Health economics of end-of-life care

The particular case of COPD and Alzheimer's disease

Kristof Faes

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'Cure sometimes, treat often, comfort always'

(Hippocrates, 460-377 BC)

DANKWOORD

DANK!

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ABBREVIATIONS

AD	Alzheimer's disease
ATCcode	Anatomic Therapeutic Classification code
BCR	Belgian Cancer Registry
CAT	COPD Assessment Test
CBSS	Crossroads Bank for Social Security
CCQ	COPD Control Questionnaire
CDR	Clinical Dementia Rating
CHF	Chronic Heart Failure
CI	Confidence limit
COPD	Chronic Obstructive Pulmonary Disease
CPR	Cardiopulmonary Resuscitation
CRF	Chronic Renal Failure
CT	Computed Tomography
CVD	Cardio-Vascular Disease
DNH	Do Not Hospitalize
DNR	Do Not Reanimate
EEG	Electroencephalography
EOLCC	End of life Care Cost
ER	Emergency Room
FAST	Functional Assessment Staging Test
FEV1	Forced Expiratory Volume in one second
GDP	Gross Domestic Product
GDS	Global DeterioratioS scale
GOLD	Global initiative for chronic Obstructive Lung Disease
GP	General Practitioner
ICU	Intensive Care Unit
IMA	Intermutualistic Agency
IQR	Inter Quartile Range
LC	Lung Cancer
MDPHCT	Multidisciplinary Palliative Homecare Team
MMRC	Modified British Medical Research Council questionnaire
NIHDI	National Institute for Health and Disability Insurance
NMR	Nuclear Magnetic Resonance

ODC	One-day Care
OOPC	Out-Of-Pocket Cost
OR	Odds Ratio
PET	Positron Emission Tomography
PIM	Prescribed Inappropriate Medication
PREM	Patient Reported Experience Measurement
PROM	Patient Reported Outcome Measurement
QALY	Quality Adjusted Life Year
RCT	Randomised Control Trial
RR	Relative Risk
SES	Socio-Economic Status
TNM	Tumor Node Metastasis
TTP	Trusted Third Parties
VPN	Virtual Private Network

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PART I

GENERAL INTRODUCTION

CHAPTER 1: GENERAL INTRODUCTION

INTRODUCTION

At the end of life, people are confronted with specific and complex healthcare challenges. Some suffer from a prolonged and painful death receiving invasive, unwanted and expensive care; others die peacefully and received the care they hoped for. Regardless of how a person dies, it is important to gain a clear insight into the final phase of life of the dying population in order to be able to optimize them, both from an individual and a societal perspective

Yet, to date evidence on costs and resource use of terminally ill patients available to inform policy makers is scarce. Limited research available to Belgian policy makers and health care payers only focuses on specific care settings or disease groups, but does not provide an overview of the current use of resources and costs of end-of-life care within the Belgian population. However, regardless of the Belgian situation, previous research in an American setting showed that approximately 10 to 25% of all healthcare expenditures can be related to the last year of life [1, 2]. Main identified factors that cause these high costs are hospitalization, the use of skilled nursing facilities and the uptake of a number of inpatient procedures. These findings, with regard to end-of-life resource use and its related costs, however, are mainly directed by evidence on those who suffer and die from cancer or are based upon small samples of cancer and non-cancer patients. Even though the severity of cancer as a disease cannot be underestimated, in the context of the development of a population wide policy, this basis is too narrow. These identified shortcomings are also the starting point for the main aims of this dissertation on the resource use and costs of the Belgian dying population:

1. Evaluation and description of the existing evidence on end-of-life care for those who suffer from COPD.

2. Describing end-of-life resource use for the full population of those who died of COPD or Alzheimer's disease.

3. Analyzing end-of-life care costs for the full population of those who died of COPD or Alzheimer's disease.

Before addressing these specific shortcomings, and in order to elucidate the relevance of these aims within the current knowledge, we will briefly describe a state of the art concerning the resources and costs used at life's end and how the uptake of specific end of life resources and costs are influenced by specific diseases.

1. ECONOMICS OF END OF LIFE CARE: A STATE OF THE ART

1.1. End-of-life care: A lack of standardization

Good quality end-of-life care is recognized as an essential component of modern health care services. In recent years a number of initiatives have been put in place to look at how we might improve the care provided at the end of life, and national indicators have been developed with the aim of helping us understand current care and supporting people's choices about where and how to die [3-5]. However, given the finite resources available for health care, it is important that there is some understanding of the costs of end-of-life care as one component of the wider picture of providing good-quality end-of-life care. Yet, as was noted by Hughes-Hallet and colleagues in a 2011 review of palliative care funding for the Department of Health (UK) "there is a lack of good data concerning costs of palliative care" [6]. However, acquiring information on the costs of end-of-life care poses significant challenges, especially given that end of life care is complex and is fragmented across many different services and providers of care. As a result of its fragmented nature, additional challenges arise concerning the concept and definition of end-of-life care. Defining the end phase of life can be ambiguous and terms are often used differently between clinical settings, healthcare professionals and researchers. There are, in addition, many different illness trajectories for dying people, and there is no accurate clinical indicator to predict time of death. As a result the concept and definitions for the end of life phase vary considerably.

Defining end-of-life care

Definitions for end-of-life care have broadened considerably over time, both in regard to the point in the illness trajectory when end-of-life care should be introduced, as well as in terms of the clinical condition on which it focuses. Terms used to describe '*care for those with a progressive life-limiting disease*' evolved over time from care of the dying to terminal care, hospice care, palliative care, and in some contexts to supportive care [7]. Moreover, terms used to describe the concept '*end of life*' are also discussed in previous literature. Terms such as end of life, terminally ill and end-stage often relate to a progressive life-limiting disease with a specific prognosis of months, weeks or days left to live. The challenge with these 'prognostic' descriptions is that prognostication is often uncertain or imprecise. Since death is often mediated by catastrophic events such as myocardial infarction and pneumonia, it is difficult to estimate exactly how long a person is going to live.

A definition of palliative care is often used to define end-of-life care. According to the World health Organization, palliative care is '*an approach that improves the quality of life of patients and their families facing the problem 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' [9]. However, palliative care and end-of-life care do not entirely coincide: palliative care is not just provided at the end of life but is '*applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications*'. And not every person with a progressive life-limiting disease who receives end-of-life care receives care that can be classified as palliative in accordance with the WHO definition. Some, often due to prognostic uncertainties, receive *therapies intended to prolong life as long as possible.* In this dissertation we opt for a pragmatic definition that looks at the period prior to death, regardless of whether the care one receives is palliative in nature or life-prolonging; and regardless of whether a person with a life-threatening illness is consciously recognized as 'end of life'. By describing the end-of-life period (stage) we use often a specific moment before death e.g., one year, six months or 30 days (state).

1.2. End-of-life care in Belgium

According to national statistics, in 2016, 1% of the Belgian population died with an average age of death for men of 78.8 years and women 83.7 years. Main causes of death were ischemic heart disease, Alzheimer's disease, cerebrovascular disease, lung cancer and chronic obstructive pulmonary disease and most of these deaths happened in a secondary health care service. Despite many deaths take place at a hospital, trend analysis show a shifting from hospital deaths towards home death and death at care homes [11-14]. Based on the analysis of Belgian death certificates between 1998 and 2007, Houttekier et.al. found that hospital deaths decreased from 55.1% to 51.7% and care home deaths rose from 18.3% to 22.6%. However, their results showed that the percentage of home deaths remained stable [11]. Although these results indicate a doubling of deaths in care homes by 2040, to date a majority of people dies in a hospital setting although a majority prefers to be cared for and to die at home.

Organization of Belgian health care

The Belgian health system is primarily funded through social security contributions and taxation and is based on the principles of equal access and freedom of choice, with a Bismarckian-type of compulsory national health insurance, which covers the whole population and has a broad benefits package. Compulsory health insurance is combined with a private system of health care delivery, based on independent medical practice, free choice of service provider and predominantly fee-for-service payment. The compulsory health insurance is managed by the National Institute for Health and Disability

Insurance (NIHDI), which allocates a prospective budget to the different (private) sickness funds to finance the health care costs of their members. All individuals entitled to health insurance must join or register with a sickness fund to receive a refund.

Persons affiliated to the Belgian National Institute for Health and Disability Insurance are entitled to reimbursement of the cost of healthcare services, treatments and fees provided that the services in question meet certain requirements. However, not every healthcare profession or service is entitled to reimbursement. A list of reimbursable services or acts for each profession, the so called nomenclature assigns a specific code (nomenclature code) to each act that determines the financial cost and is used as a base for the reimbursement of healthcare costs. Nomenclature codes can be divided into acts which are assigned to ambulatory care i.e. outpatient care and institutionalized care i.e. inpatient care. Inpatient or institutionalized care refers to any medical service or act that requires an hospitalization or an act which is provided during an admission and stay into a hospital. To qualify as an inpatient, a patient must be under the care of a physician while staying overnight in the hospital. Outpatient or ambulatory care includes all acts that does not require an overnight stay in a hospital or medical facility. Outpatient care is mainly administered in a medical office, hospital, nursing home facility or at home.

In Belgium, end of life care and palliative care is provided at home, nursing homes, day centers, hospitals and palliative care units.

Inpatient end of life care

In Belgium, inpatient end of life care is provided in hospitals which offer two different types of palliative care services. First, end of life care can be provided to patients residing at a specialist palliative care unit and second to those who are staying on a non-specialized palliative care unit (i.e., general ward). The specialist palliative care unit is a specific hospital unit that delivers specialized palliative care to those who are suffering from an incurable illness and will die relatively soon. Here, patients, who can no longer stay in an acute hospital or cannot be looked after at home any more, are offered individual specialized and coordinated total end-of-life care by a multidisciplinary specialized palliative care team. For those in need of adapted end of life care and staying outside these specialized palliative care units a multidisciplinary mobile palliative care team or palliative support team is available. This inpatient mobile palliative care team does not deliver palliative care itself but advises non-specialized palliative care teams of the department the patient has been admitted to on the end of life care that needs to be provided. This mobile palliative care team is also tasked with continuous training and awareness-raising about specific end of life care amongst hospital staff.

Outpatient end of life care

Belgium has region-bound home care which is a separate secondary care service provided by a multidisciplinary palliative home care team (MDPHCT) consisting of a physician, home care nurses and psychologist. A referral to a MDPHCT is mainly requested by the patient's general practitioner (GP) depending on individual context, relatives, involved home care nurses, palliative care nurses in the hospital, or specialists. In Belgium a 'palliative status', defined by a physician is a primary eligibility criteria for receiving a reimbursement of costs related to the palliative phase.
Unlike other countries, in Belgium, there is no formal recognition of hospices within the current health services. Moreover, specialized end of life care in long-term care facilities is provided by a primary physician, supported by nurses, the facility's palliative support team and the inpatient palliative care unit of the associated hospital. As a result, the primary physician and the community based palliative care team play an important role in the provision of end of life care at home or in a nursing home [39].

1.3. End-of-life care characteristics

Despite end of life care is still characterized by a high intensity of resource use resulting in exuberant costs, the use of specialized inpatient and outpatient palliative care results in a decreased use of hospitalization, emergency department and intensive care unit admissions and lower healthcare costs at life's end. However, people at the end of life still commonly receive inappropriate invasive and life prolonging procedures or treatments. Studies examining end of life resource use indicate that patients nearing death are prone for receiving medication, mechanical ventilation, medical imaging or diagnostic interventions which are not focused on their specific end-of-life needs or are still resuscitated during their final phase of life.
For example, studies, mainly based upon those suffering from cancer, examining end of life resource use have shown that up to one third of patients nearing death received chemotherapy or mechanical ventilation during the last month of life and twelve percent was resuscitated during this period [15].
Moreover, it is generally acknowledged that medical management at the end of life should focus on optimizing quality of life and minimizing symptoms rather than on extending the duration of life. This shift from preventative and curative care to symptomatic care impacts drug use during the end-of-life period. Although a number of medications such as analgesics, anti-emetics, sedatives, anxiolytics and anticholinergics are found suitable in improving specific end of life symptoms, the number of inappropriate medications prescribed at the end of life (PIM) remains high and medical end-of-life management is characterized by polypharmacy [48-52]. More specific, the use of PIMs and

polypharmacy results in unwanted drug-drug interactions, adverse effects and increased healthcare costs [53]. However, differences in care services provided, availability of specialized palliative services in a inpatient or outpatient healthcare setting as well as the cause of death and comorbid conditions all contribute to differences in medication use during the end-of-life period [54]. Especially the provision of palliative care and use of palliative care services are associated with changes in drug utilization that are consistent with increased use of symptom-controlling medications and decreased medication expenditures [55, 56]. Moreover, proximity to death and age impact medication cost and utilization at the end-of-life in community-dwelling terminal patients [57].

Although healthcare expenditures can be reduced if diagnostic procedures are performed when a true benefit is shown, or, when end-of-life discussions are promoted, as a result of good healthcare planning, the evidence on the use of both imaging and invasive diagnostic procedures at the end of life is scarce. As diagnostic procedures have no diagnostic purpose in end-of-life patients, they can be justified only in view of the management of acute symptoms, evaluation of disease progression, and assessment of treatment effect. The use of diagnostic procedures, however, is still widespread despite the present guidelines. Results of an Italian study on the frequency and cost of diagnostic procedures in end-of-life cancer patients (2018) show that diagnostic imaging and testing increases and results in higher healthcare costs when nearing death [58].

Earlier research also pointed out that those staying in a hospital setting are characterized by a high intensity and costs of end of life care use when compared to those who are cared for at home [16-20]. However, the specific use of resources at life's end and its related costs are mainly characterized by local factors and the availability of resources on these places of care as well as by specific patients' and professionals' preferences and characteristics [21]. Notwithstanding, there are some general findings concerning end-of-life care use and healthcare costs related to hospital and home-based palliative care.

Hospital based end of life care

Since more than 50% of those suffering from a life-limiting disease die in an acute care setting, healthcare resources they use and the costs they generate are characterized by this setting.
A hospitalization of a terminally ill patient happens in many cases through an emergency service and takes mainly place during the last 6 months of life or preceded by an acute deterioration of the patient's condition [23]. In spite of the fact that the number of hospital admissions increases exponentially as the end of life approaches, the recognition of a terminal diagnosis is an important influencing parameter

[24]. The recognition of a terminal diagnosis or end-of-life phase is associated with a decreased number of admissions but is characterized by a longer length of stay [25].

Notwithstanding that the recognition of a terminal diagnosis influences hospital admission, an important part of the hospitalization cost is caused by a stay at an intensive care unit (ICU). Although ICU is an important cost driver of end-of-life care costs, it is borne by a small number of patients approaching the end of life and is strongly influenced by specific patient's and healthcare system factors. Specifically, in cancer patients, ICU use decreases with age and is more often used by male and single patients. However, its use increases with the number of comorbidities, but decreases when the primary physician is a medical oncologist [26].

Although hospitalized patients receive care adapted to their specific 'acute' healthcare needs, the care they receive when nearing death is strongly focused on preserving life or treating an acute exacerbation of their disease. As a result, a large number of hospitalized patients in need of appropriate end-of-life care are subject to intensive treatments or die at a non-palliative care unit despite the availability of palliative care units and inpatient palliative support teams available in hospitals. Moreover, evidence on the number of terminal patients receiving adapted end-of-life care on a specific ward e.g., medical or surgical ward is limited. Nevertheless, these services also offer the possibility of receiving adapted end-of-life care. Previous studies within the Belgian context suggest that the implementation of palliative care models, such as available and performed on a palliative care unit or by palliative support teams, on non-palliative units has a positive effect on end-of-life care costs [22]. Though, specific figures on the number of people using specific palliative care models on non-palliative care units remain relatively limited for the Belgian context.

Although a 2017 meta-analysis concluded that specialist palliative care interventions are associated with only a small effect on quality of life, its use results in a reduction of hospital costs, a reduced number of admissions, a shorter length of stay and a reduced use of specific hospital services [27-31]. However, a comparison of palliative care use between Belgian hospital wards indicated that, due to legal staffing levels, palliative care offered at a palliative care unit is more expensive than palliative care provided in an acute ward. Yet, terminal patients receiving palliative care in the acute ward generate lower costs as compared to terminal patients receiving usual care [22]. In addition to the use of specialized palliative care offered at a palliative care unit or a hospital unit, a hospitalized patient can use specific specialized palliative care offered by specialized palliative support teams available within the healthcare institution. Hospital-based specialist palliative care consultation teams reduce hospital costs and are found to be nine to twenty-five percent less costly than usual care [32].

Home based end of life care

Despite the fact that in many countries over 50% of terminal ill people prefer to be cared for and to die at home and despite efforts and policies to enable more to die at home, in Belgium, only a quarter of all deaths takes place at home [11]. More precisely, the desire to provide high-quality and cost-effective end-of-life care is causing healthcare systems to shift from a hospital-centric to a community-centric view that provides end of life care to patients in their homes.

Homecare at the end of life has been shown to improve patient well-being, to reduce acute care use, and to lower overall healthcare costs [33-37]. As a result, end of life homecare is an identified priority in many national end of life care policies , and is seen as a sustainable alternative to costly institutional end of life care.

Moreover, earlier research on home-based palliative care has shown that it improves patient health outcomes, increases satisfaction, leads to a higher number of hospice transitions from the home or hospital and decreases health care costs and unnecessary hospital-based spending [33, 41-44]. However, the timing of initiation of community-based palliative care might affect these outcomes. Although, initiation of community-based palliative care before the last six months of life is associated with a lower rate of unplanned hospitalizations and costs, earlier initiation shows a trend toward a longer length of stay when admitted to the hospital compared with initiation in the final month of life [45].

General practitioners play a key role in providing home-based palliative care as they are the closest to the community and easiest to access. Although there is no evidence available on the effect of a general practitioner on end of life care costs, it might be assumed that, they are in the best position to provide maximum support and care within the available resources resulting in lower end of life care costs. However, home-based palliative care can also be provided by a specialized home-based palliative care team known as a ‘multidisciplinaire begeleidings equipe’.

In-home palliative team care for individuals nearing end-of-life (at home and in long term care) reduces health care costs and improves health outcomes for patients nearing the end of life. An economic analysis and budget impact analysis for an Ontario cohort of decedents (2014) showed that the population impact of in-home palliative team care is potentially large due to a reduction of acute care utilization [46]. Particularly, the deployment of community-based specialized palliative care teams reduces acute care use such as hospitalizations and emergency admissions and reduces hospital deaths at the end of life [47].

However, most people in Belgium, when faced with the prospect of dying with an advanced illness, die in a hospital setting, though the majority of people prefers to die at home [38-40].

1.4. One size does not fit all - Different trajectories of dying

According to Statistics Belgium, during the last five years, each year over 110.000 people died in Belgium. Approximately seven percent of these were the result of sudden death e.g., accident or suicide. The remaining deaths were attributed to non-communicable diseases including heart diseases, cancer, stroke, chronic lung diseases, chronic liver disease or dementia [59]. However, due to the fact that end-of-life care, and more specific palliative care services, are primarily focused on oncological patients, inequalities of end-of-life care for equally needy non-cancer patients increase. The inequality in focus of end-of-life care between cancer and non-cancer patients is mainly caused by the fact that cancer patients are recognized by a well predicted and specific disease and end-of-life trajectory in contrast to those who suffer from other non-communicable diseases such as chronic obstructive pulmonary disease or dementia.

Different trajectories for different diseases

Based on the Glaser and Strauss's 'Dying Trajectory Theory' (1968) four distinct types of death expectations can be defined. The four trajectories are (a) certain death at a known time, (b) certain death at an unknown time, (c) uncertain death but a known time when the certainty will be stablished and (d) uncertain death and an unknown time when the uncertainty will be resolved. Their trajectory theory of death suggests that a broad categorization scheme can capture the nature of clinical course before death [60]. However, in a more recent study of older Medicare descendants, Lunney, Lynn, and Hogan (2002) found four distinct trajectory groups at end-of-life (Figure 1) [61, 62].

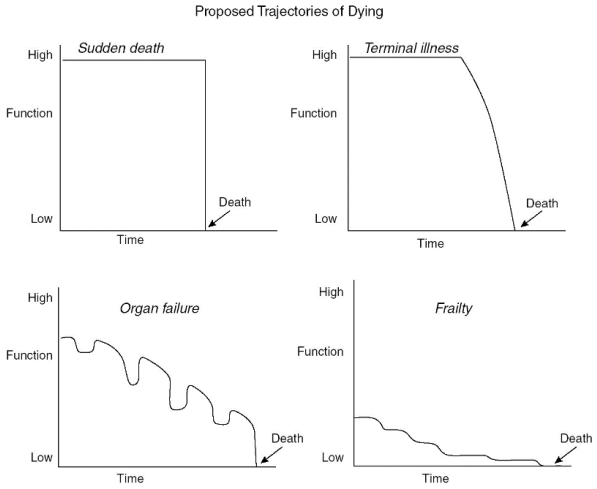


Figure 1. Proposed Trajectories of Dying (Lunney, Lynn and Hogan, 2002)

First, a scenario of terminal illness which is recognized by a long disease trajectory followed by a shorter phase of sharp decline, occurring over weeks to months. Many patients with a terminal illness will be functioning reasonably well until the final decline. The onset of their end-of-life phase is signaled by a progressive inability to function. This trajectory fits well with traditional specialist palliative care services which concentrate on providing comprehensive services in the last weeks or months of life for people with cancer. Resource constraints, however, can limit their availability and acceptability.

Second, a scenario which is recognized by long term limitations and intermittent serious episodes. This trajectory is marked by a steady decline in physical function with severe symptom crises. Each exacerbation decreases the patient's baseline function until death and deteriorations are generally associated with a hospital admission and intensive treatment. This clinically intuitive trajectory comprises conditions such as heart failure and chronic obstructive pulmonary disease. Patients are usually ill for many months or years with occasional acute, often severe, exacerbations.

A third trajectory, is recognized by a progressive disability from an already low baseline of cognitive or physical functioning and may be cut short by death after an acute event such as an infection or progression of another disease. It is usually associated with dementia or old age and frailty.

Finally, about 10-15% of all deaths follow a sudden death trajectory. In this trajectory the end-of-life phase is abrupt with no preceding decline. Examples are myocardial infarction, trauma, intracerebral or large vessel catastrophe [61, 62].

Because different dying trajectories exist, different models of end-of-life care will also be appropriate. The typical model of cancer end-of-life care might therefore not suit people who have a gradual, progressive decline with unpredictable exacerbations such as chronic obstructive pulmonary disease or those who suffer from a prolonged deterioration such as dementia. People who suffer from these non-communicable diseases e.g., COPD and dementia may have similar and more prolonged needs pressing as hard as those who suffer from cancer. However, uncertainty about the prognosis and the failure to recognize or late recognition of the terminal phase often result in a lack of timely initiation of adapted end-of-life care. As a result of a late recognition of the terminal phase or inaccurate prognosis, the care received by these patient groups is often not aimed at responding to their specific end-of-life needs and consequently results in intensive and expensive use of possibly inappropriate healthcare services. A strategic overview of used healthcare resources and associated costs generated by these patients may help policies and healthcare providers to conceptualize, formulate and develop an adapted policy regarding end-of-life care for those who die from non-cancer diseases.

End-of-life care in non-communicable diseases

To date, non-communicable diseases, such as COPD and dementia, are associated with the majority of causes of death in the western world. However, there is a significant difference in the attitudes of healthcare professionals and patients toward accepting COPD and dementia as a terminal disease and cause of death, compared to other terminal illnesses such as cancer. The estimated number of people dying from COPD and dementia, however, may be higher than reported by national yearly statistics [63-67]. Since the estimated cause of death is often based on death certificates, which often fail to list COPD or dementia as the immediate cause of death. Physicians tend to report the immediate cause of death, without reporting the underlying one, reflecting a lack of recognition and inaccurate perception of the terminal nature of the disease.

One of the causes for failure to recognize COPD or dementia as a terminal disease is “prognosis paralysis”, defined as a lack of ability to determine prognosis due to the uncertain nature of the disease. This paralysis frequently results in prognostic uncertainty and inadequate end-of-life care due to delaying or not recommending palliative care, as well as exposing patients to uncontrolled symptoms, over-procedural and pharmacologic treatment, futility of care, and unnecessary suffering [68-72].

In community settings, for example, palliative support teams and the integration of palliative care into nursing homes offers a potential solution to provide, in a way that aligns with patients’ preferences and needs, appropriate end-of-life care with adequate reimbursement and lower healthcare costs for those

dying of COPD or dementia. However, to date, prognostic markers that are being used to determine COPD or dementia patients who are eligible for receiving adapted end-of-life care are inaccurate and often lack of a standardized assessment of the terminal status.

During the last decades, most western countries have promulgated laws considering limits of medical care for terminally ill patients, from the view of patient autonomy and dignity. The laws determine patients' rights for decision-making regarding the kind of care they prefer; and under certain conditions, the right to avoid care; as well as protecting the healthcare provider from lawsuits when providing end-of-life and not life-prolonging care. Because COPD and dementia are frequently not considered as a terminal disease, most patients with these diseases do not take advantage of these legislative approved opportunities and do not declare their preferences for future care [73-75]. Such is the case with advance directives, an important aspect to provide timely and adapted end-of-life care. However, the lack of knowledge and negative attitudes towards advance directives, strengthened by concerns regarding lack of perceived benefits to those with COPD or dementia, prevents advanced care planning [75, 76]. Even when advance directives and do not resuscitate (DNR) or do not hospitalize (DNH) orders exist, healthcare professionals often lack the confidence to follow these directives and to provide end-of-life care because of potential sanctions by health authorities, as well as fear of prosecutions due to improper use of pain control drugs. The routine of curative care provides a safe and protected climate for healthcare professionals, thus avoiding uncomfortable and distressing discussions regarding death.

This phenomenon has, beside social and ethical implications, a vast number of implications concerning the development and elaboration of an appropriate end-of-life policy and moreover, raises the question as which and to what extent, to date, COPD and dementia patients at the end of life use the available healthcare resources.

1.5. End-of-life care and chronic obstructive pulmonary disease

What is chronic obstructive pulmonary disease?

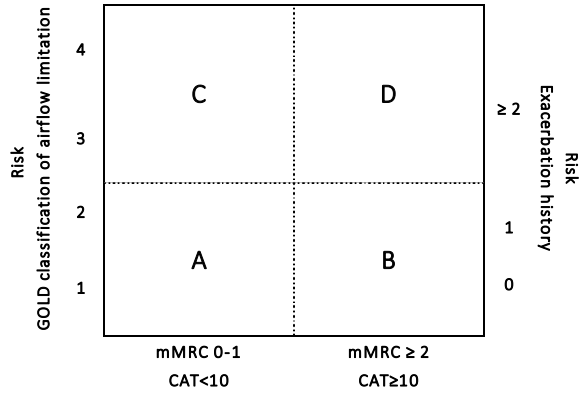
Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation. In most patients, COPD is associated with significant concomitant chronic diseases, which increase its morbidity and mortality. The global initiative for chronic obstructive lung disease defines COPD as follows:

> *"(...) a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that*

is characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person."

In a follow–up to the 2011 United Nations high level political declaration on non-communicable diseases, in 2012, the World Health Assembly endorsed the "25 by 25 goal", which focuses on reduction of premature deaths from COPD by 25% by the year 2025 [77, 78]. However, despite this initiative, experts report that COPD remains a growing and neglected global epidemic [78-81]. According to the European COPD Coalition estimates, the global prevalence of COPD is 11.7% (8.4%-15%) resulting for the European Region in 66 million people in 2015 [82, 83]. According to the global burden of diseases study, COPD accounted for 3.2 million deaths worldwide in 2015 [84]. Whereas COPD is currently rated the fourth most common specific cause of death globally it is predicted to be the third by 2030 [85].

The course of COPD is characterized by 4 stages which range from mild to very severe COPD. According to the Global initiative for chronic obstructive lung disease (GOLD) the presence and severity of the spirometric abnormality, the nature and magnitude of symptoms, the history and future risks of exacerbations and the presence of comorbidities determine the stage of COPD. The most common ways to determine these stages of COPD are the GOLD staging system, the BODE-index and some specific lung function tests (e.g., gas diffusion tests, 6-minute walk tests or spirometry). The GOLD staging system uses the forced expiratory volume in one second (FEV1) test, the Modified British Medical Research Council (mMRC) questionnaire, the COPD Assessment Test (CAT™) and the COPD Control Questionnaire (CCQ) to categorize the severity of COPD into stages [86].



Classification of airflow limitation severity in COPD (post-bronchodilator FEV_1) in patients with $FEV_1/FVC<0.70$

GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

Symptoms
(mMRC or CAT score)

Patient category	Characteristics	Spirometric classification	Exacerbations per year	mMRC	CAT
A	Low risk: less symptoms	GOLD 1-2	≤1	0-1	<10
B	Low risk: more symptoms	GOLD 1-2	≤1	≥2	≥10
C	High risk: less symptoms	GOLD 3-4	≥2	0-1	<10
D	High risk: more symptoms	GOLD 3-4	≥2	≥2	≥10

Source: Adapted from the *Global Strategy for Diagnosis, Management and Prevention of COPD 2018*, Global initiative for chronic Obstructive Lung Disease (GOLD)

Furthermore, the BODE Index (body mass, obstruction of airflow, dyspnea and exercise capacity), is used to better understand how COPD affects a person's life and the severity of the symptoms [87].

Moreover, COPD often coexists with comorbidities that may have a significant impact on prognosis or the recognition of COPD as a primary cause of death [88-90]. Some comorbidities arise independently of COPD where others may be related to it. Comorbidities such as cardiovascular diseases, osteoporosis, depression and anxiety, skeletal muscle dysfunction, metabolic syndrome and lung cancer occur frequently in COPD patients and may influence treatment, mortality and resource use in COPD patients. Importantly, comorbidities with symptoms also associated with COPD may be overlooked e.g., cardiovascular disease or lung cancer. As a result, COPD might be negatively impacted by these comorbid conditions [91]. The combination of physical deterioration and existence of comorbidities in those who progress to the very severe or end-stage phase of the disease, require complex and comprehensive care, especially, during the last phase of life.

COPD related end-of-life care: a reverse focus

COPD patients at the end of life suffer from several symptoms e.g., a poor prognosis, intolerable dyspnea, low levels of self-efficacy, disability, poor quality of life and higher levels of anxiety and depression which are comparable to those who suffer from cancer [92]. These symptoms affect patients' quality of life and can be a source of concern for family and carers as most patients are likely to be housebound and may need continuous support and care. Evidence of palliative care provision for cancer patients indicate that it improves quality of life and reduces health care costs. However,

currently, compared to those who suffer from cancer, there appears to be a lack of palliative care provision or access for patients with end-stage COPD. The reasons why COPD patients do not receive palliative care are complex and a number of barriers can be noted why it is not always provided to this vulnerable group of patients: the inadequate information provision about the likely course of COPD at diagnosis; lack of consensus regarding who should initiate appropriate end-of-life care and in which setting; palliative care discussions which are conflicting with the goals of chronic disease management; and a lack of understanding of the meaning of 'end of life' within the context of COPD [93]. These barriers may partly be related to the prognostic accuracy of patients' survival which poses a challenge for healthcare professionals, including general practitioners and specialist, and for patients with end-stage COPD, as they are, in contrast to cancer patients, less likely to engage in the discussion of end-of-life care planning (advanced care planning). Furthermore there might also be a lack of specific end-of-life resources, time, increased workload and fear which constraints the use of palliative care programs in a specific health care system [92]. As a result those in an advanced stage of the disease still pursue intensive medical treatment although they may also benefit from the simultaneous holistic care approach of palliative care services, medical services and social services to improve their quality of life [94].

Apart from the end-of-life period, COPD patients have a very variable use of healthcare resources ranging from non-COPD-related hospital admissions to a large number of COPD-related admissions over a relatively long time period [95]. The main reasons for admission are acute exacerbation of COPD or a lung infection and complications of other chronic comorbidities [96]. The presence of comorbidities and exacerbations results in an increase of resource use and healthcare costs at the end-of-life. Mainly the use of acute hospitalization, an increased use of ICU and specific drug use at the end of life are responsible for a high end of life cost. End-stage COPD patients are most frequently hospitalized, spending on average 14 days in the hospital during the last 6 months of life [97, 98]. Most of these hospitalizations are characterized by a stay at the intensive care unit where patients receive invasive ventilation. Ventilation use is indeed particularly prevalent in COPD patients at the end of life and is usually preceded by an exacerbation. Ventilation received by COPD patients varies, depending on the severity of the exacerbation, from non-invasive ventilation to invasive ventilation on an ICU [98-100]. Due to a hospitalization during the last months of life, most COPD patients die in hospital. As a result of this, only a limited number of patients has contact with their GP during their last months of life.

In general, current evidence stated that acute hospital visits, ICU admissions, physician visits and use of invasive interventions and medication are the key drivers of resource use in terminal COPD patients which are mainly caused by concomitant diseases related to advanced age or smoking and by a lack of discussion of end-of-life preferences between the patient and healthcare professional (e.g., advance

care planning). Moreover, in current evidence, specific cost items concerning end-of-life care are not well described. As such, it remains difficult to derive specific cost drivers, resources and influencing factors for COPD patients at life's end [94] and it may be suggested that resources used at the end of life and costs of end-of-life care in COPD patients should systematically be described by specific resources and in relation to specific comorbidities so that the understanding of specific cost drivers in end-of-life care of COPD patients could be improved and the effect of comorbidities on end of life resource use could be explained.

Moreover, the varying course of COPD, the presence of specific symptoms as well as the presence of different co-morbidities in COPD patients, cause difficulties regarding the prognosis of the end-of-life phase in COPD. As a result, COPD patients are often excluded from receiving appropriate end-of-life care such as palliative care. Notwithstanding the fact that previous research in a cancer population showed that the use of palliative care services available in the hospital or at home led to a reduction in end-of-life costs, the evidence with regard to the effect of palliative care services within a COPD population is limited or non-existent. Due to the degenerative nature of the disease and the desire to die at home COPD patients often reside at home during the last phase of the disease. Although community-based palliative care affects end-of-life costs positively in cancer patients, evidence regarding a COPD population is lacking. Moreover, the difference in disease progression and prognostication between those who die from cancer and those who die from COPD, an extrapolation of the results regarding the effect of a community-based palliative care service in a cancer population is impossible. As a result, a population-wide analysis regarding the use of community-based palliative care services by COPD patients at the end of life occurs.

1.6. End-of-life care and dementia

What is dementia?

According to the World Health Organization, 50 million people suffer from dementia worldwide and is projected to triple by 2050 to 152 million [101]. It is a major cause of disability characterized by a range of symptoms and associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities. Although there are several types of dementia, the most frequent cause of dementia is Alzheimer's disease which accounts for 60 to 70 percent of the cases [102]. The life expectancy of a person with dementia is unpredictable, and can progress for up to around 10 years after diagnosis. It is estimated that 33% of the people with dementia will be at one time in the advanced stage of the disease. Although dementia is sometimes not perceived as a terminal illness, it will shorten life expectancy. Mostly, other conditions or illnesses caused by the psychological and

physical decline, such as pneumonia or other infections, are described as the primary cause of death. The World Health organization (WHO) describes dementia as follows [103]:

> "*Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation. This syndrome occurs in a large number of conditions primarily or secondarily affecting the brain.*"

The course of dementia is characterized, based on the Mini-mental state examination, by three stages which range from mild to moderate to very severe or advanced dementia [104]. However, often a more exact stage is assigned, based on a person's symptoms. The most common scale is the global deterioration scale or Reisberg Scale (GDS). The GDS divides the disease process into seven stages based on the amount of cognitive decline. This staging is most relevant for people who have Alzheimer's disease, since some other types of dementia (i.e. frontotemporal dementia) do not always include memory loss [105]. Other scales used to determine the stage of dementia are: the Functional Assessment Staging Test (FAST) and the Clinical Dementia Rating scale (CDR) [106].

Alzheimer's disease related end-of-life care

Dementia accounts for increasing health resource use and has significant social and economic implications in terms of direct medical costs, direct social costs and the costs of informal care. In 2010, the total global societal costs of dementia was estimated to be US$ 604 billion. Which was 1.0% of the worldwide gross domestic product (GDP), or 0.6% if only direct costs were considered. Although dementia causes physical and emotional burden to the patient, family and caregivers, the economic burden of dementia to patients and family at the end-of-life should not be underestimated. In high-income countries, informal care (45%) and formal social care (40%) account for the majority of costs, while the proportionate contribution of direct medical costs (15%) is much lower [107]. The increased demand for end-of-life care for people with dementia will be associated with major social and economic costs, but what is the current state of resources used and related costs of such care?

The course of dementia is characterized by a progressive decline and often results in death due to an acute event such as an infection or progression of another disease [108]. Although palliative care is mainly focused on those who are in an advanced stage of the disease, it is presumed that it should be

initiated early in the disease course. Since dementia is characterized by a progressive decline, those with mild dementia often reside at home. However, when dementia progresses to a moderate and advanced level, burden of the informal caregiver increases [109]. As a result of the increase in informal caregiver burden, those suffering from dementia are often admitted to a nursing home and/or admitted to a hospital when acute diseases such as infections arise. Therefore, end-of-life care in dementia patients should be organized in different healthcare settings, at home, nursing home and hospital. Due to this 'compartmentalization' of end-of-life care in dementia patients, the general practitioner (GP) is seen as an end-of-life care coordinator [110, 111]. Despite a GP is seen as a suitable healthcare provider to initiate and organize appropriate end-of-life care at home or nursing home there are still some barriers that keep them from organizing this care in those settings. Main barriers GP's are confronted with are: the compartmentalization in healthcare, a lack of communication and collaboration between different care providers, lack of 24-hour availability and their own uncertainty about their knowledge and abilities regarding palliative care [112-114] . Notwithstanding a GP is seen as a primary care provider of end-of-life care in a home situation or nursing home, the influence of a community-based palliative care team and the services, with regard to the provision of palliative care, available in a nursing home should not be underestimated. Although evidence shows that a community-based palliative support team has a positive effect on lowering end-of-life care costs in a home situation, there is only scarce evidence that shows that this is also the case for those who suffer from dementia. Furthermore, evidence that shows that providing appropriate end-of-life care in a residential setting such as a nursing home has a positive effect on the costs related to the end of life is also limited. Simoens et al. (2013) analyzed costs of terminal patients in Belgian nursing homes and found that the cost of usual care exceeded the costs of palliative care due to a longer length of stay in hospital. However, they did not focus solely on those who died of dementia [115]. Moreover, a study comparing place of death by Mitchell et al. found that only 5-7% of those who stayed in a nursing home were referred to a hospice, compared with 10.7% of those residing in a home care setting. Furthermore, they were more likely to be admitted to a hospital due to an acute illness [72, 116].

Those transferred to the hospital suffering from end-stage dementia are at higher risk of receiving invasive or inappropriate non-palliative interventions, receive poor pain control, have feeding tubes inserted and are confronted with inappropriate laboratory tests and treatments at the end of life which do not improve prognosis and life-expectancy [117].

Although these before mentioned barriers are seen in a number of serious illnesses, they are amplified in those who suffer from advanced dementia due to challenges in dementia patients related to their cognitive impairment which may hinder treatment or adherence to treatment. Moreover, 'prognostic paralysis' is seen as an important reason why dementia patients do not receive appropriate end-of-life

care. Although, the prognosis of advanced dementia patients is often based on their level of inability to eat, the MMSE is used to identify end-stage dementia patients who could have most benefit from a palliative care provision [118, 119]. However, prognostication is a complex and challenging task that relies primarily on clinical judgement and advanced dementia is often not viewed as a terminal diagnosis. As a result of 'prognostic paralysis' and 'neglecting a terminal condition', end-stage dementia patients often receive inappropriate end-of-life care.

With respect to medical management, there is some evidence that invasive procedures are limited in end-stage dementia patients [120]. Yet, central line insertion is found in a small number of end-stage dementia patients, and significantly more patients have a measurement of blood gases and diagnostic tests to follow up an acute event of, for instance, a pneumonia. Moreover, significant more dementia patients at life's end are documented with urinary catheter and nasogastric tube insertion but have less palliative medications prescribed or use less palliative care services when compared with those without a dementia diagnosis [117].

Given the increasing prevalence of people dying with dementia, palliative care for those suffering from end-stage dementia is extremely relevant. However, there is increasing evidence that patients with diseases other than cancer have difficulty accessing specialist palliative care services. Difficulties associated with diagnosing the terminal phase of the illness (prognostication); issues relating to communication; medical interventions; availability of palliative care services at home or nursing home and the appropriateness of a palliative care intervention for those suffering from end-stage dementia are therefore five key elements why end-stage dementia patients receive not the appropriate level of palliative care.

Although current evidence indicates that those who suffer from dementia might benefit from receiving specialized palliative care, there is no evidence available that indicates to what extent the recognition of Alzheimer's disease results in receiving appropriate care such as palliative care. The recognition of Alzheimer's disease as a life-threatening illness can lead healthcare professionals to provide appropriate care for this group in the final phase of life. Furthermore, it can be argued that the recognition and improvement of the prognosis criteria that lead to more appropriate end-of-life care have a positive influence on end-of-life costs in Alzheimer's disease patients.

Current evidence indicates that patients suffering from dementia generate lower total medical costs at the end of life compared to those suffering from cancer. However, this evidence is non-existent within the Belgian health care system, as a result an analysis of medical costs within the Belgian care context is recommended. As a result of the specific disease progression of dementia and the specific place of care where dementia patients receive their care, it can be assumed that a GP plays an important key

role in delivering appropriate end-of-life care. GPs, however, are limited by a number of barriers that limit the initiation of palliative care and that end-of-life care costs relate differently to dementia patients than in cancer where the last phase of life can be better predicted and the provision of specialized palliative care is more used.

2. HEALTH ECONOMIC EVALUATION OF END OF LIFE CARE

It is important to ascertain what proportion of healthcare costs is assigned to the specific end-of-life period and what end-of-life care interventions are most cost-effective for those suffering from COPD or dementia. However, investigating and analyzing end-of-life care and its related costs is challenging due to important methodological limitations related to socioeconomic, demographic and patient specific factors.

2.1. Economic evaluation of health care

Health economic evaluation can be described as a comparative analysis of two or more healthcare interventions whereby costs and health effects are analyzed [121]. It comprises a range of techniques that can be used to gather evidence and make comparisons on costs and effects of different healthcare interventions. Since it is recommended to collect data on costs and effects simultaneously in health economic evaluations, the process is long and expensive. Existing medical literature is often used to provide data on the health care effects. When using existing medical literature, data may not be accurate and certain assumptions may have to be made.

Health economic analyses can be classified according to the type of comparison of the costs and effects. Depending on the type of analysis, the assessment of the outcome ranges from non-assessment through assessment in non-monetary, naturalistic units to monetary assessment. The choice of method of analysis depends on the research question and must be justified. A number of health economic evaluation techniques can be distinguished:

(1) Cost-minimization analysis. Cost-minimization is an economic study in which two or more therapeutic interventions with the same effectiveness or efficacy are compared in terms of net costs in order to establish the cheapest alternative.

(2) Cost-effectiveness analysis. The cost-effectiveness analysis is an economic study in which the costs are expressed in monetary units and the results in non-monetary outcomes (e.g. life years gained, hospital days, days in good wellbeing, reduction of aggressiveness of care, reduction of anxiety).

(3) Cost-utility analysis. Cost-utility analysis has the same principle as a cost-effectiveness analysis. Costs are assessed in monetary units and the effect is measured as a utility-adjusted outcome, the quality adjusted life year (QALY). A QALY combines life expectancy and quality of life. This analysis is recommended when quality of life is an important aspect of the intervention.

(4) A cost-benefit analysis. A cost-benefit analysis assesses all effects, including health effects, in monetary units. A disadvantage of the cost-benefit analysis is that a monetary assessment of clinical

results must be made. Nevertheless, since costs and effects are measured in monetary units, it is possible to calculate whether an intervention delivers an overall gain to society. Two methods of assessing effects of the intervention in monetary terms can be used. The human capital approach and the willingness to pay approach.

(5) A cost-analysis. A cost-analysis measures and evaluates costs of specific actions or alternatives in healthcare but does not evaluate the specific effects of the alternatives. As such, it does not constitute a full-economic evaluation. The large literature on cost of illness, or burden of illness falls in this category. A cost-analysis describes the cost of disease to society [122].

