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UNIVERSITY OF TARTU
Press

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Dissertation accepted for the commencement of the degree of Doctor of Philosophy in Medicine on October 18, 2017 by the Council of the Faculty of Medicine, University of Tartu, Estonia.

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Commencement: December 14, 2017

Publication of this dissertation is granted by the University of Tartu.

ISSN 1024-395X
ISBN 978-9949-77-616-0 (print)
ISBN 978-9949-77-617-7 (pdf)

University of Tartu Press
www.tyk.ee

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I. Jürisson M, Vorobjov S, Kallikorm M, Lember M, Uusküla A. The incidence of hip fractures in Estonia, 2005–2012. Osteoporosis International 2015; 26:77–84.
II. Jürisson M, Pisarev H, Kanis JA, Borgström F, Svedbom A, Kallikorm R, Lember M, Uusküla A. Quality of life, resource use, and costs related to hip fracture in Estonia. Osteoporosis International 2016; 27:2555–2566.
III. Jürisson M, Raag M, Kallikorm R, Lember M, Uusküla A. The impact of hip fracture on mortality in Estonia: a retrospective population-based cohort study. BMC Musculoskeletal Disorders 2017;18(243):1–10
IV. Jürisson M, Raag M, Kallikorm R, Lember M, Uusküla A. The impact of comorbidities on hip fracture mortality: a retrospective population-based cohort study. Archives of Osteoporosis 2017; 12:76
V. Borgström F, Lekander I, Ivergård M, Ström O, Svedbom A, Alekna V, Bianchi ML, Clark P, Curiel MD, Dimai HP, Jürisson M, Kallikorm R, Lesnyak O, McCloskey E, Nassonov E, Sanders KM, Silverman S, Tamulaitiene M, Thomas T, Tosteson ANA, Jönsson B, Kanis JA. The International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) – quality of life during the first 4 months after fracture. Osteoporosis International 2013; 24:811–823.
VI. Svedbom A, Borgström F, Hernlund E, Ström O, Alekna V, Bianchi ML Clark P, Diaz-Curiel M, Dimai HP; Jurisson M, Kallikorm R, Lember M, Lesnyak O, McCloskey E, Sanders KM, Silverman S, Solodovnikov A, Tamulaitiene M, Thomas T. Toroptsova N, Uuskula A, Tosteson ANA, Jönsson B, Kanis JA. Quality of life for up to 18 months after low energy hip, vertebral, and distal forearm fractures – Results from the ICUROS. Accepted for publication in Osteoporosis International on November 13, 2017

The contribution of Mikk Jürisson to the original publications:

PAPERs I, II, III, IV: Proposing the research question, participating in the design and conduction of the study, participating in the data collection and analysis, drafting the manuscript and preparing final revisions in the manuscript before submission for publication.

PAPERs V, VI: Participating in the design and conduction of the study, participating in the data collection and analysis, revising and approving the manuscript before submission for publication.

LIST OF ABBREVIATIONS

BMD	bone mineral density
BMI	body mass index
CCI	Charlson comorbidity index
DALY	disability-adjusted life year
EHIF	Estonian Health Insurance Fund
HRQoL	Health related quality of life
ICD	International classification of diseases
ICUROS	International Costs and Utilities Related to Osteoporotic Fractures Study
IQR	inter-quartile range
IRR	incidence rate ratio
QALY	quality-adjusted life year
SD	standard deviation
SIR	age-standardized incidence rate
TTO	time trade off method
VAS	visual analogue scale

1. INTRODUCTION

Hip fracture is one of the major public health problems (Kanis *et al.*, 2013). Clinical consequences of fracture include short and long-term morbidity characterized by pain, limitation of function, decreased health-related quality of life (HRQoL), and increased mortality (Teng, Curtis and Saag, 2008). Hip fracture is the most serious osteoporotic fracture, and its consequences measured in mortality, morbidity and cost approximate to all other fragility fractures combined (Hernlund *et al.*, 2013). To outline the magnitude, every 6–7th woman over 50 years will experience a hip fracture (Kanis *et al.*, 2013), a figure close to the risk of coronary heart disease (Berry *et al.*, 2012). The related hospitalization cost is comparable to that of myocardial infarction and stroke (Singer *et al.*, 2015). Moreover, the all-cause mortality at 1 year after hip fracture exceeds the population-expected mortality by 3–4 times (Abrahamsen *et al.*, 2009; Haentjens *et al.*, 2010), the risk comparable to the severest life-threatening diseases such as metastatic cancer or dementia (Quan *et al.*, 2011; Todd *et al.*, 2013). In addition, less than half of all survivors recover in full (Melton, 2003).

However, public awareness of the problem is low, and identifying individuals with a high risk of fracture remains a challenge (Harvey *et al.*, 2017). Besides, there is a marked heterogeneity of hip fracture prevention and care among European countries (Hernlund *et al.*, 2013; Svedbom *et al.*, 2013). Given the aging population and a projected increase in hip fractures, a change in policy is warranted (Cheng, Levy and Lefaivre, 2011; Hernlund *et al.*, 2013). Awareness of the disease and its consequences must be increased to attenuate the public health impact (Harvey *et al.*, 2017). Quantifying the hip fracture burden on patients and society is important to raise awareness, identify the most vulnerable at-risk groups, draw attention to gaps and inequalities in care provision, and guide prevention policies and interventions (Kanis *et al.*, 2013; Harvey *et al.*, 2017).

The health and economic burdens of hip fracture were modeled recently for all European countries (Ström *et al.*, 2011; Hernlund *et al.*, 2013; Svedbom *et al.*, 2013). In 2010, the number of people with incident hip fractures was estimated at 615,000 and prevalent fractures at 3.3 million in Europe, 3/4 of the fractures were among women. The cost of hip fractures amounted to 20 billion euros, 2/3 of that incurred in those aged above 80 years. For comparison, the societal cost of lung cancer has been estimated at 19 billion and breast cancer at 15 billion euros in Europe (Luengo-Fernandez *et al.*, 2013), dementia at 105–160 billion (Gustavsson *et al.*, 2011; Wimo *et al.*, 2011; Olesen *et al.*, 2012; DiLuca and Olesen, 2014), Parkinson's disease at 14 billion (Gustavsson *et al.*, 2011; Olesen *et al.*, 2012; DiLuca and Olesen, 2014), stroke at 27–64 billion (Leal *et al.*, 2006; Gustavsson *et al.*, 2011; Olesen *et al.*, 2012; DiLuca and Olesen, 2014), and coronary heart disease at 45 billion (Leal *et al.*, 2006). Overall, the reduced survival, reduction in HRQoL and high costs pose a significant clinical and economic burden on the European population (Hernlund *et al.*, 2013; Papadimitriou *et al.*, 2017).

According to the limited data on hip fracture in Estonia, the number of people ≥50 years of age with incident hip fractures was estimated at 1600 each year, and prevalent fractures as high as 7300 persons a year (Hernlund *et al.*, 2013; Svedbom *et al.*, 2013). The disease burden was estimated at 1400 quality-adjusted life years (QALY) lost each year. The first-year hip fracture cost burden was estimated at 5580 euros per patient, and the total societal cost at 15 million euros or 12 euros per person. For comparison, the healthcare cost of lung cancer has been estimated at 7 euros and breast cancer at 13 euros per person in Estonia (Luengo-Fernandez *et al.*, 2013). The hip fracture costs were projected to increase by 17% by 2025 (Hernlund *et al.*, 2013; Svedbom *et al.*, 2013).

However, the epidemiologic and cost data for estimating disease burden in the study were incomplete for deriving sound estimates for policy. For example, the hip fracture incidence for Estonia was derived from a regional estimate (Haviko, Maasalu and Seeder, 1996) and using the unpublished hip fracture rates from Finland (Svedbom *et al.*, 2013), the mortality estimate was derived from Sweden (Kanis *et al.*, 2003; Johnell *et al.*, 2004; Borgström *et al.*, 2007), and the HRQoL loss estimate from a systematic review (Peasgood *et al.*, 2009). Resource use and cost data were adjusted from neighboring countries, Finland and Sweden (Nurmi *et al.*, 2003; Borgström *et al.*, 2006; World Bank, 2008). The need for reliable country-specific estimates was evident.

This series of studies was undertaken to assess the health and economic impact (incidence, loss of HRQoL, resource use and costs, and excess mortality) of hip fracture in Estonia, to enable estimation of the total societal burden and improve future predictions. The results can be used as a platform for prioritization of hip fracture in health and social policy agendas, draw attention to gaps and inequalities in care, and suggest that implementation of fracture prevention programs and optimal post fracture rehabilitation and social care are warranted. The results can also be used in economic evaluations for selecting cost-effective interventions for hip fracture prevention and care. To our knowledge, this is the first population-based research in Eastern Europe that provides comprehensive country-specific estimates of the impact of hip fracture.

2. LITERATURE REVIEW

2.1. Hip fracture as a public health problem

Hip fracture is a major public health issue associated with excess morbidity, mortality, disability, and subsequent hospital and social costs as well as impairment in HRQoL (Melton, 2003; Johnell and Kanis, 2006; Borgstrom *et al.*, 2013). Hip fracture is usually a clinical consequence of osteoporosis that increases with age, and it is estimated that up to 6% of men and 21% of women 50–84 years have osteoporosis (Hernlund *et al.*, 2013). To outline the magnitude, the lifetime probability of hip fracture at the age of 50 ranges from 4% to 25% (Ström *et al.*, 2011) and the excess all-cause mortality from 5% to 40% during the first year after fracture (Haentjens *et al.*, 2010). In addition, less than half of all survivors regain the level of function they had prior to the fracture (Melton, 2003). Hip fracture is the most serious osteoporotic fracture: it accounts for the highest excess mortality, disability, and subsequent health care and social costs (Melton, 2003; Johnell *et al.*, 2004; Johnell and Kanis, 2006; Borgstrom *et al.*, 2013; Hernlund *et al.*, 2013; Kanis *et al.*, 2013). The burden of hip fractures has increased considerably throughout the world over the last few decades as the number of elderly persons has increased (Johnell and Kanis, 2006). Given the aging of the population globally, hip fractures will become an increasing public health problem (Johnell and Kanis, 2006; Cheng, Levy and Lefaivre, 2011; Kanis *et al.*, 2013).

Hip fracture is usually a low-energy or fragility fracture that may be defined as a fall from a standing height or less, or trauma that in a healthy individual would not give rise to fracture (Melton *et al.*, 1997; Hernlund *et al.*, 2013). About one-third of elderly individuals fall annually, with the result that 5% will sustain a fracture and 1% will suffer a hip fracture (Hernlund *et al.*, 2013). The risk of falling increases with age and is somewhat higher in elderly women than in elderly men (Hernlund *et al.*, 2013). The leading cause of hip fracture in persons aged 50 years and over is considered osteoporosis, defined as a value for bone mineral density (BMD) $\leq$2.5 standard deviations (SD) below the young female adult mean (Kanis *et al.*, 2002). However, not all hip fractures occur at osteoporotic BMD values (Melton *et al.*, 1997; Johnell *et al.*, 2005; Roux and Briot, 2017). Other risk factors include female sex, premature menopause, advanced age, previous fragility fracture, glucocorticoid therapy, family history of hip fracture, a low bodyweight, smoking, and excessive alcohol consumption (Kanis *et al.*, 2002). The hip fracture could be a result of poor health: the severe pre-fracture conditions such as diabetes, cardiac disease, cancer, dementia, Parkinson's disease, chronic obstructive pulmonary disease, stroke, hypothyroidism, low muscle strength, poor walking ability are all risk factors for falls (Jørgensen *et al.*, 2014).

Hip fracture is a fracture of the proximal femur, either through a femoral neck or through a trochanteric region (pertrochanteric fracture) (Hernlund *et al.*,

2013). Subtrochanteric fractures (in a region up to 5 cm distal to lesser trochanter) are also defined as hip fractures (Lix, Azimaee and Osman, 2012) and included in most hip fracture incidence and mortality studies (Brauer and Coca-Perraillon, 2009; Cheng, Levy and Lefaivre, 2011; Dimai *et al.*, 2011; Michaëlsson *et al.*, 2014; Omsland *et al.*, 2014), despite that most of these are not low-energy fractures (Nieves *et al.*, 2010). Hip fracture nearly always necessitates hospitalization and surgical intervention (Kanis *et al.*, 2013).

A hip fracture can have a profound impact on physical function and activity (Kerr *et al.*, 2017). The impact accumulates over time through a cycle of impairment, as fracture leads to long term decline in physical function, including loss of muscle, activity avoidance and reduced physical capacity, which in turn leads to greater risk of fracture and further physical restrictions. The cycle of impairment is complex, as other physical, psychosocial and treatment-related factors, such as comorbidities, fears, and beliefs about physical activity and fracture risk influence physical function and everyday activity (Kerr *et al.*, 2017).

Patients experiencing a hip fracture are at considerable risk for premature death (Magaziner *et al.*, 1997; Abrahamsen *et al.*, 2009; Klop *et al.*, 2014). Up to 20% of patients die in the first year following hip fracture (Abrahamsen and Vestergaard, 2010; Haentjens *et al.*, 2010). It is estimated that approximately 30% of excess deaths are causally related to hip fracture, and most excess deaths are a result to serious life-threatening comorbidities (Kanis *et al.*, 2003). The diseases associated with excess mortality are dementia, cancer, diabetes and cardiac disease (Hu *et al.*, 2012; Martinez-Laguna *et al.*, 2017). Other risk factors for the excess mortality include advanced age, male sex, poor preoperative health status, poor walking capacity, poor activities of daily living, poor mental state, and multiple comorbidities (Hu *et al.*, 2012). A number of these factors are also related to frailty that is defined by weight loss, weakness, poor energy, slow walking, and low physical activity (Fried *et al.*, 2001; Ensrud *et al.*, 2007). Frailty is associated with falls, disability, hospitalization, and mortality (Xue, 2011; Romero-Ortuno and Kenny, 2012).

2.2. Measures of hip fracture burden

Disease burden is the impact of a health problem in a given area that can be compared across diseases, geographies and time to inform policy and health system performance, prioritize investments in research, and monitor progress (Kassebaum *et al.*, 2016). In order to quantify the burden of disease and facilitate rational decision making for resource allocation, it is important to estimate the impact of a disease using measures that can be compared across diseases, interventions, populations, and time (Drummond *et al.*, 2015).

The impact of hip fracture has been measured by disease frequency, the cost of illness, excess mortality, and summary measures of population health that combine mortality with morbidity (Hernlund *et al.*, 2013).

2.3. Incidence of hip fracture

There are marked geographical differences in hip fracture incidence worldwide (Kanis, Odén and McCloskey, 2012). The highest rates of hip fracture in women have been observed in Northern Europe, e.g., Scandinavian countries (540–570/100 000) and Ireland (410/100 000), whereas the lowest rates are in the developing countries, e.g., Ecuador (73/100 000) (Kanis, Odén and McCloskey, 2012). The difference in incidence is approximately 10-fold, whereas the reasons for this variation are not well known (Kanis, Odén and McCloskey, 2012). It is hypothesized that the hip fracture rates correlate with the degree of urbanization across geographies and cultures (Ballane *et al.*, 2014). Within countries, the age-standardized incidence in women is approximately two times higher than that in men (Kanis, Odén and McCloskey, 2012).

While the total number of individuals affected by hip fracture may be expected to increase globally, incidence rates appear to be stabilizing, with age-adjusted decreases being observed in many European countries and in the US, the trend being more pronounced in women than in men (Brauer and Coca-Perraillon, 2009; Abrahamsen and Vestergaard, 2010; Korhonen *et al.*, 2013; Siggeirsdottir *et al.*, 2014). It is assumed that hip fracture rates decrease due to the improvement in nutritional status, increases in BMD and body mass index (BMI), osteoporosis medication use, and lifestyle interventions such as smoking cessation and fall prevention (Ballane *et al.*, 2014). Conversely, in the developing countries (Asia, South America) the continuous rise of hip fracture rates is still prevailing, though the absolute risks are still smaller (Ballane *et al.*, 2014). A better understanding of the variations and trends in hip fracture rates can provide important clues to etiology and prevention of fractures (Cheng, Levy and Lefaivre, 2011; Cooper *et al.*, 2011).

Data on recent trends in hip fractures from Eastern European countries are limited. However, the difference in incidence between Eastern and Western European countries has been noted before, for example in 1995–2004 the incidence was significantly higher in Western than in Eastern Germany, and differences between East and West have decreased since unification (Icks *et al.*, 2013). Recent data from Poland indicate a relatively low incidence in both women and men (Wilk *et al.*, 2013), whereas Lithuania and Russia have moderate rates (Lesnyak *et al.*, 2012; Tamulaitiene and Alekna, 2012). The difference in risks between Western and Eastern Europe is greater in women than in men (Kanis, Odén and McCloskey, 2012).

Geographically, Estonia lies between the high-incidence Scandinavian countries and low to moderate-incidence Eastern European countries (Cheng, Levy and Lefaivre, 2011; Kanis, Odén and McCloskey, 2012; Kanis *et al.*, 2017). The hip fracture incidence data for Estonia are available for women, and the age-standardized (to the WHO world population) risk for women ≥ 50 years is estimated at 225 cases per 100 000 person-years (Haviko, Maasalu and Seeder, 1996; Kanis, Odén and McCloskey, 2012). Another report imputed data from the unpublished Finnish incidence rates estimated that 1600 hip fractures (75%

in women) are sustained in Estonia each year, with the age-standardized (to the EU standard population) incidence at 238/100 000 in men and 440/100 000 in women (Svedbom *et al.*, 2013). The number of incident fractures was assumed to increase by 400 by 2025 (Svedbom *et al.*, 2013). Along with countries with comparable risk estimates (Poland, Mexico, Spain, USA) Estonia belongs to the medium risk tertile of countries (Kanis, Odén and McCloskey, 2012).

2.4. Resource use and cost related to hip fracture

The cost of illness is a measure of burden quantified in monetary terms, encompassing the resource use and financial cost related to the disease (Larg and John R. Moss, 2011). Cost-of-illness studies have been used to generate public interest, to inform the planning of health services and encourage policy debate, and prioritizing research (Larg and John R. Moss, 2011). It has also been argued that for health policy decisions, the cost estimates are easy to relate to, compared to the use of health measures (DiLuca and Olesen, 2014). In addition, costs of illness are an input in economic evaluations (Hodgson, 1994; Drummond *et al.*, 2015), and it is preferable to use country-specific estimates as the costing studies are context-specific and cannot be used to inform policy debate in other populations (Drummond *et al.*, 2015).

Several studies have assessed the costs related to hip fracture (Tamulaitiene and Alekna, 2012; Ireland and Kelly, 2013; Castelli *et al.*, 2015; Marques *et al.*, 2015; Leal *et al.*, 2016). However, most studies estimate only the direct health care costs (Tamulaitiene and Alekna, 2012; Lambrelli *et al.*, 2014; Lüthje *et al.*, 2014; Castelli *et al.*, 2015; Leal *et al.*, 2016) or focus on a too short period after the fracture (Tamulaitiene and Alekna, 2012; Castelli *et al.*, 2015). It has been estimated that the direct health care costs account for only 30–60% of the total hip fracture costs (Borgström *et al.*, 2006; Lüthje *et al.*, 2014), and other costs should be accounted for when evaluating the economics and the total burden on society (Dimai *et al.*, 2012; Hernlund *et al.*, 2013; Marques *et al.*, 2015). Overall, country-specific cost estimates are scarce (Hernlund *et al.*, 2013; Svedbom *et al.*, 2013).

The annual hip fracture related total cost has been estimated at 20 billion euros in Europe, 2/3 of that incurred in age above 80 years, and 2/3 accrued in the first year after fracture (Hernlund *et al.*, 2013). For comparison, a societal cost of lung cancer has been estimated at 19 billion euros in Europe, dementia at 105–160 billion, Parkinson's disease at 14 billion, stroke at 27–64 billion, and coronary heart disease at 23 billion (Leal *et al.*, 2006; Gustavsson *et al.*, 2011; Wimo *et al.*, 2011; Olesen *et al.*, 2012; Luengo-Fernandez *et al.*, 2013; DiLuca and Olesen, 2014). The highest hip fracture costs are incurred in the age group over 80 years (Hernlund *et al.*, 2013). Denmark had the highest annual hip fracture cost (25,117 euros per hip fracture patient or 103 euros per person), Bulgaria the lowest cost (1826 euros per patient or 3 euros per person) (Hernlund *et al.*, 2013).

