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POTENTIAL OVERTREATMENT DURING LIFE-LIMITING ILLNESS AND END OF LIFE IN OLDER ADULTS

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Potential overtreatment during life-limiting illness and end of life in older adults

Thesis for Doctoral Degree (Ph.D.)

By

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To my late grandfather

The efforts finally bore fruit

The best way out is always through

Robert Frost - A Servant To Servants

Popular science summary of the thesis

Ageing is a complex process that ultimately leads to death. With improved public health in many parts of the world over the past century, age-related chronic diseases and neurodegenerative disorders have emerged as leading causes of death, often following a foreseeable end-of-life trajectory. As death nears, the focus of medical care typically shifts from prolonging life to managing symptoms and providing comfort. Treatments that take a long time to show benefits become less relevant, especially for older individuals. Yet, such treatments are frequently continued for patients nearing the end of their lives, a practice termed *potential overtreatment*. Overtreating older individuals close to death can compromise their quality of life, expose them to unnecessary risks of adverse events, disrupt their care, and may not align with their end-of-life preferences. However, not *all* treatments at the end of life are overtreatment, some are adequate, beneficial and in line with patient preferences when evaluated on a case-by-case basis.

The overarching aim of this doctoral thesis was to evaluate the quality of end-of-life care in older adults, with a particular focus on potential overtreatment and life-limiting illness, using nationwide administrative healthcare data. By leveraging these accessible and high-quality data sources, we aimed to assess the extent, determinants, and consequences of potential overtreatment during life-limiting illness and end of life of older adults. We contributed to addressing the overarching aim with four individual studies, each exploring different facets of potential overtreatment.

In **Study I**, we investigated the prevalence of potential overtreatment at the end of life among older people with solid cancer. This task proved challenging because nearly half of the measurements we identified, so called quality indicators, could not be calculated using the Swedish administrative and healthcare registers. Since the data were originally collected for administrative rather than research purposes, vital patient outcome information was missing, impeding our calculations. Nonetheless, based on the indicators we were able to measure, we estimated that approximately one third of older patients with solid cancer experienced potential overtreatment during their last month of life.

Next, in **Study II**, we described the patterns of unplanned hospitalisations during the last year of life for older individuals. We specifically focused on unplanned hospitalisation, as opposed to planned care transitions, because they have greater potential to disrupt care processes, disorganise care and lead to adverse events. Our observations revealed that patients with different illness trajectories, such as cancer, organ failure and dementia, exhibited distinct patterns of unplanned hospitalisation in their final year of life. This differentiation became especially pronounced in the three months preceding death. Patients with cancer and organ failure, had the highest frequency of unplanned hospitalisation while older individuals with dementia, had a modest rise in unplanned admissions, predominantly in their final month of life.

In **Study III**, we examined the initiation and continuation of endocrine treatment, a systemic treatment for breast cancer, during the final three months of life. We found that among older women with metastatic breast cancer (where cancer spread to other organs) over one-third continued endocrine treatment and five per cent initiated treatment during the last three months of life; potentially beyond a point where the treatment could provide meaningful benefits. Additionally, our findings suggest that social and treatment-related factors, such as multi-dose dispensing, influence these treatment patterns.

Lastly, in **Study IV**, we studied the consequences of a potential drug-drug interaction between commonly used antidementia drugs, specifically cholinesterase inhibitors, and non-steroidal anti-inflammatory drugs, in individuals with life-limiting illness. We discovered a nine-fold increase in the risk of peptic ulcer (sores in the stomach) when these two types of drugs are concurrently prescribed, with women and older individuals being disproportionately affected.

In conclusion, our findings suggest that older adults and those with life-limiting illness may be exposed to various forms of potential overtreatment towards the end of their lives. We derived this conclusion from nationwide administrative and healthcare datasets, which do not record patients' preferences or allow for individual assessment of treatment appropriateness. Nonetheless, overly intensive care near the end of life typically contradicts patient preferences and increases the risk of adverse events. In this thesis, we argued against potential overtreatment neither to ration healthcare nor from economic reasons. Instead, our emphasis was on ensuring patients achieve the highest possible quality of life, spend their final months in alignment with their wishes, and avoid unnecessary and avoidable risks.

Sammanfattning

Åldrande är ett komplext fenomen som oundvikligen leder till döden. Med förbättrad folkhälsa i många delar av världen under det senaste århundradet har åldersrelaterade kroniska sjukdomar och neurodegenerativa sjukdomar blivit alltmer tongivande dödsorsaker, med en ofta förutsägbar sista del av livet. När döden närmar sig ändras vanligtvis de medicinska behandlingsmålen från att förlänga livet till att hantera symtom och bevara patientens komfort. Läkemedel och medicinska procedurer med 'lång tid till nytta' har då inte längre en plats i behandlingsrepertoaren. Dock fortsätter sådana behandlingar ofta för patienter ända till livets slut, ofta kallat potentiell överbehandling. Överbehandling av äldre personer nära döden kan minska deras livskvalitet, öka risken för oönskade händelser, orsaka oordning i vårdförloppet och är ofta inte i linje med hur patienterna önskar tillbringa sina sista månader. Viktigt att notera är att inte alla behandlingar vid livets slut är överbehandling. Vissa är adekvata och fördelaktiga när de utvärderas utifrån individuella behov.

Den övergripande målsättningen med denna doktorsavhandling var att utvärdera vårdkvaliteten för äldre personer vid livets slut, med särskilt fokus på potentiell överbehandling och sjukdomar med begränsad livslängd, med hjälp av nationella administrativa hälso- och sjukvårdsdata. Med hjälp av dessa lättillgängliga och högkvalitativa data syftade vi till att bedöma omfattningen, bestämningsfaktorerna och konsekvenserna av potentiell överbehandling vid sjukdomar med begränsad livslängd och vid livets slut för äldre vuxna. Vi bidrog till att adressera den övergripande målsättningen med fyra individuella studier som undersökte olika aspekter av potentiell överbehandling.

I **Studie I** undersökte vi förekomsten av potentiell överbehandling vid livets slut bland äldre personer med solida tumörer. Detta visade sig vara utmanande eftersom nästan hälften av de mått vi identifierade, så kallade kvalitetsindikatorer, inte kunde beräknas med hjälp av svenska administrativa och hälso- och sjukvårdsregister. Eftersom dessa data inte samlades in för forskning utan snarare för administrativa ändamål saknades viktig information om patientutfall, vilket omöjliggjorde beräkningar. Baserat på de indikatorer vi kunde mäta uppskattade vi emellertid att ungefär en tredjedel av äldre patienter med solida tumörer utsattes för potentiell överbehandling under sin sista månad i livet.

I **Studie II** beskrev vi mönstren av oplanerade sjukhusinläggningar under det sista året i livet för äldre individer. Vi fokuserade på oplanerade sjukhusinläggningar, i motsats till planerade sådana, eftersom det förstnämnda har större potential att bringa oordning i vårdförloppet och leda till oönskade händelser. Vi såg att patienter med olika sjukdomsförlopp, såsom cancer, organsvikt och demens, hade olika mönster av oplanerade sjukhusinläggningar under det sista året i livet. Skillnaderna mellan sjukdomsförloppen blev allt tydligare vid den tredje månaden före döden. Patienter med

cancer och organsvikt hade den högsta belastningen av oplanerade sjukhusinläggningar, medan äldre personer med demens hade en blygsam ökning av oplanerade inläggningar, främst under sin sista månad i livet.

I **Studie III** undersökte vi påbörjandet och fortsättningen av endokrin behandling, en systemisk behandling för bröstcancer, under de sista tre månaderna i livet. Vi rapporterade att bland äldre kvinnor med metastaserande bröstcancer, där cancern hade spridit sig till andra organ, fortsattes endokrin behandling av mer än en tredjedel av studiepopulationen och påbörjades av fem procent under de sista tre månaderna i livet, potentiellt bortom en punkt där den kunde erbjuda meningsfulla fördelar. Vi fann också potentiell bevis för att sociala och behandlingsrelaterade faktorer (till exempel apodos) påverkar behandlingsmönstren.

Slutligen, i **Studie IV**, studerade vi konsekvenserna av en potentiell läkemedelsinteraktion mellan vanligt förekommande demensläkemedel (så kallade kolinesterashämmare) och icke-steroida antiinflammatoriska läkemedel för patienter med sjukdom med begränsad livslängd. Vi upptäckte en niofaldig ökning av risken för magsår när dessa två typer av läkemedel föreskrevs samtidigt, med en oproportionerlig påverkan på kvinnor och äldre personer.

Sammanfattningsvis indikerar våra resultat att äldre vuxna och svårt sjuka individer potentiellt utsätts för olika former av överbehandling nära livets slut. Vi drar denna slutsats genom att använda administrativa och hälso- och sjukvårdsdata som inte registrerar patientens önskemål eller möjliggör utvärdering av behandlingens lämplighet på individuell patientnivå. Dock är potentiellt överdriven vård nära döden i allmänhet i strid med patientens preferenser och utsätter patienter för risker för oönskade effekter. I denna avhandling argumenterar vi mot potentiell överbehandling, inte för att ransonera sjukvård eller av ekonomiska skäl, utan snarare för att möjliggöra för patienter att uppnå sin högsta möjliga livskvalitet och tillbringa sina sista månader enligt sina önskemål, utan onödiga och undvikbara risker.

Abstract

Background. A growing body of evidence suggests that older patients are subject to potential overtreatment at the end of life, characterised by disease modifying therapies, preventive medications, and frequent care transitions. This occurs even though many older patients express a preference for symptom management and tend to avoid curative therapies near death. Nowadays age-related chronic diseases and neurodegenerative conditions are the top causes of death leading to a more foreseeable trajectory of decline at the end of life compared to compared to those who die suddenly or prematurely due to global pandemics. However, drugs and procedures, with longer time-to-benefit than the seriously ill older patients' life expectancy, are still administered causing potential adverse events, deteriorated quality of life and higher dependency.

Aim. The present doctoral thesis aimed to evaluate the quality of end-of-life care in older adults, with a focus on potential overtreatment and life-limiting illness. The four individual studies of the thesis contributed to this aim from different, yet complimentary aspects.

Study I. We identified overtreatment indicators in the existing literature and discovered that nearly half of them cannot be appropriately measured in administrative and healthcare data in Sweden. However, based on the 15 unique indicators that we could measure, we estimated that one third (36.9%) of patients with solid cancer received care in their last month of life deemed as potential overtreatment. Cancer-specific treatments were the most common form of potential overtreatment (27.0%), followed-by potentially futile non-cancer specific treatments (12.3%), and hospital transitions (9.4%).

Study II. We found that older decedents had an average 1.7 unplanned hospitalisations during their last year of life, which corresponded to an incidence rate of 175 per 100 person-years. Those with a cancer trajectory had the highest incidence rate at 231 per 100 patient-years, whereas individuals on a trajectory of prolonged dwindling had the lowest rate at 99 per 100 patient-years. Unplanned hospitalisations were unevenly distributed throughout the last year of life. From the third month before death, the incidence rate started to increase, which is the point where the different patterns of hospitalisation between illness trajectories became evident.

Study III. We reported that endocrine treatment, which is a systemic disease modifying treatment, was initiated by 5% in the last three months of life and continued by 39% of the older decedents with hormone receptor-positive metastatic breast cancer. We found several factors linked to continuation of treatment, for example, higher age (RR_{85+} years: 1.25 [1.12-1.41]), higher education ($RR_{\text{tertiary education}}$: 0.89 [0.81-0.98]), and multi-dose drug dispensing (RR: 1.22 [1.13-1.32]). Initiation of treatment was associated with, for instance, number of hospitalised days ($RR_{\text{1-14 inpatient days}}$: 1.81 [1.12-2.91]) and CDK4/6 use (3.16 [2.25-4.44]).

Study IV. Based on a self-controlled case series analysis, we discovered that the concomitant dispensation of cholinesterase inhibitors (ChEIs) and non-steroidal anti-inflammatory drugs (NSAIDs) resulted in a heightened risk of peptic ulcer disease (adjusted IRR: 9.0, 95% confidence interval: 6.8-11.8, E-value: 17.5) compared to periods without treatment. This risk was over and beyond the risks observed for NSAIDs alone (IRR 5.2, 4.4-6.0, E-value: 9.8). We found no evidence of increased risks associated with the use of ChEIs alone (IRR 1.0, 0.9-1.2, E-value: 1.2).

Conclusions. Our findings suggest that older adults and seriously ill individuals are potentially exposed to various types of treatment near the end of life that may be deemed as overtreatment, which warrants further attention from policy makers, healthcare professionals, researchers, and the society as a whole. Overly intensive care, fuelled by disease modifying treatments, preventive therapies and frequent transitions close to death is generally against the preferences of older people. Important to note that reducing or eliminating these types of treatments is not about rationing healthcare or denying treatment, but rather about ensuring that patients spend their last months in good quality care, characterised by symptom management and avoidance of unnecessary and preventable risks factors and adverse effects.

Keywords: Adverse effects, Ageing, End-of-life care, Life-limiting illness, Medications, Older people, Overtreatment, Palliative care, Quality indicators, Quality of care, Sweden

List of scientific papers

I. **Szilcz M**, Wastesson JW, Morin L, Calderón-Larrañaga A, Lambe M, Johnell K. Potential overtreatment in end-of-life care in adults 65 years or older dying from cancer: applying quality indicators on nationwide registries. *Acta Oncologica*. 2022;61(12):1437-1445.

II. **Szilcz M**, Wastesson JW, Johnell K, Morin L. Unplanned hospitalisations in older people: illness trajectories in the last year of life. *BMJ Supportive & Palliative Care*. 2021;bmjspcare-2020-002778.

III. **Szilcz M**, Wastesson JW, Calderón-Larrañaga A, Morin L, Lindman H, Johnell K. Endocrine treatment near the end of life among older women with metastatic breast cancer: a nationwide cohort study. *Frontiers in Oncology*. 2023;13

IV. **Szilcz M**, Wastesson JW, Calderón-Larrañaga A, Prieto-Alhambra D, Blotiere PO, Maura G, Johnell K. Cholinesterase inhibitors and non-steroidal anti-inflammatory drugs and the risk of peptic ulcers: a self-controlled study. *Accepted. Journal of the American Geriatrics Society. 2023*

Contents

List of abbreviations

ATC	Anatomical Therapeutic Chemical classification system
CDK4/6	Cyclin-dependent kinase 4 and 6 inhibitors
ChEIs	Cholinesterase Inhibitors
CI	Confidence Interval
DDDs	Defined Daily Doses
GEE	Generalised Estimating Equations
ICD	International Classification of Diseases
IQR	Interquartile Range
ISCED-97	International Standard Classification of Education 1997
IRR	Incidence Rate Ratio
LISA	Longitudinal integrated database for health insurance and labour market studies
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OECD	Organisation for Economic Co-operation and Development
RCT	Randomised Controlled Trial
RR	Risk Ratios
UK	United Kingdom
USD	United States Dollar
WHO	World Health Organization

1 Introduction

Life expectancy has continuously increased over recent decades due to improving population health in many parts of the world. This increase in the ageing population has led to a growing demand for healthcare for age-related chronic diseases, such as cancer and neurodegenerative conditions like dementia.[1,2] The transition from infectious diseases to chronic diseases as main causes of death has prolonged the end-of-life period. Since chronic conditions often have a lengthy and, at times, predictable end-of-life trajectory, it allows for the provision of anticipatory palliative care. As death approaches, medical treatment goals gradually transition from prolonging life to managing symptoms and alleviating disease burden to ensure high quality of life.[3–7] This shift in treatment goals is usually in line with patient wishes who prefer spending their last days with family and, if possible, dying at home.[8–13] Generally, treatments that may cause more harm than benefit are often referred to as *potential overtreatment*. Such treatments might include, but are not limited to, overly aggressive procedures, burdensome care transitions, systematic drug treatments and futile medication use that have no benefits (e.g., preventive treatments) or may result in drug-drug interactions. At the end of life, overtreatment can compromise the quality of care for patients and their families and it places an unnecessary burden for healthcare systems and society.

The quality of end-of-life care has primarily been studied in clinical settings. Consequently, national estimates are seldom reported in literature. However, by utilising nationwide register data, it is possible to measure various aspects of overtreatment at end of life. This allows for studying large, representative samples and ensures a high degree of precision when analysing specific patient groups and treatments.

In this thesis, first, our focus was on evaluating the nationwide prevalence of potential overtreatment in older individuals diagnosed with solid cancer in Sweden. We first gathered published quality indicators from the scientific literature, which specifically measure interventions suggestive of overtreatment, and investigated their applicability to administrative and health register data in Sweden (**Study I**). Next, we compared a crucial quality of care indicator, namely healthcare transitions (e.g., hospitalisations) at the end of life, across different illness trajectories. This study had a unique focus on unplanned hospitalisations. (**Study II**). Thirdly, we explored the extent of questionable and potentially inappropriate medication use and the determinants associated with initiating and continuing treatment. For this we selected the potential overtreatment of systematic hormone therapy in a breast cancer population (**Study III**). Lastly, we assessed the consequences of one selected potential overtreatment in a specific life-limiting illness. Among persons using the anti-dementia drugs cholinesterase inhibitors, we investigated their risk of peptic ulcer when they concurrently used non-steroidal anti-inflammatory drugs, by using an advanced epidemiological self-controlled study design (**Study IV**).

2 Literature review

2.1 End of life at old age

2.1.1 Ageing

Ageing is a complex phenomenon.[14] From a biological perspective, ageing is characterised by random molecular and cellular damage that begins at conception.[15] This damage accumulates over time and affects all organ systems, leading to great variation until death. Notable functional changes generally occur between 60 and 70 years of age.[16] For example, ageing results in increased arterial stiffness in the cardiovascular system, diminished aerobic capacity in the pulmonary system, decreased synaptic plasticity in the neurologic system, glomerulosclerosis in the kidneys, immunosenescence (i.e., increased susceptibility) in the immune system, liver shrinkage, and other irreversible alterations.[17] These cumulative changes eventually lead to a decline in physical function, manifesting as slower walking speed, reduced mobility, loss of independence in activities of daily living, falls and continence problems.[18, 19] As individuals approach the end of their lives, these effects of ageing intensify. The vulnerability to common age-related diseases and symptoms, such as cardiovascular disease, cancer, osteoarthritis, diabetes mellitus, osteoporosis, dementia, depression, frailty, and multiple chronic conditions, increases.[18] In addition to physical and cognitive deficits, ageing also triggers psychological and social consequences. Emotional and existential concerns can emerge due to the prospect of impending death, social isolation, and loss of autonomy.[20] However, the ageing process varies greatly among individuals.[21] While some may retain their physical and cognitive functions until the end of their lives, others may experience a severe decline in these areas. Regardless, the ultimate outcome of ageing remains the same for all: death.

2.1.2 Disease burden of older people

Factors contributing to the ageing of populations are the advancements in diagnostic methodologies, lifesaving interventions and enhanced medical technology. These innovations have enabled the prevention and treatment of diseases that were once fatal.[22] The World Health Organization predicts that by 2050, approximately two billion people will be 60 years and older, marking an increase of one billion from 2020.[23] This demographic shift, characterised by ageing-related diseases, presents unparalleled challenges in terms of delivering suitable healthcare and long-term support for older adults.[24] The rise in global life expectancy holds considerable significance from a public health standpoint. The added years of life are anticipated to encompass both periods of independence and dependence.[25] As a result, not only will the healthy years increase in the future, but also the life-years marked by poor health and high care need. To measure poor health and care need at old age a variety of measures exist. In line with the multi-systemic nature of ageing, these ill-health measures typically involve several dimensions

of health status. While no single metric can comprehensively represent health in old age, they are useful in detecting changes in health status. The following two chapters introduce two related measures, multimorbidity and frailty.

2.1.2.1 Multimorbidity

Multimorbidity is a crucial concept that plays a significant role in the complex care needs of older individuals. In most epidemiologic studies, multimorbidity is defined as the coexistence of two or more chronic health conditions within an individual.[26] The presence of multiple chronic conditions is especially common among older adults, who are more susceptible to age-related health issues. Research indicates that globally, more than half of individuals aged 60 years and above experience multimorbidity.[27] Nonetheless, it is essential to interpret such estimates with caution due to the considerable variation in the underlying population and the methods of measuring multimorbidity.

To standardise the measurement of the number of diseases at old age, Calderón-Larrañaga et al. developed a consensus-based operationalisation that meets the criteria of chronicity and identifies clinically relevant diseases categories.[28] Their study found that 89% of a Swedish population aged 60 or older had two or more chronic conditions, while over half (56%) had four or more. The most frequently observed conditions were hypertension (69%), dyslipidemia (46%) and chronic kidney disease (38%).[28] Importantly, the prevalence of multimorbidity increases with age. Several studies have shown that over 80% have chronic coexisting conditions after the age of 70.[26] This suggest that the concept of multimorbidity becomes increasingly relevant as individuals progress through life.

One of the most widely-used measures of multimorbidity is the Charlson comorbidity index, introduced in 1987.[29] The original intent behind this index was to predict one-year mortality, but since its inception, it has frequently been used to account for multimorbidity in epidemiological studies. The Charlson comorbidity index was adapted for register-based research in the Swedish context in 2021 by Ludvigsson and colleagues.[30] The index assigns scores to selected diseases, ranging from low (e.g., myocardial infarction: one point) to high for severe disease (e.g., metastasis: six points). Consequently, the Charlson comorbidity index does not directly equate to the number of diseases.

The adage "The whole is greater than the sum of the parts" resonates with multimorbidity, where the collective implications are more substantial than the cumulative effects of individual diseases.[31, 32] Multimorbidity profoundly affects patient outcomes, such as quality of life, and healthcare utilisation, introducing unique challenges.[33] The interplay between multiple chronic conditions can lead to a complex network of physiological dysfunctions. For instance, a study of community-dwelling older adults in the United States identified 291 unique disease combinations.[34] Hypertension paired with arthritis, as

well as combinations involving cardiovascular disease or diabetes, emerged as the most prevalent disease combinations. The study also demonstrated that as the burden of multimorbidity increased, overall health deteriorated correspondingly. Furthermore, the presence of comorbidities often necessitates multiple medications, elevating the risk of drug interactions, adverse effects, and treatment-related complications.[35]

The complex health profile of patients with age-related multimorbidity challenges healthcare providers, patients, and their families alike. The burden of managing numerous conditions — including regular healthcare visits, diagnostic tests, and treatments — can impose significant physical and emotional strains on individuals. Simultaneously, it demands that healthcare practices, especially primary care, ensure effective care coordination.[36] Patients express the need for a comprehensive and integrated approach that considers the unique needs and goals of each patient, promotes effective symptom management, and optimises care coordination.[37] Looking forward, given the projected increase in life expectancy,[23] managing the complex burden of multimorbidity will gradually result in a greater need for palliative care and prevention of unnecessary and potentially harmful treatments. Such considerations warrant attention in research, healthcare, and social policy domains.[38]

2.1.2.2 Frailty

Another important concept encompassing both the burden of multimorbidity and functional impairment is the geriatric syndrome known as frailty. While frailty is associated to multimorbidity — most frail individuals are multimorbid — not all multimorbid individuals are necessarily frail.[39] Frailty can be characterised as a state marked by depleted reserves and increased vulnerability to stressors, resulting from a lifetime of cumulative decline across multiple physiological systems.[40] Multiple measurements exist for frailty,[41] but the Frailty Phenotype and Frailty Index are the most commonly used. Frailty Phenotype categorises individuals as non-frail, pre-fail and frail based on meeting none, one to two, or at least three of the following criteria: weakness, slow gait, low physical activity, exhaustion, and unintended weight loss.[42] The Frailty Index is the ratio of health deficits in an individual, based on a measure of least 30 health deficits.[43] While the cut-off values for this index remain a topic of debate, a value of 0.25 is typically indicative of frailty.[44] However, the Frailty Phenotype and Frailty Index cannot be operationalised using routinely collected data, which often lack specific criteria details. In 2018, Stow and colleagues defined a frailty trajectory at the end of life using electronic health records, suggesting that routinely collected data can be helpful in identifying people with frailty and palliative care needs.[45] At the same time, Gilbert et al. developed the Hospital Frailty Risk Score specifically for register data,[46] paving the way for measurements of frailty in nationwide register data. This risk score has since been validated across numerous settings and disease groups.[47-56]

Frailty is prevalent among older adults. A systematic review and meta-analysis estimated an incidence of 43 new cases per 1000 person-years among community-dwelling adults 60 years or older, though rates varied based on sex, frailty measures and country income level.[57] Among those 50 years and older, frailty prevalence ranged between 12%-24% depending on the diagnostic criteria.[58] Substantially higher estimates (52%) were reported for nursing home residents.[59] Women have a higher (15-29%) prevalence of frailty than men (11%-20%).[58] Interestingly, women appear to tolerate frailty better than men, given their consistently lower mortality rates across different frailty levels.[60] Additionally, older adults with comorbidities, low socioeconomic status and poor health behaviour are especially at risk of frailty.[44]

Frailty correlates with several negative outcomes, such as mortality, hospitalisation, falls, and diminished quality of life, even when considering other concurrent diagnoses.[40, 61] Healthcare service use, such as hospitalisation, of older people poses risks for iatrogenic harms (i.e., caused by the processes of care) that might exacerbate their functional impairment and frailty. For instance, a study of 503 older patients (aged 75 or older) found that 12% experienced iatrogenic harms, of which 82% of could have been preventable with mobilisation, physical therapist, less urinary catheterisation, and decreased diaper use.[62] Additionally, the concurrent use of multiple medications has a correlation with frailty,[63] exhibiting a dose-response relationship; the risk of frailty amplifies with the consumption of an increasing number of drugs.[64, 65] This is especially important because older people with frailty are vulnerable to drug treatments and have higher risks of complications (including intolerance to systemic disease-modifying therapy).[66] Individuals with frailty tend to prefer less aggressive care at the end of life, though preferences can change over time.[67] Recognising frailty as an important syndrome at the end of life can guide clinicians in discussing prognosis and treatment preferences.[68] Avoiding intensive interventions that might deteriorate the functional impairment of older persons and a strong focus on quality-of-life enhancement is especially appropriate for people with frailty syndrome.[69]

2.1.3 Life-limiting illnesses and illness trajectories

Life-limiting illnesses refer to often progressive, severe health conditions that are incurable. As a result, these illnesses drastically shorten a person's life expectancy and diminish their quality of life.[70] They impair physical, emotional, and functional capabilities, ultimately leading to death. In older age, the primary causes include organ failures (e.g., heart, liver, or kidney disease), cancer, dementia, and other neurological conditions.[23] Among these, cardiovascular diseases, including ischemic heart disease and stroke, are the leading causes of death, reaching 19 million deaths globally in 2019.[71] Cancer follows as the second leading cause of death with approximately ten million deaths worldwide in the same year.[72, 73] Although the number of cancer survivors is rising due to advancements in early detection, treatment options, and improved care models,[74] cancer still largely remains a life-limiting illness. Similarly, neurodegenerative disorders like dementia

accounted for close to ten million deaths worldwide.[75] This thesis mainly focuses on cancer and dementia.