Economic evaluation requires also the identification and measurement of costs related to the intervention. Costs can be described as direct, indirect and intangible costs. Direct costs refer to medical and non-medical costs. Direct medical costs are defined as the medical care cost for treatment, rehabilitation or terminal care, while direct non-medical costs refer to costs such as transportation cost to and from the health care provider, specific household expenditures related to the disease and costs related to informal care. Indirect costs are used to refer to productivity loss due to the illness or death. Furthermore, intangible costs refer to discomfort due to the disease or health care status but are rarely quantified in monetary terms.

2.2. Economic evaluation of end-of-life care

End-of-life care is not a singular entity with a universal experience and well agreed upon course of care. Prognostication is poor and imprecise for most conditions, and patients and caregivers cope with illness for years, often with different trajectories of functional decline and needs which may impede the recognition of the terminal phase [125] .

Since these patterns of decline, as well as socio-economic and demographic factors of patients at the end-of-life, differ, different measures to assess the full spectrum of patients' end-of-life period is needed. Besides these different patterns and socio-economic and demographic factors, it is also important to consider the health care system which covers different healthcare settings. Although, a direct comparison of end-of-life spending across different healthcare systems is difficult due to differences in population sample, components of costs, definitions of end-of-life and time frames in which data are collected, some insights can be learned by comparison of the distribution of components of spending across different healthcare systems [126].

The pattern of decline (related to the diagnosis), patient characteristics, health care system and health care setting play an important role and face different challenges in health economic evaluation of end-of-life care.

Perspective

The perspective of which health economic evaluation is performed is the point of view from which the costs and benefits are recorded and assessed. Apart from the societal perspective, which represents the most comprehensive approach, a health system or health insurance perspectives is possible. Since for most patients with life-threatening diseases the time before death is characterized by months to years of physical and emotional distress, progressive functional dependence, frailty and high family support, they are often bound to use several different service providers such as hospitals, physicians, home care, hospices, emergency care or long term care facilities and skilled nursing facilities. When conducting an health economic evaluation in end-of-life, this perspective should be clearly described. If several perspectives are included in the analysis, the results should be presented separately for each perspective.

Health economic data in end-of-life care

Most of the current understanding of end-of-life expenditure is based on analyses using administrative databases that cover most of the formal care expenses [126]. Administrative databases provide an opportunity to analyze costs of end-of-life care, but they often lack important variables such as socio-demographic and patient characteristics. Direct medical costs at the end-of-life are influenced by socio-demographic characteristics, patient characteristics, geographic region and the availability of present health services and local resources. However, these influencing factors are determined by the present health care system.

Health economic outcome parameters in end-of-life care

Three outcome parameters can be chosen when evaluating the economic effects of end-of-life care interventions. First, the outcome can be measured economically oriented such as a number of hospital days or days at a palliative care unit. A second way to measure outcomes of end-of-life care is based on a clinical outcome and third, the outcome can focus on health related quality of life. These three types of outcome aim to assess the success of end-of-life care on individuals, to help managing service delivery and monitoring quality, and to support priority setting by comparing the effectiveness and cost-effectiveness of different end-of-life interventions.

The gold standard measure of outcome in economic analysis is presumed to be quality adjusted life years or QALY [141]. Although there are arguments against its use in evaluating healthcare technologies and interventions, it is widely used in practice and there is consensus that its use in resource allocation decision making is appropriate. Nevertheless, its use in evaluating end-of-life care is discussed.

3. IMPORTANCE OF HEALTH RESOURCE AND ECONOMIC EVALUATION OF END OF LIFE CARE

Medical care in the final period of life accounts for a considerable share of health care expenditures and most of the evidence is based on studies in those suffering from cancer. The evidence regarding resources used and costs generated for those who suffer from non-cancer diseases remains scarce. Hence, there is a growing interest in examining the current state of healthcare use and costs across a full national population and there is a need to identify opportunities for improvement and reducing costs at the end of life without compromising the quality of care. Despite this growing international interest, only a few studies investigated resource use and costs for end-of-life patients in Belgium and described only a specific population such as cancer patients or focused only on specific places of care e.g., hospital or nursing home [17, 22, 115, 142, 143].

To date, there is only a small number of literature analyzing resource use and costs in end-of-life COPD and Alzheimer's disease patients and knowledge about the impact of resources and costs used by these patients at the end-of-life is crucial for national and international policymakers due to an increasing prevalence of those dying from COPD or Alzheimer's disease.

Current evidence showed that, apart from the varying course of COPD and the presence of specific symptoms, the presence of different co-morbidities influence the uptake of specific end-of-life resources in those dying of COPD. Moreover, previous research also indicated that the typical model of cancer end-of-life care might not suit for people who have a gradual, progressive decline with unpredictable exacerbations such as chronic obstructive pulmonary disease or those who suffer from a prolonged deterioration such as Alzheimer's disease. It was also previously stated that people who suffer from non-communicable diseases e.g., COPD and Alzheimer's disease may have similar and more prolonged needs pressing as hard as those who suffer from cancer. However, uncertainty about the prognosis and the failure or late recognition of the terminal phase often result in a lack of timely initiation of adapted end-of-life care.

Due to the differences between the end-of-life trajectories of cancer, COPD and Alzheimer's disease and difficulties in recognizing Alzheimer's disease as a life-limiting disease and the presence of lung cancer and cardio-vascular diseases in those suffering from COPD, end-of-life care received by those suffering from COPD or Alzheimer's disease is often not aimed at responding to their specific end-of-life needs and consequently results in intensive and expensive use of healthcare services. However, a full population analysis of direct medical end-of-life care costs between those dying from cancer, COPD and Alzheimer's disease are lacking.

Finally, COPD patients are often excluded from receiving appropriate end-of-life care such as palliative care. However, previous research in a cancer population showed that the use of palliative care services available in the hospital or at home lead to a reduction in end-of-life costs. Due to the lacking evidence with regard to the effect of palliative care services within a COPD population and due to the desire to die at home COPD patients often reside in a hospital during the last phase of the disease. Although it was found that home-based palliative care affects end-of-life costs positively in cancer patients, evidence regarding a COPD population is lacking.

Furthermore, economic evaluation of end-of-life care develops slowly and the evidence base remains small. While current results indicate that palliative care is cost-saving for those dying of cancer, these results are based on heterogeneous methods and evaluation is often poor and based on specific samples. Early identification and prognostication of the end of life phase and the provision of appropriate end-of-life care and palliative care are assumed to improve quality of life of patients and their families. However, most of the evidence is based on evaluations of specific or small cohorts, full-population national evaluations are lacking and those suffering from non-cancer diseases are also found to be in need of appropriate end of life care. As a result, filling this evidence gap is increasingly important to facilitate good resource allocation decisions for those suffering from non-cancer related diseases such as COPD or Alzheimer's disease.

4. RESEARCH AIMS

The present dissertation has two main objectives:

1. To examine resource use and costs in the final months of life of those dying from chronic obstructive pulmonary disease and Alzheimer's disease.

2. To examine if specialized palliative care is related with changes in end-of-life care costs in those suffering from non-cancer related diseases.

These objectives have several specific research aims:

1. To summarize and discuss resource use and costs of end-of-life care in those suffering from COPD by means of a systematic review.

2. To describe and compare end-of-life resource use during the last six months of life between COPD patients dying of COPD, cardiovascular diseases and lung cancer.

3. To describe and compare medical resource use in the final six months of life in people dying with and of Alzheimer's disease.

4. To determine and compare total end-of-life care costs and specific cost-components associated with changes in end-of-life care costs during the last year of life between cancer, COPD and Alzheimer's disease.

5. To examining to what extend the use of a palliative home care team results in changes on direct medical expenditures during the last month of life in those dying with COPD.

CHAPTER 2: METHODS AND OUTLINE

1. METHODS AND DATA

To address the research aims a systematic review of current evidence was executed and quantitative analyses were preformed using seven different full-population national databases and one disease registry which were linked into one comprehensive database:

1.1. Systematic review of current evidence

We conducted a systematic literature review to describe the existing evidence about resource use and costs of COPD patients in their final months of life. We performed a comprehensive literature search in Medline, Web of Science and Econlit AND combined search terms to identify resource use and costs during the end-of-life period of COPD patients. Furthermore the included studies were screened for back-references to detect potential studies not-identified through the initial search strategy. Study identification occurred following the PRISMA guidelines and included potentially relevant studies for data extraction if they complied with the following criteria: (1) study population of adults diagnosed with COPD, (2) presence of a focus on an end-of-life period, and (3) description of resource use and/or costs during the end-of-life period. Since all selected studies appeared to have retrospective designs, quality appraisal was executed consistent with "A checklist for retrospective database studies – ISPOR".

1.2. Administrative databases

We used a total of eight national population-level databases to describe resource use and costs of end-of-life care in COPD and dementia patients (Table 1) and linked them into one common database. The data of this comprehensive full-population linked database include healthcare data retrieved from the Intermutualistic Agency (IMA), diagnostic characteristics of cancer decedents from the Belgian Cancer Registry (BCR) and sociodemographic, socio-economic and death certificate data retrieved from Statistics Belgium. The procedures for obtaining and linking these data is presented in the third chapter.

Table 1 Overview of population-level databases identified as relevant for end-of-life care research

Database administrators	Database name	Population	Information provided in database
Inter Mutualistic Agency (IMA)	Population Database	Every Belgian citizen who is a member of one of the seven (compulsory) Belgian sickness funds, information in Population Database is updated twice each year from 2002 onwards	Socio-demographic characteristics (age, sex, date of death, place of residence, family composition, use of supportive measures)
	Pharmanet Database		Medication supply characteristics (substance, quantity, prescriber, expenses, refunds, delivery date)
	Medical Claims Database		Health and medical care use characteristics (quantity of use, reimbursement, supplier, supplier institution, length of treatment)
Belgian Cancer Registry	Cancer registry	Every new cancer diagnosis of Belgian residents, registered by oncological care programs and laboratories for anatomic pathology	Diagnostic characteristics (date of diagnosis, type of cancer, TNM gradation)
Statistics Belgium	Death certificate database	Every Belgian decedent with a registered death certificate	Direct and indirect causes of death (in ICD-10 codes), socio-demographics about the deceased, place of death
	Demographic dataset	Every Belgian citizen	Nationality group, household composition
	Socio-economic survey (SES) 2001 and Census 2011	Every Belgian citizen, information gathered from multiple external administrative databases using social security number (Census 2011)	Highest attained education level, occupation, housing comfort
	IPCAL dataset	Every Belgian citizen	Net income by category
Identified but not used in our research			
Belgian Ministry of Health	Minimal Hospital Dataset	Every hospital admission in non-psychiatric general hospitals	Medical, nursery and personnel data for in-hospital care

Derived from: Maetens, A., De Schreye, R., Faes, K. et.al. (2016). Using linked administrative and disease-specific databases to study end-of-life care on a population level. BMC Palliative care.

1. The Intermutualistic Agency databases

The IMA manages the databases that include all reimbursement data of health care consumption from all Belgian healthcare insurance organisations. Since health insurance is legally mandatory in Belgium, reimbursement data of all legal residents are available. From IMA four databases are linked: (1) a population database containing socio-demographic data of all insured persons; (2) a health care database containing health care use and cost (of reimbursement) data; and (3) a pharmaceutical database containing delivered medication and related cost data and (4) a hospital care database containing hospital use and costs data. These were linked with socio-demographic, socio-economic and death certificate data from Statistics Belgium.

2. The Statistics Belgium databases

Statistics Belgium manages the national demographic database, derived from the population registry and data from the Socio-Economic Survey 2001 and Census 2011, nationwide full population surveys based on the tradition of population count . The demographic database contains information about the highest educational level attained, the last held occupation (as a measure of socio-economic position)

and housing characteristics. Finally a database containing fiscal data (i.e. net taxable household income), also managed by Statistics Belgium, was linked to allow additional socio-economic insights.

3. The Belgian Cancer Registry

The Belgian Cancer Registry was identified as a database to identify people who died with cancer. All Belgian oncological care programs of hospitals and laboratories for anatomic pathology are legally bound to register each new cancer diagnosis with the cancer registry. The latter manages a database with diagnostic information on all incidences of cancer i.e. date of diagnosis, type of cancer and TNM (tumor node metastasis) classification of malignant tumors.

1.3. Setting, measures and determination of Chronic obstructive pulmonary disease and Alzheimer's disease

Setting

The Belgian health system is primarily funded through social security contributions and taxation and is based on the principles of equal access and freedom of choice, with a Bismarckian-type of compulsory national health insurance, which covers the whole population and has a very broad benefits package. Compulsory health insurance is combined with a private system of health care delivery, based on independent medical practice, free choice of service provider and predominantly fee-for-service payment. All individuals entitled to health insurance must join or register with a sickness fund.

The reimbursement of services provided depends on the employment situation of the patient (self-employed or employed, until 2007), the type of service provided, the statute of the person who is socially insured (preferential reimbursement or not) as well as the accumulated amount of user charges already paid.

Patients in Belgium participate in health care financing via co-payments, for which the patient pays a certain fixed amount of the cost of a service, with the third-party payer covering the balance of the amount; and via co-insurance, for which the patient pays a certain fixed proportion of the cost of a service and the third-party payer covers the remaining proportion. There are two systems of payment: (1) a reimbursement system, for which the patient pays the full costs of services and then obtains a refund for part of the expense from the sickness fund, which covers ambulatory care; and (2) a third-party payer system, for which the sickness fund directly pays the provider while the patient only pays the coinsurance or co-payment, which covers inpatient care and pharmaceuticals.

Measures

In the IMA healthcare and pharmaceutical databases, healthcare and medication data are coded as nomenclature and Anatomical Therapeutic Chemical Classification (ATC) codes. In order to answer the research questions, specific nomenclature numbers were interpreted and aggregated into meaningful resource use, procedures, medication categories and specific cost components.

Measures for resource use included hospitalization, emergency room (ER), intensive care unit (ICU), palliative care unit, one-day-care (ODC), nursing home and skilled nursing facilities, home care, palliative home care, and contacts with general practitioner, specialist and physiotherapist.

Measures of specific procedures and medication associated with the treatment or end of life phase included the use of medical equipment e.g. invasive and non-invasive ventilation, gastric tubing, cardiopulmonary resuscitation (CPR), medical imaging (computed tomography (CT), nuclear magnetic resonance imaging (NMR), positron emission tomography (PET)), electroencephalography (EEG)), and medication i.e. oxygen, opioids, sedatives, morphine and other specific drugs.

Different cost components included inpatient and outpatient costs which were further broken down in specific cost components. Specific cost components included total cost, total inpatient cost, total outpatient cost, total hospitalization cost and costs of intensive care unit, palliative care unit, D-ward, G-ward, specialized psychogeriatric ward, other wards, emergency room, nursing home, multidisciplinary primary care, general practitioner, specialist, home nursing care, other healthcare professionals, medication, pharmaceutical deliveries, medical supplies, medical imaging, clinical biology, physiotherapy, surgery, other medical procedures, mental/psychiatric care and palliative care. For each specific cost component we determined the direct medical out-of-pocket cost, insurance cost and total cost (i.e. sum of out-of-pocket cost and insurance cost).

A more detailed description of the different resource categories and cost components used in the following chapters of this dissertation and how they were determined is included as a supplemental file to this work. (A detailed list of used acts can be provided on request.)

1.4. Determination of Chronic obstructive pulmonary disease and Alzheimer's disease using health administrative databases

To determine those who died of COPD and Alzheimer's disease we used the primary cause of death as mentioned on the death certificate. However, as highlighted in the general introduction of this dissertation, COPD and Alzheimer's disease are underreported on the death certificate. Therefor, we expanded our population of COPD and Alzheimer's disease patients with those who died with COPD or Alzheimer's disease using a specific algorithm. COPD and Alzheimer's disease patients were identified

algorithmically using health claims and medication data from 2002 through 2015. Yet, since the IMA database contains no information regarding medical diagnoses or any disease specific information a validated algorithm based on medication and clinical activities was used to identify those deaths who had COPD or Alzheimer's disease and had no indication of it on the death certificate. This algorithm was further expanded with those deaths for which COPD or Alzheimer's disease was recorded on the death certificates as an intermediate or associated cause of death but excluding the deaths for which COPD or Alzheimer's disease was the underlying cause of death. Following algorithms were used to determine COPD and Alzheimer's disease patients using health claims and medication data:

FINAL ALGORITHM CHRONIC OBSTRUCTIVE PULMONARY DISEASE

ATCcode=((R03BB04 OR R03BB05 OR R03BB06 OR R03BB07 OR R03AL04 OR R03AL03 OR R03AK06 OR R03AK07 OR R03AK08 OR R03AK10 OR R03AK11) NOT (R03DC01 OR R03DC03))

FINAL ALGORITHM ALZHEIMER'S DISEASE

ATCcode=(N06DA01 OR N06DA02 OR N06DA03 OR N06DA04 OR N06DX01 OR N06DA52)

1.5. Prospective versus retrospective design

Studying direct costs can be done prospectively or retrospectively depending on the relationship between the initiation of the study and the data collection. In prospective studies patients are identified when entering a specific phase of their disease e.g., terminal phase. This means that the process of data collection needs to be done by following-up the patient over time. This approach provides an unbiased look at care. On the other hand, care can be retrospectively assessed. Using a retrospective design has several disadvantages such as an absence of data about potential confounding factors if the data was recorded in the past and can only be carried out when sufficient data are available. Moreover, retrospective data may have been collected for other purposes different from those of an economic evaluation. However retrospective designs have also several advantages. The major advantage of retrospective studies is that they are less expensive and time consuming than those performed prospectively because all relevant events have already occurred at the time the study is initiated [123]. Furthermore, they allow for easy identification of cohorts of relevant patients e.g., patients at the end-of-life [124].

For health economic analyses of end-of-life care, both a prospective and a retrospective study approach can be adopted.

According to Steinhauser et.al. (2005) literature reveals great variety in the operationalization of the end-of-life phase. Four factors can be described in defining the end-of-life scope [127]. First, the disease category or disease trajectory can be described as a delimiting factor in determining the end-of-life phase. Nevertheless, many patients at the end-of-life suffer from comorbidities which can impede correct categorization. Second, clinical criteria among diagnostic groups can be determinative but should be handled with caution. For example, in chronic obstructive pulmonary disease, which disease trajectory is marked by a steady decline in physical function with severe symptom crises, commonly used prognostic criteria, including measures of air-flow limitation such as FEV_1, degree of hypoxia, complications such as cor-pulmonale and recent hospitalization requiring ventilation, have all been found to be unreliable in determining a specific end-of-life phase [68]. Third, a care setting can play a guiding role defining the specific end-of-life phase. For example, a hospice or palliative care unit stay can presume that a patient is in the end-of-life phase. However, the available services do not reach all those who could benefit from hospice or palliative care [128]. Because of this, a number of patients at the end of life do not receive appropriate end-of-life care or will not be included in the research sample. And finally, prognostication can be used to determine the end-of-life phase [68]. Although clinicians can prognosticate mortality more accurately the closer the patient gets to death, they can rarely say with certainty whether a patient will live for another day, week or month.

The uncertainty surrounding the prognosis and the fact that patients may be unaware of their status as terminally ill or receiving hospice or palliative care render it difficult to identify patients who clearly have a limited life expectancy [129, 130] .

The retrospective approach is an important tool to describe the last days and months of life. An advantage of using a retrospective design in end-of-life research is that the end-of-life phase is clearly defined and the nonresponse bias of being unable to collect information is minimized [131]. Moreover, a retrospective approach allows all patients who come to the end-of-life to be studied. And finally, retrospective designs facilitate the development of measures of real-life performance [124].

A retrospective approach involves use of proxies or existing databases such as medical record databases, disease registries or administrative databases. More specific, use of administrative databases and disease registries creates an opportunity to study costs of end-of-life care and proxies can be used to describe quality of care. Nevertheless, researchers interested in using administrative databases to conduct health economic research in end-of-life often run into different barriers. According to Wang et.al. (2014) clinical big data users face a large spectrum of challenges, including but not limited to sample size, selection bias, interpretation problem, missing values, dependence problems and data handling methodologies [132]. Administrative data itself has limitations such as adequacy, accuracy,

completeness, nature of the reporting sources and other measures of the quality of the data. However, administrative databases and disease registries are not specifically designed for research purposes, researchers can realize significant benefits such as managing specific individual and population health and optimizing end-of life care from an economic perspective.

2. OUTLINE OF THIS DISSERTATION

The findings of this research are divided into two sections matching the two research objectives. Part II and III concerns an evaluation of health resource use and health economic evaluation of end-of-life care across a Belgian population of COPD and dementia decedents. Chapter 4 gives an overview of the current evidence on resource use and costs in end-stage COPD patients. Chapter 5 compares resource use between those who had a primary cause of death of COPD with COPD patients who had a primary cause of death of cardiovascular diseases or lung cancer during the last months of life and chapter 6 describes end-of-life resource use between those who died of or with Alzheimer's disease. Chapter 7 contains a cost comparison of those who died of cancer, COPD and dementia. In chapter 8, we analyzed the effect of providing palliative care in a community-based setting on direct medical end-of-life care costs in COPD patients.

Finally, this dissertation contains, in Part IV, a discussion of the results, including methodological concerns, strengths and limitations and implications for policy and future research.

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CHAPTER 3: ADMINISTRATIVE AND DISEASE SPECIFIC DATABASES TO STUDY END OF LIFE

Chapter based on:

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ABSTRACT

Background: The use of full-population databases is under-explored to study the use, quality and costs of end-of-life care. Using the case of Belgium, we explored: (1) which full-population databases Provide valid information about end-of-life care, (2) what procedures are there to use these databases, and (3) what is needed to integrate separate databases.

Methods: Technical and privacy-related aspects of linking and accessing Belgian administrative databases and disease registries were assessed in cooperation with the database administrators and privacy commission bodies. For all relevant databases, we followed procedures in cooperation with database administrators to link the databases and to access the data.

Results: We identified several databases as fitting for end-of-life care research in Belgium: the InterMutualistic Agency's national registry of health care claims data, the Belgian Cancer Registry including data on incidence of cancer, and databases administrated by Statistics Belgium including data from the death certificate database, the socio-economic survey and fiscal data. To obtain access to the data, approval was required from all database administrators, supervisory bodies and two separate national privacy bodies. Two Trusted Third Parties linked the databases via a deterministic matching procedure using multiple encrypted social security numbers.

Conclusion: In this article we describe how various routinely collected population-level databases and disease registries can be accessed and linked to study patterns in the use, quality and costs of end-of-life care in the full population and in specific diagnostic groups.

Keywords: End-of-life, Data linkage, Administrative databases, Disease-specific databases, Full-population

USING LINKED ADMINISTRATIVE AND DISEASE SPECIFIC DATABASES TO STUDY END OF LIFE CARE ON A POPULATION LEVEL

Background

It has been argued that there is a particular challenge for end-of-life care research to develop a public health approach [1] which would include, among other things, the need for a focus on total populations instead of individuals at risk or those receiving a certain health care service. This means that many, often 'hidden', publics also need to be studied [1, 2]. End-of-life care research indeed often suffers from selection bias, recall bias and non-response bias [3–5] and difficult-to-reach populations tend to be under-represented due to ethical and practical considerations [6].

Administrative data can provide a major opportunity in this respect. They allow not only the monitoring of usage, quality and costs of end-of-life care on a population level [7], but also identifying populations dying of or dying with a specific disease such as cancer, chronic obstructive pulmonary disease (COPD) or Alzheimer's disease in order to evaluate patterns of end-of-life care within and across different trajectories of dying [8]. Many healthcare institutions generate, store and exchange large amounts of individual patient data [9]. Increasing digitalization in recent years has further facilitated and improved this process [10]. Although big data serve administrative purposes particularly (e.g. billing, tracking of health care reimbursement) they can provide useful research material from a public health perspective [11]. They often have a well-defined population and include subgroups or difficult-to-reach populations [6]. Because administrative data registrations are usually standardized and continuously collected they enable trend analyses and longitudinal studies. Moreover, since the data have already been collected, they are relatively inexpensive when compared with original data collections [2, 12]. The expanding availability and quality of data input make them increasingly interesting to use in health research. Although full-population databases have been used to study end-of-life care since the late nineties (e.g. in Australia [13] and Canada [14]), the use of such data in end-of-life care research is still under-explored.

End-of-life care researchers may face several challenges when using administrative data. Administrative data are, for instance, not specifically designed for research purposes and therefore not directly usable for the evaluation of quality of care or quality of dying. They are not structured in readily available variables for analysis and may often lack the essential disease-specific or relevant socio-demographic information needed in end-of-life care research. Additionally, healthcare data, socio-demographic data, socio-economic data and clinical data gathered on every citizen are stored in separate databases that are owned and handled by different organizations. Also, data security and confidentiality must be publicly guaranteed when using administrative databases for healthcare research. The challenge is thus

to collect, link, integrate, store and process them so that they provide a useful input for end-of-life care research.

Using the case of Belgium, we describe how several full-population data sources can be accessed, linked, handled and stored in order to obtain a rich database for evaluating the use, quality and costs of end-of-life care. Our research questions are: (1) what data and databases are available that provide information about end-of-life care, (2) what are the procedures to obtain/use these data, (3) what is needed to integrate separate databases, and (4) what variables are available in these databases to study use, quality and costs of end-of-life care.

Methods

To address our research aims we systematically collected the necessary information in four phases:

1.First, we had to identify what databases provide information on the health care use, quality and costs near the end of life. We aimed to retrieve healthcare use data from all decedents for the two years prior to their death. A group of end-of-life researchers and health economics experts explored what data are available on healthcare and medication use that additionally (1) allow identification of people dying with or from cancer, Alzheimer's disease or COPD; and (2) provide relevant socio-economic and demographic information that is known from literature to influence end-of-life care patterns. Health claims data were used as the starting point as they provide critical data about patterns in formal care and medication prescription at the end of life. Other administrative databases and disease registries were explored to supplement the health claims database.

2.Once the databases and the data handling organizations were identified, the associated access procedures and permissions as well as linking possibilities were explored.

3.To complete the linking procedure, technical aspects and privacy protection measures were determined, explored and followed.

4.Finally, we composed an overview of available variables through this process. We examined how they can be used to study use, quality and costs of end-of-life care.

Results

Identification and selection of databases

A total of seven population-level databases handled by three different organizations were identified as providing the necessary information (Table 1).

The Inter Mutualistic Agency (IMA) manages the databases that included all reimbursement data of health care consumption from all seven healthcare insurers. Since health insurance with one of these insurers is legally mandatory in Belgium, reimbursement data of all legal residents are available in the IMA database. Moreover, thorough quality procedures result in reliable usability of the database for healthcare research. The IMA manages three databases: (1) a population database containing socio-demographic data of all insured persons; (2) a health care database containing health care use and costs data of both ambulatory and hospital care and (3) a pharmaceutical database containing medication prescription and costs data. The databases thus provide information on an individual level across the entire Belgian population. The IMA databases contain no information regarding medical diagnoses or any disease specific information.

The Belgian Cancer Registry was identified as a database to identify people who died with cancer. All Belgian oncological care programmes of hospitals and laboratories for anatomic pathology are legally bound to register each new cancer diagnosis with the cancer registry. The latter manages a database with diagnostic information on all incidences of cancer i.e. date of diagnosis, type of cancer and TNM (tumour node metastasis) classification of malignant tumours [15].

However, the cancer registry data does not make it possible to distinguish between those who died 'from' cancer and those who died 'with' cancer. Additionally, since no similar registries were available to identify those who died with or from Alzheimer's disease and COPD we identified the death certificate data as a necessary additional database. Death certificate data in Belgium are collected by three administrations (corresponding to the three semi-autonomous regions in the country, i.e. Brussels, Flanders and Wallonia) and are integrated by Statistics Belgium into one national database for cause of death statistics. This database provides the causes of death and associated causes of death (coded in ICD-10 [10th revision of the International Statistical Classification of Diseases and Related Health Problems] codes) for all decedents.

Statistics Belgium also manages the national demographic database, derived from the population register [16] and containing for example the household composition of every citizen and data from the Socio-Economic Survey 2001 and Census 2011, nationwide full population surveys based on the tradition of population count [17]. The database contains information about the highest educational

level attained, the last held occupation (as a measure of socio-economic position) and housing characteristics, which are all socio-economic factors that have been identified in previous studies as affecting end-of-life care patterns [18–20]. Finally a database containing fiscal data (i.e. net taxable household income), also managed by Statistics Belgium, was identified as providing additional socio-economic variables of influence on end-of-life care patterns.

For more specific clinical data, the Minimal Hospital dataset, providing clinical information associated with hospitalizations, was looked at for possible inclusion. This dataset has high quality data and provides diagnostic information (in ICD-codes), which allows for a more exact clinical description of the study population. It is however limited to in-hospital data, limiting the study population. Additionally, clinical information can be abstracted from health care claims data using specific algorithms. Obtaining cause of death information and using healthcare claims data makes up for the lack of clinical data. Therefore inclusion of the Minimal Hospital dataset was found to be unnecessary.

The combination of identified databases would provide information on formal health care and medication prescription, causes of death, main diagnosis (through the cancer diagnostic information of the cancer registry and algorithmic estimation methods in the IMA databases), and various relevant socio-demographic and socio-economic information.

Access procedures

Two types of approval were needed for every database: (1) internal approval from database administrator organizations and (2) approval from the relevant Belgian Privacy Commission bodies.

1.To obtain access to the IMA and cancer registry databases several steps are required. First, a declaration of interest needs to be set up between researchers and IMA and cancer registry programme managers. Research goals, databases, variables and linking possibilities (see Data linkage procedure) need to be discussed. After IMA and cancer registry programme managers agree on cooperation, the research project (research goals and requested data) is presented to IMA and cancer registry directory boards for approval.

To obtain access to the databases administered by Statistics Belgium, no formal approval of the directory board is required, since Statistics Belgium is legally committed to providing data for research. Based on the requested data, variables and linking possibilities (see Data linkage procedure) the statisticians of Statistics Belgium deliver non-binding advice. Data requests should be filed directly to the Privacy Committee.

All involved partners then discuss the final selection of data and variables and initiate preparations for the linking procedure. The linking of the databases is a main issue for approval by the involved Privacy Commission bodies.

2.We needed the approval of two separate national sectoral committees for privacy protection for access to the various databases and the database integrating all databases: the 'Sectoral Committee of Social Security and Health, Section Health' and the 'Statistical Supervisory Committee'. Both are subcommittees of the Belgian Commission for the Protection of Privacy. The former is responsible for privacy protection of health care data (IMA and cancer registry databases), the latter for privacy of national statistical data (Statistics Belgium databases). The application to the Sectoral Committee of Social Security and Health, Section Health consists of two phases. Phase 1 is the submission of the application and a first assessment by the committee in a plenary meeting. The primary investigator of the study presents the research goals and data linkage procedure to the committee at this plenary meeting. In our application special attention was given to the selection of different variables to receive data with sufficient detail for analysis, but at the same time reducing the risk of re-identification of deceased individuals and their families in order to preserve privacy. Changes in the linking procedure and storage on a separate server were requested (see section on data linkage for more details). Phase 2 is the formal approval during a second plenary meeting of the committee, after having received additional information from the applicant. In our case, the committee requested an additional risk analysis to ensure privacy of the included individuals, which was not requested in the first phase. Formal approval was granted only after a third plenary meeting. The full process took six months from application to formal approval.

The Statistical Supervisory Committee application procedure consists of one phase in which the application is assessed and discussed on a plenary meeting. Formal approval was granted after the first meeting.

Data linkage procedure

All eligible databases needed to be linked into one integrated database for analysis; a common unique identifier (i.e. social security number) made deterministic linking possible. Although the death certificate database does not contain this unique identifier, Statistics Belgium performed a linkage between the death certificate database and the national registry database based on date of birth, sex, and municipality of residence in order to include this unique identifier as a variable. Unique linkage was possible for 98.4 % of deaths.1

For privacy reasons, Trusted Third Parties (TTPs) 'eHealth' and 'Crossroads Bank for Social Security (CBSS)' were responsible for the simple deterministic one-to-one record linkage of the IMA, cancer registry and Statistics Belgium databases. The linkage procedure (Fig. 1) consisted of 13 steps of data-coding or decoding and data transfers needed to ensure that none of the involved parties would have access to both the sensitive data and the social security numbers or to their own databases enriched with data from one of the other parties. Only the researchers have access to the complete linked database without unique identifiers using a Virtual Private Network (VPN) connection with secure token.

Linkage of all data for deaths in 2012 (including health care information about the two years prior to death) were completed in a first phase of the project. In a second phase all data for all deaths 2010-20xx are linked, where data from subsequent years will be added upon availability. A major consideration in the decision to adopt this phased approach is the size of the linked database. The linked database (deaths in one year) will be used for the initial analysis, after which a selection of variables and/or information can be made. Variables with too many missing data or variables that are inaccurate can be dropped. Additionally, the initial analysis will inform on what health care interventions or medications are suitable for further analyses. Finally, based on this first analysis phase, detailed information can be aggregated. The second and third delivery will therefore include more cases with more condensed information per case.

Since all databases depend on submission by individual organizations or institutions, a two-year delay is common. Linkage can only be initiated after all data are complete.

Available information and data handling

Variables selected in this study include data on health care use, prescribed medication, demographics, socio-economics and use of special reimbursement rules. A complete list of variables can be found in Additional file 1: Table S1.

Several steps were necessary to make the data analysis-ready:

1. In the IMA databases, health care and medication data are coded as nomenclature and Anatomical Therapeutic Chemical Classification (ATC) codes. In order to answer research questions, nomenclature numbers had to be interpreted and possibly aggregated by the researchers into meaningful categories.

2. Due to privacy concerns, no raw dates (e.g. date of birth, prescription date) were provided by database administrators. Dates of medication delivery or health service provision were therefore transformed into a number of days before death. Combinations of these recoded

dates and nomenclature or ATC codes are used to determine whether certain interventions occur within a certain time period before death.

3.Since no data were provided on diagnosis in the current set of linked databases (only causes of death are available), algorithms were used to abstract diagnostic information from health care and medication prescription data. Algorithms were developed to identify people with COPD or Alzheimer's disease, based on treatments and medication received. The algorithms were developed using existing evidence [21–23] and were validated by medical experts and medical data experts from the IMA. They were then applied by the IMA, prior to the linking procedure, because data were used that were not available to the researchers; data provided to the researchers were limited to two years prior to death, while data used for identification of patients with Alzheimer's disease went back to six years before death. Combinations of the algorithmic identification of diagnosis and the causes of death (including the associated causes) can be used to identify relevant disease groups in the analyses.

Discussion

Summary of main results

In linking information from seven different datasets we managed to obtain a database that can provide information about patterns in the use, quality and costs of end of life care at the level of the full population and their associations with various clinical, socio-demographic, socio-economic and environmental factors. The process of obtaining this involved detailed identification of databases fitting the study aims, negotiation with and formal approval of three database administrators, three supervisory bodies and two national privacy commissions and eventual linking of all databases through two Trusted Third Parties (TTPs) using multiple encrypted social security numbers.

We believe that the described process can be particularly helpful to researchers in other countries in compiling similar population-level databases on end-of-life care. A number of considerations (limitations, strengths and opportunities) and recommendations can be made based on our experience.

Limitations of our study

Our study involved a systematic and thorough exploration of how several databases providing information on end-of-life care can be accessed, handled and linked into an integrated and enriched database. However, an important limitation is that linkage with information on patient-related outcomes of healthcare services, such as specific Patient Reported Outcome Measures (PROMs) was

not explored in our study. Even though PROMs are important indicators to evaluate whether increased healthcare expenditure results in better health outcomes, their inclusion in a population-level database is only meaningful if there is sufficient standardization in the measurement methodology. In Belgium, a common coding system for PROMs is lacking and would be time-consuming to perform. [24] Future efforts could be made to include PROMs at a population level.

Opportunities of the collected database

Our efforts resulted in a population-level database with detailed information about formal end-of-life care, the costs of care and demographic, socio-economic and diagnostic information on decedents. The opportunities provided by such a database to study use, quality and costs of end-of-life care are considerable. The main overall advantage is that data are population-level and therefore not subject to sample bias such as in surveys or medical records studies of selected groups of patients. Compared to primary data collection, using linked routinely collected databases as in our case is less expensive and less time-consuming. In the end-of-life care context specifically, primary data collection can be burdensome for patients and caregivers. Furthermore, in routinely collected databases, high-quality data are available on the spot, although they are not deliberately collected for research aims.

Although the linked database does not include certain types of information that are important in evaluating quality of care, such as patient-specific preferences of care, psycho-social information, patient or family reported outcomes and experiences or information about pain and symptom management or communication aspects [25], the full-population data have the potential to provide robust and population-level measures of the quality of end-of-life care using specific claims-based quality indicators. These quality indicators, e.g. mapping inappropriate end-of-life care, have been used in various studies as measures for the quality of end-of-life care [26]. If preceded by an adequate validation process, they can provide a detailed image of the quality of end-of-life care by regions or health care providers [26]. The linked database also contains data on all direct medical costs and reimbursed service and medication use, which offers opportunities to study direct medical costs and patterns in the use of specific end-of-life care for full populations. Policy measures that support palliative care include financial compensation directed towards the patient (e.g. monthly lump sum to cover additional costs for palliative home patients). Using this database, patterns in the uptake of these measures can be mapped and compared between population or pathology groups. As the linked database contains individual data, these data can be aggregated on multiple levels, which makes longitudinal, disease-, treatment- or provider-specific analyses possible. As a result, it is also possible to evaluate the influence of certain policy measures and governmental support programmes. Without the

rich population-level data we collected it would be impossible to answer these example research questions without facing major issues of reliability, generalizability, feasibility and costs.

Data allow us to follow back the treatment history and costs of those treatments up to two years before death. Although a shorter period before death may be sufficient to study several aspects of end-of-life care in specific disease groups, for other (particularly non-cancer) longer time periods are warranted. The decision to request all health care and medication data up to two years before death (irrespective of when the diagnosis was made) was also made for practical reasons as going further back would substantially increase storage and analysis requirements.

Limitations of the collected database

A limitation of these types of routinely collected population-level data is that services not covered by insurers are not included. Researchers from other countries that wish to compile a similar database need to remember that what is not covered by insurance (and hence not found in the data) may be country- or even region-specific. In Belgium, data are relatively complete, for health care services in the hospital, nursing homes and at home. Nevertheless use of certain services cannot be identified because there is no individual reimbursement (e.g. mobile hospital palliative care teams) or such reimbursement is not regulated or generalized (e.g. consultations of a psychologist). Secondly, total out-of-pocket spending is not available in the integrated database. This results in an overall underestimation of the total cost of end-of-life care. Nevertheless, administrative data are an essential source of information for studies on the financial burden of end-of-life care for the health care budget and are valuable for policymakers in informing their decisions on health care policy [8].

The linkage process is crucial in obtaining a useful population-level database. It enables the enriching of the population-level data on formal end-of-life care and the costs of that care with putative demographic, socio-economic and diagnostic information for the study of end-of-life care patterns. This allows the development of explanatory models and the provision of public health information to policy makers, for example on social differences and differences between pathology groups. It can support discussions on the organization of the health care system, based for instance on possible existing inequities.

The flip side is that the linking can create additional difficulties in the process of obtaining the data. While deterministic linking is relatively easy to complete on a technical level (even without identical unique identifiers a deterministic linking is possible based on a combination of variables), the main challenges for researchers lie in the fact that 1) several separate organizations have to be convinced to cooperate and 2) special attention needs to be given to privacy-related issues.

Databases across health and social care may not always contain a unique identifier variable, or not always contain accurate and fully available information that allows identifying unique persons. In such cases where the possibility to perform deterministic linkage is limited the method of probabilistic linking can present a solution. In this approach the likelihood of a correct linking is calculated and a linking is done when the likelihood is sufficiently large [27]. Several tools have been developed to perform this probabilistic linking [28]. Nevertheless, a lack of accurate and fully available personal identifiable information constrains a probabilistic linking method.

A final consideration for researchers who wish to have access to similar data in their country is that establishing and maintaining good relationships with database administrators is crucial. Gaining access to administrative data is an iterative process that requires a lot of preparatory work. Database administrators are the researchers' access points to the data and have all the information about internal procedures. Strict procedures need to be followed, in close cooperation with database administrators. We were able to arrange an updated dataset where data from subsequent years will be added upon availability in the same approval and agreement, which limits the time of going through all necessary permissions each time an updated dataset is needed. Since administrative data are often not gathered with the intention of research, or only for internal use, the process of making the data analysis-ready can take time. Researchers must adapt to how data are registered and stored, before they can effectively use them for research.

Conclusion

Linking and accessing various routinely collected population-level databases involves challenges but offers substantial opportunities to study patterns in the use, quality and costs of end-of-life care both in the full population and for specific diagnostic groups. This study has identified that it is possible to combine data from different databases in order to obtain a rich database for such analysis, including information about all reimbursed care and medication as well as disease, demographic, socio-economic and environmental information. While some aspects may be specific to the Belgian context, our study has a much broader application as most developed countries collect similar population-level databases. The process described in our study can be a helpful aid for researchers in these countries to compile similar data and eventually develop an international comparative end-of-life care research agenda using administrative health care data.

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Table 1 Overview of population-level databases identified as relevant for end-of-life care research

Database administrators	Database name	Population	Information provided in database
Inter Mutualistic Agency (IMA)	Population Database	Every Belgian citizen who is a member of one of the seven (compulsory) Belgian sickness funds, information in Population Database is updated twice each year from 2002 onwards	Socio-demographic characteristics (age, sex, date of death, place of residence, family composition, use of supportive measures)
	Pharmanet Database		Medication supply characteristics (substance, quantity, prescriber, expenses, refunds, delivery date)
	Medical Claims Database		Health and medical care use characteristics (quantity of use, reimbursement, supplier, supplier institution, length of treatment)
Belgian Cancer Registry	Cancer registry	Every new cancer diagnosis of Belgian residents, registered by oncological care programs and laboratories for anatomic pathology	Diagnostic characteristics (date of diagnosis, type of cancer, TNM gradation)
Statistics Belgium	Death certificate database	Every Belgian decedent with a registered death certificate	Direct and indirect causes of death (in ICD-10 codes), socio-demographics about the deceased, place of death
	Demographic dataset	Every Belgian citizen	Nationality group, household composition
	Socio-economic survey (SES) 2001 and Census 2011	Every Belgian citizen, information gathered from multiple external administrative databases using social security number (Census 2011)	Highest attained education level, occupation, housing comfort
	IPCAL dataset	Every Belgian citizen	Net income by category
Identified but not used in our research			
Belgian Ministry of Health	Minimal Hospital Dataset	Every hospital admission in non-psychiatric general hospitals	Medical, nursery and personnel data for in-hospital care

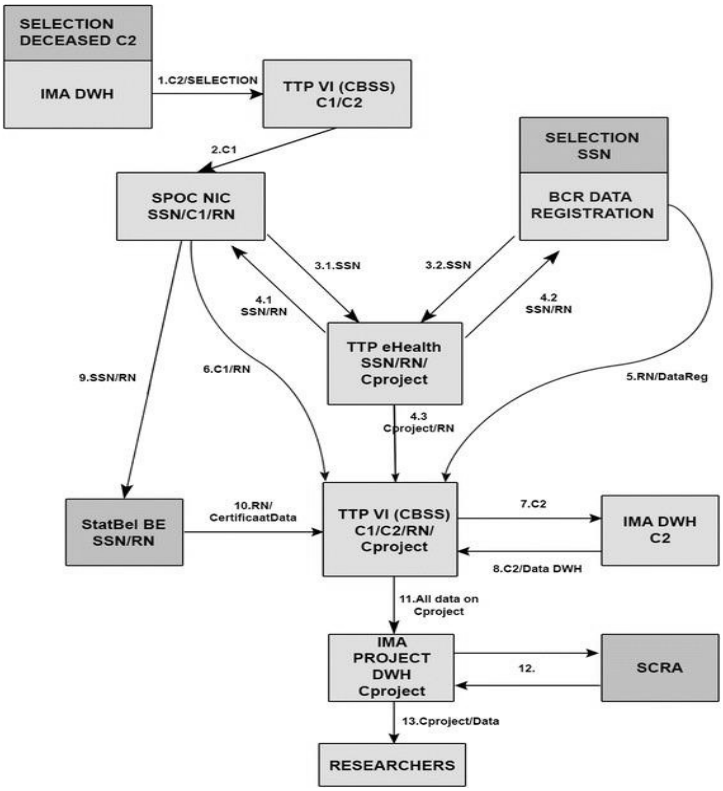

Figure 1

Step-by-step overview of linkage procedure. IMA DWH: InterMutualistic Agency Data Warehouse; TTP VI CBSS: Trusted Third Party Crossroads Bank for Social Security; SPOC NIC: Single Point of Contact National InterMutualistic College; BCR: Belgian Cancer Registry; TTP eHealth: Trusted Third Party eHealth; StatBel BE: Statistics Belgium; SCRA: Small Cells Risk Analysis; SSN: Social Security Number; C1/C2: coding 1/2; Explanatory note: The linkage procedure consisted of 13 steps (cf. arrows Fig. 1). Step 1: All cases from Belgian decedents since January 1, 2010 are selected in the IMA databases with their specific identifier coded (C2). These are then decoded (C1) by the TTP VI (CBSS). Step 2: The security officer of the National InterMutualistic College decodes the identifiers (C1) into actual social security numbers. Step 3.1: The IMA subset of social security numbers is sent by secure means to the separate TTP eHealth. Step 3.2: TTP eHealth receives the social security numbers from all cases in the Cancer Registry selected for the study (decedents since January 1, 2010). Step 4.1 and 4.2: To avoid any party from having access to both the sensitive data and the social security numbers, the established principle of random transport numbers (RN) is used. TTP eHealth assigned these RNs for the selected cases from IMA (4.1) and BCR (4.2) and provides these RNs to both data agencies in order to transmit the sensitive data safely to the TTP VI (CBSS). Step 4.3: TTP eHealth recodes the social security numbers into a final code that can be made available to the researchers (Cproject). These are sent, with the RNs as a cross reference coding, to the TTP VI (CBSS). Step 5: The selected cases and the corresponding requested data from the Cancer Registry are securely transmitted to the TTP VI (CBSS). Step 6: The selected IMA cases (but not yet the corresponding requested data) are securely transmitted to the TTP VI (CBSS). Step 7: The selected cases are transferred to the IMA datawarehouse (based on C2) so as to allow the selection of all data corresponding to these cases. Step 8: The selected cases and the corresponding requested data from IMA are securely transmitted to the TTP VI (CBSS). Step 9: The social security numbers and corresponding RNs are transferred safely to Statistics Belgium in order to allow selection of the correct cases. A social security number has already been attributed by Statistics Belgium to every case in the death certificate data (which do not contain the social security numbers) based on a deterministic linkage between the death certificate database and the national registry database based on date of birth, sex, and municipality of residence. Step 10: Statistics Belgium sends the requested data from the selected cases to TTP VI (CBSS) who links these with the data from IMA and Cancer Registry using the RNs. Step 11: The TTP VI (CBSS) recodes all data one final time based on the Cproject coding. Step 12: A small cells risk analysis is performed to minimize the risk of re-identification based on a combination of variables. Step 13: The complete linked database is stored on a separate IMA data server, which is only accessible to the researchers through a Virtual Private Network (VPN) connection with secure token.