In Estonia, the annual hip fracture cost (at 2010 prices) was estimated at 5580 euros per patient, and the total societal cost burden at 15 million euros or 12 euros per person (Svedbom *et al.*, 2013) that is comparable to other common conditions in the elderly. For comparison, the direct healthcare cost of lung cancer has been estimated at 4 euros and breast cancer at 7 euros per person in Estonia (Luengo-Fernandez *et al.*, 2013). The hip fracture costs were projected to increase by 17% by 2025 (Hernlund *et al.*, 2013; Svedbom *et al.*, 2013). However, the results were incomplete for deriving sound estimates for policy. Hip fracture cost was estimated using the price level adjusted cost in Finland (Nurmi *et al.*, 2003; World Bank, 2008). Likewise, using Swedish data for the proportion of patients who transition to nursing homes after fracture may have overestimated the nursing home costs and underestimated the informal care cost for countries outside Scandinavia (Hernlund *et al.*, 2013). For example, 30% of fracture cost in Austria is due to family care (Dimai *et al.*, 2012), compared to only 3–20% in Sweden (Borgström *et al.*, 2006). Indirect cost was omitted, underestimating the economic burden despite the relatively old age of patients (Hernlund *et al.*, 2013).

2.5. Hip fracture related excess mortality

Patients who fracture their hip are at considerable risk of premature death (Abrahamsen *et al.*, 2009; Haentjens *et al.*, 2010). The pooled all-cause mortality risk of hip fracture patients from 75 cohorts and 64 300 patients (mean age 81 years) was as high as 13% at 1 month, 16% at 6 months, 25% at 1 year, and 35% at 2 years after fracture (Hu *et al.*, 2012). For comparison, the 1-year mortality for heart failure is estimated at 7–17% (Maggioni *et al.*, 2013), and for myocardial infarction at 6% (Smolderen *et al.*, 2017). Mortality studies almost always note increased mortality soon after the fracture, within the first 3–6 months (Johnell *et al.*, 2004; Abrahamsen *et al.*, 2009; Haentjens *et al.*, 2010; Michaëlsson *et al.*, 2014).

As hip fracture is usually not recorded as an underlying cause of death (Calder, Anderson and Gregg, 1996), the mortality impact of hip fracture can be examined by comparing the observed all-cause mortality among hip fracture patients to the expected mortality in non-fracture controls; the absolute risk difference represents excess or attributable mortality (Teng, Curtis and Saag, 2008). The pooled results of hip fracture patients aged 70 years or above from Western European countries, Australia, and the USA suggest that the cumulative excess risk of death over the first year after hip fracture varied widely from 3% to 43%, depending on age at the time of fracture, and sex (Haentjens *et al.*, 2010). The cumulative risk at 1 year was 2.9 times higher among hip fracture women and 3.7 times in men compared to the age-matched controls (Haentjens *et al.*, 2010). Although the relative risk decreased in subsequent years, it did not return to that of age- and sex-matched reference groups even 10 years post-fracture (Haentjens *et al.*, 2010). The excess risk increased with advancing age,

although this differential became less pronounced over the following years due to increased mortality, unrelated to hip fracture, in the reference populations (Abrahamsen *et al.*, 2009; Haentjens *et al.*, 2010). The excess risk was higher among men than women (Abrahamsen *et al.*, 2009; Kannegaard *et al.*, 2010; Ekström *et al.*, 2015), notably among the oldest age categories (≥80 years) (Haentjens *et al.*, 2010). This leaves hip fracture men with significantly higher mortality than women because the risk of death in a general population is also higher in men (Hernlund *et al.*, 2013).

Estimates of hip fracture mortality in Eastern Europe are scarce (Sebestyén *et al.*, 2008; Kurtinaitis *et al.*, 2012). However, the data in this region suggests a sex-specific difference in the incidence of hip fractures between Eastern and Western Europe (Icks *et al.*, 2013; Wilk *et al.*, 2013), and the age and sex-specific all-cause mortality rates in Eastern Europe differ from those in Western countries (Eurostat, 2017). The number of hip fracture deaths in the first year after fracture in Estonia has been estimated at 65 (37 women, 27 men) (Svedbom *et al.*, 2013). This conservative estimation is based on assumption that only 30% of excess deaths are attributable to hip fracture and the majority (70%) are related to pre-existing comorbidities (Kanis *et al.*, 2003; Tosteson *et al.*, 2007) and therefore not included in the estimate. If the impact of comorbidities was smaller, up to 1.5% of all deaths (up to 225) could be related to hip fracture in Estonia (Kanis *et al.*, 2003; Hernlund *et al.*, 2013), an estimate comparable to that for breast and stomach cancer or self-harm (Wang *et al.*, 2016; Institute for Health Metrics and Evaluation University of Washington, 2017).

2.6. The impact of comorbidities on hip fracture related excess mortality

Hip fracture patients often have significant comorbidities, so that not all deaths associated with hip fracture are due to the fracture event (Kanis *et al.*, 2003; Hernlund *et al.*, 2013). Numerous studies have demonstrated that the presence of severe pre-fracture comorbidities or poor health status is a negative predictor of survival after hip fracture (Roche *et al.*, 2005; Luise *et al.*, 2008; Abrahamsen *et al.*, 2009; Hu *et al.*, 2012; Hindmarsh *et al.*, 2014; Melton *et al.*, 2014; Anthony W. Ireland, Kelly and Cumming, 2015). Therefore, it is assumed that the excess mortality after hip fracture is a sum of two components. Some excess deaths are a result of the higher prevalence of pre-fracture comorbidities in that patient group, i.e., elevated background risk of death. Other deaths are causally related to the fracture, directly or indirectly by accelerating death from other diseases, i.e., the deaths that would not happen without sustaining a fracture (Kanis *et al.*, 2003). Better understanding the impact of comorbidities on mortality following hip fracture is essential for identifying those patients who are candidates for interventions to reduce the excess risk of death (Luise *et al.*, 2008; Teng, Curtis and Saag, 2008; Abrahamsen *et al.*, 2009). However, the

impact of comorbidities on extent and duration of excess mortality is still controversial (Abrahamsen *et al.*, 2009).

Several large cohort studies have demonstrated that the pre-fracture comorbidities have a leading role in excess mortality (Kanis *et al.*, 2003; Farahmand *et al.*, 2005; Tosteson *et al.*, 2007). For example, Kanis et al, compared the risk of all-cause death among hip fracture patients to that in the general population, and suggested that the immediate elevated 6-months period risk (30% of all excess deaths) was associated with a fracture, whereas the following long term residuum (70% of deaths) accounted for comorbidity-related deaths (Kanis *et al.*, 2003). However, the comorbidity data were not collected for the study. Tosteson et al demonstrated that much of the short-term and all of the long-term excess risk of death can be explained by poor health status, and not by fracture event (Tosteson *et al.*, 2007). In contrast, Vestergaard et al demonstrated that the adjustment for age, sex and comorbidities only reduced the excess risk a little, implying that most of the short and long-term excess risk is due to the fracture and its complications (Vestergaard, Rejnmark and Mosekilde, 2007). Similar to that, several studies have demonstrated that after adjustment for comorbidities the hip fracture patients were 2–3 times more likely to die than controls (Empana, Dargent-Molina and Bréart, 2004; Grønskag *et al.*, 2012; Klop *et al.*, 2014; Michaëlsson *et al.*, 2014; Padrón-Monedero *et al.*, 2017). The controversy has also been sustained by use of different study methods. For example, stratification by the comorbidity status generally demonstrated a dose-response relationship between comorbidities and excess deaths (Magaziner *et al.*, 1997; Farahmand *et al.*, 2005; Vestergaard, Rejnmark and Mosekilde, 2007), whereas adjustment for comorbidities derived pooled results (Empana, Dargent-Molina and Bréart, 2004; Tosteson *et al.*, 2007; Vestergaard, Rejnmark and Mosekilde, 2007; Grønskag *et al.*, 2012; Klop *et al.*, 2014). Likewise, the studies using conditional risks account for the deaths within short periods over the follow-up (Kanis *et al.*, 2003), whereas the cumulative risks account for all accumulating deaths (Vestergaard, Rejnmark and Mosekilde, 2007; Kannegaard *et al.*, 2010; Hindmarsh *et al.*, 2014).

2.7. Summary measures of population health

Incidence and mortality have traditionally been the most common indicators for evaluation of the burden of disease in a population (Mckenna *et al.*, 2005). However, large increases in life expectancy have led to the development of new summary measures of population health that capture both duration and quality of life lost (Fox-Rushby, 2002; Murray *et al.*, 2015; Kassebaum *et al.*, 2016). Disability-adjusted life year (DALY) is a composite measure that combines the prevalence and severity of non-fatal conditions with premature mortality and measures a gap between population and a normative standard of lifespan in full health (Murray *et al.*, 2012). Assessment of DALYs has revealed that hip

fracture can lead to an average 3% loss of healthy life-years in elderly people and that 70% of the burden is related to disability (Papadimitriou *et al.*, 2017).

The use of DALYs has limitations. To derive the severity of disease DALY incorporates the preference based disability weights (Salomon *et al.*, 2015), whereas the proposed weights are based on expert opinion rather than on patient or populations opinion (Sassi, 2006). Further, the severity estimates are constant and sometimes inconsistent (Sassi, 2006). For example, the hip fracture weights used in the Global Burden of Disease study were estimated at 0.26 (i.e., 26% health loss compared to the state of perfect health) for a short-term fracture, 0.06 for a treated long term, and 0.40 for an untreated long-term fracture (Salomon *et al.*, 2015), whereas the National Osteoporosis Foundation has proposed different weights, 0.47 for the first year and 0.17 for the second year after fracture (Kanis *et al.*, 2001). The inconsistency might compromise the ability of DALY to detect change (Papadimitriou *et al.*, 2017).

QALY is a composite measure in which the length of life is adjusted with the HRQoL (Drummond *et al.*, 2015). Unlike DALY, the severity of disease in QALY is elicited directly by choice methods or indirectly using pre-scored questionnaires (Arnold *et al.*, 2009). QALY was developed for estimating health gain to inform resource allocation (Weinstein, Torrance and Mcguire, 2009); QALY loss is an unconventional reverse application to measure health loss from a disease (Lips and van Schoor, 2005) (Figure 1).

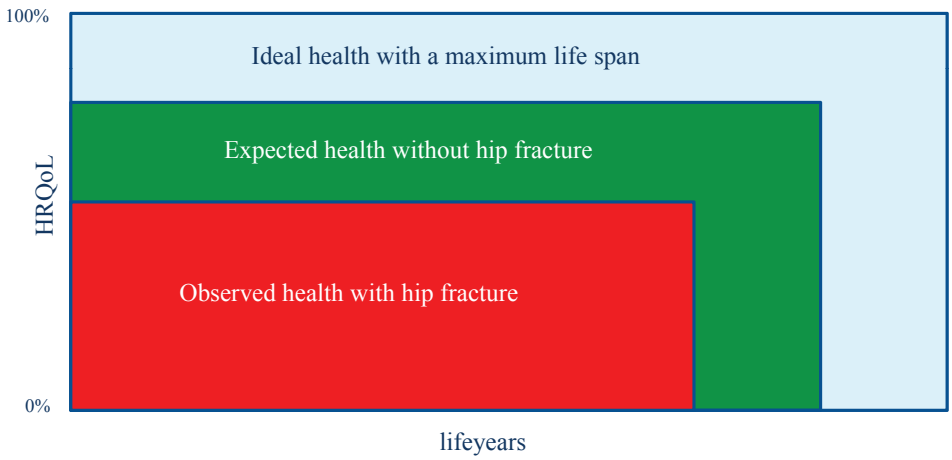

Figure 1. Loss of quality-adjusted life years (QALY). Blue box represents the normative duration and quality of life, based on the highest age- and sex-specific life expectancy estimates worldwide, green stands for the expected health without hip fracture (pre-fracture QALY), and red for the observed health with fracture (post-fracture QALY). Adapted from Fox-Rushby, et al (Fox-Rushby and Cairns, 2005)

The reasons for using QALY loss for estimating the hip fracture burden stems from its applicability for primary data collection (Fox-Rushby, 2002), higher responsiveness (Sassi, 2006), the use of study results in health economic evaluations (Weinstein, Torrance and Mcguire, 2009; Drummond *et al.*, 2015), and the need to measure the loss of HRQoL against its pre-fracture levels, and not to the normative standard (Borgstrom *et al.*, 2013; Hernlund *et al.*, 2013). The recent study estimated the total annual hip fracture related QALY loss of 1400 in Estonia, primarily incurred by prior fractures and patients aged over 75 years (Svedbom *et al.*, 2013). Mean health-related QALY loss during the first year after fracture was estimated at 0.23 (Svedbom *et al.*, 2013). The estimate was similar to other European countries (Hernlund *et al.*, 2013) as the HRQoL loss estimate was based on the pooled data (Peasgood *et al.*, 2009).

2.8. Health-related quality of life

To obtain QALYs precise estimates of HRQoL are required. Direct health valuation methods derive HRQoL by mapping preferences for a disease status directly onto the HRQoL scale by means of choice (time-trade-off, TTO) or visual analog scale (VAS) (Arnold *et al.*, 2009). Indirect methods derive HRQoL via a generic HRQoL questionnaire (e.g., EUROQoL-5D, EQ-5D), whereas the responses are converted onto HRQoL (utilities) using the described direct valuation methods (Arnold *et al.*, 2009). The differences in EQ-5D valuation estimates between populations are remarkable (Szende, Oppe and Devlin, 2007). Therefore, the transferability of HRQoL utilities across countries is limited, and choosing a method, instrument, and country value set is crucial for minimizing measurement bias and informing health policy (Knies *et al.*, 2009). The EQ-5D questionnaire has been recommended for inclusion in hip fracture trials (Haywood *et al.*, 2014) but has not been validated with the Estonia's population utility weights (EuroQol, 2017). The UK population-based HRQoL value set is considered to be the most robust and is recommended by the EUROQoL group in the absence of country-specific value sets (Szende, Oppe and Devlin, 2007). The HRQoL values that are generated range from –0.59 to 1, where 1 represents full health, 0 represents death, and values below 0 represent health states worse than death (Dolan, 1997).

The estimates of HRQoL after hip fracture are scarce. The profound loss in quality of life was demonstrated among Australian hip fracture women over 75 years (Salkeld *et al.*, 2000). Using a TTO and EQ-5D questionnaire with UK utility weights, the fracture which resulted in admission to a nursing home was valued at 0.05 (i.e., the value of health was only 5%), and a fracture maintaining independent living in the community at 0.31. Of note, the respective medians were lower, 0 and 0.13 (IQR 0.0, 0.65), implying a large variation among patients. Of women surveyed, 80% would rather be dead than experience the loss of independence and admission to a nursing home (Salkeld *et al.*, 2000). Tosteson, at al, assessed the HRQoL in fracture women over 50 years in the

USA using a TTO method and estimated the respective mean at 0.63 (Tosteson *et al.*, 2001). However, the relatively high estimate can be explained by late measurement, between 1–5 years after fracture. The following systematic reviews revealed a wide range of empirical HRQoL estimates, mostly due to differences in valuation methods and instruments, health state descriptions, and the background and perspective of respondents (Brazier and Green, 2002; Peasgood *et al.*, 2009). The pooled estimates from 12 studies were 0.76 at pre-fracture, 0.27 at 1 week, 0.54 at 4 months, and 0.58 at 1 year; the annual HRQoL loss was estimated at 0.24 QALY (Peasgood *et al.*, 2009). The HRQoL impact of hip fracture extended for at least 3 years (Tarride *et al.*, 2016).

In the meta-analysis of 14 studies the pooled pre-fracture HRQoL estimate of 0.76 was dependent on age (higher in younger and lower in older patients) and elicitation method (higher with an EQ-5D questionnaire, lower with TTO and VAS); recalled pre-fracture estimate was higher than that collected prospectively (Si *et al.*, 2014). A country, sex and fracture history had no significant impact on pre-fracture HRQoL. The immediate post-fracture estimate was rather high at 0.32, whereas those at 1 year (0.60) and subsequent years (0.66) came as expected. Post-fracture estimates were lower in patients with previous fracture, those ended in a nursing home, and in men. The estimates used in the meta-analysis were mostly derived from the Western European countries, the USA and Japan.

With the purpose of estimating the burden and to fill parts of the data gap The International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) was initiated to collect the comparable HRQoL estimates in 2007 in 11 countries worldwide (Australia, Austria, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain, the UK, and the USA), with the 4-months interim results published in 2013 (PAPER V) (Borgstrom *et al.*, 2013). Based on the 1273 patients' data the HRQoL after hip fracture was lower than expected in most countries, and the recovery over 4 months was modest. For example, the Lithuanian EQ-5D estimates were 0.80 before, 0.01 right after, and 0.36 at 4 months, implying that the average Lithuanian patient lost 0.21 QALY or 79% of the expected HRQoL over the first 4 months (PAPER V, Table 3). The final ICUROS results are published in PAPER VI.

2.9. Critical review of the literature

The marked differences in hip fracture incidence are present across Europe, whereas the reasons for the difference are not entirely clear; it is hypothesized that the socioeconomic inequalities may contribute to that. It is also known that the total hip fracture cost is increasing, whereas the data on costs and inequities in service use are insufficient for policy. The country-specific data on HRQoL loss are scant, and the data on the impact of comorbidities on excess mortality is controversial.

In conclusion, there are important gaps in the knowledge on hip fracture incidence, excess mortality, costs, and loss of HRQoL in Europe. Of importance, more data are available for the advanced Western European and North American countries, whereas the data for Eastern Europe are incomplete. We assume that for estimating the health and economic impact of hip fracture Estonia should be classified as an Eastern European country, as the risk factor and disease pattern in general is more characteristic to the Eastern Europe (GBD 2013 Risk Factors Collaborators *et al.*, 2015; Forouzanfar *et al.*, 2016; Kassebaum *et al.*, 2016) and the status of economic development is comparable (OECD, 2017). In general, the topic of health and economic impact of hip fracture has a country-specific context, whereas the impact of comorbidities on hip fracture mortality is a research question of a broader clinical importance.

3. AIMS OF THE RESEARCH

The overarching aim of the research was to assess the health and economic impact of hip fracture among individuals aged over 50 years in Estonia in 2005–2016. The specific aims were:

1. To assess the incidence of hip fractures (PAPER I);
2. To estimate the impact of hip fracture on health-related quality of life over 18 months after the fracture (PAPERs II, V, VI);
3. To estimate the impact of hip fracture on resource consumption and cost over 18 months after the fracture (PAPER II);
4. To assess the impact of hip fractures on all-cause mortality over 10 years (PAPER III);
5. To assess the impact of pre-fracture comorbidities on excess mortality (PAPER IV).

4. MATERIALS AND METHODS

4.1. Outline of the research project

The project was led by the Institute of Family Medicine and Public Health and the Institute of Clinical Medicine, University of Tartu. Research commenced in 2010 with Estonia joining the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) for estimating the quality of life and costs related to osteoporotic fractures across the world (PAPERs II, V, VI). A series of studies were conducted to fulfill the aims set for the research project. The ecologic study design was chosen for assessing the incidence and time trends (PAPER I), a (hospital based prospective) cohort study was used to assess the HRQoL and societal costs (PAPERs II, V, VI), and a population-based retrospective age- and sex-matched cohort study to assess the excess mortality (PAPERs III–IV). The thesis is focused on analysis and interpretation of Estonian data (PAPERs I–IV), and the results from PAPERs V–VI are presented for an international comparison.

Data sources:

(i) Face to face and phone interviews with hip fracture patients (for ICUROS);
(ii) Estonian Health Insurance Fund (EHIF) administrative database (Estonian Health Insurance Fund, 2015) for all studies. Estonia has a universal public health insurance system, covering >94% of the population. Since its inception in the early 2000s, the EHIF has maintained a complete record of inpatient and outpatient health care services. The EHIF electronic database contains information on characteristics of the person (sex, age at health care service utilization), health care utilization (date of service, primary and other diagnoses, treatment type (in- or outpatient), a specialty of the provider), medication use, and the date of death;
(iii) Statistics Estonia (data on source population age and sex distribution) for the incidence and mortality studies.

The study series (research aims and methods) is outlined in Table 1.