The severity, progression and patterns of physical function decline vary among individuals. While some undergo a gradual deterioration, others experience periods of exacerbation or remission.[76, 77] Lunney et al.[78] identified physical functional decline trajectories to help caregivers better anticipate the end-of-life care needed based on the underlying disease. This research was expanded upon by Lynn et al.[79] and Murray et al.[80] They categorised end-of-life trajectories into four distinct groups:[78-80]

1. **Cancer**, marked by a rapid and evident decline.
2. **Organ failure**, characeterised by a longer period of functional limitations and intermittent decline.
3. **Prolonged dwindling**, commonly seen in older individuals with neurodegenerative conditions like dementia or frailty.
4. **Sudden causes of death**, where individuals face no decline in function before an unexpected death (e.g., accident).

Based on data from the National Cause of Death Register in Sweden, among adults who died at the age of 65 years or older, about 29% belonged to the cancer trajectory, 39% organ failure, 25% dementia and 8% sudden death between 2007-2015.[81]

However, Gill et al. [82] have critiqued these illness trajectories, suggesting that the root cause of death might not reliably predict the course of functional impairment in the last year of life. Similarly, Steinhauser proposed that the illness experience is more influenced by disease severity, emotional, and social factors than by a specific diagnosis.[83] In 2019, Morgan et al.[84] identified only two simplified trajectories. Patients with cancer, organ failure and cardiovascular disease comprising one group, and patients with dementia and neurological conditions comprising the other group. Individuals in the first group may experience rapid functional decline necessitating swift care support and adaptations. The second group may experience prolonged functional decline that requires sustained patient care options. Regardless, the four illness trajectories offer helpful knowledge about the heterogeneous healthcare resource usage,[78-80] comorbidity patterns, and end-of-life symptom burden.[85, 86]

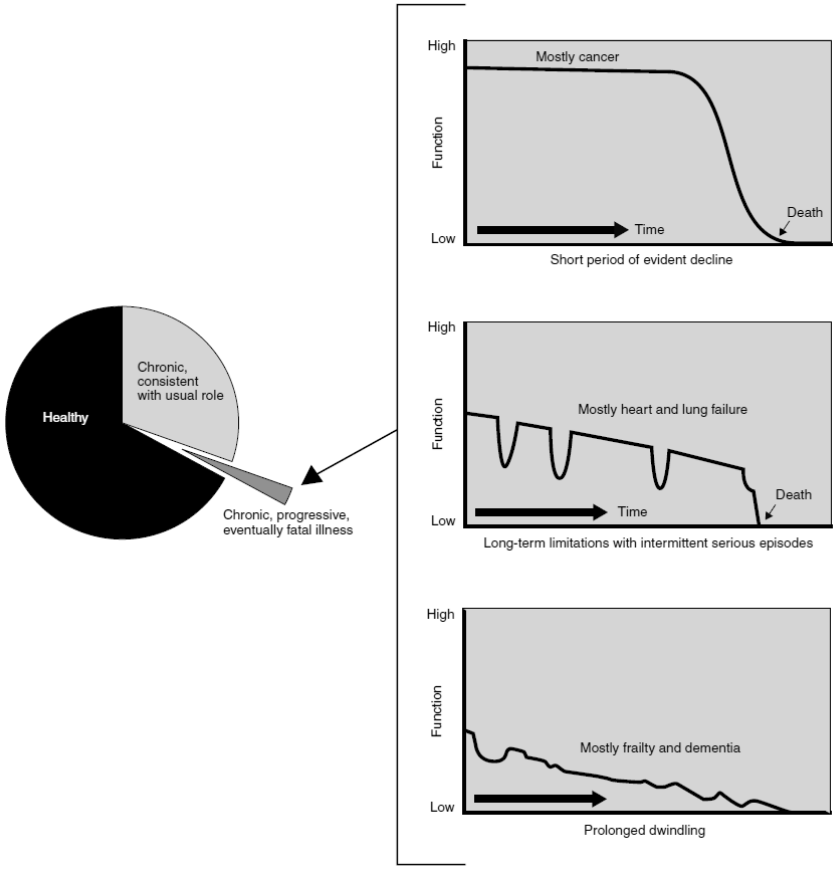

Figure 1. Chronic Illness in the Elderly Typically Follows Three Trajectories, originally published by Lynn et al.[79] Reprinted with permission from RAND corporation (Santa Monica, CA). The pie chart highlights the trajectories of physical function decline as the last part of the disease course. The figures show three illness trajectories (note that sudden death is not shown here) with different pattern of decline which all require different prioritisation of care. For cancer, Lynn et al. highlights hospice care, for organ failure they stress the importance of advance care planning and home services, while for those with the prolonged dwindling trajectory urges supportive home services, and care in long-term care facilities.

As the end approaches in a person's life, regardless of the trajectory of decline, certain symptoms become increasingly universal. Examples include pain, fatigue, anorexia, nausea, breathlessness, and individuals may also grapple with spiritual questions.[87] A systematic review found that dyspnoea, pain, and respiratory secretions were prevalent in more than half of the patients during their last two weeks of life.[88] Furthermore, a qualitative study involving patients, caregivers and healthcare professionals found that the most common symptoms of terminal illnesses include pain, agitation, breathlessness, and nutritional or hydrational concerns and difficulties (e.g., enteral feeding, thirst, artificial hydration).[89] Unfortunately, some symptoms, notably pain, are not always effectively managed at the end of life.[90] Moreover, a study involving patients in acute care hospitals found that symptom prevalence tends to rise with an increase in the comorbidity

burden.[91] This is particularly true for patients who opt for less aggressive symptom management, often in pursuit of maintaining mental clarity.

Research on end-of-life care focus on and compare specific life-limiting illnesses given their shared characteristics and similar care requirements. In Sweden, for instance, the quality of end-of-life care has been compared across various illnesses, such as between cancer and dementia,[92] heart disease and cancer,[93] stroke and cancer,[76] and lung disease and lung cancer.[77] Additionally, in research, life-limiting diseases are also frequently described as palliative care amendable conditions, meaning that individuals diagnosed with these diseases would significantly benefit from palliative care services.[94, 95]

2.1.4 End-of-life care and palliative care

End-of-life and palliative care disciplines are particularly affected by ageing societies. Sleeman and colleagues have projected that by 2060, about half of all deaths worldwide will be due to palliative care-amendable conditions.[96] Thus, they advocate for global action to integrate palliative care more thoroughly into the healthcare systems. Historically, palliative care programs were limited to inpatient units for patients nearing death. However, over the past two decades, there has been a significant effort to extend palliative care to outpatient and community settings, promoting earlier intervention.[97]

The World Health Organization currently defines palliative care as: "*Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.*"[98] This definition is broader than World Health Organization's previous one, which emphasised that palliative care was primarily for patients unresponsive to disease-modifying therapies, thus limiting it to the disease's final stages.[99] The current definition emphasises the significance of introducing palliative care early in the course of a terminal disease.[98] This approach is also widely endorsed in the research community.[95] Furthermore, in 2014, the World Health Assembly recognised palliative care "*as an integrated treatment throughout the life course*" due to its positive effects on patient quality of life and healthcare systems, such as reducing unnecessary healthcare services.[94] Importantly, the definition of palliative care incorporates end-of-life care, which is usually restricted to the last year or six months of life.[100]

Ideally, palliative care should permeate most aspects of care delivery to cater to the needs of seriously ill patients, from diagnosis to end of life.[101] To provide a "state-of-the-science synopsis of the literature", Hui and Bruera complied the latest evidence in 2020 concerning the various specialist palliative care delivery models, particularly for patients with cancer (**Figure 2**).[102]

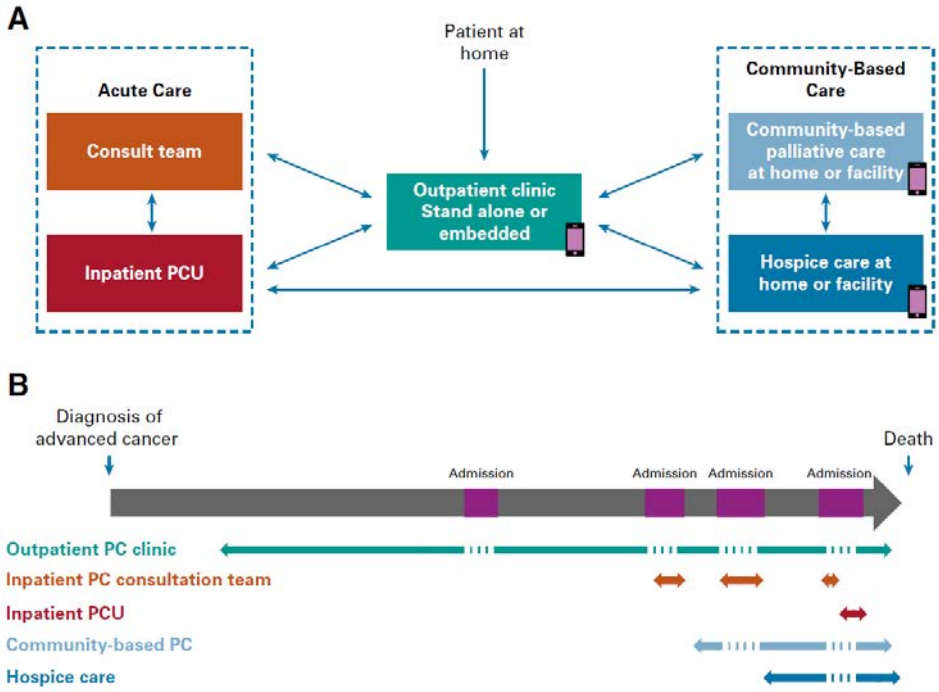

Figure 2. Schematic overview of specialist palliative care models in relation to cancer disease progression. Originally published by Hui and Bruera, 2020.[102] Reproduced with permission. Panel A shows the care in different setting. Outpatient clinics are at the centre because they coordinate care. Telehealth outreach is indicated by a phone icon. The Panel B shows care anytime along the disease course. The figure shows how the different palliative care models complement each other. Patient engagement opportunities are highlighted by the arrows.

In their review, they list five palliative care delivery models.[102] The first is outpatient palliative care clinics (standalone or embedded clinics, telehealth interventions or enhanced primary palliative care), focusing on patients with early-stage disease to manage symptoms, facilitate coping, support disease understanding, and engage family members. Second, inpatient palliative care consultation involves teams of physicians, nurses, and psychosocial professionals caring for hospitalised patients with limited expected survival. The third, acute palliative care units, address patients' comprehensive well-being, with teams potentially overseeing interventions such as pain management, sedation, discharge planning, or goals-of-care discussions. Fourth, community-based palliative care entails in-person visits, telephone support, and equipment provision, either at the patient's home or in nursing facilities. The fifth, hospice care, caters to patients with a life expectancy of less than six months, although many die within a week of admission. Collectively, these palliative care methods cater to distinct patient groups and complement each other throughout a terminal illness's progression.[102]

A systematic review of early palliative care interventions for cancer and non-cancer life-limiting diseases identified several benefits, including enhanced quality of life, patient and caregiver satisfaction, survival benefits and costs reductions.[103] In a pivotal randomised controlled trial, Temel et al. found that early palliative care integration increases survival and well-being at the end of life of patients with lung cancer.[104] Similarly, a Cochrane systematic review, based on seven small trials with more than 1600 patients, concluded that early palliative care interventions enhance the quality of life and symptom relief compared to standard care for patients with advanced cancer.[105] Another systematic review, published in Lancet Oncology, found that early palliative care is more advantageous than on-demand palliative care consultation combined with psychosocial support for quality of life improvement.[106] Moreover, a meta-analysis also reported findings of improved survival of patients who received outpatient speciality palliative care.[107] This challenges the prevalent misconception that accepting palliative care entails compromising survival.

Ensuring that the patient's preferences guide the entire end of life, even if they lose decision-making capability, is vital. Advance care planning facilities individuals in preplanning their care. In 2017, white paper commissioned by the European Association for Palliative Care Board defined advance care planning as: "*Advance care planning enables individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and health-care providers, and to record and review these preferences if appropriate.*"[108] Still, the available knowledge of some aspects of advance care planning is currently insufficient. Rietjens and colleagues, in their 2021 review, identified a need for more clarity regarding the initiation of advance care planning discussions, patient and family preferences and support for healthcare professionals to overcome challenges in implementing these practices.[109] Nonetheless, advance care planning has been linked with improved end-of-life preference documentation, better communication between the care team and patients, and an increased likelihood of patients dying at their preferred location.[110]

2.1.5 End-of-life care and palliative care in Sweden

In Sweden, life expectancy has increased steadily for both women and men since the mid-19th century.[111] By 2020, the average life expectancy reached 84 years for women and 81 years for men. By the age of 65, women can expect to live an additional 21 years, while men can expect 19 more years.[112] It is projected that half of women and men born in 2021 will live to at least 93 years. Such demographic shifts will present challenges for the healthcare system, including palliative care, especially considering that four out of five people may benefit from palliative care.[112, 113]

Palliative care in Sweden is provided within the healthcare sector and is organised by regions and municipalities.[114] However, the organisation and delivery models of palliative

care vary across the country. The most common models are specialised palliative care units that can provide care in a hospital setting or long-term care facilities, such as hospices or nursing homes. There are also advanced mobile teams comprising cross-functional members, such as physicians, nurses, physiotherapists, occupational therapists, counsellors, who provide care in the community setting. These models align with the acute and community-based models described by Hui and Bruera (see **Figure 2**).[102] Relatives are encouraged to participate in the palliative care planning and have the right to information, as well as psychological and financial support if they choose to care for their dying relative at home (up to 100 days per seriously ill person).[114] Sweden also has a well-established long-term care system, organised by municipalities, that caters to older people and those with functional impairments. National policies prioritise care in ordinary housing, focusing on assistance with daily living activities to promote community living. The Social Services Act regulates the rights to long-term care. In 2021, 15% of people aged 65 and older used some form of long-term care.[114] Municipalities typically provide healthcare and rehabilitation in ordinary homes (except in municipalities in Region Stockholm, where the region is the responsible party). About 80% of those services are directed towards individuals aged 65 and older.[114] Guidelines and recommendations for these services are regularly updated by the National Board of Health and Welfare.

Sweden's national palliative care guidelines were first published in 2012 by the organisation "Regionala Cancercentrum i samverkan".[115] In 2013, The Swedish National Board of Health and Welfare expanded the knowledge base of these guidelines, incorporating both local and national recommendations primarily aimed at policymakers.[116] These guidelines were updated in 2016 to emphasise end-of-life care for patients with untreatable diseases.[117] In the same year, The Swedish National Board of Health and Welfare conducted a quality assessment, revealing the guidelines yielded improvements, but further progressions are warranted in some selected areas.[118] These areas included reducing the heterogeneity of care provision, offering ongoing training to personal, increasing the proportions of people who undergo pain assessment and end-of-life conversations to reach equal care across county councils, regions and municipalities.[118] Advanced directives were scarcely mentioned in the report, leading some to consider Sweden as "advance care planning-naïve on a collective level".[119, 120] In 2021, guidelines underwent a third revision, expanding their scope beyond just end-of-life care to encompass the entire care process for untreatable diseases, in line with international developments. It also includes recommendations on the different types of conversation during the care processes of a person with a fatal disease.[121] However, unlike many European countries, the Swedish healthcare system neither recognises legally binding advance directives nor permits the appointment of proxy decision-makers.[119]

Comparable to the United States,[122] public understanding of palliative care in Sweden remains limited despite continuous advancements in palliative care guidelines.[121, 123] A public survey conducted by Swedish researchers from the "DöBra" (in English: *DieWell*) project revealed that 41% had no knowledge and 43% had only some understanding of palliative care. Common misconceptions included the belief that palliative care is exclusively associated with death or is only provided just before death. The survey showed that women, older people, and the highly educated were more knowledgable.[124] The DöBra project aims to enhance collective awareness about end-of-life care through public engagement, striving to understand the values and preferences of the Swedish population concerning end-of-life care.[120, 125]

2.2 Overtreatment at the end of life

2.2.1 Overview

The maxim *primum non nocere* ("first, do no harm") is typically incorporated into the modern "Hippocratic" oath in some form.[126] It embodies the ethical principle of nonmaleficence, emphasising the importance of avoiding unnecessary harm to the patients, which is especially important in end-of-life situations.[127] Almost all medical interventions come with risks, ranging from minor discomforts like a blood sample to severe repercussions, possibly leading to fatal consequences. However, the intervention becomes justifiable when the potential benefits outweigh the potential harms.[128] To guide decision-making in the latter stages of a disease, Holmes and colleagues developed a framework for assessing medication appropriateness.[129] This framework visualised (see **Figure 3**) four central concepts in a form of a pyramid: life expectancy, time to benefit, target, and goals of care. When life expectancy is long and the primary care goal is curative, there are numerous treatment options, symbolised by the pyramid's base. However, as life expectancy decreases and care goals shift towards palliation, the number of suitable medication options diminishes, depicted by the pyramid's apex. During the end-of-life care of older, frail persons with multimorbidity, ensuring alignment among these four pyramid pillars becomes challenging due to the lack of concrete evidence of adverse consequences in real-world scenarios. This complicates the adherence to *primum non nocere* and the avoidance of unnecessary harm, or put differently, *potential overtreatment*, making it a subject for debate, discussion, and research.

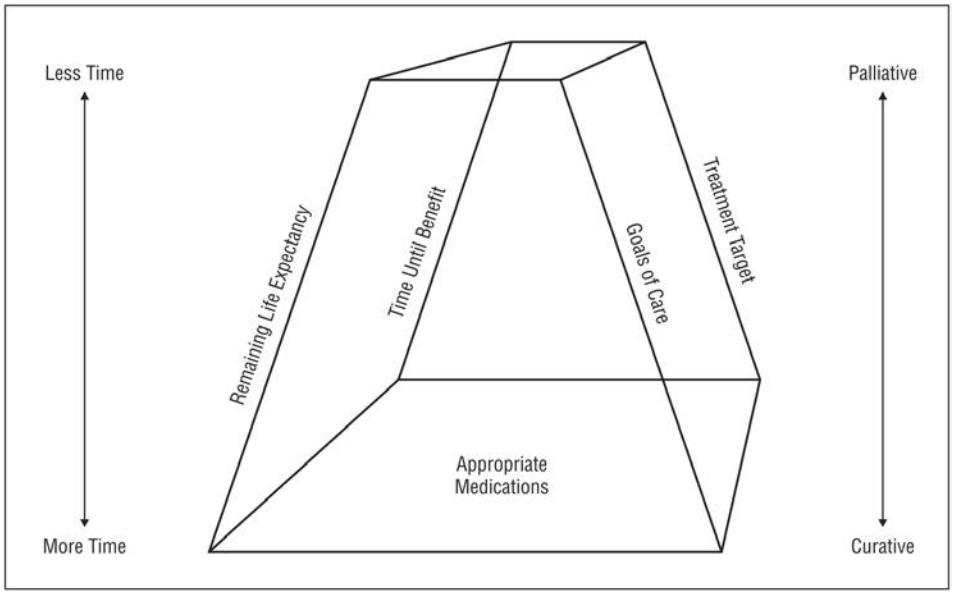

Figure 3. Originally published in Holmes et al. 2006.[129] Reprinted with permission.

Discussions on potential overtreatment during end-of-life care began with the "treatment-limitation debate" at the end of the 1980s, focusing on the potential harms of mechanical ventilation and resuscitation for terminally ill patients.[130, 131] These life-sustaining measures were controversial, as they seemed to offer limited clinical benefit, only extending life marginally, often at the cost of significant discomfort. Soon, a similar debate arose concerning the use of chemotherapy during end-of-life care. Medical professionals questioned the ethical implications of administering chemotherapy to critically ill patients, especially after previous treatments yielded minimal benefits.[132, 133] The American Society of Clinical Oncology later listed "cancer-directed treatment" (i.e., chemotherapy, among others) for advanced solid tumour patients with low-performance status or who did not benefit from previous therapies among interventions that are "costly, widely used, and not supported by high-level clinical evidence".[134] In 2010, the American Institute of Medicine published a landmark report discussing unnecessary or futile interventions and diagnostic practices.[135] This growing realisation and discussions of potential overtreatment ultimately led to campaigns like the Choosing Wisely, launched by the American Board of Internal Medicine Foundation, spotlighting the issue of overtreatment. The campaign started in 2012 and was widely disseminated among physicians and patients.[136] Since then, overtreatment is gaining increasing attention.

Defining overtreatment is inherently difficult. Related terms such as aggressive-, non-beneficial-, questionable-, futile-, excessive-, low-value-, no-value-, unwanted- and unnecessary care have been used interchangeably, resulting in ambiguity.[137] DuMontier and colleagues sought to clarify the concept of overtreatment (and undertreatment), among older people in an oncology setting.[138] Via a scoping literature review, they identified 71 articles published until 2018 that used the term overtreatment. Only a small fraction of studies (~6%) provided clear definitions. In the remaining cases, DuMontier et al. inferred implicit definitions based on the context. They discovered two broad categories of overtreatment, each used by approximately half of the articles. The first revolves around intensive treatment causing more harms than good, and the second concerns intensive treatment that older adults cannot benefit from in their remaining life. The researchers expressed concerns that these categories overemphasise disease-specific treatment and survival while they overlook critical outcomes that are more important for older persons (e.g., quality of life, preferences, and values). Thus, they proposed their definition of overtreatment: "*Treatment of a cancer in an older patient that would not likely lead to symptoms in his/her remaining lifetime or intensive treatment of a cancer in a vulnerable older patient in whom there would be a greater net benefit from less intensive therapy.*"[138] However, we deem that this definition lacks aspects of care transitions that are also important part for older individuals and their relatives.[139] In our point of view, overtreatment broadly incorporates interventions, treatments, diagnostics, and care processes that all have elements of providing "*care in the absence of a clear*

medical basis for use or when the benefit of therapy does not outweigh risks,"[140, 141] or according to "*the patient's own preferences, cannot possibly help.*"[142]

Examples of potential overtreatment in end-of-life care include but are not limited to the following. First, there is inappropriate drug use near death, such as anticancer agents (e.g., intravenous chemotherapy, targeted therapy or immunotherapy),[143, 144] initiations or continuations of preventive drug treatments (e.g., statins, antihypertensives, bisphosphonates) that are only effective in the long-term and can cause adverse events in a relatively short period, particularly among older adults.[145, 146] Second, there are inappropriate procedures at the end of life, often with life-sustaining intentions, such as mechanical ventilation, hemodynamic support, or surgery.[147] Third, frequent transitions between care settings can also be problematic at the end of life. For example, non-elective/unplanned hospital admissions often lead to deaths in hospitals, contrary to patient wishes.[148, 149] These three main forms of overtreatment are discussed in detail in subsequent subsections after a general overview of the adverse outcomes and drivers of overtreatment.