Table 2 Considerations for researchers planning to link databases

Topics	Considerations
Exploring relevant databases	Are my research questions clear and well-defined? What data are needed to answer them?
	What is/are my study population(s)? What data are needed to identify it?
	What database(s) contains the core data and could thus be selected as a starting point?
	When a starting database is chosen, what data are lacking to fully address the research questions? Where can we find them?
	How can we establish contact with the database administrators of the databases? Obtain principal approval from all administrators (e.g. by presenting the study to the board of directors)
	What is the cost associated with each database?
Variable selection	What specific variables do we need from the selected databases to answer our research questions?
	Are the variables we want available and linkable between the different databases?
	Does the preferred selection of variables complicate the linking procedure considerably? Balance the gain in information with the increase in complexity and time.
	What is the required level of detail for each variable? Balance the preferred level with what is allowed in terms of data protection (e.g. through small cells risk analysis to determine risk of re-identification based on a combination of variables)
	Do we have sufficient storage capacity and analysis hardware to store and analyze all the data we want?
Access procedures	What ethical and privacy procedures need to be followed to link and access the selected database?
	What technical procedures need to be followed to link and access the selected databases?
Infrastructure	How will data be stored safely? Is infrastructure provided by researchers or by database administrators? What is the cost for this infrastructure?
	How will data be protected? Physical and digital protection need to be guaranteed.
	How can data be accessed in a safe and easy way? What hardware and software do we need to access and analyze the requested data?

PART II

HEALTH RESOURCE USE EVALUATION OF END OF LIFE CARE ACROSS A BELGIAN POPULATION OF COPD AND ALZHEIMER'S DISEASE DECEDENTS

CHAPTER 4: RESOURCE USE AND HEALTH CARE COSTS OF COPD PATIENTS AT THE END OF LIFE: A SYSTEMATIC REVIEW

Chapter based on:

Faes K, De Frene V, Cohen J, Annemans L. Resource Use and Health Care Costs of COPD Patients at the End of life: A Systematic Review. J Pain Symptom Manage. 2016;52(4):588-99.

ABSTRACT

Context: Patients with COPD in their final months of life potentially place a high burden upon healthcare systems. Concrete knowledge about resources used and costs incurred by those patients at the end-of-life is crucial for policymakers.

Objective: The aim of this systematic review was to describe the resources used and costs incurred by patients with COPD at the end-of-life.

Methods: We performed a comprehensive literature search in Medline, Web of Science and Econlit. We screened 886 abstracts, and subsequently reviewed 80 full-text manuscripts. Inclusion criteria were at least one type of resource use and/or cost outcome reported in adults diagnosed with COPD during an end-of-life period. Subsequently, we performed quality appraisal consistent with the ISPOR checklist for retrospective database studies and accomplished comprehensive data extraction.

Results: Nine manuscripts fulfilled the inclusion criteria. Two, five and two studies described a European, North American and Asian healthcare setting, respectively. All studies had a retrospective design and were published between 2006 and 2014. We observed a very variable resource use, an increased number of hospitalizations, ICU stay, primary care consultations and medication prescriptions, as well as a lack of utilization of formal palliative care services in end-of-life COPD patients. Specific cost items were not well described.

Conclusion: The extensive and variable resource use and related costs of COPD patients during their final months of life is caused by different elements of the healthcare system. The use of palliative care services is presumed to be effective in cost reduction at the end of life.

Keywords

End-of-life, chronic obstructive pulmonary disease, COPD, systematic review, resource use, costs

RESOURCE USE AND HEALTH CARE COSTS OF COPD PATIENTS AT THE END OF LIFE: A SYSTEMATIC REVIEW

Introduction

Chronic obstructive pulmonary disease (COPD) is an important health problem present in about 7.6% of the adult population (1). It is an irreversible disease characterized by cough, wheezing, dyspnea, a higher frequency of pneumonia and lung infections, as well as a progressive deterioration of patients' general condition. Patients with COPD also have typical comorbid diseases, such as muscle wasting, cardiovascular disease, depression, reduced fat-free mass, osteopenia and chronic infections (2).

COPD is a major cause of death with a global mortality rate of more than 3 million in 2012, which represents 6% of all deaths globally that year (3). Strikingly, the World Health Organization predicts that COPD will become the third leading cause of death worldwide by 2030 (4) and, according to the European COPD coalition, this disease is expected to increase from 270,000 deaths in Europe in 2005 to 338,000 deaths by 2030 (5). Mortality in COPD patients depends on disease severity, the number of comorbidities and the number of exacerbations in the last year of life (6-8). The presence of comorbidities and exacerbations moreover leads to increased resource use and costs, together with the severity level of disease (9-11). As such, COPD patients in their final months of life may put a high burden on different health care systems. To date, there is only a small number of literature analyzing resource use and costs in end-of-life COPD patients. Nevertheless, knowledge about the impact of resources and costs used by COPD patients at the end-of-life is crucial for national and international policymakers. It is thereby important to understand that the unpredictability regarding the prognosis of COPD and the use of life-sustaining treatments in COPD patients poses different challenges in end-of-life decision-making when compared with those of, for instance, the better studied domain of cancer (12).

We conducted a systematic literature review to describe the existing evidence about resource use and costs of COPD patients in their final months of life.

Methodology

Search strategy and inclusion criteria

The aim of this review is to describe resource use and associated costs towards the end-of-life in COPD patients. We performed a comprehensive literature search in Medline, Web of Science and Econlit. We combined search terms to identify resource use and costs (i.e., costs, health expenditures, health care costs, economics, terminal cost, palliative cost, terminal care economics, health resources, health care utilization, health care resource utilization) in end-of-life period (i.e., end of life, terminal, palliative, end

of life care, terminal care, hospice care, palliative care, terminally ill, end-stage COPD, last 2 years, last year, advanced COPD) of COPD patients (i.e. chronic bronchitis, chronic obstructive pulmonary disease, pulmonary emphysema, COPD, chronic obstructive airway disease, COAD, chronic airflow obstruction, end-stage lung failure, end-stage lung disease). Despite our extended search strategy, we only found a small number of eligible studies. Hence, we decided to extend the "end-of-life period" by adding the search terms 'severe', 'very severe', 'stage 4' and 'GOLD stage 4' since GOLD stage 4 of COPD is associated with a higher mortality rate (13) and severe as well as very severe COPD patients are more likely to die due to respiratory failure (14). Additionally, included studies were screened for back-references to detect potential studies not-identified through our initial search strategy.

Study identification occurred as given in figure 1. Screening of titles and abstracts of studies identified during the literature search was executed. Subsequently, the full-text of potentially relevant articles was evaluated. Studies were included for data extraction if they complied with the following criteria: (1) study population of adults diagnosed with COPD, (2) presence of a focus on an end-of-life period, and (3) description of resource use and/or costs during the end-of-life period. We excluded studies (1) in which COPD was not mentioned, (2) without a specific description of an end-of-life period, and (3) in which neither resource use nor costs were reported. In a 25% random sample of initially selected studies the selection based on title and abstract was performed by two reviewers (KF and LA) who compared the results of their selection and discussed the reasons for discrepancies.

Studies fulfilling our inclusion criteria underwent comprehensive quality appraisal and data extraction. The following data were extracted:

1. General study characteristics (*e.g.*, year of publication, setting, objectives and study design),
2. Baseline characteristics (*e.g.*, age or age at death, gender and number of comorbidities),
3. Sample characteristics (*e.g.*, sample size, data source),
4. Duration of the end-of-life period,
5. Resource utilization during the end-of-life period [*e.g.,* interventions (inpatient and outpatient), physician visits, hospital admissions (i.e., admissions at ER, ICU and a ward), drugs, palliative care services, nursing home, hospice care, home care],
6. Cost perspective of economical evaluation and costs of COPD patients during the end-of-life period,
7. Main findings of resource use and/or costs during end-of-life in COPD patients.

Since all selected studies appeared to have retrospective designs, quality appraisal was executed by two reviewers (KF and VDF) consistent with "A checklist for retrospective database studies – ISPOR" (15). This checklist was developed to evaluate the quality of studies using health-related retrospective

databases in which disease registries and national survey data are registered. This checklist consists of 27 questions covering five issues: (1) data source, (2) research design, (3) study population and variable definitions, (4) statistics, and (5) discussion and conclusion. It should be mentioned, however, that not each question of this checklist was applicable to all studies included in our review. Questions concerning a treatment effect were out of scope.

Results

Our literature search, including the expanded search, resulted in 1224 studies. After removing duplicates, 886 studies were screened on title and abstract. Thereof, 80 were found potentially relevant for full-text screening, which resulted in eight eligible studies. Through using the back-reference strategy, one extra study was found.

Study characteristics

Study characteristics are described in Table 1. All included studies had a retrospective design and were published between 2006 and 2014. Six studies described resource use alone, two mentioned resource use as well as costs and one focused specifically on drug expenditures at the end-of-life. Two, five and two studies described a European, North American and Asian healthcare setting, respectively.

Decedents were mainly retracted from administrative databases, medical records or hospital medical records in which they were identified as COPD patients according to the International Classification of Disease codes or based on linked death certificates where cause of death was described as COPD.

Seven studies compared decedents with COPD as an underlying cause of death with non-COPD decedents. The underlying cause of death of those non-COPD decedents was mostly cancer. None of the included studies mentioned GOLD stages of COPD at time of death and six studies included co-morbidities of COPD patients at the end-of-life.

Six studies mentioned explicitly the number of male or female patients suffering from COPD, but only two of these described differences in resource use between genders. Two studies reported no information at all about gender.

Seven studies mentioned a specific timeframe of the end-of-life period which ranged between the last three years and the last two weeks of life.

As shown in Table 2, all studies reported outcomes related to resource use during end-of-life. Eight studies focused on outcomes related to hospital use such as number of hospital admissions, length of stay and ICU admissions. Five studies used nursing home, home care and physician visits as outcome. Four studies included outcomes related to drugs *(e.g.*, Oxygen, Opioids, Benzodiazepines or Sedatives)

and four studies reported specific interventions (*e.g.*, invasive or non-invasive ventilation and CPR) in the last months of life. Only one study described hospice use as outcome. Finally, four studies did describe outcomes related to palliative care in end-of-life of COPD patients.

Costs were only mentioned in three studies. Thereby the focus was not on the cost of COPD as such but on total health care costs incurred by COPD decedents during their last period of life (*e.g.*, last years, months, weeks).

Resource use in end-of-life COPD patients

Apart from the end-of-life period, COPD patients have a very variable use of healthcare resources ranging from non-COPD-related hospital admissions to a large number of COPD-related admissions over a relatively long time period (16). A majority of hospitalizations are for other reasons than COPD. Mostly, underlying diseases are the common diseases among elderly or diseases related to smoking (16). The main reasons for admission are acute exacerbation of COPD or a lung infection and complications of other chronic comorbidities (17). On average, the use of hospital care increases almost exponentially as the end of life approaches (16).

Differences in resource use in COPD patients during their last months of life are due to the presence of comorbidities and exacerbations at the end-of-life. Andersson et.al. (2006) studied 2266 Swedish individuals who died from COPD and who were admitted to a hospital during their last 13 years of life. Up to 50% of their hospital admissions were for other reasons than COPD (16). Moreover, the study by Goodridge et.al. (2008) shows that 68.3% of COPD patients have two or more comorbidities during their last 12 months of life (18). The likelihoods of receiving home care services (OR = 0.74, 95% CI=0.56-0.97) and specialized home care services such as palliative care (OR = 0.29, 95% CI=0.19-0.45) and physiotherapy (OR = 0.09, 95% CI=0.03-0.25) are significantly lower for persons in rural locations than for those in urban settings (19). (Table 1)

Hospital use in end-of-life COPD patients. Results of a Danish nationwide study, conducted by Husted et.al. (2014) show that during the last year of life, COPD patients have a median number of two hospitalizations with a median length of stay of 14 days (20). According to the study by Au et.al. (2006) among Medicare-eligible veterans about 61.3% of 1490 COPD patients are hospitalized during the last six months of life with a median length of stay of 14 days as well (21). Teno et. al. (2013) found that among 91,517 Medicare beneficiaries who died of COPD in 2009, 83% was hospitalized during the last 90 days of life, 20% had three or more hospitalizations during the last 90 days of life, and almost 40% had an ICU stay in their last month of life (22). According the results by Au et.al. (2006) and Chou et.al. (2013) median length of stay at an ICU varies between five and eight days (17, 21) with a median

ventilator support of five days (17). During the last six weeks of life, COPD patients were frequently admitted for an unrelated condition (21).

Use of ventilation is particularly prevalent in COPD patients at the end-of-life. According to Husted et.al. (2014) 14% of COPD patients receives invasive ventilation during the last 3 years of life and 24.4% receives non-invasive ventilation during the last six months (20). Furthermore, results of the study by Teno et.al. (2013) show that of the 91,517 COPD deaths 13% was set on mechanical ventilation during the last 30 days of life (22). Subsequently, the study by Lau et. al. in Hong Kong shows that nearly 50% of 242 in hospital COPD deaths are initiated on either invasive (10.3%) or non-invasive (38.4%) ventilation in their last two weeks of life (23). Husted et.al. (2014) suggest that non-invasive ventilation is an indicator of approaching the last six months of life (20).

Palliative care services. According to a comparative study between cancer and non-cancer deaths in Hong Kong conducted by Lau et. al. in 2010 only 3.6% of COPD patients received palliative care services during their last six months of life (23). Furthermore, the study by Goodridge et.al. (2008) shows that very few patients who died with COPD utilized palliative care services that are available in acute care hospitals (5.1%) or home care settings (2.8%) (18).The authors suggest that their results indicate that palliative care services are not well-utilized for those dying from COPD (18). Lack of utilization of formal palliative care services means that a majority of COPD patients does not benefit from symptom management expertise and a consistent approach of a palliative care interdisciplinary team at the end of life (18).

General practitioner contacts. According to the study conducted by Husted et.al. (2014) 46.5% of Danish COPD patients have seven or more contacts with a general practitioner during the last 3 years of life. Although the number of contacts with a general practitioner remains stable when approaching end-of-life, COPD patients have a number of five consultations until one year before death (20). Furthermore, results of Au et.al. (2006) show that 77.5% of 1490 patients who died of COPD between April 1997 and September 2001 have at least one primary care visit in the last six months of life (21).

Drug use in end-of-life COPD patients. Drug use during the last year of life differs among causes of death and socio-demographic characteristics (24). Specifically, during the last year of life an increasing number of comorbidities results in a 60% increase in prescriptions for those with five or more comorbidities and women have higher levels of mean medication use than man (39.0 vs 34.8) (24). According to Fahlman et.al. (2006) who described prescription drug spending for Medicare and choice beneficiaries in the last year of life, COPD patients had 47.2 prescriptions in the last year of life and increases as they approach end-of-life (24). According to Au et.al. 25% and 17% of COPD patients in their last six months of life receive a prescription for an opiate or benzodiazepine respectively. (21)

Differences in end-of-life resource use between cancer and COPD patients.

As compared with cancer patients, several differences in healthcare use can be found (table 3). Goodridge et.al. (2008), who compared resource use between COPD patients and lung cancer patients during the last 12 months of life, found that COPD patients were less likely to be hospitalized, were hospitalized less often and had shorter length of stay than those with lung cancer and found no differences in the number of physician visits (18). Nevertheless, Au et.al. (2006) suggest that, compared with COPD patients during the last six months of life, lung cancer patients were more likely to have been hospitalized (61.3% for COPD vs 68.6% for lung cancer), nevertheless, COPD patients were more admitted to an ICU (32.6% for COPD and 18.3% for lung cancer) with more ICU days (5 for COPD and 3 for lung cancer). During the last six months of life, 77.5% of COPD patients and 70.2% of lung cancer patients had, respectively, 2.36 and 1.87 primary care visits (21).

The study by Lau et.al. (2010), comparing non-cancer and cancer deaths, shows that COPD patients at the end-of-life have less DNR orders in place (84.3% vs 95.6%) and more CPR performed (14.5% vs 4.4%) than cancer patients (23). According to Au et.al. (2006) COPD patients also have less prescriptions for opiates (25% vs 49%) and benzodiazepines (17% vs 26%) as compared with lung cancer patients (21). Results of Au et.al. (2006) indicate that end-of-life care in COPD patients is more consistent with prolongation of life than palliation (21).

Since end-of-life care in COPD patients is focused on prolongation of life, end-of-life COPD patients receive more invasive interventions . According to Chou et.al. (2013) in Taiwan most common invasive procedures used in end-of-life care of COPD patients are feeding tube placement (93%), Foley catheter insertion (86%) and, invasive ventilation (52%). Over 33% of COPD patients also receive computed tomography examinations and around 10% receive bronchoscopy or panendoscopy during their end-of-life (17).

Costs in end-of-life COPD patients

Due to heterogeneity in the reported costs a direct comparison between the studies is not opportune. Nevertheless some findings can be summarized.

Au et.al. (2006) found that COPD patients during their last six months of life have a mean total cost of $34,911 ± $39,791 (median: $22,495, Interquartile range [IQR: $11,232-$39, 792]), with a mean outpatient cost of $2422 ± $2767 and a mean inpatient cost of $31,935 ± $39,739. If compared with lung cancer patients mean total cost of COPD patients in their last six months of life is $8793 higher than mean total cost of lung cancer patients ($26 118). This significant difference ($p<.001$) is mainly attributed to acute hospital use, more specifically an increased ICU admission rate in COPD patients

(21). Despite of a low use of hospice care and palliative care services, mean daily costs of COPD patients who receive palliative care are significant lower ($250) than mean daily costs of COPD patients who do not receive palliative care ($440) during their last year of life ($p < .001$) (17).

Drug expenditures of COPD patients in the last year of life are significantly correlated with female gender and higher number of comorbidities and are highly dependent on socio-demographics, insurance characteristics and disease state. According to Fahlman et.al. (2006) COPD patients have a total drug expenditure of $2141, including high out-of-pocket expenses ($753) in their last year of life (24).

Discussion

This systematic review details studies that characterize and quantify health resource use and related costs incurred for the care of COPD patients approaching life's end. Despite some heterogeneity in the findings, several common observations can be made. First, patients who died from COPD have a very variable use of the healthcare system, ranging from non-COPD-related hospital admissions to a large number of admissions because of other concomitant diseases (16-18, 21, 23). Secondly, decedents with COPD utilize less palliative care services that are available in acute care hospitals or home care settings. Finally, COPD patients were more demanding on the public health care system and receive more invasive interventions in the last months of their lives.

We highlighted the extensive use of acute care in COPD patients at the end-of-life as well as the impact of this care on health systems. More specifically, acute hospital visits, ICU admissions, physician visits and use of invasive interventions and medication were found to be the key drivers of resource use and costs of terminal COPD patients. The extensive use of resources in the final months of life in COPD patients is mainly caused by concomitant diseases related to advanced age or smoking. The presence of two or more comorbidities increases hospital use and having more than 5 comorbidities increases medication prescriptions by 60% (24).

Use of invasive ventilation, low use of analgesics and invasive treatment showed that end-of-life care in terminal COPD patients is focused on prolonging life. Although COPD patients have similar clinical symptoms and needs as cancer patients, COPD patients receive more medical care aiming at prolonging life, receive little symptom relief management and have little access to palliative care (23, 25, 26).

Our findings may suggest that providing palliative care to patients with COPD may improve end-of-life care, while reducing costs by minimizing unwanted ICU care. A possible explanation for low use of palliative care in COPD patients may include different factors such as provider failure to recognize the imminent death of patients with COPD, the perception that palliative care services are available only to

cancer patients, the assumption that the provided care is sufficient, or the belief that a terminal COPD patient already received palliative care elsewhere, such as in a long term care facility (18).

Given that the use of a specific intervention is affected by disease stage, the individual's functional status, and the best evidence available at that time, not every intervention can be labeled as futile care.

Specific cost items were not well described in the included papers. As such, we could not derive specific cost drivers and influencing factors. According to the study by Simoni-Wastila et al. (2009) costs in COPD patients were mainly due to long term care, pharmacy and inpatient costs (27). We suggest that costs of end-of-life care in COPD patients should systematically be described by specific resource so that understanding of specific cost drivers in end-of-life care of COPD patients could be improved. Knowing specific cost drivers in end-of-life care could encourage policymakers to establish cost-effective end-of-life care in terminal COPD patients.

Limitations

Despite our comprehensive search and expanded search strategy, we only found nine articles fulfilling the inclusion criteria. Most studies were performed in a non-European setting which makes it difficult to generalize our findings to a European context. While two studies described resource use and costs in a European setting, the study samples were derived from national administrative databases. Despite different healthcare systems described in the included studies, some similar findings of resource use in terminal COPD patients could be found. Due to different healthcare financing systems, combining or summarizing costs was impossible. Nevertheless, described costs showed the impact of palliative care on costs in end-of-life COPD patients.

It should be noted that all included studies used a retrospective design. Using a retrospective design has several disadvantages such as an absence of data about potential confounding factors if the data was recorded in the past. However retrospective designs have also several advantages. Firstly, they allow for easy identification of cohorts of relevant patients. Secondly, a retrospective approach allows all patients who come to the end-of-life to be studied. Finally, retrospective designs facilitate the development of measures of real-life performance (28). Such performance measures may become key elements in benchmarking quality of end-of-life care.

Conclusion

This review indicates that the terminal disease trajectory for COPD patients is associated with a high number of resource use and related costs in the final months of life. Our findings also seem to suggest that end-of-life care for COPD patients is focused on prolonging life, with a prevailing tendency towards aggressive care. As a result, end-of-life care of terminal COPD patients causes an excessive economic

burden on healthcare budgets. Therefore, and particularly keeping in mind the projected rise in cases over the coming years, rational improvements in end- of-life care for people with COPD are essential, both from a quality and a cost perspective.

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Figure 1. Process of study inclusion

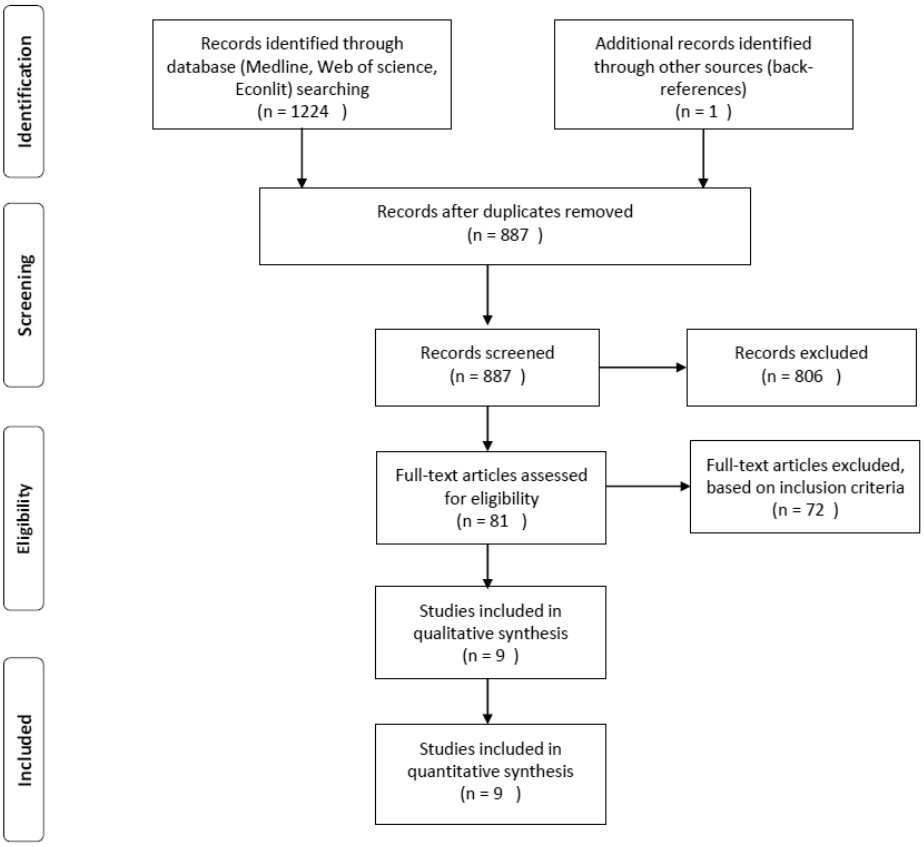

Table 1. Summary tables of included studies

Study (year)	Country	Study design	End-of-life period	No of patients		COPD patient characteristics	Source	Key findings resource use	Key findings costs
				COPD[1]	non-COPD				
Lau et. Al. (2010) (23)	China	Retrospective study	Last 6 months - last 2 weeks	242	cancer (n=183); CRF[2] (n=239); CHF[3] (n=175)	Mean no. Comorbidities (SD): 1.8 (1.2)[4] Male: female ratio: 3:1	Hospital records	*Last 6 months:* • COPD patients on non-invasive ventilation: 45.5%[4] • COPD patients on invasive ventilation: 9.9%[4] • COPD patients received palliative care: 3.6% [4] • Cancer patients received palliative care: 79.2%[4] *Last 2 weeks:* • COPD patients on non-invasive ventilation: 38.4%[4] • COPD patients on invasive ventilation: 10.3%[4]	
Andersson et. Al. (2006) (16)	Sweden	Retrospective study	Not specified	2331	-	Average age of death: 78.6 for men and 77.2 for women.	Swedish Inpatient Register and Swedish Mortality Register	*Hospital admissions 13 years before death:* • All causes : 28,189 (n=2266) • COPD as underlying or contributing cause of admission: 14,440 (n= 1914) • COPD as underlying cause of admission: 8815 (n=1530)	

[1] Chronic obstructive pulmonary disease
[2] Chronic renal failure
[3] Chronic heart failure
[4] P<.001

Study (year)	Country	Study design	End-of-life period	No of patients		COPD patient characteristics	Source	Key findings resource use	Key findings costs
				COPD [1]	non-COPD				
Goodridge et. Al. (2008) [18]	Canada	Retrospective cohort study	Last 12 months	615	Lung cancer (n=483)	*Co-morbidity (last 12 months of life):* • 0-1 condition: 31.7%[1] • 2 or more conditions: 68.3% Age groups COPD: ≤ 70 years: 11.5%[1] 71-79 years: 25.6% 80-85 years: 23.1% >85 years: 36.9% Male: 59% Female: 41%	Administrative health data	*Palliative care use* • Within hospital : 5.1%[1] • From home care : 2.8%[1]	
Goodridge et. Al. (2010) [19]	Canada	Retrospective cohort study	Last 12 months	615	Lung cancer (n=483)	Age: 77 Male: 57% Urban: 24.1% Rural: 28.2% *Comorbidities:* 0-1 comorbidity Urban: 45.4% Rural:49.1% ≥2 comorbidity Urban: 54.6% Rural: 50.9%	Administrative health data	*Type of home care last 12 months of life (rural vs urban)* • Palliative care : OR=0.29 (95% CI=0.19-0.45) • Physiotherapy : OR=0.09 (95% CI=0.03-0.25) • Any home care : OR=0.74 (95% CI=0.56-0.97)	

[1] P < .05

Study (year)	Country	Study design	End-of-life period	No of patients		COPD patient characteristics	Source	Key findings resource use	Key findings costs
				COPD [1]	non-COPD				
Teno et. Al. (2013) [22]	United States	Retrospective cohort study	Not specified	(2000) n=79 284; (2009) n=91 517	Cancer (2000) n=49735; Cancer (2009) n= 55362; Dementia (2000) n=59065; Dementia (2009) n= 67861	Mean age (2000): 80.2 (2009): 81.4 Female (2000): 49.6%, (2009): 56.2%	Medicare denominator file	*Hospitalisation (2009)* • Hospitalisation last 90 days : 82.8% (95% CI: 82.6-83.1) • ≥ 3 hospitalisations last 90 days : 19.1% (95% CI : 18.8-19.3) • ICU last 30 days : 39.9% (95% CI : 39.6-40.2) *Mechanical ventilation last 30 days:* 13% (95% CI: 12,7-13,2)	
Au et. Al. (2006) [21]	United States	Retrospective cohort study	Last 6 months	1490	Lung cancer (n=459)	Mean age: 71.7 Charlson index: 3.14 ± 2.30 [1]	Medical Records	*VA inpatient resource use (last 6 months)* • Hospital admission: 61.3% • Hospital days, median (IQR) : 14 (6-28) • ICU utilization, No. (%) : 32.6%[1] • ICU days, median (IQR) : 5 (2-11)[1] *Outpatient medication last 6 months:* • Opioids : 25% [1] • Benzodiazepines : 17% [1]	*Costs in last 6 months of life, $* • Mean outpatient costs ±SD : 2422 ± 2767 [1] • Mean inpatient costs ±SD : 31 935 ± 39 739 [1] • Mean total costs ±SD : 34 911 ± 39 791 [1]

[1] P < .001

Study (year)	Country	Study design	End-of-life period	No of patients		COPD patient characteristics	Source	Key findings resource use	Key findings costs
				COPD [1]	non-COPD				
Chou et. Al. (2013) [17]	Taiwan	Retrospective study	Not specified	91 (palliative care n=17; non-palliative care n=74)	-	*Median age:* • *All: 82.1* • *Non-palliative: 81.9* • *Palliative: 83.8* *Male:* • *All: 73.6%* • *Non-palliative: 75.7%* • *Palliative: 58.8%* *Mean no. of comorbidities* • All: 2.3 • Non-palliative: 2.3 • Palliative: 2.4	Medical Records and Bureau of National Health Insurance	*Medical care utilization (all patients, n=91)* • *Median days hospital stay (range) 16 (1-61)* • *Median days of ICU stay (range) : 8 (1-42)* • *Median days of ventilator usage (range) : 5 (0-42)* *Invasive procedures* • *Feeding tube : 93%* • *Foley catheter : 86%* • *Invasive ventilation : 52%* • *Computed tomography : 35%* • *Bronchoscopy : 9%* • *Panendoscopy : 11%*	*Cost between COPD patients with and without palliative care: Total medical cost, $, (range) (P=.12)* • *Palliative care: 4509 (1883-17033)* • *No palliative care : 3918 (324-21867)* *Mean daily cost, $, (range) [1]* • *Palliative care : 250 (128-446)* • *No palliative care : 444 (118-1479)*

[1] P < .001

Study (year)	Country	Study design	End-of-life period	No of patients		COPD patient characteristics	Source	Key findings resource use	Key findings costs
				COPD [1]	non-COPD				
Fahlman et. Al. (2006) [24]	United States	Retrospective study	Last year and last month	401	Cancer (n=1431), Dementia (n=154), Diabetes (n=322), Heart condition (n=1484), Kidney (n=87), Stroke (n=447), other (n=332)	Female: 48.9% *Age at death:* • 65-74: 31.9% • 75-79: 25.8% • 80-84: 19.7% • 85-89: 16% • 90+ : 6.5% *Charlson comorbidities* • 0-1 : 10,7% • 2-4 : 72,1% • 5+ : 17.2%	Prescription claims and Centers for Medicare and Medicaid Services denominator file and 1990 Census	*Last year of life* • Mean number of prescriptions : 47,2 (95% CI: 43,7-50,7) • Female : 39.0 (95% CI: 37.8-40.3) • Male : 34.8 (95% CI: 33.7-35.9)	*Medication costs* *Last month of life, $* • Mean out of pocket by user : 97 (95% CI : 84-109) • Mean amount paid by insurer : 99 (95% CI : 80-115) • Mean amount claimed per user by pharmacy : 259 (95% CI : 228-289) *Last year of life, $* • Mean out of pocket by user : 753 (95% CI : 678-829) • Mean amount paid by insurer : 835 (95% CI : 737-933) • Mean amount claimed per user by pharmacy : 2141 (95% CI : 1960-2321)
Husted et. Al. (2014) [20]	Denmark	Retrospective study	Last 3 years	3013	Lung cancer (n=3635)	Average age: 77.3 Male: 44.3% Female: 55.7%	Danish health registers	*Hospital admissions during the last year of life* • Number of hospitalisations (IQR): 2 (3) • Days with hospitalisation (IQR): 14 (25) *Last 6 months of life* • Non-invasive ventilation: 24.4% • Invasive ventilation : 13.9% *Last 3 years of life* • No of contacts with general practitioner: 0 contacts : 10.2% 1-6 contacts : 43.3% 7 or more contacts : 46.5% Median number (IQR) of contacts last year before death : 5 (8)	

Table 2. Aspects of resource use in COPD patients at the end-of-life described in included studies

Aspects of resource use	N of studies	References
Hospital use		
Hospital admissions	7	(16, 18-23)
Length of stay	8	(16-23)
ICU admissions	4	(17, 21-23)
Nursing home	3	(18, 19, 22)
Home care	2	(18, 19)
Physician visits	4	(18-21)
Drugs	4	(17, 21, 23, 24)
Interventions		
NIV	3	(17, 20, 23)
IV	4	(17, 20, 22, 23)
CPR	2	(17, 23)
Hospice	1	(22)
Palliative care services	3	(18,19,23)

Table 3. Resource use in end-of-life among patients with COPD and Cancer

Study (Year)		COPD	Cancer	P-value
Goodridge et.al. (2008) (18)	Number of patients	602	433	-
	Median number physician visits (IQR) [2]	28 (28)	27 (22)	-
	% with any hospitalization (last 12 months)	80.4	94.2	.05
	Median average length of stay (IQR) [2]	5.71 (9,58)	7 (8)	.05
Au et.al. (2006) (21)	Number of patients	1490	459	-
	% Primary care visits [1]	77,5	70,2	.001
	Mean no. primary care visits ±SD [1]	2.36±2.64	1.87±2.36	<.001
	No hospital admissions (%)[1]	913 (61.3)	315 (68.6)	.004
	No ICU utilization (%) [1]	486 (32.6)	84 (18.3)	<.001
	Median ICU days (IQR) [1]	5 (2-11)	3 (1-6)	<.001
	Opioids (%) [1]	25	49	<.001
	Benzodiazepines (%) [1]	17	26	<.001
Lau et.al. (2010) (23)	Number of patients	242	183	-
	No of patients CPR performed (%)	35 (14.5)	8 (4.4)	-
	No of patients DNR order in place (%)	204 (84.3)	175 (95.6)	-
	Mean (SD) no of ICU admissions [1]	0.2 (1.0)	0.04 (0.3)	-

[1] Last 6 months of life ; [2] Last 12 months of life

CHAPTER 5: RESOURCE USE OF COPD PATIENTS AT THE END OF LIFE

Chapter based on:

Faes, K., J. Cohen, and L. Annemans. Resource use during the last 6 months of life among COPD patients: a Population level study. J Pain Symptom Manage. 2018 Jun 11.

ABSTRACT

Context Chronic obstructive pulmonary disease (COPD) patients often have several comorbidities, such as cardiovascular diseases (CVD) or lung cancer (LC), which might influence resource use in the final months of life. However, no previous studies documented resource use in end-of-life COPD patients at a population level, thereby differentiating whether COPD patients die of their COPD, CVD or LC.

Aim To describe end-of-life resource use in people diagnosed with COPD and compare this resource use between those dying of COPD, CVD and LC.

Methods We performed a full-population retrospective analysis of all Belgian decedents. Those who died of COPD were selected based on the primary cause of death. Those who died with COPD but with CVD or LC as primary cause of death were identified based on a validated algorithm expanded with COPD as intermediate or associated.

Results Resource use among 13.086 patients dying of or with COPD was studied. Those who died of COPD received less opioids, sedatives and morphine; used less palliative care services; and received more invasive and non-invasive ventilation as compared to the other 2 groups. Those who died of LC had more specialist contacts, hospital admissions and medical imaging as compared to those who died of COPD or CVD. Those who died of CVD used less palliative care services when compared to those who died of LC and had a comparable use of hospital, ICU, home care, opioids, sedatives and morphine as those who died of COPD.

Conclusion The presence of lung cancer and cardiovascular diseases influences resource use in COPD patients at life's end. We recommend that future research on end-of-life care in COPD systematically accounts for specific comorbidities.

Keywords End-of-life care; COPD; Resource use; Full-population; Lung cancer; Cardiovascular diseases; Comorbidities

RESOURCE USE DURING THE LAST 6 MONTHS OF LIFE AMONG COPD PATIENTS: A POPULATION LEVEL STUDY

Background

Chronic obstructive pulmonary disease (COPD) is an important health problem, present in about 7.6% of the adult population and is responsible for an increasing proportion of deaths worldwide (1). Although COPD is seen as a chronic life-limiting disease, the scarce data for COPD patients seem to indicate that many do not receive appropriate end of life care (2). Compared to patients with a diagnosis of lung cancer, who have clinical symptoms that are often comparable to those of COPD patients, the latter relatively use more intensive resources at the end of life (2). Part of this difference is due to the prognostication of death in COPD patients: it is usually more difficult to predict the end of life phase due to the slower decline and less-recognizable end-stage phase (3, 4).

Moreover, since COPD patients often have several comorbidities, such as heart failure, ischemic heart disease, pulmonary hypertension, metabolic syndrome and diabetes, COPD-related mortality is probably underestimated because of the difficulties associated with identifying the precise cause of death (5, 6). In particular, cardiovascular diseases and lung cancer are the leading causes of death in those diagnosed with COPD (7-12), mainly because the population with COPD consists to a large extent of former or active smokers and smoking being a known risk factor for lung cancer and cardiovascular diseases. As the clinical course of lung cancer is more predictable and marked by a lower use of health care services and less aggressive treatment at the end of life than in cardiovascular diseases or COPD without lung cancer, it is likely that end-of-life care and resource use in the final months of life within the population of COPD patients will vary strongly depending on what comorbidities they have.

No previous studies have described resource use in end-of-life COPD patients at a population level, thereby differentiating whether COPD patients die of their COPD, of cardiovascular diseases or of lung cancer, which likely correspond to different dying trajectories. This differentiated evaluation of end-of-life resource use could result in important insights to provide appropriate end-of-life care such as palliative care in the whole population of persons diagnosed with COPD.

This population-based retrospective study aims to describe end-of-life resource use in people diagnosed with COPD and compare this resource use between those dying of COPD, those diagnosed with COPD but dying of cardiovascular diseases and those diagnosed with COPD but dying of lung cancer. The following specific research questions are addressed:

1. Which resources and with what intensity are used during the last 6 months of life of COPD patients?

2. How does resource use and intensity differ between those COPD patients who died of COPD, of cardiovascular diseases and of lung cancer?

Materials and methods

The present study is a retrospective, full population analysis of Belgian decedents in which resource use during the last six months of life is compared between (1) those who died of COPD, (2) those who died of cardiovascular disease and with COPD and (3) those who died of lung cancer and with COPD during 2012.

Data sources

A total of seven population-level databases were linked into one common database. The data include healthcare data retrieved from the Intermutualistic Agency (IMA), and sociodemographic, socio-economic and death certificate data retrieved from Statistics Belgium. A more detailed description of these databases and the procedures for obtaining and linking these data is presented elsewhere (13). The IMA manages the databases that include all reimbursement data of health care consumption from all Belgian healthcare insurance organisations. Since health insurance is legally mandatory in Belgium, reimbursement data of all legal residents are available. From IMA three databases are linked: (1) a population database containing socio-demographic data of all insured persons; (2) a health care database containing health care use and cost (of reimbursement) data; and (3) a pharmaceutical database containing delivered medication and related cost data. These were linked with socio-demographic, socio-economic and death certificate data from Statistics Belgium. Statistics Belgium manages the national demographic database, derived from the population registry (14) and data from the Socio-Economic Survey 2001 and Census 2011, nationwide full population surveys based on the tradition of population count (15). The demographic database contains information about the highest educational level attained, the last held occupation (as a measure of socio-economic position) and housing characteristics. Finally a database containing fiscal data (i.e. net taxable household income), also managed by Statistics Belgium, was linked to allow additional socio-economic insights.

Study population

The study population consists of all persons who died with or of COPD in Belgium during the year 2012. Patients who died of COPD were selected based on the primary cause of death as recorded on the death certificate (ICD10-code: J41-44). Those who died with COPD and of cardiovascular diseases or lung cancer (further described as 'Subgroup dying of Cardiovascular diseases' or 'Subgroup dying of lung cancer') were first identified as dying with (i.e. having a diagnosis of) COPD based on a validated

algorithm using medication data from 2 years before death. This validated algorithm was based on existing evidence on algorithms (16-18) to identify different therapeutic options in COPD and subsequently discussed with four experts in COPD treatment and administrative healthcare databases which resulted in an adapted version of the algorithm. The adapted version of the algorithm was finally discussed with healthcare experts in COPD treatment and resulted in the final algorithm based on prescriptions with ATC-code of R03BB04, R03BB05, R03BB06, R03BB07, R03AL04, R03AL03, R03AK06, R03AK07, R03AK08, R03AK10, R03AK11 and the exclusion of a prescription with ATC-code of R03DC01, R03DC03 in order to exclude those suffering from asthma or a COPD-asthma overlapping syndrome.

This algorithm was further expanded with those deaths for which COPD was recorded on the death certificates as an intermediate or associated cause of death but not the underlying (=primary) cause of death (supplemental file 1). The underlying cause of death was then used to identify those dying of cardiovascular diseases (ICD10-codes: I00-I99) or lung cancer (ICD10-codes: C33, C34).

Measures

The primary study outcome was to describe resource use in the last six months of life of COPD patients.

In the IMA healthcare and pharmaceutical databases, health care activities and medication data are coded respectively as nomenclature codes for reimbursement purposes and Anatomical Therapeutic Chemical Classification (ATC) codes. In order to answer the research question, specific nomenclature numbers were interpreted and aggregated into meaningful resource use, procedures and medication categories.

Measures for resource use during the last six months of life included hospitalization, emergency room (ER), intensive care unit (ICU), palliative care unit, one-day-care, nursing home and skilled nursing facilities, home care, palliative home care, and contacts with general practitioner, specialist and physiotherapist.