Table. 1. Study series outline*

Objective	Data source	Study design	Patient inclusion period	Sampling	Case definition	Number of individuals	Follow-up time	Main outcome	Measures	Statistical analysis
PAPER I: – To assess the incidence and trends of hip fractures	EHIF**; Statistics Estonia	Ecological study	2005–2012	All individuals ≥50 years with a heath care utilization bill meeting the case definition	Case definition based on hip fracture specific diagnosis codes (S72.0–2) on inpatient health care claim submitted to EHIF by health care provider. No diagnosis of hip fracture within preceding 12 months.	10 704 cases; (1340/year)	NA	Hip fracture (incidence)	Annual crude incidence, age-standardized incidence, age-specific incidence of hip fractures in men and women	Descriptive analysis. Linear regression
PAPER II: – To estimate the impact of hip fracture on HRQoL over 18 months after the fracture	Research study (primary data collection)	Prospective cohort study	2010–2012	Consenting adults ≥50 years receiving acute hip fracture care at East Tallinn Central Hospital and Tartu University Hospital	Patients diagnosed with hip fracture (S72.0–2) at admission	205 recruited; 45 died; 37 lost to follow-up	Total 18 months	HRQoL**	HRQoL (at baseline, and 4, 12, 18 months after fracture)	Descriptive analysis. Mann-Whitney non-parametric test and χ^2 test as appropriate
– To estimate the impact of hip fracture on resource consumption and cost over 18 months after the fracture	Research study (primary data collection) ; EHIF							Resource allocation, costs	Resource allocation, direct, indirect and informal costs at 4, 12, 18 months after fracture	
PAPER III: – To assess the impact of hip fractures on all-cause mortality over 10 years PAPER IV: – To assess the impact of pre-fracture comorbidities on excess mortality	EHIF	Retrospective cohort study	2005–2013	Hip fracture group (cases): All individuals ≥50 years with a health care utilization claim meeting the case definitions; reference group: age and gender matched (to cases) randomly selected individuals	Case definition based on hip fracture specific diagnosis codes (see above) listed as primary diagnosis on inpatient health care claim; no previous evidence of hip fracture. Reference individuals alive and without evidence of hip fracture prior to case patient's index date of fracture	8298 cases (922/year), 5552 died; 33 191 reference individuals, 14 037 died	Total 10 years; mean 4.3 years	All-cause mortality	Crude and adjusted (for CCI**, age) cumulative mortality in both groups, excess mortality. Age, sex, CCI score group, and disease-specific excess mortality	Descriptive analysis. Wilcoxon rank-sum non-parametric test and χ^2 test as appropriate. Poisson regression

*The data from PAPER II (Estonian data) have also been used for an international comparison (PAPERs V, VI, not detailed in Table 1)
**CCI: Charlson comorbidity index; EHIF: Estonian Health Insurance Fund; HRQoL: health-related quality of life

4.2. The incidence of hip fractures (PAPER I)

4.2.1. Data and case definitions

For this ecological time-trend study we obtained the medical claims data from the EHIF. We analyzed data from 2005 to 2012 to identify all individuals aged 50 years or older who sustained hip fractures. We documented 10,704 new hip fracture cases among persons aged 50 years or older occurring in 2005–2012. The case definition of hip fracture was based on identification of the hip fracture specific diagnosis codes (The International Classification of Diseases, Tenth Revision (ICD-10), codes: S72.0 – fracture of femoral neck, S72.1 – pertrochanteric fracture, and S72.2 – subtrochanteric fracture) on the health care bill submitted to the EHIF by the health care provider. These codes must have been listed as the primary or secondary diagnosis on the electronic inpatient health care claim submitted to the EHIF. An incident case of hip fracture and the index date of the diagnosis was assigned to cases that had no previous evidence of a diagnosis of hip fracture (i.e., no health care claims related to care with the diagnosis of S72.0, S72.1, and S72.2) within the preceding 12 months. The validity and reliability of this method of a case definition to ascertain incident hip fracture cases from a population-based administrative database have been demonstrated (Lix, Azimaee and Osman, 2012). Data obtained from the EHIF database included the characteristics of the person receiving care due to hip fracture (age, gender) and an identification code which allows longitudinal tracking of the medical care provided to this person, i.e. pseudo-identification.

4.2.2. Statistical analysis

The numbers of individuals with hip fractures across different age and sex categories were presented. Data on source population age and sex distribution was obtained from Statistics Estonia (Statistics Estonia, 2015c). The annual incidence of hip fractures (crude incidence, age-standardized incidence, and age- specific incidence in women and men) together with the confidence intervals were estimated. The age-specific incidence rates for men and women were calculated in 5-year age groups using the number of hip fractures in that specific age group, divided by the population size within that specific age group, and was expressed per 100 000 persons in that age group. To adjust for age differences in the population through the study period, standardized incidence rates (SIR) were estimated using direct standardization to the WHO world standard population (WHO, 2015). χ^2 test was used for categorical variables to explore differences in rates between men and women over the study period. Trends in rates over time were assessed using linear regression analysis. All statistical analysis was performed using Stata version 11.2.

4.2.3. Ethical considerations

The study procedures were in accordance with local data protection regulations. The study was based on pre-existing records containing only non-identifiable data about individuals, it was exempt from ethical review, and the informed consent was not obtained. The study was approved by the Tartu University Research Ethics Committee.

4.3. Quality of life, resource use, and costs related to hip fracture (PAPERs II, V, VI)

We followed a cohort of hip fracture patients in Estonia for 18 months after fracture. The study was part of the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) with the objective of estimating the quality of life and costs related to osteoporotic fractures in several countries across the world (PAPERs V, VI). All countries participating at ICUROS (Austria, Australia, Estonia, Spain, France, Italy, Lithuania, Mexico, Russia, the UK, the USA) followed the same study protocol and data collection instruments. We present the method used in Estonia (PAPER II), and highlight the major differences with ICUROS (PAPERs V, VI) if any.

4.3.1. Setting and patients

A convenience sample of 205 consenting patients with low-energy trauma hip fractures attending the departments of traumatology and orthopedics of Tartu University Hospital and East Tallinn Central Hospital was recruited from November 2010 to October 2012. Patients were followed up at 4, 12 and 18 months after the fracture or until death. Patients aged ≥ 50 years diagnosed with hip fracture who were interviewed within 2 weeks after fracture were eligible for inclusion. Patients with fractures caused by comorbidities, e.g., cancer, patients with multiple fractures, patients with cognitive disabilities (judged not to be able to complete the questionnaire), and previously institutionalized patients were excluded. Out of 707 hip fracture patients hospitalized over the study recruitment period in the two study centers 562 patients were not included in the study. This includes patients not invited (patients who were admitted for care in periods when recruitment team was not operating; n=336), patients accessed but deemed to be ineligible (n=198), and patients who refused study participation (n=28). In the case of any new fracture during follow-up, the participation was discontinued and the patient excluded from further data collection.

No formal statistical power calculation was conducted. Recruiting 200 patients with hip fracture was judged to be an appropriate target sample size to produce stable country estimates of HRQoL and cost based on the experience of

previous similar study from Sweden (Borgström *et al.*, 2006). The recruiting hospitals provided about 40% of the hip fracture inpatient care in Estonia in 2012 (PAPER I).

For comparison, the patients for ICUROS were recruited from 52 hospitals, ranging from 1–2 (the UK, the USA, Italy, Lithuania, Estonia) to 8 (Austria, Australia) hospitals per country.

4.3.2. Data collection

Patient interviews

Baseline data were collected by trained interviewers at the hospital during the initial inpatient stay in face to face interviews. Interviews were conducted using a structured questionnaire based on the ICUROS study clinical research form (CRF) (available in English and Russian) (PAPER V). The questionnaire was translated into Estonian; the team of researchers discussed the translations and agreed the "best fits" for items. The Estonian translation was also compared to the original CRF (English version) by back-translation. The CRF elicited information on socio-demographic characteristics (date of birth, gender, education, working/living status, income), history of previous osteoporotic fractures, history of contacts with health care services for the hip fracture episode, use of non-prescription drugs, social care, informal care, working status, HRQoL, and contact information. At the first interview in addition to current (after fracture) HRQoL assessment, recall-based pre-fracture estimation of the HRQoL was obtained.

Follow-up data were collected by study researchers during follow-up at months 4, 12 and 18 post-fracture via phone interviews. Data on fracture-related use of social care (days of living in nursing home, hours of home help by social worker per week, use of assistive devices, transportation) and informal care (hours of home help by relatives and friends per week) were collected from patient interviews using 4 weeks' recall.

Data from the EHIF database

Data on fracture-related health services utilization and costs were extracted from the EHIF database for all recruited hip fracture patients. In addition, data on patients aged over 50 years treated in the same departments during the recruitment period but not recruited in the study (non-participants) were extracted. For each patient data were extracted for the index hip fracture episode (ICD codes S72.0 – 2 on the health care claim), and for health services/ medications provided 12 months before and up to 18 months after the index episode (dates, services provided, treatment type (in- or outpatient), specialty of the provider, costs), and the date of death. Data on prescription drugs considered relevant for the treatment of osteoporosis (bisphosphonates, denosumab, strontium ranelate, teriparatide, estrogens/receptor modulators, calcium, vitamin D supplements, analgesics and NSAIDs) (Borgström *et al.*, 2006; Borgstrom *et*

al., 2013) (ATC-code, date of purchase, cost, cost-sharing (patient/EHIF)) were extracted. For study participants, the extracted data contained personal identification codes; for non-participants, the data contained pseudo-identification codes which allowed longitudinal tracking of the medical care provided to an individual but did not permit personal identification. For non-participants, information on age and gender was extracted in addition to health care utilization data.

4.3.3. Measures

HRQoL loss

The indirect method to measure HRQoL from the EQ-5D-3L (EuroQol, 2017) was used applying preference-based utility values from a UK study (Dolan, 1997). The HRQoL loss in QALYs was calculated as the area under the curve using the trapezoid method (Walters, 2009). The HRQoL loss was estimated among surviving patients who completed the study period and whose HRQoL estimates were available.

Disease burden

To estimate the health burden by hip fracture patient, the mean hip fracture related QALY loss was calculated by adding the lost life years (until the end of study follow-up) of patients whose death was attributable to hip fracture to the HRQoL loss estimate in survivors. The lost life years attributable to fracture was based on a difference between observed and expected number of deaths (excess mortality). Expected number of deaths was calculated from the Estonian life tables (Shkolnikov, Barbieri and Wilmoth, 2013).

Comorbidities

Data on comorbidities was assessed using the Charlson comorbidity index (CCI) to measure the burden of disease and case mix (Charlson *et al.*, 1987). We used the revised coding algorithm that has been validated for estimating comorbidity burden using ICD-10 coded administrative data (Quan *et al.*, 2005), and the updated disease weighting suggested by Quan (Quan *et al.*, 2011). The CCI assessment for all hip fracture patients (participants and non-participants) was based on the EHIF health service claims of the index episode and all in- and outpatient health care claims (not only hip fracture care related) from the 12 months before the fracture (Toson, Harvey and Close, 2015).

Resource use and cost

We considered fracture-related resource use and costs using a societal perspective (Tan-Torres Edejer *et al.*, 2003). Data on fracture-related health care services and prescription drug use were obtained from the EHIF database using ICD-10 codes. Inpatient care was categorized as specialty care (traumatology and orthopedics), nursing care, and rehabilitation (e.g., physiotherapy, occupational

therapy) conducted during an overnight stay. Outpatient care comprised family practitioner's / nurse's office and home visits, visits to specialty physicians, home nursing, and rehabilitation. Nursing care is part of the health care system in Estonia and can be delivered either in licensed nursing care institutions (hospitals) or in patients' homes (Estonian Health Insurance Fund, 2015). Patient charges for specialty care were added to each claim from the EHIF (Estonian Health Insurance Fund, 2015). Information on use of non-prescription drugs (e.g., analgesics, calcium and vitamin D supplements) was collected at each follow-up from patient interviews, using 4 weeks recall at each follow-up data collection time point, and extrapolating the reported use over the respective follow-up period.

Data on fracture-related use of social and informal care (4 weeks' recall) reported by patients were extrapolated over the respective follow-up period, excluding the days of inpatient care, if any. To obtain the cost of social care, unit costs of living in nursing home or costs of a home visit by a social worker were attributed to the self-reported service use (City of Tallinn, 2015; Ministry of Social Affairs, 2015). The cost of assistive devices (walking aids, hygiene, home modifications) was based on data provided by patients during interviews. To estimate the cost of informal care, a replacement cost method was used by assigning a cost of home help by a social worker (City of Tallinn, 2015).

The indirect cost (the value of lost production related to sick leave and early retirement) was estimated using the human capital approach by assigning a self-reported net income level and tax for the time spent in the study that patients would have worked had they not sustained a fracture (Drummond *et al.*, 2015). Data on the number of days on fracture-related sick leave was collected using 4 weeks' recall and extrapolated using the assumption that the leave started from the beginning of the respective follow-up period. The working status was recorded at each follow-up interview and if retirement was reported, it was assumed to having commenced in the middle of the relevant follow-up period.

All costs were presented in euros at 2014 prices, adjusted for the Estonian consumer price index (Statistics Estonia, 2015a).

For ICUROS, most countries extracted the health services use data from administrative databases, whereas some relied on patients' interviews only. However, no cost data for ICUROS (except for Estonia) have yet been published for details.

4.3.4. Statistical analysis

We presented the number of hip fracture patients enrolled, the number of patients in the study at 4, 12 and 18 months, and the number of patients who dropped out by reason, gender (number, proportion of women), age, CCI (mean, proportion by score group, disease components), level of education and income, and working and living (living alone or with partner) status. Age-standardized (to the WHO world standard population) mortality rates at 12 and 18 months after the fracture were estimated (WHO, 2015).

We followed a general rule to include all patients in the analysis while the relevant data for a specific outcome measure were available. The healthcare resource utilization and cost data from the health insurance database were available for all recruited patients (including patients who died or were lost to follow-up) until the end of the study or until death. The patient-reported data on HRQoL, social care, informal care and working status were available for all patients until the end of the final follow-up period for the patient.

We presented EQ-5D estimates at 0, 4, 12 and 18 months stratified by age, gender, and CCI. To estimate the HRQoL loss in QALYs over 18 months, we estimated the difference between linearly interconnected HRQoL time-point estimates and pre-fracture level, using the assumption that the patient would have remained at the pre-fracture level of HRQoL had the fracture not occurred (Borgstrom *et al.*, 2013). The follow-up periods varied in duration (from 4 to 8 months); to increase comparability between periods, we calculated the mean HRQoL loss in 6-month periods by linearly interpolating the 6-month estimate. EQ-5D and HRQoL loss estimates were presented as means with 95% confidence intervals. Acknowledging the skewed distribution of utilities and HRQoL loss estimates we used box plots to summarize the data (presenting the medians, quartiles, and range). We also presented the proportion of fully recovered patients (who achieved at least 100% of pre-fracture HRQoL) at 4, 12 and 18 months.

Health care, social care and informal care resource utilization was presented as the number of patients receiving care and the mean number of service units for patients who used the resource in question (admissions, bed days, visits, and hours per week) along with 95% confidence intervals, by follow-up period (0–4 months, 5–12 months, and 13–18 months), and cumulative use over 18 months. Work related data were presented as the number of patients and days on sick leave, and the number of patients on early retirement. The average cost and cost structure per hip fracture patient were presented for the follow-up periods and as a cumulative cost over 18 months.

To interpret generalizability of results, the case mix (gender, age, comorbidity, and mortality) was compared between study participants and non-participants aged over 50 years receiving hip fracture care at the two recruiting hospitals (based on data from the EHIF) during the recruitment period. We used a Mann-Whitney non-parametric test for the differences in age, CCI score, HRQoL, and costs, χ^2 test for categorical variables (age groups, CCI score groups, and disease components), 95% CI-s for mortality rates. Age, CCI, and HRQoL were compared between patients who died or were lost to follow-up and those remaining in a study using a Mann-Whitney non-parametric test.

Statistical testing was conducted at significance level 0.05. All statistical analysis was performed using Stata version 12.1.

In ICUROS, the HRQoL was presented as a mean, and the comparisons were conducted using parametric tests (t-test, χ^2 test as appropriate). In the primary analysis for ICUROS, a complete case approach (all patients who completed the study) was applied. To explore the potential impact from loss of follow-up, two

additional approaches were implemented: an available case analysis (all patients with available data at a certain time point were included in the analysis for that time point), and a multiple imputation (a method where multiple imputations are made for each missing value based on a model) (Rubin, 1987). The imputation model comprised all available EQ-5D results, sex, and age.

4.3.5. Ethical considerations

The study procedures were in accordance with local data protection regulations. The informed consent was obtained from all participants, and the patients could withdraw from the study at any time on their own request. The study was approved by the Tartu University Research Ethics Committee.

4.4. Hip fracture related excess mortality, and the impact of comorbidities on excess mortality (PAPERs III and IV)

We used a population-based retrospective cohort study to examine the excess all-cause mortality after hip fracture over a 10-year follow-up period. The data on all-cause mortality in men and women aged ≥50 years with incident hip fracture (cases) were compared to this of the reference group (a random sample of age- and sex-matched subjects with no known history of hip fracture prior to the index date). The excess mortality risk related to the hip fracture over a 10-year follow-up period was estimated using Poisson regression. The impact of comorbidities on excess mortality was explored using an adjustment for the CCI score, and stratification by CCI score groups and components (Quan *et al.*, 2005, 2011).

4.4.1. Setting, data source, and participants

For this study, the study subjects' demographic characteristics, clinical characteristics, and outcome data were ascertained from the EHIF (Estonian Health Insurance Fund, 2015). The sample frame included all insured individuals, including those with no record of health care services provided during January 1, 2004 – December 31, 2013. Health care utilization data on all patients (aged ≥50 years) hospitalized with incident hip fractures during the period January 1, 2005-December 31, 2013 were identified (case group, n=8298). The case definition was based on the hip fracture specific diagnosis codes (see above), listed as the primary diagnosis on the electronic inpatient health care claim. The index date of diagnosis was defined as the first day of care indicated in the claim; patients with a diagnostic code primary for hip fracture and no known previous evidence of hip fracture were selected for inclusion (Lix, Azimaee and Osman, 2012). The hip fracture patients were matched by sex and age (year of

birth) in a 1:4 ratio (reference group, n=33,191). Reference group subjects were alive and without evidence of hip fracture prior to the case patient's index date of fracture. Study subjects were assigned a unique identifier decoupled from personal identification information to enable longitudinal tracking of care and mortality while maintaining patient privacy.

4.4.2. Identification of pre-fracture comorbidity

Clinical characteristics and comorbidities were captured for the 365-day period prior to the index date for case patients and their matched controls. Comorbidities were defined as any secondary or other diagnoses coded at the index hip fracture claim and/or diagnoses of any type on hospital or outpatient health care claims during the year preceding the index date (Radley *et al.*, 2008; Toson, Harvey and Close, 2015). We applied a restriction to outpatient claims, such that a comorbid condition could be flagged during the preceding period only if it appeared two or more times at least 7 days apart (Tosteson *et al.*, 2007; Radley *et al.*, 2008).

The comorbidity status for both groups was computed using the CCI. The index is based on the hazard ratios of individual life-threatening comorbidities for 1-year mortality presented as disease weights, and the CCI score represents the person's mortality-predicting disease burden (Charlson *et al.*, 1987; Quan *et al.*, 2011). For example, a person with a score of 2 might have 2 individual diseases with a weight of 1 or 1 disease with a weight of 2. We used the revised coding algorithm described by Quan et al., and subsequently validated for estimating comorbidity using ICD-10 coded administrative data (Quan *et al.*, 2005). We also updated disease weighting to reflect advances in chronic disease management and treatment outcomes since the introduction of the original Charlson index in 1987 (Quan *et al.*, 2011). The updated CCI consists of 12 comorbidities (CCI components) (Table 1 in PAPER IV). Comorbidities are weighted from 1 to 6 for mortality risk, and then summed to form the total CCI score (groups ranging from 0 to ≥3). The updated CCI has demonstrated comparable predictive utility for mortality using ICD-10 coded administrative data (Quan *et al.*, 2011) and has been validated among hip fracture patients (Toson, Harvey and Close, 2015).

4.4.3. Follow up and identification of outcome

The primary outcome for this study was all-cause mortality. We followed all study subjects (belonging to the case and reference groups) until the study end (4th May 2016). Dates of death were obtained from the EHIF database. Although the EHIF database captures provision of healthcare services country-wide, loss to follow-up upon emigration from Estonia is possible, albeit rare, among those 50 years or older (estimated to be less than 0.5% per year) (Statistics Estonia, 2015b).

4.4.4. Statistical analysis

The hip fracture group and the reference group were described by group size, mean age, age range, and 10-year groups, CCI mean score, score groups, and range. Age of men and women with hip fracture was compared by non-parametric Wilcoxon rank sum test. CCI in hip fracture group was compared to reference group by Wilcoxon rank sum test, distribution of age groups and CCI groups was compared with χ^2 test. 95% confidence intervals for mean differences of age and CCI were calculated.

Cumulative risk of death was estimated separately in 10 strata defined by sex and five age categories (50–59, 60–69, 70–79, 80–89, 90+ years old at index date), the risks were weighted by the size of respective groups to present generalized results (aggregated over sex and age). To capture the rapid and extensive changes in mortality during the first 3–6 months following a hip fracture [1, 5], we divided the 10-year follow-up period into graduated discrete intervals as follows: shorter periods proximal to the index date and wider intervals afterwards, with cut-points at each 0.5 months during the first three months, at each month during the rest of the first year; at each three months during the second year; and on each year from the third to the tenth year. Within each age and sex subset Poisson regression was used to estimate mortality rates for each of those intervals (to smooth the variability of data thin plate regression spline was used for estimating the impact of comorbidities in PAPER IV (Wood, 2003)) among hip fracture cases and controls. Two regression models were considered: crude, containing only the interaction between the group (hip fracture or reference/control) and follow-up time interval, and adjusted, including main effects of hip fracture, CCI score and groups, age, and follow-up time interval. Age adjustment within age groups was used to account for residual confounding (Sjölander and Greenland, 2013). Interval-specific mortality rates were transformed to calculate cumulative risks. Excess risks and risk ratios (RR) were calculated as differences or ratios in cumulative risks in both study groups. Bootstrap percentiles were used to compute 95% confidence intervals (CI) for cumulative and excess risks. Using bootstrapping (and splines used in the analysis for PAPER IV) resulted in slightly different excess mortality estimates in PAPERs III and IV.