There are many consequences of overtreatment noted in literature, from both patient and healthcare provider perspectives. From a patient standpoint, overtreatment may harm by impairing quality of life and causing substantial discomfort,[104, 150-153] contrary to wishes of most patients and their family.[154, 155] A systematic review and meta-analysis indicated that six per cent of harm related to drugs, diagnostic and medical procedures could have been prevented (i.e., resulted from a modifiable cause), with 12% being severe or fatal.[156] Another meta-analysis reported 11% preventable harm in care settings of older patients, with 58% attributed to prescribed drugs.[157] To summarise and conceptualise the negative harms of overtreatment (and overuse of medical services), Korenstein et al. identified six domains with short and long-term consequences for the patients: physical, psychological, treatment burden, social, financial, and dissatisfaction with the care.[158] Furthermore, overtreatment may, counter-intuitively, result in undertreatment.[159] An example of such scenario in an end-of-life context is aggressive life-prolonging treatments and the simultaneous underuse of appropriate palliative care services. From a healthcare provider's perspective, overtreatment wastes valuable resources, leading to unnecessary expenses. In 2013, overuse was estimated to cost 270 billion USD in the US, according to a conservative estimate.[160] In Organisation for Economic Co-operation and Development (OECD) countries, approximately 10% of hospital spending is due to preventable and unnecessary harm and mistakes caused at the point of care.[161]

The reasons for overtreatment vary. Emanuel and Fuchs identified seven critical factors of what they call a "perfect storm of overutilisation". [162] Four related to physician and three to patients. First, they mention the culture of physicians trained to highly value extensive tests and diagnostics. Second, fee-for-service payments encourage more interventions regardless of costs and consequences. Third, marketing campaigns targeted at

physicians about new technologies that often lack comparative effectiveness studies coupled with the abundance of constantly emerging new information. Fourth, physicians fear malpractice, which makes them do more interventions than what is necessarily appropriate. Fifth, patients value more care and equate it with better care. Sixth, direct marketing to customers may influence them to request more treatment (only applicable to United States and New Zealand where direct-to-consumer advertising is legal at the time of this thesis). Lastly, physicians and patients are unaffected (in many countries entirely but in some countries only partially) by the costs of care, which again lead to more care. Emanuel and Fuchs argue that these contributing factors are intertwined and augment each other. Hicks added four other contributing factors to this list.[163] First is the fragmented care systems where patients are cared for inefficiently, for example emergency department visits of cancer patients without acute problems. Second, the complexity of care where several physicians see the same patients might result in test and diagnostic duplications. Third, unintended consequences of quality measures to monitor the quality of healthcare. Fourth, treatment guidelines often focus on what to do rather than what to refrain from or when to stop specific interventions. Ooi added two more factors.[164] First, the expanding disease definitions due to advancements in early diagnosis enabled unnecessary treatment of diseases at earlier stage that was previously deemed as part of normal ageing. Second, the discomfort of uncertainty surrounding all interventions that are difficult to predict whether they will be helpful for the patient persuades more interventions, some of which will turn out to be inherently unnecessary.

At the end of life, additional factors might contribute to overtreatment. Studies have shown that both patients and clinicians often overestimate the patient's life expectancy.[165] This can prompt treatments that have benefits extending beyond a patient's lifespan.[166, 167] Further, clinicians may overestimate the benefit and underestimate the harms of the treatments because of cognitive biases (e.g., framing effects, impact, and affect bias).[168] Treatments based on poorly informed decisions can lead to false hope and unexpected complications.[169] Importantly, medical services at the end of life are considered appropriate if they improve quality of life or align with patient preferences.[170]

Patient preferences are pivotal in medical decision-making.[171, 172] Mulley posits that these preferences often go unnoticed, terming it a "silent misdiagnosis".[173] Below we present two case stories from the literature to provide examples of preference misdiagnosis. Mulley brings up the example of a 78-year-old woman who undergoes mastectomy due to breast cancer but suffers from psychological effects afterwards. She was not fully informed about alternative treatment options. Had she known that hormone therapy might have slowed down the progression of the disease and she likely had died due to other causes by the time cancer would have caused adverse effects, she would have opted for hormone therapy. This resulted in an unnecessary surgery. Similarly, Mason warns against routine clinical practices that disregard individual values.[174] They bring up

the example of a 74-year-old woman with systemic sclerosis who preferred avoiding invasive tests. When she learned that hypertension and interstitial lung disease are common complications for her condition, she agreed to undergo echocardiogram and computed tomography even when she felt good. However, the tests showed pulmonary nodules; thus, she was referred to an invasive upper endoscopy, which found scleroderma, and caused stress for the patient. Mason called this a "teachable moment" of the cascades of follow-up tests because even if the tests had revealed early fibrosis, an asymptomatic patient would not undergo immunosuppressive therapy due to its toxicity and minimal improvements for interstitial lung disease due to scleroderma.

Towards the end of life, people generally prefer fewer medical interventions.[67] Fried and colleagues discovered that patients' views about treatment burdens and probable outcomes are key determinants of patient priorities, which remain consistent across different diseases.[154] Regarding the stability of such end-of-life preferences, a systematic review found that around 70% of patients' preferences remained unchanged.[175] Those more ill or involved in advance care planning had the most stable preferences.[175] Additionally, family members perceive better end-of-life care quality when patients had fewer hospitalisations in their last months or died outside of the hospital.[155]

2.2.2 Inappropriate drug use

Inappropriate drug use at the end of life may refer to specific drugs deemed to be disadvantageous or lacking in benefit for certain patient groups.[176] Inappropriate drug use may also refer to the quantity (e.g., polypharmacy) or combination of medicines (e.g., drug-drug interactions, drugs with synergic adverse event profiles) that a person takes concurrently.[177] An example of such drugs that are often deemed inappropriate is the use of anticancer agents, especially the widely-researched chemotherapy, [143, 144, 150] very close to death. Near death anticancer agents can be "worse than the disease" due to their high toxicities and detrimental effect on quality of life.[178] The concept of polypharmacy typically focuses less on specific drugs and more on the number of medications a patient takes concurrently.

Concurrent use of five,[179] or, according to some studies, ten,[180, 181] drugs is often defined as polypharmacy, though a consensus on this definition does not exist.[182, 183] Polypharmacy is sometimes necessary for managing multiple conditions in one individual.[184] As a result, polypharmacy is not inherently inappropriate,[185] especially if the correct medications are prescribed.[186] However, it is frequently seen as inappropriate,[187] especially if it arises from a prescribing cascade, where additional drugs are prescribed to manage the adverse effects of other drug(s).[188]

The primary concerns of polypharmacy are drug-drug interactions,[189, 190] and adverse drug reactions,[191-194] which can lead to hospitalisations.[195] Ageing-associated changes in the pharmacodynamics and pharmacokinetics of medications also increase the risk for these

adverse reactions.[196] Interestingly, a systematic review of systematic reviews from 2020 on the negative outcomes of polypharmacy in older people reported mixed evidence regarding the association between polypharmacy and adverse drug reactions.[197] The authors attributed these contradictory findings to the inclusion of both appropriate and inappropriate polypharmacy in the primary studies they reviewed. Regardless, the potential adverse consequences of polypharmacy are of concern, given its high prevalence in older age groups (**Figure 4**). A 2022 systematic review reported a prevalence of 37% to 54% for polypharmacy in a population aged 65 or older.[198] This high prevalence makes polypharmacy a significant concern when considering inappropriate drug use in older people.

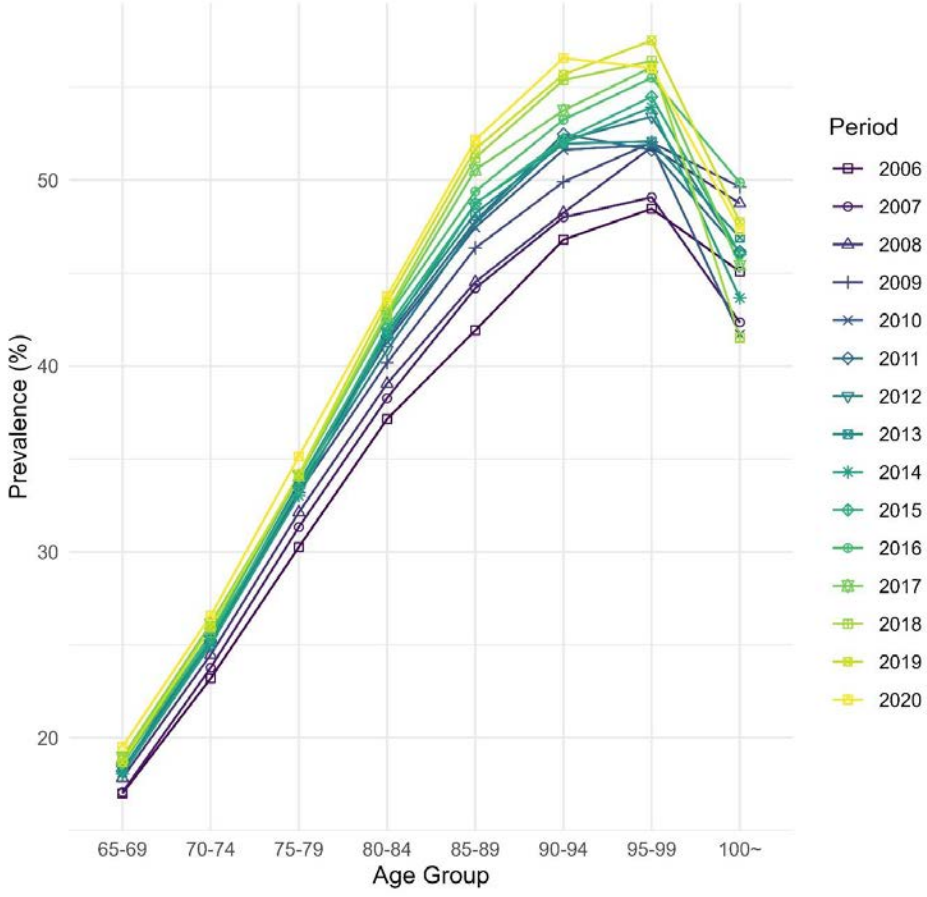

Figure 4. Prevalence of polypharmacy across age groups and calendar years among persons aged 65 years or more in Sweden, 2006–2020. Source: National Prescribed Drug Register and Total Population Register. A random sample of 10% of the entire population aged 65 years and older was selected for inclusion each year. The total number of individuals included across the study period was 2,935,147. Polypharmacy was defined as five or more dispensed drugs during a three-month period each year. The figure was produced by Tianyi Miao.

Prescribing for older people is notably challenging, especially at the end of life. As an individual nears death, the array of drugs considered appropriate narrows, as depicted by Holmes et al. in **Figure 3**.[129] Clinicians must weigh the "time to benefit" (i.e., whether the patient has time to benefit from the treatment) against the remaining life expectancy of the patient.[199, 200] Over the recent decades, several prescribing criteria have been developed to assist in ensuring proper drug administration for older people. One systematic review identified 23 validated explicit potentially inappropriate medication lists for the general population aged 65 and older.[201] However, many of these criteria are not clinically relevant in an end-of-life context.[202, 203] Drugs deemed inappropriate for older adults might be suitable for symptom relief at the end of life. Conversely, drugs that are usually appropriate for the elderly might be seen as inappropriate at the end of life due to limited expected benefits and potential side effects.[204] Recognising this gap in guidance for practitioners, Morin et al. developed consensus-based criteria to identify adequate, questionable, or inadequate drugs to continue or initiate for older adults at the end of life with life-limiting illnesses.[205] Using their criteria, Morin and colleagues assessed end-of-life prescribing in Sweden and discovered that 32% continued and 14% initiated medications of questionable benefit.[206]

2.2.3 Inappropriate procedures

Inappropriate procedures refer to interventions, whether surgical or invasive diagnostic tests, that are often performed with the intent of life-sustenance for older individuals with life-limiting illnesses nearing death. While life-sustaining interventions might prolong life, they often provide minimal benefit and can amplify patient suffering. For example, continuing blood transfusion requires healthcare visits and laboratory tests, posing risks to patients such as fluid overload, adverse reactions or alloimmunisation. [207] Similarly, total parenteral nutrition at the end of life necessitates regular laboratory evaluations and liver and pancreas function check-ups. At the same time, patients require ongoing central venous access, and face risks like sepsis and thrombotic occlusion.[207, 208] Likewise, mechanical ventilation, a focal point in the overtreatment debate,[130, 131] prolongs the dying process with considerable discomfort. Typically, the patients and relatives prefer palliative extubation to permit a natural and dignified death.[209] Another example is radiotherapy, where the line between palliative and curative treatment is blurred.[210] While short-fraction and single-dose radiotherapy might provide pain relief at the end of life, it is frequently overused. Rossi et al. estimated that 30% of radiotherapy expenditure were for end-of-life patients who did not benefit from the treatment in their last month of life.[211] Toole found that 70% of patients with cancer at Indiana University had their last radiotherapy session within ten days of death, while some received their last treatment on their death day.[212] Instead of focusing on curative treatments, end-of-life care should prioritise symptom relief and pain management.[90]

Similarly, surgeries near the end of life are often deemed aggressive and non-beneficial.[147] Surgical procedures necessitate hospital stays, which is often against patients' and their relatives' preferences near the end of life.[13, 213, 214] On the one side of the debate, Millis and Suwanabol argue that certain surgical procedures, like bowel resections and gastric bypasses, are essential in specific situations, preventing the need for rehospitalisation and avoiding painful deaths.[215] Additionally, other surgeries, such as ascites and pleural drainage, might be deemed appropriate for end-of-life care considering the patient's conditions.[216] On the other side of the debate, these interventions need to balance the progressively worsening quality of life and the accelerating deterioration of symptoms close to death.[217] Clapp highlights that surgical overtreatment occurs because "*circumstances culminate to make it seem sensible — required, even — for those involved.*"[218]

Inappropriate procedures are common at the end of life.[147, 219] Yet, uncertainties persist around current estimates. In a systematic review and meta-analysis, Cardona-Morell et al. reported that an average of 30% of patients underwent potentially non-beneficial active life-sustaining interventions at the end of life, including blood transfusion, radiotherapy and dialysis.[147] Koroukian et al. estimated cancer-directed treatments (inclusive of surgery and radiation therapy) to be as prevalent as 26% at the end of life of older adults with metastatic cancer, based on Medicare data linked with Surveillance, Epidemiology, and End Results database in the US.[219] Notably, these estimates are non-generalisable and non-transferable as they only pertain to specific populations and selected diseases. Of note, it is often uncertain whether patients have sufficient life-expectancy to realise the future advantages of potentially inappropriate procedures, and whether their potential future benefits surpass their immediate risks for seriously ill patients.[220] Above all, research indicates that enhancements in symptom management are essential for patients nearing death, especially concerning pain and psychological distress.[89, 221]

2.2.4 Care transitions and place of death

Care transitions, such as emergency department visits and hospital admissions, become increasingly frequent towards the end of chronic disease trajectories.[149, 151, 222-225] Unanticipated and abrupt exacerbation of symptoms or disorganised care with inadequate symptom management can result in hospitalisations. De Korte-Verhoef reported that respiratory (31%), digestive (17%), and cardiovascular symptoms (17%) were the most common causes of hospitalisation during the last three months of life.[226] However, not all end-of-life hospitalisations serve palliative and symptom-alleviating purposes. Reyniers et al. noted that 26% of end-of-life hospitalisation were intended for curative and life-prolonging measures.[227]

When patients are hospitalised near death, they are at risk of receiving care with insufficient quality.[228] Hospitalisation disrupts care continuity and can have detrimental functional and psychological consequences for patients at the end of life,[151] especially affecting the oldest and most vulnerable.[229] Hospitalisations can trigger mechanisms for overdiagnosis and overtreatment,[155] and are substantial contributors to aggressive end-of-life care.[219] Typically, patients and relatives prefer to avoid care transitions towards the end of life.[230] This is particularly relevant as patients have a higher risk of dying in hospitals, even though home is often the preferred place of death.[8-12] However, Gerber and colleagues highlighted that these preferences might vary throughout the disease trajectory.[231]

The place of death profoundly shapes the end-of-life quality and experience. Death can occur in various settings, including homes, hospitals, and long-term care facilities. The home is commonly the most preferred place of death.[8-13] This might be attributed to older individuals' attachment to their homes, which is centred on familiarity, privacy, control and proximity to family.[232] Dying at home is associated with a higher quality of death and satisfaction among relatives.[233, 234] However, Pollock argues that the emphasis should not be solely on home death; aspects like pain management and family presence play pivotal roles in enhancing the quality of the dying experience.[235] Meier et al. reinforced this by reporting that pain-free status was the most prevalently cited (81%) component of "good death."[236]

Despite these preferences, hospitals remain the most common place of death in Western countries. For example, in cancer populations aged 65 and above, the percentages of those who died in hospitals are as follows: Canada (52%), Belgium (51%), Norway (45%), England (41%), Germany (38%), and Sweden (46%).[81, 237] Pivodic et al. investigated the place of death across 14 countries among those who died with palliative care amendable diseases.[238] They found that South Korea (85%), Hungary (66%), France (64%) and the Czech Republic (64%) were the countries with the highest proportions of hospital deaths. For individuals with dementia, Reyniers also investigated 14 countries but found generally lower in-hospital-deaths than in cancer or other populations: lowest in the Netherlands (2%) and highest in South Korea (74%)[239]

Although in-hospital deaths are associated with more aggressive end-of-life care,[219] they are not always unnecessary or overly aggressive. Based on focus group discussions with the relatives and caring team, hospital deaths are deemed "justified" if they align with patient preferences, the current care setting is ill-equipped for the patient, or if acute conditions arise.[240] In fact, Robinson et al. argue that the emphasis on home death as an indicator of "good death" has deterred policy to an extent where the improvement of end-of-life care experience in hospital seems neglected.[241] Hoare et al. further suggest that metrics other than the place of death are needed, as the location alone does not assess the quality of the dying experience.[242] However, until a universally recognised

indicator emerges to guide researchers and policymakers better, interventions like home palliative care, early palliative care referrals, and caregiver support can promote home deaths,[243] aligning more with patient preferences.[8-13]

2.3 Indicators of quality of care at the end of life

2.3.1 Quality of care

According to the World Health Organization, quality of care is defined as "*the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge*." They further define seven elements of quality of care: effective, safe, people-centred, timely, equitable, integrated and efficient.[244] However, from the perspective of end-of-life care this definition might not fully capture the importance of patient preferences. Steffen[245] provided a more nuanced definition in alignment with this perspective: quality of care may also be defined as the capacity to attain goals of care defined by the collaboration between patient and physician. Achieving quality care based on this definition might be challenged by changing patient preferences as the disease advances, but in general extending survival becomes less important than preserving a high quality of life.[173, 175]

In 2015, the Institute of Medicine's Committee on *Approaching Death: Addressing Key End-of-Life Issues* published a report that emphasised patient and family-centredness at the end of life: "*care near the end of life should be person-centred, family-oriented, and evidence-based.*"[246] The committee emphasised that providing care according to predetermined protocols and without a personal treatment can deprive patients of their fundamental dignity and self-governance. They also underscored the importance of the individual's specific personal background and distinct physical, emotional, mental, cultural, spiritual or religious, financial, and social circumstances. Delivering high-quality, patient-centric end-of-life care should also embrace the values, goals of care, and preferences of patients, aiming to sustain their quality of life while navigating the challenges of progressing illness, at the same time providing support to both family and caregivers. The committee summarised these requirements into twelve core components of quality end-of-life care. The committee inherently enabled quality measurement by defining what quality end-of-life care is. Most importantly, the committee urged using and developing quality measures to ensure accountability.[246]

2.3.2 Quality indicators

Measuring quality of care at the end of life presents challenges. The most frequently utilised method for measuring care quality employs quality indicators. These indicators are explicitly defined measurements, consisting of a numerator and denominator, offering the potential to shed light on end-of-life care quality.[247-250] The numerator represents the number of patients that fulfil the pre-set criteria, while the denominator denotes the total number of populations at risk.[251, 252] Originally, quality indicators were developed to measure the quality of care at an aggregated level, such as healthcare region or nationwide. Although quality indicators are the most frequently used assessment method, they do not always provide explicit answers to complex questions.[251, 252] Nevertheless, they

serve to highlight problem areas within care systems or, conversely, show well-performing care domains.[249] Ideally, quality indicators should be anchored to a specific gold standard that dictates the expected performance for providers. This threshold may be established by decision-makers or the target level might reflect the best performing region in the country.[253] Employing quality indicators augments transparency, paves the way for care enhancement, and allows for the longitudinal monitoring of care quality.[250]

There exists a plethora of quality indicators tailored for end-of-life care, applicable in both clinical and population-based settings.[254, 255] These indicators are predominantly retrospective in design, meaning care provided to patients who have passed away is analysed. Such a design has its limitations in clinical settings where patients with life-limiting illnesses and poor prognosis are identified prospectively.[256] However, there is available evidence that prospective and retrospective indicators might show similar results.[257] Chassin delineated healthcare quality problems into three domains measurable by quality indicators:[258] (1) underuse, when care providers forego to give patients medically necessary care or follow proven practices; (2) misuse, when patients do not benefit from appropriate treatment because of preventable problems or incorrect diagnosis (i.e., medical errors resulting in harm caused by the treatment), (3) overuse when the care services are provided without medical justification, or the potential for harm exceeds the potential for benefit, or a treatment that a fully informed patient would forgo. Overuse has two building blocks. One is overdiagnosis, when a diagnosis is given for a medical condition that would never have caused any symptoms or problems. The second is overtreatment,[140, 141] which is the central concept of the present doctoral thesis, extensively discussed in chapter 2.2. Quality indicators can offer robust empirical evidence, empowering key stakeholders and decision-makers to initiate further inquiries or targeted interventions in specific domains of (in)appropriate care.

2.3.3 Quality indicators in Sweden

To identify quality indicators for palliative care and end-of-life situations, Lind et al. conducted an extensive review of the Swedish policy documents in 2015.[259] Their review revealed that out of the 240 quality indicators that they found across 14 national guidelines, merely eleven indicators were related to palliative care and end-of-life context. They further noted that only three indicators (pain assessment, registration in the Swedish Register of Palliative Care register, and opioid prescription) specifically target end-of-life care. Established in 2005, the Swedish Register of Palliative Care has since been employed to report quality indicators for both cancer and other conditions.[92, 93, 260] However, not all deaths are recorded in this register (66% and 87% of all deaths and cancer deaths in 2015, respectively). Additionally, there have been reports of validity concerns.[261]

The most recent Swedish palliative care guidelines include nine quality indicators for end-of-life care.[121] Eight of these can be directly accessed from the Swedish Register of Palliative Care. Six hold national gold standard targets. Only one pertains to overtreatment: "Two or more inpatient admissions in the last 30 days of life".[121] In Sweden, the high quality routinely collected administrative and healthcare data present an excellent opportunity to measure quality of care by utilising some of the internationally developed and population-based quality indicators.[255] However, there is much heterogeneity in the definition of these quality indicators. Also, some indicators remain to be validated by experts. Most importantly, it remains unclear whether the established quality indicators can be implemented and operationalised within Swedish routinely collected registers. This might be due to temporal, regional or practice differences in procedures or diagnosis code registration patterns. For example, in Sweden, the Z51.5 International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code for palliative care has sometimes been used to describe that the patient is dying instead of that palliative care is provided,[117] which is misleading when used to operationalise a quality indicator.[262]

2.3.4 Knowledge gaps

Quality indicators highlight problematic areas in the quality of care, offering key stakeholders a chance to delve deeper into identified deficiencies. Despite the abundance of indicators that can be used to measure the quality of end-of-life care,[255] few indicators target specifically potential overtreatment measures. This has resulted in notable lack of literature on potential overtreatment estimates, particularly from nationwide data. Most overtreatment estimates are derived from studies focused on specific disease populations or from systematic reviews that encompass studies with diverse populations and settings using various indicators of overtreatment.[147] Consequently, our understanding of the epidemiology of overtreatment on the population level remained limited in the age of "big data" where registers contain a large amount of readily available information.

