self-harm in people with type 2 diabetes mellitus. The results did not support a causal association between the use of GLP-1 receptor agonists and the risk for these cases.

After reviewing the available evidence from pre-clinical studies, clinical trials, post-marketing surveillance and the published literature, the PRAC considered that **no update to the product information is warranted**.*

[*Meeting highlights from the Pharmacovigilance Risk Assessment Committee \(PRAC\) 8-11 April 2024](#)

[EU regulator rules out link between weight-loss drugs and suicidal thoughts](#)

CGTN - April 13, 2024

Wegovy pens move along a packaging line at Novo Nordisk's facility in Hillerod, Denmark, March 8, 2024.

/Reuters The European Union drug ...

... drugmaker Novo Nordisk rose more than 2 percent after the **European Medicines Agency (EMA)** released its findings. Novo said it will continue ...

[No link between Ozempic, Wegovy and suicide, EU drug regulators say](#)

The Washington Post - April 12, 2024

... (David J. Phillip/AP) Drug regulators in Europe have found no evidence that popular diabetes and weight-loss drugs like Ozempic and Wegovy ...

David J. Phillip/AP) **Drug regulators** in **Europe** have found no evidence that popular diabetes and weight-loss drugs like Ozempic and Wegovy ...

[EMA Probe Finds No Link Between GLP-1s And Suicidal Thoughts & Actions](#)

Pink Sheet RSS Feed - April 12, 2024

After reviewing the evidence from non-clinical studies, clinical trials, post-marketing surveillance data and other studies, the European ...

After reviewing **the** evidence from non-clinical studies, clinical trials, post-marketing surveillance data and other studies, **the** European ...

[EU Probe Finds No Added Suicide Risk Linked to Novo's Wegovy](#)

BNN Bloomberg - April 12, 2024

... (Bloomberg) -- The **European** Union's **drug regulator** found no added risk of suicide or self-harm for

GLP-1 receptor agonists and risk of suicide- and self-harm-related events among T2DM patients

Association between exposure to GLP-1 receptor agonists and risk of suicide-related and self-harm-related events

First published: 07/03/2024 Last updated: 15/04/2024

EU PAS number: EUPAS1000000052

Signal in July 2023 / Study started in Sep 2023 / Results provided to PRAC in **Oct 2023**

JAMA Internal Medicine | [Original Investigation](#)

GLP-1 Receptor Agonist Use and Risk of Suicide Death

Peter Ueda, MD, PhD; Jonas Söderling, PhD; Viktor Wintzell, PhD; Henrik Svanström, PhD; Laura Pazzagli, PhD; Björn Eliasson, MD, PhD; Mads Melbye, MD, DrMedSci; Anders Hviid, DrMedSci; Björn Pasternak, MD, PhD

Published in **Sep 2024**

Glucagon-like peptide-1 receptor agonists and risk of suicidality among patients with type 2 diabetes: active comparator, new user cohort study

Samantha B Shapiro,^{1,2} Hui Yin,¹ Oriana Hoi Yun Yu,^{2,3,4} Soham Rej,^{5,6} Samy Suissa,^{1,2,7} Laurent Azoulay^{1,2,8}

Published in **Feb 2025**

Compared to SGLT-2 inhibitors users (in the UK),

Risk of suicide-related and self-harm events – Adjusted HR 1.10 (0.86-1.41)

Risk of suicide-related events (only) – Adjusted HR 1.08 (0.83-1.39)

Compared to SGLT-2 inhibitors users (in Sweden & Denmark),

Risk of suicide death and nonfatal self-harm events – Adjusted HR 0.83 (0.70-0.97)

Risk of suicide death – Adjusted HR 1.25 (0.83-1.88)

Compared to SGLT-2 or DPP4 inhibitors users (in the UK),

Risk of suicidal ideation, self-harm and suicide events – Adjusted HR 1.02 (0.85-1.23)

Risk of suicidal ideation, self-harm and suicide events – Adjusted HR 0.91 (0.73-1.12)

Frailty and polypharmacy among adults with selected cancers at diagnosis

Geriatric Medicines Strategy

Vision

- Ensure high-quality, thoroughly evaluated medicines for older populations.
- Enhance informed prescription through improved availability of data.

Key actions

1. Medicines Development

- Provide tailored scientific advice for geriatric medicine development.
- Identify and validate tools for assessing "frail" patients.
- Integrate geriatric requirements into guidelines.

2. Medicines Evaluation

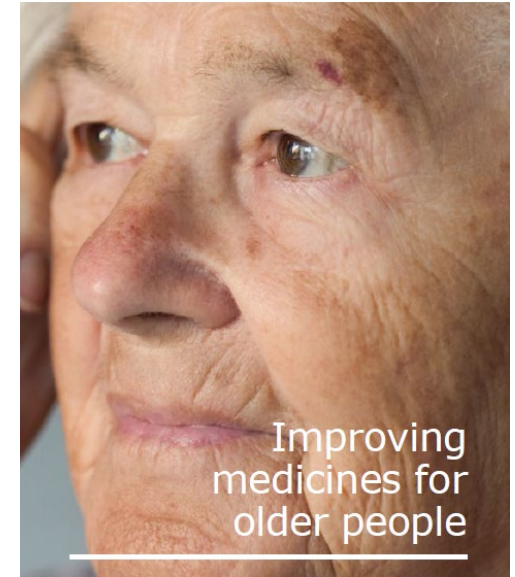
- Assess safety and efficacy in older adults during evaluations.
- Record and analyse geriatric-specific study data.
- Incorporate geriatric considerations into post-authorisation safety measures.