The stratification by CCI groups (0, 1–2, ≥3) was performed by comparing the excess risk of cases in one score group to that of reference subjects in the respective score group, e.g. CCI 1–2 hip fracture / CCI 1–2 reference. Stratification by the individual CCI components was done in a similar fashion. In the CCI component-specific analysis everyone's CCI score was reduced by the respective amount corresponding to the CCI component (if present). The number of patients in CCI groups 1–2 and ≥ 3 was relatively small in the age group of 50–59 years. The respective age group was excluded from the CCI component-specific risk assessment for dementia and cancer, as no patients with these conditions were present.

All analyses were performed in R (versions 3.1.1 to 3.3.1) (Wickham, 2009; Calaway *et al.*, 2015; Calaway, RevolutionAnalytics and Weston, 2015; R Core Team, 2015; Canty and Ripley, 2016; Carstensen *et al.*, 2016; Dowle *et al.*, 2016; Wickham and Francois, 2016).

4.4.5. Ethical considerations

The study procedures were in accordance with local data protection regulations. The patient privacy was maintained by assigning a personal identifier (pseudo-identification code) to enable longitudinal tracking of diagnoses, care, and mortality. The study was approved by the Tartu University Research Ethics Committee.

5. RESULTS

5.1. The incidence of hip fracture (PAPER I)

We documented 10 704 incident hip fracture cases among persons aged 50 years or older occurring in 2005–2012 (Table 1 in PAPER I). Most fractures occurred in women (70%). Among women, we found exponential increases of fractures with age, with over half (58%) of all fractures in women occurring in the oldest age group (80+ years) and this accounted for 41% of all hip fractures in Estonia. Among men, 43% of all hip fractures occurred in the two youngest age groups of 50–69 years. The total number of fractures remained relatively constant over the study period in both genders, however, in the 80+ age group (which contributed to as much as 49% of all fractures) we observed an increase in both genders (p=0.012 for women, p=0.017 for men). Over the study period, the mean age of a fracture patient increased by 1.6 years (from 79.0 years [SD 9.7] to 80.6 years [SD 9.4]) in women (p<0.001) and by 3.4 years (from 69.7 years [SD 11.3] to 73.1 years [SD 11.5]) in men (p=0.001).

The crude incidence for the entire observation period was 319.8 per 100 000 person-years (95% CI 312.5 to 327.0 per 100 000) in women and 218.8 per 100 000 person-years (95% CI 211.2 to 226.3 per 100 000) in men, resulting in a female to male incidence rate ratio (IRR) of 1.46 (95% CI 1.31 to 1.63) (Figure 2). Women had significantly higher crude rates over the study period (p<0.001). No changes in the crude incidence over the period of observation were observed among either gender (p=0.681 for women, 0.704 for men).

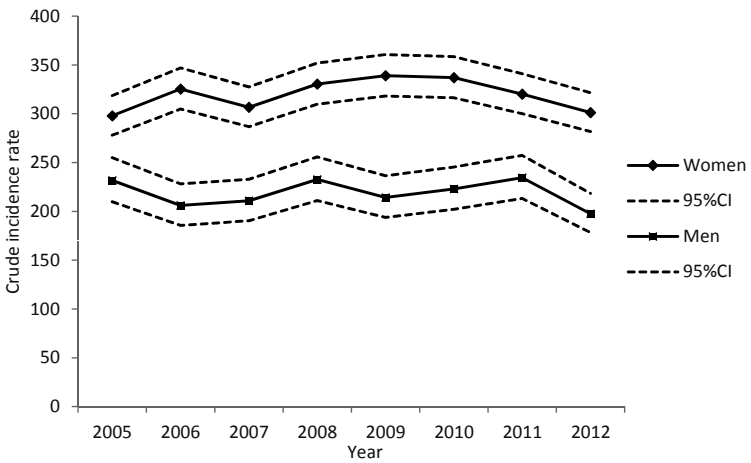

Figure 2. Crude hip fracture incidence (per 100 000 person years) in women and men, 2005–2012 (Figure 1, PAPER I)

However, there were no significant sex differences in SIR: the SIR for the entire observation period was 209.2/100 000 (95% CI 204.2 to 214.2) in women and 215.6/100 000 (95% CI 208.2 to 223.1) in men, resulting in a female to male

IRR of 0.97 (95% CI 0.84 to 1.11) (Figure 3). Although SIR for both sexes decreased during the study period, the change was not statistically significant for neither sex (p=0.058 for women, 0.177 for men). For the period of 2009–2012, we observed an accelerated 16% decrease in the hip fracture rate in women (p=0.008).

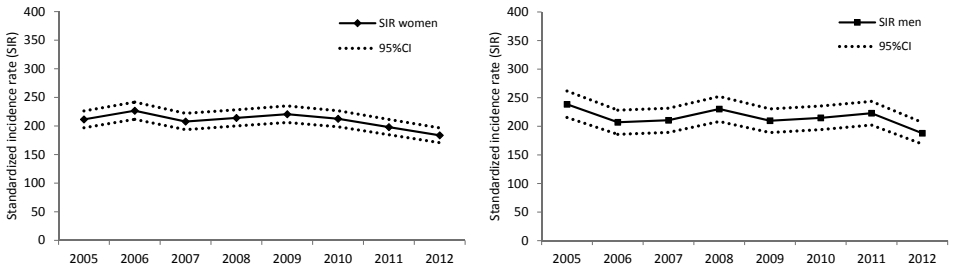

Figure 3. Standardized hip fracture incidence rates (per 100 000 person years) in women and men, 2005–2012 (Figure 2, PAPER I)

We observed exponential increases in hip fracture incidence with age in both genders: over the period of observation the incidence rate ratio (IRR) 70–79/50–59 years was 9.1 (95% CI 8.8–9.5) in women and 3.4 (95% CI 3.2–3.5) in men, and 80+/50–59 years 34.3 (95% CI 33.7–35.0) in women and 9.1 (95% CI 8.9–9.3) in men (Figure 4). We also observed marked sex differences in age-specific rates: over the period of observation the female to male IRR was 0.41 (95%CI 0.38 to 0.45) in the 50–59 age group, 0.59 (95%CI 0.57 to 0.62) in the 60–69 age group, 1.12 (95%CI 1.08 to 1.17) in the 70–79 age group, and 1.57 (95%CI 1.54 to 1.60) in the 80+ age group. Among men, we observed a declining trend over the study period in the age groups of 50–59 years (p=0.030) and 60–69 years (p=0.007). Among women, we observed a non-significant decline in incidence in all age groups above 60 years.

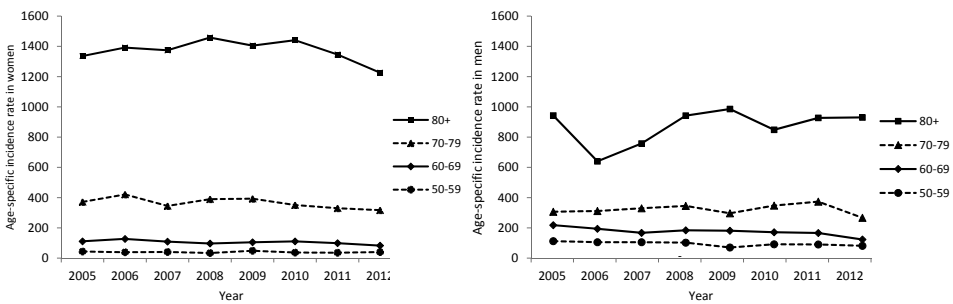

Figure 4. Age-specific hip fracture incidence (per 100 000 person years) in women and men, 2005–2012 (Figure 3, PAPER I)

5.2. Quality of life, resource use, and costs related to hip fracture (PAPERs II, V, VI)

Of the 767 patients with hip fractures who were treated at the two clinics during the study period, 205 (26.7%) participated in the study. Characteristics of participants and non-participants are presented in Table 2.

All participants were hospitalized because of the fracture and 189 (92%) were admitted via an emergency department; 45 (22%) reported osteoporotic fracture during the last 5 years; the majority had only primary (70, 34%) or secondary (100, 49%) education, low net income (181, 88%; low defined as ≤ 500 euros per month), and almost half (96, 47%) of the patients were living alone. 13 (6%) (mean age 61.7, range 50.1–77.7 years) were working (all full time) before the fracture. On average, study participants were interviewed within 3.9 (SD=2.5) days of the first healthcare contact for the fracture.

The retention rate throughout the study was 60% (154 patients (75%) at 4 months, 128 patients (62%) at 12 months and 123 patients (60%) at 18 months) (82% after excluding those deceased during the follow-up amongst those who were lost to follow-up). Among those not followed up (82 patients, 40%) 45 (22%) died, 33 (16%) were lost, 1 patient withdrew consent, and 3 sustained a new fracture. Patients who died during follow-up were older (82.4 vs 77.0 years, p=0.002) and had higher CCI score (1.7 vs 1.0, p=0.002) than those who remained in the study. Patients who were lost to follow-up were statistically non-significantly younger (73.6 years, p=0.13) and had similar CCI score (0.95, p=0.85) compared to retained patients.

Non-participants were on average 1.7 years older (p=0.008) and had a higher CCI score than participants (p=0.004); predominately reflecting a higher prevalence of heart failure (p=0.051) and dementia (p=0.0003). Age-standardized mortality at 12 and 18 months was (statistically non-significantly) higher among non-participants.

For comparison, 2,406 hip fracture patients were enrolled in ICUROS from 2007 to 2014 (PAPER VI). After excluding 184 (8%) patients who died during the follow-up, 246 (10%) who were not reachable, and 561 (23%) patients due to withdrawal, new fracture during the follow-up, or incomplete EQ-5D data, 1415 patients (59%) were eligible for (complete case) analysis. No comparison group for assessing generalizability was available for the pooled ICUROS sample.

Table 2. Characteristics of clinical study participants and non-participants in Estonia (patients with hip fracture aged ≥50 years attending two hospitals) (Table 1, PAPER II)

Characteristic	Study participants	Non-participants*	p-value study participants vs non-participants
Number of hip fracture patients	205	562	
Women (%)	72	68	0.302
Mean age, years (SD)	77.5 (9.9)	79.2 (10.5)	0.008
Age groups (%)			
50–59	9	6	0.005
60–69	11	13	
70–79	32	23	
80–89	42	45	
≥90	5	13	
Charlson index score			
mean (SD)	1.1 (1.3)	1.5 (1.5)	0.004
range	0–5	0–8	
Charlson index score groups (%)			
0	51	42	0.006
1–2	37	38	
3–4	11	17	
≥5	2	3	
Charlson index components (%)			
Congestive heart failure	33	41	0.051
Any malignancy	10	10	0.999
Chronic pulmonary disease	8	10	0.296
Rheumatologic disease	4	3	0.287
Diabetes mellitus with chronic complications	2	4	0.326
Renal disease	2	4	0.326
Hemipegia or paraplegia	2	2	0.996
Dementia	1	8	0.0003
Other	0	1	0.891
Age-standardized mortality rate per 1,000 person-years (95% CI)			
12 months	57 (35–129)	125 (78–190)	
18 months	53 (32–115)	90 (60–130)	

*Includes data on patients not invited (patients who were admitted for care in periods when recruitment team was not operating; n=336), on patients accessed but deemed to be ineligible (n= 198), and refused study participation (n= 28).

HRQoL

The HRQoL estimates and loss in QALYs among survived patients are presented in Figure 5. The mean HRQoL was 0.67 (95% CI 0.63–0.71) before fracture, 0.07 (95% CI 0.01–0.12) after fracture, 0.42 (95% CI 0.36–0.47) at 4 months, 0.54 (95% CI 0.49–0.60) at 12 months, and 0.60 (95% CI 0.54–0.65) at 18 months. The mean HRQoL loss was estimated at 0.16 QALYs in the first 6 months, 0.09 in the following 6 months, and 0.06 in the last 6 months, resulting in a mean total of 0.31 QALYs lost during 18 months. Thirty percent of survived patients were fully recovered at 4 months, 41% at 12 months, and 49% at 18 months. There was a tendency for lower HRQoL among older participants, those with higher CCI scores, and women (Figure 2, PAPER II).

For comparison, the respective pooled ICUROS results were 0.77 (SD 0.27) (vs 0.67 in the Estonian study), –0.11 (SD 0.37) (vs 0.07, respectively), 0.49 (SD 0.38) (vs 0.42), 0,59 (SD 0.37) (vs 0.54), and 0.66 (SD 0.34) (vs 0.60) (Table 2, PAPER VI). The pooled results indicated a larger 18-months HRQoL loss, 0.42 QALYs, mostly due to larger loss over the first 6 months. The HRQoL point estimates from the available case and multiple imputation approaches were similar to the complete case analysis.

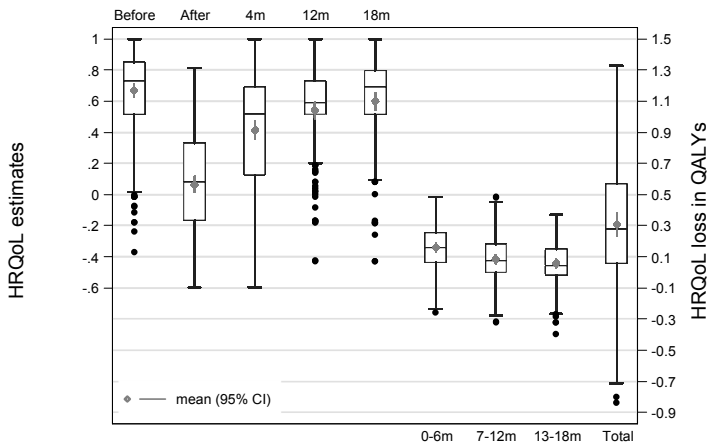

Figure 5. Health-related quality of life estimates before, directly after, and at 4, 12 and 18 months after fracture (left-hand panels); and (right-hand panels) health-related quality of life lost in QALYs (between 0–6, 7–12, 13–18 months, and total) among survived hip fracture patients. Box plots present the medians, quartiles, and range (Figure 1, PAPER II)

Patients who died during a particular follow-up period had lower HRQoL at the start of the period than patients who completed that period, albeit the differences were not statistically significant (mean HRQoL: pre-fracture 0.63 vs 0.66 (p=0.52), after fracture –0.06, vs 0.09 (p=0.07), at 4 months 0.35 vs 0.42 (p=0.35) and at 12 months 0.39 vs 0.54 (p=0.23)). There was no difference in HRQoL in patients who were lost to follow-up in a given period and patients who completed the period (mean HRQoL: pre-fracture 0.73 vs 0.66 (p=0.69), after fracture 0.01 vs 0.09 (p=0.4), at 4 months 0.42 vs 0.42 (p=0.79).

Disease burden

The mean hip fracture related QALY loss that accounts for HRQoL loss of survivors and lost life years of patients whose death was attributable to hip fracture was estimated at 0.16 (95% CI 0.14–0.19) QALYs in the first 6 months, 0.12 (95% CI 0.10–0.15) in months 7–12, and 0.11 (95% CI 0.08–0.14) in months 13–18. The accumulated QALY loss during 18 months was 0.39 (95% CI 0.32–0.47). The number of observed vs expected deaths in the QALY calculation was 25 vs 6.5 in months 0–6, 12 vs 5.7 in months 7–12, 8 vs 5.9 in months 13–18, and 45 vs 18.1 in the 18 months' follow-up period.

Resource use

The average utilization of health care resources per patient utilizing a specific resource is presented in Table 3, and the utilization of non-medical and indirect resources in Table 4. In months 0–4 after fracture, all patients were admitted to specialty care (traumatology or orthopedics), with a mean number of admissions and mean length of stay of 1.6 (95% CI 1.5–1.7) and 15.2 (95% CI 13.2–17.2) days, respectively. Forty percent (82/205) of patients were admitted to inpatient nursing (on average for 32.5 days), whereas 8% (17/205) were admitted to a rehabilitation department. Although 58% (119/205) of patients had at least one outpatient care visit, only 5% of patients visited either rehabilitation or nursing outpatient care. Up to 65% of patients (133/205) used some type of fracture-related medications: 53% used analgesics, 18% used calcium and vitamin D supplements, 8% used bisphosphonates. Alendronate accounted for over 90% of the bisphosphonate use. Among the 45 patients who reported previous osteoporotic fractures in the last five years, 2 were on bisphosphonates before the index fracture.

The proportions of patients receiving medical care decreased in subsequent study periods. During months 5–12 and 13–18 after fracture 8% (14/185) and 5% (9/168) were admitted to the hospital, respectively, and 27% (50/185) and 15% (25/168) received outpatient care. Utilization of outpatient rehabilitation and nursing care remained low (8% of patients). The proportion of patients using analgesics was stable whereas the proportion of calcium and vitamin D users increased to 30% in months 13–18, while 13% were on bisphosphonates during the follow-up. No use of estrogen receptor modulators, strontium ranelate, and teriparatide was recorded.

Fewer than 2% of patients were institutionalized during the follow-up, and the proportion receiving home help by social workers remained below 10% over the study despite some increase in months 5–18 post-fracture. Use of informal home help by relatives and friends was high (reported by 84% of patients) during the follow-up, with an average of 15.4 (95% CI 13.7–17.3) hours of help per week. Eighty-eight percent of patients used assistance devices during the first 4 months, but use decreased to 13% during months 12 to 18. Among the 13 patients working before the fracture, 10 were off work due to sick leave (at least once) or took early retirement due to the fracture during the study period.