Measures of specific procedures and medication associated with the treatment or end of life phase included the use of medical equipment.

Patient characteristics included age at death, sex, cause of death, urbanization level of the municipality of residence, educational level , household type, housing comfort and net taxable income.

The period of 180 days before death was defined for analysis purpose based upon the dates related to the specific nomenclature numbers or medication prescription dates.

Statistical Analysis

To investigate potential differences we compared patient characteristics and resource use of patients who died of COPD and patients who died with COPD using chi square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Resource data were analysed using a general linear model for continuous variables and logistic regression for binary variables, with dying of vs with COPD as an independent variable and controlling simultaneously for various covariates (age, gender, household type, attained educational level and urbanisation level of the municipality of residence). We set the significance level at $p \leq .05$ to address hypothesis testing.

We calculated odds ratio estimates for dichotomous outcomes and maximum likelihood estimates for continuous outcomes of each given type of resource use for those who died with COPD and of cardiovascular disease and those who died with COPD and of lung cancer compared to those who died of COPD during a 180 days period before death. All analyses were made using SAS version 9.3 for the analyses.

Results

In 2012, 109,034 people died in Belgium of which 107,847 (98.91%) were insured with one of the seven sickness funds and hence had data about reimbursed health care and medication; for 1,187 deaths, mainly Eurocrats, NATO employees, those working abroad and homeless or illegals, such data was not available.

Characteristics of the studied populations

A total of 23,376 persons (21.7 % of all deaths) died with a diagnosis of COPD. Of these 19,504 (83.4%) died with but not of COPD and 3,872 (16.6%) died of COPD (Table 1). Among those who died with COPD, 2,866 (14.7%) had lung cancer and 5,955 (30.5%) had cardiovascular disease as their primary cause of death. Those who died of COPD had an average age of 78.9 years (SD=10.0 years). The majority (61.4%) were men. Those dying of COPD were slightly younger than those dying with (but not of) COPD and did not differ in terms of sex ratio. Among patients who died with (but not of) COPD those who died of lung cancer were predominantly men and younger as compared to those who died of cardiovascular diseases ($p<.0001$). All groups were comparable for urbanisation level of the municipality of residence ($p=.002$) and educational level ($p<.0001$). Those dying of COPD substantially more often lived in a collective household (i.e. nursing home) ($p<.0001$) (Table 1).

Resource use in the studied populations

As shown in table 2 and 3, those who died of COPD were more likely to be admitted to an ICU (28.7% versus 12.5%) or to have a stay in a nursing home (31.3% versus 6.9%) ;were less likely to receive opioids, sedatives and morphine (table 3) and less likely to use palliative care services at a palliative care unit (2.1% versus 16.5%) or at home (6.2% versus 28.5%) (table 2) when compared to those who died of lung cancer. Furthermore, when compared to the other two groups, those who died of COPD were more likely to receive non-invasive ventilation, oxygen and COPD drugs (table 3).

As shown in table 2, those who died of lung cancer had a higher proportion of specialist contacts (84.9% versus 54.5% and 60.9%) as compared to the other 2 groups. They also had a higher proportion of hospital (88.9% versus 76.8% and 75.6%) and one-day care (outpatient) admission (44.8% versus 7.4% and 9.7%) and received more medical imaging (97.3% versus 80.8% and 79.8%).

Those who died of cardiovascular disease were at higher risk of being reanimated when compared to the other 2 groups (table 3) and were less likely to use palliative care services at a palliative care unit (1.6% versus 16.5%) or at home (4.5% versus 28.5%) when compared to those who died of lung cancer (table 2). When compared to those who died of COPD, those dying of cardiovascular diseases had a comparable use of hospital, ICU and home care services and had a comparable use of opioids, sedatives and morphine (table 2,3).

Finally, there was no difference between the three groups for emergency room admission, general practitioner contacts, gastric tube, urinary tract catheter and spirometry. Overall, those who died of cardiovascular diseases had a comparable resource use during the last 6 months as compared to those who died of COPD.

Discussion

This population-level study shows that the presence of lung cancer and cardiovascular diseases influences resource use in COPD patients at life's end. COPD patients who have a primary cause of death of lung cancer use less intensive resources during the last 6 months of life as compared to those who have a primary cause of death of COPD or cardiovascular diseases, are more prone for using palliative care services offered in a palliative care unit or at home and receive more medication that provides symptomatic benefits to patients at the end of life. COPD patients who died of their COPD and those who died of a cardiovascular disease have a comparable resource use although the latter receive less non-invasive ventilation and have a higher chance of being reanimated.

Earlier results show that patients who died from COPD have a very variable use of the health care system ranging from a large number of hospital admissions because of other concomitant diseases to a low use

of palliative care services available in acute care hospitals or home care settings. More specifically, acute hospital visits, ICU admissions, physician visits and use of invasive interventions and medication were found to be the key drivers of resource use in terminal COPD patients (2). We found that, of all Belgian residents who died of COPD, 76.8% were admitted to hospital and 28.7% to the ICU during the last 6 months of life which seems substantially higher than the 61.3% and 18.3% reported for the years 1997-2001 in the USA by Au et.al (19), but lower than the 82.8% of all COPD deaths in Medicare (older than 65 years) in the USA having had a hospital admission during the last 90 days of life and 39.9% having had an ICU admission in the last 30 days as reported by Teno et al (20). Moreover, physician visits, invasive ventilation and opioids used by persons who died of COPD found in our study seems to be higher than that described by previous studies (19, 21, 22).

The use of palliative care services in persons with COPD found in our study seems to be lower than that described by previous studies. We found that 2.1% and 6.2% of those dying of COPD received palliative services at a palliative care unit or at home. Teno et al.found that during the last 90 days of life, 39% of Medicare beneficiaries who died with a diagnosis of COPD received hospice care (20). As compared with the results of Goodridge et al., in Canada, 5.1% of those who died of COPD received palliative care services at a palliative care unit and 2.8% at home (22). Of all Belgian residents who died with COPD and of lung cancer 16.5% received palliative care services at a palliative care unit and 28.5% at home during the last 6 months of life. These results are in line with the results of Goodridge et al. who found that, respectively, 27% and 28.6% of those who died with COPD and of lung cancer in Canada received palliative care services within the hospital or at home (22). No previous studies have examined end-of-life resource use of COPD patients who died of cardiovascular diseases. Although a cardiovascular disease such as a cardiac arrest or severe stroke may often result in a sudden death , our findings suggest that a cardiovascular disease may influence overall resource use during the last months of life among those suffering from COPD.

Although previous studies show the importance of comorbidities in studying end-of-life care and more in particular analysing resource use, they paid no attention to the specific influence of comorbidities in end-of-life resource use. Moreover, study participants, in previous research, were mainly identified as COPD patients or lung cancer patients (2). Yet, our study suggests that the trajectories of dying of COPD or with COPD differ and may be influenced by the presence of lung cancer or cardiovascular diseases, which are prevalent comorbidities in COPD patients. Our findings seem to suggest that the presence of lung cancer and cardiovascular diseases within COPD patients affect treatment decisions during the dying process and particularly may result in different choices for aggressive versus palliative treatment, advanced directives and place of death.

The influence of lung cancer and cardiovascular diseases in COPD suggested in our study also has important implications for future research. The manner in which the population of COPD patients is selected (e.g. based on only underlying cause of death or diagnosis) will have an important influence on the findings. The scarce previous research mainly focused on those dying with COPD and controlled for the number of comorbidities (19, 21, 22). Although the number of comorbidities influences resource use in COPD patients, it is mainly the presence of a specific disease such as lung cancer or cardiovascular diseases which influences the use of palliative care services in COPD patients at life's end. Therefore, future research should clearly describe which sample of COPD patients is investigated and which specific comorbidities are taken into account, to increase the generalizability and comparability of the results. Including all those with a diagnosis of COPD (and not only a cause of death) but excluding those with lung cancer and/or cardiovascular disease (two main comorbidities of COPD) will give a clearer picture of resources use in COPD.

We acknowledge several limitations of our study. First, we used administrative databases in this retrospective study. Therefore we were not able to examine the relation between specific patient preferences, reported outcomes and medical decisions. Both, patient preferences and the nature of medical decisions can influence patterns of medical service use. Moreover, resource use during end of life in COPD patients might also be influenced by the level of the disease severity or the number of exacerbations which could influence decisions regarding specific end of life care plans. However, due to the use of administrative databases and a lack of specific diagnostic information available on medical files in our study, we could not account for specific confounders such as the number of exacerbations or the disease level. Nevertheless, a retrospective design allowed us to measure the real-life performances in end-of-life care of COPD patients (23). A second limitation of using linked administrative and health care databases is that these types of routinely collected population-level data do not include services not covered by insurers. However, in Belgium data are relatively complete for health care services in the hospital, nursing homes and at home. Nevertheless use of specific services such as mobile hospital palliative care teams cannot be identified because of a lack of individual reimbursement or regulation (13). Third, to identify those who died with COPD we not only used intermediate and associated causes of death indicated on the death certificates but also a validated algorithm to identify COPD patients. However, using the algorithm, it was impossible to determine the specific level of the disease from our data since only dispensing data and not prescription data were available. Although there is no standard validated algorithm, the use of pharmacy data to identify COPD patients in administrative databases was found adequate in previous studies. Smidth et.al. concluded that an algorithm based on administrative data could be used as a tool for identifying patients with COPD (16). Moreover, Mapel et.al. found that pharmacy utilization data could be used to help identify

persons at risk for having undiagnosed COPD, even without any information about smoking status (24).Lastly, our results are limited in that they do not provide any insights into the relative contribution of lung cancer and cardiovascular diseases to the increased resource use in COPD patients at the end of life.

Conclusion

During the last 6 months of life COPD patients used resources that were more focused on preservation of life and used less resources and medication that provide benefits to their specific end of life care needs. However, our results show an influence of lung cancer and cardiovascular diseases on end of life resource use of COPD patients: COPD patients who had a primary cause of death of lung cancer used less intensive resources during the last 6 months of life as compared to those who had a primary cause of death of COPD or cardiovascular diseases and were more prone for using palliative care services offered in a palliative care unit or at home. Those who died with COPD and had a primary cause of death of lung cancer received more medication that provide symptomatic benefits to patients at the end of life as compared to those who died of COPD and with COPD and of cardiovascular diseases. Moreover, those COPD patients who died of cardiovascular diseases showed a comparable use of resources during the last 6 months of life as those who died of COPD.

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Table 1. Characteristics of patients dying with COPD and dying from COPD

		All deaths	Dying of COPD	Dying with COPD			P-value
				All deaths	Dying of Lung Cancer	Dying of Cardiovascular diseases	
		(N=107847)	(n= 4231)	(n= 19401)	(n= 2876)	(n= 5979)	
Mean age		77.9	78.8	76.6	70.8	80.3	*<.0001*
Age group (%)							*<.0001*
	18-64	17283 (16.03)	429 (10.14)	3265 (16.83)	832 (28.93)	528 (8.83)	
	65-74	15737 (14.59)	833 (19.69)	3826 (19.72)	893 (31.05)	925 (15.47)	
	75-84	32118 (29.78)	1596 (37.72)	6557 (33.8)	866 (30.11)	2099 (35.11)	
	85-94	36674 (34.01)	1273 (30.09)	5277 (27.2)	281 (9.77)	2211 (36.98)	
	95+	5576 (5.17)	100 (2.36)	466 (2.4)	4 (0.14)	216 (3.61)	
Gender (%)							*<.0001*
	Male	53461 (49.57)	2597 (61.38)	11884 (61.25)	2160 (75.1)	3455 (57.79)	
	Female	54386 (50.43)	1634 (38.62)	7517 (38.75)	716 (24.9)	2524 (42.21)	
Cause of death (%)							*<.0001*
	Malignancies	26464 (24.6)	0 (0)	6241 (32.2)	2876 (100)	0 (0)	
	Nervous system	9048 (8.4)	0 (0)	719 (3.71)	0 (0)	0 (0)	
	Circulatory system	30878 (28.6)	0 (0)	5979 (30.82)	0 (0)	5979 (100)	
	Respiratory system	11112 (10.3)	4231 (100)	1742 (8.98)	0 (0)	0 (0)	
	Liver and kidney diseases	2906 (2.7)	0 (0)	539 (2.78)	0 (0)	0 (0)	
	Other	27439 (25.4)	0 (0)	4181 (21.56)	0 (0)	0 (0)	
Educational level (%)							*<.0001*
	No education	8156 (7.56)	400 (9.45)	1577 (8.13)	225 (7.82)	528 (8.83)	
	Primary education	34528 (32.02)	1548 (36.59)	6591 (33.97)	889 (30.91)	2257 (37.75)	
	Lower secondary education	24434 (22.66)	896 (21.18)	4528 (23.34)	754 (26.22)	1279 (21.39)	
	Upper secondary education	15717 (14.57)	501 (11.84)	2738 (14.11)	466 (16.2)	737 (12.33)	
	Higher education	9925 (9.2)	267 (6.31)	1561 (8.05)	243 (8.45)	382 (6.39)	
Mean Net taxable income		16792.45	15621.38	16413.29	17029.92	15975.89	*<.0001*
Household type (%)							*<.0001*
	Single person household	33117 (31.15)	1380 (32.65)	5898 (30.47)	806 (28.05)	1887 (31.58)	
	Married with no children living in	32655 (30.71)	1408 (33.32)	7356 (38.01)	1379 (48)	2152 (36.02)	
	Married with children living in	8246 (7.76)	246 (5.82)	1508 (7.79)	291 (10.13)	385 (6.44)	
	Living together with no children living in	2617 (2.46)	121 (2.86)	623 (3.22)	100 (3.48)	169 (2.83)	
	Living together with children living in	1017 (0.96)	33 (0.78)	182 (0.94)	36 (1.25)	38 (0.64)	

	One-parent family	5723 (5.38)	211 (4.99)	999 (5.16)	121 (4.21)	303 (5.07)	
	Other household type	2562 (2.41)	95 (2.25)	433 (2.24)	53 (1.84)	149 (2.49)	
	Collective household	20382 (19.17)	732 (17.32)	2356 (12.17)	87 (3.03)	892 (14.93)	
Housing comfort (%)							*<.0001*
	High	39447 (41.44)	1392 (37)	7479 (42.55)	1257 (48.11)	2155 (39.49)	
	Average	20258 (21.28)	809 (21.5)	3266 (18.58)	369 (14.12)	1102 (20.19)	
	Low	25608 (26.9)	1153 (30.65)	5102 (29.02)	785 (30.04)	1601 (29.34)	
	None	9869 (10.37)	408 (10.85)	1731 (9.85)	202 (7.73)	599 (10.98)	
Urbanisation (%)							*0.0019*
	Very high	34086 (31.61)	1374 (32.47)	5899 (30.41)	867 (30.15)	1706 (28.53)	
	High	29551 (27.4)	1145 (27.06)	5408 (27.87)	807 (28.06)	1680 (28.1)	
	Average	27321 (25.33)	1061 (25.08)	5349 (27.57)	797 (27.71)	1670 (27.93)	
	Low	13593 (12.6)	562 (13.28)	2333 (12.03)	349 (12.13)	797 (13.33)	
	Rural	1487 (1.38)	66 (1.56)	266 (1.37)	42 (1.46)	84 (1.4)	

Table 2. Resource utiliziaton during the last 180 days of life among patient dying of COPD and dying with COPD by specific cause of death

RESOURCE	Dying of COPD	Dying with COPD		P-value[c]	Subgroup dying of Lung Cancer vs Dying of COPD		Subgroup dying of Cardiovascular diseases vs Dying of COPD		Subgroup dying of Dying of Lung Cancer vs Cardiovascular diseases	
		Subgroup dying of Lung Cancer	Subgroup dying of Cardiovascular diseases							
	(n= 4231)	(n= 2876)	(n= 5979)		OR [a](CI95%)	LR[b]	OR[a] (CI95%)	LR[b]	OR [a](CI95%)	LR[b]
Hospital admission,%*[d]	76.8	88.9	75.6	<.0001	2.1 (1.8-2.4)		0.9 (0.8-1.0)		2.2 (1.9-2.6)	
Hospital days, mean (CI 95%)	18.0 (17.5-18.6)	13.4 (12.9-13.9)	15.3 (14.8-15.7)	<.0001		-4.3†		-3.0†		-1.3†
Emergency room admission,%*	68.6	70.1	67.1	0.014	1 (0.9-1.1)		0.9 (0.9-1.0)		1.1 (1.0-1.2)	
ICU admission,%*	28.7	12.5	27.6	<.0001	0.2 (0.2-0.3)		1 (0.9-1.1)		0.2 (0.2-0.3)	
LOS ICU, mean (CI 95%)	5.1 (4.8-5.4)	3.4 (3.1-3.8)	3.7 (3.6-3.9)	<.0001		-2.0†		-1.3†		-0.7†
Palliative care unit admission,%*	2.1	16.5	1.6	<.0001	8.9 (7.0-11.4)		0.7 (0.6-1.0)		12.0 (9.5-15.3)	
LOS PCU, mean (CI 95%)	6.5 (5.3-7.7)	8.5 (7.8-9.1)	5.4 (4.4-6.4)	<.0001		1.9†		-1.1		2.9†
ODC admission,%*	7.4	44.8	9.7	<.0001	7.6 (6.6-8.8)		1.4 (1.2-1.6)		5.4 (4.8-6.1)	
Nursing home stay,%*	31.3	6.9	26.7	<.0001	0.4 (0.3-0.4)		0.6 (0.6-0.7)		0.6 (0.5-0.7)	
Home care,%*	47.0	63.9	47.5	<.0001	2 (1.8-2.2)		1.0 (0.9-1.0)		2.1 (1.9-2.3)	
Palliative home care,%*	6.2	28.5	4.5	<.0001	5.9 (5.1-6.9)		0.7 (0.6-0.8)		8.6 (7.3-10.0)	
Number of palliative home care days, mean (CI 95%)	66.4 (58.4-74.5)	35.0 (32.1-37.9)	59.4 (51.3-67.5)	<.0001		-30.1†		-8.1†		-22.1†
GP contact,%*	96.6	96.6	97.0	0.5341	1.4 (1.1-1.9)		1.1 (0.8-1.3)		1.4 (1.0-1.8)	
Number of GP contacts, mean (CI 95%)	12.4 (12.1-12.7)	12.3 (12.0-12.7)	11.8 (11.6-12.0)	0.0004		1.4†		-0.8†		2.2†
Specialist contact,%*	54.5	84.9	60.9	<.0001	3.5 (3.1-3.9)		1.4 (1.3-1.5)		2.5 (2.5-2.9)	
Number of specialist contacts, mean (CI 95%)	2.8 (2.7-2.9)	4.8 (4.7-4.9)	3.2 (3.1-3.3)	<.0001		1.6†		0.5†		1.1†
Physiotherapist contact,%*	71.1	61.3	61.3	<.0001	0.6 (0.5-0.7)		0.6 (0.6-0.7)		1.0 (0.9-1.1)	

Number of physiotherapist contacts, mean (CI 95%)	36.5 (35.2-37.8)	22.1 (21.0-23.3)	28.0 (27.1-29.0)	<.0001	-15.9†	-8.1†	-7.9†

* Row percentages; CI: confidence limits

[a] Odds Ratio were obtained by logistic regression controlled for age, gender, household type, attained educational level and urbanization level of the municipality of residence (each specific resource use was controlled for this fixed set of covariates)

[b] Likelihood Ratio were obtained by a general linear model controlled for age, gender, household type, attained educational level and urbanization level of the municipality of residence (each specific resource use was controlled for this fixed set of covariates)

[c] P-value univariate analysis

[d] Hospitalization can include ICU and ER admissions. (ER admissions were only included in hospitalization when followed by a hospital stay of more than 1 day)

ICU: Intensive care unit; LOS: Length of stay; ODC: One-day care; GP: General practitioner

† P <.05 versus dying of COPD

NOTE: Subgroups might differ: LOS, number of care and care days were calculated conditionally a decedent used the care or not.

Table 3. Procedures and medication use during the last 180 days of life among patient dying of COPD and dying with COPD by specific cause of death

Procedures	Dying of COPD	Dying with COPD		P-value[c]	Subgroup dying of Lung Cancer vs Dying of COPD		Subgroup dying of Cardiovascular diseases vs Dying of COPD		Subgroup dying of Dying of Lung Cancer vs Cardiovascular diseases	
		Subgroup dying of Lung Cancer	Subgroup dying of Cardiovascular diseases							
	(n= 4231)	(n= 2876)	(n= 5979)		OR [a](CI95%)	LR[b]	OR[a] (CI95%)	LR[b]	OR [a](CI95%)	LR[b]
Invasive ventilation,%*	20.9	5.7	21.2	<.0001	0.1 (0.1-0.2)		1.1 (1-1.2)		0.1 (0.1-0.2)	
Days of invasive ventilation, mean, (CI 95%)	8.1 (7.6-8.6)	5.3 (4.4-6.2)	5.3 (5.0-5.6)	<.0001		-3.4†		-2.7†		-0.7
Non-invasive ventilation,%*	50.9	37.9	22.5	<.0001	0.6 (0.5-0.7)		0.3 (0.3-0.3)		2.2 (2.0-2.4)	
Days of non-invasive ventilation, mean, (CI 95%)	60.2 (56.5-63.9)	26.3 (22.8-29.7)	39.6 (35.8-43.4)	<.0001		-45.1†		-14.9†		-30.2†
Gastric tube,%*	0.6	0.5	0.5	0.8683	0.8 (0.4-1.5)		0.9 (0.5-1.6)		0.8 (0.4-1.6)	
Urinary tract catheter,%*	1.1	0.5	0.7	0.0084	0.5 (0.3-1.0)		0.6 (0.4-1)		0.9 (0.5-1.7)	
CPR,%*	2.4	0.6	5.9	<.0001	0.2 (0.1-0.3)		2.7 (2.1-3.3)		0.1 (0.04-0.1)	
Medical imaging,%*[d]	80.8	97.3	79.8	<.0001	7.1 (5.6-9.1)		0.9 (0.8-1.0)		7.6 (6.0-9.7)	
RX-thorax,%*[d]	78.0	89.9	74.5	<.0001	2.2 (1.9-2.6)		0.8 (0.7-0.9)		2.7 (2.4-3.2)	
Number RX-thorax, mean, (CI95%)	7.7 (7.4-8.1)	5.1 (4.8-5.3)	6.2 (6.0-6.5)	<.0001		-4.0†		-1.1†		-2.9†
Spirometry,%*	1.1	1.8	1.1	0.0205	1.0 (0.7-1.6)		1.1 (0.7-1.5)		1.0 (0.7-1.4)	
Medication										
Oxygen,%*	26.8	19.4	10.3	<.0001	0.6 (0.5-0.7)		0.3 (0.3-0.4)		1.9 (1.6-2.1)	
Opioids,%*[e]	47.3	79.5	44.4	<.0001	4.0 (3.6-4.5)		0.9 (0.8-1)		4.5 (4.0-5.0)	

Sedatives,%*	35.0	54.9	35.1	<.0001	1.9 (1.7-2.1)	1.0 (0.9-1.1)	1.8 (1.7-2.0)
Morphine,%*[e]	13.5	47.7	11.7	<.0001	4.9 (4.4-5.6)	0.9 (0.8-1.0)	5.7 (5.0-6.3)
COPD drugs,%*	90.2	80.9	70.6	<.0001	0.4 (0.4-0.5)	0.3 (0.2-0.3)	1.7 (1.5-1.9)

* Row percentages; CI: confidence limits

[a] Odds Ratio were obtained by logistic regression controlled for age, gender, household type, attained educational level and urbanization level of the municipality of residence (each specific resource use was controlled for this fixed set of covariates)

[b] Likelihood Ratio were obtained by a general linear model controlled for age, gender, household type, attained educational level and urbanization level of the municipality of residence (each specific resource use was controlled for this fixed set of covariates)

[c] P-value univariate analysis

[d] Medical imaging was determined using specific nomenclature codes charged for RX, NMR, CT and PET-scan. To determine RX-thorax only specific nomenclature codes charged for RX-thorax were used. (RX-thorax is included in Medical imaging)

[e] To identify Opioids ATC-codes starting with N02A% were used. To identify Morphine a more specific ATC-code N02AA% was used.

† P <.05 versus dying of COPD

CPR: cardiopulmonary resuscitation

NOTE: Subgroups might differ: LOS, number of care and care days were calculated conditionally a decedent used the care or not.

CHAPTER 6: RESOURCE USE OF INDIVIDUALS DYING OF ALZHEIMER'S DISEASE

Chapter based on:

Faes, K., J. Cohen, and L. Annemans. Resource Use During the Last 6 Months of Life of Individuals Dying with and of Alzheimer's Disease. J Am Geriatr Soc, 2018.

ABSTRACT

Background Because of its protracted nature Alzheimer's disease (AD) is often seen as a predisposing or contributing factor, rather than an underlying cause of death. This could result in a differentiated nature and intensity of care at life's end.

Aim To compare resource use during the last 6 months of life between those who were diagnosed with AD but for whom AD was not formally identified as the underlying cause of death (i.e."dying with AD") and those who had AD as underlying cause of death (i.e."dying of AD").

Methods We performed a full-population retrospective analysis on linked healthcare, population and death certificate data of all Belgian decedents in the year 2012. Those who died of AD were selected based on the underlying cause of death. Those who died with AD were selected using a validated algorithm.

Results Those who died of AD had less hospital use compared to those dying with AD, were less often admitted to a palliative care unit but received palliative home care services slightly more often and had a comparable use of physiotherapy, non-invasive ventilation, medical imaging, sedatives, oxygen and opioids as those who died with AD.

Conclusion During the last 6 months of life, those dying of AD used less intensive resources such as ICU,CPR or invasive ventilation than those dying with AD, which could suggest the effect of a recognition of an end-of-life phase. Overall, AD patients used rather rarely palliative care services, suggesting a need for more efforts to encourage palliative care in AD patients.

RESOURCE USE DURING THE LAST 6 MONTHS OF LIFE OF INDIVIDUALS DYING WITH AND OF ALZHEIMER'S DISEASE

Background

During the past century improvements in health care have contributed to people living longer and healthier lives which resulted in an increase in the number of people with non-communicable diseases such as dementia. In 2015, 46.8 million people worldwide were living with dementia and their number is expected to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050 [1]. Dementia is a general term comprising different types of mental decline. The most common type of dementia is Alzheimer's disease (AD) which accounts for an estimated 60 to 80 percent of cases [2].

The end-stage of Alzheimer's disease lasts on average as long as two years [3] and patients may develop apraxia, dysphagia and, at a later stage, often have a reduced mobility which increase the risk of infections [4]. These infections, such as pneumonia, might increase mortality in AD patients and are often seen as an underlying cause of death. As a result, dementia is often seen as a predisposing or contributing factor to the terminal infections rather than a cause of death [5]. Moreover, prognostic markers to identify the last 6 months of life in AD e.g. functional dependency, recurrent hospitalizations and weight loss are not able to predict the final months of life [6]. Given the lack of a formal recognition of AD as a life-threatening disease, reliable prognostic markers and variability in survival in AD patients, clinicians do not see AD as a primary cause of death or a disease of which one could die [6]. Not recognizing dementia as a possible cause of death might result in a limited chance to obtain support or access to tailored treatment, formal end-of-life care and healthcare services or might result in receiving care and services on a general basic level not adjusted to their specific end-of-life needs [7, 8].

Hence, the recognition of dementia as a possible cause of death could have important implications in terms of resource use at the end of life, including palliative care.

As a result, it can be hypothesized that within those suffering from AD, those patients who were diagnosed with AD but for whom AD was not formally identified as the underlying cause of death on the death certificate have a different resource use pattern during the final months of life than those patients who died of AD and had AD indicated as the underlying cause of death on the death certificate.

In order to fill this current gap in our knowledge about the management of patients with dementia at the end of life, the aim of this study is to describe, at a population level, medical resource use in the final months of life in people suffering from AD and compare this resource use between those who were diagnosed with AD but for whom AD was not formally identified as the underlying cause of death on the

death certificate (i.e. dying with AD) and those who had AD indicated as the underlying cause of death on the death certificate (i.e. dying of AD).

Material and methods

The present study is a retrospective, full population analysis of Belgian patients who died with or of AD during 2012.

Data sources

A total of eight population-level databases were linked into one common database. The data include healthcare data retrieved from the Intermutualistic Agency (IMA); sociodemographic, socio-economic and death certificate data retrieved from Statistics Belgium and cancer diagnosis data retrieved from the Belgian Cancer Registry. A more detailed description of these databases and the procedures for obtaining and linking these data is presented elsewhere [9]. The IMA databases include all reimbursement data of health care consumption and pharmaceuticals prescriptions from all Belgian healthcare insurance organisations. Since health insurance is legally mandatory in Belgium, reimbursement data of all legal residents are available. Moreover, thorough quality procedures result in good reliability of the database for healthcare research [10]. The statistics Belgium databases include socio-demographic data from the population registry [11] , socio-economic data from the Socio-Economic Survey 2001 and Census 2011 and death certificate data of all deaths [12].

Study population

The study population consists of all persons who died with AD in Belgium during the year 2012. We compared the end-of-life resource use between those who were diagnosed with AD but for whom AD was not formally identified as the underlying cause of death on the death certificate (conveniently labeled 'dying with AD') and those who had AD (ICD10-codes: F00 and G30) indicated as the underlying cause of death on the death certificate (labeled 'dying of AD'). Diagnosis of AD was identified algorithmically using medication data from 2002 through 2012. This validated algorithm was based on existing evidence and discussed with experts in AD treatment and administrative healthcare databases (see Appendix 1). The final algorithm was further expanded with those deaths for which AD was recorded on the death certificates as an intermediate or associated cause of death but excluding the deaths for which AD was the underlying cause of death.

Measures

The primary study outcome is the resource use in the last six months of life of AD patients thereby differentiating whether AD patients had AD indicated as an underlying cause of death on their death certificate or not.

All health care (coded as nomenclature codes) and medication data (coded as Anatomical Therapeutic Chemical Classification (ATC) codes). were interpreted and aggregated into meaningful resource use, procedures and medication categories.
Patient characteristics included age at death, sex, urbanization level of the municipality of residence, highest obtained educational level, household type, housing comfort and net taxable income.

Periods of 180, 90 and 30 days before death were defined for analysis purpose based upon the dates related to the specific nomenclature numbers or medication prescription dates.

Statistical Analysis

To investigate potential differences we compared patient characteristics and resource use of AD patients who had AD as a primary cause of death noted on the death certificate (i.e. “dying of AD”) and who had no notification of AD or had AD noted as an intermediate or contributing cause of death on their death certificate (i.e. “dying with AD”) using chi square tests for categorical variables and Wilcoxon rank sum tests for continuous variables and calculated relative risks of having each given type of resource use for those who died with compared to those who died of AD during a 180, 90 and 30 days period before death. Additionally, we analysed resource data using a general linear model for continuous variables and logistic regression for binary variables, with dying of vs with AD as a dependent variable and controlling simultaneously for various covariates (age, sex, household type, housing comfort, attained educational level, urbanization level of the municipality of residence, net taxable income, having a cancer diagnosis, comorbidity index (Charlson), level of care need and place of death). We set the significance level at $p \leq .05$ to address hypothesis testing and performed all analyses using SAS version 7.13 HF1 (7.100.3.5419) (64-bit).

Results

In 2012, 109,034 people died in Belgium of which 107,847 (98.9%) were insured with one of the seven sickness funds and hence had data about reimbursed health care and medication; for 1,187 deaths, mainly those working for the European Government (covered by an insurance Scheme of the European Union), homeless persons and those with unauthorized immigration, such data was not available.

A total of 11,410 persons (10.6 % of all deaths) died with or of AD. Of these 8,804 (77.2 %) died with but not of AD and 2,606 (22.8 %) died of AD, the average age was 85 years (SD=6.6 years), and a majority were women, married and lived in an urban region (Table 1). Although those who died with AD had a higher comorbidity index as compared to those who died of AD, both groups only differed marginally in terms of age, sex, educational level, household, housing comfort and had a comparable mean net taxable income.

For almost all types of resource use and procedures, utilization during the final 6 months of life tended to be similar or higher in those who died with AD compared to those who died of AD (table 2). Those dying with AD showed a higher probability of having at least one hospital admission (61.07% versus 40.48%, p<0.0001), had more ICU stays (8.75% versus 1.96% had at least one ICU stay, p<0.0001), more home care services use (32.42% versus 25.44%, p<0.0001) and were more often admitted to a palliative care unit (2.19% versus 1.23%, p=0.0019). Moreover, those dying both with and of AD had a mean number of 12 contacts with a general practitioner during the last 6 months of life. Finally, a greater proportion of those dying with AD had specialist contacts as compared with those who died of AD (40.78% versus 27.86% had at least one contact during the last 6 months of life, p<0.0001). However, those dying with AD received slightly less often palliative home care services (5.47% versus 6.79%, p=0.0113) with a lower number of palliative home care days during the last 6 months of life (63.2 days versus 83.5 days). Moreover, those dying with AD stayed slightly less in a nursing home compared to those who died of AD (70.1% versus 80%, p<0.0001).

In both groups, all resources increased when approaching death (See Figure 1a,b Appendix 2). Yet, home care use and specialist contacts decreased.

In terms of procedures applied during the last 6 months, those who died with AD received more invasive ventilation (p<0.0001), were more resuscitated (p=0.0002) and had higher use of medical imaging (p<0.0001) as compared with those who died of AD (table 3). In terms of medication, those dying with AD slightly more often used opioids (p=0.0541), morphine (p<0.0001) and sedatives (p<0.0001) as compared with those who died of AD. The use of these medications increased substantially during the final 6 months of life in both groups (See Figure 2 Appendix 2). The use of dementia drugs was lower in those dying of AD versus those dying with AD (p<0.0001) and their use moreover remained stable in those who died with AD but decreased in those who died of AD during the last 6 months of life.

Discussion

Our observational study of all individuals who died from Alzheimer disease's (AD) is the first, to our knowledge, to describe resource use on a full population level during the last 6 months of life thereby comparing patients who were diagnosed with AD but for whom AD was not formally identified as the

underlying cause of death on the death certificate (i.e. dying with AD) and those who had AD indicated as the underlying cause of death on the death certificate (i.e. dying of AD). Our results indicate that palliative care services available at home or a palliative care unit are not always considered in the care plans for AD patients, and hospitalization, intensive care and emergency room admissions near the end of life remain common in those who die with or of AD. Those who died with AD had a similar or higher resource use during the last 6 months of life when compared to those who died of AD. However, they received less often palliative home care services and were slightly more often admitted to a palliative care unit.

The high use of intensive resources at the end of life of those with AD found in our study may be a result of the disease course of AD. In contrast to many other diseases with a predictable prognosis such as cancer, which reach an advanced stage followed by a predictable downhill course over weeks or months, the prognostication of AD is more difficult. This corroborates previous findings that the end of life phase in non-communicable diseases, specifically AD, is often not recognized or neglected due to the absence of prognostic markers or difficulties in diagnosing [13]. However, our results indicate that AD patients at life's end have frequent contacts with their general practitioner and this creates an opportunity for recognizing end-stage AD and discussing end-stage approaches. Nevertheless, previous research shows that GPs encounter different difficulties when discussing end-of-life care in AD patients [14, 15]. However, the recognition of an end-of-life phase and a timely initiation of palliative care may improve end-of-life care and, moreover, the quality of life in AD patients.

Our study also revealed important differences, within the group of persons with AD, between those dying of AD (AD as an underlying cause of death noted on the death certificate) and those dying with AD (diagnosed with but not dying of AD). Those who died with AD had more intensive resource use than those who died of AD . However, the differences in resource use could be related to the fact that both groups differ in terms of disease severity or the number of comorbidities. Based on the Charlson comorbidity index we found that those who died with AD had more severe comorbidities compared to those who died of AD which indicates that those who died with AD were more prone to receive resources related to these co-existing diseases. Moreover, those who died with AD more often died in a hospital as compared to those who died of AD, indicating as well that those who died with AD received treatments or care adjusted to these specific co-existing diseases. Nevertheless, the found differences suggest an importance of an adequate recognition of the end-of-life phase in those who suffer from AD.

Despite indications of a better recognition of the dying phase in those dying of AD, the absolute percentage of patients using palliative care services among those dying of AD is still rather low. It possibly points to a need for better (and earlier) identification of patients who can benefit from palliative

care and increased awareness of the benefits of palliative care in AD. Next to recognition of the dying phase, identification of those who could benefit from palliative care provision would thus also be needed to improve end-of-life care in AD. A systematic review by Coventry et.al. (2005) concluded that validated prognostic models to predict for whom palliative care would be beneficial are currently lacking for routine clinical use in dementia patients [16]. However, Aminoff and Adunsky (2006) found that the use of the Mini-Suffering State Examination Scale can help to identify those who could benefit from palliative care provision [17].

Several possible limitations of our study have to be acknowledged. The recognition of the end of life situation in AD patients might be influenced by a number of confounders e.g. the level of the disease severity, the presence of specific comorbidities or the place of death/care which could influence decisions regarding specific end of life care plans. However, due to the use of administrative databases and a lack of specific diagnostic information in our study, we could not account for specific confounders such as the number and characteristics of the palliative care practitioners or the number of specific comorbidities based on specific diagnostic information available on medical files. Nevertheless, based on a specific algorithm using intermediate and associated causes of death as mentioned on the death certificate we were able to measure the Charlson comorbidity index (CCI). After controlling simultaneously for a number of possible confounders, we found that the differences in resource use between those who had AD as an underlying cause of death and those who had not was maintained. (in supplemental file)

The use of death certificate data to identify those who died of and with AD entails certain limitations. First, clinicians might often recognize AD as a contributor to death but might not prioritize the diagnosis in individuals with different comorbidities. Therefore, it should be noted that in individuals with different comorbidities, different doctors might choose different diagnoses to report as a cause of death. Moreover, another well-known weakness in using death certificates concerns the under reporting of AD on death certificates as a main and contributory cause of death [18, 19]. However, our additional use of a validated medication-based algorithm partly mitigated that limitation in identifying those with AD. The combination of the death certificate and medication data resulted in a more accurate number of those dying with AD [20]. The adequacy of the use of an algorithm based on pharmacy data, when claims data and pharmacy data of more than 3 years were used, to accurately identify those dying with AD has been confirmed in previous research [21, 22]. Yet, due to the lack of a gold standard to identify those dying with AD [23], our results may still be affected by the choice of grouping resulting in a more heterogeneous group with more differing morbidities for which they were treated. Despite these limitations, our study has a number of exceptional strengths. The use of a full population linked administrative and healthcare database resulted in a large sample size and has large statistical power

which made the study of resource use in AD patients at the end-of-life possible. Moreover, the completeness of the unique linked database ensures the representativeness in a real world setting. Furthermore, the completeness and independent data collection minimizes the effect of selection bias due to non-response and loss to follow-up (attrition) or influences of the diagnostic process determined by the study [24].

Conclusion

Our results showed that, based on a retrospective analysis using a full population linked database, those who died of AD (i.e. AD as an underlying cause of death) used less resources as compared with those who did not have AD indicated as an underlying cause of death on the death certificate, suggesting that the recognition of end-stage AD as an end-of-life condition may influence the use of less intensive resources such as palliative care services and, hence, the appropriateness of end-of-life care. Besides the importance of and difficulties in recognizing end-stage AD, we found that the level of home palliative care in those patients dying of AD is low, pointing to a need for more efforts to encourage its timely use in those suffering of AD. Moreover, recognizing AD as a disease of which one could die and the related recognition of the end-stage phase are therefore important factors to provide end-of-life care adapted to the specific needs of those who suffer from AD.

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Table 1. Characteristics of patients dying with Alzheimer's disease and dying from Alzheimer's disease

		All deaths (N=107847)	Dying both with or of AD (n= 11410)	Dying with but not of AD (n=8804)	Dying of AD (n=2606)
Mean age		77.9	84.9	84.9	85.1
Age group (%)	18-64	17283 (16.0)	108 (1.0)	72 (0.8)	36 (1.4)
	65-74	15737 (14.6)	582 (5.1)	450 (5.1)	132 (5.1)
	75-84	32118 (29.8)	4298 (37.7)	3379 (38.4)	919 (35.3)
	85-94	36674 (34.0)	5868 (51.4)	4513 (51.3)	1355 (52.0)
	95+	5576 (5.2)	554 (4.9)	390 (4.4)	164 (6.3)
Gender (%)	Male	53461 (49.6)	4115 (36.1)	3284 (37.2)	831 (31.9)
	Female	54386 (50.4)	7295 (63.9)	5520 (62.7)	1775 (68.1)
Cause of death (%)	Malignancies	26464 (24.6)	874 (7.7)	874 (9.9)	0 (0.0)
	Nervous system	9048 (8.4)	4303 (7.7)	1697 (9.3)	2606 (100.0)
	Circulatory system	30878 (28.6)	2821 (24.7)	2821 (32.1)	0 (0.0)
	Respiratory system	11112 (10.3)	1103 (9.7)	1103 (12.5)	0 (0.0)
	Liver and kidney diseases	2906 (2.7)	179 (1.6)	179 (2.0)	0 (0.0)
	Other	5763 (5.3)	427 (3.7)	427 (4.9)	0 (0.0)
	Residual	21676 (20.1)	1703 (14.9)	1703 (19.3)	0 (0.0)
Place of death (%)	Hospital	52497 (48.7)	3493 (30.6)	3106 (35.3)	387 (14.9)
	Nursing home/skilled nursing facility	25141 (23.3)	6308 (55.3)	4515 (51.3)	1793 (68.8)
	Other	30209 (28.0)	1609 (14.1)	1183 (13.4)	426 (16.4)
Charlson comorbidity index (%)	0	82240 (76.3)	7916 (69.4)	5570 (63.3)	2346 (90.0)
	1	13796 (12.8)	2676 (23.5)	2492 (28.3)	184 (7.1)
	2	8578 (8.0)	607 (5.3)	536 (6.1)	71 (2.7)
	≥3	3233 (3.0)	211 (1.8)	206 (2.3)	5 (0.2)
Educational level (%)	No education	8156 (7.6)	929 (8.1)	709 (8.1)	220 (8.4)
	Primary education	34528 (32.0)	4364 (38.3)	3408 (38.7)	956 (36.7)
	Lower secondary education	24434 (22.7)	2488 (21.8)	1939 (22.0)	549 (21.1)
	Upper secondary education	15717 (14.6)	1330 (11.7)	1025 (11.6)	305 (11.7)
	Higher education	9925 (9.2)	874 (7.7)	648 (7.4)	226 (8.7)
Mean Net taxable income		16792.5	16282.1	16132.5	16788.9
Household type (%)	Single person household	33117 (31.2)	2328 (20.4)	1877 (21.4)	451 (17.3)
	Married/living together with no children living in	35272 (33.2)	3385 (29.7)	2619 (29.8)	766 (29.4)
	Married/living together with children living in	9263 (8.7)	495 (4.3)	364 (4.1)	131 (5.0)
	One-parent family	5723 (5.4)	429 (3.8)	319 (3.6)	110 (4.2)
	Other household type	2562 (2.4)	243 (2.1)	186 (2.1)	57 (2.2)
	Collective household	20382 (19.2)	4514 (39.6)	3425 (39.0)	1089 (41.8)
Housing comfort (%)	High	39447 (41.4)	4211 (40.5)	3259 (40.3)	952 (41.2)
	Average	20258 (21.3)	2508 (24.1)	1948 (24.1)	560 (24.2)
	Low	25608 (26.9)	2674 (25.7)	2111 (26.1)	563 (24.4)
	None	9869 (10.4)	995 (9.6)	760 (9.4)	235 (10.2)
Urbanisation (%)	Very high	34086 (31.6)	3509 (30.8)	2698 (30.7)	811 (31.1)
	High	29551 (27.4)	3347 (29.4)	2604 (29.6)	743 (28.5)
	Average	27321 (25.3)	3028 (26.5)	2405 (27.3)	623 (23.9)
	Low	13593 (12.6)	1300 (11.4)	924 (10.5)	376 (14.4)
	Rural	1487 (1.4)	133 (1.2)	102 (1.2)	31 (1.2)

Table 2. Resource utiliziaton during the last 180,90 and 30 days of life among patient dying with Alzheimer's disease and dying from

	WITH not FROM (n=8804)			FROM (n=2606)			*RR* (CI)		
RESOURCE	**180 days**	**90 days**	**30 days**	**180 days**	**90 days**	**30 days**	**180 days**	**90 days**	**30 days**
Hospital admission*	61.1	53.1	36.5	40.5	32.9	17.7	1.5 (1.4-1.6)	1.6 (1.5-1.7)	2.1 (1.9-2.3)
Hospital days, mean (CI 95%)	16.5 (16.1-16.9)	15.1 (14.7-15.4)	10.0 (9.7-10.2)	17.1 (16.2-18.0)	16.0 (15.1-16.7)	10.7 (10.1-11.4)			
ICU admission*	8.8	7.5	5.9	2.0	1.7	1.2	4.5 (3.4-5.9)	4.6 (3.4-6.2)	4.8 (3.4-6.7)
LOS ICU, mean (CI 95%)	3.4 (3.1-3.6)	3.4 (3.1-3.7)	3.4 (3.1-3.7)	2.8 (2.0-3.7)	2.8 (1.8-3.8)	3.2 (1.9-4.6)			
Palliative care unit admission*	2.2	2.1	2.0	1.2	1.2	1.2	1.8 (1.2-2.6)	1.8 (1.2-2.6)	1.8 (1.2-2.6)
LOS PCU, mean (CI 95%)	8.2 (7.2-9.3)	8.1 (7.1-9.1)	7.4 (6.4 -8.4)	6.3 (4.1-8.6)	6.3 (4.1-8.6)	6.0 (3.6-8.4)			
ODC admission*	4.6	2.3	1.2	1.9	1.1	0.4	2.5 (1.8-3.3)	2.5 (1.7-3.6)	3.2 (1.7-6.2)
Nursing home stay*	70.1	69.7	68.2	80.0	79.8	78.5	0.9 (0.9-0.9)	0.9 (0.9-0.9)	0.9 (0.8-0.9)
Home care*	32.4	27.5	20.1	25.4	21.7	16.7	1.3 (1.2-1.4)	1.3 (1.2-1.4)	1.2 (1.1-1.3)

Palliative home care*	5.5	5.3	5.1	6.8	6.8	6.7	0.8 (0.7-1.0)	0.8 (0.7-0.9)	0.8 (0.6-0.9)
Number of palliative home care days, mean (CI 95%)	63.2 (57.2-69.2)	40.5 (37.4-43.6)	18.8 (17.8-19.9)	83.5 (72.6-94.4)	50.7 (45.3-56.1)	22.1 (20.4-23.7)			
GP contact*	97.1	95.1	85.9	96.5	94.6	88.7	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Number of GP contacts, mean (CI 95%)	12.4 (12.2-12.5)	7.9 (7.8-8.0)	4.6 (4.5-4.7)	12.3 (12.1-12.6)	8.2 (8.0-8.4)	4.9 (4.8-5.0)			
Specialist contact*	40.8	24.2	8.5	27.9	15.7	5.5	1.5 (1.4-1.6)	1.5 (1.4-1.7)	1.6 (1.3-1.9)
Number of specialist contacts, mean (CI 95%)	2.2 (2.1-2.3)	1.6 (1.6-1.7)	1.2 (1.2-1.3)	1.8 (1.7-1.9)	1.5 (1.4-1.5)	1.2 (1.1-1.2)			
Physiotherapist contact*	47.9	41.5	32.8	37.8	31.8	24.0	1.3 (1.2-1.3)	1.3 (1.2-1.4)	1.4 (1.3-1.5)
Number of physiotherapist contacts, mean (CI 95%)	26.4 (25.5-27.2)	17.6 (17.0-18.1)	9.1 (8.9-9.4)	27.3 (25.5-29.2)	18.3 (17.3-19.4)	9.2 (8.7-9.7)			

* Row percentages; CI: confidence limits; ICU: Intensive care unit; LOS: Length of stay; ODC: One-day care; GP: General practitioner

NOTE: Subgroups might differ: LOS, number of care and care days were calculated conditionally a decedent used the care or not.