3. Stakeholder Engagement

- Collaborate with geriatric experts and organizations.
- Maintain updated resources and conduct workshops on ageing-related healthcare.



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SCIENCE MEDICINES HEALTH



An agency of the European Union 

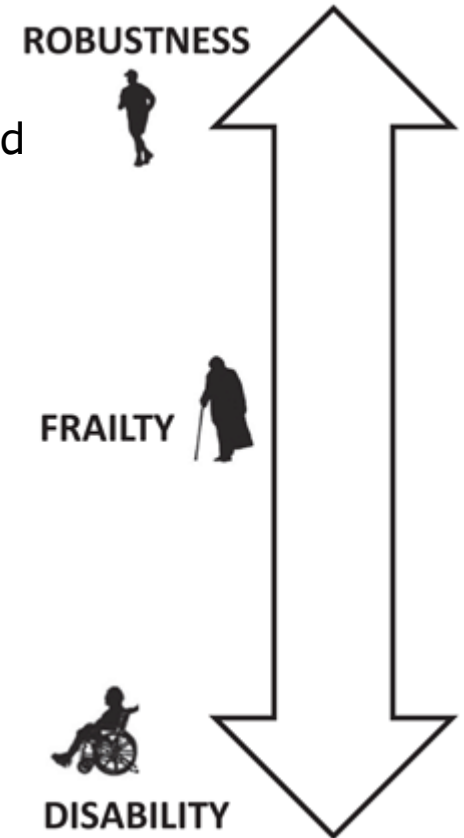
Reflection paper on physical frailty

The problem

- Frailty is a clinical syndrome characterised by a decrease in physiological resilience, and increased susceptibility to stressors. Originally a feature of age-related decline.
- Frailty and polypharmacy are major factors for older adults due to increased risks of treatment complications, hospitalisation, and mortality.
- Historically, older and frail populations are underrepresented in trials, limiting generalisability of results.

Why account for frailty in studies

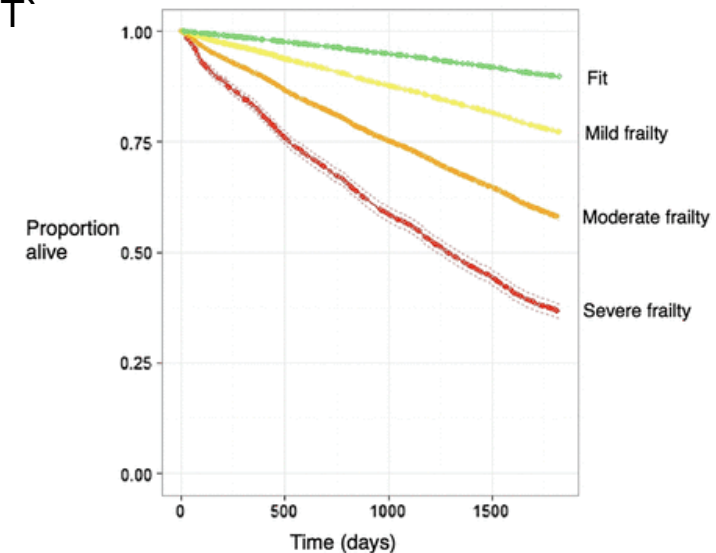
- Predefine frailty subgroups and stratify trial participants.
- Use frailty metrics to inform dose adjustments and predict adverse events.
- Integrate results into trial outcomes to better reflect real-world populations.



Reflection paper on physical frailty

Challenge

- No consensus definition
- Clinical frailty evaluation requires MDT **Comprehensive Geriatric Assessment**
 - Physical and cognitive function, nutritional status, multimorbidity, medications and SE factors
- Several frailty instruments have been tested and validated
 - **Short Physical Performance Battery**: Comprehensive, long-term prognostic accuracy (RCT)
 - **Gait Speed**: Easier to implement but less multifaceted (RCT)
 - **ECOG** performance status scale (RCT)
 - eFI / eFRAGICAP (database)
 - Hospital frailty risk score (database)
 - etc.





Study Report

P2-C1-009

DARWIN EU[®] – Frailty and polypharmacy among adults with selected cancers at the time of diagnosis

Study Objectives and Design

Objectives

1. Estimate the prevalence of frailty and polypharmacy in adults aged 18+ with selected cancers at diagnosis.
2. Describe the characteristics of adults with cancer, focusing on frailty and polypharmacy categories.

Study Design

- **Type:** Population-based cohort study.
- **Data Sources:** Six (CPRD GOLD, UK; IQVIA DA Germany and Belgium; SIDIAP, ES; IPCI, NL; EBB, Estonia).
- **Population:** Adults aged 18+ with one of ten cancers (lung, breast, ovary, endometrium, prostate, pancreas, colorectal cancer, lymphoma, leukaemia and myeloma) diagnosed between 2017-2022. Excludes those with prior cancer diagnoses.

Key Variables

- **Frailty Score:**
 - Components: 36 including polypharmacy, chronic diseases, disabilities, symptoms (based upon eFI)
 - Frailty levels: Fit, Mild, Moderate, Severe.
- **Polypharmacy:**
 - Standard: ≥ 5 medications prescribed within 90 days pre-diagnosis.
 - Extreme: ≥ 10 medications prescribed within the same period.