Table 3. Utilization of health care resources per hip fracture patient receiving care, by study period and cumulatively (Table 2, PAPER II)

		0–4 months			5–12 months			13–18 months			Cumulative		
Resource	Measure	Patients N=205	Mean	(95% CI*)	Patients N=185	Mean	(95% CI*)	Patients N=168	Mean	(95% CI*)	Patients N=205	Mean	(95% CI*)
Inpatient care													
All	admissions	205	2.2	(2.0–2.3)	20	1.6	(1.4–2.1)	11	1,5	(1.3–2.1)	205	2.4	(2.2–2.6)
	bed-days		29.2	(25.8–32.9)		28.3	(12.5–50.9)		29.0	(17.6–42.2)		33.5	(29.4–38.8)
Specialty care	admissions	205	1.6	(1.5–1.7)	14	1.5	(1.2–1.7)	9	1.4	(1.1–2.1)	205	1.7	(1.6–1.9)
	bed-days		15.2	(13.2–17.2)		25.4	(9.9–45.4)		22.4	(10.4–38.1)		17.9	(15.0–21.3)
Nursing care	admissions	82	1.2	(1.1–1.3)	5	1.2	(1.0–1.4)	4	1.0		86	1.3	(1.1–1.4)
	bed-days		32.5	(28.3–37.3)		29.6	(9.0–50.2)		29.3	(9.5–51.3)		34.1	(29.7–39.8)
Rehabilitation	admissions	17	1.4	(1.1–1.9)	6	1.0					19	1.5	(1.2–1.8)
	bed-days		12.0	(10.5–13.7)		10.2	(8.8–11.8)					13.9	(12.0–15.9)
Outpatient care													
All	visits	119	1.9	(1.7–2.2)	50	1.9	(1.6–2.4)	25	1.6	(1.2–2.4)	140	2.6	(2.2–3.0)
Family practitioner	visits	71	1.4	(1.3–1.6)	29	1.2	(1.0–1.3)	7	1.1	(1.0–1.3)	89	1.6	(1.4–1.9)
Specialty care	visits	80	1.4	(1.3–1.6)	28	1.9	(1.5–2.4)	18	1.5	(1.2–1.9)	100	1.9	(1.7–2.2)
Nursing care	visits	8	1.9	(1.3–2.5)	3	2.0	(1.0–3.0)	1	4.0		10	2.5	(1.5–3.7)
Rehabilitation	visits	3	1.3	(1.0–1.7)	3	1.3	(1.0–1.7)	2	1.0		7	1.4	(1.0–1.9)
Drug use													
All	patients	133			122			105			162		
Bisphosphonates	patients	16			17			18			26		
Denosumab	patients				1			1			1		
Oestrogens	patients	1			3			2			3		
Analgesics (prescription and non- prescription)	patients	108			98			90			150		
Prescription NSAIDs	patients	58			64			44			95		
Prescription opioids	patients	30			28			25			52		
Non-prescription analgesics	patients	36			24			32			63		
Calcium and vitamin D (prescription and non-prescription)	patients	37			41			50			77		

*Bootstrapped bias corrected and accelerated 95% confidence intervals

Table 4. Utilization of direct non-medical and indirect resources per hip fracture patient utilizing resources, by study period and cumulative, among hip fracture patients aged ≥ 50 years (Table 3, PAPER II)

		0–4 months			5–12 months			13–18 months			Cumulative		
Resource	Measure	Patients N=154	Mean	(95% CI*)	Patients N=128	Mean	(95% CI*)	Patients N=123	Mean	(95% CI*)	Patients N=154	Mean	(95% CI*)
Nursing home / home for elderly	bed-days last month	2	28.0	(28.0–28.0)	3	25.7	(23.3–28.0)	1	28.0		3	25.7	(23.3–28.0)
Home help by social worker	hours per week	3	2.7	(1.0–3.7)	12	9.3	(5.3–14.0)	10	4.9	(2.5–9.6)	14	7.8	(4.4–12.6)
Assisting devices	patients	135			33			16			143		
Walking aids	patients	130			29			10			139		
Hygiene	patients	25			4			5			34		
Other	patients	3			4			3			10		
Transportation	units last month	3	2.3	(2.0–3.0)	3	1.7	(1.0–3.0)	2	1.0	(1.0–1.0)	6	1.8	(1.2–2.4)
Informal care	hours per week	121	16.2	(14.0–18.3)	87	16.3	(13.8–18.9)	91	14.6	(12.6–17.1)	128	15.4	(13.7–17.3)
Work related	patients	10			4			6			10		
Sick leave	days last month	7	23.4	(14.9–28.3)	0			0			7	23.4	(13.1–28.3)
Retired	patients	3			4			6			6		

*Bootstrapped bias corrected and accelerated 95% confidence intervals

Table 5. The average cost and cost structure per hip fracture patient by study period and accumulated (costs in euros, at 2014 prices) among hip fracture patients aged ≥ 50 years in Estonia (Table 4, PAPER II)

	0–4 months		5–12 months		13–18 months		Cumulative	
Resource	Mean	(95% CI*)	Mean	(95% CI*)	Mean	(95% CI*)	Mean	(95% CI*)
Health care								
Inpatient care	3722	(3368–4075)	412	(177–756)	208	(75–419)	4342	(3620–5249)
Outpatient care	39	(32–47)	20	(12–32)	7	(3–15)	66	(47–94)
Pharma-ceuticals	21	(16–27)	37	(27–48)	37	(28–48)	95	(71–123)
Social care								
Nursing home / home for elderly	22	(0–53)	141	(0–283)	37	(0–184)	199	(0–519)
Home help by social worker	2	(0–6)	104	(47–195)	33	(12–70)	140	(59–271)
Assisting devices	15	(10–28)	1	(0–3)	0	(0–0)	17	(10–31)
Transportation	4	(1–9)	9	(0–24)	3	(1–7)	15	(2–41)
Informal care								
Home help by relatives, friends	521	(439–619)	1231	(1005–1471)	901	(748–1068)	2653	(2192–3159)
Indirect cost								
Loss of production	221	(108–386)	177	(52–406)	223	(73–438)	620	(233–1230)
Total cost	4566	(3974–5249)	2130	(1322–3217)	1449	(940–2251)	8146	(6236–10717)

Costs

The average cost and cost structure per hip fracture patient are presented in Table 5. The mean cumulative 18-month cost related to hip fracture was 8146 (95% CI 6236–10717) euros per patient. Most costs were related to health care and informal care, 56% and 33% respectively, whereas social care and indirect costs accounted for less than 5% and 8%, respectively. Fifty-six percent of the costs (including 84% of health care costs) were incurred in the first 4 months. Health care costs comprised 83% of the total costs in the first 4 months, decreasing to 17% during months 13–18. In contrast, the proportion of informal care cost increased from 11% in the first period to 62% in the last period. The proportion of social care cost was only 1% in the first period, increasing only moderately thereafter. The proportion of indirect cost increased gradually from 5% to 15%.

5.3. Hip fracture related excess mortality (PAPER III)

We documented 8298 incident hip fracture cases among persons aged 50 years and older, hospitalized in 2005–2013 in Estonia (Table 1 in PAPER III, Table 1 in PAPER IV). 71% of fractures occurred in women. The mean patient age was 78.0 years, and men were younger than women (72.2 vs 80.4). In total, 51% of fractures occurred among those 80 years and older, primarily among women. The mean CCI score was 0.94 (SD 1.36), whereas men were healthier (CCI 0.88, SD 1.38) than women (CCI 0.96, SD 1.36). 39% patients had at least 1 life-threatening pre-fracture comorbid condition, and 11% had CCI score ≥3. Congestive heart failure was the most prevalent comorbid condition (22%), followed by dementia (8%) and cancer (6%). The age- and sex-matched reference group subjects (n=33 191) were healthier than the hip fracture patients: the mean CCI score was 0.66 (SD 1.13) ($p<0.0001$) (men 0.59 (SD 1.11), women 0.69 (SD 1.13)), and the prevalence of comorbidities was smaller (30%, $p<0.0001$).

Absolute risk of death

The average follow-up time was 4.3 years (3.4 years among hip fracture patients and 5.0 among the reference group). 5552 (67%) cases (1564 men, 3988 women) and 14037 (42%) reference individuals (3514 men, 10523 women) died during the 10-year follow-up period. The crude risk of death of hip fracture patients was high compared to the matched reference subjects: 17.5% (95% CI 16.8–18.1%) vs 2.0% (95% CI 1.9–2.1%) at 3 months, 28.3% (95% CI 27.629.0%) vs 7.8% (95% CI 7.6–8.0%) after 1 year, 54.4% (53.6–55.2%) vs 29.8% (95% CI 29.4–30.1%) in 5 years, and 78.2% (95% CI 77.2–79.2%) vs 55.6% (95% CI 55.0–56.2%) in 10 years from fracture. The average age- and CCI-adjusted cumulative 10-year risk of all-cause death was 77.6% (95% CI 76.7–78.8%) in the hip fracture group and 56.5% (95% CI 56.0–57.3%) in the

reference group, and women had higher risk than men in both study groups (Figure 6).

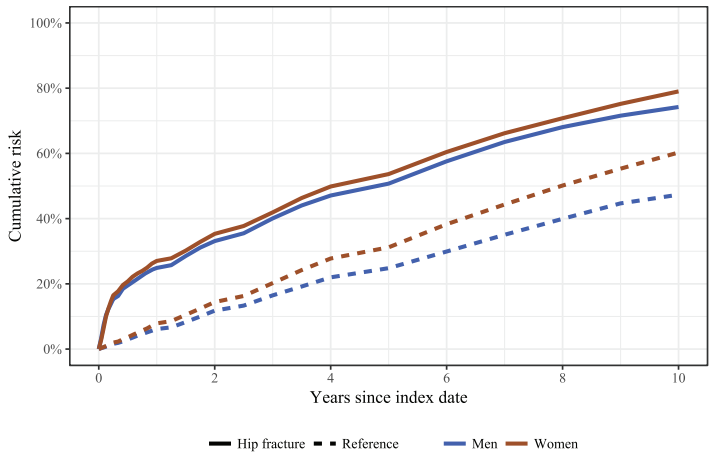

Figure 6. Sex-specific cumulative 10-year risk of all-cause mortality (adjusted for age and Charlson index score) by study group in men and women ≥ 50 years in Estonia, January 1, 2005-May 4, 2016 (Figure 1, PAPER III)

The mortality increased with age (Figure 7). For example, among 60–69-year-old men the 1-year risks were 15.9% (95% CI 14.2–18.4) in hip fracture group and 2.5% (95% CI 2.2–3.2) in the reference group, whereas in the group of ≥90 years the respective risks were 68.3% (95% CI 62.0–75.2) and 22.5% (95% CI 20.3–25.3).

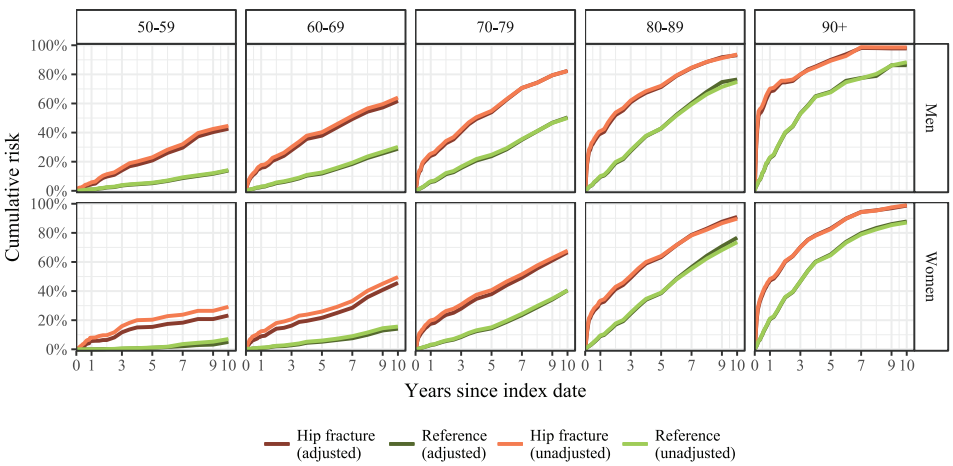

Figure 7. Age group-specific cumulative risk of all-cause mortality (crude, and adjusted for age and Charlson index score) by study group in men and women ≥ 50 years in Estonia, January 1, 2005–May 4, 2016 (Figure 2, PAPER III)

The proportion of deaths in the hip fracture group attributable to the exposure (attributable risk fraction) in 10 years from fracture was 27.2% (95% CI 25.9–28.5%), i.e., one in four deaths in the case group was attributable to the fracture (Figure 6). The attribution was higher in younger and lower in older patients (Figure 7). For example, in the group of 50–59-year old patients, 2/3 of deaths in men and 4/5 in women were attributable to hip fracture, whereas in over 90-year old women every 10th patient died from the fracture.

Excess risk of death

The crude excess risk of death after hip fracture compared to the reference subjects was pronounced, stable and persistent, reaching 22.6% (95% CI 21.4–23.8%) after 10 years after a fracture. The CCI-adjusted cumulative excess risk was 18.9% (95% CI 18.3–19.5) already by month 3, 25.3% (95% CI 24.6–26.2) after 5 years, and as high as 21.1% (95% CI 20.0–22.5%) after 10 years from the fracture. The excess risk was higher in men than in women (Figure 8).

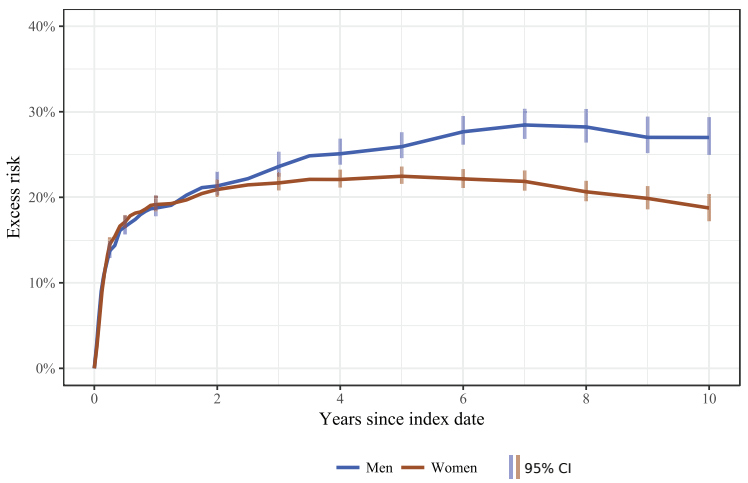

Figure 8. Excess cumulative 10-year risk of all-cause mortality following hip fracture among men and women age ≥ 50 years (adjusted for age and Charlson index score) in Estonia, January 1, 2005–May 4, 2016 (Figure 3, PAPER III)

The sex difference was present in all age groups (Figure 9). Two characteristic excess mortality patterns were revealed. In younger age groups (50–79 years) the excess risk was gradually accumulating. For example, in the 60–69-year-olds, the 3-month excess risk was moderate (men 8.1%, 95% CI 6.5–9.9%; women 4.6% (95% CI 3.3–6.2%), but increased to 30% in 10 years (men 32.8%, 95% CI 28.0–38.1%, and women 31.5%, 95% CI 26.1–37.6%). However, in older patients, the excess risk was immediate and high but decreased over time. In all age- and sex-specific groups, the excess risk was present until the end of follow-up.

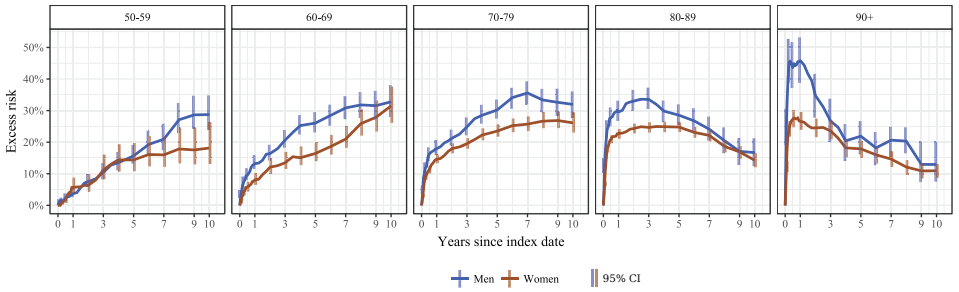

Figure 9. Age group-specific 10-year cumulative excess risk of death following hip fracture among those ≥50 years old (adjusted for age and Charlson index score), men and women in Estonia, January 1, 2005–May 4, 2016 (Figure 4, PAPER III)

Relative risk of death

The adjusted relative risk of all-cause death among hip fracture patients versus age- and sex-matched controls is presented in Table 6. At 1 year, the hip fracture patients were between two and 10 times more likely to die than their age- and gender-matched reference subjects, depending on age and sex. The long-term relative risk was higher in younger age groups (women greater than men) where the absolute risk in the respective reference groups was lower, and decreased with advancing age. The relative risk remained elevated over 10 years in all age- and sex-specific comparisons.

Table 6. Age group specific and average 10-year relative risk (risk ratio (RR) comparing hip fracture cases to reference group) of all-cause death after hip fracture in men and women ≥ 50 years, adjusted for age and Charlson index score (Table 2, PAPER III)

		3 months		1 year		5 years		10 years	
Sex	Age group	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Men	50–59	*		5.6	3.3–10.2	4.0	3.2–4.9	3.1	2.6–3.7
	60–69	10.6	7.3–18.1	5.9	4.8–7.5	3.2	2.9–3.6	2.1	1.9–2.4
	70–79	10.0	7.8–13.2	3.9	3.4–4.5	2.3	2.1–2.4	1.6	1.5–1.7
	80–89	9.9	8.2–12.4	4.0	3.6–4.6	1.7	1.6–1.8	1.2	1.2–1.3
	90+	8.0	6.3–11.0	3.1	2.7–3.7	1.3	1.3–1.4	1.2	1.1–1.3
	Weighted average	9.5	8.4–10.9	4.1	3.8–4.4	2.0	2.0–2.1	1.6	1.5–1.6
Women	50–59	*		*		14.6	7.7–44.0	4.6	2.6–8.1
	60–69	14.6	8.6–34.8	9.8	6.8–15.0	4.1	3.4–5.0	3.3	2.8–3.9
	70–79	14.9	11.5–19.3	6.0	5.3–6.8	2.6	2.5–2.8	1.6	1.6–1.7
	80–89	9.1	8.2–10.1	3.5	3.3–3.7	1.7	1.6–1.7	1.2	1.2–1.2
	90+	5.3	4.6–6.1	2.3	2.1–2.5	1.3	1.2–1.3	1.1	1.1–1.2
	Weighted average	8.3	7.7–9.0	3.4	3.3–3.6	1.7	1.7–1.8	1.3	1.3–1.3

* Respective risk ratios had too high variance and were not reliable

5.4. The impact of comorbidities on hip fracture related excess mortality (PAPER IV)

The excess mortality, when not adjusted for CCI, was 15.1% (95% CI 14.5–15.6) in 3 months, 21.3% (95% CI 20.6–22.0) in 1 year, 25.3% (95% CI 24.6–26.2) in 5 years, and 21.9% (95% CI 21.0–22.9) in 10 years (Figure 10). CCI–adjusted cumulative excess risk was 14.2% (95% CI 13.7–14.8) in 3 months, 20.2% (95% CI 19.5–20.9) in 1 year, 24.0% (95% CI 23.2–24.8) in 5 years, and 20.2% (95% CI 19.2–21.2) in 10 years. Therefore, after adjustment for the effect of CCI score, the aggregated average excess mortality decreased by 0.9% at 3 months, 1.1% at 1 year, 1.3% at 5 years, and 1.7% at 10 years. Thus, the 10-year risk fraction attributable to comorbidities on the average hip-fracture related excess mortality was up to 8% or 1/12, and 1 out of 12 excess deaths was related to pre-fracture, life-threatening comorbidities.

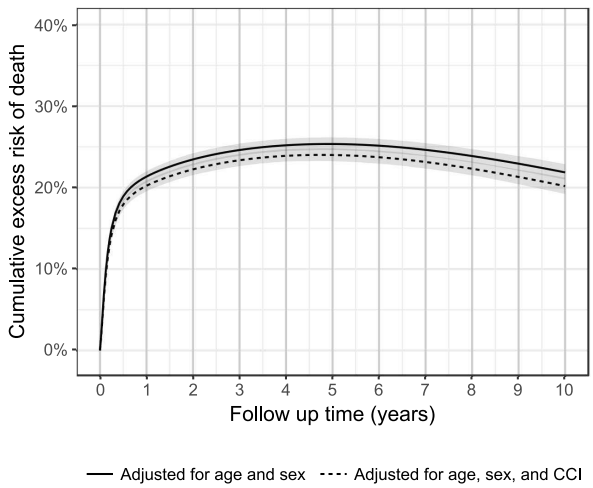

Figure 10. The excess cumulative risk of all-cause mortality following hip fracture among patients aged ≥ 50 years (adjusted for age and sex [solid line], and age, sex, and Charlson index score [dotted line]), over the 10-year follow-up (2005–2016) (Figure 1, PAPER IV)

Stratification by CCI score groups revealed an association for CCI groups and excess mortality. Hip fracture patients with CCI of 0 had an excess risk of 11.6% (95% CI 11.1–12.1) at 3 months, 17.1% (95% CI 16.5–17.8) in 1 year, 23.2% (95% CI 22.2–24.1) in 5 years, and 21.9% (95% CI 20.7–23.1) in 10 years from fracture compared with reference subjects with a CCI score of 0 (Figure 11). The presence of pre-fracture comorbidities that are strongly associated with risk of death (i.e. having a weight of 1 or higher in CCI) was associated with increased excess mortality over 5–7 years. At 3 months, the excess risk in the CCI 1–2 group was 18.9% (95% CI 17.9–19.8%), and in the ≥3 group 23.5% (95% CI 22.1–25.0), whereas in 1 year the respective risks

were as high as 25.8% (95% CI 24.6–27.0%) and 30.3% (95% CI 28.3–32.2%). The excess risk of patients with comorbidities declined over time below that of CCI 0 but did not disappear in any CCI group.

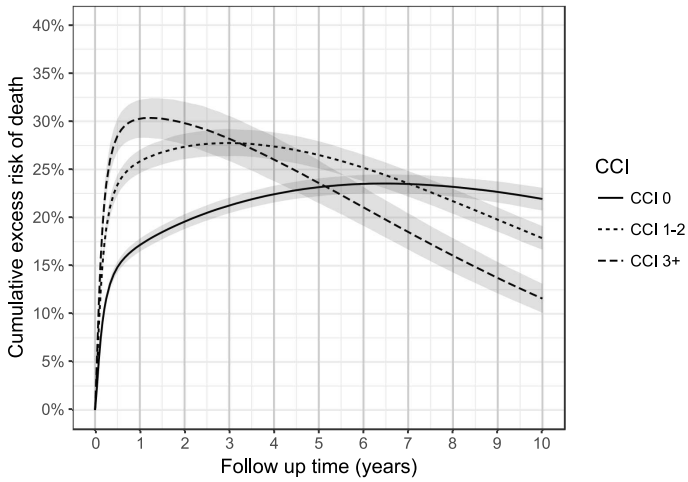

Figure 11. The excess cumulative risk of all-cause mortality following hip fracture by Charlson index score group (adjusted for age and sex) among patients aged ≥ 50 years, over the 10-year follow-up (2005–2016) (Figure 2, PAPER IV)

Overall, the stratification yielded some differences in excess mortality pattern across age groups and was more uniform for CCI components. In younger age groups the effect of comorbidities on excess mortality accumulated gradually and was long lasting (up to 10 years) (Figure 12). For example, among the 60–69-year age group the excess risk in the CCI 0 group was 9.5% (95% CI 8.2–10.8) at 1 year, 21.0% (95% CI 18.6–23.2) at 5 years, and 28.7% (95% CI 25.5–32.4) at 10 years, whereas in the CCI 1–2 group the respective risks were 21.2% (95% CI 17.9–24.7), 39.8% (95% CI 35.0–45.0), and 43.3% (95% CI 37.9–48.9). In the older groups (≥ 80 years) the impact was relatively modest and short (1–3 years). The effect of comorbidities was not dependent on the underlying comorbid condition, except for dementia (Figure 13). The 1-year average excess risk in dementia patients was 18.0% (95% CI 14.9–21.1) higher compared to those without dementia, whereas the excess risk in congestive heart failure patients was 6.5% (95% CI 5.1–8.0) higher than among those with no congestive heart failure. Patients with dementia were older than other patients (mean age 83.2 (SD 7.7)) and had the highest short-term excess risk of all-cause death. However, the excess risk in dementia patients declined fast and fall below that without dementia after 3 years from the fracture.