Furthermore, there are essential knowledge gaps in various domains of overtreatment. One such important domain pertains to care transitions at the end of life. Although several overtreatment indicators measure the frequency of care transitions (e.g., hospitalisation) at the end of life, most studies did not distinguish between planned or unplanned hospitalisations.[149, 222-225] This has led to ambiguous estimates and patterns of hospitalisation, complicating interpretations from an overtreatment perspective. The distinction between planned and unplanned hospitalisation is essential because the latter potentially suggests a worse quality of care due to their disruptive effects.[151] Even if hospitalisations align with patient preferences, they can negatively impact end-of-life experiences.[151, 155, 228, 229, 263] Identifying unplanned hospitalisation patterns for different

disease trajectories at the end of life can enhance the development of preventive strategies for these patient groups.

Another area needing more research is the domain of potentially inappropriate drug use. One widely recognised potentially inappropriate medication at the end of life, chemotherapy, is frequently discussed within the research community.[264–268] However, other, less futile systematic anticancer treatments near death (e.g., hormone therapy) were less investigated in the literature. This resulted in a limited understanding of the extent of other systematic anticancer treatments used (i.e., continued or initiated) near death. Consequently, epidemiological determinants of such questionable, potentially inappropriate drugs in disease populations, where these drugs are preferred curative treatment options, were unknown. Revealing potential driving factors behind questionable systematic curative treatment use at the end of life may help reduce potential negative consequences.

Lastly, there is a scarcity of information on the impact of overtreatment on patient outcomes, especially concerning the severe consequences for older individuals. While much research has focused on end-of-life experiences, emphasising the quality of life for patients and their families, there is a paucity of epidemiological evidence on the possible consequences of overtreatment, such as adverse events. Also, some studies reported mixed evidence regarding the adverse event outcomes of drug use at the end of life.[197] Understanding what consequences specific drug-drug interactions entail can improve our understanding of their risks at the end of life, which need to be weighed against the potential benefits of the drugs to avoid overtreatment.

3 Research aims

The overarching aim of this doctoral thesis was to evaluate the quality of end-of-life care in older adults, with a particular focus on potential overtreatment and life-limiting illness, using nationwide administrative and healthcare data. We set out to assess the extent, determinants, and consequences of potential overtreatment during life-limiting illness and end of life of older adults. We contributed to addressing the overarching aim with the following four individual studies.

Study I aimed to investigate how well universal quality indicators of broadly defined potential overtreatment can be measured in a cohort of patients with solid cancer based on Swedish nationwide administrative and healthcare data. We aimed to present tentative estimates of the nationwide prevalence of overtreatment.

Study II aimed to describe the longitudinal unplanned hospitalisation patterns during the end of life of patients with different illness trajectories. Our objective was to use administrative and healthcare data in a cohort of older adults with illness trajectories of cancer, organ failure, prolonged dwindling (i.e., dementia) and those who died a sudden death to compare their frequency and pattern of unplanned hospitalisations during the last year of life.

Study III aimed to assess the extent of questionable potentially inappropriate endocrine therapy use at the end of life of patients with metastatic breast cancer. We set out to study their patterns of initiation and continuation of endocrine therapy during the last year of life. We also explored the determinants contributing to a higher propensity of initiating and continuing treatment during their last three months of life.

Study IV aimed to estimate the consequences of potentially inappropriate drug use in patients with life-limiting illness, specifically, the potential drug-drug interaction of non-steroidal anti-inflammatory drugs and cholinesterase inhibitors and their subsequent risks of peptic ulcer.

4 Materials and methods

4.1 Data sources

All the studies incorporated in this thesis utilised routinely collected administrative and healthcare data. This means that the data used in these studies were gathered as a part of standard administrative or care procedures, without any specific pre-defined research purposes.[269, 270] In total, data from seven different registers were linked at the individual level using pseudonymised identifiers.[271] Each register is described in detail below.

4.1.1 Total Population Register

The Total Population Register, started in 1968, is maintained by Statistics Sweden with an aim to provide population statistics. The register is vital in epidemiological research conducted in Sweden because it enables researchers to calculate disease statistics at the population level. The register contains information about, for example, personal identity number, birth, death, emigration, immigration, country of birth, sex, and citizenship. The Total Population Register may overestimate the population due to emigrants failing to report leaving the country. In 2015, over-coverage was estimated to be 0.1% of Nordic citizens and 4-8% of individuals born outside of the Nordic countries.[272]

4.1.2 National Cause of Death Register

The National Board of Health and Welfare has been responsible for the National Cause of Death Register since 1994. The register is complete and available for research since 1952. It practically records all deaths in Sweden (0.9% was missing in 2015), and almost all (96%) registered an underlying cause of death. The register is updated on an annual basis.[273]

Death certification is a two-step process in Sweden. First, the death is reported to the Swedish Tax Agency by the physician who confirmed the death. Second, a medical death certificate containing the underlying cause of death and up to 48 contributing causes of death is sent to the National Board of Health and Welfare. The ICD-10, has been used to code the causes of death since 1997.[273]

The registry defines the underlying cause of death as "*the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury*", in line with ICD-10.[273] In practice, the underlying cause of death is identified via stringent rules. Between 1987 and 2017, the Automated Classification of Medical Entities software aided physicians in selecting the underlying cause of death. After 2017 the Multicausal and Unicausal Selection Engine has been in use in Sweden.[273] Unlike the underlying cause of death, the contributing causes of death identification do not have strict rules and are not reported in order of importance. Besides the underlying and contributing causes of death, the register contains information on, for example, sex, date of birth, place of death, and civil status.[273]

4.1.3 National Patient Register

The National Board of Health and Welfare maintains the Swedish National Patient Register. It has complete national coverage of inpatient care since 1987 and specialised outpatient care since 2001, but to date, no primary care data. Almost all, >99%, somatic and psychiatric hospital discharges are registered. The outpatient diagnoses coverage is lower than inpatient data but still above 80%. According to external validation, the inpatient register has an overall 85%-95% positive predictive value of the diagnoses discharge codes. The register contains information about, for example, sex, age, date of admission and discharge, planned/unplanned admission, main diagnosis, secondary diagnoses, injuries, medical or surgical procedures, department of admission and provenance. Since 1997, the diagnoses have been coded according to the ICD-10 classification, while the procedures are coded according to the Swedish variant of the NOMESCO Classification of Surgical Procedures (in Swedish: "KVÅ" - klassifikation av vårdåtgärder).[274]

4.1.4 National Prescribed Drug Register

The National Prescribed Drug Register in Sweden is maintained by the National Board of Health and Welfare since its inception in July 2005.[275] The register utilises the Anatomical Therapeutic Chemical (ATC) system to categorise the dispensed drugs and provides monthly updates to the National Board of Health and Welfare. It is important to note that over-the-counter drugs and drugs administered in hospitals are not included in the register, and there are partial gaps in information related to vaccines and drugs used in nursing homes. Notably, the register does not collect data on the indication of treatment but does provide prescriber-written free text, often containing dosage information. The register covers 85% of all sold defined daily doses (DDDs), leaving the remaining 15% to be accounted for by over-the-counter medications (12% of DDDs) and drugs administered in hospitals (3% of DDDs).[275] The extensive data collected by the register includes various details such as sex, age, date of prescription, date of dispensing, type of dispensing (e.g., multi-dose), total dose, prescribed daily dose (free text), number of DDDs dispensed, ATC code, generic name, costs, and characteristics of prescribers, making it a valuable resource for research and analysis in the healthcare domain.[276]

4.1.5 National Register of Care and Social Services for the Elderly and Persons with Impairments

The National Register of Care and Social Services for the Elderly and Persons with Impairments, also known as the Swedish Social Service Register, is an important resource managed by the National Board of Health and Welfare. It is the sole register in Sweden that collects data about care home residency and the nature of long-term care provided to older individuals. By law, the responsibility for funding the care of older people lies with the Swedish municipalities, and they are obligated to supply information to the register

on a monthly basis. The register's inception dates to 2007, but its quality from an epidemiological research perspective was poor until 2013 compared to the other nationwide registers. The quality deficit was mainly due to inconsistent reporting by several municipalities. Nevertheless, the register's quality has improved significantly, and the most recent data, indicates that 99.7% of municipalities reported at least one person to the register in 2019, up from 84.5% in 2013.[277]

The register contains a plethora of variables concerning care in nursing homes or in the homes of older individuals. These variables encompass living arrangements, diverse home care types (including services, personal care, social participation, meal service, and more), monthly home care hours, short-term residence status, daytime activities, and other forms of support. It is worth noting that the coverage of these variables varies, with home care hours having a 95% coverage rate, and home care types ranging from 91% to 99%. As the quality of data continues to improve over the years, the Swedish Social Service Register stands as a valuable resource for epidemiologists, and policymakers to address the needs of the older people and individuals with impairments in Sweden.[277]

4.1.6 Longitudinal integration database for health insurance and labour market studies

The Longitudinal integration database for health insurance and labour market studies (in Swedish: Longitudinell Integrationsdatabas för Sjukförsäkrings- och arbetsmarknadsstudier [LISA]), was established in 2003 by Statistics Sweden as a response to the escalating sick leave rates. LISA offers researchers access to a wide variety of information dating back to 1990. Covering the population aged ≥16 years since 1990, and individuals aged ≥15 years since 2010, this database is important for understanding various socio-economic factors of the population. Its comprehensive data encompasses education, income (from employment, capital, and allowances), occupation, and employment status on a calendar-year basis. Detailed information on sick leave and disability pension, unemployment benefits, disposable income, social welfare payments, civil status, and migration details is also available as the data is often compiled from various other registers. LISA has a 95% coverage on occupation and more than 98% coverage on education, with an accuracy rate of 85%. Updated annually with a 15-month delay, the register ensures compulsory participation, making it a robust and reliable resource for statistical purposes. For researchers, LISA proves helpful, as it allows them to include these socioeconomic variables in their analyses as covariates, exposures, or outcomes.[278]

4.1.7 Swedish Register of Education

The Swedish Register of Education, initiated on December 31st, 1985, serves as a tool for educational planning at both national and regional levels, as well as for resource allocation planning. The register provides statistics used for international comparisons, facilitating

insights into the education system's efficacy and progress. With yearly updates, the register employs the SUN2000 nomenclature, aligned with the International Standard Classification of Education (ISCED-97), to code educational attainment since January 1st, 2001. Educational institutions consistently report information on completed education to Statistics Sweden. Data on immigrants' education primarily originates from surveys or population and housing censuses. The register serves as a valuable resource for researchers, particularly in determining the highest attained education, a pivotal socioeconomic variable of end-of-life research.

4.1.8 Overview or registers

The **Table 1** below contains a summary of information about the registers utilised in this thesis.

Table 1. Overview of register used in the studies

Register	Register holder	Start	Completeness	Geographical coverage	Content	Externally validated
Total Population Register[273]	Statistics Sweden	1968	The over-coverage has been estimated to 0.1 % for Nordic citizens but substantially higher for individuals born outside the Nordic countries (potentially 4–8 %)	Nationwide	Sex, date of birth, country of birth, municipality of residence, living arrangement, civil status, year of first and last immigration, year of last emigration	Yes
National Cause Of Death Register[273]	National Board of Health and Welfare	Complete since 1952	99% of all deaths are documented and 96% has an underlying cause of death	Nationwide	Sex, date of birth, underlying and contributing causes of death (ICD-10), place of death, civil status	Yes
National Patient Register[274]	National Board of Health and Welfare	Inpatient care coverage complete since 1987 Specialised outpatient care since 2001	99% of all somatic and psychiatric hospital discharges are registered. Outpatient diagnoses coverage lower than inpatient data but above 80%	Nationwide	Sex, age, date of admission and discharge, planned/unplanned admission, main diagnosis, secondary diagnoses, injuries, medical or surgical procedures, department of admission, provenance, destination.	The inpatient register part has an overall positive predictive value of diagnosis of 85%-95%

Register	Register holder	Start	Completeness	Geographical coverage	Content	Externally validated
National Prescribed Drug Register[275, 276]	National Board of Health and Welfare	July 2005	85% of all sold defined daily doses (DDDs) are covered by the register The remaining 15% are Over-the-counter medications (12% of DDDs), drugs administered in hospitals (3% of DDDs)	Nationwide	Sex, age, date of prescription, date of dispensing, type of dispensing (e.g., multi-dose), total dose, prescribed daily dose (free text), number of DDDs dispensed, ATC code, generic name, costs, characteristics of prescribers	Yes
National Register of Care and Social Services for the Elderly and Persons with Impairments[277]	National Board of Health and Welfare	2007	99.7% of municipalities reported at least one person to the register in 2019, up from 84.5% in 2013.	Nationwide, varying quality in some municipalities	Living arrangements, diverse home care types (including services, personal care, social participation, meal service, and more), monthly home care hours, short-term residence status, daytime activities, and other forms of support	No
Longitudinal integration database for health insurance and labour market studies (LISA)[278]	Statistics Sweden	2003	95% coverage on occupation and more than 98% coverage on education	Nationwide	Education, income, occupation, sick leave and disability pension, unemployment benefits, disposable income, social welfare payments, civil status, and migration	Yes
Swedish Register of Education[279]	Statistics Sweden	1985 (annual updates from 2000), earlier versions have been produced in the 1930 and 1970 census	Population aged 16-74 years old registered as resident in Sweden at 1 January each year. From 2007, information for the group 75+ is also collected	Nationwide	Highest educational attainment	Yes

4.2 Study designs and populations

All studies included in this thesis, apart from **Study IV**, were nationwide retrospective cohort studies, where participants were selected at the time of their death. **Study IV** was a self-controlled case series, where participants were selected if they experienced both the exposure and outcome. The studies follow a wide-to-specific pattern. In **Study I & II,** we analysed large cohorts of decedents with important implications for public health. In **Study III & IV,** we used clinically relevant patient populations in particular disease areas to provide clinically useful recommendations. All studies were based on administrative and healthcare register data. The following subsections introduce the study designs and populations of each constituent studies.

Table 2. Overview of the studies

	Design	Population	Data sources	Period
Study I	Retrospective cohort	Older decedents with solid cancer	Total Population Register National Cause of Death Register National Patient Register National Prescribed Drug Register Swedish Register of Education	2013-2015
Study II	Retrospective cohort	Older decedents	Total Population Register National Cause of Death Register National Patient Register National Prescribed Drug Register Swedish Register of Education	2015
Study III	Retrospective cohort	Older women decedents with metastatic breast cancer	Total Population Register National Cause of Death Register National Patient Register National Prescribed Drug Register Swedish Register of Education Social Services Register LISA	2016-2020
Study IV	Self-controlled-case series	Seriously ill older adults with life-limiting illness	Total Population Register National Cause of Death Register National Patient Register National Prescribed Drug Register Swedish Register of Education	2007-2020

Abbreviations: LISA = Longitudinal integration database for health insurance and labour market studies

4.2.1 Retrospective cohort study design

Studies I-III utilised a nationwide retrospective cohort study design, which is widespread in end-of-life research. These types of studies are often called mortality follow-back or studies of decedents because individuals are followed back from their time of death to collect information on the care they received near death. The period people are followed

back usually depends on the research question but often one year, six months or one months before death. The main underlying assumption of this study design is that care received by those who died is comparable to the care received by those who are perceived dying.

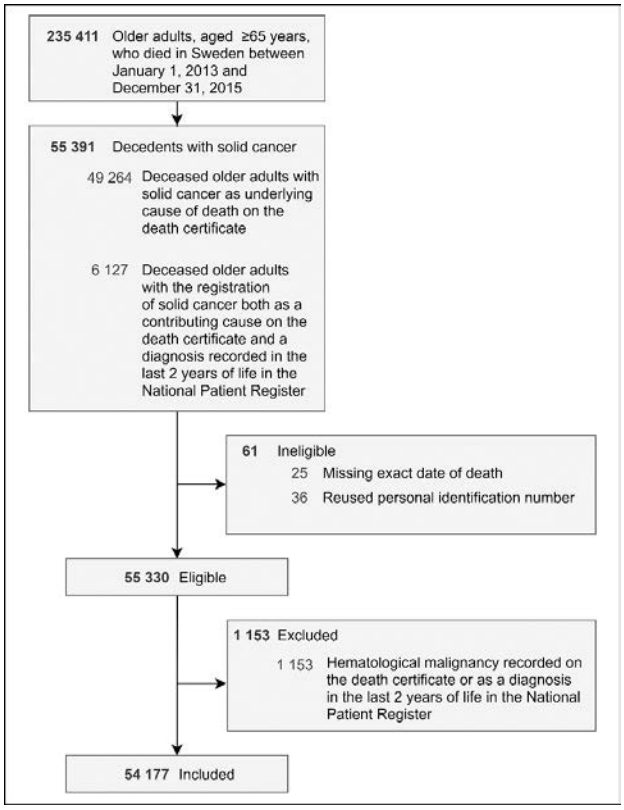

Figure 5. Flowchart diagram of Study I

In **Study I**, we identified all older adults (aged ≥65 years) who died due to solid cancer during the study period from 1 January 2013 to 31 December 2015, totalling 55,391 individuals. We selected decedents who had solid cancer as the underlying cause of death (obtained from death certificate data) or as both a contributing cause of death and a hospital diagnosis within the last two years of life (ICD-10 codes C00–C80, excluding C77–C79). To ensure a homogeneous population, we excluded patients under 65 years old and those with haematological malignancies (ICD-10 codes C81–C95). The exclusion of individuals with haematological malignancies was necessary because they might experience a rapid functional decline towards the end of life, making survival predictions more unreliable compared to patients with solid cancer. To maintain homogenous data, we excluded older adults with unconfirmed malignancies or individuals who were not identified as cancer patients before their death. This involved excluding decedents with cancer mentioned as a contributing cause of death but without a reported cancer diagnosis in the National Patient Register, as well as those whose cancer diagnosis was reported during a hospital stay but not listed as a cause of death. The final study population consisted of 54,177 included decedents.

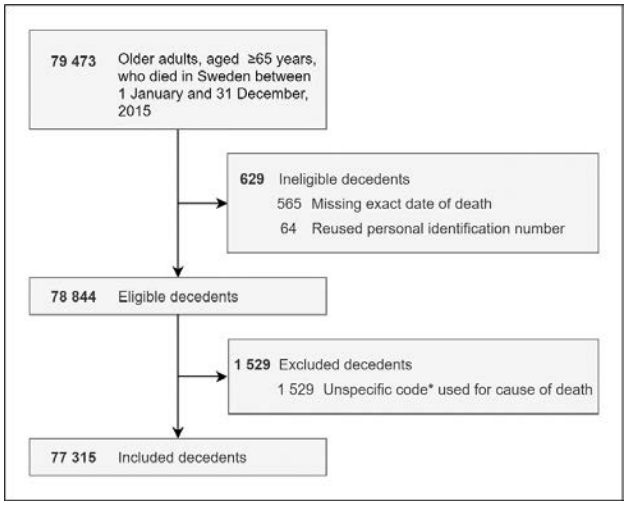

Figure 6. Flowchart diagram of Study II.
*Unspecific ICD-10 codes are B99, R96, R98, and R99

The **Study II** was a retrospective cohort study involving older adults aged 65 years or older, who died in Sweden between January 1 and December 31, 2015. Participants were excluded from the study if their precise date of death was unknown (n=565), if their unique personal identifier had been reassigned to someone else (n=64), or if the cause of their death remained unknown (n=1,529), unreported, or vague. The final study population included 77,315 decedents.

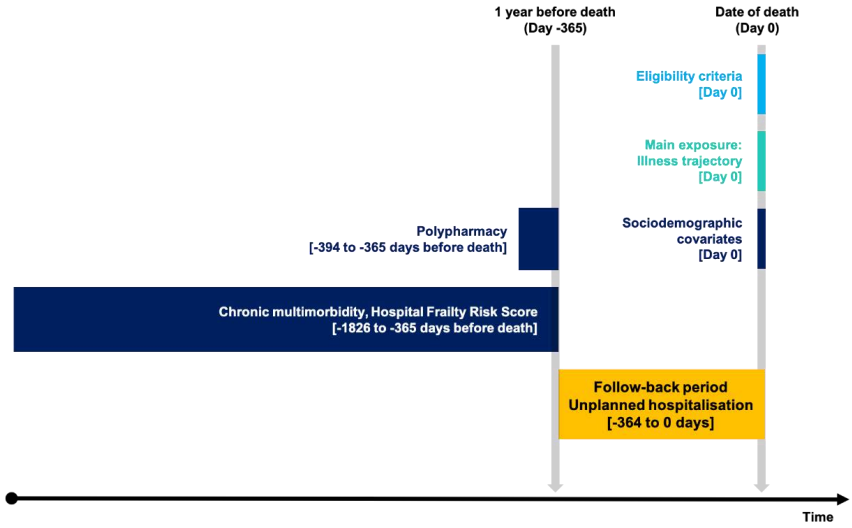

Figure 7. Study design of Study II

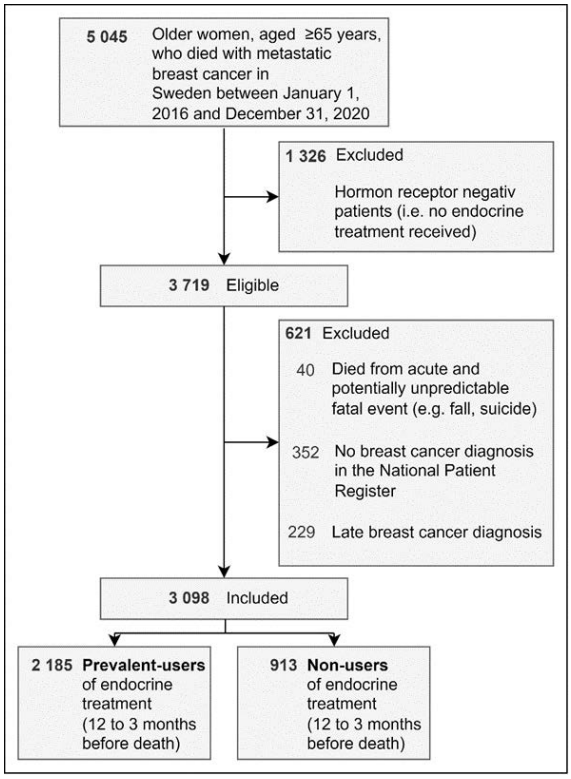

Figure 8. Flowchart diagram of Study III

Study III, was a retrospective cohort study that focused on older women aged 65 years and above, who had hormone receptor-positive metastatic breast cancer, and died in Sweden between January 1, 2016, and December 31, 2020 (n = 5,045).

Inclusion criteria for the cohort were as follows: women had to have a documented diagnosis of breast cancer (ICD-10 code C50) on their death certificate, and their metastatic condition (ICD-10: C78-79) needed to be registered in either the National Patient Register or Cause of Death Register. Those without any endocrine treatment records were excluded from the study (n=1,326). The remaining individuals were assumed to be hormone receptor-positive, similarly to previous research.[280] Furthermore, the study excluded individuals (n=40) whose cause of death was deemed potentially acute and unpredictable (e.g., falls, suicide, stroke without history of ischemic heart disease). This was done to ensure that only patients whose death might have been anticipated by clinicians were included. Additionally, patients without a registered breast cancer diagnosis (n=352) and those first diagnosed within three months of their death (n=229) were excluded to include only patients who were likely considered to be near death at the time of prescription. The final study population included 3,098 women.

The study population was then divided into two groups. Patients who had at least one endocrine treatment dispensation during the period from twelve to three months before their death were classified as "prevalent users" (n=2,185), while the rest were categorised as "non-users" (n=913). This division was necessary to identify which patients were at risk of continuing or initiating endocrine treatment during that specific timeframe.