Components of the RWE frailty score

Disease States

- Anaemia
- Arthritis
- Atrial fibrillation
- Chronic kidney disease
- Cerebrovascular disease
- Diabetes
- Foot problems
- Fragility fracture
- Heart failure
- Heart valve disease
- Hypertension
- Hypotension
- Ischaemic heart disease
- Osteoporosis
- Parkinsonism and tremor
- Peptic ulcer
- Peripheral vascular disease
- Respiratory disease
- Skin ulcer
- Thyroid disease
- Urinary system disease

Symptoms/signs

- Dyspnoea
- Dizziness
- Falls
- Memory and Cognitive problems
- Sleep disturbance
- Urinary incontinence
- Weight loss and anorexia

Disability

- Activity limitation
- Hearing impairment
- Housebound
- Mobility transfer
- Requiring care
- Social vulnerability
- Visual impairment

Significant coding exercise to define frailty in this way

Outcomes and analysis

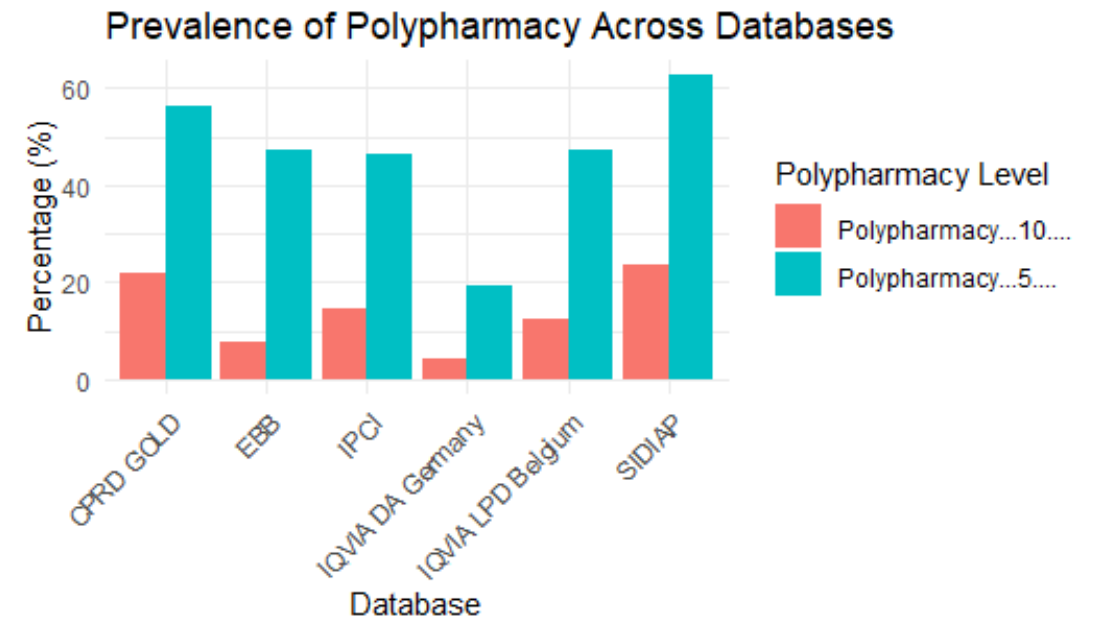
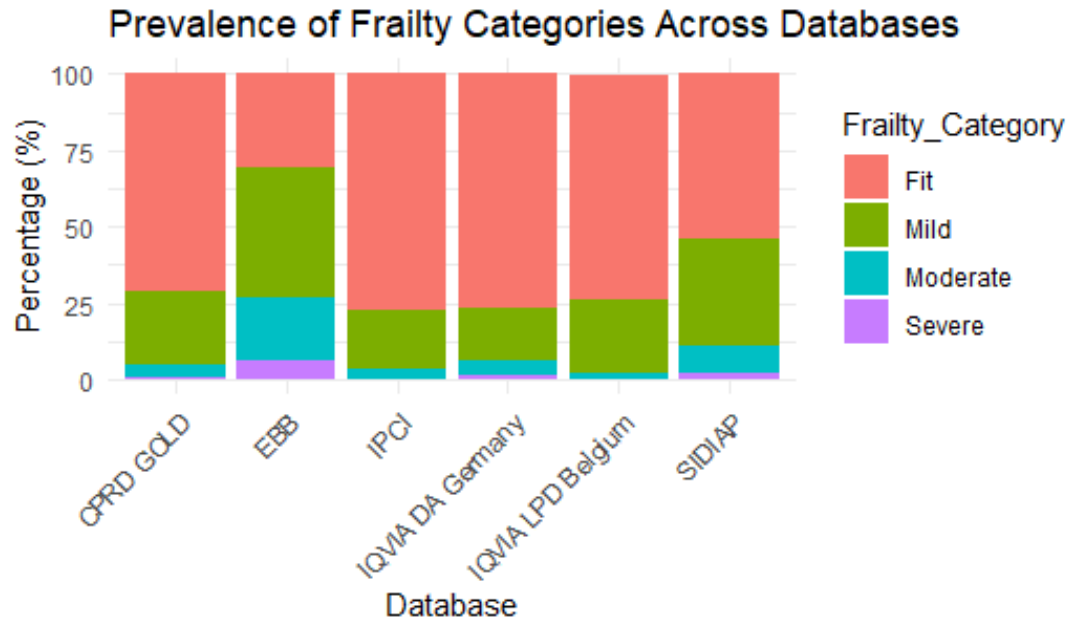
Outcomes

- **Hospitalisation:** Percentage hospitalised after one-year post-cancer diagnosis.
- **Mortality:** Percentage died after one-year post-cancer diagnosis.

Data Analysis

- **Prevalence Estimation:** Frailty, frailty categories, and polypharmacy by cancer type.
- **Stratification:** By age group (18-44, 45-64, 65-74, 75-84, 85+), sex, and pre-/post-2020 (COVID-19 impact).
- **Patient-Level characterisation:** Analyses per frailty and polypharmacy category, including age, sex, medical history, and medication use.

