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The interrelationship of multimorbidity and COPD: the impact on health care resources and the analysis of the possibility of change

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Dauginių ligų ir LOPL sąsajos: įtaka sveikatos priežiūrai ir pokyčio galimybės analizė

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ABBREVIATIONS

ACIC – Assessment of Chronic Illness Care questionnaire
CHRODIS – The European Union Joint Action on Chronic Diseases and Promoting Healthy Ageing Across the Life Cycle co-funded by the European Union
CHRODIS PLUS – The European Union Joint Action on Implementing Good Practices for Chronic Diseases co-funded by the European Union
CI – confidence interval
COPD – chronic obstructive pulmonary disease
CVD – cardiovascular diseases
3D – three-dimensional
EFA – exploratory factor analysis
EQ VAS: EuroQol-visual analogue scales for recording the patient's self-rated health on a vertical visual analogue scale
EQ-5D: EuroQol 5D questionnaire - a standardised instrument developed by the EuroQol Group as a measure of health-related quality of life
EU – European Union
EUR - euros
GLM – generalised linear models
HR – hazards ratio
IMCM – integrated multimorbidity care model
KMO - Kaiser-Meyer-Olkin criterion
MM – multimorbidity, multimorbid
N – number
NCD – non-communicable chronic diseases
NICE – National Institute for Health and Care Excellence (United Kingdom)
MULTIPAP – Intervention for improving Drug Prescription in Primary Care Patients with Multimorbidity and Polypharmacy
OR – odds ratio
PACIC+ – the Patient Assessment of Care for Chronic Conditions+
SD – standard deviation
SWOT – strengths, weaknesses, opportunities, threats
US – United States of America
VULSK or Vilnius site – Vilnius University Hospital Santaros Klinikos
WHO – World Health Organization

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Paper II. Puteikis, Kristijonas; Mameniškienė, Rūta; **Jurevičienė, Elena**. Neurological and psychiatric comorbidities in chronic obstructive pulmonary disease // International journal of chronic obstructive pulmonary disease. Auckland: Dove Medical Press Ltd. ISSN 1178-2005. 2021, vol. 16, p. 553-562. DOI: 10.2147/COPD.S290363.

Paper III. Jurevičienė, Elena; Onder, Graziano; Visockienė, Žydrūnė; Puronaitė, Roma; Petrikonytė, Dovilė; Gargalskaitė, Urtė; Kasiulevičius, Vytautas; Navickas, Rokas. Does multimorbidity still remain a matter of the elderly: Lithuanian national data analysis // Health policy: Elsevier Ireland Ltd. ISSN 0168-8510. eISSN 1872-6054. 2018, Vol. 122, no 6, p. 681-686. DOI: 10.1016/j.healthpol.2018.03.003.

Paper IV. Nedzinskienė, Laura; **Jurevičienė, Elena**; Visockienė, Žydrūnė; Ulytė, Agnė; Puronaitė, Roma; Kasiulevičius, Vytautas; Kazėnaitė, Edita; Burneikaitė, Greta; Navickas, Rokas. Structure and distribution of health care cost across age groups of patients with multimorbidity in Lithuania // International journal of environmental research and public health. Basel: MDPI. ISSN 1661-7827. eISSN 1660-4601. 2021, vol. 18, no. 5, art. no. 2767, p. [1-13]. DOI: 10.3390/ijerph18052767

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1. INTRODUCTION

The number of people having non-communicable diseases (NCD) has recently increased dramatically, primarily due to the ageing population. It means more years living with disability and multimorbidity, impaired physical function, lower quality of life, higher mortality and increasing utilization of limited health care resources [1]–[5]. With increasing life expectancy, the prevalence of multimorbidity (MM), defined as two or more concurrent chronic diseases, is estimated to range from 13% to 95%, depending on the specific age and population group [5], and the proportion is higher in older populations [6], [7]. MM affects patients and their families, as it is associated with lower quality of life, greater disability risk, and premature death of patients [6]. It reduces quality of life of patients' family members and caregivers and is also challenging for overworked health care workers and places a financial burden on health and social care systems [7].

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent chronic diseases, causing high morbidity and mortality in the adult population [8]–[11]. Both death rates and the prevalence of COPD steeply increase with age. More than three million people died from COPD worldwide in 2015, an increase of 11.6% compared with 1990, despite a decrease in the age-standardised rate of 41.9% [12]. However, COPD remains a significant contributor to the disease burden globally when measured in disability-adjusted life-years [13]. Patients suffering from COPD are more likely to be diagnosed with various comorbidities, such as allergic, cardiovascular diseases (CVD) or cerebrovascular diseases, and different neurological or psychiatric conditions [14]–[18]. Therefore, COPD can lead to high medical expenses and challenges in providing multidisciplinary care [19].

Most studies exploring comorbidities in COPD include heterogeneous disorder groups, and therefore broad patterns of disease clustering are reported. Still, the clustering of the comorbidities in COPD patients remains under-investigated [20], [21]. Varying methodologies in defining the inclusion criteria, databases used, differences in clustering methodologies also lead to mixed published outcomes. Other MM clusters and their prevalence and impact on mortality could be helpful when planning health care interventions targeting patients with the most prevalent chronic obstructive airway diseases and multiple chronic conditions [21]–[27].

It is already known that psychiatric disorders, impaired cognition, poor sleep and an increased risk of stroke are relevant issues in COPD patients [28]–[34]. However, it is not clear whether different neurological and psychiatric

comorbidities tend to manifest together and what patterns emerge among individuals with COPD. This information could be valuable for neurologists and psychiatrists when providing medical services to patients with COPD.

It is well-known that the proportion of patients with more than one chronic condition increases with age, hitting 85% in over 85-year-olds [2]. However, many of the processes leading to MM starts much earlier. Although MM association with age has been previously reported, limited data are available about its distribution across different age groups. Age group under 45 is usually excluded from MM studies, therefore, this group is extremely under-investigated [35]–[37].

There is well-established evidence that health care costs are associated with increasing age. Some studies argue that proximity to death is a more critical determinant of health expenditure than ageing alone. Yet, there is ample evidence in the literature of a positive association between MM and health care costs [38], [39]. However, a comprehensive assessment of health care costs in different age groups and its association to MM complexity in patients with MM in Lithuania is still lacking.

MM patients can be complex, particularly because they are more likely to have problems with self-care, mobility, and daily functioning than patients with one chronic disease and cognitive impairment and frailty [40]. This often results in more challenging health care. It is clear that the paradigm of "one patient and one disease" no longer fits the medical necessities and needs of most patients, and a more holistic, patient-centred view needs to be developed [2], [41]–[43]. Many health care systems still focus on a traditional disease-oriented approach. Consequently, MM patients frequently experience fragmented care [11], [44] and receive complex drug regimens and polypharmacy, which increase the risk of inappropriate prescribing, adverse drug reactions, and poor medication adherence.

Recently, large real-world data sets from different sources have become the key target for investigations in health care. Medicine now aims to tailor, adjust, and personalise health care to individuals' and populations' specific characteristics and needs [45].

Several interventions and models of care for MM patients have been developed during the past years to address this problem [46]–[49]. However, most of the available models have been developed within clinical trials and have not been implemented in real-life conditions or specifically focused on health care aspects without considering other relevant dimensions such as social and community resources, therefore not providing comprehensive frameworks adaptable to different health care settings.

As regards the implementation of NCD policies, Lithuania with a 74% rate of implementation is among 20 countries reporting the highest rates. The majority of implemented policies include clinical guidelines, graphic warnings on tobacco packaging, and NCD risk factor surveys [50]. The real-life implementation of care management programmes for MM patients is still lacking. In 2016 a systematic review [51] found only 19 publications in the scientific literature that assessed integrated care models for MM, and only one of these was from Europe. Palmer et al. [52] highlighted that the applicability of the integrated multimorbidity care model (IMCM), developed by The European Union (EU) Joint Action on chronic diseases and promoting healthy ageing across the life cycle in 2014-2016 (CHRODIS), will depend on the country's type of health care system and that the guidelines should be interpreted and applied according to the specific setting.

This thesis is based on six published research articles. Its overall aim was to investigate the interrelationship of COPD, MM and other factors proposing the implementation of IMCM as a potential solution to increase the quality of care. Paper I analyses the prevalence and clustering of COPD comorbidities, and the impact of clusters on all-cause hospitalisations. Paper II focuses on neurologic and psychiatric comorbidities in COPD examining gender and age differences and grouping of the illnesses. Paper III identifies age breakpoints for the occurrence of multiple chronic diseases, increased hospitalisations and higher utilisation of reimbursed medications. Paper IV investigates the distribution, change and interrelationship of health care costs in MM. Paper V describes the country-adjusted methodology for implementing the Integrated Multimorbidity Care Model (IMCM) developed during the EU Joint Action CHRODIS. This thesis focuses on implementation methods adjusted to the primary health care unit in Vilnius University Hospital Santaros Klinikos (VULSK). Paper VI reveals the immediate results of IMCM implementation piloted in five centres in Italy, Lithuania, and Spain during the EU Joint Action on implementing good practices for chronic diseases in 2017-2020 (CHRODIS-PLUS). The thesis aimed to present the immediate impact of IMCM on healthcare quality at VULSK Family Medicine Centre.

2. LITERATURE REVIEW

2.1 Multimorbidity

Health care systems face the challenge of the population ageing and an increasing number of NCD per patient. MM meaning a co-occurrence of two or more chronic diseases in the same individual at the same period has become common in older adults in high-income countries. The increased prevalence of MM worldwide leads to the high utilisation of limited health care resources, lower quality of life, and higher mortality [3], [4], [53]–[57]. MM has a high prevalence, especially in older individuals, where it affects more than 60% of people aged 65 or over [1], [5].

CVD, cancer, diabetes mellitus, and dementia are the most common chronic diseases among older adults [58], [59]. MM commonly includes chronic progressive cardiopulmonary and metabolic diseases, such as heart failure, atrial fibrillation, stroke, diabetes, renal failure, osteoarthritis, and COPD, which involve organs that play a crucial role in providing the body with oxygen and nutrients. Some of them share common risk factors such as cigarette smoking and have similar underlying mechanisms, including low-grade inflammation, hypercoagulability, and some degree of endothelial dysfunction [60], [61]. Many clinically relevant diagnoses need to be considered, particularly as there is a large overlap of symptoms in these diseases.

Multiple conditions themselves influence each other, and their treatments may interact. Also, some interactions between the conditions and treatment may occur [62]. The most frequent methods used for determining MM patterns are hierarchical cluster analysis (HCA) and exploratory factor analysis (EFA). The HCA clusters tend to contain diagnoses similar to each other, but are dissimilar from those in other clusters; no diagnosis can be included in more than one cluster. In contrast, the EFA is primarily used for testing hypothesised relationships between observed measures and allows the inclusion of any diagnosis in multiple factors as they can present significant correlations with more than one factor [63], [64].

2.2 COPD, comorbidities and multimorbidity

COPD is one of the most frequent chronic respiratory conditions and a leading cause of death worldwide [65], [66]. Its prevalence, mortality and associated burden have been increasing throughout the years when adjusted for population growth and ageing.

COPD is characterised not only by airflow limitation and lung parenchyma destruction, but also have systemic manifestations. Smoking, hypoxia, and systemic inflammation are discussed as the main factors influencing the interactions between COPD and comorbidities [67]–[72]. Genetic risk factors, accelerated ageing, and gender differences are important contributors to key features of the individual's disease pathology in COPD [73]. Changes in immune systems with ageing may also be associated with COPD pathogenesis [73]–[75]. The ageing lung is characterised by several physiological and structural changes, including declining lung function, decreased mucociliary clearance, decreased antioxidant levels, senile emphysema and altered extracellular matrix proteins [74]. Disturbance of extracellular matrix can have important consequences leading to lung tissue remodelling [73], [76]. Anti-ageing molecules also are reduced in diseases of accelerated ageing, including COPD, atherosclerosis, cardiac failure, type 2 diabetes, metabolic syndrome, osteoporosis, chronic kidney disease and Alzheimer's disease. The same microribonucleinic acids that have been implicated in cellular senescence are found to be abnormal in atherosclerosis, Alzheimer's disease, diabetes, and COPD. Epigenetic changes in methylation and acetylation of desoxyribonucleinic acids and histone proteins may also have an impact on COPD and comorbidities [74], [77], [78].