Table 3. Procedures and medication use during the last 180,90 and 30 days of life among patient dying with Alzheimer's disease and dying from

	WITH not FROM (n=8804)			FROM (n=2606)			*RR* (CI)		
Procedures	**180 days**	**90 days**	**30 days**	**180 days**	**90 days**	**30 days**	**180 days**	**90 days**	**30 days**
Invasive ventilation*	5.4	4.9	4.4	0.9	0.9	0.8	6.1 (4.0-9.2)	5.6 (3.7-8.5)	5.4 (3.5-8.4)
Days of invasive ventilation, Mean, (CI 95%)	2.0 (1.0-6.0)	2.0 (1.0-6.0)	2.0 (1.0-5.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)			
Non-invasive ventilation*	10.2	9.5	8.6	10.1	9.7	8.5	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.2)
Days of non-invasive ventilation, Mean, (CI 95%)	7.0 (4.0-13.0)	6.0 (4.0-9.0)	4.0 (3.0-6.0)	5.0 (4.0-9.0)	5.0 (4.0-7.0)	4.0 (4.0-6.0)			
Gastric tube*	1.0	0.9	0.5	1.0	1.0	0.5	1.0 (0.6-1.5)	1.0 (0.6-1.5)	1.0 (0.6-2.1)
CPR*	0.8	0.8	0.7	0.1	0.1	0.1	6.8 (2.1-21.6)	6.5 (2.0-20.7)	5.8 (1.8-18.6)
Medical imaging*	66.0	57.7	44.1	47.0	38.1	23.3	1.4 (1.3-1.5)	1.5 (1.4-1.6)	1.9 (1.8-2.0)
Medication									
Oxygen*	4.0	3.3	2.6	4.8	4.5	3.7	0.8 (0.7-1.0)	0.7 (0.6-0.9)	0.7 (0.6-0.9)
Opioids*	42.7	39.8	34.5	44.9	42.1	37.2	1.0	1.0	1.0

							(0.9-1.0)	(0.9-1.0)	(0.9-1.0)
Sedatives*	23.2	19.8	15.2	12.2	9.9	6.3	1.9 (1.7-2.1)	2.0 (1.8-2.3)	2.4 (2.1-2.8)
Morphine*	9.3	8.5	7.2	6.6	6.4	5.5	1.4 (1.2-1.6)	1.3 (1.1-1.6)	1.3 (1.1-1.6)
Dementia drugs*	52.4	43.0	24.5	28.7	21.6	11.0	1.8 (1.7-1.9)	2.0 (1.8-2.1)	2.2 (2.0-2.5)

* Row percentages; CI: confidence limits; ICU: Intensive care unit; LOS: Length of stay; ODC: One-day care; GP: General practitioner

NOTE: Subgroups might differ: LOS, number of care and care days were calculated conditionally a decedent used the care or not.

Supplemental file - Multivariate analysis of resource utilization during the last 180,90 and 30 days of life between those dying with Alzheimer's disease versus dying from

	Subgroup dying with vs Dying from 180 days		Subgroup dying with vs Dying from 90 days		Subgroup dying with vs Dying from 30 days	
RESOURCE	OR [a](CI95%)	LR[b]	OR [a](CI95%)	LR[b]	OR [a](CI95%)	LR[b]
Hospital admission	1.75 (1.56-1.95)	-	1.66 (1.48-1.87)	-	1.72 (1.49-2.01)	-
Hospital days	-	-1.04*	-	-1.27*	-	-1.07*
Emergency room admission	1.47 (1.33-1.64)	-	1.42 (1.27-1.59)	-	1.48 (1.29-1.70)	-
ICU admission	3.54 (2.59-4.84)	-	3.16 (2.25-4.45)	-	2.73 (1.83-4.07)	-
LOS ICU	-	0.57	-	0.42	-	-0.02
Palliative care unit admission	0.70 (0.46-1.06)	-	0.66 (0.43-1.01)		0.62 (0.40-0.96)	
LOS PCU	-	0.95	-	1.12	-	0.87
ODC admission	1.89 (1.38-2.60)	-	1.80 (1.20-2.69)	-	2.54 (1.27-5.10)	-
Nursing home stay	0.46 (0.40-0.54)	-	0.46 (0.40-0.53)	-	0.49 (0.43-0.56)	-
Home care	1.69 (1.47-1.95)	-	1.70 (1.46-1.97)	-	1.71 (1.45-2.01)	-
Palliative home care	1.17 (0.91-1.52)	-	1.16 (0.88-1.49)	-	1.11 (0.86-1.45)	-
Number of palliative home care days	-	-12.62	-	-7.08*	-	-2.58*
GP contact	1.28 (0.97-1.67)	-	1.32 (1.07-1.64)	-	1.12 (0.96-1.31)	-
Number of GP contacts	-	0.52*	-	0.15	-	0.04
Specialist contact	1.60 (1.44-1.78)	-	1.58 (1.39-1.79)	-	1.54 (1.26-1.89)	-
Number of specialist contacts	-	0.29*	-	0.10	-	0.07
Physiotherapist contact	1.30 (1.17-1.44)	-	1.29 (1.59-1.43)	-	1.26 (1.12-1.41)	-
Number of physiotherapist contacts	-	0.87	-	0.15	-	0.17

Procedures						
Invasive ventilation	4.60 (2.93-7.21)	-	3.87 (2.46-6.08)	-	3.62 (2.25-5.82)	-
Days of invasive ventilation	-	1.23	-	1.15	-	0.68
Non-invasive ventilation	1.10 (0.94-1.29)	-	1.06 (0.90-1.25)	-	1.13 (0.95-1.34)	-
Days of non-invasive ventilation	-	4.08*	-	2.17*	-	0.53
Gastric tube	1.10 (0.69-1.74)	-	1.10 (0.68-1.76)	-	1.32 (0.67-2.58)	-
CPR	5.50 (1.71-17.72)	-	5.36 (1.66-17.31)	-	4.71 (1.45-15.27)	-
Medical imaging	1.66 (1.49-1.85)	-	1.63 (1.46-1.82)	-	1.83 (1.60-2.08)	-
Medication						
Oxygen	0.91 (0.72-1.14)	-	0.81 (0.64-1.03)	-	0.82 (0.63-1.07)	-
Opioids	0.84 (0.76-0.92)	-	0.82 (0.75-0.91)	-	0.80 (0.72-0.88)	-
Sedatives	1.55 (1.34-1.78)	-	1.48 (1.27-1.73)	-	1.55 (1.28-1.88)	-
Morphine	1.15 (0.96-1.38)	-	1.08 (0.90-1.31)	-	1.03 (0.84-1.26)	-
Dementia drugs	2.49 (2.24-2.76)	-	2.47 (2.21-2.77)	-	2.22 (1.93-2.56)	-

* P ≤.05 versus dying of AD

ICU: Intensive care unit; LOS: Length of stay; ODC: One-day care; GP: General practitioner; CPR: cardiopulmonary resuscitation

[a] Odds Ratio were obtained by logistic regression controlled for age, sex, household type, housing comfort, attained educational level, urbanization level of the municipality of residence, net taxable income, having a cancer diagnosis, comorbidity index, level of care need and place of death

[b] Likelihood Ratio were obtained by a general linear model controlled for age, sex, household type, housing comfort, attained educational level, urbanization level of the municipality of residence, net taxable income, having a cancer diagnosis, comorbidity index, level of care need and place of death

[The level of care was determined on the presence of a specific nomenclature code available in the healthcare data.
(In Belgium, the level of care burden is based upon the total KATZ-score. This score determines which level of care is provided to the specific patient and determines the amount of refund based upon a specific nomenclature code.)]

PART III

ECONOMIC EVALUATION OF END OF LIFE CARE

CHAPTER 7: COST OF DYING

Chapter based on:

Faes, K., J. Cohen, and L. Annemans. The Cost of Dying: A Real-world Population Level Economic Analysis of Different Dying Trajectories. (To be submitted)

ABSTRACT

Background Evidence on end-of-life care costs (EOLCC) at a full population level remains scarce and specific cost-components that drive the costs in different disease groups are poorly evaluated. It remains unknown what differences exist in direct medical EOLCC between people dying of different causes of death and which cost-components incur a high inpatient or outpatient cost.

Aim To compare direct medical EOLCC and cost-components for those dying of COPD, Alzheimer's disease (AD) and cancer across different cost-components.

Methods A retrospective full population cohort study design was used, analyzing linked health claims, pharmaceutical, registry and population databases for all deaths in Belgium in 2015. Based on claims codes and ATC-codes, different cost-components were determined and direct medical EOLCC were compared by calculating expenditures of all medical care within the last year of life.

Results Total direct medical EOLCC of those dying of cancer is substantially higher than of those dying of COPD or AD. Dying of COPD and AD results in lower total inpatient cost in the final year of life. Dying of AD results in a higher total outpatient cost and is characterized by higher home nursing care and GP costs compared to the two other conditions. Out-of-pocket EOLCC for COPD and AD is higher than for cancer. Total and inpatient insurance cost for COPD and AD was lower than for cancer and outpatient insurance costs for AD was found higher.

Conclusion Compared to cancer, dying of COPD and AD results in a lower total, inpatient and outpatient direct medical cost but generates a higher direct medical cost related to intensive care, GP, nursing home care and nursing home. We suggest that improvements of prognosis and recognition of the end-stage in COPD and AD and a further elaboration of home-based palliative care services for these groups can lead to a reduced use of acute services and a reduction of EOLCC.

THE COST OF DYING: A REAL-WORLD POPULATION LEVEL ECONOMIC ANALYSIS OF DIFFERENT DYING TRAJECTORIES

Background

Chronic illnesses such as cancer, chronic obstructive pulmonary disease and dementia are among the leading causes of death in the western part of the world (1). Moreover, it is suggested that over the coming years the prevalence of these diseases is predicted to increase as a result of the ageing population and the greater longevity of people with chronic conditions. Consequently, this epidemiological trend could have major economic consequences for health care systems since previous studies on end-of-life care costs showed that approximately 10 to 25% of all healthcare expenditures could be related to the last year of life (2, 3).

Previous research has observed that certain socio-demographic factors such as age, sex, ethnicity or race as well as time before death influence the level of health care expenses during the last months of life (4, 5). Cause of death also seems to play an important role in the level of health care costs before death. Previous research indicated that expenses before death are highest for cancer and lowest for cardiovascular diseases (6). However, it remains under investigated what differences exist in direct medical end-of-life care costs between people dying of different causes.

Hitherto research has been descriptive in nature using cost estimates or focusing on specific samples or health care settings and has been often restricted to limited comparisons of small samples of specific causes of death mainly directed by evidence on those who suffer and die of cancer or based on small samples comparing healthcare costs of cancer and non-cancer patients. Evidence on end-of-life care costs at full national population level remains scarce and specific cost-components that drive the costs in different disease groups also remains poorly evaluated (7).

Fassbender et al. found that the primary cost in the last year of life were inpatient care for those dying of a terminal illness, skilled nursing facilities for those with organ failure and nursing homes and long-term care for those with frailty. However, no studies have evaluated what specific parts of inpatient or outpatient care drive the costs in different dying trajectories (8).

The objective of this study, therefore, was to determine and compare total end-of-life care costs and specific cost-components influencing end-of-life care costs during the last year of life on a full national population level between three leading causes of death in western societies i.e. cancer, COPD and dementia.

Methods

Design

The present study is a retrospective population-level cohort study . Medical expenditures during the last 360 days of life are compared between three cohorts: those who died of cancer, COPD and Alzheimer's disease in Belgium in 2015.

Setting

For all individuals in the three cohorts all reimbursed health care use and dispensed medication up until 360 days before death was reconstructed. Since health insurance is legally mandatory in Belgium, reimbursement data of all legal residents are available. Moreover, thorough quality procedures result in good reliability of the database for healthcare research.

The Belgian health system is primarily funded through social security contributions and taxation and is based on the principles of equal access and freedom of choice, with a Bismarckian-type of compulsory national health insurance, which covers the whole population and has a broad benefits package. Compulsory health insurance is combined with a private system of health care delivery, based on independent medical practice, free choice of service provider and predominantly fee-for-service payment. The compulsory health insurance is managed by the National Institute for Health and Disability Insurance (NIHDI), which allocates a prospective budget to the different (private) sickness funds to finance the health care costs of their members. All individuals entitled to health insurance must join or register with a sickness fund. Patients in Belgium participate in health care financing through official co-payments and diverse supplements. There are, based on the fee-for-service payment mechanism, two systems of payments: a direct payment, where the patient pays for the full cost of the service and then obtains a reimbursement; and a third-party payer system where the sickness fund pays the provider directly and the patient is only responsible for paying any co-payments, supplements or non-reimbursed services. Hospital financing knows a dual remuneration structure according to the type of services provided: accommodation costs, nursing activities in the nursing units, operating room, and sterilization are financed via a fixed prospective budget system; while medical services, polyclinics and medico-technical services and paramedical activities are mainly paid via a fee-for-service system to the service provider. Pharmaceuticals are exclusively distributed through community and hospital pharmacies and (except for over-the-counter medicines) are partly or fully reimbursed.

Participants

The study population consists of all persons who died of cancer, COPD and Alzheimer's disease (AD) in Belgium during the year 2015 and were selected based on the primary cause of death as recorded on

the death certificate. The period of 360 days before death was defined for analysis purpose based upon the dates related to the specific nomenclature codes or medication dispension dates.

Data sources and linkage

To study direct medical costs of end-of-life care between cancer, COPD and Alzheimer's disease, we used a health care payer and patient perspective and analyzed health care costs incurred by the Belgian third-party payer, the NIHDI and costs incurred by patients (co-payment).

For the study we linked data from seven administrative databases administered by the Intermutualistic Agency (IMA) and Statistics Belgium and one disease registry namely the Belgian Cancer Registry (BCR). A more detailed description of these databases and the procedures for obtaining and linking these data is presented elsewhere (9).

IMA is a Belgian central agency which collects all reimbursement data of health care consumption from all seven sickness funds. Since in Belgium, health insurance is legally mandatory, all reimbursement data of all Belgian citizens is available in the IMA database. Three databases managed by IMA were used in our study: (1) a population database containing socio-demographic data; (2) a health care database containing all reimbursed health care use and associated costs data; and (3) a pharmaceutical database containing all reimbursed dispensed medication and associated costs data. These were linked with four databases from Statistics Belgium: (1) the national demographic database (e.g. containing the household composition of every citizen), (2) the census 2011 (national dataset based on an information extraction from multiple external administrative databases at various administrative levels), (3) the death certificate data and (4) fiscal data about personal income. Finally the data were linked to the BCR database containing diagnostic information (date of diagnosis, type of cancer, and primary cancer type) of all new cancer diagnoses collected by all Belgian hospitals that provide oncological care.

Measures

In order to answer the research question, specific claims codes (called nomenclature codes) were interpreted and aggregated into specific cost-components. We calculated total medical cost as well as total inpatient, outpatient and medication cost. Inpatient (or institutionalized) cost includes any medical service or act that requires an hospitalization or an act which is provided during an admission and stay into a hospital. To qualify as an inpatient, a patient must be under the care of a physician while staying overnight in the hospital.

Outpatient (or ambulatory) cost includes all acts that does not require an overnight stay in a hospital or medical facility. In Belgium, outpatient care is mainly administered in a medical office, hospital, nursing home facility or at home. These inpatient and outpatient costs were further broken down in specific

cost components. For each specific cost-component we calculated the mean out-of-pocket cost, mean insurance cost and mean total cost (i.e. sum of out-of-pocket cost and insurance cost).

Statistical analysis

To investigate potential differences between those who died of Cancer, COPD and AD we compared patient characteristics and medical expenditures. Direct medical cost data were analyzed using a general linear model with medical expenditure as a dependent variable and the disease leading to death (cancer, COPD or AD) as an independent variable, controlling for various potential confounders (age, sex, educational level, household composition, comfort level housing, comorbidity index). Costs were calculated as the sum of all costs of all services received during the last 360 days of life and indexed to 2017. We calculated the adjusted person-level mean cost for each cost component and used a gamma distribution (10) to define differences of each given cost component for those who died of COPD and those who died of AD compared to those who died of cancer and supplementary for those who died of COPD compared to those who died of AD during a 360 days period before death. We set the significance level at $p \leq .05$ to address hypothesis testing and performed all analyses using SAS version 9.3.

Results

A total of 108,959 persons (about 1% of the total population) died during the year 2015. Of these 24.3% died of cancer, 3.8% of COPD and 2.4% of AD (Table 1). For the entire deceased population during the year 2015, total medical cost amounted to 3.4 billion euros of which 55.7% inpatient costs and 44.3% outpatient costs. 6.5% of total direct medical end of life care costs was related to the out of pocket cost and 93.5% was paid by the public insurer. Respectively, 34.2%, 4.2% and 2.0% of total direct medical cost during the last year of life was related to cancer, COPD and AD patients.

Total direct medical cost of the last year of life in cancer decedents amounted to € 42,163 (95% CI 41,790 – 42,536) and was mainly determined by an inpatient cost which was mainly characterized by a high cost related to hospitalization, inpatient specialist care, medication, clinical biology and specific medical and surgical procedures. For COPD decedents, total direct medical cost amounted to € 35,209 (95% CI 34,406 – 36,013) and was dominated mainly by a high inpatient cost (€ 21,602 (95% CI 20,848 – 22,356)) which in turn was characterized by a high hospitalization (€ 20,682 (95% CI 19,963 – 21,402)), inpatient specialist care (€ 3,172 (95% CI 3,035 – 3,308)), clinical biology (€ 1,143 (95% CI 1,106 – 1,180)) and surgical procedures (€ 1,132 (95% CI 1,044 – 1,221)) cost. AD decedents generate a mean total direct medical cost of €26,358 (95% CI 25,821 – 26,894) of which 68.7% consisted of outpatient costs. This outpatient cost was in turn characterized by a high cost related to direct medical nursing home (€ 11,555 (95% CI 11,269 – 11,841)) and home nurse (€ 2,352 (95% CI 2,129 – 2,575)) costs. In all 3 groups,

the largest share of the total direct medical end-of-life care costs was borne by the public insurer (respectively for cancer, COPD and AD decedents 93.5%, 93.7% and 92.7%; Table 2).

Total cost

Multivariable analyses controlling for several covariates and possible confounders indicate that, compared to cancer decedents, COPD decedents generate € 7,200 lower total cost, € 4,509 lower total medication cost, and € 3,432 lower total outpatient cost , but a higher inpatient cost related to intensive care, specialist care, clinical biology, physiotherapy and surgery. Dying of AD lowered total costs with € 15,549, total medication costs with €6,286, and inpatient costs with €16,687 but increased total outpatient costs with €1,138 when compared to cancer decedents (Table 3a,b).

Out of pocket cost (OOPC)

COPD decedents incur €562.76 lower total, €620.47 lower inpatient, €57.66 higher outpatient and € 15.85 higher medication expenses during the last year of life when compared to cancer decedents (Table 3a). AD decedents caused € 842.15 lower total, €1,257.05 lower inpatient, €241.22 lower medication and €414.9 higher outpatient expenses than cancer decedents. (Table 3b).

Insurance cost (IC)

In line with the total costs, the total IC, total inpatient IC and total medication IC for COPD and AD decedents was significantly lower than for cancer. AD decedents generated significant higher outpatient IC when compared to cancer decedents. Specifically, AD decedents generated a €723.99 higher outpatient IC than cancer decedents which was characterized by a significant higher cost for nursing home medical care (€9,902.96), home nurse medical care (€160.93) and general practitioner (€30.35). COPD decedents generated both a lower total outpatient and inpatient IC when compared to cancer decedents, but were characterized by generating a significant higher IC for intensive care, physiotherapy, surgical procedures, home nursing and GPs (Table 3a,b).

Discussion

Our study shows that – accounting for age, gender, educational level, household composition, comfort level of housing and comorbidities – direct medical costs during the last year of life differ between different causes of death and that total medical healthcare cost of those dying of cancer is substantially higher than that of those dying of COPD or AD. Dying of COPD and AD results in a lower total inpatient cost in the final year of life when compared with dying of cancer. Our results also revealed that, compared to cancer, out-of-pocket costs during the last year of life for COPD and AD was higher. In line

with the total costs of care, the total and inpatient insurance cost for COPD and AD was lower than for cancer, whereas the outpatient insurance costs for AD was found higher.

Our study adds several findings to those from previous research. While previous research found that inpatient care (i.e. related to a hospital admission/stay) is a primary cost driver for different trajectories of dying (8), our study, which is to our knowledge the first in-depth analysis of a full national population of cancer, COPD and AD decedents, showed that this only applies to cancer and COPD. However, dying of COPD generates a lower total hospitalization cost than dying of cancer but is characterized by a higher ICU cost. We found that dying of AD generates a relatively higher total medical outpatient cost mainly characterized by a high nursing home, home care and medication cost and lower inpatient medical care cost when compared to those dying of cancer.

Our results show that, compared to those who die of cancer, those who die of COPD or AD generate lower total direct medical costs. Firstly, these differences might partly be explained by the specific end-of-life trajectory (11). COPD is characterized by different stages and patients may often suffer from a number of exacerbations and comorbidities that may have a significant impact on costs at the end of life. Acute exacerbations often result in the uptake of acute services provided at the hospital and those suffering from more than 5 comorbidities generate 60% higher costs. The course of dementia, on the other hand, is characterized by a progressive decline and often results in death due to an acute event such as an infection or progression of another disease. Due to a prolonged decline and related informal caregiver burden, AD patients often reside in an outpatient setting e.g. a nursing home or at home where they receive a number of outpatient medical care acts.

Secondly, the possibility of treatments can be a cost-driving factor. The lack of recent successes in treatment of AD could explain the relatively lower medication and specialist cost. Moreover, the provision of chronic and long-term medical care to AD patients will result in higher outpatient costs. In COPD various analyses report diagnosis primarily in later stages. However, patients who fall into later stages classically exhibit less response to treatment modalities and suffer from a more progressive decline influenced by a number of exacerbations. As a result of this, COPD patients require changes in treatment modalities which result in increases of pharmacotherapy costs and are characterized by an increased number of acute hospital admissions due to acute exacerbations.

Thirdly, prognostic uncertainty and a lack of recognition of the end-stage contribute to different cost patterns. In those dying of COPD prognostic paralysis has been identified in previous research as a possible cause for a relatively high use of intensive resources in end-stage COPD patients. Furthermore, earlier research found that a lack of recognition of the end-stage in those dying of AD results in a relatively low use of specialized palliative care services offered in hospital or at home (12-14). Due to

the fact that over 50% of terminal ill people prefer to be cared for and to die at home and due to efforts and policies to enable more to die at home, improvements in prognostication and recognition of end-stage COPD and AD results in an increase in the use of specialized palliative care services and a higher need for home based health care services at the end of life. At the same time, it is expected that a higher outpatient cost and more specifically a higher out-of-pocket outpatient cost will be generated.

A relevant remaining question for health care policy is what part of these end-of-life care costs could be avoided. In Belgium end-of-life care is still 'treatment-oriented' and the use of specialized palliative care services by those suffering from COPD and AD is low. Although many people with life-limiting illnesses prefer to be cared for and die at home, a significant number dies in the hospital. However the use of specialized palliative care services available at home has been found to decrease the use of hospital based services, increase home death and to reduce overall costs at the end-of-life(17-19).

Moreover, improving prognosis in COPD and AD and improvement in the recognition of the final stage of life in these diseases, partly associated with a timely treatment and development of more effective and affordable cancer, COPD and AD treatment options as well as avoiding unnecessary hospitalizations due to acute unforeseen exacerbations and concomitant diseases, could lead to a more pronounced reduction of end-of-life care costs in those dying of cancer, COPD and AD.

Our study has a number of specific strengths compared to previous studies conducted in other healthcare jurisdictions. First, in contrast to previous research, our results are based on a full national population of cancer, COPD and AD decedents instead of a small or specific sample of cancer, COPD and AD decedents (12, 15). Moreover, the use of a linked full national population database in which all medical healthcare expenses were available on a person and single act-level allowed us to analyze specific inpatient and outpatient cost-components which resulted in a more detailed and comprehensive overview of all medical care costs generated during the last year of life instead of an estimated and more general total cost. Second, although the use of a retrospective design and the cause of death mentioned on the death certificate for end of life care research has been criticized (16-19), the strength of using a retrospective design and cause of death indicated on the death certificate, is that the selection of cases is not dependent on inaccurate physician prognostication of survival and that time frames in relationship to death are well known.

Nevertheless, our study has certain limitations. First, we used administrative databases and cost data to capture direct medical costs in the last year of life and examined only patients who died of cancer, COPD and AD. Earlier research indicated that a retrospective analysis looking only at those who died, and hence not at those who were equally ill but survived, leads to an overestimation of the actual end-of-life care costs (20). Additionally, the lack of certain disease specific information (e.g. the degree of

illness), patient preference data, and specific provider characteristics could also influence the uptake of specific resources, and influencing average costs (21). Previous results showed that end of life care intensity was negatively influence by a higher availability of bed capacities but was positively influenced by end-of-life care training in younger professionals and associated with the physician's age and specialty (22). Nevertheless, the extensive availability of patient and socio-demographic characteristics linked to the specific person-level medical expenses allowed us to make a distinct evaluation of 'real-world' cost differences between those who died of cancer, COPD or AD. Our real-world based results might be considered to represent well actual routine practice and provide valuable insights on the range and distribution of costs caused by the end-of-life phase. Finally, the limitation of using routinely collected population-level healthcare data is that services not covered by the national health insurance were not included. However, in Belgium, data are relatively complete for health care services in the hospital, nursing homes and at home.

Conclusion

Direct medical costs differ between different causes of death. Total medical healthcare cost in the last year of life of cancer is higher than that of COPD or Alzheimer's disease. In COPD, the total inpatient and outpatient costs in the last year of life is lower than in cancer; in AD the outpatient cost is higher mainly due to costs for out-of-hospital services such as family physician consultations, home nursing and nursing home care.

However, development of more effective and affordable cancer, COPD and AD treatment options, avoiding unnecessary hospitalizations due to acute unforeseen exacerbations and concomitant diseases, improvements in prognosis and recognition of the final stage in COPD and AD and improvements in the availability of home-based specialized palliative care services might result in a reduction of end-of-life care costs in those dying of cancer, COPD and AD.

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Table 1. Characteristics of patients dying of Cancer, COPD and Alzheimer's disease

		All deaths (N=108959)	Cancer (n= 26493)	COPD (n= 4140)	Alzheimer's disease (n= 2589)	*P-value*
Mean age		78.7	73.8	78.7	85.8	*<.0001*
Age group (%)						*<.0001*
	18-64	16313 (14.97)	6027 (22.75)	454 (10.97)	20 (0.77)	
	65-74	15764 (14.47)	6440 (24.31)	846 (20.43)	130 (50.2)	
	75-84	30600 (28.08)	8268 (31.21)	1510 (36.47)	844 (32.66)	
	85-94	39340 (36.11)	5307 (20.03)	1216 (29.37)	1433 (55.35)	
	95+	6544 (6.01)	415 (1.57)	114 (2.75)	162 (6.26)	
Gender (%)						*<.0001*
	Male	53139 (48.77)	14815 (55.92)	2555 (61.71)	850 (32.83)	
	Female	55820 (51.23)	11678 (44.08)	1585 (38.29)	1739 (67.17)	
Cause of death (%)						*<.0001*
	Malignancies	26493 (24.31)	26493 (100.00)	0 (0.00)	0 (0.00)	
	Nervous system	9854 (9.04)	0 (0.00)	0 (0.00)	2589 (100.00)	
	Circulatory system	30665 (28.14)	0 (0.00)	0 (0.00)	0 (0.00)	
	Respiratory system	11611 (10.66)	0 (0.00)	4140 (100.00)	0 (0.00)	
	Liver and kidney diseases	2955 (2.71)	0 (0.00)	0 (0.00)	0 (0.00)	
	Other	27381 (25.13)	0 (0.00)	0 (0.00)	0 (0.00)	
Educational level (%)						*<.0001*
	No education	8109 (7.44)	1733 (6.54)	366 (8.84)	205 (7.92)	
	Primary education	33322 (30.58)	6821 (25.75)	1442 (34.83)	897 (34.65)	
	Lower secondary education	25287 (23.21)	6819 (25.74)	954 (23.04)	556 (21.48)	
	Upper secondary education	16877 (15.49)	4944 (18.66)	548 (13.24)	353 (13.63)	
	Higher education	10781 (9.89)	3465 (13.08)	285 (6.88)	233 (9.00)	
Household type (%)						*<.0001*
	Single person household	32941 (30.68)	7908 (29.88)	1298 (31.38)	398 (15.38)	
	Married with no children living in	31888 (29.70)	10772 (40.7)	1353 (32.71)	732 (28.28)	
	Married with children living in	7793 (7.26)	2680 (10.12)	260 (6.29)	103 (3.98)	
	Living together with no children living in	2767 (2.58)	980 (3.7)	115 (2.78)	35 (1.35)	
	Living together with children living in	1104 (1.03)	358 (1.35)	35 (0.85)	7 (0.27)	
	One-parent family	5836 (5.44)	1402 (5.3)	182 (4.4)	74 (2.86)	
	Other household type	2402 (2.24)	453 (1.71)	87 (2.1)	56 (2.16)	
	Collective household	22627 (21.08)	1917 (7.24)	806 (19.49)	1183 (45.71)	
Housing comfort (%)						*<.0001*
	High	42927 (44.30)	12563 (51.61)	1486 (39.74)	1033 (43.79)	
	Average	18921 (19.53)	3618 (14.86)	738 (19.74)	517 (21.92)	
	Low	26169 (27.01)	6413 (26.34)	1144 (30.6)	583 (24.71)	
	None	8887 (9.17)	1749 (7.18)	371 (9.92)	226 (9.58)	
Urbanisation (%)						*0.0894*
	Very high	33419 (30.67)	7958 (30.04)	1293 (31.23)	841 (32.48)	

	High	29865 (27.41)	7637 (28.83)	1146 (27.68)	731 (28.23)
	Average	27914 (25.62)	6928 (26.15)	1071 (25.87)	613 (23.68)
	Low	13752 (12.62)	3309 (12.49)	524 (12.66)	334 (12.9)
	Rural	1528 (1.40)	383 (1.45)	60 (1.45)	34 (1.31)
Charlson comorbidity index (%)					
	0	82615 (76.75)	20830 (78.62)	3634 (87.78)	2311 (89.26)
	1	14313 (13.30)	768 (2.9)	367 (8.86)	202 (7.8)
	2	8768 (8.15)	4390 (16.57)	122 (2.95)	69 (2.67)
	≥3	1949 (1.82)	505 (1.9)	17 (0.41)	7 (0.27)

Table 2. Mean unadjusted costs of medical care during the last year of life

		Unadjusted costs								
		Total cost (€)			Insurance cost (€)			Out of pocket cost (€)		
		Cancer (n= 26493)	COPD (n= 4140)	AD (n= 2589)	Cancer (n= 26493)	COPD (n= 4140)	AD (n= 2589)	Cancer (n= 26493)	COPD (n= 4140)	AD (n= 2589)
All costs										
	Total cost	42163.5	35209.8	26358.2	39416.5	33001.7	24435.2	2747	2208.1	1923,0
Inpatient costs										
	Total inpatient cost	25237.3	21602.4	8246.4	23531.8	20499.9	7780.2	1705.5	1102.5	466.1
	Hospitalisation (Total)	24046.8	20682.8	7912.2	22812.9	19922.6	7589	1234	760.2	323.2
	Intensive care unit	1387.6	3534.4	109.2	1331.7	3435.9	105.9	55.9	98.6	3.3
	Palliative care unit	2100.1	226	121.5	2035.4	220.4	118.3	64.7	5.7	3.2
	D-ward	13499.2	8876.3	1105.5	12859.7	8543.1	1061.5	639.5	333.2	44
	G-ward	2745.7	5009.2	4696.1	2632.4	4829.4	4510.8	113.3	179.8	185.3
	Psychogeriatric ward	109.6	198.7	786.4	104.7	192.3	746.8	4.9	6.4	39.6
	Other wards	4204.7	2838.2	1093.6	3849	2701.7	1045.7	355.7	136.5	47.9
	Healthcare professionals									
	General practitioner	35.3	17.6	12.3	31.5	16.3	10.9	3.7	1.3	1.4
	Specialist	3813.6	3172	836.2	3207.1	2934.3	743.8	606.6	237.8	92.3
	Other healthcare professionals	15.5	12	3	14.3	11.2	2.8	1.2	0.8	0.2
	Medication	1717.5	626.1	161.8	1556.5	498.3	123.4	161	127.8	38.4
	Other pharmaceutical deliveries	463.3	94.7	21.3	463	94.6	21.3	0.2	0.1	0
	Medical supplies	435.1	222.9	95.9	346.8	181.4	75.4	88.3	41.5	20.5
	Clinical Biology	1248	1143.6	406.3	1205.4	1123.8	400.9	42.7	19.8	5.4
	Medical imaging	780.3	587.6	182.9	697.4	554.9	173.7	82.9	32.7	9.2
	Fysiotherapy	195.6	335.3	116.7	142.9	261.9	84.7	52.7	73.5	32

	Surgical procedures	1033	1132.8	118.8	844.4	1100	112.3	188.6	32.9	6.4
	Other medical procedures	1286.1	842.6	190.5	1116.2	765.9	165.2	169.9	76.7	25.3
	Other costs	316.5	212.1	95.5	27.2	33	18.8	289.3	179.1	76.7
Outpatient costs										
	Total outpatient cost	16926.2	13607.3	18111.8	15884.7	12501.8	16654.9	1041.5	1105.5	1456.9
	ER	78.2	93.6	43.2	64	82.7	38	14.3	10.9	5.2
	Nursing home (total)	1647.3	3890.4	11555.1	1647.2	3890.3	11554.7	0.1	0.1	0.4
	Healthcare professionals									
	General practitioner	621.8	735.9	673.4	552.9	650.5	584.9	68.8	85.4	88.5
	Specialist	2700.7	860.5	293.7	2444.3	775.9	261.9	256.5	84.6	31.8
	Home nurse	2210.2	2391.8	2352.2	2199.1	2380.4	2338.7	11.1	11.4	13.6
	Other healthcare professionals	322.7	324.6	385.9	285	300.4	371.8	37.7	24.2	14.1
	Medication	5672.2	2306.4	987.2	5370.5	1958	804.8	301.7	348.4	182.4
	Other pharmaceutical deliveries	278.1	23.3	12.8	264	21.4	9.3	14	1.9	3.5
	Medical supplies	117.4	39	11	86.6	25.2	8.8	30.9	13.8	2.2
	Clinical Biology	830.6	232.2	143.6	760.4	212.5	129.4	70.1	19.7	14.2
	Medical imaging	730.4	164.9	66.7	689.7	157	62.6	40.7	7.9	4.1
	Fysiotherapy	284.6	588	261.4	243	510.4	222	41.6	77.6	39.5
	Surgical procedures	111.7	115.5	23.5	101	107.2	23	10.7	8.3	0.5
	Other medical procedures	1423.3	586.4	69.9	1393.1	574	67.2	30.2	12.4	2.7
	Other costs	786.1	1624.7	1316.2	553.2	1192.7	245.7	232.9	432	1070.5
Medication costs										
	Total medication cost	7389.7	2932.5	1149.1	6927.1	2456.4	928.2	462.7	476.1	220.9

COPD: Chronic obstructive pulmonary disease; AD: Alzheimer's disease - Detailed description of all cost components is included as a supplemental file to this manuscript

Table 3a. Multivariable analysis examining the association between cause of death and costs in the last year of life by cost category (gamma distribution)

		COPD versus Cancer		
		Out of pocket cost	Insurance cost	Total cost
		Cost(€)	*Cost(€)*	*Cost(€)*
All costs				
	Total cost	-562.8*	-6,638.1*	-7,200.8*
Inpatient costs				
	Total inpatient cost	-620.5*	-3,147.6*	-3,768.1
	Hospitalisation (Total)	-486.3*	-3,020.2*	-3,506.4
	Intensive care unit	44.4*	2,113.8*	2,158.2*
	Palliative care unit	-59.0*	-1,777.1	-1,836.1
	D-ward	-311.6*	-4,276.4*	-4,588*
	G-ward	65.7	2,074.0*	2,139.8*
	Psychogeriatric ward	0.6	45.1	45.6
	Other wards	-226.5*	-1,199.5*	-1,426.0*
	Healthcare professionals			
	General practitioner	-2.5	-15.3*	-17.8*
	Specialist	-377.0*	-251.6*	-628.6*
	Other	-0.4	-2.7*	-3.1*
	Medication	-30.7*	-1,048.6*	-1,079.3*
	Other pharmaceutical deliveries	-0.1	-359.9*	-360.1*
	Medical supplies	-46.1*	-159.3	-205.4*
	Clinical Biology	-23.2*	-85.0*	-108.1*
	Medical imaging	-51.4*	-139.9*	-191.4*
	Fysiotherapy	20.2*	115.1*	135.4*
	Surgical procedures	-160.1*	269.5*	109.4*

	Other medical procedures	-95.2*	-334.4*	-429.6*
	Other costs	-115.2*	13.9	-101.4*
Outpatient				
	Total outpatient cost	57.7*	-3,490.4*	-3,432.8*
	ER	-3.3*	17.8*	14.4*
	Nursing home	0.0	2,188.1*	2,188.1*
	Healthcare professionals			
	General practitioner	16.6*	94.6*	111.3*
	Specialist	-174.1*	0*	-174.2*
	Home nurse	1.2*	195.6*	196.8*
	Other	-13.7	20.3*	6.6*
	Medication	46.6*	-3,477.3*	-3,430.7*
	Other pharmaceutical deliveries	-12.1*	-241.1*	-253.2*
	Medical supplies	-16.8*	-61.2*	-78,0*
	Clinical Biology	-51.4*	-553.2*	-604.6*
	Medical imaging	-33.7*	-535.6*	-569.3*
	Fysiotherapy	36.4*	268.9*	305.3*
	Surgical procedures	-1.7*	8.2*	6.5*
	Other medical procedures	-18.3*	-791.5*	-809.8*
	Other costs	195.4*	638.3*	833.7*
Medication costs				
	Total medication cost	15.9*	-4,525.8*	-4,510.0*

COPD: Chronic obstructive pulmonary disease

*p<.05

Detailed description of all cost components is included as a supplemental file to this manuscript

Table 3b. Multivariable analysis examining the association between cause of death and costs in the last year of life by cost category (gamma distribution)

		AD versus Cancer		
		Out of pocket cost	Insurance cost	Total cost
		Cost(€)	*Cost(€)*	*Cost(€)*
All costs				
	Total cost	-842.2*	-14,706.7*	-15,548.9*
Inpatient				
	Total inpatient cost	-1,257.1*	-15,430.7*	-16,687.8*
	Hospitalisation (Total)	-927.6*	-14,916.4*	-15,844.0*
	Intensive care unit	-53.0*	-1,209.9	-1,263.0
	Palliative care unit	-62.3*	-1,896.4*	-1,958.6*
	D-ward	-605.4*	-11,634.3*	-12,239.6*
	G-ward	74.9*	1,928.9	2,003.8
	Psychogeriatric ward	32.2	610.9*	643.1
	Other wards	-314.1	-2,715.7*	-3,029.8*
	Healthcare professionals			
	General practitioner	-2.5*	-20.3*	-22.8*
	Specialist	-529.1*	-2,427.9*	-2,957.0*
	Other	-1.0	-11.4*	-12.4*
	Medication	-121.0*	-1,414.0*	-1,535.0*
	Other pharmaceutical deliveries	-0.2*	-435.1*	-435.3*
	Medical supplies	-66.9	-267.1*	-333.9
	Clinical Biology	-38.1*	-790.7*	-828.8*
	Medical imaging	-75.7*	-517.5*	-593.2*
	Fysiotherapy	-20.9	-57.3	-78.1
	Surgical procedures	-189.1*	-722.0*	-911.1*

	Other medical procedures	-150.5*	-936.3*	-1,084.8*
	Other costs	-214.2*	-2.0*	-216.3
Outpatient				
	Total outpatient cost	414.9*	724.0*	1,138.9*
	ER	-8.9*	-25.2	-34.2*
	Nursing home	0.3	9,903.0*	9,903.3*
	Healthcare professionals			
	General practitioner	19.4	30.4*	49.8*
	Specialist	-229.1*	-2,182.4*	-2,411.5*
	Home nurse	2.7*	160.9*	163.6*
	Other	-25.3*	83.7*	58.4*
	Medication	-120.3*	-4,631.5*	-4,751.7*
	Other pharmaceutical deliveries	-10.9*	-254.1	-265.0
	Medical supplies	-29.3*	-78.4*	-107.7*
	Clinical Biology	-57.1*	-635.1*	-692.2*
	Medical imaging	-37.6*	-630.2*	-667.8*
	Fysiotherapy	-1.6*	-17.9*	-19.5*
	Surgical procedures	-10.3*	-79.7*	-90.1*
	Other medical procedures	-27.9*	-1,320.0*	-1,347.9*
	Other costs	844.4*	-305.5*	538.9*
Medication costs				
	Total medication cost	-241.2*	-6,045.5*	-6,286.7*

AD: Alzheimer's disease

*p<.05

Detailed description of all cost components is included as a supplemental file to this manuscript

Table 3c. Multivariable analysis examining the association between cause of death and costs in the last year of life by cost category (gamma distribution)

		COPD versus AD		
		Out of pocket cost	**Insurance cost**	**Total cost**
		Cost(€)	*Cost(€)*	*Cost(€)*
All costs				
	Total cost	279.4*	8068.7*	8348.1*
Inpatient				
	Total inpatient cost	636.6*	12283.1*	12919.7*
	Hospitalisation (Total)	441.4*	11896.2*	12337.6*
	Intensive care unit	97.5*	3323.7*	3421.1*
	Palliative care unit	3.3	119.3	122.6
	D-ward	293.8*	7357.8*	7651.6*
	G-ward	-9.2*	145.1*	136.0*
	Psychogeriatric ward	-31.6*	-565.8	-597.5*
	Other wards	87.58	1516.2	1603.8
	Healthcare professionals			
	General practitioner	-0.04*	5.0*	5.0*
	Specialist	152.1*	2176.3*	2328.4*
	Other	0.6*	8.7*	9.3*
	Medication	90.2*	365.4*	455.7*
	Other pharmaceutical deliveries	0.1*	75.1*	75.2*
	Medical supplies	20.8*	107.7*	128.5*
	Clinical Biology	14.9*	705.7*	720.7*
	Medical imaging	24.2*	377.6*	401.8*
	Fysiotherapy	41.0*	172.5*	213.5*

	Surgical procedures	29.04	991.5*	1020.5*
	Other medical procedures	55.3*	601.9*	655.2*
	Other costs	98.99	15.9*	114.9
Outpatient				
	Total outpatient cost	-357.2*	-4214.4*	-4571.7*
	ER	5.59	43.0*	48.6*
	Nursing home	-0.3	-7714.9*	-7715.2*
	Healthcare professionals			
	General practitioner	-2.8*	64.3*	61.5*
	Specialist	55.1*	2182.4*	2237.3*
	Home nurse	-1.56	34.7*	33.1*
	Other	11.6*	-63.5	-51.9
	Medication	166.8*	1154.2*	1321.1*
	Other pharmaceutical deliveries	-1.2*	13.1*	11.9*
	Medical supplies	12.5*	17.2*	29.7*
	Clinical Biology	5.7	81.9*	87.7*
	Medical imaging	3.9*	94.6*	98.4*
	Fysiotherapy	38.1	286.7*	324.8*
	Surgical procedures	8.6*	87.9*	96.6*
	Other medical procedures	9.6*	528.5*	538.0*
	Other costs	-650.0*	943.8*	294.9*
Medication costs				
	Total medication cost	257.1*	1519.7*	1776.7*

AD: Alzheimer's disease; COPD: Chronic obstructive pulmonary disease

*p<.05

Detailed description of all cost components is included as a supplemental file to this manuscript

CHAPTER 8: THE EFFECT OF SPECIALIZED PALLIATIVE HOME CARE ON END OF LIFE CARE COSTS

Chapter based on:

Faes, K., J. Cohen, and L. Annemans. A specialized multidisciplinary palliative home care team affects direct medical costs of COPD patients. (To be submitted)

ABSTRACT

Context Specialized home-based palliative care can improve patient health outcomes and decreases unnecessary hospital-based spending. However, evidence about the effects of specialized palliative home care for COPD patients is limited.