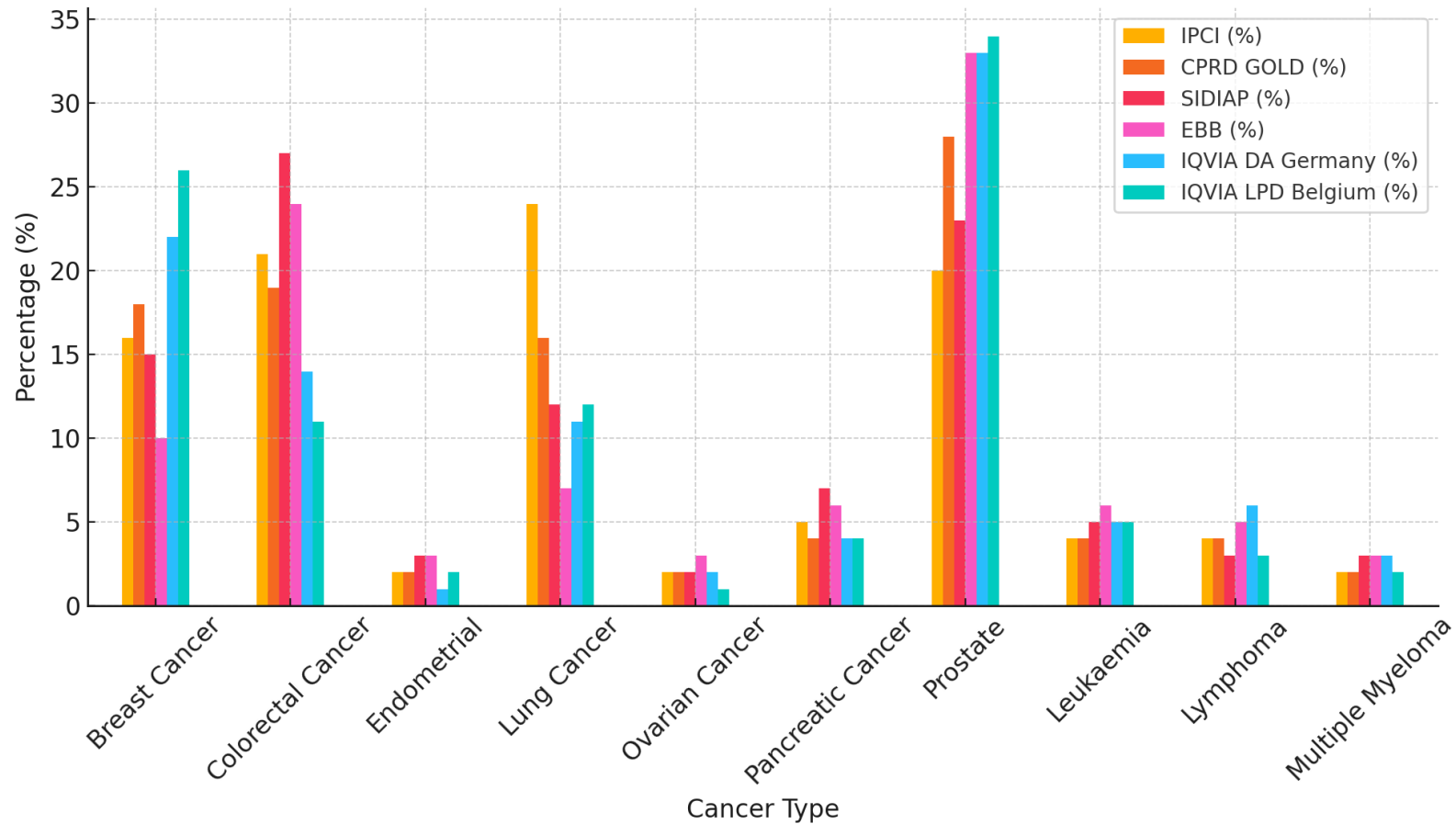
Prevalence of frailty categories and polypharmacy (aged ≥ 65) for any cancer



- The study involved 350,203 individuals, 66% were ≥ 65 yrs
- The highest frailty rates are observed in EBB, while the lowest are in IQVIA DA Belgium/IPCI.
- Frailty prevalence varies by database. For example, IPCI shows 1.8% moderate frailty in ages 65-74 vs 20.5% in EBB. Severe frailty shows a similar pattern.