MM is common in COPD patients, increasing with age and low socioeconomic status [20], [21], [56], [74]. Many COPD patients have more than two comorbidities. Therefore, MM occurs in many of them. Addressing the most prevalent chronic diseases may not necessarily address those that impact essential outcomes [20], [22], [23]. Comorbidities not only increase the burden that people with COPD suffer, but also decrease their quality of life [79]. COPD should be considered as the pulmonary component of MM [80].

The presence of COPD itself, as well as other comorbidities themselves, contribute to poor health outcomes in COPD patients [21], [81]–[86]. Reported comorbidities of COPD patients include a variety of chronic and acute conditions. The studies of COPD patients have reported a higher risk of myocardial infarction, congestive heart failure, metabolic syndrome, hypertension, lung cancer, depression, other psychiatric disorders, chronic kidney diseases, osteoporosis, and diabetes mellitus [81], [85]–[90]. Psychiatric disorders impaired cognition, poor sleep, and an increased risk of stroke are relevant issues among patients with COPD [14], [17], [91]–[97].

Controlled studies provide information about the specific neurological or psychiatric risks that patients with COPD face. However, the interpretation of

reports addressing the increased prevalence of individual comorbidities is often limited because of methodological issues [98]. Non-identical definitions of COPD, variability in selected patient samples, data sources, and measured outcomes render very different comorbidity prevalence results. As current findings indicate that comorbidities in COPD tend to cluster in discrete groups, it might be thus more beneficial to examine MM patterns among patients with COPD rather than the risks of the discrete comorbidities themselves [99]–[101]. A similar approach has already led to the identifying different clinical patterns of COPD [102]–[106]. Outlining the comorbidity profiles in patients with COPD could help acknowledge the additional health conditions present in these individuals. This could improve the personalisation of care and facilitate a multidisciplinary approach to treatment protocols [107].

2.3 Age-breaking points and multimorbidity

MM has become recognised as the most common medical status [108]. A focus on one disease in one patient no longer fits the medical exigences and needs of most patients, thus a more comprehensive, patient-centred view needs to be developed [2], [41]–[43].

According to a study by the University of Sherbrooke (Canada) [109], nearly half of the patients between 45 and 64 years of age have five or more chronic diseases. The prevalence of MM in this age group is almost 30% higher than in patients under 45. A more recent Sauver et al. study [110] investigated more than 100 000 patients and showed that the prevalence of two or three diseases in the same individual increases rapidly mostly at 40-45 years of age. These and other recent studies suggest that the number of people who developed MM before the age of 65 was more than four times greater than the number of people who developed MM after 65 [110]. MM develops much earlier nowadays, although data on age breaking points when MM increase steeply are lacking [111].

The expenditures associated with managing multiple chronic illnesses are overwhelming [110], growing with age [112] and are higher compared to patients with one chronic disease [35], [36], [39], [112], [113]. Zulman et al. [57] showed a statistically significant positive association between MM and health care costs. In contrast, Hopman et al. [113] emphasised that extensive health care utilisation is related not only to the number and types of chronic conditions, but also to patient‘s age and income.

A study by Navickas et al. [59] in Lithuania showed a significant increase in the prevalence of MM in the adult population ranging from less than one percent at the age of 18-24 to more than sixty percent at the age of 85 years and older. Higher usage of health care resources was also demonstrated in patients with two or more chronic illnesses than in single-disease subjects [112].

2.4 The costs of multimorbidity

With all scientific advances and increasing economic welfare, most people in developed countries live longer, but the costs are high. The Health Profile for England 2018 [114] report summarises the trends of longer life while also increasing the number of years living with MM and disability. The trend projects that children under five will be outnumbered by those over 65 globally. With increasing life expectancy, the prevalence of MM is also rising, and it is estimated to range from 13% to 95% depending on the specific age and population group [115], and the proportion is higher in older populations [116], [117]. Due to the progressive increase in the proportion of older adults, health care systems face severe organisational and financial challenges [118], [119]. CVD, diabetes mellitus, cancer and dementia are the most common chronic diseases among older adults [58], leading to impaired physical function, dependence, high care costs, and shorter survival [114]. There is well-established evidence that health care costs are associated with increasing age. Some studies argue that proximity to death is a more important determinant of health expenditure than ageing alone. However, there is ample evidence in the literature of a positive association between MM and health care costs [38], [39], [120]. Costs significantly increase with each additional chronic disease due to the high need for physicians, hospitals, and social services. Older adults with MM use significantly more prescription medications and have higher expenditures related to them [39].

The costs of MM were calculated in several patient cohorts in Switzerland [35], Germany [121], Taiwan [122], and the United States (US) [57], [123], but not in nationwide studies. Analyses showed disproportionately higher direct costs for health care services and indirect costs of truancies, and reduced workforce participation [38], [123]. Only one in five US patients has multiple chronic diseases; however, but they account for 78% of health expenditure [57]. The German study [121] of up to 2000 patients aged over 72 was based on patient-reported interviews and showed that every other disease increases health care costs. The Swiss study [35] of more than 250.000 patients aged 65

and more revealed 5.5 times higher costs for MM patients; each additional chronic disease was associated with an increase of 3.2 outpatient consultations and increased costs by 33%. MM patients were 5.6 times more likely to be hospitalised, requiring more nursing services. Based on data from the Taiwan Health Insurance Database, a five-year study of up to one million patients by Kuo et al. [122] also confirmed higher health care costs of MM. They revealed a strong association of MM with lower socioeconomic status. Therefore, patients with MM constitute a target population for which prevention could result in the most-significant savings.

The health care system in Lithuania is based on compulsory social health insurance, financed by salary contributions paid by employers and employees to the National Health Insurance Fund (NHIF). State funds cover medical services such as primary and secondary care, hospitalisation, prescriptions, rehabilitation and services during pregnancy and childbirth. Navickas et al. [59] showed a steep rise of MM at the age of 45–55 years in the adult population in Lithuania. The identification of the earliest age-breaking points might also be valuable in looking for the targets for intervention [124].

2.5 Interventions and models of care for patients with multimorbidity

Several interventions and models of care for patients with MM have been developed recently.

The patient-centred 3D approach [46] developed by Salisbury et al. focuses on patients' quality of life and promotes self-management towards agreed goals. The method has been developed based on health, depression, and drugs. The randomised clinical trial lasted seven months. More than 1,500 patients were included, but the primary outcome of improving patients' quality of life was not reached, possibly due to the short duration.

The Ariadne principles [47] were developed during a multistage feedback process using a practical case example and designed for primary care practice. They were focused on realistic treatment goals, based on holistic assessment, repeated re-assessment, and patients' preferences.

The MULTIPAP intervention [48] was a cluster-randomised clinical trial implementing the Ariadne principles in a population of patients with MM and polypharmacy aged 65-74 in Spain. The sample size was more than 500 patients. They used e-training for general practitioners and patient-centred interviews. More than a hundred general practitioners were trained. The intervention improved medication appropriateness, but the difference in the quality of life was not significant [125].

The NICE guidelines for the clinical management of MM [49] were developed in the United Kingdom seeking to reduce polypharmacy, multiple appointments and unplanned care. The guidelines describe how to identify patients eligible for MM management, frailty assessment, management of risk factors, evaluation of risks and benefits, etc. Recommendations for establishing patients' goals and priorities, reviewing treatments, and different management approaches are also provided.

The CHRODIS project [126] developed the IMCM, based on the Chronic Care Model [127] and the Innovative Care for Chronic Conditions Model [128]. The IMCM aims to overcome the care fragmentation and focuses on several limitations currently faced in treating MM patients mostly due to a lack of integration between primary and hospital care services as well as between health care professionals from different specialities. Although health care professionals were not trained to handle patients with MM, they are used to manage single chronic diseases by following official clinical guidelines for specific conditions. Their experience in patient-centred care or shared-decision making that takes the patient's preferences, needs, and expectations into account also might be insufficient.

The IMCM includes sixteen components across five domains (i.e., care delivery, decision and self-management support, technology, and community/social resources) [51], [52]. This model was developed not as ready-made for implementation, but to serve as a flexible model to be adapted to national or local peculiarities so that each implementing site can select and assess which dimension(s) to implement and how. The potential applicability of the IMCM has been already assessed through a theoretical case study of an older adult with diabetes and mental health diseases showing a potential [129].

This initiative continued with CHRODIS-PLUS to pilot the implementation of the IMCM based on the common methodology in different health care settings in Europe (Italy, Lithuania and Spain) [130]. The impact of the IMCM pilot implementation was assessed and local adaptations of the model based on the results obtained at each pilot site were provided. For this, the perspectives of the patient and the health system stakeholders regarding the quality of provided care were agreed upon as key common indicators.

3. THE AIM AND OBJECTIVES OF THE STUDY

The thesis is part of international MM research started in 2014 within the framework of the European projects CHRODIS and CHRODIS PLUS and is focused on Lithuanian data.

The study aimed:

- to analyse the prevalence of COPD comorbidities, the interrelationship between MM, COPD and other factors, and assess the impact of MM on all-cause hospitalisations and health care costs;
- to adapt, implement and evaluate the IMCM in a Lithuanian primary health care institution.

The objectives of the thesis were:
1-To investigate the prevalence of COPD comorbidities (Papers I-II).
2-To evaluate MM patterns (clustering) and their interrelationship with COPD (Papers I-II).
3-To determine the impact of MM clusters on hospitalisations (Paper I).
4-To define the age breakpoints for the occurrence of MM. (Paper III).
5-To analyse the interrelationship between multiple chronic conditions, hospitalisations and heavy medication usage (Paper III).
6-To explore changes in the structure of health care costs in patients with multiple chronic diseases (including COPD). (Paper IV).
7-To elaborate country-adjusted methodology for implementing the IMCM, developed by the EU CHRODIS project (Paper V).
8-To implement the IMCM in the Family Medicine Centre of VULSK and assess the primary impact of the implementation on the quality of health care (Paper VI).

3.1. Scientific novelty and practical value of the thesis

This doctoral research, which resulted in six published papers, is the first complex study on MM patterns in Lithuania, focusing on COPD. It was based on real-life data from the national database of the National Health Insurance Fund (NHIF). To our knowledge, it is the first nation-wide study in Europe analysing the interrelationship between multiple chronic diseases, the impact of ageing and the utilisation of health care resources looking for better pathways for patients suffering from COPD and MM. Earlier studies mostly covered a few regions of the country or were focused only on some parts of the scope of this research.

To reduce the increasing burden of COPD, improved and personalised treatment strategies are needed. According to the statement of the Forum of International Respiratory Societies in the second edition of the Global Impact of Respiratory Diseases, research should increase the understanding of the interactions of risk factors and comorbidities tackling to affect the severity of the disease and management of COPD in the context of MM, such as sleep apnoea, cardiovascular disease, depression, osteoporosis, diabetes, lung cancer, ageing and frailty [99], [100]. The knowledge of interactions among chronic diseases and holistic patient management is essential. This study has increased the understanding of the interrelationship among major chronic conditions and provided practical recommendations for managing MM.

Overhelming the lack of comprehensive assessments of health care costs in different age groups and their association with MM complexity in Lithuania, this research provided the most important targets for the intervention to slow down the growth of expenditures for health care.

The IMCM developed during the European Joint Action CHRODIS (2014-2017) required adjustment to the Lithuanian health care system and the pilot implementation of the model was foreseen during the European Joint Action CHRODIS PLUS [126]. There were no management programmes for MM implemented in Lithuania and the European experience in Europe was also too limited. With the support of the international team, the country-adjusted methodology was developed, the first pilot IMCM was implemented in a primary health care setting, and the primary impact of the intervention was evaluated.