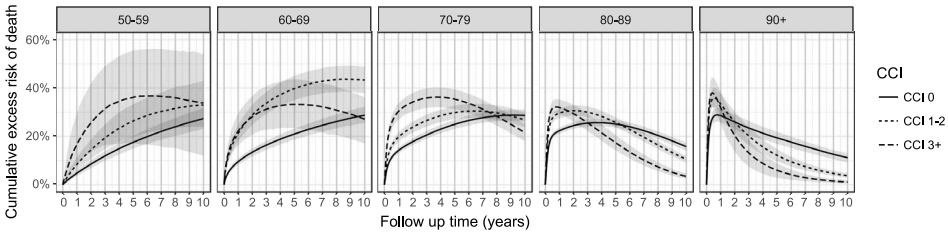

Figure 12. Age group-specific cumulative excess risk of death following hip fracture by Charlson index score group among those ≥50 years old (adjusted for sex), over the 10-year follow-up (2005–2016) (Figure 3, PAPER IV)

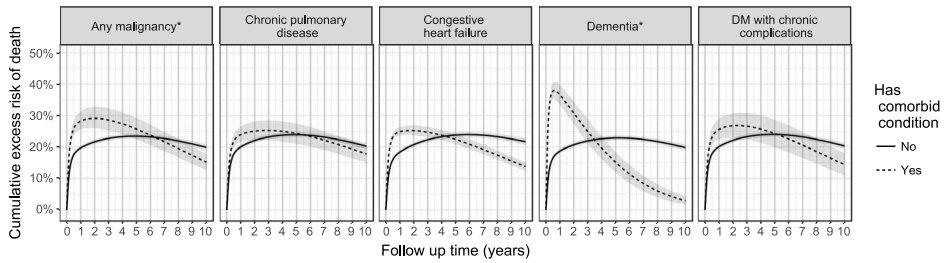

Figure 13. Excess cumulative risk of all-cause mortality following hip fracture by Charlson index components (adjusted for age, sex and other CCI components) among patients aged ≥ 50 years, over the 10-year follow-up (2005–2016) (*due to the small number of patients, the 50–59-year age group was excluded from analyses for dementia and any malignancy) (Figure 4, PAPER IV)

6. DISCUSSION

6.1. The incidence of hip fracture

Incidence in women and men

Compared to other countries, the SIR in Estonian women was low: it was comparable to that in Poland and Romania which reported the lowest rates in Europe (Grigorie *et al.*, 2013; Wilk *et al.*, 2013). The SIR in Estonian women was lower than those reported in the neighboring countries of Lithuania, Russia, and Finland (Lesnyak *et al.*, 2012; Tamulaitiene and Alekna, 2012; Korhonen *et al.*, 2013), and also lower than in many other European countries (Ahlborg *et al.*, 2010; Cooper *et al.*, 2011; Dimai *et al.*, 2011; Kanis, Odén and McCloskey, 2012; Grigorie *et al.*, 2013; Icks *et al.*, 2013; Nilson *et al.*, 2013; Siggeirsdottir *et al.*, 2014) and in the US (Brauer and Coca-Perraillon, 2009; Ettinger *et al.*, 2010). The difference in incidence was predominantly attributable to the lower incidence among the elderly (80+ years) (Bjørgul and Reikerås, 2007; Péntek *et al.*, 2008; Brauer and Coca-Perraillon, 2009; Dodds *et al.*, 2009; Abrahamsen and Vestergaard, 2010; Ström *et al.*, 2011; Dimai *et al.*, 2011; Tamulaitiene and Alekna, 2012; Lesnyak *et al.*, 2012; Støen *et al.*, 2012; Korhonen *et al.*, 2013; Nilson *et al.*, 2013). The age-standardized incidence in women in this study was comparable to the previous regional estimate (Haviko, Maasalu and Seeder, 1996; Kanis, Odén and McCloskey, 2012).

In contrast to women, the SIR among Estonian men was higher than that reported in Eastern and Central European (Lesnyak *et al.*, 2012; Tamulaitiene and Alekna, 2012; Grigorie *et al.*, 2013; Wilk *et al.*, 2013) and most Western European countries (Singer *et al.*, 1998; Dodds *et al.*, 2009; Maravic *et al.*, 2011; Hernlund *et al.*, 2013; Piscitelli *et al.*, 2013). The SIR in men was comparable to that in Finland, Hungary, Czech, and the US (Péntek *et al.*, 2008; Brauer and Coca-Perraillon, 2009; Ettinger *et al.*, 2010; Kanis, Odén and McCloskey, 2012; Stepan *et al.*, 2012; Korhonen *et al.*, 2013), but lower than that in Scandinavia and Austria, countries with the highest incidence worldwide (Bjørgul and Reikerås, 2007; Abrahamsen and Vestergaard, 2010; Dimai *et al.*, 2011; Kanis, Odén and McCloskey, 2012; Støen *et al.*, 2012; Nilson *et al.*, 2013). Among men aged 50–59, Estonia had one of the highest hip fracture rates in Europe, comparable to that in Russia and Sweden (Singer *et al.*, 1998; Kanis *et al.*, 2000; Bjørgul and Reikerås, 2007; Péntek *et al.*, 2008; Dodds *et al.*, 2009; Ström *et al.*, 2011; Tamulaitiene and Alekna, 2012; Lesnyak *et al.*, 2012; Støen *et al.*, 2012; Grigorie *et al.*, 2013; Korhonen *et al.*, 2013). Clearly, cross-country/study comparisons are limited by methodological differences across studies (study design and source of data, case definition and ascertainment of cases, age range and stratification, study year and period of observation).

The phenomenon of population aging has recently been observed in Estonia, and the population structure has become comparable to that of more stable aged populations in Europe (Eurostat, 2017). In line with longer survival, the mean

age of individuals sustaining hip fractures has increased. However, there are significant gender differences in life expectancy at age 65 (20.3 years for women and 15.3 in men in 2015), and the 80+ age group consists predominantly of women, with the female to male ratio being 3.0 in 2015 (Statistics Estonia, 2015c). In line with this, the large difference between crude and standardized rates of hip fractures in women can be explained by differences in the age structure of the Estonian population compared with the WHO world standard population (Statistics Estonia, 2015c; WHO, 2015). Given the stable age-specific hip fracture rates, the observed increase in the absolute numbers of hip fractures in the 80+ age group is largely attributable to the demographic changes, i.e., the increasing number of old people. This result corresponds to other recent findings (Ahlborg *et al.*, 2010). The number of hip fractures might still increase in the coming decades as the number of people aged 80+ in Estonia is projected to increase by 50% by 2050 (UN, 2015).

We found no sex differences in hip fracture rates in Estonia after age standardization. Worldwide, the standardized hip fracture rates in men are approximately half that noted in women, and where higher rates are observed in women, higher rates are found in men and vice versa (Kanis, Odén and McCloskey, 2012). Our observation suggests that Estonia remains an exception to the general pattern of sex-specific hip fracture distribution.

It is hard to delineate the factors associated with the relatively low incidence of hip fractures among women. Data on health behavior for elderly Estonians are scant. We know that the prevalence of overweight in women aged 50+ in Estonia have constantly been among the highest in Europe (Eurostat, 2017) whereas smoking and alcohol consumption is low (Tekkel and Veideman, 2013), and these factors could have reduced the average risk of hip fracture. In addition, given that older age was associated with high level of physical activity in everyday work in Estonia (Tekkel and Veideman, 2013), we could speculate that work related high physical activity (due to poor socio-economic status) among elderly Estonian women relatively early in the life course may have reduced the risk of fracture later in life (Johnell *et al.*, 2007; Kanis *et al.*, 2017; Petit *et al.*, 2017; Rosengren *et al.*, 2017). Interestingly, the modest vitamin D levels (Kull *et al.*, 2009) and low hip fracture rates in Estonian women contrast with the findings of good vitamin D levels (Kuchuk *et al.*, 2009; Wahl *et al.*, 2012) but high hip fracture incidence in the neighboring Scandinavian countries, the controversy is partly explained by the higher socio-economic prosperity in Scandinavia (Kuchuk *et al.*, 2009; Rosengren *et al.*, 2017). In summary, there is currently an inconsistent evidence of differences between hip fracture rates in Eastern and Western Europe (Kanis, Odén and McCloskey, 2012; Icks *et al.*, 2013) which might build to the socio-economic hypothesis, but our results are in line with this theory.

The reasons for a relatively high hip fracture rate in Estonian men remain obscure. We hypothesize that the high incidence in the younger age groups of 50–69 (that accounted for over 40% of hip fractures in men) could be associated with greater risk of alcohol-related falls. We know that heavy alcohol intake is a

risk factor for hip fractures (Kanis *et al.*, 2005; Berg *et al.*, 2008). Estonia is a country where heavy drinking among men is common (Popova *et al.*, 2007); in the age group of 50–54 years, alcohol is the leading factor for disease burden, preempting dietary risks, smoking and high blood pressure (Forouzanfar *et al.*, 2016; Institute for Health Metrics and Evaluation University of Washington, 2017). In this context, mortality from external causes and incidence of injuries are high in Estonia (Institute for Health Metrics and Evaluation University of Washington, 2017; National Institute for Health Development, 2017): for example, the rate of traumatic spinal cord injury in Estonian men is among the highest in Europe, and alcohol consumption precedes over 40% of cases (Sabre *et al.*, 2012). However, there is conflicting evidence to this theory as the hip fracture rates in men differ across Eastern Europe despite a similar pattern of alcohol use (Lesnyak *et al.*, 2012; Tamulaitiene and Alekna, 2012).

Incidence trends

As in several Western European countries and the US which have recently reported stabilizing or declining trends of hip fracture, mostly among women (Bjørgul and Reikerås, 2007; Brauer and Coca-Perraillon, 2009; Abrahamsen and Vestergaard, 2010; Cheng, Levy and Lefaivre, 2011; Cooper *et al.*, 2011; Dimai *et al.*, 2011; Maravic *et al.*, 2011; Støen *et al.*, 2012; Nilson *et al.*, 2013; Icks *et al.*, 2013; Korhonen *et al.*, 2013; Siggeirsdottir *et al.*, 2014; Lucas *et al.*, 2017), we too observed a 16% decrease in SIR in women since 2009, the change is predominantly attributable to the decline among the oldest age group. The period of declining incidence in our study was too short to make long term conclusions on trends, but the finding was confirmed in the recent study with an extended follow-up (Laius *et al.*, 2017). Recent studies have suggested that reduction in fractures can be explained by reductions in falls-related comorbidity (Jørgensen *et al.*, 2014). Data from Estonia are in line with this hypothesis: over the period of this study, the life expectancy at 65 in Estonian women increased from 18.1 to 20.3 years (2.2 years) (Statistics Estonia, 2016), indicating an improved general health and prevention and treatment of chronic diseases. A decrease in incidence corresponds temporally with an increased availability of BMD testing and the expanding use of bisphosphonates (Svedbom *et al.*, 2013; Laius *et al.*, 2017). We might also speculate that the impact of various socio-economic factors during the life course feed through as a cohort effect towards healthier older populations (Cooper *et al.*, 2011; Kanis *et al.*, 2017; Rosengren *et al.*, 2017).

Limitations and strengths

As the data collected for administrative purposes, we had no data on potentially important other risk factors. The inclusion of claims with secondary inpatient hip fracture diagnoses could have resulted in an overestimation of the incidence in the analysis (Lix, Azimaee and Osman, 2012). This clearly could not be driving the differences in hip fracture occurrence among men and women. Yet, the strength of our analysis lies in the use of a data source with nationwide

coverage. We had a large sample size of the representative population and standardized recording of health events (hip fracture contemporaneously across the period of observation), which avoids problems of imperfect recall and incomplete records.

Further, we do not expect significant misclassification of hip fracture based on the incident case definition used, as the hip fracture rates were calculated based on the number of subjects with hip fractures and not simply on the number of admissions. While the used case definition adjusted for multiple registrations per fracture during one year, it might have slightly underestimated the true incidence as about 9% of patients experience a second hip fracture during that period (Ryg *et al.*, 2009). We also have considered the possibility of sex-specific over- or under-ascertainment of incident cases leading to the observed uncommon female to male SIR ratio (Lix, Azimaee and Osman, 2012). In general, it has been demonstrated that administrative data are a valid source for ascertaining hip fracture cases (Lix, Azimaee and Osman, 2012), and after careful analysis of the diagnosis, reporting, and case ascertainment process we conclude that the observed results are unlikely to be a product of measurement bias. Finally, the study period was too short to draw conclusions on temporal trends in hip fracture rates in men.

6.2. Quality of life, resource use, and costs related to hip fracture

Health-related quality of life

To start with, the pre-fracture HRQoL among hip fracture patients was low: it was comparable to that in Spain and Mexico which reported the lowest HRQoL estimates from ICUROS (Table 3, PAPER V). It was also lower than the pooled estimate of 0.78 (95% CI 0.75 – 0.80) reported in a recent meta-analysis (Si *et al.*, 2014). For comparison, the EQ-5D Estonian population estimate for the age group of 55–64 years is 72.7 in men and 72.0 in women, and no estimates are available for the older age groups (Tekkel and Veideman, 2013). The marked decrease after fracture resulted in a post-fracture HRQoL of 0.07, an estimate close to death, that was comparable to generally low estimates from the ICUROS study and significantly lower than the pooled estimate of 0.31 (95% CI 0.22–0.39) (Si *et al.*, 2014). The mean HRQoL nearly reached the pre-fracture levels by the end of follow-up, however, over half of patients (51%) did not recover in full. Accordingly, the HRQoL loss in QALYs after fracture was substantial (patients lost on average 48% of the expected HRQoL in the first 6 months). Our results agree with previous findings that hip fractures are associated with substantial reductions in HRQoL (Borgström *et al.*, 2007; Borgstrom *et al.*, 2013; Si *et al.*, 2014).

The (non-significant) differences in HRQoL and HRQoL loss by age and CCI score were expected as older people with more comorbidities usually have lower HRQoL. It was also expected that the patients who died were older, had

higher CCI scores and lower HRQoL than surviving patients. Given that we did not see significant differences in age, CCI score and HRQoL between those retained and not in the study, we believe that our results are not strongly affected by the low retention rate.

Comparing the Estonian results to those from ICUROS, we observed a slightly lower pre-fracture HRQoL and poorer recovery estimates (at 4, 12, and 18 months) in Estonia, resulting in lower QALY loss. The post-fracture HRQoL (0.07) was higher in Estonia compared to ICUROS pooled estimate of –0.11. The severity of fractures may systematically differ between the participating centers. However, as the patients who died during the follow-up were not included in the pooled (complete case) analysis, and the institutionalized patients were excluded at onset (the proportion of patients who lived in a nursing home at a time of fracture might have been high (10 to 30%) in some affluent participating countries (Brennan (nee Saunders) *et al.*, 2003; Osnes *et al.*, 2004; Harris *et al.*, 2010; Haywood *et al.*, 2014; Anthony W Ireland, Kelly and Cumming, 2015)), the average hip fracture patient from ICUROS may have been healthier and with better recovery potential than the average Estonian patient in the study. Therefore, it is likely that the observed HRQoL differences between the Estonian and the pooled ICUROS results were related to selection bias. However, there is no proof to the hypothesis as the ICUROS HRQoL estimates from the complete case, available case, and multiple imputation analyses were similar, and no comparison group was available to assess bias.

Resource use

Comparing the resource use and cost to other studies is difficult as there are differences in socio-economic characteristics, health systems, price adjustments, and study methods (only a few include social and informal costs) (Borgström *et al.*, 2006). However, large disparities may still be noted in the context of population aging.

The utilization of fracture related specialty care services during the first months was comparable to that in Sweden (Borgström *et al.*, 2006; Canto *et al.*, 2011) and Australia (Anthony W Ireland, Kelly and Cumming, 2015). One difference of note was low use of bisphosphonates, indicating a large gap between current use and the proportion of the population that could be considered eligible for treatment based on fracture risk (Ström *et al.*, 2011). Compared to the similar Swedish study (Borgström *et al.*, 2006) our results showed the low use of rehabilitation, nursing care and social care (particularly after 4 months after fracture). The use of inpatient rehabilitation (9% of patients) was also low compared to that in Lithuania (33%) (Tamulaitiene and Alekna, 2012). We know that at 4 and 12 months after fracture up to 2/3 of patients (70% and 59% respectfully) were not fully recovered and could therefore assume that a substantial proportion of patients still had difficulties in mobility, self-care, and normal activities at that time. Hence, the use of rehabilitation, nursing care, and social care may potentially be insufficient to meet the needs of patients with

low HRQoL. We could speculate that the high excess mortality revealed in the study could be reduced by provision of adequate long-term care post fracture.

Cost

The hip fracture related 18-month societal cost of 8146 euros (annual cost of 6696 euros) was higher than the previous 1-year estimate of 5580 euros (at 2010 prices) that was equal to 40% of the EU average hip fracture cost (Hernlund *et al.*, 2013). The new estimate is approximately half of the European average, comparable to that in Malta or Spain (Hernlund *et al.*, 2013). For comparison, the 2-year direct health care cost of myocardial infarction in Estonia has been estimated at 8704 euros and stroke at 6937 euros per patient (Männik, Pisarev and Kiivet, 2015), and the annual societal cost of Parkinson's disease at 2305 euros per patient (Vois, 2015). The preliminary annual estimate for the total economic burden of incident hip fractures for Estonia is approximately 8 million euros or 6 euros per person, comparable to the direct health care costs for colorectal, lung, or breast cancer (Luengo-Fernandez *et al.*, 2013; Estonian Health Insurance Fund, 2017).

Comparing the cost structure to that in Sweden (Borgström *et al.*, 2006), significant differences were revealed. In our study the proportion of social cost was below 5%, compared with almost 30% in Sweden. The proportion of informal care cost exceeded that in Sweden. A remarkably high use of informal care in Estonia may partly be explained by the shortage of social care. In line with our findings, a large proportion of informal care cost was also noted in a recent study from Austria (Dimai *et al.*, 2012). Another important finding was an increasing proportion of indirect cost, confirming the understanding that despite the advanced age of hip fracture patients, the cost of productivity should not be omitted from hip fracture economic evaluations (Hernlund *et al.*, 2013). In this context, it may be noted that the human capital approach may overestimate costs of productivity losses (Larg and John R Moss, 2011).

Limitations and strengths

A cautious approach should be applied in generalizing results to the total hip fracture population in Estonia as we collected data in two hospitals. However, these hospitals provide 40% of hip fracture inpatient care in Estonia, and we assume that the patients admitted and quality of care do not significantly differ from the other clinics (The World Bank Group, 2015). Further, the modest sample size increases the likelihood of type II error (for example the statistically non-significant differences in HRQoL by age, gender and CCI).

Our results are prone to selection bias – both in relation to recruitment (our sample comprised only 27% of all hospitalized patients with hip fracture at the recruiting hospitals) and retention (60%). We acknowledge that low recruitment rate cannot be explained solely by excluding the previously institutionalized and cognitively impaired patients. Non-participants were significantly older, had higher comorbidity burden and a higher risk of death. One might speculate that this would lead to moderately overestimating HRQoL loss (since recruitment of

younger and milder cases might have resulted in higher HRQoL before fracture) and underestimating costs. However, the cost consequences of fracture might be lower among previously institutionalized patients who already incur the cost of nursing care before fracture. 22% of patients died and 16% were lost during the follow-up, thus the data on social and informal care use for these patients were not available for the non-completed periods. As the respective costs for the patients who died in each period might have been higher than for patients who remained in the study, exclusion of those costs from analysis probably resulted in a slight underestimation of average hip fracture cost.