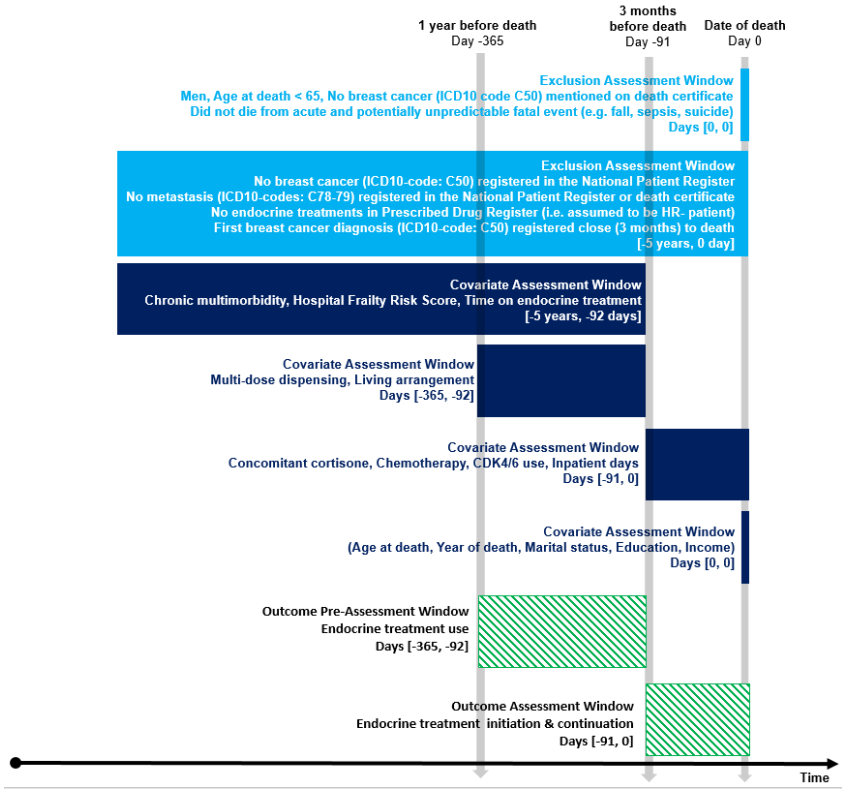

Figure 9. Study design of Study III

4.2.2 Self-controlled case series design

The self-controlled case series study design is widely used in pharmacoepidemiologic investigations of adverse drug reactions. This design includes patients who have experienced both the outcome of interest and the treatments under examination. The self-controlled case series method allows us to estimate the incidence rate ratio of the outcome during time-varying exposure periods in comparison to non-treatment periods. Unlike cohort designs that rely on comparisons between different individuals, this method uses patients as their own controls, effectively eliminating potential confounding factors that remain constant within each individual (e.g., genetic factors). As a result, this study design focuses on determining when the adverse event is more likely to occur, rather than who is more susceptible to experiencing it, which is the approach of cohort studies.

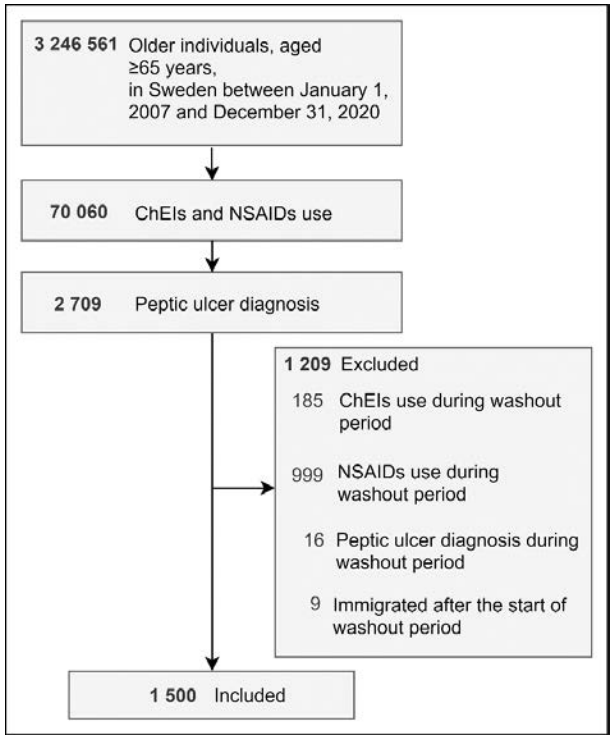

Figure 10. Flowchart diagram of Study IV

In **Study IV**, the source population consisted of all older adults aged ≥65 in Sweden between 2007 and 2020, totalling 3,246,561 individuals. From this population, we identified patients who received new prescriptions for either cholinesterase inhibitors (ChEIs) or non-steroidal anti-inflammatory drugs (NSAIDs), either concomitantly or separately, and were diagnosed with an incident peptic ulcer during the study period from 1 January 2007 to 31 December 2020. The observation period commenced on 1 January 2007 for patients aged 65 years or older at that date, and for those who turned 65 years during the study period, it began on their 65th birthday. The observation period ended upon reaching the end of the study period, death, or emigration.

To ensure a clear temporal sequence between drug exposures and outcomes, we excluded patients who had used ChEIs or NSAIDs, or had peptic ulcers during a one-year washout period preceding their observation period. Additionally, individuals who immigrated after the start of the washout period were excluded from the analysis. The final study population comprised 1500 cases.

4.3 Measurements

4.3.1 Quality indicators, outcomes, and exposures

4.3.1.1 Quality indicators

In **Study I**, we initially identified quality indicators for end-of-life cancer care based on a systematic review conducted by Henson and colleagues in 2019.[255] To update this list, we applied their search algorithm and inclusion criteria to find recently published quality indicators up until August 2020. Specifically, we focused on indicators that suggested potential risks outweighing the benefits of care, specifically indicators related to overtreatment in a broad sense, which primarily referred to medications, procedures, and hospital transitions. Next, we examined the feasibility of using these indicators with routinely collected administrative and healthcare data in Sweden. We excluded indicators that could not be effectively measured due to their reliance on procedures, specific in-hospital drug treatments, hospital transitions, or time frames that were not available in the data. Finally, we categorised the indicators into three main groups: (1) cancer-specific treatments, (2) hospital transitions and place of death, and (3) potentially futile treatments not limited to cancer.

We identified a total of 354 quality indicators concerning end-of-life cancer care. Among these indicators, 145 (41%) specifically addressed the issue of overtreatment. After evaluating their feasibility with nationwide Swedish administrative data, we found that 82 (57%) of the overtreatment indicators could be effectively operationalised. The reasons for indicators being non-operationalisable included instances where procedures or hospital drug treatments could not be identified in the available data (52%), care transitions or visits not being captured in the data (24%), a period too short for proper evaluation (e.g., drug treatments in the last 3 days of life) (21%), or other reasons (4%).

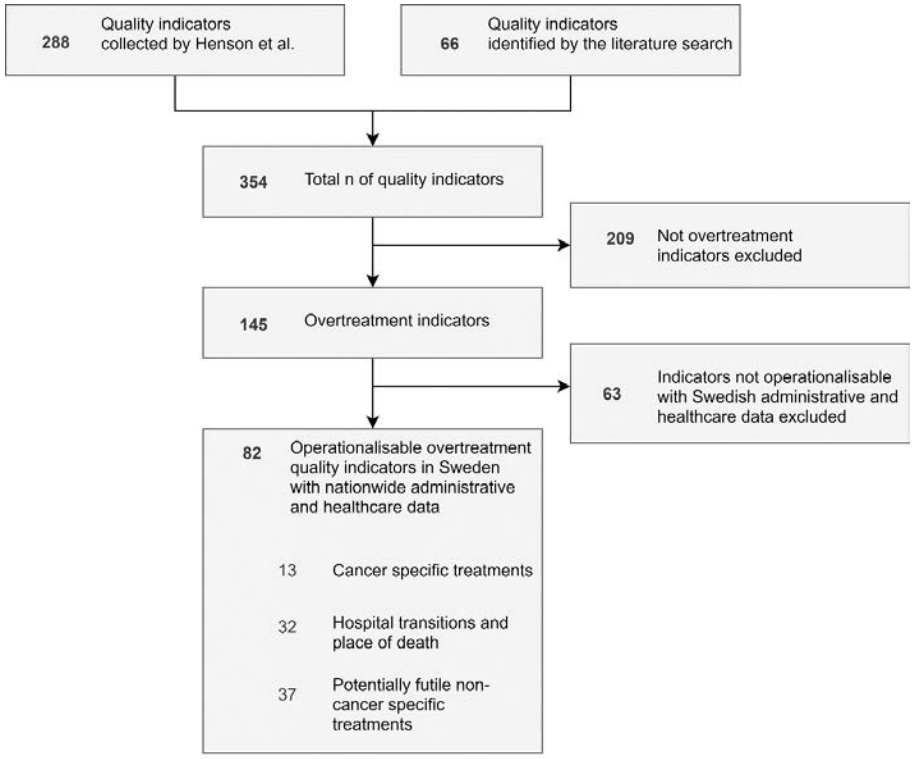

Figure 11. Flowchart of potential overtreatment indicator identification

Out of the 82 selected overtreatment indicators, 13 (16%) focused on cancer-specific treatments, 32 (39%) were related to hospital transitions and places of death, and 37 (45%) addressed potentially futile non-cancer specific treatments. Many indicators showed overlap, as they targeted the same procedure. In this study, we measured 15 unique quality indicators.

Table 3. Measured quality indicators of overtreatment at the end-of-life care in Study I

Numerator (number of people who died with solid cancer who received/had…)	**Denominator** (number of people who died with solid cancer…)
Cancer-specific treatments	
1. Tube feeding or intravenous feeding	People with gastro-intestinal cancer excluded
2. One or more chemotherapy (antineoplastic) treatments	
3. New chemotherapy (antineoplastic) regimen	People who did not receive chemotherapy before excluded
4. Surgical and invasive diagnostic procedures	
Hospital transitions and place of death	
5. More than one emergency room visit	
6. More than one hospitalisation	
7. Calculation: Non-general practitioner visits in last six months averaged across all cases with at least three non-general practitioner visits	
8. Died in hospitals	
9. Calculation: Per cent of days spent at home versus hospital*	
Potentially futile non-cancer specific treatments	
10. Blood transfusion(s)	
11. Port-a-cath installed	
12. Initiation of a new anti-depressant treatment	
13. Cardiopulmonary resuscitation performed	
14. Continued the use of often inadequate drugs	People <75 years of age excluded
15. Initiated the use of often inadequate drugs	People <75 years of age excluded

4.3.1.2 Illness trajectories and unplanned hospitalisation

In **Study II**, the main exposure, illness trajectories, were defined based on the causes of death mentioned on death certificates. The causes of death were classified into four distinct patterns of illness trajectories at the end of life, as proposed by Lunney et al.[78] These trajectories are as follows: Cancer, characterised by a short period of functional decline. Organ failure, marked by a longer period of functional limitations with intermittent acute decompensations. Prolonged dwindling, typical of older individuals with neurodegenerative conditions and/or frailty. Sudden death, which does not fit into any of the above-mentioned trajectories.[82] To determine a single illness trajectory for each decedent in cases where the causes of death were compatible with multiple trajectories, we utilised a rule-based algorithm based on previous research.[78, 281] The following hierarchy was applied: cancer > prolonged dwindling > organ failure > sudden death. This means that when multiple trajectories are present, the faster progressing trajectory is considered to have the greatest impact on the burden of functional decline over time. For example, cancer is placed at the top of the hierarchy because research has shown that a cancer diagnosis tends to dominate other co-occurring diseases when listed as multiple causes of death. [82, 282]

Creating clear-cut categories for complex events leading to death has been acknowledged as conceptually and operationally challenging by other researchers. [78, 80, 283] One difficulty in delineating illness trajectories is that some decedents may follow none, some, or all of these trajectories simultaneously. However, since detailed longitudinal data on physical and cognitive changes near the end of life are often not available in routinely collected data, these four groups of illnesses have been found to be a reliable approximation for understanding the pattern of late-life functional decline and care needs at the end of life.[284]

In **Study II**, we captured the outcome, unplanned hospital admissions, throughout the last year of life in the National Patient Register. Non-elective admissions in the National Patient Register were categorised as unplanned hospitalisations. To prevent counting transfers between hospital units as distinct admissions, consecutive hospitalisations occurring within a one-day timeframe were combined into a single episode.

4.3.1.3 End-of-life drug exposure patterns

In **Study III**, we looked at end-of-life drug exposure patterns of endocrine treatment. The use of endocrine treatment was identified using ATC codes (specifically, subgroup level 'L02' or everolimus [ATC: L01EG02]) from the National Prescribed Drug Register. To determine treatment exposure, we employed a text parsing algorithm that calculated the prescribed daily dose based on the input provided by the prescriber. A detailed explanation of this method can be found elsewhere.[180]

For our study, we applied four previously established patterns of end-of-life treatment:[206]

1. Treatment continuation: defined as the dispensing of endocrine treatment during the last three months of life, following its prior use during the period twelve to three months before death.
2. Treatment discontinuation: endocrine treatment dispensed during the twelve to three months before death but not during the last three months of life.
3. Treatment initiation: identified when endocrine treatment was dispensed during the last three months of life, following a washout period of twelve to three months before death.
4. No use: absence of any endocrine treatment dispensing during the last twelve months of life.

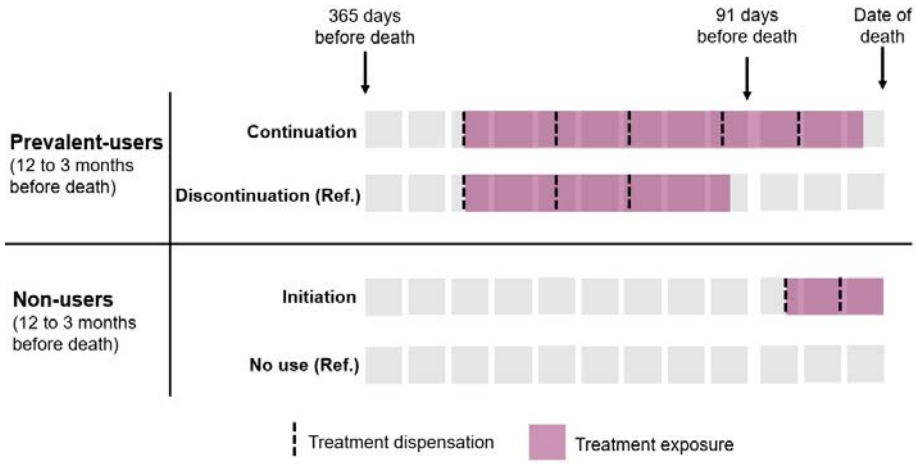

Figure 12. Treatment patterns at the end of life

4.3.1.4 Peptic ulcer cases and concomitant drug exposures

In **Study IV**, the peptic ulcer outcome was determined using the ICD-10 codes: K25 for gastric ulcer, K26 for duodenal ulcer, and K27 for peptic ulcer at an unspecified site. The K28 code was excluded as it refers to recurrent ulcers after gastroenterostomy in the Swedish ICD-10 codes, which was deemed irrelevant for the population of interest. For our study, we considered only the first occurrence of peptic ulcers since recurrent events of peptic ulcers are not independent.

In **Study IV**, we considered two main exposure drugs and their combination. ChEIs and NSAIDs were identified using the ATC codes ('N06DA02' for donepezil, 'N06DA03' for rivastigmine, 'N06DA04' for galantamine, 'M01A' for NSAIDs) from the National Prescribed Drug Register.

To determine the duration of drug use, we used a text parsing algorithm based on the prescriber's free text input to calculate the prescribed daily dose. Further details on this method can be found elsewhere.[180] After calculating the length of use, we considered the time from the dispensing date until the end of the prescribed daily dose, adding a 30-day grace period. Overlapping drug exposure periods were then consolidated into a single drug exposure window. Based on these drug exposure windows, we established four mutually exclusive exposure risk periods: ChEIs alone, NSAIDs alone, a combination of ChEIs and NSAIDs, and a reference non-treatment period.

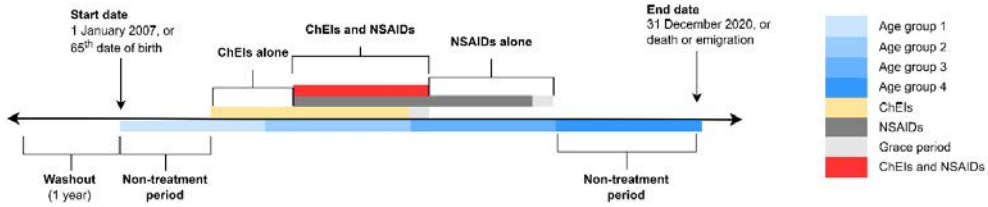

Figure 13. Study design of Study IV.

4.3.2 Individual characteristics

4.3.2.1 Sociodemographic characteristics

We extracted sex and age at death from the Cause of Death Register in **Studies I-III**. We used the Total Population Register to cross-validate these variables. In **Study IV,** where the cases were alive at the time of inclusion, we extracted sex and age at outcome ascertainment from the Total Population Register.

In **all Studies**, we defined marital status ('married', 'single/divorced', 'widowed') from the Swedish Total Population Register. Furthermore, we defined education as the lifetime highest attained educational level, and categorised into 'primary', 'secondary', and 'tertiary' education based on the International Standard Classification of Education 1997 system [279] using the Swedish Register of Education.

Table 4. Categorisation of the levels of education variable

Category	International Standard Classification of Education 1997
Primary education	Primary level of education (1)
Secondary education	Lower secondary education (2A)
	Upper secondary education ≤2 years (3C)
	Upper secondary education 3 years (3A)
	Post-secondary non tertiary education (4)
Tertiary education	Post-secondary education <3 years (5B)
	Post-secondary education ≥3 years (5A)
	Post-graduate education (6)

Income, used solely in **Study III**, was defined based on income quintiles of the latest individual disposable income obtained from The Longitudinal integration database for health insurance and labour market studies (LISA) owned by Statistics Sweden.

4.3.2.2 Hospital Frailty Risk Score

In **Studies I & III**, we estimated the Hospital Frailty Risk Score[46] based on the data captured in the National Patient Register during the period ranging from five years to three months before death. Data from the last three months of life were deliberately omitted because it corresponded to the outcome assessment window. In **Study II**, the variable was measured during the period ranging from five to one year before death. This was necessary because we aimed to avoid collecting covariate information during the same time when the outcome (unplanned hospitalisation) was assessed. In **Study IV** (the self-controlled case series), we did not use the Hospital Frailty Risk Score because frailty has a large genetic component,[285, 286] which is accounted for in self-controlled study design.

The Hospital Frailty Risk Score we utilised in our studies was developed and validated by Gilbert et a. in 2019.[46] They established this measure to capture individuals with frailty in routinely collected administrative and healthcare data. They first performed a cluster analysis to capture patients with frailty characteristics. Second, they created the Hospital Frailty Risk Score according to the ICD-10 codes that characterised frailty patients. Finally, they validated the measure on a national (UK) cohort of patients and a local patient cohort with information on their Fried Phenotype and Rockwood Frailty Index, two commonly used clinical frailty measures.[42, 43] Later, in 2022, Gilbert et al. validated the Hospital Frailty Risk Score in France, using a cohort of ≈1 million older people. They found that it predicts 30-day mortality and prolonged length of hospital stay.[287] The tool has been externally validated in many other settings and disease groups with varying results. For example, in Canada,[47-50] Australia,[51-53] US,[54] Switzerland,[55] and Sweden.[56]

4.3.2.3 Chronic Multimorbidity

We measured chronic multimorbidity in **Studies II, III & IV** based on the work of Calderón-Larrañaga et al., published in 2017.[28] In **Study I**, we did not measure comorbidity because we did not perform any analyses that would have needed covariate adjustment. The team of Calderón-Larrañaga, consisting of geriatricians, general practitioners, and epidemiologists, selected chronic conditions that "*(a) left residual disability or worsening quality of life or (b) required a long period of care, treatment, or rehabilitation*." They suggested a list of 60 clinically important chronic conditions that can be measured based on ICD-10 codes using nationwide administrative and healthcare data. Morin et al. adapted and extended the identification of chronic conditions suggested by Calderón-Larrañaga and colleagues.[281] Morin et al. identified drugs that suggest chronic diseases, enabling researchers to recognise some of them via the National Prescribed Drug Register.

In **Study II**, we captured chronic multimorbidity in the National Patient Register and the Prescribed Drug Register during the period ranging from 5 to 1 year before death. While in **Study III**, we used a period ranging from five years to three months before death. This variation was due to the different outcome assessment windows between the studies. In **Study IV**, we captured multimorbidity during the three years before the outcome occurrence using solely the National Patient Register. The reason for a shorter assessment window and the omission of the National Prescribed Drug Register was a trade-off for a longer follow-up period.

4.3.2.4 Other covariates

Several covariates are essential in the given studies but are not included in all the studies. For example, in **Study I**, we defined primary cancer diagnosis using ICD-10 codes from the underlying cause of death variable of the National Cause of Death Register. We stratified the results across primary cancer sites (and age groups).

Table 5. Primary cancer diagnosis categorisation

Primary cancer diagnosis	ICD-10 codes
Head or neck	C00–C14
Digestive tract	C15–C26
Respiratory tract	C30–C39
Melanoma	C43–C44
Breast	C50
Female genital organs	C51–C58
Male genital organs	C60–C63
Urinary tract	C64–C68
Other	C40–C41, C45–C49, C69–C80
Multiple Primary Tumours*	

*Reported only for the decedents who did not have solid cancer listed in the underlying cause of death, but had more than one solid cancer listed among their contributing causes of death.

Another example is polypharmacy. Polypharmacy was included only in **Study II** as a covariate. We assessed polypharmacy and categorised it as 0-4, 5-9 and 10 or more drugs dispensed during weeks 56-53 before death. It was calculated as the average number of prescription drugs (at the therapeutic/pharmacological subgroup level of the ATC classification system) that the decedents were exposed to across each of the four weeks preceding the last year of life.

In **Study III**, we defined a living arrangement ('community-dwelling', 'nursing home') variable using the Longitudinal integration database for health insurance and labour market studies (LISA, i.e., Swedish Social Service Register). Nursing home residency was considered permanent if registered at least once in the Swedish Social Service Register between one year and three months before death. We refrained from defining nursing

home residency status in the other studies included in this thesis because those studies used data from earlier (i.e., before 2016) where the quality of the register was subpar.[277]

Also, in **Study III**, we defined multi-dose drug dispensing. Multi-dose drug dispensing is when patients receive machine-dispensed drugs packed in disposable bags.[288] Multi-dose drug dispensing scheme was associated with polypharmacy because older people tend to have fewer drug reviews when they use this scheme.[289] We identified the variable between one year and three months before death using the Swedish Prescribed Drug Register.

4.4 Statistical analyses

In each of the four studies, the participants' characteristics were presented using either absolute numbers and percentages for categorical variables and means and standard deviations or medians and interquartile ranges for continuous variables, as deemed appropriate. We performed all analyses with SAS software version 9.4[290] and R statistical software version 3.6.1 and 4.0.5.[291]

4.4.1 Prevalence of potential overtreatment at the end of life (Study I)

In **Study I**, we measured 15 unique, published quality indicators of end-of-life cancer care. To ensure accuracy, the denominators of the quality indicators varied, including only the population eligible for treatments based on the original quality indicator. For time-specific quality indicators, we measured the indicators during two distinct periods: the last month of life and the last three months before death. These timeframes align with previous studies in end-of-life care literature.[292] Moreover, we determined the overall and category-specific (i.e., cancer-specific treatments, hospital transitions, and potentially futile non-cancer specific treatments) prevalence of overtreatment using indicators estimated specifically for the last month of life.

To explore potential variations in end-of-life overtreatment patterns, we computed the overall and category-specific proportion of individuals who fulfilled one or more overtreatment quality indicators, stratified by primary cancer site and age groups. In post-hoc sensitivity analyses, we excluded decedents with acute and potentially unexpected causes of death using a previously published algorithm.[145] Additionally, we limited the study population to decedents whose care team knew about their solid cancer diagnosis, indicating that their death was likely anticipated. Decedents were excluded if solid cancer was only reported as a contributing cause of death or recorded as the underlying cause of death without a solid cancer hospital diagnosis in the last two years of life. Finally, we excluded decedents whose first solid cancer diagnosis occurred close to their death (within three months). These population restrictions aimed to ensure that the decedents were perceived to be at the end of life by their treating physicians.