4. RESEARCH DESIGN AND METHODS

4.1. Ethical approval

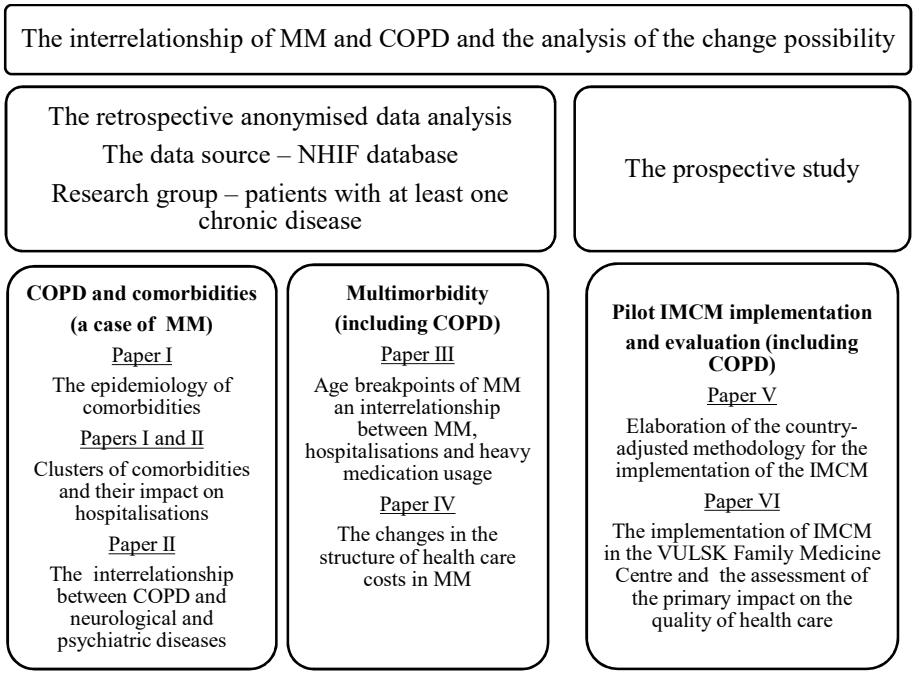
The study was approved by the Vilnius Regional Ethics Committee for Biomedical Research (protocol code: LNLP-1, date of approval: 31 March 2020) for Papers I, II and IV and by the Lithuanian Ethics Committee for Biomedical Research (protocol code: POL 400, date of approval: 1 August 2018) for Paper VI.

Before the adoption of the general data protection regulation (25 May 2018), ethical approval for anonymised generalised data analysis was not required (Paper III). Paper V does not contain any information requiring ethical approval.

4.2. Study design and data sources

The thesis was based on two parallel studies: the retrospective analysis of the diseased Lithuanian population and the implementation of a health care management model for MM patients. Figure 1 presents the general research scheme.

The data of the retrospective study were obtained from the NHIF database as a part of a database of the CHRODIS project [126].



COPD – chronic obstructive pulmonary disease, MM – multimorbidity, NHIF – the National Health Insurance Fund

Figure 1. The general research scheme.

The Lithuanian national health care system relies on compulsory health insurance and seeks to provide universal access for all country's residents. The NHIF database encompasses about 98% of inpatient cases and 90% of outpatient visits (up to 100% of primary health care visits) in Lithuania, covering the entire territory of the country with about 7000 users (health care institutions) of the system. The database contains demographic data and entries on the primary and secondary health care services provided, emergency and hospital admissions, and prescriptions of reimbursed medications for chronic diseases. The information is based on documentation from health care providers. Each visit or service is associated with a disease code of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) and a corresponding standardised cost that is established by the state. Selected anonymised variables were extracted from electronic health records of the NHIF of Lithuania for the period from 1 January 2012 to 30 June 2014. The identified period was chosen due to the reliability of the data, which was

achieved by updating national rules and regulations for medical coding as of 2012 [133].

The prospective study of the IMCM implementation was performed under the framework of CHRODIS [126] and CHRODIS-PLUS projects. The model for the care of patients with MM [52] was adapted and applied in five pilot sites (two in Spain, one in Italy and two in Lithuania). The effectiveness of the IMCM implementation on clinical and process outcomes was tested. [134].

Vilnius site implemented the IMCM in the Family Medicine Centre of VULSK. The centre provides primary care for more than 12,000 patients and a significant proportion of them have MM. The data for the study were obtained using the Assessment of Chronic Illness Care (ACIC) and the Patient Assessment of Care for Chronic Conditions+ (PACIC+) questionnaires. The Vilnius site implementation team discussed a joint position from several team members for the ACIC questionnaires pre- and post-implementation of the IMCM. The demographic and the PACIC+ data were acquired from patients of the Family Medicine Centre of VULSK as a part of the long-term study. The data on the PACIC+ and ACIC questionnaires from the rest four European pilot sites were obtained under the framework of CHRODIS-PLUS.

Table 1. Summary of study designs, study population and outcomes for the papers

	I	II	III	IV	V	VI (Vilnius site)
Study population	Lithuanian diseased adult population (at least 1 chronic disease), aged 40 to 79	Lithuanian diseased adult population (at least 1 chronic disease), aged 40 to 79	Lithuanian diseased adult population (at least 1 chronic disease)	Lithuanian diseased adult population (at least 1 chronic disease)	Not applicable	Patients with MM, aged 40 and older from VULSK Family Medicine Centre
Population size	353,780 4,834 for COPD	353,780 4,834 for COPD	452,578	452,769	Not applicable	195 45 for PACIC+
Baseline	Entry of chronic disease code under observation period, age 40-79	Entry of chronic disease code under observation period, age 40-79	Entry of chronic disease code under observation period	Entry of chronic disease code under observation period	Not applicable	At least 2 chronic diseases
Observation period	From 1 January 2012 to 30 June 2014	From 1 January 2012 to 30 June 2014	From 1 January 2012 to 30 June 2014	From 1 January 2012 to 30 June 2014	Not applicable	From 1 February 2019 to 31 January 2020
Outcome	Prevalence Odds ratio Clustering Hospitalisation	Prevalence Odds ratio Patterns	Age breakpoints	Distribution, change and interrelationship of health care costs	Country adjusted implementation methodology	Impact on quality of healthcare of the pilot implementation
Exclusion criteria	A COPD code without a recorded pulmonologist's consultation of and the usage of broncholitics for less than six months per year	A COPD code without a recorded pulmonologist's consultation of and the usage of broncholitics for less than six months per year	Not applicable	Not applicable	Not applicable	Not applicable

Controls	Gender, patients without COPD code	Gender	Single chronic disease	Single chronic disease	Not applicable	Pre and post implementation
Statistical analysis	Descriptive statistics, odds ratios for associations, Chi-square tests for proportion, agglomerative hierarchical clustering with Ward linkage for cross-sectional phenotype identification. The Jaccard coefficient was used as a measure of similarity because of the dichotomous nature of the variables.	Descriptive statistics, exploratory factor analysis for neurological and psychiatric MM profiles, chi-square test for proportion, and Mann-Whitney U test for differences	Descriptive statistics, Chi-square test for proportion, Student's t-test for differences, segmented linear regression for break points	Descriptive statistics, generalised linear models (GLM) with gamma distribution and log link function	Survey Scope analysis Risk stratification (SWOT)	Descriptive statistics, Mann-Whitney test for the ACIC, Student's paired t-test for the PACIC+. Cohen's d formula for effect size, linear regression models
Stratification	Yes, by gender, by COPD presence	Yes, by gender	Yes, by disease number: patients with 1 chronic condition vs. patients with at least 2 chronic diseases	Yes, by disease number: patients with 1 chronic condition vs. patients with at least 2 chronic diseases	Not applicable	Yes, by implementation site

4.3. Study population

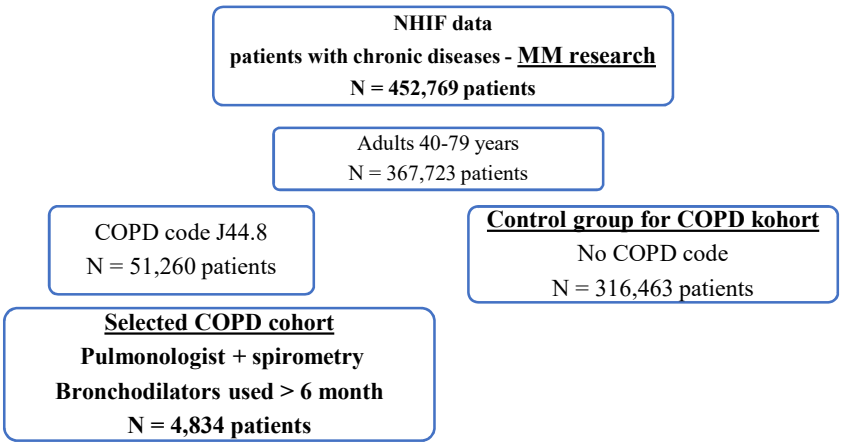
The initial patient cohort (Papers I-IV) consisted of 452,769 patients (18 years or older) who had been diagnosed with at least one chronic condition from the 32 chronic diseases list used by Barnett et al. and, thus, involved chronic diseases with the highest prevalence and the highest impact on patients [59], [61] (Table 2).

Table 2. The list of selected chronic conditions associated with ICD-10-AM diagnostic codes

	Chronic Diseases with ICD-10-AM Diagnostic Codes
1	Cancer C00–C96
2	Anaemia D50
3	Hypothyroidism E02; E03; E89.0
4	Diabetes E10.0–E10.9; E11.0–E11.9
5	Obesity E66
6	Dyslipidaemia E78
7	Dementia F00.0–F00.9; G30.0–G30.9; F01.0–F01.9; F02.0–F02.8; F03
8	Mental disorders F20.0–F20.9; F30.0–F39; F40.00–F40.9; F41.0–F41.9; F42.0–F42.9; F43.0–F43.9
9	Parkinson disease G20
10	Multiple sclerosis G35
11	Epilepsy G40.00–G40.91
12	Sleep apnoea G47.3
13	Back Pain G54.1; G54.4; G55.1; M51
14	Glaucoma H40–H42
15	Blindness H53–H54
16	Hearing loss H90.0–H90.8; H91.0–H91.9
17	Hypertension I10–I15
18	Ischemic heart disease I20–I25
19	Arrhythmias I44–I49
20	Heart failure I50.0–I50.9
21	Intracranial bleeding I61–I62
22	Stroke I63-I64; I69
23	Chronic obstructive pulmonary disease J44.0–J44.9; J96
24	Asthma J45.0–J45.9
25	Inflammatory bowel disease K50; K51
26	Psoriasis L40.0–L40.9
27	Rheumatoid arthritis M05–M06

28	Gout M10.0–M10.99
29	Osteoarthritis M15–M19
30	Systemic lupus erythematosus M32
31	Osteoporosis M80–M82
32	Renal failure N18–N19

For Papers I-II, during the first step of patient selection for the current study, data of patients aged 40 to 79 have been extracted, resulting in a sample of 353,780 individuals. To include only patients with a reliable diagnosis of COPD, several criteria during the following step were used. To be considered having COPD, patients had been diagnosed with this disorder (code J44.8 in the ICD-10-AM, "Other specified chronic obstructive pulmonary disease"), have a record of being prescribed medication for COPD (for at least 6 months a year) and have had at least one consultation by a specialist in pulmonology and spirometry. No-COPD patients were defined as all patients those having no COPD-related entry in the NHIF database (Figure 2).



COPD – chronic obstructive pulmonary disease, MM – multimorbidity, N – number, NHIF – the National Health Insurance Fund

Figure 2. The flow diagram summarising the process of enrolment

There were 4,834 individuals meeting the enrolment criteria (1.37% of the initial sample aged 40 to 79) and only their data were used for further analysis. Among the excluded patients, 316,463 had no diagnosis of COPD, 46,426 had a diagnosis of COPD, but did not meet the required criteria. As the manifestation of COPD usually starts after 40 years of age, only patients aged

40–79 years were included. Many outliers were found in patients aged 80 and older, and this group was excluded from further analysis.