Methodological issues in HRQoL measurement could also contribute to a possible overestimation of HRQoL loss. First, the initial interview took place right after fracture and patients might have recalled their pre-fracture health better than it was. Second, the assumption that the HRQoL pre-fracture level remained constant during the follow-up had the fracture not occurred may not hold in life, because in older age health might deteriorate over time, reducing the difference between pre-fracture and follow-up estimates. Third, it is possible that most of the HRQoL improvement after fracture happened not in a linear fashion over 4 months, but faster, and therefore the HRQoL loss during the first 4 months was overestimated. Furthermore, we used the EQ-5D UK population values (Dolan, 1997) to determine HRQoL. The country comparisons of EQ-5D value sets have shown that there are considerable differences in HRQoL estimations (Knies *et al.*, 2009). Thus, from an Estonian perspective, the use of a UK value set increased the uncertainty of HRQoL estimations in our study.

It is worth noting that as costs and QALYs were censored after 18 months the true disease burden might be underestimated. Furthermore, we need to acknowledge the uncertainty related to the proportion of deaths attributable to hip fracture in the calculation of total hip fracture related QALYs lost.

The strength of our analysis lies in a study design that enabled prospective collection of cost data from a societal perspective. Simultaneous collection of HRQoL and resource use permitted inferences to unmet needs of care in some patient subgroups. Another strength is the use of EHIF data for assessing fracture related health resources and costs.

6.3. Hip fracture related excess mortality

Excess mortality

Previous studies have demonstrated an immediate elevated risk of mortality after hip fracture (Kanis *et al.*, 2003; Johnell *et al.*, 2004; Vestergaard, Rejnmark and Mosekilde, 2007; Abrahamsen *et al.*, 2009; Haentjens *et al.*, 2010; Kannegaard *et al.*, 2010; Klop *et al.*, 2014, 2017; Omsland *et al.*, 2014), however, the evidence of persistence is not universal (Tosteson *et al.*, 2007; Rapp *et al.*, 2008; Abrahamsen *et al.*, 2009; LeBlanc *et al.*, 2011; Michaëlsson *et al.*, 2014). Our results are in line with the meta-analysis suggesting that the excess mortality is extensive already in the first months after fracture and persists for at

least 10 years (Haentjens *et al.*, 2010). After adjustment for age and pre-fracture comorbidities, hip fracture was associated with a 21% 10-year cumulative excess risk of death (RR 1.4), i.e., more than 1 in 4 deaths among hip fracture patients was attributable to the fracture. To describe the magnitude of a public health problem, the 1-year average relative risk of all-cause death after hip fracture (4.1 in men, 3.4 in women) was comparable to that of diseases with the highest mortality, such as dementia, cancer, heart failure (Quan *et al.*, 2011), and mental disorders (Nordentoft *et al.*, 2013).

It is a common knowledge that the hip fracture excess mortality increases with age (Haentjens *et al.*, 2010). In younger age groups (50–79 years) the excess was mild at the onset but increased in a linear fashion over the follow-up. For example, in the 60–69-year-old patients, the excess risk increased over 10 years gradually to as high as 30% and became 2–3 times higher than in the reference group. This mortality pattern has been described before, suggesting that in younger and healthier patients a hip fracture can trigger a chain of events leading to frailty, disability, and death (Teng, Curtis and Saag, 2008). In contrast, in older age groups (≥80 years) hip fracture had an immediate marked impact on excess mortality. For example, in the group of men ≥90 years old, the excess risk at 3 months was as high as 45%, 8 times higher than in men without fracture. Over half of patients died already within 3 months, and by 12 months over two-thirds of the men had died. This mortality pattern suggests that a hip fracture accelerates the chain of lethal events among older subjects and brings deaths from other pre-existing conditions forward (Magaziner *et al.*, 1997; Empana, Dargent-Molina and Bréart, 2004). It is important to note that the excess risk persisted throughout the 10-year period and did not disappear in any age- or sex-specific group. Our results are in line with the collective evidence confirming that excess mortality increases with age, and is higher in men than in women (Abrahamsen *et al.*, 2009; Haentjens *et al.*, 2010).

Compared to the pooled estimates (Haentjens *et al.*, 2010) the excess risk of death in younger (50–79 years) age groups was rather high, particularly in the first months and years after fracture. For example, in the 70–79-year-old men the excess risk in our study reached as high as 18% within 1 year, and 30% within 5 years, whereas in the meta-analysis the respective estimates were lower (11% and 20%). Likewise, in women of the same age, we found the excess risk to be 14% in 1 year and 24% in 5 years, versus 5% and 13% in the meta-analysis. It is difficult to explain the reasons for increased mortality in these groups, but insufficient case management upon discharge and low utilization of rehabilitation, nursing care, and social care could be potential contributors. However, excess mortality study results are difficult to compare due to differences in study design and sources of data, ascertainment of cases and controls, determination of death, differences in follow-up time, adjustment for confounding, and presentation of results (Abrahamsen *et al.*, 2009; Haentjens *et al.*, 2010).

The average excess risk among men in our study did not exceed that among women during 3 years following the fracture; this can be explained by the different age distribution of fractures in men and women. We know that most

hip fractures in Estonian men occur at a younger age (50–79 years), whereas over half of fractures in women occur among those ≥80 years. Due to the considerable age difference between sexes (8.2 years) women experienced an elevated risk of death in both study groups (see Figure 6), and the weighted average excess risk in both groups was influenced by the higher-weighted age groups, with younger groups in men and older groups in women.

The possible reasons for the greater mortality in men than in women following hip fracture are still poorly understood (Abrahamsen *et al.*, 2009). Previously described risk factors in older men include multi-morbidity, smoking, lower dietary protein, greater height combined with the use of antidepressants leading to a greater impact upon falling, whereas the traditional risk factors in women (rheumatoid arthritis, use of benzodiazepines and corticosteroids) were not related to hip fractures in men (Cauley *et al.*, 2016). It has also been suggested that men have higher rates of pneumonia and septicemia than women (Wehren *et al.*, 2003), or more severe medical comorbidities prior to the hip fracture (Endo, Yoshimi; Aharonoff, Gina; Zuckerman, Joseph; Egol, Kenneth; Koval, 2005; Holt *et al.*, 2008). However, in our study the CCI score was lower in men than in women in both study groups, suggesting that men were healthier than women. It is possible that the lower CCI score in men was related to their younger age compared to women. Our study adjusted for CCI, yet the excess risk was higher in men than in women.

The impact of comorbidities on excess mortality

We also analyzed the impact of comorbidities on excess mortality in detail. Most subjects, in both the hip fracture and reference groups, had no comorbid conditions contributing to the CCI, therefore adjusting for the CCI had little impact on the overall average excess risk either short or long-term (maximum difference between adjusted and unadjusted excess risks was 1.7% at 10 years of follow-up). A low comorbidity effect upon adjustment has also been shown in some other studies where CCI-related comorbidity was not highly prevalent (Farahmand *et al.*, 2005; Vestergaard, Rejnmark and Mosekilde, 2007; Michaëlsson *et al.*, 2014). Our results imply that only 1 out of 12 excess deaths was related to pre-fracture, life-threatening comorbidities, suggesting that comorbidities may not be the primary target for improving survival after hip fracture. The results are in line with a Danish study which found that the major causes of excess mortality in hip fracture patients were linked to the fracture event and not to pre-existing comorbidity (Vestergaard, Rejnmark and Mosekilde, 2007).

We also show that the mortality effect of fracture varies across CCI groups. Among the people without the concomitant disease(s) (CCI 0 group), the average excess risk was profound and durable, implying that hip fracture is an independent risk factor for short and long-term all-cause mortality. The average excess risk of patients with up to two or three co-morbid conditions (CCI groups 1–2 and ≥ 3) exceeded that in the CCI 0 group over 5–7 years, and a clear dose-response for the association of CCI score and short-term excess

mortality was observed. It is likely that the comorbidities modify the effect of hip fracture on all-cause mortality.

The effect of comorbidity was age-dependent. In younger patients (50–79 years) without comorbid conditions (CCI of 0) the excess risk gradually accumulated over the 10-year follow-up period, adding up to 20–30% to the patient's background risk of death without fracture. The presence of pre-fracture comorbidities (CCI groups 1–2 and ≥ 3) almost doubled that excess risk, both short- and long-term. This inflating impact of comorbidities on hip-fracture related excess mortality has been described before (Luise *et al.*, 2008; Abrahamsen *et al.*, 2009; Hu *et al.*, 2012; Anthony W. Ireland, Kelly and Cumming, 2015; Cauley *et al.*, 2016). In older patients (≥ 80 years) the dose–response relationship between CCI score and risk of death was immediate but shorter than in younger patients. Over time, the excess risk in CCI groups 1–2 and ≥ 3 groups decreased below that of CCI 0 as the risk of death, unrelated to hip fracture, increased in the respective reference groups. It is likely that age is an effect modifier for an association for comorbidity and hip-fracture related excess mortality, suggesting that the interaction of comorbidity and hip fracture depends on age-related factors (Knol and VanderWeele, 2012).

We also assessed the effect of specific comorbid conditions (diseases; individual CCI components) on excess mortality. The excess mortality attributable to the most prevalent diseases (malignancy, chronic pulmonary disease, congestive heart failure, diabetes with complications) exceeded the excess mortality of those without that specific disease by 5–10% over the first 4–5 years after a fracture, being essentially similar to that in a CCI score-specific analysis. The only exception was dementia which had the highest and shortest excess risk (up to 20% over 2–3 years) among all conditions. The prevalence of dementia was higher among fracture patients (8%, vs 2% among reference subjects), the patients were older and probably frailer than those without dementia. A higher prevalence of dementia among hip fracture patients than in the general population has been noted before (Yiannopoulou *et al.*, 2012) and the survival of such patients is lower (Scandol, Toson and Close, 2013). We expect this patient group will increase with population aging, and further research is required to alleviate the post-fracture implications of dementia (Chaudhry, Devereaux and Bhandari, 2013).

The conclusions derived from our research are three-fold. First, hip fracture is a strong independent risk factor for death. This result is of clinical importance implying that a substantial proportion of hip-fracture related deaths can be avoided by preventing a fracture and its complications and improving post-fracture rehabilitation and social care. Second, the impact of life-threatening comorbidities on aggregated hip-fracture related excess mortality is likely to be modest, depending on the (low) prevalence of the comorbid conditions. Third, the mortality impact of comorbidities in CCI groups is age and time-dependent: in younger patients, the comorbidities almost doubled the excess risk of death from fracture for over 10 years, in older patients the increment was shorter and

modest. It is likely that age modifies the effect of comorbidities and hip fracture on excess mortality.

Limitations and strengths

We acknowledge the limitations of our study. It is possible that the excess risk of death in our analysis was slightly overestimated due to measurement bias. Our data collection started from 2004, and some subjects with unascertained fractures before 2004 might have been misclassified as incident cases (fracture group) or non-fracture patients (reference group). This misclassification might have resulted in slightly overestimating mortality in both groups. However, as the risk for further hip fracture after previous hip fracture is over 2-fold (Klotzbuecher *et al.*, 2010; Hernlund *et al.*, 2013) and a subsequent fracture is associated with increased mortality risk (Bliuc *et al.*, 2009), the overestimation would have been higher in the fracture group, resulting in a slightly overestimated excess mortality.

We did not assess the impact of hip fracture complications and post-fracture care (such as anesthesia, surgery, or inadequate rehabilitation) on excess mortality, or the causes of death. Thus, we cannot discriminate between hip fracture and its complications. Neither did we assess the impact of other confounding factors such as frailty, social deprivation, behavioral factors (low BMI, smoking, alcohol consumption), previous fragility fracture, and the type of fracture (Ensrud *et al.*, 2007; Hu *et al.*, 2012; Hernlund *et al.*, 2013; Cenzer *et al.*, 2016; Ray *et al.*, 2016; Thorne *et al.*, 2016). Nursing home or facility residence, poor preoperative walking capacity, poor activities of daily living and poor mental state have been identified as strongly predictive factors for the excess mortality (Hu *et al.*, 2012) suggesting that frail and disabled elderly are at higher immediate risk of death after hip fracture (Tosteson *et al.*, 2007; Cenzer *et al.*, 2016). It is possible that additional adjustment for these factors could reduce the hip fracture related excess mortality (Magaziner *et al.*, 1997; Tosteson *et al.*, 2007; Vestergaard, Rejnmark and Mosekilde, 2007; Solbakken *et al.*, 2017), while the impact of CCI-related comorbidities on the excess mortality remains unchanged. We used data from the (administrative) health insurance database that covers the overwhelming majority of the Estonia's population. However, we are not aware of any data documenting the completeness of the database. Finally, we did not account for changes in hip fracture mortality in the population over time.

CCI as a measure of co-morbid conditions has its strengths but also limitations. We used the CCI as a well-accepted comorbidity burden index for adjustment of concomitant diseases (Luise *et al.*, 2008; Radley *et al.*, 2008; Neuhaus *et al.*, 2013; Hindmarsh *et al.*, 2014; Smith *et al.*, 2014; Toson, Harvey and Close, 2015). We chose the CCI because of its adaptability to large population databases using diagnostic codes from the ICD-10 (Hindmarsh *et al.*, 2014). It has also been documented that excess deaths among hip fracture patients can mainly be explained by the conditions predominantly responsible for mortality in the general population, i.e. those represented in the CCI (Melton

et al., 2014). However, the CCI does not allow to account for disease severity (Hindmarsh *et al.*, 2014; Toson, Harvey and Close, 2015). In addition, we know that as a composite index it does not discriminate well between diseases, i.e. it equates the entities. Models incorporating comorbidities as individual variables have performed better in predicting mortality than the weighted index (Toson, Harvey and Close, 2015), and clinicians are more likely to identify and respond to a medical diagnosis than (even a validated) calculated index (Anthony W. Ireland, Kelly and Cumming, 2015). In our analysis, the CCI disease-specific excess mortality patterns were comparable to those of CCI 1–2 and ≥ 3 group specific mortality, with the exception of dementia.

Two potential limitations are related to differential misclassification of comorbidity diagnoses. First, the comorbidity data for both groups were collected at the time of, and for 1 year before, the index date of a hip fracture case. It is possible that some reference subjects did not visit a physician over that period (for example, 81% of publicly insured individuals had a visit to a family physician, and 65% to a specialist in 2015) (Estonian Health Insurance Fund, 2015), whereas all cases were hospitalized for the incident fracture. That might have resulted in underascertainment of comorbidities in the reference group. However, we believe that people with severe life-threatening conditions would have received health care, and including data from hospitalization episodes (including primary and secondary diagnoses) within the 12-months recall period into CCI for individuals in the reference group might mitigate some of this bias. Further, we speculate that potential differential misclassification described above might lead to overestimating the effect of comorbid conditions on mortality and thus support our main finding of hip fracture as a major independent risk factor for death.

Second, the fact that we used an updated version of the CCI could have resulted in measurement bias. Quan et al found that five of the original Charlson conditions were not associated with increased mortality in the general population, and they were removed from the updated score (Quan *et al.*, 2011). Inline with that, Toson et al showed that the updated version was comparable to the older version for predicting 1-year mortality in hip fracture patients (Toson, Harvey and Close, 2015). However, it was recently found that some of the omitted conditions (myocardial infarction, cerebrovascular disease, and peripheral vascular disease) were associated with increased mortality in the hip fracture population (Toson, Harvey and Close, 2015). If this were true, it is possible that using an older version of CCI could have given larger effects on risk adjustment, and we might have potentially underestimated the effect of life-threatening comorbidities on excess risk of death. Further research is needed to identify specific diseases most responsible for the hip-fracture excess mortality.

To our knowledge, this is the first population-based study to estimate the impact of comorbidities on hip-fracture related excess mortality in Eastern Europe. The strength of our analysis lies in the use of a data source with nationwide coverage and complete follow-up (EHIF data). We had a large sample size of a representative population (given the >94% population coverage

of the EHIF), long follow-up, and standardized recording of health events across the period of observation, which avoids problems related to imperfect recall and incomplete records. The large sample size provided a high number of events (deaths) over the long follow-up period even in older age groups to increase the precision of estimates, and the high frequency of observations allowed for assessment of rapid and extensive changes during the first months after fracture. We believe that our results allowing inferences to other hip fracture populations ≥50 years of age.

6.4. Summary of the discussion

To finalize, the study series demonstrates a marked health and economic impact of hip fracture on patients and society. The results serve as a platform for prioritization of hip fracture in health and social policy agenda, draw attention to gaps and inequalities in care, and imply that implementation of fracture prevention programs and optimal post fracture rehabilitation and social care are warranted. The results will also be used in economic evaluations for selecting cost-effective interventions for hip fracture prevention and care. To estimate a societal burden of hip fractures in Estonia, further research is required to estimate the number of prevalent hip fractures, the number of QALYs lost in the population and the total societal cost. This will enable to compare the burden across countries and other conditions and determine future predictions in the light of population aging.

In the light of results, a suggestion was derived for improving a methodology for comorbidity research. Despite a high all-cause mortality, a hip fracture is not included in any common comorbidity index (Charlson *et al.*, 1987; Elixhauser *et al.*, 1998; Klabunde *et al.*, 2000; de Groot *et al.*, 2003). The reasons for non-inclusion remain obscure, but low disease awareness and lack of mortality data at the time of index development could be among the potential reasons. The inclusion of a hip fracture in the indices containing the severest life-threatening conditions will increase the precision of mortality risk estimates in clinical research.

7. CONCLUSIONS

1. The age-standardized hip fracture incidence in Estonian women ≥ 50 years was among the lowest, and the rate in men among the highest in Europe. The increasing number of fractures was a result of population aging.
2. The impact of hip fracture on the quality of life was substantial. After a fracture, the HRQoL was only 7%, i.e., the estimate close to death. The HRQoL before fracture and during the recovery was low in Estonia, and less than half of patients recovered in full.
3. Fracture-related specialty and primary care use was comparable to that in Sweden, but the use of rehabilitation, home nursing, and social care after discharge was low. The shortfall may explain the high use of informal care. The hip fracture related societal cost was >8000 euros per patient, comparable to that for myocardial infarction and stroke.
4. Hip fracture is a strong independent risk factor for death. The aggregated risk of all-cause death at 1 year after fracture was 28%, being 20% or 3–4 times higher than that without fracture. This excess mortality is comparable to that for dementia and cancer. In younger patients (50–79 years), the excess mortality gradually increased over 10 years, suggesting that a fracture may induce a long-term progressive decline in health leading to death. In older patients (≥80 years) the excess risk was immediate, as a fracture may have accelerated the chain of lethal events and bring the death from other conditions forward. The excess mortality in younger patients in Estonia was higher than in the Western countries. A substantial proportion of hip-fracture related deaths could be avoided by preventing a fracture and its complications and improving post-fracture care.
5. In patients with comorbidities, a fracture may accelerate the chain of lethal events and bring the death from other conditions forward. A clear dose response for the association of co-morbid conditions' quantity and excess mortality was observed. Patients with dementia had the highest excess risk of death from hip fracture, probably because of older age (83.2 years) and frailty. However, the impact of comorbidities on aggregated excess mortality was modest, depending on their low prevalence. Therefore, comorbidities may not be the primary target for improving survival after hip fracture.

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8. SUMMARY IN ESTONIAN

Reieluukaela murru tervise- ja majandusmõju Eestis

Reieluukaela murd kui rahvatervise probleem

Reieluukaela murd vanemas eas on üks olulistest rahvatervise probleemidest (Kanis *et al.*, 2013). Reieluukaela murd on enamasti luuhõrenemisest tingitud haprusmurd, mis tekib kukkumisel seisvast asendist ilma olulise traumata (Hernlund *et al.*, 2013). Reieluukaela murruga kaasnevad lühi- ja pikaajalised vaevused, tegevuspiirangud, elukvaliteedi langus ja suur suremus (Teng, Curtis and Saag, 2008). Arenenud maades saab iga kuues üle 50-aastane naine eluea jooksul reieluukaela murru (Kanis *et al.*, 2013) ning sellega seotud haiglaravi kulud on võrreldavad müokardi infarkti või insuldi vastavate ravikuludega (Singer *et al.*, 2015). Kuni 20% haigetest sureb aasta jooksul peale murdu (Abrahamsen and Vestergaard, 2010; Haentjens *et al.*, 2010). Seega ületab reieluukaela murruga haigete ühe aasta suremus üldsuremuse 3–4-kordselt (Abrahamsen *et al.*, 2009; Haentjens *et al.*, 2010) ja on võrreldav suremusega metastaatilise vähi või dementsuse korral (Quan *et al.*, 2011; Todd *et al.*, 2013). Murrueelne elukvaliteet taastub vähem kui pooltel haigetest (Melton, 2003).