Aim To describe how and to what extend the provision of a palliative home care team (MDPHCT) influences direct medical expenditures during the last month of life in those dying with COPD.

Methods We performed a full-population retrospective matched cohort study comparing all Belgian COPD decedents having received support from a PHC team to a comparable control group not having done so. We calculated person-level mean cost for each cost-component and used propensity score matching to compare both cohorts.

Results Using a MDPHCT lowers total costs in the last month of life with €1,979; and increases total outpatient costs with €1,047. The difference in total costs is mainly due to €3,027 lower total inpatient costs and is caused by a lower hospitalization costs and lower expenditures for specialist care, medication and pharmaceutical deliveries, medical-diagnostic treatments and procedures. Higher expenditures of total outpatient costs are mainly generated by expenditures related to GP contacts, home nursing care and physiotherapy and a difference in medication spending.

Conclusion Our results show that a MDPHCT is a sustainable alternative to costly institutional end of life care and show that, for COPD patients at life's end, a shift to more home-based specialized palliative care could reduce the high cost of dying.

Keywords Palliative care; Community-based palliative care team; COPD; Direct medical costs; Full-population; Administrative database

A SPECIALIZED MULTIDISCIPLINARY PALLIATIVE HOME CARE TEAM AFFECTS DIRECT MEDICAL COSTS OF COPD PATIENTS

Background

Due to escalating health care costs at the end-of-life caused by hospitalizations, providing end-of-life care at home has become important to reduce public health care expenditures. Home-based healthcare at the end of life has been shown to improve patient's well-being, to reduce acute care use, and to lower overall healthcare costs [1-5]. As a result, end of life home-based care was identified as a priority in many national end of life care policies, and is seen as a sustainable alternative to costly institutional end of life care. The desire to provide high-quality and cost-effective end-of-life care is therefore causing healthcare systems to shift from a hospital-centric to a community-centric view that provides specialized palliative care to patients at home.

Previous evidence showed that home based palliative care has a positive effect on end-of-life care costs. A 2017 meta-analysis concluded that specialist palliative care interventions are associated with only a small effect on quality of life but results in a reduction of hospital costs, a reduced number of admissions, a shorter length of stay and a reduced use of specific hospital services [6-10]. Moreover, terminal patients receiving specialized palliative care generate lower costs when compared to those receiving usual care [11]. Furthermore, evidence shows that providing home-based palliative care improves patient health outcomes, increases satisfaction, leads to a higher use of palliative care services and decreases unnecessary hospital-based spending [1, 12-15].

Although evidence shows that home-based palliative care has a positive effect on lowering end-of-life care costs in a home situation, there is only scares evidence that this is also the case for those who suffer from COPD. Furthermore, it is indicated that providing appropriate end-of-life care e.g., palliative care has a positive effect on end-of-life care costs is limited Moreover, most of the evidence describing direct medical care costs at the end of life is based on specific or small samples of COPD decedents.

Therefore, in this study, we examine the effect of palliative home care on the costs with regard to the last month of life. The following research question is asked: How and to what extend influences the provision of palliative home care direct medical care expenditures during the last month of life in those dying with COPD.

Design

The present study is a retrospective population-level matched cohort study of all those who died with COPD between 2010 and 2015 in Belgium. Using linked data from seven administrative databases,

medical expenditures during the last 30 days of life were compared between those who died with COPD and received care from a specialized home-based palliative care team during the last 6 months before the last 30 days of life and those who received usual care during this period and did not use any specialized palliative care during the last 2 years of life. To reduce selection bias between both groups and to balance measured covariates across both groups, we applied a propensity score matching.

Setting

For all individuals in the two cohorts all reimbursed health care use and dispensed medication up until 30 days before death was reconstructed. Since health insurance is legally mandatory in Belgium, reimbursement data of all legal residents are available. Moreover, thorough quality procedures result in good reliability of the database for healthcare research.

The Belgian health system is primarily funded through social security contributions and taxation and is based on the principles of equal access and freedom of choice, with a Bismarckian-type of compulsory national health insurance, which covers the whole population and has a broad benefits package. Compulsory health insurance is combined with a private system of health care delivery, based on independent medical practice, free choice of service provider and predominantly fee-for-service payment. The compulsory health insurance is managed by the National Institute for Health and Disability Insurance (NIHDI), which allocates a prospective budget to the different (private) sickness funds to finance the health care costs of their members. All individuals entitled to health insurance must join or register with a sickness fund to receive a refund.

Belgium has region-bound palliative home care which is a separate secondary care service provided by a multidisciplinary palliative home care team (MDPHCT) consisting of a physician, home care nurses and psychologist. A referral to a MDPHCT is mainly requested by the patient's general practitioner (GP) depending on individual context, relatives, involved home care nurses, palliative care nurses in the hospital, or specialists. In Belgium a 'palliative status', defined by a physician is a primary eligibility criteria for receiving a reimbursement of costs related to the palliative phase. The reimbursement of specialized palliative care was up till 2018 restricted to patients with a three months life expectancy. From 2018 on, this law is altered to the surprise question of predicted death between six and twelve months.

Participants

The study population consists of all persons who died with or of COPD in Belgium between 2010 and 2015. Patients who died of COPD were selected based on the primary cause of death as recorded on the death certificate (ICD10-code: J41-44). Since COPD is often not indicated as a primary cause of death

on the death certificate and those suffering from COPD often die of a cardiovascular disease, we extended our population with those who died with COPD.

Those who died with COPD were first identified as dying with (i.e. having a diagnosis of) COPD based on a validated algorithm using medication data from 2 years before death. This validated algorithm was based on existing evidence on algorithms (16-18) to identify different therapeutic options in COPD and subsequently discussed with four experts in COPD treatment and administrative healthcare databases which resulted in an adapted version of the algorithm. The adapted version of the algorithm was finally discussed with healthcare experts in COPD treatment and resulted in the final algorithm based on prescriptions with ATC-code of R03BB04, R03BB05, R03BB06, R03BB07, R03AL04, R03AL03, R03AK06, R03AK07, R03AK08, R03AK10, R03AK11 and the exclusion of a prescription with ATC-code of R03DC01, R03DC03 in order to exclude those suffering from asthma or a COPD-asthma overlapping syndrome. This algorithm was further refined with those deaths for which COPD was recorded on the death certificates as an intermediate or associated cause and had a primary cause of death of cardiovascular diseases (ICD10-codes: I00-I99) indicated.

We defined those who received specialized palliative home care between the last seven and one month before death as receiving a minimum of one home visit from a MDPHCT. A MDPHCT was defined based upon the nomenclature code indicating a MDPHCT visit.

Data sources and linkage

To study direct medical expenditures of end-of-life care between COPD patients receiving specialized palliative care from a MDPHCT, we used a health care payer and patient perspective and analyzed health care costs incurred by the Belgian third-party payer, the NIHDI and costs incurred by patients (co-payment).

For the study we linked data from seven administrative databases administered by the Intermutualistic Agency (IMA) and Statistics Belgium and one disease registry namely the Belgian Cancer Registry (BCR). A more detailed description of these databases and the procedures for obtaining and linking these data is presented elsewhere [19].

IMA is a Belgian central agency which collects all reimbursement data of health care consumption from all seven sickness funds. Since in Belgium, health insurance is legally mandatory, all reimbursement data of all Belgian citizens is available in the IMA database. Three databases managed by IMA were used in our study: (1) a population database containing socio-demographic data; (2) a health care database containing all reimbursed health care use and associated costs data; and (3) a pharmaceutical database containing all reimbursed dispensed medication and associated costs data. These were linked with four

databases from Statistics Belgium: (1) the national demographic database (e.g. containing the household composition of every citizen), (2) the census 2011 (national dataset based on an information extraction from multiple external administrative databases at various administrative levels), (3) the death certificate data and (4) fiscal data about personal income.

Measures

Exposure/non-exposure

The exposure group consisted of those dying with COPD who received specialized palliative home care between the last seven and one month before death as receiving a minimum of one home visit from a MDPHCT. Using specific nomenclature codes, we could identify the uptake and timing of a MDPHCT in those dying with COPD. Those who died with COPD and did not use any form of palliative care between seven and one month before death as well as those who used palliative care during the last month of life were excluded.

The non-exposure or control group consisted of all those dying with COPD and did not have any uptake of specialized palliative care during the last 2 years of life.

Outcome

In order to measure relevant cost outcomes, specific claims codes (called nomenclature codes) were interpreted and aggregated into specific cost-components. We calculated total medical cost as well as total inpatient, outpatient and medication cost during the last 30 days of life and indexed to 2017.

Inpatient (or institutionalized) cost includes any medical service or act that requires an hospitalization or an act which is provided during an admission and stay into a hospital. To qualify as an inpatient, a patient must be under the care of a physician while staying overnight in the hospital.

Outpatient (or ambulatory) cost includes all acts that does not require an overnight stay in a hospital or medical facility. In Belgium, outpatient care is mainly administered in a medical office, hospital, nursing home facility or at home. These inpatient and outpatient costs were further broken down in specific cost components. For each specific cost-component we calculated the mean total cost (i.e. sum of out-of-pocket cost and insurance cost).

Propensity score matching and Statistical analysis

To investigate potential direct medical cost differences we stratified COPD decedents by having received palliative home care provided by a MDPHCT (exposure) and those who received usual care (non-exposure). We calculated the person-level mean cost for each cost component and used propensity score matching to match those who received specialized palliative home care by a MDPHCT to those

who did not. The propensity score was calculated using baseline covariates that were considered relevant predictors for receiving palliative home care. We included socio-demographic covariates such as age, household type, educational level, income, level of housing comfort and level of urbanization and included relevant resource use from 360 days prior to the uptake of a MDPHCT such as the number of hospital and emergency room admissions, the number of GP, specialist and physiotherapist contacts, the number of RX-thorax and the length of stay at a hospital and intensive care unit, which were all found to be predictors of level of disease in COPD, to calculate the propensity and used a greedy one to one case-control propensity score matching algorithm to match. A Wilcoxon rank sum test was used to test for significant differences in costs between the exposure and non-exposure group. All analyses were performed using SAS version 9.3.

Results

Between 2010 and 2015, in Belgium, 58,527 people died with COPD. Of those 1,751 (2.99%) people used a MDPHCT during the last 2 years of life and 422 (0.72%) during the last 210 to 30 days before death. Patient characteristics and resources used before the initiation of an MDPHCT are summarized in Table 1.

After matching, of those who died with COPD and whether or not used a MDPHCT during the last 210 up to 30 days before death, for a number of relevant confounders and care use prior to the use of a MDPHCT, our results showed (Table 2) that total direct medical costs in the last month before death for those who used a MDPHCT between 180 days and 30 days before death and a comparable group that did not use, amount to, respectively, €4,963 and €6,942. Of this, respectively, 45% and 75.8% is generated by inpatient medical care which is mainly characterized by a total hospitalization cost of €4,994 and a specialist care cost of €1,003 for those who receive no MDPHCT and €2,156 and €1,048 for those who do not. 55% and 24.2% of total direct medical costs is caused by a direct outpatient medical care which, in both groups, is generated by direct total medical expenses related to home nurse care, GP contacts and physiotherapy.

The results in table 3 show that the use of a MDPHCT lowers total direct medical costs with €1,979. Despite this reduction, we determined that total direct medical outpatient costs is €1,047 higher when using a MDPHCT compared to no use. Our results show that the difference in total direct medical costs between COPD patients who use a MDPHCT and those who do not use, is mainly due to €3,027 lower total inpatient costs.

This difference in inpatient costs is mainly caused by a lower hospitalization costs and lower medical costs related to expenditures for specialist care, medication and pharmaceutical deliveries, medical-diagnostic treatments and procedures e.g. clinical biology, medical imaging, physiotherapy and medical

procedures. Higher expenditures of total direct medical outpatient costs, on the other hand, are mainly generated by expenditures related to GP contacts, home nursing care and physiotherapy as also a difference in medication spending.

Notwithstanding that the out-of-pocket costs for medication is lower in those who received a MDHPCT compared to those who did not, total medication expenditures for those who received a MDHPCT is €30.3 higher.

Discussion

Our study shows that, in COPD patients, the use of an MDPHCT during the last six to one month before death entails a significant decrease in the total direct medical cost for both patient and insurer. However, our results show that this decrease only applies to the direct inpatient medical costs and that the use of an MDPHCT increases the direct medical outpatient costs for both insurer and patient compared to no use of an MDPHCT. More specifically, the use of home or community-based specialized palliative care, such as an MDPHCT, reduces expenditures for hospitalization, specialist care, pharmaceutical deliveries, clinical biology, medical imaging, physiotherapy and medical procedures and also increases the medical cost for outpatient GP contacts, home nursing care, physiotherapy and medication spending during the last month of life in COPD patients.

Our results confirm previous limited 'general' results with regard to the use of home or community-based specialized palliative care teams. Spillsbury et.al (2017) found that community-based specialist palliative care was associated with a decrease hospital costs during the last year of life. They also stated that it was associated with a reduction of inpatient averaged hospital costs of 9% per hospitalized decedent per day and found reductions for COPD decedents one to 2 months before death [12]. Although they extensively described hospitalization costs for specific diseases, no description of other relevant cost-components were presented for COPD. A previous economic analysis by Pham and Krahn concluded that in-home palliative team care for individuals nearing end of life reduced health care costs and improved health outcomes for patients nearing the end of life and stated that the population impact of this intervention could be potentially large [20]. However, they not specifically described different cost-components in COPD patients. However, a lack of specific results on the effect of community-based specialized palliative home care teams on end-of-life care costs in COPD patients, endorses the importance of our results and we could only describe our results in the light of existing general conclusions.

A lower cost for hospitalization for those who use an MDCPHT can be explained by the specific nature of an MDCPHT. In Belgium, a MDCHPT cooperates with the usual caregivers of the patient (physician, nurse, etc.) and provides support and specialized advice at request of the professionals involved. Due

to the extramural nature of the MDCHPT, the patient will receive minimal in hospital care and a reductions in hospitalization costs can be explained. An MCPHT in Belgium also has a supportive character for the care providers involved such as GP and home nurses. The care with regard to the palliative COPD patient is therefore also provide by an informal care provider. As such, the positive difference in outpatient costs, which is mainly characterized by a higher outpatient cost for GP and home nursing care, can also be explained.

Our results show that the use of an MDCPHT entails a significant decrease for the patient's expenses. However, this positive difference in part of the patient receiving an MDCPHT is not found in the expenditures for outpatient care. Although a palliative (COPD) patient in Belgium is entitled to an increased allowance, the found increased outpatient costs, when using an MDCPHT, can be explained by a high medication cost, which is also determined in our results, for which not a full increased reimbursement exists. Moreover, since care in the final stage of life for a palliative COPD patient, due to the extramural nature of a MDCHPT, is mainly provided in a home setting, GPs and home nurses remain the first providers of this care and explains the increase in costs for care provided by them.

In contrast to the lower hospitalization costs, our results show an increase in the direct medical costs related to a palliative care unit. This result can be explained by the determination of a palliative status, deterioration of the general condition or the presence of co-morbidities in COPD patients or burden of the informal caregiver. Earlier research showed that the prognosis of the final phase in COPD patients is difficult to determine and that informal caregivers of COPD patients are often overburdened during the end-stage. This explains the necessity of an admission to a hospital or PCU and the increase of related direct medical costs.

Limitations

Our results were obtained by using administrative / insurance data and did not contain information about the specific severity of the disease, nor about the specific framework in which the patient was cared for. As a result, these elements could not be included in the matching and a certain heterogeneity between both groups might be possible. However, a propensity score matching was carried out based on relevant socio-demographic, socio-economic variables and resources used before the initiation of a MDPHCT. The inclusion of a CCI and level of care need in the matching process resulted in a one-on-one matching of COPD patients with a comparable socio-demographic, socio-economic situation, a comparable level of care need, a comparable comorbidity index and comparable prior resource use.

Furthermore, our results only relate to reimbursed medical care. Although COPD patients in their last month of life can also use specialized palliative care which is not provided in the form of an MDPHCT

our results clearly indicate that the use of an MDPHCT reduces expenditures related to inpatient medical care.

The use or not of an MDCPHT in our study was determined based upon a specific nomenclature code which gives rise to an increased reimbursement and support of an MDPHCT. Conferment of a palliative status, which is limited to patients with a life expectancy of 3 months, is often the basis for awarding reimbursed specialist palliative care by an MDPHCT. However, previous research showed that the recognition of the end-stage COPD is complicated by the specific course of the disease and that this often leads to a curative approach of the disease.

Conclusion

Our results show that end of life home or community-based care could be a sustainable alternative to costly institutional end of life care and show that, for COPD patient at life's end, a shift to a community-centric view that provides specialized palliative care to patients at home, could reduce the high cost of dying in COPD patients.

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Table 1. Patient characteristics and independent variables following propensity score weighting

		MDPHCT =0 (n= 384)	MDPHCT =1 (n=384)
Mean age		80.77	78.16
Age group (%)			
	18-64	6.25	10.94
	65-74	14.32	19.79
	75-84	41.93	40.89
	85+	37.5	28.39
Gender (%)			
	Male	63.28	60.68
	Female	36.72	39.32
Educational level (%)			
	No education	10.42	7.55
	Primary education	32.29	34.38
	Lower secondary education	23.96	26.04
	Upper secondary or higher education	20.57	21.88
Household type (%)			
	Single person household	23.96	23.44
	Married or living together with no children living in	46.88	50.78
	Married or living together with children living in	6.77	8.07
	Other household type	22.4	17.71
Housing comfort (%)			
	High	38.28	44.27
	Average	18.23	14.32
	Low	25	26.82
	None	8.59	7.29
Income category (%)			
	Lowest 40%	8.07	12.5
	Middle 20%	60.42	57.81
	Highest 40%	31.51	29.69
Urbanisation (%)			
	Very high	28.65	29.69
	High	26.3	26.56
	Average	29.95	27.34
	Rural	13.28	15.89
Charlson comorbidity index (%)			
	0	88.54	87.24
	1	8.33	7.29
	≥2	3.13	5.47

Specific resource use 180-720 days before death (mean)	Number hospital admissions	3.02	3.06
	Mean LOS hospital	34.82	35.5
	Number GP contacts	28.61	27.64
	Number Specialist contacts	6.86	7.61
	Mean LOS ICU	1.05	0.96
	Number RX-thorax	5.01	5.31
	Number ER admissions	1.57	1.68
	Number fysiotherapist contact	60.92	64.72
	Number invasive ventilations	0.29	0.29

Table 2. Mean costs of medical care during the last 30 days of life by receiving MDPHCT

		Mean costs					
		Total cost (€)/SE		Insurance cost (€)/SE		Out of pocket cost (€) /SE	
		MDPHCT =0	MDPHCT =1	MDPHCT =0	MDPHCT =1	MDPHCT =0	MDPHCT =1
All costs							
	Total cost	6,942 (319.8)	4,963 (213.5)	6,595 (306.0)	4,761 (203.3)	346.9 (21.8)	201.8 (17.7)
Inpatient							
	Total inpatient cost	5,259 (338.2)	2,233 (222.4)	5,004 (323.9)	2,110 (211.5)	254.6 (20.7)	122.6 (15.9)
	Hospitalisation (Total)	4,994 (316.8)	2,156 (215.9)	4,821 (307.3)	2,067 (207.8)	172.0 (14.0)	88.6 (12.8)
	Intensive care unit	1,160 (190.2)	179.5 (57.8)	1,129 (185.3)	175.2 (56.6)	30.2 (6.1)	4.2 (1.5)
	Palliative care unit	117.8 (46.7)	585.1 (117.6)	115.0 (45.8)	565.7 (113.9)	2.7 (1.0)	19.4 (4.1)
	D-ward	2,062 (199.9)	1,048 (157.2)	1,992 (194.2)	1,002 (150.8)	68.9 (7.4)	46.9 (10.9)
	G-ward	1,354 (172.3)	303.2 (71.7)	1,298 (165.6)	287.1 (67.8)	55.6 (9.5)	16.1 (4.6)
	Psychogeriatric ward	37.2 (37.2)	0.0 (0.0)	36.0 (36.0)	0.0 (0.0)	1.2 (1.2)	0.0 (0.0)
	Other wards	263.1 (62.9)	39.7 (23.4)	249.7 (59.8)	37.7 (22.2)	13.4 (3.8)	2.0 (1.2)
	Healthcare professionals						
	General practitioner	5.7 (1.6)	7.7 (2.4)	5.6 (1.6)	6.6 (6.2)	0.2 (0.1)	1.1 (0.4)
	Specialist	1,003 (109.3)	228.3 (31.8)	959.8 (108.2)	198.4 (28.0)	43.1 (7.6)	30.0 (10.2)
	Other	1.3 (0.6)	0.2 (0.1)	1.1 (0.5)	0.2 (0.1)	0.0 (0.0)	0.0 (0.0)
	Medication	227.8 (35.6)	89.3 (17.0)	184.7 (33.8)	74.0 (16.3)	43.1 (5.3)	15.4 (1.8)
	Other pharmaceutical deliveries	46.9 (13.4)	5.7 (2.0)	46.9 (13.4)	5.7 (2.0)	0.0 (0.0)	0.0 (0.0)
	Medical supplies	38.5 (11.8)	13.2 (9.8)	32.0 (10.4)	11.5 (9.0)	6.5 (1.8)	1.7 (0.9)
	Clinical Biology	301.4 (18.4)	123.8 (11.9)	296.6 (18.0)	119.5 (11.3)	4.7 (2.1)	4.3 (2.2)
	Medical imaging	179.8 (13.2)	49.5 (5.9)	173.0 (12.7)	45.9 (5.5)	6.8 (1.9)	3.6 (1.2)
	Fysiotherapy	81.0 (7.8)	32.7 (5.1)	64.0 (6.4)	25.1 (4.1)	16.9 (1.7)	7.7 (1.4)
	Surgical procedures	437.1 (82.4)	49.8 (13.7)	435.1 (82.3)	46.8 (13.6)	2.0 (1.8)	3.0 (1.7)
	Other medical procedures	254.3 (32.5)	55.9 (11.1)	241.8 (32.0)	48.1 (9.8)	12.5 (2.5)	7.8 (3.2)
	Other costs	61.0 (9.9)	21.9 (3.6)	14.0 (5.9)	0.1 (0.1)	47.0 (7.4)	21.8 (3.6)
Outpatient							
	Total outpatient cost	1,683 (68.8)	2,730 (82.5)	1,591 (67.9)	2,650 (81.7)	92.3 (7.4)	79.2 (6.2)
	ER	21.4 (1.7)	11.6 (1.4)	19.0 (1.5)	10.6 (1.3)	2.5 (0.3)	1.0 (0.2)
	Nursing home	123.3 (16.1)	69.5 (11.8)	123.3 (16.1)	69.5 (11.8)	0.0 (0.0)	0.0 (0.0)
	Healthcare professionals						
	General practitioner	156.7 (8.5)	250.9 (10.6)	141.7 (8.3)	244.8 (10.5)	15.0 (1.2)	6.1 (1.0)
	Specialist	119.4 (11.1)	58.1 (8.3)	110.7 (10.6)	53.6 (7.9)	8.7 (1.0)	4.5 (0.6)

Home nurse	527.7 (35.7)	1,272 (49.4)	527.1 (35.7)	1,271 (49.4)	0.7 (0.3)	0.3 (0.1)
Other	37.8 (9.6)	90.1 (21.5)	37.6 (9.6)	88.9 (21.4)	0.2 (0.1)	1.2 (0.7)
Medication	252.9 (15.9)	421.6 (30.3)	217.2 (15.0)	375.6 (29.7)	35.6 (1.6)	46.0 (2.2)
Other pharmaceutical deliveries	2.5 (0.9)	5.0 (3.7)	1.9 (0.7)	4.7 (3.6)	0.6 (0.5)	0.3 (0.3)
Medical supplies	1.4 (0.3)	2.3 (0.5)	1.2 (0.3)	2.2 (0.5)	0.2 (0.1)	0.1 (0.0)
Clinical Biology	37.0 (2.7)	30.4 (2.6)	33.2 (2.5)	27.2 (2.4)	3.8 (0.4)	3.1 (0.3)
Medical imaging	20.0 (2.9)	8.1 (2.1)	18.9 (2.8)	7.6 (2.0)	1.1 (0.3)	0.4 (0.1)
Fysiotherapy	70.0 (6.7)	127.6 (9.7)	62.5 (6.2)	123.1 (9.5)	7.5 (0.9)	4.6 (0.9)
Surgical procedures	9.5 (1.6)	4.2 (1.0)	9.5 (1.6)	4.1 (1.0)	0.1 (0.0)	0.1 (0.1)
Other medical procedures	71.1 (21.5)	72.3 (25.6)	69.9 (21.5)	71.9 (25.6)	1.1 (0.2)	0.4 (0.1)
Other costs	138.7 (12.8)	151.5 (15.0)	118.1 (11.1)	137.4 (14.1)	20.6 (6.9)	14.0 (5.0)
Medication costs						
Total medication cost	480.7 (37.4)	510.9 (38.7)	401.9 (35.8)	449.6 (37.9)	78.8 (5.2)	61.3 (2.7)

Table 3. Differences in mean costs between the use of a MDPHCT during the last 180 and 30 days before death.

		MDPHCT VS no MDPHCT		
		Out of pocket cost	Insurance cost	Total cost
		Cost(€)	*Cost(€)*	*Cost(€)*
All costs				
	Total cost	-145.1*	-1,834*	-1,979*
Inpatient				
	Total inpatient cost	-132.0*	-2,894*	-3,026*
	Hospitalisation (Total)	-83.4*	-2,755*	-2,838*
	Intensive care unit	-26.0*	-954.4*	-980.4*
	Palliative care unit	16.6*	450.7*	467.3*
	D-ward	-22.0*	-991.2*	-1013*
	G-ward	-39.4*	-1012*	-1051*
	Psychogeriatric ward	-1.2	-36.0	-37.2
	Other wards	-11.5*	-212.0*	-223.5*
	Healthcare professionals			
	General practitioner	1.0*	1.0	2.0
	Specialist	-13.1*	-761.4*	-774.5*
	Other	0.0	-1.0	-1.1
	Medication	-27.7*	-110.7*	-138.4*
	Other pharmaceutical deliveries	0.0	-41.1*	-41.1*
	Medical supplies	-4.8*	-20.5*	-25.3*
	Clinical Biology	-0.4*	-177.1*	-177.6*
	Medical imaging	-3.2*	-127.0*	-130.3*
	Fysiotherapy	-9.3*	-39.0*	-48.2*
	Surgical procedures	1	-388.3*	-387.3*
	Other medical procedures	-4.8*	-193.7*	-198.5*
	Other costs	-25.2*	-13.9*	-39.1*
Outpatient				
	Total outpatient cost	13.1*	1,060*	1,047*
	ER	-1.4*	-8.4*	-9.8*
	Nursing home	0	-53.8	-53.8
	Healthcare professionals			
	General practitioner	-8.9	103.1*	94.2*
	Specialist	-4.2*	-57.1*	-61.3*

	Home nurse	-0.4*	744.4*	744.0*
	Other	0.9	51.4	52.3
	Medication	10.3*	158.4*	168.7*
	Other pharmaceutical deliveries	-0.3	2.8	2.5
	Medical supplies	-0.1	1	0.9
	Clinical Biology	-0.6	-5.9*	-6.6*
	Medical imaging	-0.7*	-11.2*	-11.9*
	Fysiotherapy	-3.0	60.6*	57.6*
	Surgical procedures	0.0	-5.4*	-5.3*
	Other medical procedures	-0.7	2.0*	1.3*
	Other costs	-6.6*	19.4	12.8
Medication costs				
	Total medication cost	-17.4*	47.7	30.3

* p≤.05

PART IV

GENERAL DISCUSSION

CHAPTER 9: GENERAL DISCUSSION & RECOMMENDATIONS

INTRODUCTION

In the final part of this dissertation, the main findings of this project are elucidated and a reflection and discussion is provided. Subsequently, important methodological considerations as well as strengths and limitations of this project are discussed. Finally, recommendations for the healthcare and policy sector will be alleged and implications and suggestions for future research are proposed.

As stated in the introduction of this dissertation, health care costs are rising rapidly when life enters a final phase, and in an age of increasing healthcare costs and limited revenues, policy makers and health care payers are very interested in how much the care provided to a terminally ill patient costs. However, as was indicated, evidence on costs and resource use of terminally ill patients available to inform policy makers is scarce and limited research available to Belgian policy makers and health care payers focuses only on specific care settings or disease groups, but does not provide an overview of the current use of resources and costs of end-of-life care within the Belgian population.

1. MAIN FINDINGS

In what follows, the main results from previous chapters are summarized in 3 separate themes that cover the main lines of this thesis: linking administrative and disease-specific databases to study end-of-life care on a population level (theme 1), health care resource use (theme 2) and costs (theme 3) of end-of-life care among the COPD and Alzheimer's disease population.

1.1. Linking administrative and disease-specific databases to study end-of-life care on a population level

Previous findings, with regard to end-of-life resource use and its related costs, are mainly directed by evidence on those who suffer and die from cancer or are based upon small samples of cancer and non-cancer patients. Moreover, limited research available to Belgian policy makers and health care payers mainly focuses on specific care settings or disease groups, but does not provide an overview of the current use of resources and costs of end-of-life care within the Belgian population. However, in chapter 3 we examined the possibilities which major opportunities administrative data can provide to identify populations dying of specific diseases such as chronic obstructive pulmonary disease or Alzheimer's disease in order to monitor, describe and evaluate patterns of resource use and costs of end-of-life care within and across different trajectories of dying on a population level.

After thorough exploration, we found that several healthcare institutions across Belgium generate, store and exchange large amounts of individual patient data. Although these 'big data' serve a more administrative purpose, we determined that they offer a number of exceptional strengths in studying end-of-life care from a public health perspective. They have a well-defined population and include sub-groups or difficult-to-reach populations such as those at the end-of-life. Since administrative data are standardized and continuously collected they enable trend analyses and longitudinal studies. Moreover, administrative data are already collected and relatively inexpensive when compared to original data collection. Besides, the expanding availability and quality of administrative data makes them very interesting to use in public health research. However, we also determined that the use of administrative data in end-of-life research is still under-explored due to different shortcomings. First, administrative data are not designed for research and as such not directly usable to evaluate the quality of dying. Secondly, they are not well structured and often specific socio-economic, socio-demographic and disease, patient or health provider specific variables, that are required in end-of-life research, are split up between different independent databases and administrators. However, we linked these different administrative databases with specific health claims databases and disease-specific registries, and were able to construct a comprehensive and usable 'linked administrative database' which can be used to study resources and costs of end-of-life care on a full population level.

After examination of the existing administrative, disease-specific and health claims databases available in the Belgian social security and healthcare system, we identified eight suitable population-level databases, managed by three different organizations, to study resource use and costs of end-of-life care for a full Belgian population of Cancer, COPD and Alzheimer's disease patients at the end-of-life. The Intermutualistic Agency (IMA) manages the databases that included all reimbursement data of health care consumption from all seven healthcare insurers i.e., a health care database containing health care use and costs data of both ambulatory and hospital care and a pharmaceutical database containing medication dispensing and cost data as well as a population database containing socio-demographic data of all insured persons. The IMA databases provide information on an individual level across the entire Belgian population but does not contain information regarding medical diagnoses or any disease specific information. The second administrator, the Belgian cancer Registry (BCR), was identified to identify people who died with cancer. The BCR manages a database with diagnostic information on all incidences of cancer i.e., date of diagnosis, type of cancer and tumor node metastasis classification of malignant tumors. Since no similar registries are available to identify those who died with or from COPD or Alzheimer's disease, the death certificate data was identified as an additional database. Death certificate data in Belgium are collected by the three semi-autonomous regions in the country and are integrated by Statistics Belgium, the third initial identified administrator, into one national database.

This database contains the causes of death and associated causes of death for all decedents. Statistics Belgium also manages the national demographic database containing nationality and household composition, data from the Socio-economic Survey 2001 and Census 2011 containing information about the educational level, occupation and housing characteristics as well as the IPCAL dataset containing fiscal data. These socio-economic and socio-demographic variables were needed since they were all described as influencing factors affecting end-of-life care patterns.

However, none of the identified databases contains any information regarding the specific diagnosis (with the exception of BCR data). To include more specific diagnostic and clinical data to the data, the Minimal Hospital dataset, which contains clinical information associated with hospitalization, was looked at for possible inclusion. However, this database is limited to in-hospital data only which restricted the study population.

Nevertheless, clinical information can be abstracted from health care claims data using specific algorithms. Obtaining cause of death information and using healthcare claims data makes up for the lack of clinical data. As such, the Minimal Hospital dataset was found unnecessary.

All these identified databases were deterministic linked into one integrated database by a common unique identifier i.e., social security number. Although, the death certificate database does not contain this identifier. Therefore, Statistics Belgium performed a linkage between the death certificate database and national registry database based on date of birth, sex and municipality of residence. Finally, unique linkage was performed for 98.4% of deaths from whom all health care information from the last two years prior to death was provided for further research described in part 2 and 3.

1.2. End-of-life resource use among those with Chronic Obstructive Pulmonary disease and Alzheimer's disease

Resource Use and Health Care Costs of COPD Patients at the End of Life: A Systematic Review

In chapter 4 we reviewed the existing evidence on end-of-life resource use among those suffering from COPD. Our findings, based on ten included studies between 2006 and 2015, illustrate that the terminal disease trajectory of COPD patients is associated with a high use of acute resources caused by the fact that end-of-life care in COPD patients is mainly focused on prolonging life with a prevailing tendency toward aggressive care.

We determined that acute hospital visits, ICU admissions, physician visits and the use of invasive interventions and medication were the key drivers of resource use of terminal COPD patients and found that the differences in resource use of COPD patients during their last months of life were mainly caused by the presence of comorbidities and exacerbations at the end of life and were influenced by the geographic setting in which terminal COPD patients received care or by the level or stage of the disease.

One of the key drivers indicated by previous literature was the use of acute hospital services. Previous results show that during the last year of life, COPD patients have a median number of two hospitalizations with a median length of stay of 14 days. However, it was also found that the proportion of those suffering from COPD being hospitalized and the number of hospitalizations increases when COPD patients near the final months of life. During the last month of life, results of the included studies indicate that hospitalization of those dying from COPD is mainly characterized by an intensive care unit stay with a median length of stay at an ICU of those dying of COPD varying between five and eight days and a median ventilator support of five days. We found that the use of invasive and non-invasive ventilation is particularly prevalent in COPD patients at the end of life. Results of the included studies show that up to 13% of COPD patients receives invasive ventilation during the last three years of life and that almost one quarter receives non-invasive ventilation during the last six months. More specific, one of the included studies on home-ventilated patients at the end of life, showed that almost two-thirds receive non-invasive ventilation with an average daily ventilation time of 12 hours during the last three months of life which indicates that the place of end-of-life care in COPD patients might also influence the nature of intensity.

Concerning drug use during the last year of life we stated that its use differs among causes of death and sociodemographic characteristics. Specifically, during the last year of life, an increasing number of comorbidities results in a 60% increase in prescriptions for those with five or more comorbidities and women tend to have higher levels of mean medication use than men. We found that ,in general, COPD patients have 47.2 prescriptions in the last year of life which increases as they approach end of life. More specific, 25% and 17% of COPD patients in their last six months of life receive a prescription for an opioid or benzodiazepine, respectively.

Based on the results of the included studies we found that, during the last three years of life, COPD patients have seven or more contacts with a general practitioner. Although the number of contacts with a general practitioner remains stable when approaching end of life, COPD patients have a number of five consultations until one year before death and over 75 per cent has at least one primary care visit in the last six months of life. Results of our review also show that very few patients who die of COPD use palliative care services that are available in acute care hospitals or home care settings which indicates

that a majority of COPD patients does not benefit from symptom management expertise and a consistent approach of a palliative care interdisciplinary team at the end of life.

Resource use during the last 6 months of life among COPD patients: a population level study

Based on the results of the systematic review described in chapter 4, we found that the terminal disease trajectory of COPD patients is associated with a high use of acute resources. The reasons, described in previous research, why COPD patients receive this inappropriate care are complex and a number of barriers were cited why appropriate end of life care is not always provided to this vulnerable group. It has previously been found that these barriers were mainly related to the prognostic accuracy of patients' survival and the existence of comorbidities. However, based on the results of our systematic review we were not able to describe the exact influence of specific comorbidities on end-of-life care resource use. Therefore, in Chapter 5 we described the results of a retrospective, full population analysis of Belgian decedents in which resource use during the last six months of life was compared between (1) those who died of COPD, (2) those who died of cardiovascular disease and with COPD and (3) those who died of lung cancer and with COPD.

Based on the analysis of linked administrative data of fiscal year 2012, we found that the presence of lung cancer and cardiovascular diseases as a primary cause of death influences resource use in COPD patients at life's end. We found that COPD patients who have a primary cause of death of lung cancer use less intensive resources during the last 6 months of life as compared to those who have a primary cause of death of COPD or cardiovascular diseases, are more prone for using palliative care services offered in a palliative care unit or at home and receive more medication that provides symptomatic benefits to patients at the end of life. Moreover, our results show that COPD patients who died of their COPD and those who died of a cardiovascular disease have a comparable resource use although the latter receive less non-invasive ventilation and have a higher chance of being reanimated.

Our results indicated that those who died of COPD were more likely to be admitted to an ICU or to have a stay in a nursing home; were less likely to receive opioids, sedatives and morphine and less likely to use palliative care services at a palliative care unit or at home when compared to those who died of lung cancer. When compared to those with an underlying cause of death of lung cancer or cardiovascular disease, those who died of COPD were more likely to receive non-invasive ventilation, oxygen and COPD drugs.

COPD patients who died of lung cancer had a higher proportion of specialist contacts as compared to those who died of COPD or cardiovascular diseases . They also had a higher proportion of hospital and one-day care admission and received more medical imaging.

We found that those who died of cardiovascular disease were at higher risk of being reanimated when compared to those with an underlying cause of death of COPD or lung cancer and were less likely to use palliative care services at a palliative care unit or at home when compared to those who died of lung cancer. When compared to those who died of COPD, those dying of cardiovascular diseases had a comparable use of hospital, ICU and home care services and had a comparable use of opioids, sedatives and morphine.

Finally, there was no difference between the three groups for emergency room admission, general practitioner contacts, gastric tube, urinary tract catheter and spirometry. Overall, those who died of cardiovascular diseases had a comparable resource use during the last 6 months as compared to those who died of COPD.

Resource use during the last 6 months of life among those dying with and of Alzheimer's disease

In Chapter 6, we examined, using a 2012 full population linked administrative and health claims database, differences in medical resource use during the final six months of life among people suffering from Alzheimer's disease and compared this resource use between those who were, based on a specific validated algorithm, diagnosed with Alzheimer's disease but for whom Alzheimer's disease was not formally identified as the underlying cause of death on the death certificate (i.e., dying with AD) and those who had Alzheimer's disease indicated as the underlying cause of death on the death certificate (i.e., dying of Alzheimer's disease).

We found that those dying with Alzheimer's disease had a higher probability of having at least one hospital admission, had more ICU stays , more home care services use and were more often admitted to a palliative care unit . Those dying with Alzheimer's disease received slightly less often palliative home care services with a lower number of palliative home care days . Those dying both with and of Alzheimer's disease had a mean number of 12 contacts with a general practitioner. However, a greater proportion of those dying with Alzheimer's disease had specialist contacts. Moreover, those dying with Alzheimer's disease stayed slightly less in a nursing home compared to those who died of AD. Those who died with Alzheimer's disease received more invasive ventilation, were more resuscitated and had higher use of medical imaging as compared with those who died of Alzheimer's disease. Those dying with Alzheimer's disease slightly more often use opioids, morphine, and sedatives. The use of these medications, however, increases substantially during the final six months of life in those suffering from Alzheimer's disease. Yet, the use of dementia drugs was lower in those dying of Alzheimer's disease and remained stable in those who died with Alzheimer's disease but decreased in those who died of.

After controlling for disease-specific, socio-economic and socio-demographic factors, the differences in resource use between those who had Alzheimer's disease as an underlying cause of death and those who had not maintained. Our results show that, when compared with those who died of Alzheimer's disease, the odds of all resources were higher except for the admission on a palliative care unit, opioids and oxygen prescriptions. Although, the odds of palliative home care was higher for those who died with Alzheimer's disease, the number of days on which those who died with Alzheimer's disease received palliative care was lower.

1.3. Direct medical End-of-life care costs among those with Chronic Obstructive Pulmonary disease and Alzheimer's disease

A Real-world Population Level Economic Analysis of Different Dying Trajectories

In chapter 7 we compared direct medical expenditures during the last 360 days of life between three cohorts: those who died of cancer, COPD and Alzheimer's disease. Our study shows that total direct medical cost of the last year of life in cancer decedents amounted to € 42,163 mainly determined by an inpatient cost. For COPD decedents, we found that total direct medical cost amounted to € 35,209 and that this was also dominated mainly by a high inpatient cost . Moreover, our results showed that AD decedents generate a mean total direct medical cost of €26,358 of which 68.7% consisted of outpatient costs. Our results showed that in all 3 groups, the largest share of the total direct medical end-of-life care costs was borne by the public insurer.