To better differentiate the diseases that co-occur with COPD during the second half of adulthood from those existing over the course of an individual's life, all comorbid disorders had to be recorded during the study period (during medical consultations or hospitalisations). Information on diagnoses of CVD (heart failure, ischemic heart disease, arrhythmia), lung cancer, diabetes, kidney diseases, and depression was drawn from the NHIF dataset of chronic conditions. They included diagnoses of tracheal or lung cancer (C33-C34), hypertension (I10-I15), type II diabetes mellitus (E11.01–E11.9, only with prescribed medication and records of endocrinologist's consultation), ischemic heart disease (I20-I25, only with records of cardiologist's consultation), arrhythmias (I44–I49, only with records of cardiologist's consultation) or heart failure (I50.0– I50.9, only with records of cardiologist's consultation). All neurological and psychiatric comorbidities were identified only by diagnostic ICD-10-AM codes throughout the medical record data. Stroke was classified as either ischemic or hemorrhagic by using codes I63-I64 and I60-I61, respectively, as proposed by Woodfield et al. (presuming that most undetermined strokes are ischemic) [135]. The definition of the diseases was based on the entry of the code. Some disorders, however, were present in single cases and/or were considered to have too little value to be explored in the context of COPD. We chose to omit such conditions from the analysis. Information about the number of hospital admissions, total hospital stays, and patient disability status was also available.

For Paper III and IV, patients aged 18 and over with at least 2 chronic diseases from the list in Table 1 during the 2.5 years' period were selected for the analysis.

Study population is not applicable for Paper V which presents the methodology of implementation and describes the characteristics of each national health care system and implementation site.

In Paper VI, the main inclusion criterion for patients was having MM, although specific inclusion criteria differed depending on the site. The participating sites were: Andalusian Department of Health in Andalusia and Aragon Department of Health in Aragon, both in Spain; Gemelli Hospital, the Catholic University of the Sacred Heart in Rome, Italy; Hospital of the Lithuanian University of Health Sciences Kauno Klinikos in Kaunas and VULSK in Vilnius, both in Lithuania. From this point on and for word-economy purposes, the geographical name will be used when referring to each implementation site.

In the Vilnius site, 195 patients from the Family Medicine Centre of VULSK eligible to the inclusion criteria (having at least two chronic diseases affecting different systems and aged between 40 and 75) were included after signing informed patient consent. Forty five of them filled the PACIC+ questionnaire pre- and post-implementation of the IMCM. The thesis analysed only the data of the PACIC+ obtained from the Vilnius site compared with the overall results from all implementing sites.

4.4 The methodology of implementation

The implementation strategy was developed during the CHRODIS-PLUS project.

Paper V describes the implementation strategy of all pilot sites, but the thesis was focused on the implementation in the Family Medicine Centre of VULSK (Vilnius site).

The assessment of the characteristics of pilot sites was performed using a questionnaire across six dimensions: general information; delivery of care and decision support; patient self-management; eHealth; community resources; and practice/programme assessment.

Risk stratification is defined as a systematic process to target, identify, and select patients at risk of worth health outcomes, and who are expected to benefit most from an intervention [3], [136], [137]. A risk stratification process was adopted in all pilot sites to ensure the focus on patients who could have the highest benefit of the intervention and maximising the impact on both quality and costs. The target cohort was defined by searching databases that routinely collect information on clinical or demographic data.

4.4.1 Implementation strategy

The implementation strategy was designed by CHRODIS-PLUS partners and experts and aimed to provide guidelines to facilitate the uptake of routine good practices, policies, and tools.

As a first step, each site established a local implementation working group comprised of organiser, experts, decision makers, front line stakeholders, and implementers. The working groups involved periodic face-to-face meetings or online meetings with specific tasks for each meeting: scope analysis; situation analysis – “strengths, weaknesses, opportunities, threats” (SWOT); development and improvement of methodology; and final development of a pilot action plan (Figure 3).

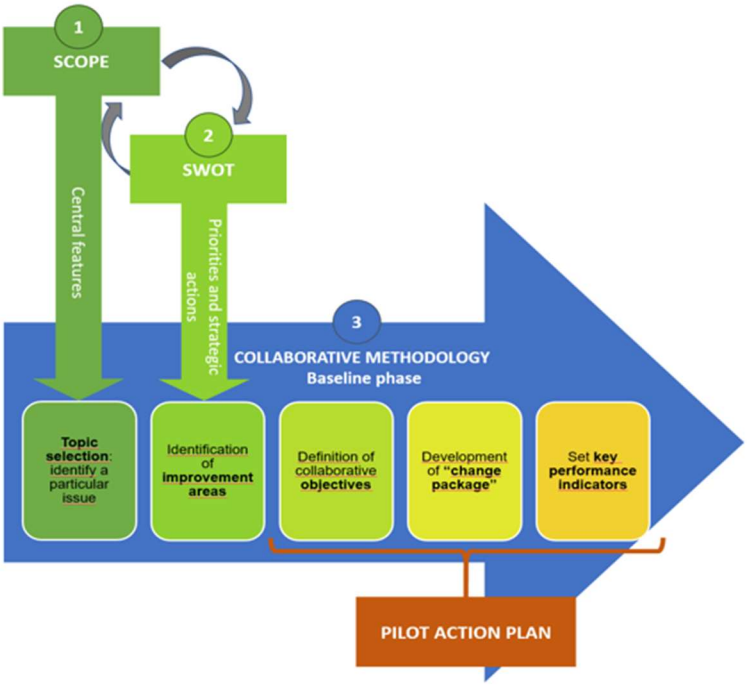


Figure 3. Description of the implementation phases conducted by the local implementation working groups

A structured group discussion was used during the scope analysis, highlighting the specific features or elements of the planned intervention identified according to the site's local needs and capabilities. Each site followed five steps: identify and describe the problem; describe the purpose of the intervention; describe the target population; analyse the intervention's components and identify the features essential to achieve the desired results; and select the components from the IMCM for the local implementation.
SWOT analysis was used to identify the respective organisations' internal strengths and weaknesses, as well as external opportunities for, and threats to, implementing the interventions based on the selected model elements. SWOT is designed to help with both strategic planning and decision making, and it is a structured method allowing the comparison of different analyses from the five sites. Every site prepared a matrix that presented the most important strengths, weaknesses, opportunities, and threats for their organisation across five dimensions: sustainability, organization, empowerment, communication, and monitoring and evaluation. A template was devised to facilitate discussion.

The methodology was developed and improved during face-to-face meetings, leading to the development of an action plan providing a set of steps and activities that need to be carried out to implement the care interventions. An adapted version of the iterative cyclic nature of the collaborative methodology [138] was used for drafting local action plans. According to this methodology, three main questions were addressed: (1) What are we trying to accomplish? (2) What changes can we make that will result in the successful implementation of the IMCM as well as an improvement? (3) How will we know that a change is an improvement? These questions were used to develop a concrete action plan, which was devised in five steps (Table 3).

Table 3. Five steps used to define Action Plans for the integrated multimorbidity care model

Action Plan Steps
Identify the specific issues to work on
The central features or elements of the intervention to work were already selected during the definition of the scope. These included components of the IMCM [52].
Detect improvement areas
Based on the SWOT analysis, the working groups identified specific areas for improvement.
Define specific objectives
According to the improvement areas detected, the working groups developed achievable and realistic objectives.
Develop the Change Package
Based on the improvement areas and the associated objectives, concrete activities were described in a "change package", which is a set of changes that lead to improvement and successful implementation of IMCM during the implementation phase. Each objective defined in the previous step requires at least one activity.
Set key performance indicators
Key performance indicators were defined to ensure that the expected impact of the interventions can be accurately measured. Depending on the site, the indicators could either be intermediate health-related outcome measures, process indicators, or both. The targets had to be achievable and measurable. Existing data was chosen to measure progress.

IMCM – Integrated Multimorbidity Care Model, SWOT – strengths, weaknesses, opportunities, threats

4.4.2 The Vilnius site intervention

Paper VI describes the intervention in each pilot site. The implementation of the IMCM followed a structured methodology, common to each participating site, but specifically adapted to their specific characteristics based on baseline situation analyses conducted before the intervention [130]. The duration of the intervention was 12 months, and assessments were performed at the beginning

and end of the intervention. All interventions were integrated as a standard practice of the respective sites.

The Vilnius site targeted components from all five domains of the model and included primary and specialised care professionals at the implementation, which was directed at 195 patients with MM, aged 40 and older. The team aimed at optimising health care resources and decreasing care fragmentation by appointing case managers and creating individualised care plans, developing consultation systems for professionals, and improving patient access to community resources [130]. VULSK adapted the IMCM prioritising heavy users of health care resources.

The perspectives of both the patient and the health system regarding the quality of provided care were agreed upon as key common indicators for all implementing sites. Self-perceived patient care was analysed through the 26-item Patient Assessment of Care for Chronic Conditions (PACIC+) survey [139], which measures specific actions or qualities of care that patients report to have experienced during their interactions with the delivery system. The health system team perspective was assessed by using the Assessment of Chronic Illness Care (ACIC) survey [140], a practical quality-improvement tool to help organisations to evaluate the strengths and weaknesses of their care delivery for chronic illnesses. Both questionnaires were collected and analysed before and after one year of IMCM implementation.

A questionnaire for the collection of basic sociodemographic patient data (i.e., gender, age, civil status, education level and employment status) was also developed. A question on perceived change (change score) was included after the implementation, the patients were asked "Concerning your chronic conditions, please rate the degree of change in the care you have received in the past 12 months". This item presented seven Likert-type response options, ranging from 1 (very much worse) to 7 (very much improved).

The ACIC (version 3.5) [140] assesses the strengths and weaknesses of delivery of care for chronic illness in seven areas: delivery system organisation (Part 1), community linkages (Part 2), self-management support (Part 3a), decision support (Part 3b), delivery system design (Part 3c), clinical information systems (Part 3d), and integration of model components (Part 4). The ACIC was applied in each site pre- and post-implementation. Items were scored from 0 (the lowest level of support) to 11 (the optimal level of support). Scores for each section were obtained by summing the values for all items within a section and dividing by the number of items within that section (range: 0-11). The overall score was derived by summing the average scores of each section and dividing by the number of sections administered (range:

0-11). The following ranges for quality-of-care levels were established: 0-2 for limited support for MM care; 3-5 for basic support for MM care; 6-8 for reasonably good support for MM care; and 9-11 for fully developed support for MM care [141]. The ACIC was completed by members of the implementation team with a good knowledge of implementation as well as site and health care system characteristics (decision maker, front-line stakeholder, or implementer). After a discussion a joint position from several team members was filled to the ACIC. This questionnaire was responsive to changes performed and correlates well with other measures of productivity and system change.

The English version of the questionnaire was used in all sites.

The PACIC+ [139] consists of 26 items. Each item was scored from 1 (almost never) to 5 (almost always). The PACIC+ allows for a scoring method derived from the "5As" model of behavioural counselling that defines five measurable outcomes: assess, advise, agree, assist, and arrange [142], allowing the measurement of the improvement in self-management support and linkages to community resources [139]. A global "5As" summary score was also calculated, based on the average of items 1-4 and 6-16. The PACIC+ was translated into several languages, thus Lithuanian, Italian and Spanish versions were used.

4.5 Outcomes

Paper I aimed to assess the epidemiology and clustering of COPD comorbidities and the impact of clusters on hospitalisations, identifying the target for future interventions.

Paper II aimed at clarifying, whether different neurological and psychiatric comorbidities tend to manifest together and in what patterns they emerge in COPD. The frequency of neurological and psychiatric comorbidities also was assessed and the associations among the diseases by extracting underlying factors that are common for several comorbid disorders were explored.

Paper III was designed to identify the earliest age breaking points where MM occurs and starts to increase rapidly and analyse the interrelationship between multiple chronic conditions, hospitalisations and heavy medication usage.

Paper IV aimed to explore the distribution, change and interrelationships of health care costs across the age groups of patients with MM in Lithuania.

Paper V aimed at explaining the methodology used to implement the IMCM and describing the five pilot sites and how they have adapted and applied the proposed methodology for local implementation. The thesis focused on

implementation methodology in VULSK. ACIC and PACIC+ questionnaires were selected for the evaluation of the primary impact on the quality of care of the intervention. Other process indicators (number of unscheduled visits, admissions to emergency unit, number and duration of hospitalisations, and avoidable hospitalisations, number of incompatible drug combinations (drug interaction rate), EQ-5D questionnaire, EQ VAS visual scale) were postponed to a long-term study.

Paper VI aimed to analyse and assess the impact of the pilot IMCM intervention across the five implementing sites in Italy, Lithuania and Spain by comparing specific indicators measured pre- and post-implementation. Immediate health related outcomes using ACIC and PACIC+ questionnaires were evaluated. The overall results of the five pilot sites and the results achieved in VULSK were incorporated into the thesis.