Reieluukaela murruga seotud tervisekaotust ≥50-aastastel on hinnatud modelleerimise teel (Ström *et al.*, 2011; Hernlund *et al.*, 2013; Svedbom *et al.*, 2013). Reieluukaela murru esmasjuhtude arvuks Euroopas on hinnatud 615 000 aastas ja murruga haigete koguarvuks 3,3 miljonit. Murruga seotud kogukulu on hinnanguliselt 20 miljardit eurot aastas. Seega on reieluukaela murru kogukulu võrreldav kopsuvähi (19 miljardit), rinnavähi (15 miljardit) (Luengo-Fernandez *et al.*, 2013) ja insuldi (27–64 miljardit) kogukuluga (Gustavsson *et al.*, 2011; DiLuca and Olesen, 2014).

Reieluukaela murru alane haigusteadlikkus on seni piiratud ning riskigruppide määratlemine keeruline (Harvey *et al.*, 2017), samuti on tervisekaotuse hinnangutes palju ebaselget. Esmashaigestumus Euroopa riikides varieerub, kuid erinevuse põhjused ei ole lõpuni selged. Reieluukaela murruga seotud kulud suurenevad, kuid andmed kulude ja tervishoiu- ja sotsiaalteenuste kasutuse kohta on puudulikud (Hernlund *et al.*, 2013). Lisaks esineb Euroopas olulisi erinevusi tervishoiuteenuste ja sotsiaalabi kättesaadavuses ja kasutuses (Hernlund *et al.*, 2013; Svedbom *et al.*, 2013). Kaasuvate haiguste mõju reieluukaela murruga seotud liigsuremusele ei ole lõpuni selge (Abrahamsen *et al.*, 2009).

Eestis esineb hinnanguliselt 1600 reieluukaela esmasmurdu aastas ja murruga haigete üldarv on 7300 (Hernlund *et al.*, 2013; Svedbom *et al.*, 2013). Esimese murrujärgse aasta kogukuluks on hinnanguliselt 5580 eurot haige kohta ja ühiskondlik kogukulu ulatub 15 miljoni euroni (12 eurot inimese kohta) aastas. Eeldatakse kulude 17%-list tõusu järgneva kümnendi jooksul (Hernlund *et al.*, 2013; Svedbom *et al.*, 2013). Samas ei ole olemasolevad epidemioloogilised ja kuluandmed piisavad tervisepoliitilisteks otsusteks. Näiteks esmashaigestumust on hinnatud piirkondliku uuringu (Haviko, Maasalu and Seeder, 1996) ja

Soome vastavate andmete põhjal (Svedbom *et al.*, 2013), suremuse hindamisel on lähtutud Rootsi andmetest (Kanis *et al.*, 2003; Johnell *et al.*, 2004; Borgström *et al.*, 2007), elukvaliteedi hinnangud põhinevad teaduskirjanduse süstemaatilisel ülevaatel (Peasgood *et al.*, 2009). Tervishoiuteenuste kasutus ja kulud on ekstrapoleeritud Soome ja Rootsi uuringutest (Nurmi *et al.*, 2003; Borgström *et al.*, 2006; World Bank, 2008).

Käesolev uurimistöö käsitleb reieluukaela murru tervise- ja majandusmõju Eestis, et võimaldada reieluukaela murruga seotud summaarse tervisekaotuse hindamist ühiskonnas ja prognoosida selle muutusi ajas. Tervisekaotuse hindamine aitab parandada haigusteadlikkust (Kanis *et al.*, 2013; Harvey *et al.*, 2017). Uuringu tulemuste põhjal saab täpsemalt määratleda sihtrühmad reieluukaela murru ja murruga seotud suremuse vähendamiseks, kirjeldada ravi- ja sotsiaalteenuste kasutust ja teha informeeritud tervise- ja sotsiaalpoliitilised otsused. Tulemusi saab kasutada ka reieluukaela murru ennetus- ja ravimeetmete kulutõhususe hindamisel. Teadaolevalt on tegemist esimese tervikliku reieluukaela murru tervise- ja majandusmõju hindamisega Kesk- ja Ida-Euroopas.

Uurimistöö eesmärgid

Doktoritöö üldeesmärk oli reieluukaela murruga seotud tervise- ja majandusmõju hindamine ≥50-aastastel inimestel Eestis 2005–2016 aastal. Alaeesmärkideks oli:

1. Hinnata reieluukaela murru avaldumust (I publikatsioon);
2. Hinnata reieluukaela murruga seotud elukvaliteedi kaotust 18 kuu jooksul pärast murdu (II, V ja VI publikatsioon);
3. Hinnata reieluukaela murruga seotud ressursikasutust ja kogukulu 18 kuu jooksul pärast murdu (II publikatsioon);
4. Hinnata reieluukaela murruga seotud liigsuremust 10 aasta jooksul pärast murdu (III publikatsioon);
5. Hinnata kaasuvate haiguste mõju reieluukaela murru liigsuremusele (IV publikatsioon).

Uurimistöö metoodika

Andmeallikad:

(i) Eesti Haigekassa andmebaas soo, vanuse, diagnooside, tervishoiuteenuste kasutuse ja kulude, ravimikasutuse, surma kohta (kõik alaeesmärgid);
(ii) Reieluukaela murruga haigete standardiseeritud intervjuud sotsiaaldemograafiliste näitajate, elukvaliteedi ja kulude hindamiseks (2. ja 3. alaeesmärk);
(iii) Statistika andmebaas rahvastiku vanuselise ja soolise jaotuse kohta (1., 4. ja 5. alaeesmärk).

Reieluukaela murru avaldumuse hindamiseks kasutati ökoloogilise uuringu meetodit (I publikatsioon). Teostati andmepäring Haigekassa andmebaasist kõigi ≥50-aastaste reieluukaela murruga hospitaliseeritud haigete kohta aastatel 2005–2012. Juhu definitsioon põhines reieluukaela murru diagnoosi koodidel (S72.0-S72.2 põhi- või kaasuva haigusena) Haigekassale esitatud raviarvetel.

Vaadeldava kaheksa aasta (2005–2012) jooksul dokumenteeriti 10704 reieluukaela murru esmasjuhtu. Hinnati tooravaldumust, vanusespetsiifilist ja vanusele standarditud avaldumust, samuti avaldumuse muutust uuringu perioodil.

Reieluukaela murruga seotud elukvaliteedi kaotust ja kogukulu hinnati prospektiivses kohortuuringus kahes Eesti haiglas ravitud patsientidel (II, V ja VI publikatsioon). Mugavusvalimi moodustasid 205 ≥ 50-aastast reieluukaela murruga haiget Tartu Ülikooli Kliinikumi (TÜK) ja Ida-Tallinna Keskhaigla (ITK) traumatoloogia ja ortopeedia osakondadest aastatel 2010–2012. Uuringus hinnati haigete elukvaliteeti, murruga seotud ressursikasutust ja kulu (tervishoiuteenused, sotsiaalabi, lähedaste abi, kaudsed kulud) uuringusse kaasamisel ning kolmel korral 18 kuu jooksul pärast murdu. Nimetatud uuring viidi läbi rahvusvahelise uuringu International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) osana, milles osales 52 haiglat 11-st riigist.

Liigsuremust hinnati rahvastikupõhises retrospektiivses kohortuuringus (III publikatsioon). Võrdlusrühmadeks olid murruga patsiendid (juhud) ning viiterahvastikuks juhtudele vanuse ja soo järgi sobitatud (reieluu murruta) isikud. Kõik andmed pärinesid Haigekassa andmebaasist perioodist 2005–2013. Uurimisgrupi moodustas 8298 esmase reieluukaela murruga haiget ja viiterahvastiku 33191 isikut. Murruhaigete üldsuremust võrreldi viiterahvastiku suremusega kuni 10 aasta jooksul. Kumulatiivset liigsuremust hinnati kohandatuna vanusele ja Charlsoni kaasuvate haiguste uuendatud indeksile (CCI) (Quan *et al.*, 2011) ning kihitatuna soo ja vanuse lõikes. CCI on komposiitindeks, mis koondab suure suremusriskiga haigused. Kaasuvate haiguste mõju liigsuremusele hinnati ka eraldiseisva analüüsiga kihitamise ja kohandamise abil (IV publikatsioon).

Uuringutel oli Tartu Ülikooli inimuuringute eetika komitee luba.

Peamised tulemused ja arutelu

Avaldumus

Vaadeldava kaheksa uuringuaasta (2005–2012) jooksul dokumenteeriti 10704 reieluukaela murru esmasjuhtu, millest 70% esines naistel. Valdav osa naiste murdudest (58%) esines üle 80-aastastel, kuid ligi pooled (43%) meeste murdudest esinesid nooremates vanusrühmades (50–69 aastat). Naiste keskmine vanus murru tekkel oli 79,8 aastat, meestel 71,2 aastat. Murdude koguarv püsis aastate lõikes stabiilsena ja suurenes vaid üle 80-aastaste vanusrühmas.

Avaldumuse toorkordaja naistel (320/100 000/aastas) oli 1,46 korda kõrgem kui meestel (219/100 000/aastas), kuid vanusele standardimisel avaldumuse sooline erinevus kadus (naistel 209, meestel 216/100 000/aastas, riskide suhe 0,97). Alates 2009. aastast oli täheldatav avaldumuse langus naistel. Seega oli murdude arvu suurenemine eakatel ja toorkordajate sooline erinevus tingitud rahvastiku vanuselisest struktuurist ja mitte haigestumuse tõusust. Võrreldes teiste Euroopa riikidega oli avaldumus Eesti naistel madal (võrreldav madalaima avaldumusega Poola ja Rumeeniaga), kuid meestel üks kõrgematest, võrreldav Skandinaavia ja Venemaaga. Naiste madal avaldumus tulenes eeskätt eakate (80+) suhteliselt madalast haigestumusest. Võimalike kaitsvate teguritena eakatel võib välja tuua ülekaalu ja madala suitsetamise levimuse, samuti

madala sotsiaalmajandusliku staatusega seostuva intensiivse füüsilise töö elu jooksul. Avaldumuse languse, mida on viimasel kümnendil täheldatud enamuses arenenud riikides, võimalike põhjustena võib välja tuua kukkumisriski vähenemise seoses terviseseisundi üldise paranemise ja linnastumisega, samuti kehakaalu tõusu ning paranenud diagnostika ja ravi võimalused. Meeste kõrge avaldumuse põhjuseks nooremates vanusrühmades (50–69 aastat) võivad sarnaselt Venemaaga olla alkoholi liigtarbimisega seotud traumad.

Tervisega seotud elukvaliteet, ressursikasutus ja kulud

Uuringu valimi moodustas 205 haiget (27% kõigist uuringuperioodil TÜK-i ja ITK-sse hospitaliseeritud reieluukaela murruga haigetest). Elukvaliteedi hinnang enne murdu oli 0,67, mis oli võrreldes kõigi osalevate riikide keskmisega (0,77) suhteliselt madal. Murrujärgne elukvaliteet oli ülimadal (0,07) ehk lähedane surmale. Taastumine oli Eestis aeglasem kui võrdlusriikides ning murrueelse elukvaliteedi saavutas vaid alla poolte uuritavatest. Uuringus leidis kinnitust, et reieluukaela murru mõju elukvaliteedile on suur.

Arvestades võimalikku selektsiooninihet võib tegelik elukvaliteet reieluukaela murru korral olla veelgi madalam. Võrdlusel uuringusse mittekaasatud haigetega selgus, et uuritavad olid 1,7 aastat nooremad ja tervemad (CCI uuritavatel 1,1, uuringusse mittekaasatuil 1,5; 18 kuu suremusmäär vastavalt 53/1000 (95% CI 32–115) ja 90/1000 (95% CI 60–130)). Seega olid uuringusse kaasatud haiged keskmisest nooremad ja tervemad, kelle elukvaliteet võis olla parem kui keskmisel haiglates ravitud reieluukaela murruga patsiendil.

Tervishoiu- ja sotsiaalabi teenuste analüüsil selgus, et haiged viibisid aktiivravil traumatoloogia ja ortopeedia osakonnas keskmiselt 15 päeva ning ligi pooled suunati edasi õendusabi osakonda. Eriarsti- ja perearsti teenuse kasutus peale murdu oli võrreldav Rootsiga. Aktiivravile järgnenud taastusravi, koduõenduse ja sotsiaalabi kasutus oli aga väga vähene ning sellega kooskõlas elukvaliteedi aeglane taastumine ja piiratud toimetulek. Esimese nelja murrujärgse kuu jooksul sai vaid 8% haigetest statsionaarset ja 1% ambulatoorset taastusravi, 4% kasutas koduõendusteenust ning sotsiaaltöötaja külastas vaid kolme haiget. Hooldekodusse suunati 2 haiget. Üle poole (53%) haigetest kasutas analgeetikume ja mittesteroidseid põletikuvastaseid aineid ning vaid 8% bisfosfonaate. Järgnevate kuude jooksul raviteenuste kasutus vähenes ja sotsiaalteenuste kasutus oluliselt ei muutunud. Minimaalset taastusravi, õendus- ja sotsiaalabi kompenseeris lähedaste abi sage kasutus: 83% kasutas lähedaste abi keskmiselt 2 tundi päevas kuni 18 kuu jooksul. Kulude hindamisel selgus, et 18 kuu kumulatiivne kogukulu oli 8146 eurot haige kohta, kusjuures poole (56%) moodustas aktiivravi ja 33% lähedaste abi, sotsiaalabi osakaal oli vaid 5%. Võimalik, et uuringusse mittekaasatud haigete murrujärgne ressursikasutus oli suurem. Uuringust selgus ka suhteliselt suur (8%) kaudse kulu osakaal, seda vaatamata haigete kõrgele vanusele.

Liigsuremus

Uurimisgrupi moodustas 8298 esmase reieluukaela murruga haiget ja viiterahvastiku 33191 vanusele ja soole sobitatud ilma eelneva murruta isikut. Reieluukaela murruga patsientidel oli rohkem kaasuvaid haigusi, kuigi erinevus ei olnud suur: 39%-l uuritavatest esines vähemalt üks eelnev raske haigus ja grupi keskmine CCI oli 0,94. Võrdlusgrupi vastavad näitajad olid 30% ja 0,66. Vanusele ja CCI-le kohandatud 10 aasta üldsuremus oli uurimisgrupis 77.6% (95% CI 76.7–78.8%) ja viiterahvastikus 56.5% (95% CI 56.0–57.3%), liigsuremus seega 21.1% (95% CI 20.0–22.5%). 27% ehk iga neljas surm murruhaigete grupis oli tingitud murrust. Liigsuremus ilmnes koheselt pärast murdu, olles 18.9% (95% CI 18.3–19.5) juba kolm kuud pärast murdu ning püsis stabiilsena järgneva 10 aasta jooksul. Kuigi naised olid vanemad kui mehed (80,4 vs 72,2 aastat) ja nende üldsuremus oli suurem, oli liigsuremus suurem meestel. Meeste suurema liigriski põhjused ei ole seni täiesti selged. Noorematel haigetel (50–69 aastat) suurenes liigsuremus järk-järgult 10 aasta jooksul, seega võib reieluukaela murd põhjustada pikaajalise progresseeruva surmaga lõppeva tervisekaotuse. Vanematel haigetel (≥ 80 aastat) esines liigsuremus aga vahetult murru järgselt näidates, et murd kiirendab oluliselt surma saabumist. Liigsuremus nooremates vanusrühmades oli Eestis ligikaudu 10% suurem kui lääneriikides, millel võib olla seos ebapiisava õendus- ja sotsiaalabiga. Uuringutulemused näitavad, et reieluukaela murd on oluline iseseisev suremuse riskifaktor ning suur osa murruga seotud liigsuremusest võiks olla välditav ennetuse, tüsistuste vältimise ja piisava murrujärgse hooldusega.

Kaasuvate haiguste mõju liigsuremusele

Sarnaselt kõrge vanusega patsientidele kiirendas murd surma saabumist ka raskete kaasuvate haigustega patsientidel. Kaasuvate haiguste ja liigsuremuse vahel esines selge annus-vastuse seos: ilma kaasuvate haigusteta (CCI 0 grupp) murruga seotud ühe aasta liigsuremus oli 17.1% (95% CI 16.5–17.8), CCI 1–2 grupis 25.8% (95% CI 24.6–27.0%) ja CCI ≥3 grupis 30.3% (95% CI 28.3–32.2%). Enamuse enamlevinud haiguste (kasvaja, kroonilise kopsuhaiguse, südamepuudulikkuse) korral oli liigsuremus 5–10% kõrgem kui ilma vastava haiguseta, kuid dementsusega haigetel oli erinevus 18%, tõenäoliselt haigete kõrgema vanuse (83,2 aastat) ja hapruse (kaalukaotus, nõrkus, aeglane kõnd, madal energiatase ja füüsiline tegevus) tõttu. Samas oli kaasuvate haiguste levimus suhteliselt madal ja gruppidevaheline erinevus väike, mistõttu CCI kohandamisel selgus, et vaid 8% reieluukaela murruga seotud liigsurmadest oli tingitud murrueelsetest kaasuvatest haigustest. Seega on võimalik, et kaasuvate haiguste mõju reieluukaela murru liigsuremusele on väike ja ei oma liigsuremuse vähendamisel kriitilist rolli.

Järeldused

1. Vanusele standarditud reieluukaela murru avaldumus ≥ 50-aastastel Eesti naistel oli suhteliselt madal, kuid meestel üks Euroopa kõrgematest. Murdude arvu suurenemine oli tingitud rahvastiku vananemisest. Sarnaselt paljudele Euroopa riikidele esines ka Eestis avaldumuse langus naistel.
2. Reieluukaela murru mõju patsiendi elukvaliteedile oli suur. Tervisega seotud elukvaliteet vahetult peale murdu oli vaid 7% ehk lähedane surmale. Elukvaliteedi taastumine oli aeglasem kui võrdlusriikides ja vähem kui pooled patsiendid taastusid täielikult.
3. Reieluukaela murru järgse eriarstiabi ja perearsti teenuse kasutus oli võrreldav Rootsiga, kuid taastusravi, koduõenduse ja sotsiaalabi kasutus oli madal. Lähedaste abi, mida kasutas üle 80% haigetest, võis osaliselt kompenseerida ebapiisavat õendus- ja sotsiaalabi. Reieluukaela murru kogukulu oli >8000 eurot haige kohta, mis on teaduskirjanduse andmetel võrreldav infarkti ja insuldi kogukuluga.
4. Reieluukaela murd on oluline iseseisev suremuse riskifaktor. Keskmine murrujärgne üldsuremus ühe aasta jooksul oli 28% ehk 20% võrra (3–4 korda) kõrgem kui ilma murruta isikuil. Selline liigsuremus on võrreldav dementsuse või metastaatilise vähi korral esinevaga. Liigsuremus nooremates vanusrühmades (50–69 aastat) oli Eestis suurem kui lääneriikides. Liigsuremuse vähendamine saab olla võimalik murru ja selle tüsistuste vältimise ning piisava murrujärgse abiga.
5. Kaasuvate haiguste ja liigsuremuse vahel esines selge annus-vastuse seos. Murd kiirendas surma saabumist kaasuvate haigustega patsientidel. Dementsusega haigetel esines suurim murruga seotud liigsuremus, ilmselt kõrgema vanuse ja hapruse tõttu. Samas oli kaasuvate haiguste levimus suhteliselt väike ja nende mõju üldsuremusele mõõdukas: ainult 8% liigsuremusest oli tingitud kaasuvatest haigustest. Seega on kaasuvate haiguste mõju reieluukaela murru liigsuremusele väike ja ei oma liigsuremuse vähendamisel kriitilist rolli.

ACKNOWLEDGEMENTS

The studies presented in the thesis were carried out at the Institute of Family Medicine and Public Health, University of Tartu, and were a teamwork with the contribution of many persons whom I am grateful to.

I wish to express my sincere gratitude to Professor Anneli Uusküla for continuously guiding and coaching me throughout the years of my studies and research. I am very grateful to Professor Riina Kallikorm and Professor Margus Lember for the introduction to the research topic and continuous guidance throughout the studies. I am also grateful that I was given a latitude to work and decide within a practical domain.

I am thankful to my colleagues and co-authors Sigrid Vorobjov, Heti Pisarev, and Mait Raag for the invaluable methodological guidance and contribution to the studies conducted for this thesis. I would also like to acknowledge the research team members in studies conducted for this thesis: Fredrik Borgström and Axel Svedbom from Karolinska Institute, and Professor John Kanis from the WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield. I would also like to thank Liz Wager and Allison Krug for editing my English.

The studies included in this thesis were financially supported by the Estonian Science Foundation [grant number 9368], the Estonian Ministry of Education and Research [grant numbers SF0180060s09], and the institutional research grants [TARTH15017I, IUT 34–17, IUT 2–8].

PUBLICATIONS

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Teadustöö

Peamised uurimisvaldkonnad:

- Osteoporoosi ja reieluukaela murruga seotud haiguskoormus
- Tervisetehnoloogiate hindamine ja majandusanalüüs

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