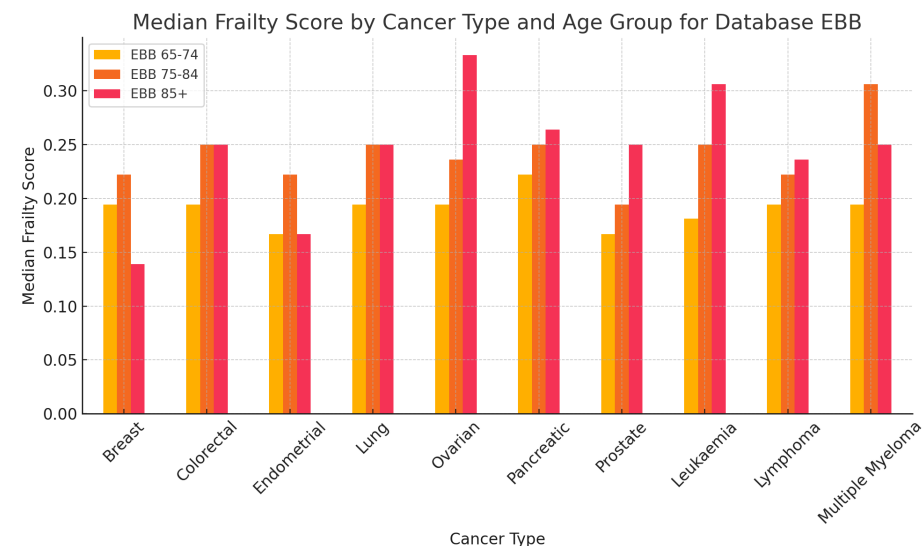
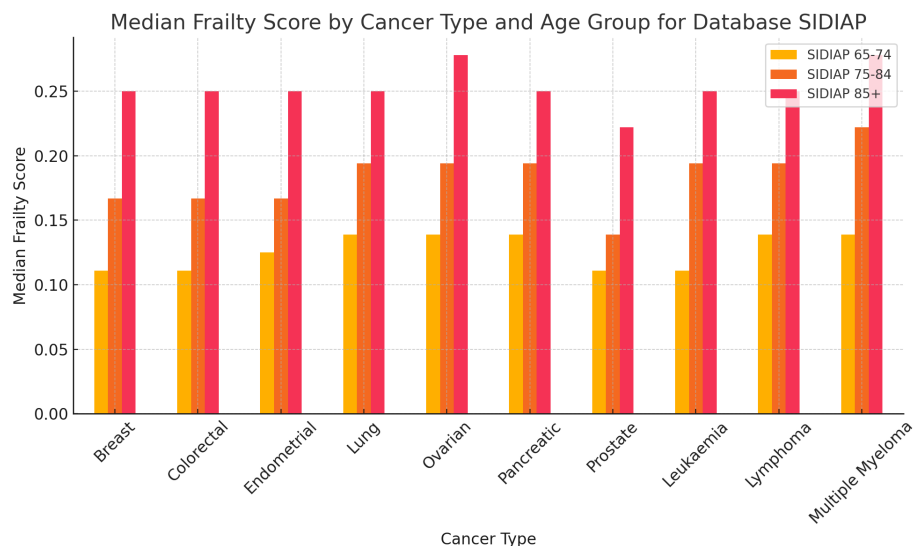
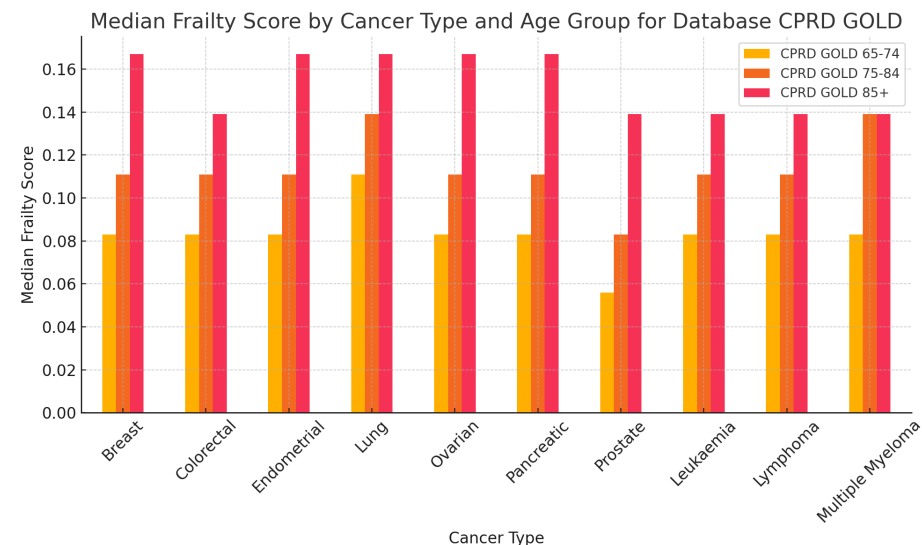
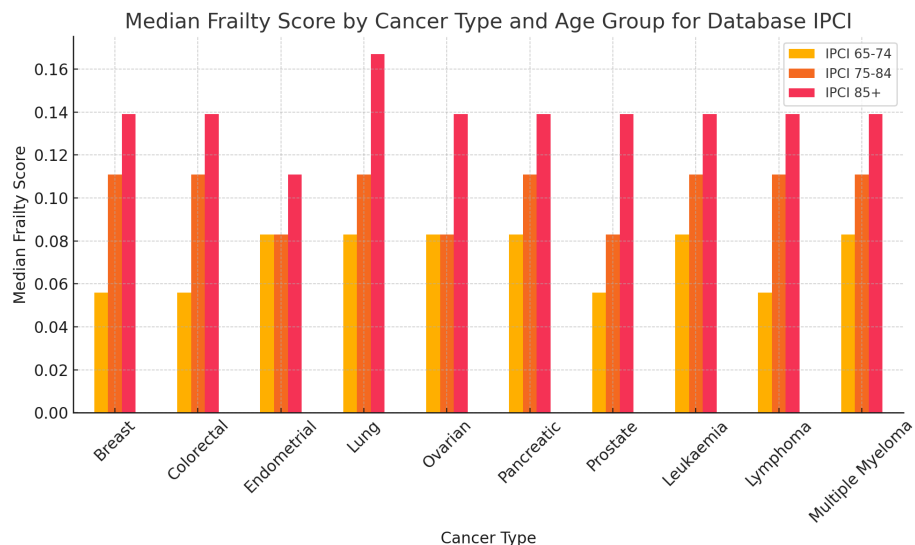
- The highest polypharmacy rates are observed in SIDIAP, while the lowest are in IQVIA DA Germany.
- Polypharmacy, increases with age. For example, among those aged 65-74, prevalence is between 19.4%-62.6% vs 38%-85.6% for 85+.