4.6 Statistical analysis

For the retrospective part of the study Data Exporter Software was used to extract the data from the NHIF database: demographic information (gender, age) of patients who were diagnosed with at least one of 32 chronic diseases (Table 2); the use of primary (overall and home visits), outpatient (specialist consultation) health care services; hospitalisations; prescribed and at least partially reimbursed medications during the analysed period.

The number of chronic diseases, the mean cost of medication, hospitalisation, primary and outpatient services, the share of health care costs and the trends of annual costs of a patient with MM were assessed in different age groups. The anonymised information was uploaded on the secured server which was developed for this study. The analysis of the anonymised data was performed according to the Lithuanian data protection regulation without explicit patient consent.

Paper I. Two analyses were carried out to assess the association between COPD and comorbidities. Descriptive statistics and odds ratios (ORs) for associations were computed. Continuous variables were expressed as mean and standard deviation (SD) and categorical variables were expressed in numbers and percentages. For these analyses, all individuals with records of CVD: heart failure (I50), arrhythmia (I44–I49), ischemic heart disease (I20, I24, I25), lung cancer (C33, C34), diabetes (E10–E14), kidney diseases (N17–N19), and depression (F31–F39) were included.

The prevalence of these comorbidities in those with and without chronic obstructive pulmonary disease was assessed. Differences in the disease prevalence were tested using Chi-square tests.

A cross-sectional analysis to quantify the relationship between COPD and other chronic comorbidities was performed. Our primary outcome was the relationship between prevalent COPD and the diagnosis of each comorbidity under study. Unadjusted ORs and 95% confidence intervals (CIs) of the associations between the outcome variable and each explanatory variable were estimated using logistic regression. Separate multivariable models were built for each disease to look for confounding or effect modification by gender, age, and place of residence.

For the patients with all records of chronic diseases from Barnett's list, agglomerative hierarchical clustering with Ward linkage for cross-sectional phenotype identification was performed. The Jaccard coefficient was used as a measure of similarity because of the dichotomous nature of the variables. Clustering of the diseases for COPD patients was performed if at least 5% of the patients were found to have a comorbidity, separately for men and women. The clusters were depicted graphically using bottom-up approach, marking the same colour as a single cluster.

All statistical analyses were performed using STATA version 11 (StataCorp. 2009. Stata Statistical Software: Release 11.0. College Station, TX, USA), STATISTICA version 10 (StatSoft, Inc Tulsa, OK, USA.) and R (version3.6.1). R packages "stat" (procedure "hclust"), "vegan", "dendextend", "pheatmap" and "fpc" were used to conduct hierarchical clustering and graphical representation. The significance level was defined as $p < 0.05$.

Paper II. The EFA was performed in search of variables underlying the neurological and psychiatric MM profiles in COPD. The EFA is the proposed method when it is assumed that distinct health conditions are causally related and represent a continuum of pathological processes [143]. The EFA was based on a tetrachoric correlation matrix from the binary comorbidity data ("1" – a condition is present, "0" – a condition is absent). To be included as variables, comorbidities had to be present in two or more percent of the patient sample or the patient subgroup in question. Being unaware of any existing guidelines for methods of selection of distinct diagnostic categories for the EFA, we grouped diagnoses by ICD-10-AM codes according to two principles. First, if one condition was predominant in a group of ICD-coded disorders, we avoided grouping it with other disorders that are heterogeneous in their etiology, mechanism and/or manifestation. Secondly, we combined

the coded disorders into groups if they had a similar impact on the patient's health or have a similar etiology.

The number of factors extracted was based on eigenvalues over 1.0 and the evaluation of a scree plot. Factor loadings were interpreted after performing an oblique oblimin rotation. A cutoff value of >0.30 was used to determine the inclusion of factor loadings into a comorbidity profile. If the Heywood phenomenon occurred (factor loading ≥1.00), the variable in question was eliminated and the procedure was repeated to improve model fit. To state the obtained sampling adequacy, we employed the Kaiser-Meyer-Olkin (KMO) criterion (<0.50 being unacceptable).

The benefit of additional stratification by age in the EFA of MM profiles is unclear [143]. Given that the patient sample was already limited to ages between 40 and 79, we did not split the study sample into additional age subgroups. However, we anticipated variation in the discrete COPD comorbidities between genders. Therefore, additional EFA was performed for male and female subgroups. Microsoft Excel 16.0 was used for descriptive statistics and the creation of graphs. IBM SPSS 23.0 was used for Chi-squared and Mann-Whitney U tests. We employed STATA 13.0 for EFA.

Paper III. For statistical analysis, we used the R statistical computing environment (version 3.2.2; R Core Team 2015) and STATISTICA (StatSoft, version 10). Continuous variables were presented as means ± standard deviation (SD) and categorical variables as frequency and percentage. The chi-square test and Student's t test were used to test the significant proportion and mean differences, respectively. We used segmented linear regression to identify breakpoints (R package "segmented") [144]. All reported p values were two-tailed and the level of significance was set at 0.05.

Paper IV. Patients' age was defined as the age in the year of data extraction and was classified into 8 categories: 18 to 24 years, 25 to 34 years, 35 to 44 years, 45 to 54 years, 55 to 64 years, 65 to 74 years, 75 to 84 years, and 85+. Patient characteristics are presented as means ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. The 95% confidence intervals (CI) were computed for health care service costs. Generalised linear models (GLM) with gamma distribution and log link function were used for the evaluation of the relationship between chronic diseases and cost. The segmented linear regression was used to identify breaking points (R package "segmented") [145]). For statistical analysis, the R statistical computing environment (version 3.4.0; R Core Team 2017) [144] and STATISTICA (StatSoft, version 10) were used. All reported *p* values were two-tailed, and the level of significance was set at 0.05.

Paper V described the implementation methodology of the IMCM and no statistical analysis was therefore applicable.

Paper VI. Descriptive statistics (frequencies and percentages, means and standard deviations) were used to characterise the participants and to summarise the results of ACIC and PACIC+ questionnaires, total and subscales scores, for each site. ACIC scores were averaged by site and time (pre- or post-intervention).

Differences in ACIC and PACIC+ scores between pre- and post-implementation assessments in each site were ascertained using the Mann-Whitney test for the ACIC and the Student's paired t-test for the PACIC+. The magnitude of change was estimated using Cohen's d formula for effect size $(mean_{t2}–mean_{t1})/SD_{t1}$) [146], with 0.50-0.79 indicating moderate change and ≥ 0.80 indicating large change.

Six linear regression models, with the difference between post and pre-implementation in all PACIC+ dimensions and total as dependent variables, respectively, were performed. As independent variables, the following variables were included in the models: gender, age, civil status (in two categories: with and without a partner), education (two categories: primary or lower and secondary or higher), employment status (inactive and active), respective baseline PACIC+ scores, and difference in ACIC dimensions 1, 2 and 4 scores. ACIC dimension 3 was not included due to strong co-linearity with other dimensions.

Calculations were performed using IBM SPSS software, version 22.0.

4.7 Considerations on patient population and study design (strength and limitations)

The retrospective study (Papers I-IV) was performed using a real-world population and capturing and quantifying the use of health services for different diseases. The use of medical records of primary and secondary health care settings used in routine work should eliminate differential misclassification due to recall or interviewer prejudice. The COPD group composed exclusively of patients diagnosed by a pulmonologist suggests that the spirometry was performed for all patients despite the absence of spirometry data in the database.

Numerous limitations ought to be stated regarding the study. The source of data consisted of medical records from the Lithuanian database of the NHIF, which had not been intentionally designed for observational studies. This

database was created for the reimbursement of health care institutions for medical services as well as for statistical needs.

It is thus possible that some conditions were under- or over-reported because of various reasons, including insurance policy to reimburse services only after a specific diagnosis is made, presumable stigmatisation of some conditions and less accurate reporting in the case of MM. The inclusion of primary, secondary, and tertiary care, as well as prescriptions and the duration of the analysed period over 2 years maximised the chances of capturing all related diagnoses. However, the possibility of missed diagnoses could not be completely excluded.

However, as we have used the list of diseases (Table 2) for data extraction, patients with any other chronic disease not mentioned in the list, were not included in the analysis [59], [61]. The list is debatable and could possibly be expanded. Different authors may propose a different list of chronic diseases, some excluding mental illnesses, accounting for worse outcomes and increased costs. Due to a lack of an established MM gold standard measure, defining the list of diseases, it is impossible to clearly define which chronic diseases should be excluded, as some of the minor ones would clearly have a different weight on the outcomes, costs, and management of the patients. Nevertheless, we have analysed the prevalence of the selected chronic diseases in the Lithuanian population in our previous work and confirmed that the chronic conditions included in the current study's definition are highly prevalent and thus meeting the criteria of chronic diseases having the highest impact on the use of health care resources [59].

Our data represents health care provider contact due to a chronic disease, not necessarily the time when the diagnosis was first made, if it was prior to 2012. In addition, there is a chance of a possible delay between the time of symptoms and the first contact, making it difficult to clearly define the time of the onset of the disease. The fact, that the whole population was screened and the analysed timeframe is over 2 years reduces the chances of significant discrepancies. Additionally, comprehensive database information relating to individual patient diagnoses, treatment, primary and outpatient visits and hospitalisations, as well as their trends over time, increase the reliability of our data. However, the period might not be long enough to cover the whole picture of some diseases, which are more prone to fast deterioration. The limited duration and scope of the database do not allow for further analysis of the association with end-of-life care.

The cross-sectional data analysis could be considered a potential limitation; hence conclusions about causality cannot be made. Since our cohort was a

sample of the study of chronic disease population, the prevalence of chronic conditions may be higher than in other studies.

The retrospective nature of our study did not allow the selection of patients with COPD according to clinical criteria. Consequently, some patients with less severe forms of COPD might have been excluded from the sample. Associations between various disorders in COPD should be regarded with caution as they depend on ad hoc grouping of nosological entities and a subjective interpretation of the possible underlying latent factors. That is, the statistical methods employed do not provide direct evidence of causative relationships between comorbidities.

The stratification by age was not performed during the clustering procedure, but the results of the prevalence analysis in different diseases correspond with the cluster analysis. Although we found a significantly higher risk of manifestations of CVD, heart failure, ischemic heart disease, lung cancer, diabetes, and kidney diseases in the COPD group, our methodology may have underestimated the overlap between these diseases. The presence of asthma code in COPD patients was associated with the level of reimbursement of medication. However, the COPD-asthma overlap syndrome could be underestimated. The lack of smoking data could be considered a potential limitation, but smoking epidemiology in Lithuania suggests that most COPD patients could be heavy smokers.

The size of the database means that the duration had to be limited. It also affected the time frame of the data, suggesting that some changes in the care might have happened during the last few years, affecting the resource usage, even though very unlikely. Last but not least, the analysis is limited to a single country. Additional database analysis of other countries could potentially validate the findings, suggesting the need for further analysis and supporting the differentiation in the reimbursement of services for the investigated patients in the MM group.

There are several strengths of the methodology in Paper V and VI. We used a process that followed a standardised procedure adaptable to the local site's needs, capabilities, and characteristics. The process was developed so that each site followed the same methodology to create a standardised implementation package that can be practically applied in different European and clinical settings. Each of the five sites participated in regular joint meetings (usually virtually) with the work package coordinators to compare strategies and identify any ambiguities in the methodology. In addition, we used SWOT analysis that can provide comparable information allowing for the identification of differences and similarities across the sites.

There are potential limitations to the implementation process described herein. The implementation process was set at 18 months to fall within the timeframe of the three-year JA CHRODIS-PLUS project. Therefore, various aspects such as the selected key indicators might reflect this relatively short intervention period. Longer interventions might have the potential to assess other relevant health-related indicators such as mortality, change in long-term functional status or frailty status, as well as cost-effectiveness data. Lithuanian sites decided to postpone the measurements of the number of visits to primary care, the number of specialist consultations, the number of emergency unit visits and hospitalisations and to postpone them to a long-term intervention foreseen by the Lithuanian Ministry of Health. The current pilot testing of the IMCM in five European sites was expected to provide primary relevant information that should help develop integrated care and treatment programs for MM patients.