After multivariable analyses controlling for several covariates and possible confounders we found that, compared to cancer decedents, COPD decedents generate € 7,200 lower total cost, € 4,509 lower total medication cost, and € 3,432 lower total outpatient cost , but a higher inpatient cost. Our results also showed that dying of AD lowered total costs with € 15,549, total medication costs with €6,286, and inpatient costs with €16,687 but increased total outpatient costs with €1,138 when compared to cancer decedents. We found that the out of pocket cost (OOPC) of COPD decedents incur €563 lower total, €621 lower inpatient, €58 higher outpatient and € 16 higher medication expenses during the last year of life when compared to cancer decedents. Furthermore, AD decedents caused € 842 lower total direct medical OOPC, €1,257 lower inpatient OOPC, €241 lower medication OOPC and €415 higher outpatient expenses than cancer decedents. In line with the direct medical total costs, the total insurance costs (IC), total inpatient IC and total medication IC for COPD and AD decedents was found significantly lower than for cancer decedents.

The use of a specialized multidisciplinary palliative home care team is associated with changes in direct medical costs of COPD patients

In chapter 8 we studied how the uptake of a multidisciplinary palliative home care team (MDPHCT) relates to differences in direct medical end-of-life care costs of COPD patients. We found that in Belgium, 58,527 people died with COPD. Of those 2.99% used a MDPHCT during the last 2 years of life and 0.72% during the last 180 to 30 days before death. Our results showed that total direct medical costs in the last month before death, for those who used a MDPHCT between 180 days and 30 days before death and those that did not use, amount to, respectively, €4,963 and €6,942. Of this, respectively, 45% and 75.8% is generated by direct inpatient medical care which is mainly characterized by a total direct medical hospitalization cost of €4,994 and a specialist care cost of €1,003 for those who received no MDPHCT and €2,156 and €1,048 for those who did not. 55% and 24.2% of total direct medical costs was caused by a direct outpatient medical care which, in both groups, was generated by direct total medical expenses related to home nurse direct medical care, GP contacts and physiotherapy. It was found that the use of a MDPHCT lowers total direct medical costs in the last 30 days of life with €1,979 . Total direct medical outpatient costs were increased with €1.047 but direct medical inpatient costs were decreased with €3.027. The lower inpatient cost was mainly caused by a lower direct medical hospitalization cost and lower medical costs related to expenditures for specialist care, medication and pharmaceutical deliveries, medical-diagnostic treatments and procedures. Higher expenditures of total direct medical outpatient costs, on the other hand, were mainly generated by expenditures related to GP contacts, home nursing care and physiotherapy as also a difference in medication spending.

2.METHODOLOGICAL CONSIDERATIONS

In following paragraphs an overview of methodological considerations is provided. First, strengths and weaknesses of administrative data, health claims data as well as disease registries used to analyze end-of-life health care resource use and costs are discussed. Second, the use of death certificates and specific algorithm to determine the cause of death has been discussed. Third, the choice of a retrospective design and the implications of this choice are discussed.

2.1. Strengths and weaknesses of the use of linked administrative data, health claims data and disease registries

Administrative databases are appealing to researchers because they offer numerous advantages [1-3]. They are pseudonymized, contain a large number of prospectively collected data, are inexpensive to use, and are available in electronic format which makes them usable in research studies in the field of end-of-life care and particularly as a replacement for medical records which are often not digitized and fully available. As a result, the use of administrative data is beneficial in research that is attempting to learn sensitive information about those nearing the end. Although such information could also be obtained directly from patients or families by surveying or interviewing them, those nearing death or suffering from an advanced level of a disease are often not able to participate due to physical, cognitive and emotional deterioration [4]. Moreover, administrative data also do not require patient authorization for use and are free from non-response and dropout, which are problems for studies that rely on surveys or interviews for their data.

Administrative databases are also particularly useful for including sizable groups of patients with rare conditions or at the end of life, who might be difficult to include due to prognostic uncertainty and specific disease trajectories and presence of different comorbidities. However, coding errors and questionable billing practices may contaminate the costs of a specific diagnosis, but the financial outlays regarding end-of-life are nevertheless real [2].

Although administrative data have many advantages serving end-of-life care research, they also have limitations which must be considered in the process of planning, executing and interpreting research findings [3].

Although the vast amount of clinical data available in Belgian administrative health care databases create an opportunity to analyze resource use and costs of end-of-life care, conducting end-of-life research based on administrative data often runs up against different barriers. Mainly, the accessibility and usability of an integral dataset remains a challenge. Although 'big data' have the potential to

improve medical care and reduce costs by bringing together multiple sources of data about individual patients, it is important to maintain public confidence by preserving data security and confidentiality [5]. Moreover, using administrative databases for research purposes faces a large spectrum of challenges[6]. Administrative data itself have limitations such as adequacy, accuracy, completeness, nature of the reporting sources and other measures of the quality of the data. Nevertheless, by digitizing, combining and effectively using administrative data, significant benefits such as managing specific individual and population health and optimizing end-of life care from a health service and economic perspective could be realized.

The use of administrative and health claims databases has been shown to be useful in other studies and permits to study health care resource use and costs across a full population [7-10]. Furthermore, by linking available and appropriate administrative databases and health claims databases, databases are enriched by the presence of specific socio-demographic and socio-economic variables and, more specifically, the related availability of individual-person-level resource use and costs. Due to a specific linking based on a unique identifier such as a social security number, detailed resource and cost categories could be determined and analyzed in function of the specific population.

2.2. Strengths and weaknesses of the specific data sets used

As described in Chapter 3, a total of 8 different available and usable databases were linked. These databases, which are managed by three different administrators, have their own strengths and weaknesses.

1. Databases administered by the Intermutualistic Agency

The Inter Mutualistic Agency (IMA) manages the databases that include all reimbursement data of health care consumption from all seven healthcare insurers [11]. A particular strength of these databases is that thorough quality procedures result in reliable usability for healthcare research. More specific, they provide information on an individual level across the entire Belgian population. However, a major limitation is that these IMA databases contain no information regarding medical diagnoses or any disease specific information.

2. Databases administered by Statistics Belgium

Statistics Belgium manages the national demographic database [13] which contains socio-demographic and socio-economic information about, for example, the highest educational level attained, the last held occupation (as a measure of socio-economic position) and housing characteristics, all socio-economic

factors that have been identified in previous studies as affecting end-of-life care patterns [14-16]. And a database containing fiscal data (i.e. net taxable household income) which provided additional socio-economic variables of influence on end-of-life care patterns.

However, these administrative databases are set up from a non-research-oriented goal and do not contain very specific data that are important in end-of-life research. Moreover, important specific variables such as race, ethnicity and religious conviction were not made available for our research due to privacy regulations. However, these variables have been shown to have a specific influence on the use of care and costs around the end of life [14, 17].

3. Specific available disease registries

As noted, the Belgian Cancer Registry (BCR) was identified as a database to identify people who died with cancer containing diagnostic information on all incidences of cancer [18]. The reason that this database was requested was to obtain a specific overview of those who died of cancer since this population was served as reference category in different studies included in this thesis.

Despite the availability of the BCR database, no similar registries were found available to identify those who died with or from Alzheimer's disease and COPD. Due to the absence of disease-specific data for those who died of COPD and Alzheimer's disease, was, based on the available data and to carry out a justified analysis, not all BCR data used within this dissertation.

In conclusion, every database has limitations by itself. First, the IMA databases provide information on health care use, but lack clinical data. Yet, diagnostic information can be invaluable in studies on health care use and costs. Second, the clinical information from BCR databases offers opportunities to study cancer population, but is limited to cancer and other disease registries concerning different life-limiting diseases such as COPD and Alzheimer's disease does not exist. Third, socio-demographics and socio-economics offer very wide information on the general population, but contain no medical or health care data and are limited to the specific variables recorded. Nevertheless, all databases contain invaluable information and by linking them we could surpass the limitations they have on their own.

The opportunities provided by the linked database to study use and costs of end-of-life care are considerable. The main overall advantage is that data are population-level and therefore not subject to sample bias such as in surveys or medical records studies of selected groups of patients. The rich amount of information that is contained in the population-level databases thus allows us to make valid statements on research questions for the full population. Compared to primary data collection, using linked routinely collected databases is less expensive and less time-consuming. In the end-of-life care context specifically, primary data collection can be burdensome for patients and caregivers.

Furthermore, in the routinely collected databases, high-quality data are available on the spot, although they were not deliberately collected for our research aims. Nevertheless, detailed information available in the population-level databases allowed us to make valid statements on the specific research questions.

Although the linked database did not include certain types of information that are important in evaluating resource use and costs of end-of-life care, such as patient-specific preferences of care, psycho-social information, patient or family reported outcomes and experiences or information about pain and symptom management or communication and treatment aspects [9], full-population data have the potential to provide robust detailed and population-level measures of resource use and costs of end-of-life care. The linked database contains data on all direct medical costs and reimbursed service and medication use, which offers opportunities to study direct medical costs and patterns in the use of end-of-life care. Moreover, as the linked databases contain individual data, these data could be aggregated on multiple levels, which makes longitudinal, disease-, treatment- or provider-specific analyses possible. As a result, it was possible to evaluate the economic impact of specific end-of-life care plans by episode and specific population [2].

The linking of different administrative and health claims databases provide an number of opportunities in studying end-of-life resource use and costs. We used a deterministic linking method to create our comprehensive full-population database, which provides clear advantages compared to a probabilistic method where risks of false connections are higher[19, 20]. A deterministic linking procedure is based on unique identifiers (e.g. social security number) or a combination of information that allows to identify a unique person (e.g., date of birth, date of death and municipality of residence) in order to connect cases across different databases [21, 22]. However, this holds several privacy, political and legal concerns. In Belgium, privacy protection is handled by different privacy committees for each sector where public data are gathered. For all studies in this dissertation, permissions were granted from (1) public health care and (2) general statistics which was approved by the Public Health Care Privacy Committee and the Statistical Supervisory Committee, after multiple iterations and in close cooperation with all parties involved. The deterministic linkage was executed by Crossroads Bank for Social Security (CBSS) and eHealth, trusted third party organizations (TTP) that guarantee safety and privacy regulations. These TTPs were recognized by all database administrators involved and technical staff of IMA, BCR, StatBel, CBSS and eHealth worked together to engineer the linkage procedure in detail. A supplementary risk analysis was conducted to assess possible security and privacy issues. Nevertheless, linking databases is time-consuming and selecting exact data from different databases is challenging.

Because administrative data have been collected for other purposes than research, they are often not available in a format that is intelligible or convenient for research. Furthermore, health claims data are often limited to services covered by the insurer. As a result, generalizability across other healthcare jurisdictions of our results is restricted by that what is not covered by insurance (and hence not found in the data). However, the used data are relatively complete for health care services in the hospital, nursing homes and at home. Nevertheless use of certain services could not be identified because there is no individual reimbursement (e.g. mobile hospital palliative care teams) or such reimbursement is not regulated or generalized (e.g. consultations of a psychologist). Secondly, total out-of-pocket spending is not available in the integrated database. This results in an overall underestimation of the total cost of end-of-life care. Nevertheless, the administrative data used and the results obtained provide an essential source of information on the financial burden of end-of-life care for the health care budget and could be valuable for policymakers in informing their decisions on health care policy [23].

Moreover, a lack of disease specific and diagnostic information causes difficulties in identifying incident cases of those suffering from COPD and Alzheimer's disease. To absorb this shortage the Minimal Hospital dataset, which includes clinical information associated with hospitalizations, was looked at for possible inclusion. This dataset has high quality data and provides diagnostic information (in ICD-codes), which allows for a more exact clinical description of the study population. It is however limited to in-hospital data, limiting the study population.

However, specific clinical information can also be abstracted from health care claims data using specific algorithms and/or causes of death noted on the death certificate. Obtaining cause of death information and using healthcare claims data makes up for the lack of a clinical diagnosis.

2.3. The use of death certificates and specific algorithms to determine COPD and Alzheimer's disease decedents

To identify those suffering or dying from COPD and Alzheimer's disease (Chapter 5 to 8) we identified the death certificate database as a necessary additional database. Death certificate data in Belgium are collected by three administrations (corresponding to the three semi-autonomous regions in the country, i.e. Brussels, Flanders and Wallonia) and are integrated and administered by Statistics Belgium into one national database for cause of death statistics. This database provides the causes of death and associated causes of death (coded in ICD-10 [10th revision of the International Statistical Classification of Diseases and Related Health Problems] codes) for all Belgian decedents.

Although the underlying cause of death cannot be seen as a diagnosis of COPD or Alzheimer's disease, using the underlying cause of death as a proxy of COPD and Alzheimer's disease might be accurate. However, death certificates have been shown to be inaccurate in recording the correct cause of death and under-reporting specific diseases such as COPD and Alzheimer's disease [24-26]. Still, for analyzing resource use and costs of end-of-life care, selection of only those people whose recorded underlying cause of death is COPD or Alzheimer's disease (i.e., those who died from COPD or Alzheimer's disease), the problem of under-reporting may be less problematic. Though, when analyzing end-of-life care from a health service and economic perspective on a full population level the use of only the underlying cause of death would underestimate the results for a full national population of COPD and Alzheimer's disease decedents. Therefore, as shown in chapter 5 and 6, an expansion of our study population to a full national population was needed. Based on existing evidence on algorithms and different therapeutic options in COPD and Alzheimer's disease we developed a specific medication based algorithm which was further expanded with those deaths for which COPD or Alzheimer's disease was recorded on the death certificates as an intermediate or associated cause of death but not the underlying cause of death. Although there is no standard validated algorithm available to use on Belgian health claims data, the use of pharmacy data to identify COPD and Alzheimer's disease patients in administrative databases was found adequate in previous studies [27-29].

Additionally, death certificates provide no information on important aspects of the end-of-life process such as preferences of place of death, choices of place of care, and course of decision-making levels, i.e., patients, family, health-care professionals, and/or health-care policy makers [30]. Moreover, it has to be noted that differences in diagnosing, reporting or certification may exist between different health care settings within a country [31]. Nevertheless, a combination of death certificates (i.e. underlying cause of death) and pharmacy based algorithms offers the opportunity to study relatively small and under-reported subpopulations such as COPD and Alzheimer's disease retrospectively.

2.4. Strengths and weaknesses of a retrospective vs a prospective design

There is a need for good-quality evidence and analysis that informs commissioning and policy decisions. However there has been a shortage of basic information about services delivered and costs generated at the end of life, and studies of effectiveness and cost-effectiveness face particular challenges [32-34].

For many aspects of healthcare, the randomized controlled trial is held up as the golden standard to obtain evidence of the value of an intervention. However, the application of prospective randomization methods at the end of life is particularly difficult in real-world situations.

To begin a discussion of prospective and retrospective measurement at the end of life, the scope of end-of-life research i.e. what time period constitutes the end of life, has to be defined [35]. As noted in the introduction, earlier research reveals great variety in the operationalization of the end phase of life. For some studies, disease category is the delimiting factor; in other instances, clinical criteria among diagnostic groups are determinative. Receiving palliative care, e.g., in a palliative care unit or home and nursing based palliative care services, may be used to define the sample and finally, many studies, particularly randomized control trials, rely on physician prognostication.

Studies conducted in patients receiving formal palliative care in outpatient or inpatient care settings (defining end of life by setting of care) offer the advantage of capturing experiences in settings specifically designed to meet the needs of dying patients. As such, they may be an obvious choice for evaluating end-of-life care. However, since end-of-life care tends to be introduced relatively late in the disease course of COPD and Alzheimer's disease patients, many of them residing at a palliative care unit or receiving palliative home care or inpatient palliative care are too ill to respond even to brief questionnaires [36, 37]. As a result, studies that define end of life only according to settings or status (e.g., palliative care unit or person receiving palliative care or hospice benefits) often include very ill patients. The inclusion of these patients in largescale prospective studies result in high study attrition.

Because of late referrals and brief lengths of stay, a majority of patients at a palliative care unit or with a palliative status, will be in a stage of imminent dying. However, the palliative care received in this period arguably constitutes only a portion of end-of-life care, which may for those living with COPD or Alzheimer's disease even start months to years before death. Additionally, certain patients, the most unfortunate ones, will need but not get palliative care. Selecting a cohort based only on receiving palliative care would be a priori ignore these people and result in an inadequate image of overall end-of-life care..

Relying on physician prognostication also causes limited usability and generalizability [4]. Although it is noted that physicians can prognosticate mortality slightly more accurately the closer the patient gets to

death, they still rather inaccurately predict whether a person with COPD or Alzheimer's disease is likely to live another day, week or month. As a result, predict whether patients are appropriate for inclusion in a longitudinal prospective study based on 'end-of-life' status is also imprecise.

Additionally, prospective interviewing if patients, families or healthcare professionals, while feasible [38], has its problems in terms of accuracy and completeness of responses [39-43]. Patients can be too ill or cognitively impaired to answer, while proxies tend to underestimate quality of life and over-estimate physical symptoms, anxiety, depression, and psychological distress [44].

Several of the difficulties in measuring end-of-life care outcomes in a prospective study can be overcome with retrospective cohort studies using routinely (and prospectively) collected data [45]. They allow defining a clear denominator since deaths are required by law to be reported by means of a death certificate [46], minimize issues of nonresponse bias or attrition. An additional advantage is its cost-effectiveness. The use of routinely collected administrative and health claims databases limits extensive data-collection efforts for the researcher and burden for the study subjects. Using death certificates generates an opportunity to identify those with COPD and Alzheimer's disease based upon the underlying cause of death. However, as was noted, COPD and Alzheimer's disease are underreported on death certificates which complicates the opportunity to include a full population of these patients. Using a specified algorithm partly solves this problem [27].

However, an important limitation of our retrospective approach based on administrative and health claims databases is that important information is lacking. A lack of disease specific information such as the level of the disease of COPD and Alzheimer's disease and a lack of care specific information such as preferences of (end of life) care and specific COPD or Alzheimer's disease treatment related choices made by patients and healthcare professionals, might have influenced our results on the economic analysis of end-of-life care [47, 48]. Future studies using administrative and health claims data can opt for the enrichment with specific disease and care related information by attempting to contact the " next of kin" or the person who was involved in the (medical) decision making during the last months or days of life. However, retrospective proxy accounts are also subject to additional bias because of issues of recall, reinterpretation of the past based on intervening events and current experience of grief and bereavement. An important concern is whether bereavement affects respondents' abilities to recall events or costs made during the end-of-life phase and that the information given may be unreliable.

A final concern related to the retrospective design we used, is that one must be aware of the differences with cohort studies and case series. These differ in how subjects are identified, and over what time period their care is observed relative to when they became eligible for the study [49]. Bach et al suggest that, if retrospective cohort studies of decedents either include different subjects or analyze events over

different time periods than cohort studies of the dying, then retrospective cohort studies are likely to produce an inaccurate portrait of terminal care. However, an advantage of using a retrospective design is that, as noted before, the selection of cases is not dependent on inaccurate physician prognostication of survival and that the time frames in relationship to death are known. When examining health service use and costs of end-of-life care in the last months of life prospectively, respondent burden is another important concern since many dying persons are unable to be interviewed in the last months of life. Moreover, incomplete enrollment is an additional important potential limitation of prospective cohort studies. Since those closest to death are unable to be interviewed because of their level of disease, a substantial number of patients would be excluded from the study and exclusion of these patients could to lead to substantial bias especially on a full population basis.

2.5. Limitations of the economic analysis performed

Existing economic evaluations of end-of-life care suffer from a specific number of limitations which also limit our results in terms of validity. First, economic evaluation is the evaluation and comparison of different treatment options on both outcomes and costs. However, palliative care is often defined as an additional service offered to patients in need which does not need the cessation of disease-focused care. Consistent with this, economic evaluations of end-of-life care are often focused on comparing specific appropriate end-of-life care such as palliative care with standard care and are mainly focused on one outcome, costs. Due to a lack and difficulties in determining the specific second outcome such as quality of care or quality of life, specific results on the effect of palliative care on these outcomes are missing [50]. Therefore, it is stated that the measurement of both costs and specific patient related outcomes together is crucial in the further development of palliative care. Due to the nature of our administrative data and a lack of specific patient reported outcomes and experiences we evaluated in chapter 8 the effect of a palliative home care team on direct medical expenditures for both the insurer and patient but were not able to evaluate the specific and important second outcome, the effect.

Based on the available health claims data we constructed specific cost-components which were aggregated costs consisting of all nomenclature codes referring to a specific healthcare service or professional. Based on existing nomenclature reference tables and Belgian tarification guidelines we constructed relevant cost categories for evaluating end-of-life care within the Belgian healthcare context. Although we used a payer perspective in chapter 7 and 8, we could only draw conclusions within this conceptual framework. However, previous guidelines on economic evaluations recommend that a societal perspective is the most optimal approach and suggest that costs should be measured from all relevant resources incorporating the cost of supplies, staff and medications as well as costs for

the provider, patient and family. However, by being limited using a payer perspective and health claims data, the overall costs in our studies are underreported.

A final important issue in our economic evaluation concerns the time window of our analysis. Although the decedent cohort study is the most popular approach to examine longer timeframes, there is a specific risk of bias in economic studies since costs adds up over time. For example, an RCT by Temel et.al. comparing palliative care patients with non-palliative care patients previously found that among palliative care patients utilization was lower after the diagnosis and in the last week of life but found higher mean total costs in the palliative care group due the positive survival effect [51]. Our analysis described in chapter 8, which were based on a full-population sample of decedents ,did not allow us to estimate the cost of those who survived after receiving palliative home care due to the lack of a time indication of death with respect to receiving palliative home care.

3. GENERAL DISCUSSION

Three main themes and objectives were handled in this dissertation: 1) providing an overview of the current state of resource use and costs in those suffering from COPD; 2) determining the level and character of end-of-life resource use within those who suffer from COPD and Alzheimer's disease and 3) examining the costs of those in the last phase of life, comparing costs between those who died of cancer, COPD and Alzheimer's disease and evaluating the effect of a multidisciplinary palliative home care team in those suffering from COPD.

3.1. Resource use at the end-of-life: The particular case of COPD and Alzheimer's disease

In Chapter 4 we showed, based on previous results, that acute hospital visits, intensive care unit admissions, physician visits, invasive ventilation and medication are the main key drivers of end-of-life resource use and that the differences in resource use of COPD patients during their last months of life are mainly caused by the presence of comorbidities and exacerbations at the end of life and influenced by the geographic setting in which terminal COPD patients receive care or by the level or stage of the disease. Yet, most of the studies that were included in this systematic review were based on non-European administrative data which were retrospectively analyzed and in which COPD decedents were drawn from administrative databases, medical records and hospital medical records in which they were identified according to the International Classification of Disease codes or based on linked death certificates where the underlying cause of death was described as COPD.

An important point of discussion regarding these previously found results on the use and intensity of the use of specific resources is that they might have been influenced by the number of exacerbations and the degree of illness. The use of administrative data did not provide insights into the general condition of the included patients and specific information regarding the medical condition or degree of illness of the included populations were not described. However, previously executed cost-of-illness studies on COPD within a European context indicated that COPD patients with grade D have more intensive use of health care provisions than those with grade A or B [52-54]. Moreover, is was previously noted that the mortality rate within the COPD population is highest for those with grade C and D and that it was mainly induced by an exacerbation and worsening of the general physical condition and dyspnea [55]. As such, the results with regard to the end-of-life care use, as described in chapters 4 to 6 should be approached with some caution notwithstanding they indicate that end of life resource use in COPD patients is characterized by intensive use of acute care facilities such as acute hospital visits, intensive care admissions, medication and invasive ventilation which in turn can be related to the specific level of disease or attributed to the number and type of exacerbations, which characterize the typical disease course of COPD, and give rise to death. However, the use of specific medical records and

hospital medical records can contribute to this, notwithstanding their use is intensive and leads to a specific demarcation of the population to be studied.

In chapter 3 we showed that the inclusion of specific medical information is possible within the Belgian context, but that this does not provide the possibility to analyze the entire COPD population. The use of the minimal hospital set would narrow the study population to only those COPD patients who had hospitalization during the last months of life and could only be an added value, especially in relation to the medical condition and degree of illness, for these patients who were admitted to a hospital. Our results, described in Chapter 5, show that this would only be an added value for the 76.8% of people who died from COPD in Belgium in 2012 (e.g., 76.8% of those who had COPD hospital admission during the last 180 days of life) and in which the cause of death 'COPD' was noted as the primary cause of death on the death certificate which in turn also gives rise to a limitation of the study population since the identification of COPD decedents based on the underlying cause of death as listed on the death certificate limits considerably the potential study population by 20 to 50% [26, 56-61].

In addition to the influence of the degree of illness and the number of exacerbations, end-of-life care use in COPD patients was found to be influenced by the presence of specific comorbidities [62-67]. We indicated, based on previously found results, that during the last year of life an increasing number of comorbidities results in a 60% increase in medication prescriptions for those with five or more comorbidities. However, results related to the specific influence of important co-morbidities such as pneumonia, lung cancer and cardiovascular diseases on end-of-life care use in COPD were lacking.

Given the limitations regarding the study of a complete national COPD population and the fact that previously results are mainly related to health systems other than the Belgian health care system, a retrospective analysis of end-of-life care use was performed in in order to investigate the specific influence of lung cancer and cardiovascular diseases within the entire COPD population. Our results showed that of the 19.401 persons who were identified as suffering from and dying with COPD, based on an algorithm and the intermediate and associated causes of death, 14.8% had been assigned a primary cause of death in lung cancer and 30.8% had cardiovascular disease. We found that COPD patients who have a primary cause of death of lung cancer use less intensive resources during the last 6 months of life as compared to those who have a primary cause of death of COPD or cardiovascular diseases, are more prone for using palliative care services offered in a palliative care unit or at home and receive more medication that provides symptomatic benefits to patients at the end of life. COPD patients who died of their COPD and those who died of a cardiovascular disease have a comparable resource use although the latter receive less non-invasive ventilation and have a higher chance of being reanimated.

An important factor that may lead to the differences in these results is the accuracy of the prognosis of COPD and the fact that, due to the specific disease progression of COPD, COPD is not seen as a disease leading to death by the patient, family and professional caregivers[68, 69] . However, it should be noted that those with COPD who died of lung cancer had a higher proportion of specialist contacts and hospital admission when compared to those who had COPD as an underlying cause of death indicated on the death certificate. A possible explanation for the difference in specialist contacts and hospital admission is that the presence of a chronic condition such as lung cancer mortgages the general physical condition and as such results in a hospital admission. Furthermore, these results also indicate that, despite a general practitioner is seen as a key figure in the recognition, initiation and monitoring of palliative care needs, medical care policies in the last 6 months are coordinated by a specialist. As such treatment of COPD as well as death and its associated place of death takes place in the hospital. Previous research indicated that a specialist, in comparison with a general practitioner, puts more focus on the 'molecular approach of the disease' and seeks an optimal treatment for the disease. As a result of this 'molecular approach', a palliative care approach is not an option and COPD patients will have limited opportunities to receive specialized palliative care [70]. An additional factor that can explain the difference in end-of-life care use among those who die from COPD and those who die with COPD and lung cancer is that, notwithstanding both groups have the same end-of-life needs, cancer is still seen as a disease in which the disease trajectory can be better predicted and where available palliative care facilities are found to be optimal for deployment in the end of life phase [71, 72]. The comparable end-of-life care use between COPD patients who die from COPD and a cardiovascular disorder can mainly be explained by the unpredictability of common cardiovascular disorders such as acute heart failure. As such, the differences between both groups in the use of CPR and non-invasive ventilation could be related to the nature of death, notwithstanding that those suffering from chronic heart failure are also bathed with a specific palliative care approach [73].

Death certificate data were used to identify those who died of Alzheimer's disease. However, the use of death certificate data to identify those who died of and with Alzheimer's disease has, in line with the identification of those who died with COPD, also certain limitations. First, clinicians might often recognize Alzheimer's disease as a contributor to death but might not prioritize the diagnosis in those with different comorbidities (e.g., pneumonia, urinary tract infection). As such, in those with different comorbidities, different clinicians might choose different diagnosis to report as cause of death. Another weakness in using death certificates concerns the underreporting of Alzheimer's disease on death certificates as a main and contributory cause of death [76, 77]. However, the use of a medication-based algorithm partly mitigated this limitation and the combined use of death certificate data and algorithm resulted in a more accurate number of those dying with Alzheimer's disease. The use of an algorithm

based on pharmacy data, using claims data and pharmacy data from more than three years has confirmed in previous research [78, 79].

Using death certificate data and a specific algorithm, the use of care during the last six months of life was described and analyzed within the Belgian Alzheimer's disease population. Our results confirm previously found results that palliative care services available at home or a palliative care unit were not always considered in the care plans for Alzheimer's disease patients, and that hospitalization, intensive care and emergency room admissions near the end of life remain common in those who die with or of Alzheimer's disease. The use of these resources may be a result of the disease course of Alzheimer's disease. The end-stage of Alzheimer's disease lasts an average of two years, and those with Alzheimer's disease may develop apraxia, dysphagia and often have reduced mobility which increase the risk of infection during this time period. Moreover, infections, such as pneumonia, might increase mortality and are often seen as the underlying cause of death. As a result, resource use in those dying with Alzheimer's disease might be influenced by the existence of an Alzheimer's disease related morbidity which impede the identification and recognition of Alzheimer's disease as a life limiting disease and finally as a primary cause of death or might be a result of the specific disease course of Alzheimer's disease which makes prognostication of the end-of-life phase more difficult. However, our results showed that 97 percent of those dying with and of Alzheimer's disease had frequent contacts with their general practitioner which could create an opportunity for recognizing the end-stage and discussing end-of-life approaches.

When compared to those who died of Alzheimer's disease, those who died with Alzheimer's disease showed a similar or higher resource use during the last 6 months of life. However, they received less often palliative home care services and were slightly more often admitted to a palliative care unit.

The found differences in resource use between those dying from and with Alzheimer's disease could also be related to the fact that the groups differ in terms of disease severity or the number of comorbidities they have. However, based on the Charlson comorbidity index, we found that those who died with Alzheimer's disease had more severe comorbidities than those who died of Alzheimer's disease which indicates that those who died with Alzheimer's disease were more likely to receive resources related to the coexisting disease.

Moreover, the results can also be influenced by the way of grouping. Even though the use of claims data and pharmacy data from more than three years is suitable to identify Alzheimer's disease patients, the lack of a golden standard algorithm complicates the study of resource use in the entire population of Alzheimer's disease and, as included in this dissertation, COPD.

Nevertheless, our results confirm the difficulty of prognostication of the end-of-life phase in Alzheimer's disease and the related effect of accurate recognition of it on end-of-life resource use.

3.2. Direct medical costs at the end-of-life

Previous research on end-of-life care costs has been descriptive in nature using cost estimates or focusing on specific samples or health care settings and has been often restricted to limited comparisons of small samples of specific causes of death mainly directed by evidence on those who suffer and die of cancer or based on small samples comparing healthcare costs of cancer and non-cancer patients. Evidence on end-of-life care costs at full national population level remains scarce and specific cost-components that drive the costs in different disease groups also remains poorly evaluated [48].

We evaluated and compared total end-of-life care costs and specific cost-components influencing end-of-life care costs during the last year of life on a full national population level between three leading causes of death in western societies i.e. cancer, COPD and Alzheimer's disease. The differences we found in direct medical costs during the last year of life between those with cancer, COPD and Alzheimer's disease might partly be explained by their specific end-of-life trajectory. As mentioned in the introduction, COPD is characterized by different stages and patients may often suffer from a number of exacerbations and comorbidities that may have a significant impact on costs at the end of life. The course of dementia, on the other hand, is characterized by a progressive decline and often results in death due to an acute event such as an infection or progression of another disease. Due to a prolonged decline and related informal caregiver burden, AD patients often reside in an outpatient setting such as a nursing home or at home where they receive a number of outpatient medical care acts. Our results are, in light of an international comparison, affected by the specific healthcare systems in which they were found. Yet, they confirm previously found results in other healthcare systems which indicate that inpatient costs are the major cost driver of end of life care in all types of dying trajectories [82]. Furthermore, previously found results also indicate that a higher outpatient cost in COPD and cancer patients is mainly driven by hospital admissions and that a higher cost in dementia patients is driven by a nursing home stay [81].

Although our results are in line with these previously found results concerning specific cost drivers of end of life care, they could be affected by the determination of inpatient and outpatient cost categories in our study. Previous literature stated that there is no consensus regarding specific cost-components relevant in the economic evaluation of end-of-life care, the determination of inpatient care is, internationally, seen as care provided to a patient residing in a hospital, nursing home or skilled nursing facility [80]. However, inpatient (or institutionalized) direct medical costs described in our study,

included any medical service or act that requires an hospitalization or an act which is provided during an admission and stay into a hospital. Outpatient (or ambulatory) costs, on the other hand, included all acts that did not require an overnight stay in a hospital or medical facility. This difference in determining inpatient and outpatient costs could have affected the final results in light of international evidence negatively. However, by splitting up total costs in specific cost-components, we found similar results as previously shown in literature [81, 82].

By using a propensity score matching technique an attempt was made to map the effect of a multidisciplinary palliative home care team on the costs in the last month of life. Notwithstanding that randomized controlled trials (RCTs) are the gold standard in scientific research and have a large internal validity, external validity is limited. As a result, the generalizability of the results to a complete population is difficult to achieve. However, by using propensity score matching, an analysis on the use of a multidisciplinary palliative home care team in a complete population of COPD decedents could be performed based on available administrative data. However, the use of a propensity score matching has limitations on confounding. Confounding occurs when the outcome of interest is correlated with the factors that influence the relationship of interest. Potential cofounding variables in palliative care research have already been described in the introduction to this dissertation and include relatively straightforward factors such as time before death or gender. In addition to these factors there are also confounding factors which are not as readily observed or measured and hence not found in our database, such as symptom burden and individual preferences for aggressive interventions at the end of life and care setting [83, 84]. As a result, the results described in chapter 8 may also have been influenced by the absence of these factors and could not be corrected for this. However, by using previously noted healthcare use of the studied populations, we could better predict the eligibility of receiving (or not) palliative home care in COPD patients. By combining specific socio-demographic and economic variables we succeeded to define for example the level of care need and as such the level of functional well-being.

Our results of the effect of a multidisciplinary palliative home care team (MDPHCT) on the end-of-life care costs with regard to the last month of life show that, in COPD patients, the use of an MDPHCT during the last seven to one month before death entails a significant decrease in the total direct medical cost for both patient and insurer. This decrease only applies to the direct inpatient medical costs. The use of an MDPHCT increases the direct medical outpatient costs for both insurer and patient compared to no use of an MDPHCT. More specifically, the use of home-based specialized palliative care, such as an MDPHCT, reduces expenditures for hospitalization, specialist care, medication and pharmaceutical deliveries, clinical biology, medical imaging, physiotherapy and medical procedures and also increases the medical cost for outpatient GP contacts, home nursing care, physiotherapy and medication spending

during the last month of life in COPD patients. These results confirm previous results with regard to the use of home-based specialized palliative care teams. It was previously been found that community-based specialist palliative care is associated with a decrease hospital costs during the last year of life and inpatient reductions for COPD decedents one to 2 months before death. A previous economic analysis concluded that in-home palliative team care for individuals nearing end of life reduced health care costs and improved health outcomes for patients nearing the end of life and stated that the population impact of this intervention could be potentially large. However, evidence describing relevant cost-components in COPD patients are lacking. The lower cost for hospitalization for those who use an MDCPHT can be explained by the specific nature of an MDCPHT. In Belgium, a MDCHPT cooperates with the usual caregivers of the patient and provides support and specialized advice at request of the professionals involved. Due to the fact that a MDCHPT is mainly focused on home support, patients will receive minimal in hospital care and a reduction in hospitalization costs can be explained. An MCPHT in Belgium has a supportive character for the care providers involved such as GP and home nurses. Care with regard to the palliative COPD patient is therefore often provided by an informal care provider. As such, the positive difference in outpatient costs, which are mainly characterized by a higher outpatient cost for GP and home nursing care, can be explained. Our results on the use of an MDCPHT also showed a significant decrease in patient's expenses. Though this reduction in patient expenses can be related to the specific use of an MDPHCT, it should be noted that a shift from direct medical costs to indirect medical costs, which are fully borne by the patient, is possible.

A positive difference in part of the patient receiving an MDCPHT is not found in the expenditures for outpatient care. Although a palliative (COPD) patient in Belgium is entitled to an increased allowance, the found increased outpatient costs, when using an MDCPHT, can be explained by a high medication cost for which not a full increased reimbursement exists. Moreover, since care in the final stage of life for a palliative COPD patient, due to the extramural nature of a MDCHPT, is mainly provided in a home setting, GPs and home nurses remain the first providers of this care and explains the increase in costs for care provided by them. Our results also showed an increase in the direct medical costs related to a palliative care unit. This result can be explained by the determination of a palliative status, deterioration of the general condition or the presence of co-morbidities in COPD patients or burden of the informal caregiver. Moreover, the involvement of an MDPHCT leads to a more targeted and faster admission on a palliative care unit. Our results showed that the prognosis of the final phase in COPD patients is difficult to determine and that comorbidities can affect the choices made in the finale phase of life.

While our results mainly confirm previous results, a number of specific limitations related to the statistical method and implemented economic evaluations of end-of-life care should be indicated within these studies. Finally, the results described above are subject to a number of limitations that can be

related to the choice of grouping. First, different groups were identified based on the cause of death, e.g., cancer, COPD and Alzheimer's disease. These 3 diseases are characterized by a specific end-of-life trajectory that has a specific influence on end-of-life decisions. Earlier research showed that the recognition of Alzheimer's disease and COPD as a life-threatening disease, the accuracy of the prognosis and the initiation of a specific home-based palliative care intervention have an influence on the use of care and related costs. Secondly, nomenclature codes, which refer to specific care actions, were used to determine different cost components. These cost-components were carefully composed based on existing reference tables and pricing guidelines. Based on specific grouping, cost categories were assigned to the specific cost-component and not every nomenclature code, to which a specific cost was linked, could be subdivided into a specific relevant cost-component. However, the strength of this grouping of relevant cost-components, based on full-population available health claims data, compared to previously reported results is that the cost associated with a specific nomenclature code is a nationally agreed cost and, in comparison with previous evidence, not based on unit costs or estimated costs [81, 82]. The results shown represent the effective and real direct medical cost of end-of-life care in Belgium.

3.3. Important limitations regarding the results on end of life care resource use and costs

In this dissertation, real-world data was used in the form of prospectively collected and retrospectively analyzed health claims data to evaluate end-of-life care of the entire population of COPD and Alzheimer's disease patients in Belgium. The advantage of using these real-life data is that we were able to describe the effective reality on a full population level. Our results are especially interesting because they reflect the real direct reimbursed clinical practice in Belgium and not the idealized practice. For health care providers as well as for patients, it is important to base their clinical decisions on evidence about real clinical and financial impact in order to better manage uncertainty [85]. However, although our results reflect reality in terms of resources used an direct reimbursed medical costs generated, there are several limitations including the degree to which claims data can accurately capture an individual's medical history and comorbidities influencing treatment decisions, because claims data are collected for the purpose of payment and not specifically for clinical research.

By using health claims data from the IMA healthcare claims database we were only able to analyze reimbursed direct medical care in our studies described in chapters 5 to 8. The different care use and cost categories were based on specific nomenclature codes that indicate which specific act or service received a reimbursement within the framework of the legally required health insurance. However, in addition to this legally reimbursed care, COPD and AD patients also receive indirect and informal care provided by professionals or family. The results with regard to receiving palliative care must therefore

be approached with caution in this context. In chapters 5 and 6 we indicated that COPD and AD patients receive little appropriate end-of-life care in the form of specialized palliative care and that this is influenced by the presence of comorbidities or the degree of recognition as a life-threatening condition. However, the palliative care studied in this context refers to specific reimbursed palliative care and not to the overall degree of palliative care received. Lack of knowledge about the different possibilities of reimbursed 'specialized' palliative care among healthcare professionals and patients can lead to a lower uptake of reimbursed specialized palliative care and as such an underestimation of our results [86-90]. In this sense, our results do not indicate to what extent the COPD and AD population received informal and / or non-reimbursed adapted end-of-life care despite the fact that a considerable proportion of these patients still might have received an answer to their specific end-of-life care needs.

Secondly, secondary data available on the death certificate and pharmanet database was used to determine the entire population of COPD and AD who have died during the period of investigation. Notwithstanding that, as indicated in chapter 3, the use of medical and hospital records could have provided us with a more accurate picture of the diagnoses of COPD and AD, chapters 5, 6 and 8 defined the COPD and AD population based on the primary and secondary causes of death as well as on a medication based algorithm. Determining both populations on the basis of causes of death and the algorithm resulted in heterogeneous groups where the need for end-of-life care could not be determined specifically. The lack of specific diagnostic and therapeutic information available in medical and hospital records did not allow us to determine to what extent the diagnosis of COPD or AD was a determining factor for receiving end-of-life care or specialized palliative care and to what extent the analyzed immediate medical reimbursed care and care use were related to COPD or AD. Given that previous research indicates that COPD and AD patients may be confronted with a number of associated or non-associated disorders that directly or indirectly impact the diagnostic and therapeutic process and as such affect health care use and costs, we could, on the basis of the available data, not correct for the severity of the disorder, the presence of the whole of comorbidities and the specific need for appropriate end-of-life care related to the two populations discussed. The results in Chapters 5 to 8 were therefore indirectly influenced by the therapeutic decisions to the multipathological character of the patient and the related decisions for initiating appropriate end-of-life care.

Third, the IMA health claims data contained the cost of dispensed and billed services and medication only, as such, indirect costs reflecting loss of patient or caregivers productivity, travel to and from treatment, over-the-counter medications, or other COPD and AD related expenses were not reflected in the results. However, we focused on reimbursed health services which are within the purview of policymakers at health plan and national levels. In addition, our analysis focused on a full national insured COPD and AD population, however, because of the retrospective nature of the data, it is

important to note that causal inferences cannot be made between the associations of the end-of-life care and costs. Costs are often driven by the acuity and choices of care; meaning that, often, COPD or AD patients will generate high costs, often a result of exacerbations or their illness rather than end-stage disease. Although we examined COPD and AD patients, which may have suffered from different disease history or pathologies, and receiving different treatment regimens, we believe that the results described in previous chapters should not be minimized given these real-world results may be indicative of further research and policy.

4. RECOMMENDATIONS FOR FUTURE RESEARCH AND POLICY

In this dissertation, a full-population analysis of end-of-life care was conducted. Based on administrative data resource use and direct medical costs related to end-of-life care in Belgium was described and evaluated. Despite the fact that these evaluations have added value with regard to the current state of evidence, specific shortcomings in the field of research have been identified. Yet, the recommendations and thoughts described below are not exhaustively but can give rise to a more thorough and complete overview of care use and costs related to the end of life.

4.1. Recommendations for research

The need of defining end of life and relevant data prospectively

A first difficulty was to detect those suffering from a life-threatening illness as well as to define the period until death. Within this study, the primary cause of death was pragmatically chosen as inclusion criteria. Time before death was defined by the number of days before death. However, this dissertation indicated that this method is subject to bias. A main criticism of this method of determining costs with regard to the end of life is the survival after specific interventions. To include the effect of survival in the analysis of costs, a prospective recording of the data need to be done. However, a prospective data collection with the aim of charting the use of care and costs of the last months or days quickly runs down to difficulties regarding prognosis. As a result, future research should primarily focus on determining accurate prognosis criteria in those with an end-of-life trajectory related to chronic diseases, e.g., COPD or frailty, e.g., Alzheimer's disease.