4.4.2 Unplanned hospitalisation patterns of illness trajectories (Study II)

In the primary analysis of **Study II**, we computed the incidence rate of unplanned hospitalisations during the final year of life. To compare the risk of unplanned hospitalisations among different illness trajectories to the average risk in the cohort, we employed a zero-inflated Poisson regression model. The zero-inflated model was necessary due to a significant number of individuals having no unplanned admissions (referred to as 'excess zeros'). To account for potential confounding factors, we selected relevant variables from the published literature based on subject-matter expertise. The adjusted analyses included age at time of death, sex, marital status (married,

single/divorced, and widowed), chronic multimorbidity, Hospital Frailty Risk Score, polypharmacy, and level of education (primary, secondary, and tertiary). To model excess zeros, the logit function used in the model was adjusted with respect to the Hospital Frailty Risk Score and the cumulative length of hospital stays between 731 and 366 days before death.

We also explored the average weekly change in the rate of unplanned hospitalisations during the last year of life based on the illness trajectory of the deceased individuals. The relative incidence rate ratios were calculated as the effect estimate for the interaction between the illness trajectory and time. To achieve this, we fitted a generalised estimating equations (GEE) model with a Poisson family and log link function. We used a restricted cubic spline with knots at nine, six, and three weeks before death and employed double-robust standard errors to estimate unbiased 95% confidence intervals. The adjustment for confounders in this analysis was consistent with the primary analysis.

In a prespecified sensitivity analysis, we identified and excluded decedents with acute and potentially unexpected causes of death using a previously published algorithm.[145] The rationale behind this analysis was that, despite the underlying illness trajectory, death can still be largely unexpected in cases where unplanned hospitalisations were clinically justified by an acute and life-threatening event. Additionally, in a post-hoc analysis, we replicated the calculation of incidence rate ratios for unplanned hospitalisations across illness trajectories during the last year of life but using regular Poisson models instead of the zero-inflated model.

4.4.3 Endocrine treatment patterns at the end of life and associated characteristics (Study III)

For the primary analysis of **Study III**, we investigated the patterns of endocrine treatment during the last year of life among decedents with metastatic breast cancer. Specifically, we measured the proportions of individuals who continued, discontinued, initiated, or did not use endocrine treatment. This allowed us to explore patient characteristics that were associated with a higher likelihood of endocrine therapy continuation compared to those who discontinued (reference category). Additionally, we examined factors associated with a higher probability of treatment initiation compared to constant no-use (reference category). For these secondary analyses, we utilised log-binomial generalised linear models. We chose the log-binomial modelling strategy over logistic regression because it provides risk ratios (RR) that offer better interpretability of results compared to odds ratios. Especially when the outcome is common in cohort studies, odds ratios might overestimate the underlying risks.[293]

Regarding sensitivity analyses, we conducted three prespecified variations of our primary analysis. Firstly, we restricted the analysis to patients aged 75 years or older, as the Morin indicators,[205] which determined that endocrine treatments were inadequate to initiate at

the end of life, were validated for this age group. Secondly, we included all patients who died with breast cancer, regardless of their metastatic status, since the ICD-10 codes (C78 and C79) used to identify metastatic patients were not validated in Sweden. However, these codes had previously been used to capture metastatic breast cancer populations in Sweden.[280, 294] Thirdly, we focused only on individuals with breast cancer (ICD-10 code: C50) as the underlying cause of death.

4.4.4 Adverse drug event in a cohort of patients with life-limiting illness (Study IV)

In **Study IV**, we employed a conditional Poisson regression model to assess the incidence rate ratio of the incident peptic ulcer diagnosis during various risk periods: use of ChEIs alone, NSAIDs alone, and the combination of ChEIs and NSAIDs. These periods were compared to the non-treatment reference period. While the self-controlled case series method inherently considers time-constant confounders, it is crucial to account for significant time-varying confounders. To address the influence of age on disease progression, we adjusted the analysis by age groups, defined by quantiles of the age at the outcome, as per the recommended approach.[295] Unfortunately, certain important confounders such as alcohol consumption and smoking were unavailable in the register data. Nonetheless, the self-controlled design helps minimise the impact of any remaining confounding factors.

To gauge the minimum effect that an unmeasured confounder would need to have on both the outcome and exposure to nullify the observed association between treatments and the outcome, we calculated E-values based on the methodology introduced by Mathur and colleagues.[296] For instance, an E-value of two implies that the unmeasured confounder could "explain away" the observed association if it doubled the risk of the outcome for either exposure status and was twice as prevalent among the exposed group compared to the unexposed group.[297]

4.5 Ethical considerations

In the present thesis, **all Studies** were conducted using pseudonymised register data, which ensures the protection of individuals' privacy. The data holders, namely the National Board of Health and Welfare and Statistics Sweden, linked the registers using the personal identification number, which they replaced with a dummy identification number ("lopnr"). This type of data cannot be linked to specific persons without additional information, such as key files. Still, there are specific ethical considerations when working with register data. The main risks for ethical issues are the probable violation of participants' integrity, respect for their autonomy and compliance with the justice bioethical principle.

4.5.1 Participants' integrity

Researchers should always safeguard the participants' integrity throughout the research process. However, researchers working with register data might violate participants' integrity in the following two instances. Firstly, improper data management might inadvertently allow unauthorised persons to gain access to the data.[298] To prevent such breaches, we took careful measures, such as storing the data on secure servers. Secondly, researchers might present the data or the results obtained from the data in a way that fails ensuring that the participants' identification remains confidential. To this end, we have taken great care to present the data in a manner that does not reveal the identity of any research subjects, reporting results only at the group level. Furthermore, in **Studies I-III**, we included only deceased individuals, further ensuring the privacy and respect of the participants.

4.5.2 Respect for autonomy

Respect for the autonomy of the research participants is essential in medical research.[299] The autonomy principle entails that a person has the right to refuse or withdraw their participation from any research study, and that informed consent collection is a moral obligation of the researchers.[300] This ethical consideration takes on even greater significance in clinical trials and prospective studies compared to register-based studies. In register-based studies, data are routinely collected for administrative purposes, and no active interventions are performed on patients. Consequently, the risks posed to participants (either psychological or physical) are virtually negligible. In extensive register-based studies, it is generally assumed that the participants would not refuse participation if the Ethical Review Authority, which acts as a representative of the public, approved the study.[301] All studies included in the thesis were approved by the Ethical Review Authority.

4.5.3 Principal of justice

Obtaining informed consent is not a prerequisite for carrying out large register-based studies if the Ethical Review Authority approves the study in Sweden. On the one hand, this contradicts the principle of justice because participants might be discriminated against due to their inability to give informed consent. On the other hand, obtaining informed consent from the participants or their relatives (for example, in cases of deceased participants) would be difficult due to administrative, time and funding reasons. Nonetheless, we think that in our studies of decedents and patients with life-limiting illness, it is unlikely for patients or relatives to request us not to use individual's pseudonymised data. Patients and relatives tend to support research,[302] and people in Sweden have high trust in medical research.[303] Additionally, register-based studies do not require direct patient interaction while increasing the knowledge and providing insight to the disease history of large populations with minimal selection bias. Also, studies investigating the effect of a harmful exposure (e.g., potential overtreatment) would not be ethically feasible in a clinical trial setting.

We adhered to the Declaration of Helsinki guideline by the Word Medical Association,[304] and the "Good research practice", published by the Swedish Research Council,[305] were considered during the research projects.

4.5.4 Ethical permits

The **Table 6** shows an overview of ethical permits of the studies included in this thesis.

Table 6. Ethical permits

	Title of the application	Date of application	Date of decision	DNR reference number
Studies I & II	Frisk till livets slut? Hälsa, funktionsförmåga, vård och läkemedelsbehandling hos äldre	2016-05-09	2016-06-08	2016/1001-31/4
Studies III & IV	Amendment to DNR: 2016/1001-31/4	2020-06-22	2020-07-15	2020-03525
	Amendment to DNR: 2016/1001-31/4	2021-04-14	2021-04-28	2021-02004

5 Results

5.1 Prevalence of potential overtreatment at the end of life (Study I)

In **Study I**, we discovered that almost half (43%) of the overtreatment indicators identified in the literature could not be measured with Swedish administrative register data primarily due to the absence of suitable methods for capturing the care procedures. Numerous indicators were overlapping and assessed similar concepts. Based on the 15 non-overlapping quality indicators that could be measured in Swedish administrative and healthcare data, we found that 36.9% (n=19,980) of older decedents with solid cancer received at least one treatment or had one hospital transition indicative of potential overtreatment during the last month of life. Cancer-specific treatments were the most common form of potential overtreatment (27.0%), followed-by potentially futile non-cancer specific treatments (12.3%), and hospital transitions (9.4%). The proportions of older patients who received care belonging to one, two and three categories of potential overtreatment were 26.3%, 9.4% and 1.2%, respectively.

Table 7. Proportion of patients with ≥ 1 overtreatment indicator during the last month of life, decedents with solid cancer in Sweden, 2013-2015, stratified by primary cancers and age groups

	Overall overtreatment (%)
Total population	36.9
Primary cancer diagnosis (ICD-10)	
Head or neck (C00-C14)	37.2
Digestive tract (C15-C26)	40.4
Respiratory tract (C30-C39)	38.4
Melanoma (C43–C44)	30.3
Breast (C50)	28.4
Female genital organs (C51–C58)	41.2
Male genital organs (C60–C63)	30.0
Urinary tract (C64–C68)	37.9
Other (C40–C41, C45–C49, or C69–C80)	38.0
Multiple Primary Tumours (>1)[a]	38.2
Age group	
65 to 74 years	45.0
75 to 84 years	37.2
85 to 94 years	28.7
95 years and older	19.6

a: Multiple Primary Tumours is reported for the decedents (n=288) whose primary cancer was defined based on the contributing causes reported on the death certificate due to not having solid cancer listed in the underlying cause of death recorded on the death certificate.

The prevalence of patients with at least one indicator of potential overtreatment during the last month of life varied by primary cancer type. The highest prevalence was for patients with female genital organ cancer (41.2%) and lowest for breast cancer (28.4%). The age-stratified analysis revealed that prevalence of potential overtreatment was

higher in younger age groups (45.0% vs 19.6% in the in the 65 to 74 years vs 95 years and older group).

Table 8. Quality indicators of overtreatment at the end-of-life care for all people aged ≥65 years who died from cancer in Sweden, 2013-2015

Numerator (number of people who died with solid cancer who received/had…)	**Denominator** (number of people who died with solid cancer…)	**No. of months before death until death**	
		Not specified	One month
Cancer-specific treatments			27.0
1. Tube feeding or intravenous feeding	N= 36,523 (People with gastro-intestinal cancer excluded)	-	1.4%
2. One or more chemotherapy (antineoplastic) treatments	N= 54,177	-	2.7%
3. New chemotherapy (antineoplastic) regimen	N= 8,893 (People who did not receive chemotherapy before excluded)	-	8.0%
4. Surgical and invasive diagnostic procedures	N= 54,177	-	24.6%
Hospital transitions and place of death			9.4%
5. More than one emergency room visit	N= 54,177	-	7.2%
6. More than one hospitalisation	N= 54,177	-	9.4%
7. Calculation: Non-general practitioner visits in last six months averaged across all cases with at least three non-general practitioner visits*	N= 34,274	7.7	-
8. Died in hospitals*	N= 54,177	49.0%	-
9. Calculation: Per cent of days spent at home versus hospital*	-	-	65.1%
Potentially futile non-cancer specific treatments			12.3%
10. Blood transfusion(s)	N= 54,177	-	9.2 %
11. Port-a-cath installed	N= 54,177	-	1.2%
12. Initiation of a new anti-depressant treatment	N= 54,177	-	2.0%
13. Cardiopulmonary resuscitation performed	N= 54,177	-	0.3%

*Quality indicator contributing neither to overtreatment category level prevalence nor the overall overtreatment prevalence measured in the last month of life.

Note: The quality indicators of "Continued the use of often inadequate drugs" and "Initiated the use of often inadequate drugs" were not presented here because they were only reported for three months before death, as was done in the original publication. [205]

5.2 Unplanned hospitalisation patterns of illness trajectories (Study II)

In **Study II**, based on an analytical cohort of 77,313 decedents, aged 65 and older, who died in 2015, we found an average 1.7 unplanned hospitalisations during the last year of life per decedent, corresponding to an incidence rate of 175 per 100 person-years.

Decedents who followed different trajectories experienced varying incidence rates of cancer and unplanned hospitalisation. Those with a cancer trajectory had the highest incidence rate at 231 per 100 patient-years, whereas individuals on a trajectory of prolonged dwindling had the lowest rate at 99 per 100 patient-years. After adjusting for available confounders, decedents with cancer faced a 1.20 (95% CI 1.18–1.21) times higher risk of unplanned hospitalisation compared to the average. On the other hand, those following the trajectory of prolonged dwindling and sudden death trajectory had lower-than-average risks of unplanned hospitalisation with incidence rate ratios of 0.66 (95% CI 0.65–0.68) and 0.79 (95% CI 0.77–0.82), respectively.

Table 9. Incidence of unplanned hospitalisation during the last year of life, by illness trajectory

	No. decedents	Incidence rate per 100 person-years	Incidence rate ratio (95% CIs)	
			Unadjusted	Adjusted[b]
Overall	77 315	175	1.0 (Ref)	1.0 (Ref)
Trajectories[a]				
Cancer	23 213	231	1.22 (1.21–1.24)	1.20 (1.18–1.21)
Organ failure	28 338	195	1.09 (1.08–1.11)	1.04 (1.03–1.06)
Prolonged dwindling	20 064	99	0.57 (0.56–0.59)	0.66 (0.65–0.68)
Sudden death	5700	131	0.73 (0.71–0.76)	0.79 (0.77–0.82)

a: The total study population was used as the reference category to compare the risks across illness trajectories to the average risk in the cohort.
b: Adjusted for sex, age, education, marital status, frailty, number of chronic diseases, polypharmacy; Decedents with missing data about education (2.1% of total) were excluded from this analysis.

Throughout the last year of life, there was a substantial increase in the rate of unplanned hospitalisations, rising from 1.5 to 26.2 per 100 patient-weeks. This increase was observed regardless of the patient's illness trajectory or age. Particularly noteworthy were the sharp rises among decedents who died suddenly (from 1.0 to 43.9 per 100 patient-weeks) and those with organ failure (from 1.8 to 38.0 per 100 patient-weeks). The incidence rate increases did not follow a linear pattern, and differences between illness trajectories were minimal until the third month before death.

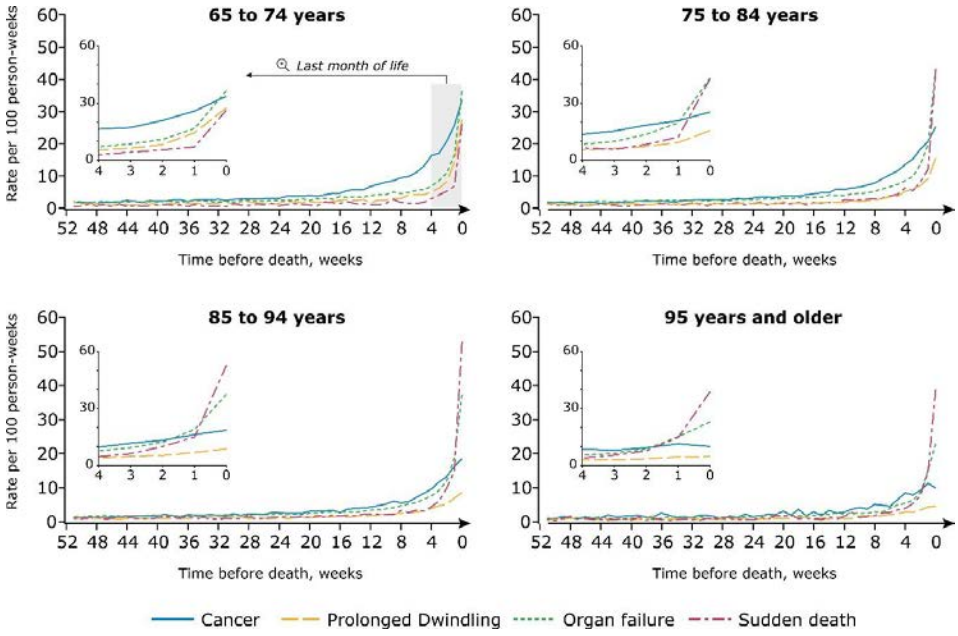

Figure 14. Incidence rate of unplanned hospitalisation throughout the last year of life, by age and illness trajectory. Originally published by Szilcz et al. 2021.[306] Reprinted with permission.

Over the final three months before death, we observed significant discrepancies in the pace of unplanned hospitalisations among various illness trajectories. Older individuals who passed away from sudden causes experienced the most rapid escalation in the likelihood of unplanned hospital admissions (relative incidence rate ratio: 1.12, 95% CI 1.11–1.13). Conversely, those who followed a cancer or prolonged dwindling trajectory had slower-than-average increments in their risks of unplanned hospitalisation.

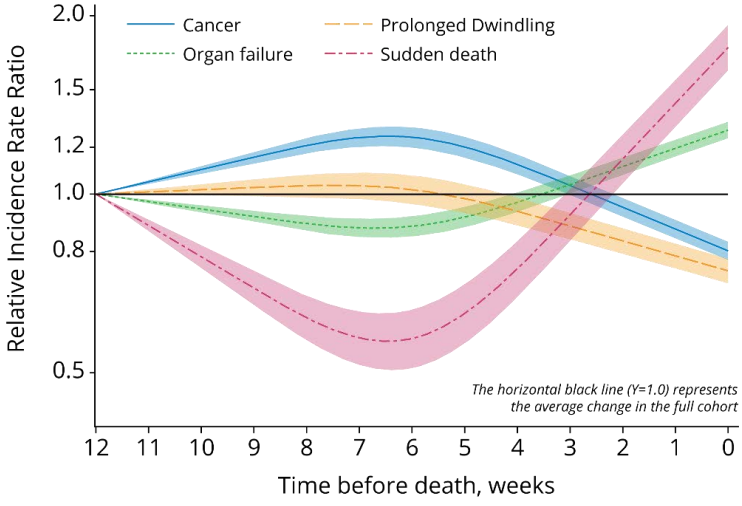

Figure 15. Change in the incidence rate of unplanned hospitalisation throughout the last 12 weeks of life, by illness trajectory. Originally published by Szilcz et al. 2021.[306] Reprinted with permission.

5.3 Endocrine treatment patterns at the end of life and associated characteristics (Study III)

In **Study III**, the final study population consisted of 3098 women with hormone receptor-positive metastatic breast cancer who died between 2016 and 2020. Median age at death was 78 years (IQR 72–85). Over the course of the final three months before death, 1,217 women continued to undergo endocrine treatment. This group corresponded to 39% of the entire studied population and 56% of those who had been using endocrine treatment (prevalent users). In contrast, 968 patients discontinued their treatment, accounting for 31% of the overall cohort and 44% of the group that had been using the treatment during last year before death. While, 157 women, making up 5% of the total cohort and 17% of those who had not previously used the treatment, began endocrine treatment in the last three months of life. Notably, a group of 756 women (24% of the entire cohort) did not use endocrine treatment at any point during the last year before their death.

Table 10. Endocrine treatment patterns at the end of life of women who died with hormone receptor-positive metastatic breast cancer, aged ≥65 years in Sweden, 2016-2020

End-of-life treatment patterns	Overall (n=3098)	Prevalent users 12 to 3 months before death (n=2185)	Non-users 12 to 3 months before death (n=913)
Continuation	1217 (39.3%)	1217 (55.7%)	-
Discontinuation	968 (31.2%)	968 (44.4%)	-
Initiation	157 (5.1%)	-	157 (17.2%)
No use	756 (24.4%)	-	756 (82.8%)

We found several factors associated to continuation of endocrine treatment compared to discontinuation. These factors include higher age (RR_{85+} years: 1.26 [1.12-1.41]), multi-dose drug dispensing (RR: 1.22 [1.13-1.32]), CDK4/6 use (RR 1.40 [1.25-1.58]), higher education ($RR_{\text{tertiary education}}$: 0.89 [0.81-0.98]), and chemotherapy (RR: 0.66 [0.49-0.90]). Fewer factors were associated to treatment initiation compared to no use. For example, we found increased probability with the number of hospitalised days ($RR_{1\text{-}14\ \text{inpatient days}}$: 1.81 [1.12-2.91]), CDK4/6 use (3.16 [2.25-4.44]), cortisone use (RR: 1.54 (1.17-2.04]) and decreased probability for earlier diagnosis of metastasis ($RR_{>3\ \text{years}}$: 0.49 [0.35-0.69])

Table 11. Relative risks estimates of factors associated with endocrine treatment continuation (N= 1217)

	%	RR (95% CI)	Adj. RR (95% CI)
Age at time of death, years			
65 to 74 years	44.0	1	1
75 to 84 years	56.2	1.29 (1.16-1.43)	1.17 (1.05-1.30)
85 years and older	67.9	1.57 (1.42-1.73)	1.26 (1.12-1.41)
Education, No. (%)			
Primary/elementary education	63.5	1	1
Secondary education	52.2	0.82 (0.76-0.89)	0.92 (0.86-1.00)
Tertiary education	48.7	0.77 (0.69-0.85)	0.89 (0.81-0.98)
Marital status			
Married	48.8	1	1
Single/divorced	52.1	1.06 (0.95-1.18)	1.03 (0.93-1.14)
Widowed	65.0	1.34 (1.23-1.46)	1.11 (1.01-1.22)
Living arrangement			
Community-dwelling	52	1	1
Nursing home	78.9	1.52 (1.41-1.64)	1.11 (1.01-1.22)
Income quintiles			
Fifth (highest)	52.5	1	1
Fourth	53.0	1.01 (0.90-1.14)	0.90 (0.82-1.00)
Third	60.6	1.15 (1.03-1.30)	0.95 (0.86-1.04)
Second	56.7	1.08 (0.96-1.22)	0.92 (0.83-1.03)
First (lowest)	56.9	1.08 (0.96-1.22)	0.96 (0.86-1.06)
Frailty			
Low (<5)	53.7	1	1
Moderate (5–10)	54.7	1.01 (0.92-1.11)	0.99 (0.91-1.08)
High (>10)	68.0	1.27 (1.16-1.40)	1.06 (0.97-1.15)
Number of chronic diseases			
0-1	51.3	1	1
2-3	55.8	1.09 (0.93-1.27)	1.06 (0.92-1.22)
4-5	53.2	1.03 (0.88-1.21)	1.01 (0.87-1.16)
>=6	58.3	1.15 (0.99-1.33)	1.01 (0.88-1.17)
Years since metastasis			
<1	60.2	1	1
1-3	53.0	0.89 (0.81-0.97)	0.96 (0.89-1.03)
>3	52.0	0.87 (0.79-0.95)	0.94 (0.86-1.02)
Multi-dose dispensing			
No	49.0	1	1
Yes	69.5	1.43 (1.33-1.54)	1.22 (1.13-1.32)
Years on endocrine treatment			
<1	56.7	1	1
1-2	55.5	0.97 (0.87-1.08)	1.01 (0.92-1.10)
>3	55.3	0.97 (0.89-1.07)	1.00 (0.92-1.08)
Inpatient days in the last 3 months of life			
No hospitalisation	64.7	1	1
1-14	53.9	0.82 (0.75-0.90)	0.93 (0.86-1.02)
15-30	54.6	0.84 (0.76-0.93)	0.97 (0.88-1.07)
>30	45.6	0.70 (0.61-0.80)	0.88 (0.77-1.01)
CDK4/6 use			
No	55.2	1	1
Yes	67.8	1.23 (1.05-1.43)	1.40 (1.25-1.58)
Hospital chemotherapy use			
No	56.8	1	1
Yes	30.5	0.54 (0.40-0.74)	0.66 (0.49-0.90)
Cortisone use			
No	58.9	1	1
Yes	50.5	0.86 (0.79-0.93)	0.96 (0.88-1.03)

Table 12. Relative risks estimates of factors associated with endocrine treatment initiation (N= 157)

	%	RR (95% CI)	Adj. RR (95% CI)
Age at time of death, years			
65 to 74 years	18.0	1	1
75 to 84 years	15.5	0.86 (0.62-1.18)	0.99 (0.74-1.32)
85 years and older	18.5	0.98 (0.65-1.50)	1.26 (0.79-1.99)
Education, No. (%)			
Primary/elementary education	19.7	1	1
Secondary education	15.9	0.80 (0.57-1.13)	0.78 (0.56-1.09)
Tertiary education	16.2	0.82 (0.58-1.17)	0.80 (0.56-1.16)
Marital status			
Married	16.5	1	1
Single/divorced	18.6	1.10 (0.79-1.54)	1.19 (0.89-1.60)
Widowed	16.7	1.02 (0.71-1.46)	1.05 (0.71-1.55)
Living arrangement			
Community-dwelling	17.7	1	1
Nursing home	9.6	0.55 (0.23-1.27)	0.76 (0.32-1.79)
Income quintiles			
Fifth (highest)	14.7	1	1
Fourth	16.7	1.13 (0.72-1.78)	0.88 (0.59-1.33)
Third	13.8	0.89 (0.52-1.54)	0.63 (0.38-1.03)
Second	23.2	1.59 (1.05-2.39)	1.14 (0.77-1.69)
First (lowest)	17.9	1.23 (0.81-1.87)	0.91 (0.59-1.40)
Frailty			
Low (<5)	18.0	1	1
Moderate (5–10)	17.2	0.96 (0.68-1.37)	1.15 (0.79-1.67)
High (>10)	11.2	0.63 (0.35-1.16)	0.73 (0.39-1.39)
Number of chronic diseases			
0-1	20.8	1	1
2-3	17.9	0.86 (0.54-1.37)	0.89 (0.59-1.34)
4-5	16.4	0.78 (0.49-1.24)	0.82 (0.54-1.23)
>=6	16.1	0.78 (0.50-1.22)	0.82 (0.53-1.28)
Years since metastasis			
<1	30.2	1	1
1-3	16.8	0.57 (0.41-0.79)	0.62 (0.45-0.85)
>3	12.1	0.41 (0.29-0.57)	0.49 (0.35-0.69)
Multi-dose dispensing			
No	17.3	1	1
Yes	16.6	0.96 (0.65-1.42)	1.19 (0.84-1.68)
Years on endocrine treatment			
<1	24.7	1	1
1-2	13.7	0.56 (0.39-0.80)	0.62 (0.44-0.88)
>3	14.5	0.59 (0.43-0.82)	0.62 (0.45-0.85)
Inpatient days in the last 3 months of life			
No hospitalisation	10.8	1	1
1-14	20.4	1.89 (1.19-3.01)	1.81 (1.12-2.91)
15-30	19.3	1.80 (1.10-2.92)	1.50 (0.90-2.48)
>30	14.9	1.34 (0.76-2.34)	1.36 (0.77-2.38)
CDK4/6 use			
No	15.9	1	1
Yes	53.1	3.35 (2.34-4.8)	3.16 (2.25-4.44)
Hospital chemotherapy use			
No	17.4	1	1
Yes	14.9	0.86 (0.48-1.55)	0.85 (0.47-1.53)
Cortisone use			
No	14.7	1	1
Yes	20.1	1.37 (1.03-1.83)	1.54 (1.17-2.04)

5.4 Adverse drug event in a cohort of patients with life-limiting illness (Study IV)

We identified 70,060 older patients using both ChEIs and NSAIDs between 2007 and 2020. Of them, 2,709 patients (3.9%) had a peptic ulcer diagnosis registered. We included 1,500 cases in the final study population, after exclusion of patient using ChEIs and NSAIDs or those who had peptic ulcer during the washout period.