The implementation study included a patient-reported experience measure (PACIC+) but lacked a quality-of-life dimension. However, previous interventions aimed at improving care for patients with MM did not change patients‘ quality of life. Instead, an improvement in patient satisfaction was observed, which can be considered in itself a relevant positive outcome [46], [147]. The methodological design of the study involved the collection of real world data, which implies some constraints such as missing data for some measures, non-representative samples, or a smaller sample size. Also, more studies are needed to confirm the validity of the results. As each site set its own inclusion criteria, participants were heterogeneous in their sociodemographic and clinical characteristics. The interventions had a common structured methodology and duration but varied in settings and health care levels. Although this could be considered a limitation, it gave the opportunity to show that the IMCM can be adapted to the characteristics of different health care systems. Moreover, despite the differences between sites, components of the five IMCM domains have been implemented and assessed. Finally, a longer follow-up would be desirable to detect changes that could occur in the long term.

5. RESULTS

5.1 Paper I

The final study group consisted of 321,297 patients aged 40–79. 1.5% of them had COPD, with prevalence increasing with age in males (69.1% vs. 34.7%) and more COPD patients lived in rural areas (35.4% vs. 27.0%). (Table 4).

Table 4. Study population characteristics

Characteristics	COPD		No COPD	
	N	%	*N*	%
Age, mean (SD)	67.2 (8.4)		63.6 (10.1)	
Age group				
40–49	126	2.6	32,341	10.2
50–59	850	17.6	76,602	24.2
60–69	1,614	33.4	97,566	30.8
70–79	2,244	46.4	109,954	34.7
Total	4,834	100	316,463	100
Gender				
Males	3,338	69.1	129,505	40.9
Females	1,496	30.9	186,958	59.1
Total	4,834	100	316,463	100
Residence				
Urban	2,285	47.3	178,203	56.3
Rural	1,711	35.4	85,391	27.0
Not reported	838	17.3	52,869	16.7
Total	4,834	100.0	316,463	100.0

COPD – chronic obstructive pulmonary disease, N – number, SD – standard deviation.

Significantly higher prevalence was found in COPD patients for CVD (heart failure, arrhythmia, ischemic heart disease), lung cancer, and kidney diseases (Table 5). The difference in COPD and non-COPD groups for diabetes and depression was not statistically significant.

Table 5. The prevalence of other comorbidities in COPD patients

Comorbidity	COPD		No COPD		*p*-value
	N	%	*N*	%	
Ischemic heart disease	4,044	83.7	204,776	64.7	<0.001
Hearth failure	3,147	65.1	115,500	36.5	<0.001
Arrhythmia	2,351	48.6	112,400	35.5	<0.001
Diabetes	609	12.6	40,975	12.9	0.472
Depression	364	7.5	23,077	7.3	0.528
Kidney diseases	278	5.8	12,366	3.9	<0.001
Lung cancer	186	3.8	1304	0.4	<0.001

COPD – chronic obstructive pulmonary disease, N – number

After adjustment for gender, age, and place of residence, the multivariate analysis showed the association of COPD with a six-fold increase in the odds of having had lung cancer (OR 6.66, 95% CI 5.68–7.82; $p < 0.0001$), a two-fold increase in the odds of heart failure (OR 2.61, 95% CI 2.46–2.78; $p < 0.0001$), and CVD (OR 1.83, 95% CI 1.69–1.97; $p < 0.0001$) compared with those without COPD (Table 6). A higher risk for arrhythmias, diabetes, kidney diseases, and depression was also found.

Table 6. ORs from multivariate logistic regression analysis of COPD patients (modified by author)

Comorbidity	OR	95% CI	*p*-value
Lung cancer	6.67	5.68 - 7.82	<0.001
Hearth failure	2.61	2.46 – 2.78	<0.001
Ischemic heart disease	2.32	2.14 – 2.50	<0.001
Arrhythmia	1.47	1.38 – 1.55	<0.001
Depression	1.5	1.34 – 1.67	<0.001
Kidney diseases	1.23	1.09 – 1.39	0.001
Diabetes	1.15	1.05 – 1.25	0.002

OR – odds ratio, CI – confidence interval

Up to 19 diseases from the list of 32 [59], [61] were eligible for the clustering inclusion criteria. The hierarchical clustering algorithm (Ward's method, h = 0.95) identified six clusters for men (Figure 1) and five clusters for women (Figure 2) in the COPD group. Clustering in patients without COPD delivered

five and four clusters, respectively. The structure of the clusters had some similarities, but a few significant differences were found.

In the male COPD group (Table 7), a cardiovascular cluster was the most prevalent, with the highest commonness of hypertension and ischemic heart disease. More than half of the COPD males were hospitalised at least once during the study period. Less dominant, but a similar frequency was found in endocrine-metabolic and asthma-musculoskeletal clusters. The incidence of gout-renal and mental disorders clusters was the lowest, but 70% of these patients had a hospitalisation history. A stroke-cancer-sensor cluster was also identified. In COPD females (Table 7), some MM clusters showed a similar frequency, but the clustering patterns were found to be different. Nevertheless, the most prevalent was the cardiovascular cluster, as it was for men. The asthma-musculoskeletal and endocrine-metabolic clusters found in COPD males appeared to compose a single cluster, including glaucoma and mental disorders, in COPD females. A dementia-stroke cluster was found in females suffering from COPD, but cancer was linked to hypothyroidism, osteoporosis and hearing loss. An anaemia cluster was found only in females with COPD. A total of 70% of females having at least one disease from the low-prevalent anaemia and dementia-stroke clusters had a hospitalisation history.

Analysing MM clusters in males without COPD (Table 7), dyslipidaemia was linked to the most prevalent cardiovascular cluster. The stroke-cancer-sensor and mental disorders clusters appeared to be the same as in COPD men. Gout was found joining the endocrine-metabolic cluster. A separate musculoskeletal cluster had a high prevalence in men without COPD. In no COPD females (Table 7), dyslipidaemia and musculoskeletal diseases were found to link to the cardiovascular cluster. The dementia-stroke cluster was found in females irrespective of COPD. The endocrine-metabolic cluster consisted only of diabetes and obesity.

The most prevalent cardiovascular cluster (heart failure, ischemic heart disease, arterial hypertension, and arrhythmia) appeared to be the same with no significant differences by gender or COPD presence. Still, hospitalisation rates were higher in the case of COPD presence (Table 7). However, dyslipidaemia was associated with CVD only in patients without COPD. In the case of COPD, clustering of dyslipidaemia with endocrine-metabolic diseases was found. This finding allows raising a hypothesis of a higher impact of hypoxemia and systemic inflammation in the pathogenesis of CVD in COPD patients rather than dyslipidaemia.

Osteoporosis and hypothyroidism were eligible to the clustering criteria only in women irrespective the presence of COPD. No evidence of asthma in

clustering trends of patients without COPD was found. Renal failure and gout met the clustering inclusion criteria only in men, but COPD was significant only for renal failure.

Table 7. Clusters by gender and COPD status

* Group with the same gender and COPD status. † Patients hospitalized at least one time in the follow-up period.

Cluster	Diseases	Patients with ≥1 Disease in the Cluster					Patients with ≥2 Diseases in the Cluster				
		Prevalence in Group *		Age	Hospitalised Patients †		Prevalence in Group *		Age	Hospitalised Patients †	
		N	%	Mean (SD)	*N*	%	*N*	%	Mean (SD)	*N*	%
Males, with COPD, *N* = 3338											
1	Ischemic heart disease, Hypertension, Heart failure, Arrhythmias	3,294	98.7	66.8 (8.4)	1,811	55.0	2,970	89.0	67.1 (8.3)	1,733	58.4
2	Obesity, Dyslipidaemia, Diabetes	1,416	42.4	64.8 (8.6)	877	61.9	394	11.8	62.2 (8.5)	295	74.9
3	Osteoarthritis, Back Pain, Asthma	1,649	49.4	65.7 (8.7)	915	55.5	515	15.4	65.3 (8.9)	291	56.5
4	Renal failure, Gout	393	11.8	68 (8)	278	70.7	53	1.6	69.5 (7.6)	43	81.1
5	Mental disorders	254	7.6	66 (8.9)	172	67.7	-	-	-	-	-
6	Stroke, Hearing loss, Glaucoma, Cancer	1,494	44.8	68.6 (7.7)	887	59.4	353	10.6	70.6 (6.8)	225	63.7
Females, with COPD, *N* = 1496											
1	Dementia, Stroke	202	13.5	71.4 (7.1)	141	69.8	24	1.6	73.3 (4.3)	17	70.8
2	Anaemia	81	5.4	68.7 (9.6)	57	70.4	-	-	-	-	-
3	Osteoporosis, Hypothyroidism, Hearing loss, Cancer	566	37.8	69.2 (7.8)	289	51.1	157	10.5	71.2 (6.8)	84	53.5
4	Ischemic heart disease, Hypertension, Heart failure, Arryhthmias	1,488	99.5	68.3 (8.2)	718	48.3	1348	90.1	68.8 (8)	697	51.7
5	Glaucoma, Mental disorders, Osteoarthritis, Back Pain, Asthma, Obesity, Dyslipidaemia, Diabetes	1,295	86.6	68.1 (8.3)	650	50.2	934	62.4	67.6 (8.4)	500	53.5
Males, without COPD, *N* = 129,505											
1	Dyslipidaemia, Ischemic heart disease, Hypertension, Heart failure, Arrhythmias	123,675	95.5	61.9 (10.1)	56,094	45.4	97,832	75.5	62.6 (10)	48,972	50.1
2	Osteoarthritis, Back Pain	41,550	32.1	61.3 (9.9)	17,810	42.9	8,448	6.5	61.6 (9.4)	3,778	44.7
3	Gout, Obesity, Diabetes	47,110	36.4	60.5 (9.8)	19,027	40.4	10,373	8.0	59.2 (9.4)	5,097	49.1
4	Mental disorders	7,658	5.9	60.5 (10.3)	3,577	46.7	-	-	-	-	-
5	Glaucoma, Hearing loss, Cancer, Stroke	47,050	36.3	65.5 (9.2)	24,207	51.4	9,204	7.1	68.4 (8.1)	5,125	55.7
Females, without COPD, *N* = 186,958											
1	Osteoarthritis, Back Pain, Dyslipidaemia, Ischemic heart disease, Hypertension, Heart failure, Arrhythmias	183,463	98.1	65.1 (9.7)	66,721	36.4	158,906	85.0	65.7 (9.4)	61,018	38.4
2	Dementia, Stroke	27,683	14.8	68.4 (9)	16,597	60.0	3,012	1.6	72.1 (6.6)	2,026	67.3
3	Obesity, Diabetes	66,817	35.7	64.4 (9.2)	23,812	35.6	12,501	6.7	62.6 (9.1)	5,777	46.2
4	Osteoporosis, Hypothyroidism, Glaucoma, Hearing loss, Cancer, Mental disorders	82,571	44.2	65.7 (9.4)	29,970	36.3	21,789	11.7	66.6 (9)	8,462	38.8

5.2 Paper II

A COPD cohort of 4,834 patients was analysed. Patient characteristics and comorbidity data are presented in Table 8. 2,767 (57.2%) were diagnosed with at least one neurological or psychiatric disorder. Among neurological and psychiatric comorbidities, most prevalent were nerve, nerve root and plexus disorders (N=1,439, 29.8%), sleep disorders (N=666, 13.8%), transient ischemic attack (N=545, 11.3%), depression (N=364, 7.5%) and ischemic stroke (N=349, 7.2%). Diagnosis of a transient ischemic attack was associated with hypertension (OR=2.218, 95% CI from 1.429 to 3.443). Recorded ischemic stroke episodes were related to hypertension (OR=2.117, 95% CI from 1.262 to 3.754) and arrhythmias (OR=1.343, 95% CI from 1.030 to 1.752).