Distribution of cancer types by database in older adults (aged ≥ 65)



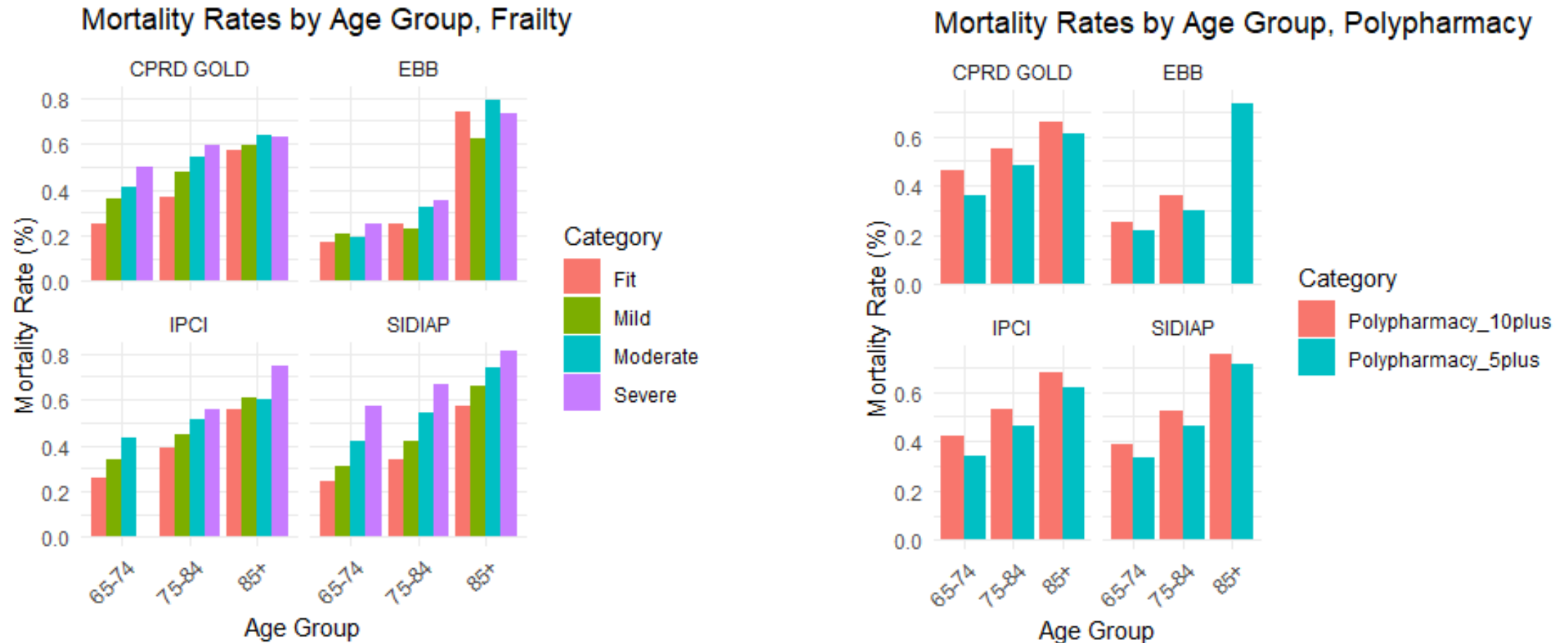
- Breast, colorectal, prostate, and lung cancers are the most prevalent across databases, though distributions vary. For example, breast cancer is more common in IQVIA LPD Belgium (26%), while colorectal cancer peaks in SIDIAP (27%).

Median frailty score by cancer type and age group (aged ≥ 65)