In comparison to periods without treatment, the utilisation of NSAIDs alone resulted in a heightened risk of peptic ulcer (adjusted IRR: 5.2, 95% confidence interval: 4.4-6.0, E-value: 9.8). This risk escalated even further when ChEIs were combined with NSAIDs (9.0, 6.8-11.8, E-value: 17.5). However, there was no observed increase in risk associated with the use of ChEIs alone (1.0, 0.9-1.2, E-value: 1.2).

Table 13. Incidence rate ratio of first peptic ulcer diagnosis stratified by exposure risk periods

Exposure risk periods	Number of events	Person-years of follow-up	Incidence rate ratio (95% CIs)	
			Unadjusted	Adjusted[a]
Non-treatment	850	12,375.8	Ref.	Ref.
NSAIDs alone	284	1,063.8	4.95 (4.26 - 5.74)	5.16 (4.44 – 6.00)
ChEIs alone	278	3,333.6	1.25 (1.08 - 1.46)	1.02 (0.86 - 1.21)
Combination of NSAIDs and ChEIs	88	169.1	10.55 (8.04 - 13.85)	8.98 (6.81 - 11.84)

[a]Estimates from the conditional Poisson regression of the self-controlled case series analysis, adjusted by age groups
Abbreviations: ChEIs = cholinesterase inhibitors; NSAIDs = Non-steroidal anti-inflammatory drugs; CI = confidence interval

In the subgroup analyses, when ChEIs and NSAIDs were used concomitantly, the adjusted IRR was found to be higher in females (10.4, 7.4-14.8, E-value: 20.4) than in males (6.9, 4.3-10.9, E-value: 13.2). Similarly, the older age group exhibited a higher adjusted IRR (12.6, 8.5-18.5, E-value: 24.6) compared to the younger age group (6.9, 4.5-10.6, E-value: 13.3).

In sensitivity analyses, where certain study design conditions were modified, consistent risk estimates were obtained for the ChEIs and NSAIDs combination. The inclusion of various pre-exposure risk periods or varied grace-periods showed similar results with no substantial difference in the risk estimates. Altering the washout window for NSAIDs preserved more cases and resulted in equivalent estimates from a larger population. Finally, accounting for time-varying use of proton pump inhibitors, antiplatelet drugs, systemic steroid, and antidepressants did not change the estimates.

6 Discussion

6.1 Main findings

We contributed to evaluating the quality of end-of-life care for older adults using nationwide administrative and healthcare data. We focused on the extent, determinants, and consequences of potential overtreatment, considering that registers lack data on some of the core principles of quality end-of-life care (e.g., patient preferences). The selected four studies reflect key dimensions of quality of care, namely, quality indicators, burdensome transitions, treatment discontinuation and inappropriate prescribing. To this end, we used quality indicators to investigate the extent of potential overtreatment at the end of life among older people with solid cancer. We described the patterns of potentially burdensome unplanned hospitalisations during the last year of life across different illness trajectories. We examined the potential overuse of endocrine treatment (initiation and continuation) and their determinants among patients with metastatic breast cancer. We studied the consequences of drug-drug interactions, namely ChEIs and NSAIDs, for patients with life-limiting illnesses. The main findings were as follows:

1. Nearly half of the overtreatment indicators described in previous literature could not be quantified using Swedish register data due to the lack of appropriate information. Based on the indicators we could measure, we estimated that one third of decedents with solid cancer were subjected to potential overtreatment during their last month of life.

2. Unplanned hospitalisations were common after the third month before death, where the differences between illness trajectories also became evident. Unplanned hospitalisations increased first among those with cancer and organ failure, while those experiencing prolonged dwindling, often linked to dementia, had a modest rise in unplanned admissions in their final month of life.

3. Endocrine treatment was initiated by five per cent in the last three months of life and continued by more than one-third of older decedents with metastatic breast cancer, potentially beyond a point where it could offer meaningful benefits. We also found several factors linked to continuation and initiation of treatment.

4. We discovered a synergic drug-drug interaction when NSAIDs and ChEIs are concurrently used that yielded a nine-fold increase in the risk of peptic ulcer. Women and older aged individuals had even further increased risks of peptic ulcer.

The detailed results of each of these four studies are discussed in their respective articles. In the subsequent sections we reflect on particular aspects that surpass the scope of the individual studies.

6.2 Parts of the puzzle

Overtreatment is broadly defined as care provided "*in the absence of a clear medical basis for use or when the benefit of therapy does not outweigh risks*."[140, 141] Such a broad concept is difficult to fully address within a single study or even within an entire doctoral thesis. In this doctoral thesis, we aspired to contribute to evaluating the extent, determinants, and consequences of potential overtreatment. The studies we chose to include in the thesis represented this effort while they investigated different yet complementing dimensions of the quality of care. In **Study I**, we measured quality indicators for overtreatment, which are frequently used to assess the quality of care and enable understanding of some aspects of the current state of end-of-life care.[247-250] However, they are "just" *indicators,* and thus, they often fall short in addressing multifaceted questions.[247] Thereby, in the following three studies, we examined key dimensions of potential overtreatment that some of the indicators of **Study I** crudely measured. In **Study II,** we investigated potentially burdensome transition measured in the form of unplanned hospitalisations, which patients and relatives usually prefer to avoid.[230] At the end of life, hospitalised patients are often subjected to low-quality care,[228] and might end up in a vicious circle of overdiagnosis and overtreatment.[155, 219] In **Study III**, we focused on discontinuation of potentially non-beneficial treatment at the end of life. Drugs with a lack of benefit during the patient's remaining short life expectancy should be avoided in light of the potential for adverse effects and polypharmacy.[179, 204] In **Study IV**, we considered potentially inappropriate prescribing of NSAIDs in a vulnerable patient population with life-limiting illness. We showed the consequences of prescribing a drug that is included in inappropriate medication criteria for older people.[307] Collectively, this thesis encompasses studies investigating a wide range of connected phenomena, all relating to some aspect of potential overtreatment.

6.3 Quality care creates quality of life

Quality and comfort care should gradually take over life-extending and disease-modifying care at the end of life.[129] People usually prefer quality of care more than extension of life.[308] In this context, the findings of **Study I**, which showed that one-third of patients might experience overtreatment at the end of life, indicate that there is room for improvement. Avoiding harm in patients with limited remaining life expectancy is vital for maintaining their dignity and preserving their functional ability. Minimising high-risk care is even more crucial at the end of life than at other stages of the disease. As Holmes et al. highlighted in their paper about medication appropriatenesss,[129] the potential benefits from treatments decrease as individuals near the end of life. This is particularly true for older patients who often grapple with multiple concurrent diseases and varying degrees of frailty.[67] However, as nearly all interventions entail some risks, ranging from negligible to dire consequences, balancing the potential for harm and benefit makes it challenging to provide quality care for patients.

Examining potential overtreatment at the end of life through a quality-of-care lens helps our understanding of the issue.[258, 309] While achieving *perfect* end-of-life care might be ideal in theory, such perfection — meaning completely free from faults and defects — would impose an unimaginable amount of financial and logistical burden on the healthcare system with opportunity costs beyond reason. However, Antoine de Saint-Exupéry (French author best known for the book The Little Prince) viewed *perfection* differently: "*…perfection is finally attained not when there is no longer anything to add, but when there is no longer anything to take away…*". Though Saint-Exupéry was discussing airplane design, his perspective serves as a great metaphor for medicine. Often, the norm is to add treatments, but in certain situations, the removal of treatments becomes the optimal course of action. In this regards, Saint-Exupéry's vision of *perfection* is what we should aim for in delivering quality end-of-life care.

Quality indicators are instrumental in assessing the performance of healthcare systems. In **Study I**, we focused on the potential overtreatment aspects of the end-of-life care within the Swedish healthcare system. This enabled expressing the quality on an aggregated Sweden-wide level, contrary to the individual patient-group perspective.[310, 311] Much of the end-of-life research have been conducted in smaller and particular diseases populations, especially when it comes to cancer and chemotherapy.[7, 150, 153, 268, 312-316] However, analysing select indicators in confined patients groups, often within single hospital setting, does not provide a holistic picture of the healthcare system. In contrast, monitoring quality nation-wide offers opportunities for regional and national evaluations and comparisons.

Our aim was not to develop new quality indicators. Instead, we aimed to collect those already established internationally, given the extensive number of indicators available for end-of-life cancer care. De Schreye et al. went through the process to develop end-of-life quality indicators specifically tailored for routinely collected data for cancer,[266] which we incorporated into our collection. They also developed indicators for Alzheimer's disease[317] and COPD.[253] Their methodology involved a literature search for candidate indicators, expert interviews to identify new indicators and validation of these indicators using the RAND/UCLA Appropriateness Method,[318] specifically in the Belgian context. Given that our collection of indicators was international in scope, there might be cultural variances in perceptions of what is deemed inappropriate.[319, 320] However, our final list predominantly comprised indicators universally recognised as potential overtreatment in most countries. For data access reasons, we did not include indicators that related to patient-reported outcomes or psycho-social aspects of care. Furthermore, we believe that quality indicators should be developed and validated with applicability to different national and international data sources in mind to facilitate widespread assessment.

Assessing the performance of end-of-life care through quality indicators can be delineated as a three-step process. The first step involves selecting and measuring the

quality indicators. We employed a data-driven selection approach for this purpose, measuring indicators of potential overtreatment that were feasible based on national administrative and healthcare data. The second step is to compare the measured indicators to established standards. Such a comparison is pivotal for a precise interpretation of the quality indicators, aiding policymakers in discerning whether a given indicator surpasses or falls short of expectations. Nevertheless, not every quality indicator has accompanying standards. In fact, none of the quality indicators we measured have national standards or targets in Sweden.[121] Typically, these national standards are determined either by a data-driven method,[252] or decision-makers, ideally grounded in high-quality scientific evidence.[321] An illustrative example of the data-driven approach is to divide regions into high and low-performing quartiles, with the latter's results serving as the relative standard to attain, akin to the methodology that De Schreye and colleagues used in Belgium.[253, 317] However, such regional comparisons need to take into account other factors that could influence the results. Factors that vary between the compared regions and might affect the care provision but are not the effect of the care provided could bias the results.[322] These factors may include but are not limited to compositional difference in structure of age, gender, care dependency, household type, net income and urbanisation of the region.

In absence of national or relative standards, we performed international comparisons and benchmarking.[323] For certain indicators, we identified similar estimates analogous to those in other countries (e.g., 1.4% "tube feeding or intravenous feeding" vs 1.3% in Belgium)[266]. For others, we found notable differences. For example, we estimated the provision of chemotherapy at the end of life to be around 3% in Sweden, which was considerably lower than in Austria (7%),[264] Germany (10%),[265] Belgium (17%)[266] or Denmark (16%).[267] However, these international comparisons have their caveats, mainly due to the lack of risk adjustment and discrepancies in measurements. Variations between estimates might stem from divergent measurement and reporting methodologies among the selected countries or inherent differences in population structures, which we did not adjust for as previously described.

The third and final step in the assessment process of the performance of end-of-life care revolves around setting objectives for the indicators. Given the presence of national or relative standards (i.e., best-performing regions) it is feasible to define such goals. Establishing priorities among these goals might be influenced by indicators that exhibit the most pronounced regional disparities, particularly where the gap between the highest and lowest-performing regions is most evident. Goal and priority setting was outside the scope of the present thesis but warrants exploration in future research endeavours.

6.4 Simpler is better?

The studies included in this thesis shed light on the problem of potential overtreatment from different aspects. However, the thesis did not investigate interventions that could mitigating such overtreatment. To provide a useful perspective, we intend to discuss options to reduce potential overtreatment, underlining that the goal is not to ration healthcare but to ensure care is evidence-based and tailored to the patient's needs. In the subsequent sections, we discuss three valuable strategies in line with this perspective: shared decision-making, deprescribing, and population-based palliative care. While these discussions are not directly derived from our findings, they are essential for interpreting our results and for addressing the challenge of potential overtreatment.

6.4.1 Alone together

Aligning treatment with a patient's preference and treatment goals should be a priority at the end of life. Shared decision-making, wherein the healthcare professionals collaborate with the patients and their families to decide on treatment goals, promotes goal-concordant care.[324] In response to our **Study I**, Björkhem-Bergman published an editorial emphasising the need for clinicians to engage more frequently in conversations with patients about their treatment preferences, and the underlying reasons for those preferences, regardless of life expectancy.[325] This editorial highlighted the importance of shared decision-making, which is based on open communication, a strong patient-clinician relationship and shared knowledge. Such an approach can potentially reduce overtreatment, enhance patients' quality of life, and contribute to a positive end-of-life experience for patients and their families.[324, 326]

However, Clapp argues that while improving communication between patients and clinicians is important, it does not necessarily eliminate the problem of overtreatment.[218] Often, patients recognise the need for a treatment, such as surgery, after consultation with a clinician who suggested it as an option.[327] In other words, this can be attributed to the problem of information asymmetry in healthcare, as described by Kenneth Arrow.[328] This means that patients often lack the specialised knowledge that healthcare professionals possess. Thus, it becomes imperative for these professionals to act in the interest of their patients (while they also act as stewards of scarce healthcare resources with professional and ethical obligation to reduce waste).[329] Yet, clinicians do not always make decisions that align with their patients' interest. For example, Zaza and colleagues found that 40% of surgeons would perform surgery on an 87-year-old woman with a terminal illness.[330] Almost all of them acknowledged previously that overtreatment is problematic at the end of life and showed a preference for comfort-oriented care. The decision to perform surgery was sometimes influenced by factors such as operating room availability and relatives' insistence on pursuing all treatment options. This underscores

the gap between the clinician's assessment of the patient's interest and their readiness to offer interventions that contradict that assessment.

Scott and colleagues identified various cognitive biases that can influence healthcare professionals' decision-making and potentially lead to overtreatment.[168] These include commission, attribution, impact, affect, availability, ambiguity, representativeness, endowment and sunken cost bias. In our **Study III**, we observed a pronounced endowment effect: there was a low percentage of patients starting treatment but a high percentage continuing treatment towards the end of life. This indicates a reluctance to begin treatments and an aversion to discontinuing them, pointing to a preference for the status quo. Hallek et al. suggest that behavioural economics interventions (e.g., active decision rules, social norms, self-commitments) aimed at physicians' biases might improve decision-making.[331] However, Kullgren and colleagues demonstrated that these interventions do not always work.[332] For instance, precommitment (i.e., the commitment in advance to a set of action) to follow the recommendations of the widely publicised Choosing Wisely overtreatment campaign[136] only led to a small and an short-lived decrease in unnecessary care.

Furthermore, insufficient communication between patients and physicians might underpin aggressive care. Douglas et al. studied the concordance of patient and oncologist-reported goals of care in a group of 206 patients and their 11 clinicians.[333] They were monitored every three months until their death. The researchers found that less than a quarter of dyads had strong goals of care agreement. The majority of patient-oncologist dyads (77%) lacked agreement. This misalignment makes it difficult to offer care that aligns with patient goals and to prevent aggressive treatments.[333] Overtreatment, therefore, seems to stem, at least partly, from mismatched expectations, inadequate communication, and imbalanced clinician-patient relationships. Engaging patients actively in their treatment strategies through shared decision-making can be instrumental in addressing potential overtreatment.

6.4.2 Atypical remedy

There is growing evidence suggesting that healthcare professionals should consider deprescribing — the act of reducing the dose or withdrawing drug treatments — to enhance the quality of life for patients.[334, 335] In our **Study IV**, we advocate for deprescribing NSAIDs in older people who use antidementia drugs, specifically ChEIs. The substantial increased risk of peptic ulcer during concomitant use of NSAIDs and ChEIs serves as a compelling case for when deprescribing interventions are needed. We recommend deprescribing NSAIDs over ChEIs because the evidence is more in favour of discontinuing NSAIDs. NSAIDs are often deemed potentially inappropriate for older individuals,[307, 336] and there are alternative treatment options available.[337] Previous studies

also indicate that deprescribing NSAIDs does not cause harm,[338, 339] and is a cost-effective intervention.[340]

The evidence-base concerning the deprescribing of ChEIs is less definitive. Morin et al., based on consensus criteria, classified antidementia drugs as often inadequate to continue and initiate for patients with an estimated life expectancy of three months or less.[205] However, patients with uncertain prognosis might face acceleration of disease progression upon discontinuation of treatment.[341] Even when treatment benefits aren't evident, stopping the treatment could lead to a marked increase in the risk of nursing home admission.[342] The 5th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia established a committee that provided evidence-based recommendations on deprescribing ChEIs. However, their guidelines are not as unequivocal as those for deprescribing NSAIDs.[343]

Deprescribing towards the end of life is also a valuable intervention for drugs that have a longer time-to-benefit than the patient's remaining life expectancy. In **Study III**, we identified a scenario where deprescribing could be beneficial. In our study, over a third of patients continued taking endocrine treatments up until the very end of life (last three months), which could be seen as a questionable clinical practice.[205] While these drugs are usually taken over extended periods, their tangible benefits at the end of life, aside from offering hope,[344, 345] remain unverified. Additionally, five per cent of our study population initiated endocrine treatment in the last three months of their lives. This clinical practice is debetable,[205] because the benefit of starting treatment is usually evaluated after three consecutive therapies.[346] While the benefits remain unclear, patients are certainly exposed to potential adverse effects that could deteriorate their quality of life as they near death.

It is important to recognise that deprescribing is not about withholding beneficial treatments from older adults. Instead, the focus is on optimising treatments to prevent potential adverse effects, enabling patients to attain the highest quality of life by minimising the impact of drug treatments. Deprescribing in a geriatric population can reduce potential overtreatment via cutting back unnecessary drug use and polypharmacy, while also improving patient outcomes.[334, 347-350] This is becoming increasingly relevant from a public health perspective, as excessive polypharmacy (i.e., the concomitant use of ten or more drugs) is on the rise in Sweden.[351]

Several trials have investigated the outcomes of deprescribing interventions. Relevant to end-of-life care, a 2021 randomised controlled trial found that supplementing vitamin D does not affect fatigue and opioid usage in palliative care patients with a survival expectancy of less than three months.[352, 353] This supports the idea of deprescribing vitamin D in patients with limited life expectancy due to a lack of notable health benefits. Evidence from other randomised controlled trials suggest that deprescribing of

antihypertensives and lipid-lowering drugs can be safely executed but have failed to demonstrate regular improvements in quality of life, fewer adverse events or extended survival.[354] Additionally, a 2021 randomised controlled trial found that STOPP/START criteria effectively decreased polypharmacy in a multimorbid population of older adults but did not reduce the likelihood of drug-related hospitalisation.[355] However, the landmark trial by Kutner et al.,[356] which assessed the safety of statin deprescribing in palliative care, observed an improved quality of life and patient satisfaction in the group that discontinued statins without any increased risk of death or cardiovascular incidents. Whether these findings can be generalised to other drugs requires further research.[357] In summary, a review by Scott et al. in 2022, concluded that while deprescribing is safe, it does not consistently reduce adverse effects or bring about improvements in outcomes significant to patients.[358] Scott and colleagues argue that the lack of effect observed was due to trial designs (e.g., focus on drugs that that rarely cause harms, small reductions in medications and low intervention intensity). Nonetheless, deprescribing can be an option to reduce inappropriate polypharmacy and thus potential overtreatment for older adults at the end of life.

6.4.3 Not only a bed-side affair

Over the past few decades, the epidemiology of end-of-life care has changed.[70] The main causes of death have diversified, there is a rising number of patients with multiple concurrent health conditions, and the complexity of illnesses near death has increased. These developments led to a more intensive care and an increased frequency of care transitions towards the end of life.[70] Current population-based efforts are moving away from the single disease perspective due to the multifaceted profile of end-of-life patients, often characterised by multimorbidity and frailty. Casarett and Teno posit that palliative care should adopt prevention strategies from population health, implementing interventions early in the disease course.[359] In other words, this is a population health-based approach to palliative care aiming to enhance patients' lives through system-wide interventions.[359]

Population health-based palliative care merges the principles of population health and palliative care.[359] It is best defined as the "*integration of palliative care principles into the fabric of health systems and care delivery*."[360] According to Casarett and Teno, this approach encompasses specialised palliative care services across various settings (outpatient, inpatient, hospice and palliative home care). It emphasises primary palliative care and supports palliative care in diverse communities and populations, aligning with the palliative care delivery models for patients with cancer as outlined by Hui and Bruera.[102]

Advance care planning, designed to determine future interventions based on individuals' wishes and preferences,[361, 362] may help reduce potential overtreatment, particularly hospitalisations.[95, 362-364] In **Study II**, we observed increasing rates of unplanned hospitalisation in the final three months, which substantially diverged between people living with different illness trajectories. Identifying these different trajectories can help tailor anticipatory care and enable earlier holistic assessment of patients' needs and concerns.[363, 364] However, proactive identification of the various care needs through advance care planning and anticipatory care requires suitable population health-based systems for logistical and financial (e.g., reimbursement) support.