Table 8. Patient characteristics and comorbidity data by gender (disorders with prevalence <1% have been omitted) (modified by the author)

	All patients		**%**	**Men**	**%**	**Women**	**%**	**p-value**
	4,834			3,338	69.1	1,496	30.9	
Recorded disability with COPD	428		8.9	343	10.3	85	5.7	<0.0001
	Median		**Range**	**Median**	**Range**	**Median**	**Range**	
Age	69		40-79	68	40-79	70	40-79	
Hospital admissions	1		0-26	1	0-26	0	0-19	<0.0001
Total hospital stay (days)	4		0-273	6	0-273	0	0-209	<0.0001
Selected comorbidities (not neurological or psychiatric)	**Code ICD-10-AM**	**N**	**%**	**N**	**%**	**N**	**%**	
Type 2 diabetes	E11.01 –E11.9	609	12.6	419	12.6	190	12.7	0.886
Heart failure	I50.0– I50.9	698	14.4	491	14.7	207	13.8	0.425
Arrhythmias	I44– I49	846	17.5	605	18.1	241	16.1	0.088
Ischemic heart disease	I20-I25	1,869	38.7	1,326	39.7	543	36.3	0.024
Hypertension	I10-I15	4,446	92.0	3,012	90.2	1,434	95.9	<0.0001
Tracheal and lung cancer	C33-C34	186	3.8	159	4.8	27	1.8	<0.0001
Neurological and psychiatric comorbidities	**Code ICD-10-AM**	**N**	**%**	**N**	**%**	**N**	**%**	

Dementia (including Alzheimer's disease)	F00-F03, G30	159	3.3	104	3.1	55	3.7	0.312
Mental and behavioral disorders due to psychoactive substance use	F10-F19	88	1.8	78	2.3	10	0.7	<0.0001
Alcohol related disorders	F10	71	1.5	66	2.0	5	0.3	<0.0001
Mood disorders	F30-F39	370	7.7	165	4.9	205	13.7	<0.0001
Depression	F32-33	364	7.5	162	4.9	202	13.5	<0.0001
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	F40-F48	292	6.0	144	4.3	148	9.9	<0.0001
Phobic and other anxiety disorders	F40-F41	158	3.3	84	2.5	74	4.9	<0.0001
Somatoform disorders	F45	98	2.0	37	1.1	61	4.1	<0.0001
Sleep disorders (all)	F51, G47	666	13.8	408	12.2	258	17.2	<0.0001
Sleep disorders not related to substance or known physiological condition	F51	298	6.2	185	5.5	113	7.6	0.007
Sleep disorders	G47	403	8.3	244	7.3	159	10.6	<0.0001
Extrapyramidal and movement disorders	G20-G26	185	3.8	107	3.2	78	5.2	0.001
Parkinson's disease	G20	128	2.6	69	2.1	59	3.9	<0.0001
Epilepsy	G40	130	2.7	95	2.8	35	2.3	0.314
Headache disorders	G43-G44	119	2.5	49	1.5	70	4.7	<0.0001
Headache disorders others than migraine	G44	110	2.3	48	1.4	62	4.1	<0.0001
Nerve, nerve root and plexus disorders	G50-G59	1,439	29.8	911	27.3	528	35.3	<0.0001
Lower back pain	G54.1; G54.4; G55.1	877	18.1	555	16.6	322	21.5	<0.0001

Brachial plexus disorders	G54.0	75	1.6	41	1.2	34	2.3	0.007
Cervical root disorders	G54.2	290	6.0	155	4.6	135	9.0	<0.0001
Thoracic root disorders	G54.3	213	4.4	122	3.7	91	6.1	<0.0001
Carpal tunnel syndrome	G56.0	76	1.6	49	1.5	27	1.8	0.384
Other mononeuropathies	G58	93	1.9	65	1.9	28	1.9	0.860
Polyneuropathies and other disorders of the peripheral nervous system	G60-G64	124	2.6	93	2.8	31	2.1	0.147
Transient ischemic attack	G45	545	11.3	290	8.7	255	17.0	<0.0001
Ischemic stroke	I63, I64	349	7.2	269	8.1	80	5.3	0.001

ICD-10-AM – International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification, N – number of patients.

The rate of distinct neurological and psychiatric comorbidities varied by men and women, the former more frequently presenting disorders related to the use of alcohol ($p<0.0001$) and ischemic stroke ($p=0.001$), the latter – to depression, anxiety and somatoform disorders, sleep, headache, nerve, nerve root and plexus disorders, and transient ischemic attack ($p<0.0001$ for all). Trends in the prevalence of comorbidity across age groups are presented in Figure 4.

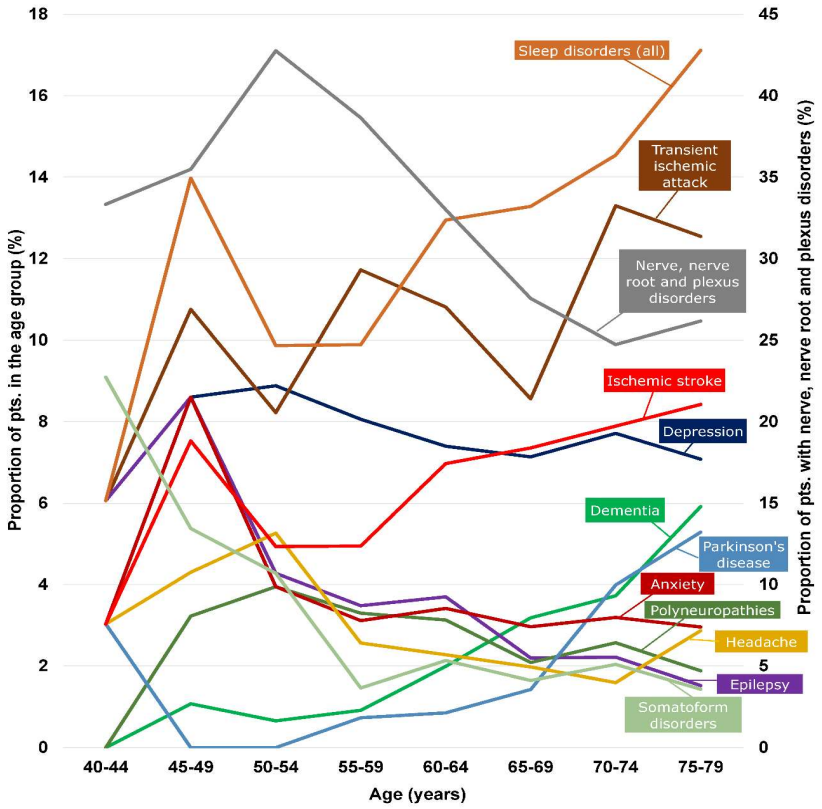


Figure 4. Prevalence of the selected disorders (overall prevalence ≥ 2%) in different age groups. Please note that nerve, nerve root and plexus disorders are plotted on a secondary axis

Results from the EFA of comorbidity patterns based on data from all patients are seen in Table 9. The KMO measure was 0.6738 (mediocre). Based on eigenvalues, two factors were extracted. The first factor grouped disorders the prevalence of which increased with age (except for epilepsy) and revealed a pattern of mainly neurodegenerative-cerebrovascular comorbidities. The second pattern matrix included psychiatric and sleep disorders. Odds ratios were calculated to better quantify the relationship between neurodegenerative-cerebrovascular disorders and epilepsy (variables in the first factor). The odds ratios of being diagnosed with epilepsy were significantly higher with co-existent Parkinson's disease (OR=3.624, 95% CI from 1.903 to 6.903), dementia (OR=4.130, 95% CI from 2.352 to 7.253), transient ischemic attack (OR=2.440, 95% CI from 1.606 to 3.707) and ischemic stroke (OR=3.051, 95% CI from 1.931 to 4.819).

Table 9. Factor loadings for the selected variables (disorders with prevalence ≥2%) when the analysis was performed with data from all patients in the sample (KMO=0.6738). Factor loadings >0.30

Comorbidity	**Factor 1**	**Factor 2**
	Dementia-epilepsy-cerebrovascular pattern	**Dementia-sleep-psychiatric pattern**
Dementia	**0.5595**	0.0492
Depression	0.2760	**0.4929**
Phobic and other anxiety disorders	-0.1090	**0.7867**
Somatoform disorders	0.0546	**0.5256**
Sleep disorders (all)	0.2165	**0.4225**
Parkinson's disease	**0.4702**	-0.0415
Epilepsy	**0.5087**	-0.1395
Headache disorders	0.2710	0.2425
Nerve, nerve root and plexus disorders	0.1476	0.2385
Polyneuropathies, other disorders of the peripheral nervous system	0.0458	0.1190
Transient ischemic attack	**0.5882**	0.0944
Ischemic stroke	**0.5686**	-0.0842

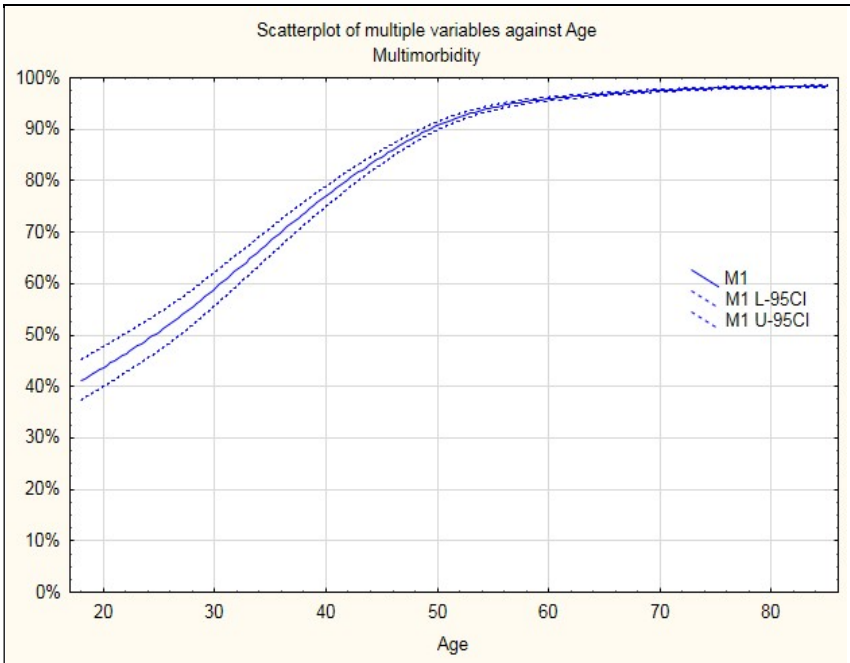
When performing the EFA with data from male patients, a Heywood case was obtained for Parkinson's disease. After omitting this variable, patterns of dementia-sleep-psychiatric comorbidities and dementia-epilepsy-cerebrovascular disease emerged with a KMO measure of 0.5923 and were similar to those obtained from the EFA of all patient data. While EFA results from female individuals pointed to mediocre sampling adequacy (KMO=0.6957), two variables were excluded before the analysis. Besides, only one factor was extracted, and the matrix's loadings did not outline a clear clinical profile.

5.3 Paper III

The cohort consisted of 452,578 patients with at least one chronic condition from the list of 32 chronic diseases (Table 1). The sample of patients with multiple (two or more) chronic conditions included 428,252 (94.63%) subjects. The proportion of women was higher than men (60.29 vs 39.71%, respectively) and men were almost five years younger than women (the mean age was 63.9 ± 14.2 vs 68.8 ± 14.0, respectively, $p<0.001$).

Age has the most significant effect on the occurrence of multimorbidity between 28 and 39.8 years of age with the proportion of subjects with one or more chronic conditions of 58 and 78%, respectively, at those age points. Still

significant, although the less pronounced impact was observed up until 50 years of age, reaching the proportion of patients diagnosed with at least two chronic conditions of 91% at the age of 50. After the age of 58, each consecutive year has a similar risk related to multimorbidity occurrence, resulting in the increase in the proportion of subjects with MM from 96% at the age of 58 to 98% at the age of 80 and over (Figure 5).