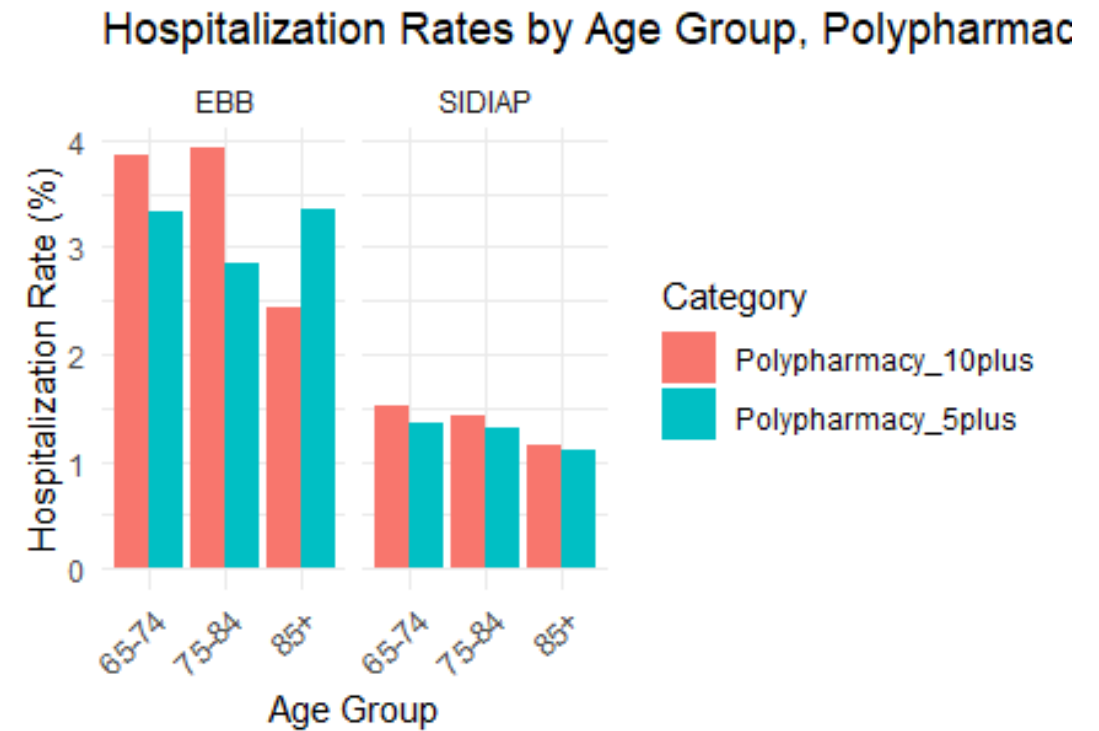
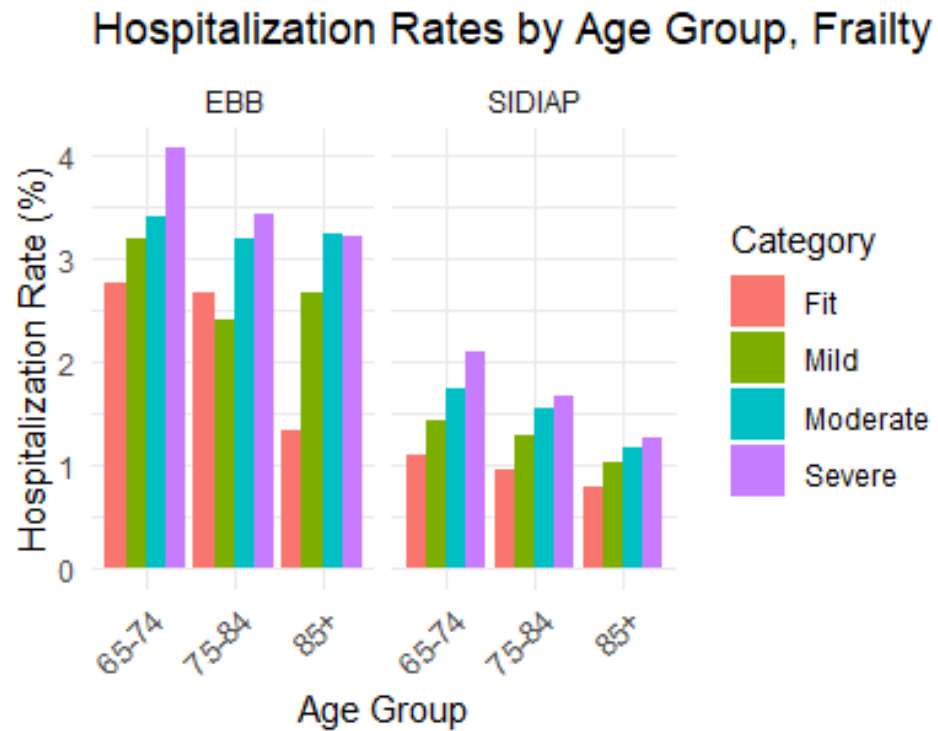
Frailty scores increase with age for specific cancer types. Differences in frailty by cancer type are evident, with certain cancers such as ovarian and multiple myeloma showing higher frailty scores in older age groups.

Mortality according to frailty and polypharmacy category (aged ≥ 65)



- Mortality risk rises with increasing frailty and polypharmacy.
- For instance, in IPCI, mortality rates increase from 0.26 for fit individuals to higher rates for those with severe frailty.
- Similar data for each cancer type has also been generated