A second problem relates to the fragmented nature of palliative care. In Belgium, specialized palliative care is provided in the hospital, at home and nursing home. Although, by using specific nomenclature codes, specialized palliative care delivered in the hospital or at home could be determined, this was not the case for specialized palliative care provided in nursing homes or non-palliative care units inside and outside the hospital (e.g., palliative care provided in non-palliative care unit or in palliative day care centers). As such, based on the data used in this dissertation, the effect of palliative care across different care settings could not be evaluated. A possible solution here lies in defining palliative care in a prospective way. By determining the complex intervention of palliative care in different care settings, and in its various forms, an analysis can be performed based on prospective data collection of resource use and costs with regard to the last months or days of life

Mixed methods for a full economic analysis of end-of-life care

In this dissertation, only a quantitative analysis was performed on the available full-population health claims data. It was argued that the lack of an important second outcome in addition to costs, the effect, was not available within the data and as such only a cost analysis could be performed. However, adding specific patient reported outcomes (PROMS) and patient reported experiences (PREMS) could offer a solution to the need for the cost-effectiveness of existing end-of-life care or palliative care interventions. However, as mentioned before, obtaining specific PROMS and PREMS from a very vulnerable group is difficult. An alternative to this can be to register specific PROMS and PREMS in a uniform manner. By integrating prospective surveys consisting of, for example, medical records, the palliative outcome scale, Euroqual EQ5D or Qualicare study related questions, on the one hand, a prognostic statement can be determined and, on the other hand, specific patient and informal caregiver-related qualitative outcomes and experiences can be determined and included in the full economic analysis of end-of-life care in Belgium.

With regard to the cost-effectiveness of specific end-of-life care interventions evidence is limited. In order to allow specific end-of-life care interventions to compete with existing cure-oriented interventions that, as appears from previous chapters, still occur frequently in non-cancer patients, a specific comparative 'effect measurement' in addition to the outcome costs must be achieved. Notwithstanding that at the moment different research actions are being taken to, similar to the current standard QALY, define a specific 'effect outcome', these studies encounter a number of specific difficulties related to the specific end-of-life population. Further developments in function of measuring quality of life in this group are therefore extremely important.

Relevant cost categories for end-of-life research

In order to determine specific resource use categories and cost-components described in this dissertation, existing reference tables and pricing guidelines were used. Nomenclature codes were interpreted pragmatically and aggregated into relevant cost- and resource use components within end-of-life care. As indicated earlier in the international literature, the determination of cost and specific care use categories is heterogeneous within the existing evidence. An international think tank in 2009 defined this problem as follows: … *There is variation in terms of who is entitled to palliative care (e.g., patient diagnoses) and when (e.g., stage of disease) and what is included in the care package and associated payments (e.g., curative, palliative, home visits, drugs) … [48].* Moreover, In 2017 Gardiner et.al. described a general overview of the most commonly used costs and care use groups and stated that these were developed for research within a specific (national) healthcare context in which the

research was carried out [80]. As such, discussion is needed to further develop specific relevant resource and cost categories for end-of-life care research.

Not only direct medical costs

Little is known about the extent to which financial burden of end of life care has shifted from the acute care public sector to families. While existing studies have reported that home-based palliative care may be less expensive than institutionalized palliative care, a full conclusion cannot be drawn due to concerns with methodological validity. Furthermore, most of the existing studies only examine public health system costs or hospital-related costs . However, by excluding out-of-pocket costs and indirect medical and non-medical costs components in end of life care, studies may underestimate the amount and type of resources consumed. According to a Canadian study, unpaid caregiver time costs constituted up to 70% of total end-of-life care costs within established home-based palliative care programs. Moreover, in 2014, Yu et.al. concluded that there was no significant difference between the societal cost for home and hospital deaths but found a change in the distribution of costs borne by different stakeholders.

In this study, health claims data and a payer perspective were used to map direct medical costs related to end-of-life care. As a result of this approach, the results with regard to the cost of end-of-life care are an underestimation of the real societal cost of end-of-life care in Belgium. However, a thorough full-economic analysis of end-of-life care requires the inclusion of direct non-medical costs as well as the indirect medical costs related to survival and the indirect non-medical costs. An important cost in this respect is the cost with regard to informal care. Since palliative care is provided by (specialist) care professionals AND informal caregivers, an important cost item in end-of-life care is an informal cost that cannot be ignored in the full-economic evaluation of end-of-life care.

4.2. Recommendations for policy

Recognizing the end-stage: urge for education

As indicated, the recognition of Alzheimer's disease as a life-threatening situation plays a crucial role in receiving specialized palliative care. It was also shown that the presence of comorbidities in COPD patients plays a specific role in receiving appropriate end-of-life care.

The presence of comorbidities and the recognition of the last phase of life result in a low use of available palliative care services by non-cancer patients. The development of specific prognostic criteria for non-

cancer patients, however, ensures that early identification of specific end-of-life care needs in non-cancer patients can be optimized.

Recognition of the dying process is the first step in end of life care provision. The process of dying is usually recognized by the change in physiology, such as, failing vital parameters, decreased movement, decreased spontaneous verbalization, decreased intake of food and fluid and skin changes which could be helpful pointers to suggest poor prognosis and very limited life expectancy. However, it is not always easy to predict impending death, and the best approach is to treat a possible reversible cause whilst accepting that the patient might be dying. Notwithstanding that, as indicated earlier in this dissertation, the use of specific outcome scales can offer a solution to this, these are not used accurately. A better education and development of an "end-of-life insight" among care professionals as well as informal care providers and patients can therefore lead to accurate advanced care planning. Advanced care planning and recognition of the end-of-life phase in a non-cancer populations by medical specialists, general practitioners and nurses can therefore lead to an early and adapted use of the palliative care

Currently, however, students graduating from medical, nursing and other health professional schools have very little training in the core precepts of pain and symptom management, advance care planning, communication, cultural competency, and end of life care coordination. As a result, there is a growing gap between the number of seriously ill patients and the number of professionals with the appropriate knowledge and skills to care for them. This lack of capacity will impact seriously ill patients in need of palliative care.

In addition to improved training for care, providers focused on particular populations such as cancer patients. However, better training across all care providers will help professionals more accurately determine when seriously ill individuals with cognitive impairment or physical illness are in need of palliative care. COPD and Alzheimer's disease patients have been subject to biases resulting in under-use of palliative care, including instances in which symptoms from their chronic health conditions are mistaken as indicators that they are nearing the end of life. It should be highlighted that the need to increase education and training opportunities for those caring for patients with non-cancer diseases is urgent. Investments in end of life and palliative care education and related policies are critical to ensuring patients have access to high quality, timely and appropriate end of life care.

Investing in specialist multidisciplinary home-based palliative care pays off

Multidisciplinary palliative homecare teams (MDPHCT) are an indispensable link for people to die at home. However, the desire to die at home, expressed by end-of-life patients, is difficult to achieve without additional specialized financial support.

We demonstrated that a multidisciplinary palliative homecare team can lead to a decrease of €1,979 in total direct medical costs which gives rise to a clearly an urgent need to invest in supporting multidisciplinary palliative home care teams from a financial point of view.

The current financing system for MDPHCTs was established at the end of the 90s and has had little or no adjustments since then. However, palliative home care has become more and more professional over the last years and palliative care needs have become more complex. The increased demand for more specific palliative guidance and support should result in better financial support for MDPHCTs to guarantee quality of end-of-life care. It is therefore appropriate to rethink the financing system of MDPHCTs and to consider the changed need for education and support for patients with COPD, Alzheimer's disease, cancer and other life-threatening conditions, as well as the severity of these disease profiles and the associated quality of care. The development of adjusted financing should primarily focus on the positive overall cost effect of MDPHCTs. However, it should be noted that the development of new financing systems within the homecare setting does not entail a shift towards out-of-pocket costs for the patient. Therefore a full health economic evaluation of palliative care should be established.

However, in order to analyze the total palliative healthcare situation, it would be appropriate to have data on patients monitored by various palliative care initiatives and services, but unfortunately these figures are not yet available today.

Need for uniform registration

An important, not to be misunderstood the most important, requirement for achieving a comprehensive economic evaluation of end-of-life care is the availability of optimal data related to end-of-life care. Notwithstanding that, as shown in this dissertation, there is already a large availability of suitable data to evaluate end-of-life care from a health resource and cost perspective, the limited availability of full-population medical data is a major shortcoming. In this dissertation we have tried to supplement the existing administrative data with medical data available in electronic medical health records (EHR). However, the addition of these data would not allow us to analyze a full population. Complete EHRs are currently only available in Belgium for patients who have had a hospital admission. However EHRs, of a full population, available from primary care and more specifically available from medical care provided by general practitioners, only provide limited medical data. In addition, it should be noted that the registration within the medical practice is strongly focused on the registration of medical data and not on these data specifically 'tailored' for the evaluation of end-of-life care. With this dissertation, I would like to highlight the importance of registering qualitative and relevant data with regard to end-of-life care and, more specifically, call for a uniform registration model to be developed, and the development of specific (pseudo)codes to put end-of-life care on the Belgian 'healthcare map'.

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APPENDIX

Additional file 1: Complete list of variables in the linked dataset (IMA – Statistics Belgium – BCR)

Flag	Variable	Description
Statistics Belgium: Death certificates database		
	Immediate cause of death	The primary disease/cause prior to death, + up to 3 underlying causes.
	Associated causes of death	Up to 3 factors that indirectly contributed to death.
Statistics Belgium: data based on demographic datasets		
	natgr	Nationality-group: indicates to which of 16 most common nationalities in Belgium someone belongs. Less common nationalities are aggregated. (e.g. EU-other, Europe-other, other)
	liprohht	LIPRO-household type: e.g. single parent, married with/without children, …
Statistics Belgium : Socio-economic survey 2001 and census 2011		
	q9a/EDU	Highest level of education.
	q16a_m/SIE	Main profession.
Statistics Belgium: Composite variables socio-economic survey 2001		
	comf	Housing comfort level, based on number of types of different rooms (e.g. kitchen, bathroom…) and heating system.
Statistics Belgium: IPCAL dataset		
	Net income	Net income in the year prior to death. Provided relative to the entire population, not in absolute numbers.
IMA: Population database		
ANON_BASE	Recoded PP0010 and SS00010	Unique identification of the rightful claimant (coded)
	PP0015	Age (based on year of birth)
	AGE05_CAT	Age of the rightful claimant in categories of 5 years, calculated on December 31 of the reference year.
	PP0020	Sex

Care region (based on NIS code)	Recoded PP0025	Care region on the hospital level (in Flanders)
PROVINCE/DISTRICT	Based on PP0025	Official place of residence at time of death
URB_CAT	Based on PP0025	Degree of urbanisation of the place of residence
	PP0030	Social status (e.g. working, retired, …)
	PP0040 (A, B, C)	Year of death
	PP1010	Indicates whether the claimant received enhanced reimbursement.
	PP2001	Indicates whether the claimant received a forfeit class B nursing care.
	PP2002	Indicates whether the claimant received a forfeit class C for nursing care.
	PP2003	Indicates whether the claimant received a forfeit class E for physiotherapy.
	PP2005	Indicates whether the claimant received the allowance for the integration of disabled persons (category III, IV, V).
	PP2006	Indicates whether the claimant received the allowance for assistance to the elderly (category III, IV, V).
	PP2007	Indicates whether the claimant received a payment for assistance of third person carers.
	PP2008	Indicates whether the claimant received an increased allowance for help from third parties. (based on degree of disability)
	PP2009	Indicates whether the claimant received a lump sum benefit for 'assistance to others'.
	PP2010	Indicates whether the claimant was hospitalised at least 120 days during the last 2 years.
	PP2011	Indicates whether the claimant was hospitalised at least 6 times during the last 2 years.
	PP3004	Reimbursement category of the family.
	PP3005	Reimbursement category of the individual.

	PP3006	Date of the first claim entitled for maximum billing (provided in days prior to death).
	PP3011	Indicates whether the claimant received special allowances for disabled persons.
	PP3014	Indicates whether the claimant was entitled for maximum billing for the chronically diseased.
	PP4002	Number of days of unemployment due to disability.
	PP4003	Number of days of disability.
	PP4004	Evaluation of degree of functional status
CHRONICAL_YN		Indicates whether the claimant had at least one chronic illness in the last year and/or was entitled to an allowance for disabled persons.
IC_AVAIL_SA11 - IC_AVAIL_SA26		Estimation of the availability of family and informal caregivers, based on age and social status of family members.
IMA: Medical claims database		
	SS00015	Relative starting date of provision
	SS00020	Nomenclature code
	SS00050	Number of cases of provision
	SS00055	Number of days of provision
	SS00060	Amount of reimbursement
	SS00065B	Caregivers' qualifications
	SS00070B	Prescribers' qualifications
	SS00075	Identification of institution of the caregiver or prescriber (coded, not nominative)
	SS00080	Department code of the institution where care was provided
	SS00085	Place of care delivery (coded)
	SS00105	Number of institution which receives the payment
	SS00110	Date of hospitalisation
	SS00115	Date of hospital discharge

NEW_YN		Indication whether provided care is performed at weekends or at night
STAY_NR		Date of hospital admission
STAY_CAT		Type of hospital admission
ADMISSION, ADMISSION_YYYY		The first day that a stay is charged at a residence
DISCHARGE, DISCHARGE_YYYY		The last day that a stay is charged at a residence
LOS		Length of stay
LOS_YYYY		The calculated length of stay in a year
	SS00120	Invoice type
	SS00125	Date of last performance
	SS00130	Invoicing performance code
	SS00135	Pharmaceutical product code
	SS00140	Specification code of provision of care
	SS00150	Billed nomenclature code
	SS00155	Prescription date
	SS00160	Patient co-payment cost
	SS00165	Supplement
	SS00170	Code implant
	SS00175	Third party payer
THIRD_YN		Indicates whether a third party payer was involved
HOSP_ADM	SS00075, SS00085, SS00105	Identification hospital admission
HOSP_TRANS	SS00075, SS00085, SS00135	Identification hospital transfer(s)
IMA: Pharmanet database		
	SS00015	Delivery date
	SS00020	Medication reimbursement category
	SS00050	Drug quantity
	SS00060	National Health and disability insurance contribution 1
	SS00070B	Profession type of prescriber

	SS00075	Type of long-term care
	SS00135	Product number
	SS00155	Date of prescription (in days before death)
	SS00160	Out-of-pocket cost
	SS00165	Reduced repayment amount / Contribution of pharmacists
	SS00180	Reduced insurance contribution
	SS00195	National health and disability insurance contribution 2
	SS00200	Fee coding
	SS00210	Supplement
PHARMACIST_C, PHARMACIST_CAT		Pharmacist C is the coded unique identification number of the supplier of the performance. Pharmacist_cat indicates the type of the supplier of the performance
UNIT		Indicates the unit to which the quantity is specified
procedure_AH_cat, procedure_group, procedure_detail, procedure_cat		Formats into categories, sub-categories and cost of the nomenclature code as they are determined by the actuary of the National Health Care insurer
Prescriber_c, prescriber_cat		Prescriber C is the coded unique identification of the prescriber's performance. PRESCRIBER_CAT indicates the type of the prescriber
atc_prod_l		The different levels of the ATC code
BCR – Cancer Registry		
	inc_death_mm	Number of complete months between incidence date and date of death
	ICD10_new	Tumour localisation (ICD-10 code)

Additional file 2: ***Determination of different cost-components***

COST CATEGORY	SUBCOST CATEGORY	INCLUSION - Codes referring to	DATABASE
Indexering costs naar 2017	deaths 2010	**1.1279531**	
	deaths 2011	**1.1093473**	
	deaths 2012	**1.0764134**	
	deaths 2013	**1.0486210**	
	deaths 2014	**1.0357705**	
	deaths 2015	**1.0316701**	
	deaths 2016	**1.0209762**	
Hospitalization	TOTAL	Verpleegdagprijs + Farmaceutische producten+ geheel honoraria	IMA/GEZ
	Intensive care unit	Verpleegdagprijs + Farmaceutische producten+ geheel honoraria	IMA/GEZ
	Palliative care unit	Verpleegdagprijs + Farmaceutische producten+ geheel honoraria	IMA/GEZ
	D-ward	Verpleegdagprijs + Farmaceutische producten+ geheel honoraria	IMA/GEZ
	G-ward	Verpleegdagprijs + Farmaceutische producten+ geheel honoraria	IMA/GEZ
	Specialized psychogeriatric ward	Verpleegdagprijs + Farmaceutische producten+ geheel honoraria	IMA/GEZ
	Other wards	Verpleegdagprijs + Farmaceutische producten+ geheel honoraria	IMA/GEZ
Emergency Room		Hoofdstuk V. Speciale technische geneeskundige verstrekkingen - Afdeling 12. Toezicht, onderzoeken en permanentie voor rechthebbenden opgenomen in een ziekenhuis en verstrekkingen verleend in de lokalen van een erkende functie voor gespecialiseerde spoedgevallenzorg - § 3bis. Honorarium voor dringende opvang in een erkende functie voor gespecialiseerde spoedgevallenzorg	IMA/GEZ
Nursing home	Residential	RVT en ROB	IMA/GEZ
	Semi-residential	Kortverblijf en dagverblijf	IMA/GEZ

Multidisciplinary primary care		Medische huizen, multidisciplinaire eerstelijnszorg	IMA/GEZ
General practitioner		Honoraria voor raadplegingen, bezoeken, adviezen en toezicht	IMA/GEZ
Specialist		Honoraria voor raadplegingen, bezoeken, adviezen en toezicht	IMA/GEZ
Nurse	NON Palliative home nurse	Thuisverpleging exclusief codes palliatieve thuiszorg	IMA/GEZ
	Palliative home nurse	Palliatieve thuiszorg exclusief codes thuisverpleging	IMA/GEZ
	TOTAL home nurse	Thuisverpleging	IMA/GEZ
Other healthcare professionals		Verzorging door bandagisten, orthopedisten, opticiens, audiciens, vroedvrouwen, logopedisten,honoraria tandheelkundigen	IMA/GEZ
Medication	INPATIENT medication cost	Specialiteiten afgeleverd aan gehospitaliseerde rechthebbenden	IMA/GEZ
	OUTPATIENT medication cost	Alle kosten farmadatabase en uit GEZdatbase: Specialiteiten afgeleverd aan niet-gehospitaliseerde rechthebbenden in de officina's en specialiteiten afkomstig van de ziekenhuisofficina, en afgeleverd aan niet ter verpleging opgenomen rechthebbenden	IMA/GEZ - FARMA
	TOTAL medication cost	Cost outpatient medication en cost inpatient medication	IMA/GEZ - FARMA
Other pharmaceutical deliveries		Magistrale bereidingen, diverse honoraria, bloed en bloedplasma, medische voeding, remgelden spoed en enterale voeding*, diverse farmaceutische verstrekkingen	IMA/GEZ
Medical supplies		medische hulpmiddelen, zuurstof, implantaten, implanteerbare defibrillatoren	IMA/GEZ
Medical imaging		Honoraria voor medische beeldvorming	IMA/GEZ
Clinical Biology		Honoraria voor klinische biologie	IMA/GEZ
Fysiotherapy		Kinesitherapie	IMA/GEZ
Surgery		Honoraria voor heelkunde	IMA/GEZ
Other medical procedures		honoraria voor speciale verstrekkingen, gynaecologie en dialyse	IMA/GEZ
Mental/psychiatric care		Psychiatrische verzorgingstehuizen, initiatieven voor beschut wonen, psychiatrische ziekenhuizen	IMA/GEZ
Palliative care		Palliatieve zorgen	IMA/GEZ

Other		all-in prijs militaire hospitaal, revalidatie en herscholing, bijzonder fonds, medisch pediatrische centra, andere kosten verblijf en transport, sociale maximumfactuur, chronische zieken, menselijk lichaamsmateriaal, bronkuren, regularisaties en herfacturaties, niet affecteerbare regularisaties per discipline, multidisciplinaire rolwagens, tabaksontwenning, MS/ALS/Huntington, magneetbandcodes, statistische codes, kadernomenclatuur, artikel 56, nomensoft, ten onrechte betaalde bedragen, maximumtarieven tandheelkunde	IMA/GEZ
Total cost		All costs	IMA/GEZ - FARMA
Total inpatient cost		All inpatient costs	IMA/GEZ
Total outpatient cost		All outpatient costs	IMA/GEZ+FARMA

SUMMARY

SUMMARY

Good quality end-of-life care is recognized as an essential component of modern health care services. However, good understanding of resources and costs used at end-of-life are important to clarify the wider picture of good-quality end-of-life care. Yet, there is a lack of good data concerning the costs of palliative care and acquiring information on resources and costs of end-of-life care poses significant challenges, especially given that end of life care is complex and fragmented across many different services and providers of care.

Medical care in the final period of life accounts for a considerable share of health care expenditures and most of the current evidence is based on studies in those suffering from cancer. While it is indicated that palliative care is cost-saving, early identification and prognostication of the end of life phase and the provision of appropriate end-of-life care and palliative care are also assumed to improve quality of life of patients and their families. However, this evidence is mainly based on evaluations of specific or small cancer cohorts and full-population national evaluations of those suffering from non-cancer diseases are lacking. Hence, there is a growing interest in examining the current state of healthcare use and costs across a full national population and there is a need to identify opportunities for improvement and reducing costs at the end of life for equally needed non-cancer patients.

However, the typical model of cancer end-of-life care might not suit for people who have a gradual, progressive decline with unpredictable exacerbations such as chronic obstructive pulmonary disease or those who suffer from a prolonged deterioration such as Alzheimer's disease. People who suffer from non-communicable diseases e.g., COPD and Alzheimer's disease may have similar and more prolonged needs pressing as hard as those who suffer from cancer. Due to uncertainty about the prognosis and the failure or late recognition of the terminal phase, end-of-life care for those suffering from COPD and Alzheimer's disease is characterized by a lack of timely initiation of adapted end-of-life care.

Due to differences between the end-of-life trajectories of cancer, COPD and Alzheimer's disease, difficulties in recognizing the end-of-life phase and the presence of comorbidities in those suffering from COPD and Alzheimer's disease results in end-of-life care not aimed at responding the specific end-of-life needs and consequently results in intensive and expensive use of healthcare services. However, full population analysis of direct medical end-of-life care costs and resource use in those dying from COPD and Alzheimer's disease are lacking.

Although economic evaluations of end-of-life care develop slowly and the evidence base remains small, filling this evidence gap is increasingly important to facilitate good-quality end-of-life care for those suffering from non-cancer related diseases such as COPD or Alzheimer's disease.

The first part of this dissertation includes a general introduction. The first chapter describes a state of the art of the current end-of-life policy. It provides more insight into the definitions used, the background of end-of-life care in Belgium and the specific end-of-life care characteristics and end-of-life trajectories of COPD and Alzheimer's disease. A distinction between hospital-based and home-based end-of-life care is also clarified. The second chapter describes the methodology used and gives an overview of this dissertation. Finally, in chapter 3, the possibilities of acquiring and linking specific secondary data sources to evaluate end-of-life care at population level are discussed.

The first objective of this dissertation is to investigate which available secondary data sources provide opportunities for evaluating end-of-life care at population level. In chapter 3 different secondary data sources were identified that offer the possibility to evaluate end-of-life care use and costs across the Belgian population. We identified a total of eight national population-level databases to describe resource use and costs of end-of-life care in COPD and Alzheimer's disease patients and linked them into one common database. The data of this comprehensive full-population linked database include healthcare data retrieved from the Intermutualistic Agency (IMA), diagnostic characteristics of cancer decedents from the Belgian Cancer Registry (BCR) and sociodemographic, socio-economic and death certificate data retrieved from Statistics Belgium. Although a fourth database, the MZG-database, was found appropriate for evaluating resource use and healthcare costs of end-of-life care, it would limit our database to hospitalized patients only. As such, a total of seven population-level databases handled by three different organizations were identified as providing the necessary information to evaluate end-of-life resource use and costs.

The second part of this dissertation describes end-of-life resource use. The first objective was to map the current state of evidence regarding resource use and the costs of end-of-life care. By means of a systematic review an overview of the current evidence on resource use and costs in end-stage COPD patients was given in chapter 4. The results of this review show that the terminal disease trajectory of COPD patients is associated with a high use of acute resources caused by the fact that end-of-life care in COPD patients is mainly focused on prolonging life

with a prevailing tendency toward aggressive care. It was determined that acute hospital visits, ICU admissions, physician visits and the use of invasive interventions and medication were the key drivers of resource use of terminal COPD patients and that the differences in resource use of COPD patients during their last months of life were mainly caused by the presence of comorbidities and exacerbations at the end of life. However, based on the existing evidence, specific cost items could not be described.

A second objective of this dissertation is to analyze the influence of specific comorbidities on end-of-life resource use in those who died with COPD. Chapter 5 compares resource use between those who had a primary cause of death of COPD with COPD patients who had a primary cause of death of cardiovascular diseases or lung cancer during the last months of life and indicates that the presence of lung cancer and cardiovascular diseases influences resource use in COPD patients at life's end. Results show that COPD patients who have a primary cause of death of lung cancer use less intensive resources during the last 6 months of life as compared to those who have a primary cause of death of COPD or cardiovascular diseases, are more prone for using palliative care services offered in a palliative care unit or at home and receive more medication that provides symptomatic benefits to patients at the end of life. COPD patients who died of their COPD and those who died of a cardiovascular disease showed a comparable resource use although the latter receive less non-invasive ventilation and have a higher chance of being reanimated.

Chapter 6 describes the third objective of this dissertation that examines the influence of the recognition of Alzheimer's disease as a life-threatening disease on resource use in the last months of life. It describes end-of-life resource use between those who died of or with Alzheimer's disease and shows that those who died of Alzheimer's disease (i.e. Alzheimer's disease as an underlying cause of death) use less resources as compared with those who did not have Alzheimer's disease indicated as an underlying cause of death on the death certificate. The results described in chapter 6 suggest that the recognition of end-stage Alzheimer's disease as an end-of-life condition may influence the use of less intensive resources such as palliative care services and, hence, the appropriateness of end-of-life care. Besides the importance of and difficulties in recognizing end-stage Alzheimer's disease, the results show that the level of home palliative care use in those dying of Alzheimer's disease is low which indicates the need for more efforts to encourage its timely use in those suffering of Alzheimer's disease. Recognizing Alzheimer's disease as a disease of which one could die and the recognition of the end-stage phase were therefore indicated as important factors to provide good-quality end-of-life care to these patients.

In the third part of this dissertation, a cost-analysis was performed in chapters 7 and 8, in which, in chapter 7 a cost comparison of those who died of cancer, COPD and Alzheimer's disease was executed. The results of this cost comparison show that total direct medical cost of the last year of life in cancer decedents amounts to € 42,163 and are mainly determined by an inpatient cost. For COPD decedents, total direct medical cost amounts to € 35,209 which was also dominated by a high inpatient cost. On the other hand, the results show that Alzheimer's disease decedents generate a mean total direct medical cost of €26,358 of which 68.7% consists of outpatient costs. In all 3 groups, the largest share of the total direct medical end-of-life care costs is borne by the public insurer. However, when compared to cancer decedents, COPD decedents generate € 7,200 lower total cost, € 4,509 lower total medication cost, € 3,432 lower total outpatient cost and a lower inpatient cost of €3,768. Dying of Alzheimer's disease lowers total costs with € 15,549, total medication costs with €6,286, and inpatient costs with €16,687 but increases total outpatient costs with €1,138 when compared to cancer decedents. Although it was shown that dying of COPD results in a lower total, inpatient and outpatient direct medical cost they generate a higher direct medical cost related to intensive care, GP, nursing home care and nursing home. In Alzheimer's disease patients, the higher outpatient cost is mainly influenced by expenditures related to out-of-hospital services such as family physician consultations, home nursing and nursing home care.

In chapter 8, we analyzed the effect of providing palliative care in a community-based setting on direct medical end-of-life care costs in COPD patients. The use of an multidisciplinary palliative home care team (MDPHCT) during the last six to one month before death entails a significant decrease of €1,979 in the total direct medical cost. This decrease, however, only applies to the direct inpatient medical costs (-€3,027). The use of an MDPHCT increases the direct medical outpatient costs for both insurer and patient with €1,047. It was shown that the use of home-based specialized palliative care, such as an MDPHCT, reduces expenditures for hospitalization, specialist care, pharmaceutical deliveries, clinical biology, medical imaging, physiotherapy and medical procedures but increases the medical cost for outpatient GP contacts, home nursing care, physiotherapy and medication spending during the last month of life in COPD patients.

Finally, this dissertation contains, in Part IV, a discussion of the results, including methodological concerns, strengths and limitations and implications for policy and future research. With this dissertation we have tried to draw attention to the lack of specific information about resource use and costs of end-of-life care in non-cancer patients such as COPD and Alzheimer's disease. We show that the presence of co-morbidities in COPD patients

and the recognition of Alzheimer's disease as a life-threatening disease complicate the accessibility to appropriate end-of-life care such as palliative care. On the other hand, we show that direct medical costs in the last year of life for cancer patients are higher than those for COPD and Alzheimer's disease and that inpatient care cannot always be seen as the most important cost component towards end of life. We therefore suggest that (1) the development of more effective and affordable cancer, COPD and Alzheimer's disease treatment options, (2) avoiding unnecessary hospitalizations due to acute unforeseen exacerbations and concomitant diseases, (3) improvements in prognosis and recognition of the final stage in COPD and Alzheimer's disease and (4) improvements in the availability of home-based specialized palliative care services might result in affordable, appropriate, accessible and customer-oriented end-of-life care for those dying of COPD and Alzheimer's disease.

SAMENVATTING

Kwaliteitsvolle levenseindezorg wordt erkend als een essentieel onderdeel van de moderne gezondheidszorg. Een goed begrip van middelen en uitgaven die hierbij worden gebruikt en gegenereerd, vormen daarbij een belangrijke component om het bredere beeld van hoogwaardige levenseindezorg te verduidelijken. Echter, vermits dat de zorg aan het einde van het leven complex en gefragmenteerd is over verschillende diensten en zorgaanbieders brengt het verzamelen van informatie over de gebruikte middelen grote uitdagingen met zich mee.

Eerdere bevindingen geven aan dat de medische zorg in de laatste levensfase goed is voor een aanzienlijk deel van de uitgaven binnen de gezondheidszorg. Echter, deze huidige bevindingen zijn gebaseerd op onderzoeken bij zij die aan kanker lijden en sterven. Hoewel eerdere bevindingen aantonen dat palliatieve zorg kostenbesparend is, wordt verondersteld dat een vroegtijdige voorspelling en identificatie van de levenseindefase en de hieraan gekoppelde verstrekking van passende zorg, ook de kwaliteit van leven van patiënten en hun families verbeteren. Deze bevindingen zijn echter voornamelijk gebaseerd op specifieke of kleine kankercohorten. Analyses van een volledige nationale populatie van mensen met niet-kankerziekten ontbreken. Als gevolg hiervan wordt de huidige praktijk en beleidsvoering van levenseindezorg sterk beïnvloedt door zij die sterven aan kanker.

Het typische levenseindetraject van kanker is echter niet geschikt voor zij die gekenmerkt worden met een geleidelijke, progressieve achteruitgang en onvoorspelbare exacerbaties, zoals chronische obstructief longlijden of zij die gekenmerkt worden met een langdurige graduele achteruitgang zoals de ziekte van Alzheimer. Mensen die lijden aan chronische aandoeningen zoals COPD en de ziekte van Alzheimer kunnen echter vergelijkbare en meer langdurige zorgbehoeften hebben die net zo intensief zijn als degenen die lijden aan kanker. Ten gevolge van de onzekerheid over de prognose en het falen of de late herkenning van de terminale fase, wordt de zorg aan het levenseinde voor deze groep van patiënten echter gekenmerkt door een gebrek aan tijdige initiatie van aangepaste levenseindezorg.

Hoewel economische evaluaties van levenseindezorg zich langzaam ontwikkelen en de evidentie klein blijft, wordt het opvullen van deze kenniskloof steeds belangrijker om een kwalitatief hoogwaardige levenseindezorg mogelijk te maken voor zij die lijden aan niet-kanker gerelateerde ziekten zoals COPD of de Ziekte van Alzheimer.

Het eerste deel van deze dissertatie omvat de algemene introductie. In het eerste hoofdstuk wordt een state of the art van het huidige levenseindebeleid beschreven. Het verschaft meer

inzicht in de gehanteerde definities, de achtergrond van levenseindezorg in België en de specifieke levenseindezorg karakteristieken en levenseindetrajecten van COPD en de ziekte van Alzheimer. Het onderscheid tussen ziekenhuis en thuis geleverde levenseindezorg worden hierin tevens ook verduidelijkt. Het tweede hoofdstuk omschrijft de gebruikte methodologie en geeft een overzicht van deze dissertatie. Ten slotte wordt in hoofdstuk 3 nader ingegaan op de mogelijkheden van het verwerven en linken van specifieke secundaire databronnen om dusdanig het zorggebruik en kosten met betrekking tot levenseindezorg op populatieniveau te evalueren.

De eerste doelstelling van deze dissertatie is om na te gaan welke beschikbare secundaire databronnen mogelijkheden verschaffen om levenseindezorg te evalueren op populatieniveau. In hoofdstuk 3 worden verschillende databronnen geïdentificeerd die de mogelijkheid bieden om levenseinde zorggebruik en kosten overheen de Belgische populatie te analyseren. We identificeerden in totaal acht nationale databanken op bevolkingsniveau om het zorggebruik en de kosten van levenseindezorg bij COPD- en Alzheimerpatiënten te beschrijven en koppelden deze in één gemeenschappelijke database. Deze uitgebreide databank bevat de volledige populatie van overledenen en omvat gegevens over het gezondheidszorggebruik die werden verkregen van het Intermutualistisch Agentschap (IMA), diagnostische gegevens van kanker overledenen van het Belgische kankerregister (BCR) en socio-demografische, socio-economische en overlijdenscertificaatgegevens die werden verkregen van Statistiek België (Statbel). Hoewel een vierde database, de MZG-database, geschikt werd bevonden voor het evalueren van het zorggebruik en de kosten, is de database beperkt tot enkel deze personen die een ziekenhuisopname hadden gekend. Finaal werd een totaal van zeven databases, die worden beheerd door drie verschillende organisaties, geïdentificeerd als noodzakelijke databases om het gebruik en de kosten van levenseindezorg te evalueren.

Het tweede deel van deze dissertatie behandelt het zorggebruik dat gepaard gaat met levenseindezorg. De eerste doelstelling hierbij was om de huidige stand van de wetenschap omtrent zorggebruik en kosten van levenseindezorg in kaart te brengen. Door gebruik te maken van een systematische review wordt in hoofdstuk 4 een overzicht gegeven van de huidige kennis met betrekking tot het zorggebruik en de kosten van COPD-patiënten in het eindstadium. De resultaten van deze review tonen aan dat het terminale ziektetraject van COPD-patiënten geassocieerd is met een hoog gebruik van acute zorg dewelke veroorzaakt wordt door een levenseindezorg die voornamelijk gericht is op het verlengen van het leven en gekenmerkt wordt door een neiging tot agressieve zorg. Er werd vastgesteld dat acute

ziekenhuisbezoeken, IC-opnames, artsenbezoeken en het gebruik van invasieve interventies en medicatie de belangrijkste componenten van het zorggebruik door terminale COPD-patiënten waren en dat deze verschillen in zorggebruik hoofdzakelijk beïnvloed werden door de aanwezigheid van comorbiditeit en exacerbaties. Op basis van het weinige bestaande bewijsmateriaal konden echter geen specifieke bevindingen worden beschreven met betrekking tot de levenseindekosten van COPD- patiënten.

De tweede doelstelling van deze dissertatie is om de invloed van specifieke comorbiditeiten op het levenseindezorggebruik te analyseren bij zij die sterven met COPD. Hoofdstuk 5 vergelijkt het zorggebruik tussen diegenen die een primaire doodsoorzaak hadden van COPD met COPD-patiënten die in de laatste levensmaanden een primaire doodsoorzaak van hart- en vaatziekten of longkanker hadden en geeft aan dat de aanwezigheid van longkanker en hart- en vaatziekten het zorggebruik beïnvloedt bij COPD-patiënten aan het einde van het leven. De resultaten tonen aan dat COPD-patiënten met een primaire doodsoorzaak van longkanker minder intensieve middelen gebruiken tijdens de laatste 6 maanden van hun leven in vergelijking met diegenen met een primaire doodsoorzaak van COPD of hart- en vaatziekten, dat ze meer gebruikmaken van palliatieve zorgdiensten aangeboden in een palliatieve zorgeenheid of thuis en meer medicatie voorgeschreven krijgen die symptomatische voordelen biedt aan het einde van hun leven. COPD-patiënten die overleden aan hun COPD en deze die overleden aan een hart- en vaatziekte vertoonden een vergelijkbaar zorggebruik hoewel de laatstgenoemden minder niet-invasieve beademing krijgen en een hogere kans hebben om gereanimeerd te worden.

Hoofdstuk 6 beschrijft de derde doelstelling van deze dissertatie waarin nagegaan wordt welke invloed de erkenning van de ziekte van Alzheimer als een levensbedreigende ziekte heeft op het zorggebruik in de laatste maanden van het leven. Het beschrijft het levenseindezorggebruik tussen zij die zijn overleden aan of met de ziekte van Alzheimer en toont aan dat personen die zijn overleden aan de ziekte van Alzheimer (Ziekte van Alzheimer als onderliggende doodsoorzaak) minder middelen gebruiken in vergelijking met zij die geen Alzheimer-indicatie hadden als onderliggende doodsoorzaak op de overlijdensakte. De resultaten die worden beschreven in hoofdstuk 6 suggereren dan ook dat de (h)erkenning van de ziekte van Alzheimer als een end-stage conditie van invloed kan zijn op het gebruik van minder intensieve zorg zoals palliatieve zorg. Naast het belang van en de moeilijkheden bij het herkennen van de levenseindefase bij de ziekte van Alzheimer, tonen de resultaten ook aan dat het niveau van palliatieve thuiszorggebruik, bij zij die lijden aan de ziekte van Alzheimer, laag is, wat tevens

ook aangeeft dat er meer inspanningen nodig zijn om het tijdig gebruik ervan te stimuleren. Het erkennen van de ziekte van Alzheimer als een levensbedreigende ziekte en de erkenning van de laatste levensfase werden daarom aangewezen als belangrijke factoren om kwaliteitsvolle levenseindezorg te garanderen.

In het derde deel van deze dissertatie worden in hoofdstuk 7 en 8 een kostenanalyse uitgevoerd waarbij, in hoofdstuk 7, de resultaten van een kostenvergelijking tussen kanker, COPD en de ziekte van Alzheimer werden beschreven. De resultaten van deze kostenvergelijking tonen aan dat de totale directe medische kosten van het laatste levensjaar bij zij die sterven aan kanker € 42.163 bedragen en voornamelijk worden bepaald door een hospitalisatiekost. Voor COPD-overledenen bedragen de totale directe medische kosten € 35.209, die ook werd gedomineerd door hoge hospitalisatiekosten. Anderzijds tonen de resultaten aan dat overledenen aan de ziekte van Alzheimer een gemiddelde totale directe medische kosten genereren van € 26.358, waarvan 68,7% uit ambulante kosten bestaat. In de drie groepen wordt het grootste deel van de totale directe medische kost aan het levenseinde gedragen door de publieke verzekeraar. Echter, in vergelijking met overledenen aan kanker, genereren COPD-overledenen € 7.200 lagere totale kosten, € 4.509 lagere totale medicatiekosten, € 3.432 lagere totale ambulante kosten en een lagere hospitalisatiekost van € 3.768. Sterven aan de ziekte van Alzheimer verlaagt de totale kosten met € 15.549, de totale medicatiekosten met € 6.286, en de hospitalisatiekost met € 16,687, maar verhoogt de totale ambulante kosten met € 1.138 in vergelijking met kanker. Hoewel werd aangetoond dat het overlijden aan COPD resulteert in lagere totale, hospitalisatie en ambulante direct medische kosten, genereren zij hogere direct medische kosten gerelateerd aan intensieve zorg, huisartsen, thuisverpleging en woonzorgcentrum. Bij patiënten met de ziekte van Alzheimer wordt de hogere ambulante kost voornamelijk beïnvloed door uitgaven gerelateerd aan de medische zorg geleverd door de huisarts en thuisverpleging en in het woonzorgcentrum.

In hoofdstuk 8 analyseerden we het effect van een multidisciplinaire begeleidingsequipe (MBE) op direct medische kosten aan het levenseinde bij COPD-patiënten. Het gebruik van een MBE gedurende de laatste zeven tot een maand voor het overlijden brengt een aanzienlijke daling van € 1.979 in de totale direct medische kosten met zich mee. Deze afname wordt echter sterk gekenmerkt door een lagere directe medische hospitalisatiekost (- € 3.027). De resultaten tonen aan dat het gebruik van een MBE de directe medische ambulante kosten verhoogt voor zowel verzekeraar als patiënt met € 1.047. Er werd tevens ook aangetoond dat het gebruik van gespecialiseerde palliatieve thuiszorg, zoals een MBE, de uitgaven voor hospitalisatie,

specialistische zorg, farmaceutische leveringen, klinische biologie, medische beeldvorming, fysiotherapie en medische procedures vermindert, maar de medische kosten voor huisartscontacten, thuisverpleging, fysiotherapie en medicatie verhoogt tijdens de laatste maand van leven.

Tot slot bevat dit proefschrift in deel IV een bespreking van de resultaten, inclusief methodologische aandachtspunten en sterktes en beperkingen en worden implicaties voor beleid en toekomstig onderzoek beschreven. Met deze dissertatie hebben we getracht de aandacht te vestigen op het gebrek aan specifieke informatie omtrent het zorggebruik en kosten van levenseindezorg in niet-kankerpatiënten zoals COPD- en Alzheimerpatiënten. We tonen aan dat de aanwezigheid van comorbiditeiten bij COPD-patiënten en de erkenning van de ziekte van Alzheimer als levensbedreigende aandoeningen de toegankelijkheid tot gepaste levenseindezorg zoals palliatieve zorg bemoeilijkt. Anderzijds tonen we aan dat de medische kosten in het laatste jaar van leven voor kankerpatiënten hoger ligt dan deze voor COPD en Alzheimer en dat zorg verleent in het ziekenhuis niet altijd gezien kan worden als de belangrijkste kostenpost naar het einde van het leven toe. We besluiten dan ook dat (1) de ontwikkeling van effectievere en betaalbare behandelingsopties voor kanker, COPD en de ziekte van Alzheimer, (2) het voorkomen van onnodige hospitalisaties als gevolg van acute onvoorziene exacerbaties en comorbiditeiten, (3) verbeteringen in de prognose en erkenning van de laatste fase van COPD en de ziekte van Alzheimer en (4) verbeteringen in de beschikbaarheid van gespecialiseerde thuiszorgdiensten kunnen resulteren in betaalbare, gepaste, toegankelijke en klantgerichte levenseindezorg voor zij die sterven aan COPD of de ziekte van Alzheimer.

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PERSONAL CONTRIBUTION

CONTRIBUTIONS OF THE AUTHOR TO THIS DISSERTATION

PART I GENERAL INTRODUCTION

CHAPTER 1: GENERAL INTRODUCTION

- Searching existing literature
- Writing the chapter

CHAPTER 2: METHODS AND OUTLINE

- Searching existing literature
- Writing the chapter

CHAPTER 3: ADMINISTRATIVE AND DISEASE SPECIFIC DATABASES TO STUDY END OF LIFE

- Searching available databases
- Discussing the linking possibilities
- Determining relevant variables from IMA, BCR and Statbel
- Writing the data request for the database administrators and privacy commission bodies
- Supervising the data request
- Writing the manuscript

PART II HEALTH RESOURCE USE EVALUATION OF END OF LIFE CARE ACROSS A BELGIAN POPULATION OF COPD AND ALZHEIMER'S DISEASE DECEDENTS

CHAPTER 4: RESOURCE USE AND HEALTH CARE COSTS OF COPD PATIENTS AT THE END OF LIFE: A SYSTEMATIC REVIEW

- Searching existing literature
- Evaluation of literature
- Writing the manuscript

CHAPTER 5: RESOURCE USE OF COPD PATIENTS AT THE END OF LIFE

- Developing relevant resource categories using IMA data
- Analyzing the results
- Writing the manuscript

CHAPTER 6: RESOURCE USE OF INDIVIDUALS DYING OF ALZHEIMER'S DISEASE

- Developing relevant resource categories using IMA data
- Analyzing the results
- Writing the manuscript

PART III ECONOMIC EVALUATION OF END OF LIFE CARE

CHAPTER 7: COST OF DYING

- Developing relevant cost-categories and cost-components using IMA data (nomenclature)
- Analyzing the results
- Writing the manuscript

CHAPTER 8: THE EFFECT OF SPECIALIZED PALLIATIVE HOME CARE ON END OF LIFE CARE COSTS

- Developing relevant cost-categories and cost-components using IMA data (nomenclature)
- Analyzing the results
- Writing the manuscript

PART IV GENERAL DISCUSSION

CHAPTER 9: GENERAL DISCUSSION & RECOMMENDATIONS

- Searching existing literature
- Writing the chapter