For population health-based palliative care to be transformative, there needs to be a shift in our cultural perception of serious illness and end-of-life care. This shift should emphasise shared decision-making, effective symptom management and a high communication standard. Casarett and Teno argue that the population health approach should encompass various settings and interaction types. Ideally, it will shape cultural views about overtreatment to the same level as smoking is today.[359]

To be a successful approach, population-based palliative care requires reliable data to depict the population nearing death. This means to look beyond the healthcare utilisation measures and incorporate elements offering a holistic view of patients' end-of-life experiences. In fact, many overtreatment indicators from **Study I**, which were comprehensive and patient-centred, were excluded as they could not be measured using Swedish administrative and healthcare data. Ideally, we should seek alternative data sources to provide a comprehensive nationwide picture of end-of-life care. Integrating patient perspectives remains an important challenge for population-based palliative care.

Several studies have begun to explore population-based approaches to palliative care.[360] For example, Ngo et al. described a system-wide implementation of advance care planning in California.[365] This involved staff training, documenting advance directives, and treatment preferences, all integrated into electronic health records, fostering inter-professional collaboration in care organisiation.[365] Since its 2017 implementation, around 6000 healthcare professionals have been trained, achieving high (89%) goal-concordant care and completion (84%) of advance directives by 2023. Other examples include Colburn and colleagues' exploration of the challenges of implementing advance care planning across 55 primary care centres.[366] Their intervention involved preparing patients and families for advance care planning, agenda-setting to align perspectives on the role of family, access to trained facilitator for discussions, and education resources. However, the intervention's effect on patient outcomes and potential overtreatment is yet to be reported. Sudore et al. summarised the steps and lessons learned from implementing advance care planning in a multi-site, health system, ran as a pragmatic trial.[367] Of note, they implemented automated cohort identification via electronic health record-based algorithms and intervention delivery. They highlighted three primary requisites for a

successful implementation: engagement of multidisciplinary key opinion leaders, standardisation, and monitoring. Another example of population-based palliative care intervention is the Improving Goal Concordant Care Initiative.[368] This intervention, which included communication training, structured electronic health record registration accessible to all physicians, and a measurement framework, is currently being implementation in ten US-based academic cancer care hospitals. They plan to assess the impact of the intervention using claim-based metrics (i.e., quality indicators) near the end of life. Casarett and colleagues also designed interventions tailored to physicians' needs, enabling them to start conversations of care goals.[369] This intervention saw an increase in the documentation of care goals from 3% in 2020 to 61% in 2022 within the Duke Health system's electronic health records. All these population-based palliative care interventions are forms of quaternary prevention, namely the "*action taken to protect individuals (persons/patients) from medical interventions that are likely to cause more harm than good*".[370, 371] Integrating this population-based approach to palliative care has the potential to redesign data collection, yielding in actionable data that results in quality improvement across domains that is important for patients. However, how the population-based approach will transform palliative care and lead to decreased levels of potential overtreatment at the end of life is yet to be seen.

6.5 All that glitters is not gold

The Nordic administrative and healthcare registers are often described as a goldmine for research.[372-375] The registers have been a catalyst for (pharmaco)epidemiologic research in the Nordic countries since their inception. However, from an end-of-life research perspective, there are some limitations that warrant in-depth discussion. The most important limitation is the lack of information on patients' preferences and regarding the intentions of care. The absence of these prevented us from assessing the appropriateness of care measured by quality indicators in **Study I**, from determining whether the unplanned hospitalisations were justifiable in **Study II,** and from establishing if the drug treatments aligned with patients' wishes in in **Study III** and **Study IV**. The lack of data on patients' preferences is not unique to our studies but is common to most large-scale register-based studies. The data are primarily collected for administrative purposes, not for research. Patient preferences, ideally form the foundation for determining whether the provided care might be considered overtreatment.[245] To be transparent about this limitation, we use the term *potential overtreatment* when describing and discussing our study results. Our findings, when interpreted in light of the studies that reported on end-of-life patient preferences,[154, 155] suggests that there may be a mismatch between patient preferences and the actual treatments they receive. The discrepancy between actual and preferred end-of-life care was highlighted in 2002 by Teno and colleagues, who found that one in three patients had goal-discordant care. Since then, several other studies published similar findings.[213, 376, 377]

A further limitation of the Swedish registers is their lack of specific information on drugs dispensed in hospitals. This deficiency might lead to artificial gaps when identifying drug exposure windows, particularly troublesome nearing death when patients tend to be frequently hospitalised.[3-7] In **Studies I & III**, we used the procedure codes (commonly known in Swedish as KVÅ) from the National Patient Register to identify in-hospital chemotherapy use. Unfortunately, the procedure codes do not provide information about the type and dosage of chemotherapy. Additionally, the KVÅ codes might have validity issues according to the register holder the Swedish National Board of Health and Welfare. This could explain why we found a low rate of end-of-life chemotherapy use in **Study I**, compared to international data.

The registers also lack information on disease severity or functional status, both of which are crucial factors for predicting life expectancy and mortality. Such data would allow end-of-life care researchers to more accurately determine if the provided care had the potential to benefit patients. Detailed clinical data usually records these characteristics and other patient-reported outcomes. However, clinical studies often involve selected populations with specific diseases and tend to have small sample sizes, limiting generalisability and our understanding of nationwide overtreatment prevalence. Despite their limitations, national healthcare and administrative registers enable large-scale studies, particularly regarding drug use and hospitalisation patterns near death, complementing clinical research.[378]

6.6 Methodological considerations

6.6.1 Data

The use of nationwide national administrative and healthcare registers in Sweden is one of the main strengths of the present thesis, yielding nationally representative studies of the older population, including hard-to-reach individuals. This register data enabled us to study the population of decedents as a whole (**Study II**) and identify select disease groups with minimal selection bias (**Studies I & III)**. Furthermore, the vast amount of data collected over a decade allowed us to identify rare adverse events in **Study IV,** while still maintaining a large enough sample size to draw conclusions.

The two main data sources for this thesis were the National Prescribed Drug Register and the National Patient Register, each with its specific limitations. The National Prescribed Drug Register's foremost limitation is that it only contains data about prescribed drug dispensation. Information on adherence (i.e., whether the individual consumed the drug) is not included. This might have led to misclassification of end-of-life treatment patterns in **Study III**. Additionally, the register records only prescribed drugs dispensed in pharmacies and machine-dispensed drugs packed in disposable bags ('apodos'). Over-the-counter drugs (9% of total drug expenditures in Sweden)[114] or pharmaceuticals administered in the hospital setting (20% of total drug expenditures in Sweden),[114] are not included. The lack of data on over-the-counter medications might have induced an underestimation of NSAIDs use in **Study IV.** However, many older adults have these drugs prescribed as part of their high-cost reimbursement scheme rather than purchasing them over the counter. The absence of data on medications administered in hospitals prompted us to measure hospital drug usage in the National Patient Register using procedure codes, potentially leading to underestimation of chemotherapy use in **Studies I & III**, as discussed in detail in section 6.5 of the thesis. A further limitation of the National Patient Register is the lack of data on primary care, which would have been valuable for insights on advance care planning, care continuity and treatments administered near death.

Another potential limitation regarding our nationwide data is that we did not include the Swedish Cancer Register. Established in 1958, this nationwide register records primary tumours. Using this register would have been of interest to us since it collects information on staging, particularly relevant for **Studies I & III**. However, there are validity concerns with the register due to potential underreporting that varies by diagnosis and age.[379] For instance, Nilsson et al. found that 13% of patients with cancer in palliative care were not listed in the Swedish Cancer Register.[380] While this register is undoubtedly useful for prospective cohort studies where patient follow-up begins at the diagnosis date, our thesis did not incorporate such studies.

It is also worth noting that we did not utilise the Swedish Palliative Care Register as it is not a nationwide healthcare register but rather a so-called quality register.[381] Nonetheless, this register contains some data that would have been relevant to our research. For example, the register records whether death was expected or if end-of-life discussions took place. This information would have enabled us to ensure that we included only patients in **Studies I–III** whose deaths were anticipated. A major limitation of this quality register is however that it covers merely 66% of all deaths in Sweden.[261] Additionally, it mainly encompasses palliative care provision during the last week of life, and some of its data are reported by staff post the patient's death.[382]

6.6.2 Study designs

The present thesis predominantly utilised the **retrospective design**, known as mortality follow-back studies. This has been, and remains, one of the most dominant and employed designs in end-of-life care research. Three of four studies (**Studies I–III**) in this thesis adhered to the principles of the retrospective cohort study design. In this approach, patients are identified at the time of death and followed back over a specific period to gather information about the care they received before death. Consequently, they are also called studies of decedents. In the early 2000s, when this study design gained popularity due to efforts to improve the quality of end-of-life care, Bach et al. voiced criticism.[256] In their article, they argued that the underlying assumption that the care received by decedents is equivalent to the care received by those who are dying (typical studied by traditional prospective cohort designs) is flawed. This is because these two types of patients differ in characteristics and the period they are observed.

Firstly, Bach et al. illustrated that patients who die in a given year are not necessarily similar to patients who are expected to die. This challenges the underlying assumption that care received by those who died corresponds to the care received by those dying. This discrepancy, due to differences in patient characteristics (e.g., stage of disease), might introduce selection effects, leading to incorrect inferences about the aggressiveness of treatment provided to patients at the end of life. Additionally, they argue that the study design underestimates the difficulties of prognostication that healthcare professionals face near death. Some patients who are expected to die survive longer, while highly functional patients might die suddenly. We made deliberate efforts to mitigate this selection bias by introducing careful measures. In **Study I**, we selected a homogenous group of patients who died from solid cancer, intentionally excluding patients with haematological cancers given their unpredictable survival rates. Moreover, we conducted extensive sensitivity analyses to ensure that the care provider perceived the patients as dying (e.g., required cancer diagnosis in the National Patient Register, or excluded those whose first cancer was recorded within three months of death). In **Study II**, we categorised patients according to illness trajectory and grouped patients who died

of a sudden cause of death. In **Study III**, we excluded decedents who died of a potentially acute and unpredictable fatal event, like suicide or falls.

Secondly, Bach et al. questioned whether the time period under evaluation in retrospective studies, which usually considers a fixed period (e.g., last months of life, last year of life), is similar to cohort studies where patients are followed up after they are considered to be dying. A mismatch might arise, as retrospective studies could, in theory, include time at risk when the patients are not yet diagnosed. This can result in immortal-time bias, which is a misclassification of the time at risk. Immortal-time bias in the case of accumulated outcome measures might particularly be a problem, leading to distorted results. In **Study II**, the outcome measure of unplanned hospitalisation was an accumulated measure. Thus, we might have misclassified exposure time for those with no condition in a portion of the last year of life. By way of example, patients diagnosed with cancer five months before death still contributed time at risk to cancer trajectory during twelve to six months before death when they were not yet diagnosed.

In response to Bach et al.'s critique, Teno and Mor defended the retrospective study design as pivotal for studying the complex nature of dying.[383] They justified its usage because it maximises the number of cases and follow-up time, compared to cohort studies. Similarly, Bernato also defended this design and its look-back period, reasoning that chronic diseases with substantial survival are so widespread that even a one-year follow-back would not introduce meaningful prediagnosis bias.[384]

Study IV employed a **self-controlled case series** study design, which has its own strengths and limitations. This method is particularly advantageous for controlling for time-invariant confounders (e.g., genetic factors), which are usually unavailable in administrative databases. However, noteworthy limitations of the study design need consideration. First, the measured effect may not encapsulate the total effect as the study design yields relative incidence estimates, corresponding to within-person variation in exposures. Second, absolute event rate estimation is impossible with this method, because only those who experienced both the outcome and exposure of interest are included. Third, as we used nationwide administrative and healthcare data, the study was limited by the available information in the data. For instance, essential data on over-the-counter medications were missing. We justified using the self-controlled case series design because the identification of a comparison group when studying adverse drug effects was deemed unfeasible.[385]

6.6.3 Precision

The use of administrative and healthcare data in our studies may have introduced some random measurement error. Inaccuracy, imprecision, coding errors, opportunistic coding, regional variations, and variations of coding practices over time in the national registries might have contributed to these errors.[386] However, the effect of such random error is

difficult to anticipate.[387] Random measurement errors in the registers is particularly important for **Study I**, as our measurements of quality indicators are only as precise as the underlying data. Any quality issues and biases in the data are carried over to the results. On one hand, random errors are expected to become more prevalent in epidemiology because of the increasing use of administrative data.[388] On the other hand, the availability of nationwide data minimises random sample error, as these nationwide studies typically include *all* individuals.

6.6.4 Internal validity

Internal validity assesses whether the observed differences are attributable to the exposure without the influence of confounding factors or systematic errors (i.e., biases).[389]

6.6.4.1 Measurement bias

Measurement or information bias is a systematic error that often arises from misclassification. There are two types of misclassification: nondifferential and differential. Nondifferential misclassification occurs when the misclassification is evenly distributed between the groups, which tends to dilute the effect estimates. In contrast, differential misclassification arises when the misclassification is unequally distributed in the groups, potentially biasing the results.

Many of the variables in our studies are susceptible to misclassification. However, we took precautionary steps to minimise such measurement bias. For example, we incorporated extensive look-back periods when categorising chronic multimorbidity and frailty. Additionally, we refrained from creating certain variables (e.g., living arrangement) from the Social Services Register in **Studies I, II & IV** due to known data limitations.[277]

6.6.4.2 Confounding

Confounding refers to the problem when the association between two variables is partially or totally influenced by a third related variable. In other words, the third variable, universally referred to as the confounder or covariate, is a common cause of the exposure and outcome but is not on their causal pathway. Unlike randomised controlled trials, where the intervention (i.e., exposure) is assigned to participants by chance through randomisation, observational research is prone to confounding. In non-experimental design, the exposures are not allocated through a randomisation procedure but via other mechanisms, which often relate to the outcome. Many potential confounders can be operationalised in administrative and healthcare datasets and accounted for during the analysis. For example, age, sex and multimorbidity, although sometimes with varying validity. When confounders are unaccounted for in the analysis, the problem of unmeasured confounding arises. Unmeasured confounding prohibits estimating causal associations because the unaccounted confounders may distort the association by over or underestimating the true effect. Simply put, in the presence of an unmeasured

confounder, the relationship between the exposure and outcome cannot be understood as strictly causal.[390]

In **Studies I–III,** we did not attempt to establish causal effects but rather to explore factors related to the outcomes. In **Study I**, we stratified the overall prevalence of potential overtreatment by sex and age groups but confounding due to disease severity remained a problem. In **Study II**, we stratified the results by age groups and controlled for potential confounding in the analysis (e.g., education, comorbidities, frailty), but we could not measure nursing home residence, which might have influenced our estimates. In **Study III,** we aimed to discover independent determinants of end-of-life drug utilisation patterns and included many factors in the analysis. The covariates included in the analysis or stratification were carefully selected a priori based on subject-matter knowledge while also considering the limitations of the available information in the registers. Yet, disease stage and adherence were unmeasured confounders. In **Study IV**, we did aim to establish causal effects with using a self-controlled case series study design. This design is exceptional in controlling for time-invariant confounding that is usually unmeasured in administrative and healthcare data. We also controlled for time-varying age and drugs potentially influencing the exposure and outcome. However, there could exists potential unmeasured time-varying factors that we failed or could not account for due to the complexity of drug prescribing in older adults. According to the paragraph above, we did not draw causal conclusions as it would require complete certainty of no unmeasured confounding. However, the calculated E-value suggested that the association could only be "explained away" by unmeasured confounding (i.e., beyond the measured confounding) if the unmeasured confounder was associated with the exposure and outcome by a risk ratio of 17.5.[296, 297]

6.6.5 External validity

External validity includes generalisability and transportability.[391] Generalisability refers to drawing conclusions for the target population based on a potentially biased sample from the same target population. Transportability, on the other hand, concerns making inferences for a target population when the sample population is partly or entirely non-overlapping.

All included studies are based on national administrative and healthcare data that includes the entire population of Sweden. The National Patient Register, the National Causes of Death Register, the National Prescribed Drug Register and the Total Population Register have nearly 100% coverage. Thus, the selection bias (also known as sampling bias), which often pertains to surveys, was not a significant threat to the external validity of our studies. However, some people were excluded during the process of assembling the final population in each study. For example, **in Study II**, we excluded people with missing exact date of death or individuals whose unique personal identifier had been

reassigned to someone else. In theory, it could be that these individuals were different in some characteristics than the target population, thereby slightly distorting our estimates. Although, the impact is likely minimal given the small number of these individuals relative to the overall study population.

Our studies are potentially transportable to other populations that do not overlap with our study populations. If our studies were replicated in other countries with similar healthcare systems, population composition and cultural values, we would expect them to find similar results. However, the findings may be limited in transportability to other countries distinct from Sweden. Therefore, our results should be used with caution when extrapolating them to settings vastly different from ours.

7 Conclusions

We evaluated the quality of end-of-life care in older adults, with a specific focus on potential overtreatment. Our findings suggest that overtreatment warrants attention in healthcare, as the patients are potentially exposed to unnecessary treatments, unplanned transitions late in the disease trajectory, and systemic disease-modifying and preventive drug therapies during the end of their life course when care should prioritise comfort and quality. Central methodological contributions of this thesis include leveraging nationwide administrative and healthcare data to quantify the extent of potential overtreatment with quality indicators, describing unplanned hospitalisation patterns across different illness trajectories, and identifying increased risks of an adverse event from a drug-drug interaction using state-of-the-art pharmacoepidemiologic methods.

We measured potential overtreatment indicators in a nationwide cohort of patients with solid cancer. Many decedents, previously diagnosed with solid cancer, were exposed to potential overtreatment during the last month of life. This might be an underestimation because nearly half of the indicators were not measurable due to missing outcomes in administrative and healthcare registers. We also reported divergent unplanned hospitalisation patterns for patients with different illness trajectories during the last year of life. Hospital transitions were especially frequent in the last three months of life, where patients with cancer and organ failure were affected the most.

We also investigated a subset of patients with metastatic breast cancer. Their end-of-life treatment patterns suggested that they continue, and some even initiate endocrine treatment, potentially past the point of benefit. Our analysis revealed differences across age, education, drug-dispensing scheme and among those with intensive treatments. Lastly, we discovered a synergistic drug-drug interaction of NSAIDs and ChEIs that augmented the risks of peptic ulcer over and beyond the risks seen with NSAIDs alone. This underscores the need to consider deprescribing NSAIDs for seriously ill older adults with cognitive impairment, in alignment with medication guidelines, to prevent unnecessary adverse events.

To summarise, our findings indicate that older adults and seriously ill individuals are potentially exposed to various types of overtreatment near the end of life. Such overly intensive care close to death is generally against their wishes and puts patients at risk of adverse events. In this thesis, we argued against potential overtreatment neither to limit healthcare nor from fiscal reasons, but rather to enable individuals to reach their highest attainable quality of life without unnecessary and avoidable risks and spend their final months according to their wishes.

8 Points of perspective

The present thesis contributed to evaluating the quality of end-of-life care in Sweden by focusing on potential overtreatment. We found evidence that overtreatment is possibly present in various forms close to the death of older individuals. However, the thesis should not be viewed in isolation. Instead, it should be interpreted and considered within the context of existing literature, clinical practice, and healthcare systems. In this section, we reflect on three main points of perspective.

From a **research perspective**, several findings need replication in different settings and among various disease populations. For example, our tentative prevalence of overall potential overtreatment measured among patients with solid cancer necessitates further validation and extrapolation. Firstly, the quality indicators should be validated with other data sources. Secondly, the validated quality indicators could be used to compare the rate of overtreatment across different settings and regions. Finally, the overtreatment quality indicators can be extended to other disease groups (e.g., dementia or other chronic diseases). Another example is our analysis of unplanned hospitalisation patterns, which should be researched from the patient's perspective, considering whether such admissions were in line with their preferences (i.e., patients might have preferred to be admitted to emergency department due to sudden exacerbation of pain or other symptoms). Moreover, our incidence rate ratio estimates of concomitant ChEIs and NSAIDs use on peptic ulcer risk should be replicated in other populations to affirm our findings and possibly achieve more precise estimates.

Furthermore, future research efforts in complementary areas are required to keep and continue growing the momentum of overtreatment research. In our opinion, research should primarily focus on establishing the harmful effects of potential overtreatment (e.g., drug-drug interactions, hospitalisations, potentially inappropriate medications) on health in older adults at the end of life. If overtreatment is not only futile, but also leads to negative outcomes, the inclination to intervene will be strengthened within different parts of the healthcare system. We believe that using advanced (pharmaco)epidemiologic design and methods play an important role, as these can provide more robust evidence where causality sometimes can be inferred, in the absence of clinical trials. Such innovative, advanced methods include, for instance, case-crossover, case-time control and case-case-time control design besides the self-controlled case-series study design utilised in **Study IV.**[392] These methods reduce constant within-person confounding by using the individuals' own time as a reference, which makes them similar to crossover clinical trials and enable them estimating counterfactuals, given no time-dependent confounding. They are particularly relevant at the end-of-life research, where it is difficult to establish comparator groups. Using these types of novel, yet easily comprehendible designs to study adverse outcomes of potential overtreatment would be a helpful piece

in the puzzle of raising awareness of the problem among clinicians and policymakers. However, the lack of patient-centred outcomes (e.g., quality of life) in administrative databases is a limitation in the field. Enriching routinely collected data with patient-centred and patient-reported outcomes is an important task for future research.

At the time of this thesis, ten years has passed since Wettermark et al.[276] published their predictions about the future of pharmacoepidemiology. Many of those predictions (e.g., post-launch monitoring of drugs, health economic evaluations of premium-priced products and the increased presence of pharmacoepidemiology in the regulatory spaces) are on their way to becoming reality. However, Wettermark also called for pharmacoepidemiologic studies of hospital-based medicines, an area that has not developed in the last ten years as expected. The pharmacoepidemiologic studies incorporating hospital drugs were scarce,[393] possibly due to the lack of reliable and easily accessible data sources. At the same time, hospital-based drugs are becoming increasingly important (e.g., immune checkpoint inhibitors)[394] for patients with cancer. Thus, a decade later, we reiterate Wettermark's call for more pharmacoepidemiologic research on hospital drugs.

Additionally, research on the effectiveness of interventions to reduce potential overtreatment is warranted. Currently, the most researched interventions to combat overtreatment are advance care planning, advance directives, and early palliative care. However, there is a need to follow these interventions in system-wide settings. The use of registry randomised controlled trials is promising for future studies.[395] Such trials are randomised, either at the individual or group level (e.g., hospital or department), but the data collection is embedded in the nationwide administrative and healthcare registries.[396] This enables a large amount of data collection, with smaller budgets on real-world populations. Although randomised registry trials are seen as the "*next disruptive technology*" they come with their own challenges (e.g., data quality or lack of relevant follow-up variables).[397]

In **clinical practice** decisions are made prospectively with limited and often uncertain information, in contrast to the studies presented in this thesis. We hope that our retrospective analyses can inform clinicians in identifying important prognostic factors and patterns of healthcare use. This could be useful for prognostic tools, with a specific focus on end-of-life patients, that supports automated patient identification and reliable life expectancy predications. Additionally, clinicians' decision-making processes at the end of life should be supported by research designed with their point of view, that is in a prospective manner. Prospective cohort studies collecting data on clinical care processes and patient-reported outcomes would be ideally suited for this purpose.

From a **healthcare policy perspective**, potential overtreatment at the end of life represents low quality of care and unnecessary costs. Although many interventions aimed

at reducing overtreatment have been implemented on a small scale, by integrating healthcare policy insights with routinely collected data, we might pave the way for system-wide implementation measures. Reducing overtreatment is in the best interest of all actors, healthcare systems and patients alike. Hence, efforts to understand the factors that generate overtreatment, such as lack of coordination and communication, are important for future research. In the realm of healthcare policy, there should be a clear emphasis on creating incentives, whether economic or regulatory, to curtail overtreatment.

Given the ageing population, future healthcare policy efforts should prioritise care continuity at the end of life as a means to mitigate overtreatment. Addressing challenges in care coordination, especially when multiple care providers and physicians see the same patients, could yield substantial benefits.[398] Policies focusing on care continuity frequently results in higher quality of care, lower costs and decreased hospital admissions and rehospitalisation.[399, 400] Care continuity can enhance trust and enable patients and physicians engaging in sensitive end-of-life discussions and soliciting treatment preferences.[401]

Death, an inevitable part of life, is an experience everyone will face. Thus, improving end-of-life care is of paramount importance for public health. At its core, policy should guarantee that all individuals receive equally compassionate and dignified care that meets their medical, physical, emotional, and spiritual needs. The ultimate objective is to minimise unnecessary suffering and promote a healthcare system that aids individuals in transitioning to death with comfort and grace.

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