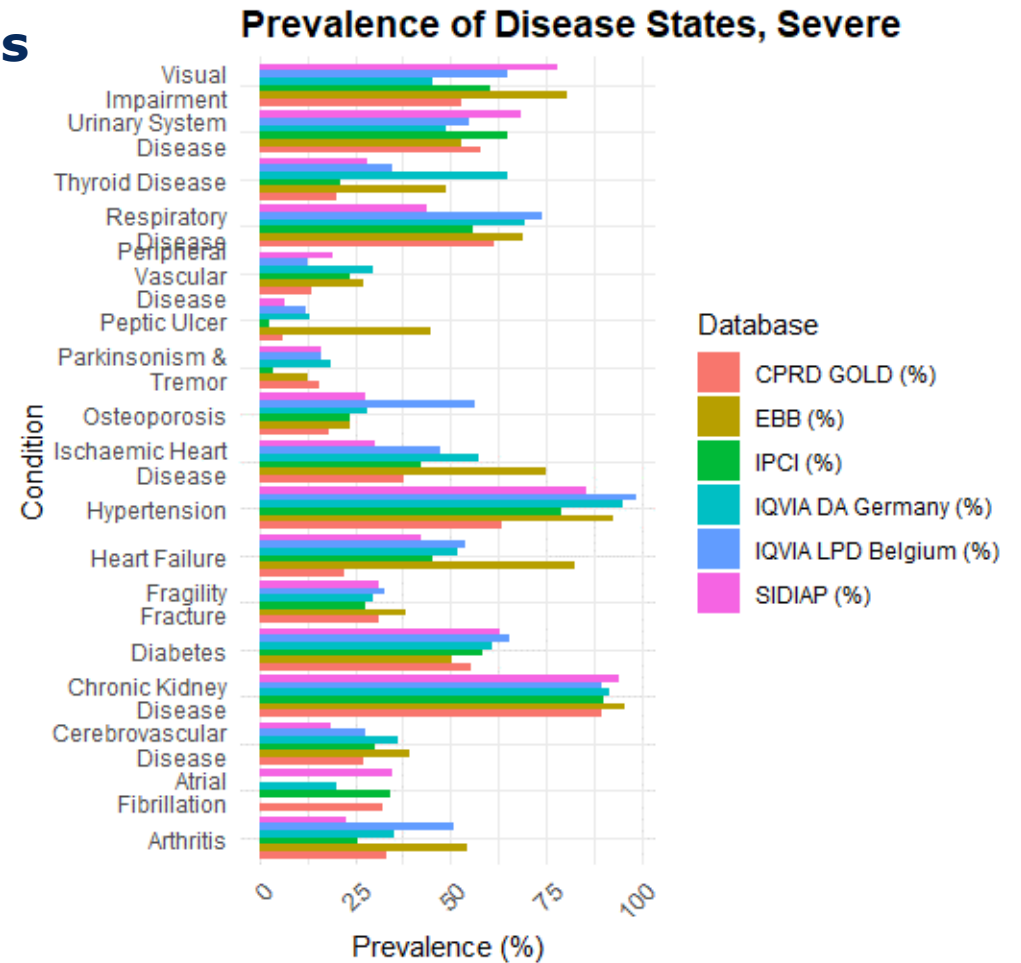
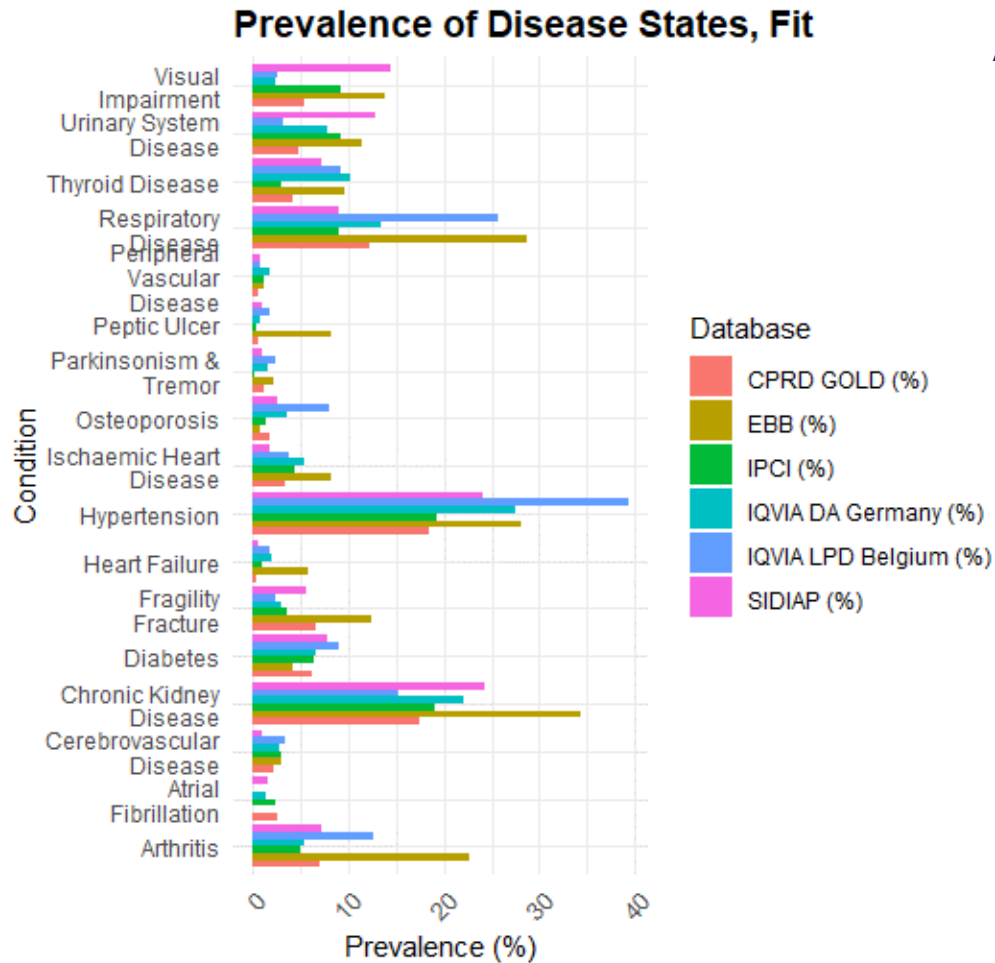
Hospitalisation according to frailty and polypharmacy category (aged ≥ 65)



- One-year hospitalisation rates increase with frailty severity and polypharmacy levels.
- For example, in SIDIAP, hospitalisation rates for ages 65-74 range from 1.10 for fit individuals to 2.09 with severe frailty.
- The patterns differ by database and decrease slightly with age.
- Similar data for each cancer type has also been generated.

Prevalence of individual deficits of the frailty score in fit vs severe frailty

All ages



- Higher prevalence: Respiratory diseases, hypertension, CKD, arthritis

- Higher prevalence: Respiratory diseases, hypertension, CKD, IHD, Visual impairment, Urinary system disease, Heart Failure, Diabetes

Summary: frailty and polypharmacy in selected cancer population

Frailty

- Most people with cancer were classified as "fit," but frailty (mild to severe) was prevalent in 23.7% to 58.3%.
- Frailty increased with age.
- Hospitalisation and mortality increased with increasing frailty.

Polypharmacy

- Polypharmacy (≥ 5) was common, especially among older adults, ranging from 19% to 56.2%.
- Polypharmacy rates increased with frailty severity and age.

Limitations

- Data quality limitations for some frailty score components were noted (e.g. disabilities), which varied across databases. Potential for improvement.
- Frailty estimates in the study are therefore **conservative** frailty measures.
- Hospitalisation data were only reliably recorded in SIDIAP and EBB, and mortality data were unavailable in two databases.

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Where do we see the role of frailty in medicines regulation?

How can RWE support complementary evidence generation on frailty?



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Thank you

daniel.morales@ema.europa.eu

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