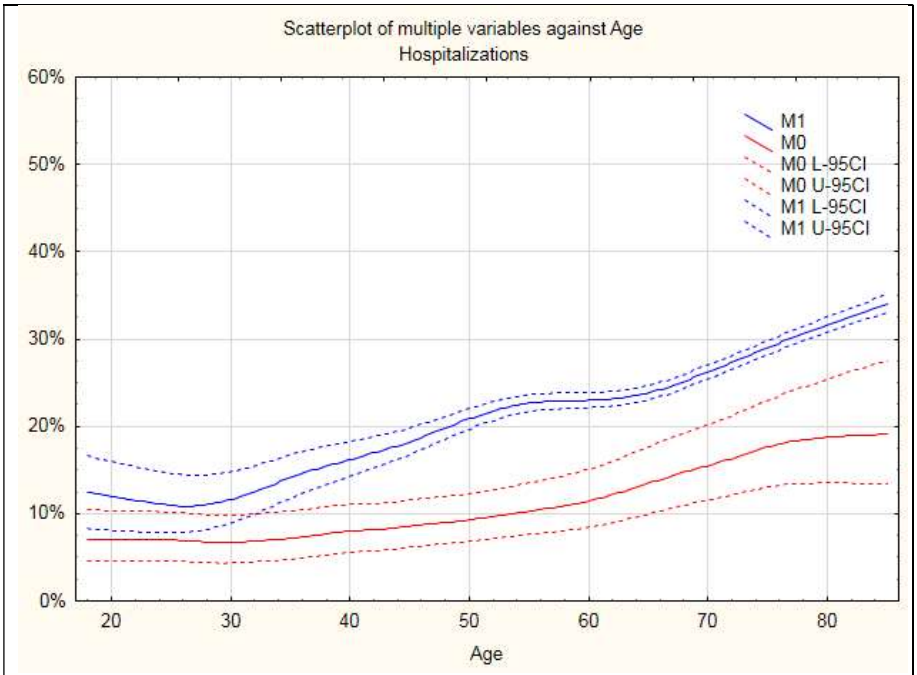


Breakpoints	**Estimate (age, years)**	**Standard Error**
Breakpoint 1	28.01	1.19
Breakpoint 2	39.85	1.54
Breakpoint 3	50.17	1.34
Breakpoint 4	58.02	2.75
Breakpoint 5	77.57	6.65

Figure 5. The relationship between age and the proportion of patients with multiple chronic conditions

Patients who are diagnosed with more than one chronic condition are heavy users of primary care and outpatient resources with minimal variability throughout the life cycle.

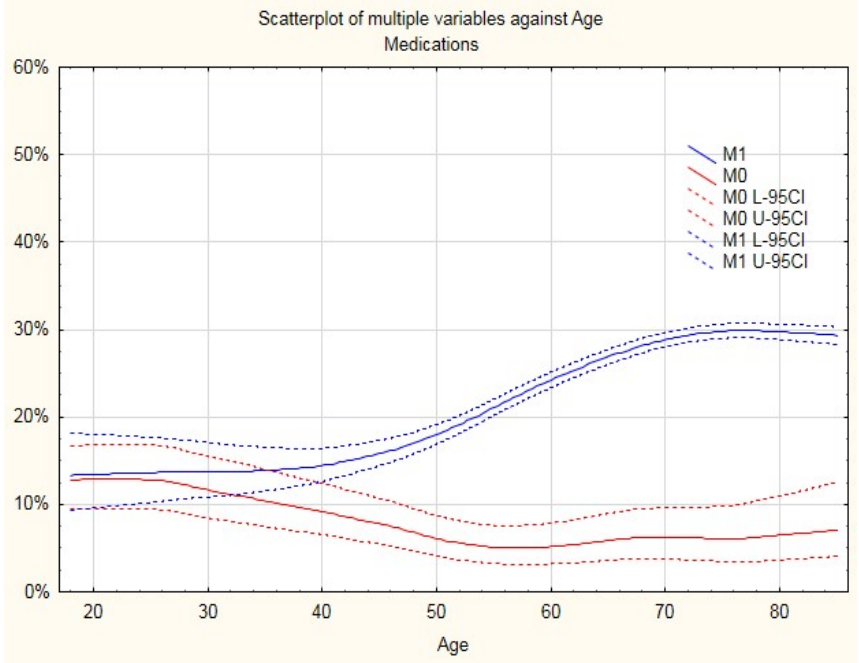
The number of hospitalisations in a single and more than one disease patients in this age group increased steeply and reached the proportion of 20% and 34%, respectively. The proportion of patients admitted to the hospital increases significantly with age in both multiple chronic conditions and one chronic condition groups. The age breaking point for the rapid increase in hospitalisations is about 29 years in both groups and grows steeply until the age of 57 years (Figure 6).



Multimorbidity	**Estimate (age, years)**	**Standard Error**
Breakpoint 1	19.86	0.35
Breakpoint 2	29.75	1.59
Breakpoint 3	56.51	0.87
Breakpoint 4	62.49	0.83
Breakpoint 5	83.7	0.37
One disease	**Estimate (age, years)**	**Standard Error**
Breakpoint 1	29.37	2.84
Breakpoint 2	57.98	6.12

Figure 6. The relationship between age and proportion of heavy inpatient (hospitalisations) care users (individuals in the top quartile of the number of hospitalisations per year (≥1)) in MM and one-disease subject groups

The proportion of patients with MM falling within the 4th quartile (using ≥EUR 312.56 per year) of expenditure on reimbursed medications increases from 15% at the age of 41 to 17% at the age of 51 and to 23% at the age of 57. At the age of 72, there is no substantial increase observed (Figure 7).



Multimorbidity	**Estimate (age, years)**	**Standard Error**
Breakpoint 1	41.09	1.37
Breakpoint 2	51.08	1.59
Breakpoint 3	57.2	1.63
Breakpoint 4	72.27	1.08
Breakpoint 5	82.83	0.6
One disease	**Estimate (age, years)**	**Standard Error**
Breakpoint 1	56.57	2.12

Figure 7. The relationship between age and proportion of heavy medication users (individuals in the top quartile of medication cost per year (≥EUR 312.56)) in multimorbid and one-disease subject groups

The proportion of patients with a single chronic disease falling within the same 4th quartile comes out at 12% at the age of 18, then declines gradually from

the age of 27 and reaches 5% at the age of 52. After the age of 56, the proportion remains almost stable without considerable increases at a later stage.

5.4 Paper IV

The sample of patients with at least one chronic disease included 452,769 patients, of which 273,016 (60.3%) were women and 179,753 (39.7%) men. Of these, 428,430 with two and more chronic diseases were classified as patients with MM and thus included in the further analysis. The mean age of all included patients was 67.83 (SD = 13.34) years, 69.71 (SD = 13.00) for females and 64.91 (SD = 13.33) for males. Patients with MM had on average 4.79 ± 2.05 chronic diseases, with the highest average number of chronic conditions of 5.25 ± 2.08 in the age group of 75–84. Notably, even in the youngest age group (18–24 years), the mean number of chronic diseases was 2.52 ± 0.84, gradually increasing with age and almost doubling at the age of 65–74.

The total cost of EUR 302,843,036.21 of all patients with MM per year was composed of primary care cost of EUR 14,194,613.70 (4.69%), outpatient cost of EUR 13,017,573.87 (4.30%), hospitalisation cost of EUR 156,078,078.78 (51.54%), and medication cost of EUR 119,552,769.86 (39.48%). Of them, EUR 93,590,567.02 (78.28%) were spent for reimbursed medication and EUR 26,834,777.81 (22.46%) for medications paid out of pocket medication). More than half of all expenses (51.54%) were allocated for hospitalisation costs and another large part (30.90%) went for reimbursed medications.

The total annual cost of health care services per patient with MM was on average EUR 707.15 (95% CI EUR 703.37–710.93). Although there was a higher proportion of women in the cohort, the annual cost was significantly higher for male patients, i.e. – EUR 756.52 (95% CI EUR 749.95–763.09) vs. EUR 631.28 (95% CI EUR 627.13–635.42), respectively ($p < 0.001$), and for patients coming from urban areas compared with those from rural areas, i.e. – EUR 688.79 (95% CI EUR 683.90–693.68) vs. EUR 674.59 (95% CI EUR 668.0–681.18) respectively ($p < 0.001$).

The assessment of the annual cost per patient with MM showed different spending for the specific health care services in different age groups. The highest average total amount of EUR 797.59 and the highest hospitalisation cost of EUR 443.00 was spent in the group aged 75–84, the highest cost of medication of EUR 304.64 was in the group aged 65–74, the highest cost for primary care of EUR 36.12 was in the group aged 65–85+, and the highest

cost for outpatient care amounting to EUR 34.76 was in the group aged 45–54.

Further analysis of the total average cost and the share of all spending for primary and outpatient visits, hospitalisation and prescribed medications calculated as a function of age showed a variably increasing trend for age groups and different health care services (Figure 8). The average total cost increased linearly and steadily from 18 to 75 years, was somewhat stable for older age and then decreased in the eldest group aged 85+ years. Services accounting for the biggest share of the average cost differed depending on the age group.

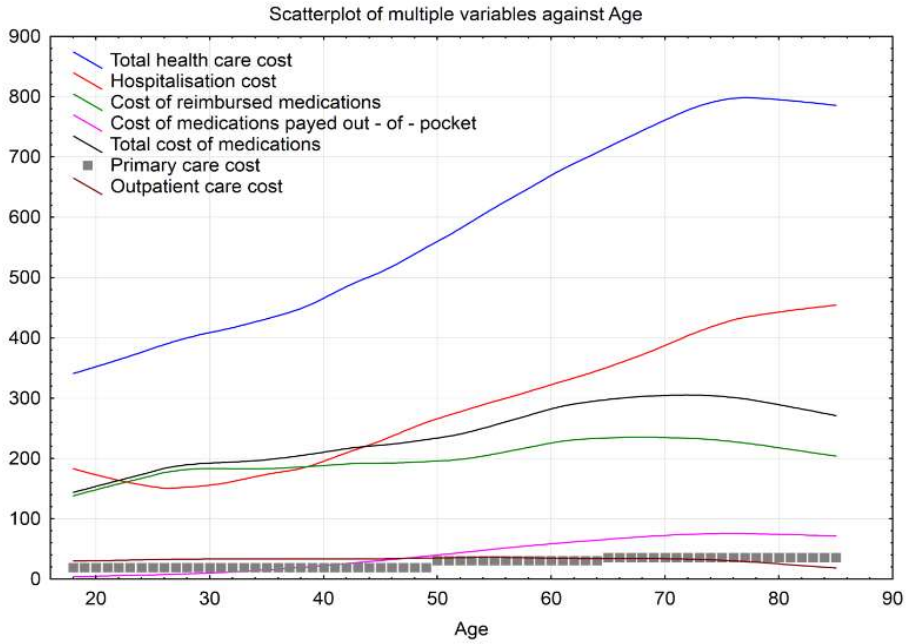


Figure 8. Trends of the mean annual cost per patient with MM in different age groups

Hospitalisation costs amounted to the highest cost for ages between 18 and 22 years and 40+ (with the minimum cost being at around 25 years of age), then increased steadily until around 79 years of age and then stabilised again. The average cost of medications increased in a similar steady fashion until around 72 years of age and stabilised afterwards. The cost of medications paid out of pocket increased more markedly than the reimbursed cost between 28 and 53 years. Importantly, although the price of medications and hospitalisation was comparable for age groups up to around 50 years, the rise of hospitalisation

cost was steeper, resulting in about 1.6 times higher average cost for the 85+ years age group. The average outpatient cost was fairly stable for the groups aged between 18 and 75 years and decreased from 75 years on.

In addition to the trends in health care costs, we estimated the age breaking points to identify the age when the costs for different health care services start to increase, decrease or become stable. Only one age breaking point indicated a decrease in health care expenses for hospitalisation at 22.09 years. All other age breaking points indicated either stable or increased expenses and the start of changes was noted in quite young patients – increased outpatient costs from age 26.53, out-of-pocket expenses from 27.82 and hospitalisation costs from age 38.64. At each age breaking point, every new illness increased costs by 1.26 times (Figure 9).

The distribution of age group shares in the total spending for MM patients' health care was similar for all services analysed. For all service categories, the relative share spent on age groups from 18 to 44 years was negligible, accounting for 3.10% of total spending, ranging from 0.13% for primary visits and 0.23% for outpatient visits to 1.33% for hospitalisation and 1.40% for medication costs. The share in the total spending gradually increased for older age groups and peaked in the group aged 65–74, accounting for 29.19% (1.39% for primary visits, 1.30% for outpatient visits, 14.77% for hospitalisation and 11.73% for medication costs), and 75–84 years, accounting for 29.53% (1.34% for primary visits, 0.99% for outpatient visits, 16.35% for hospitalisation and 10.85% for medication costs) (Figure 9).

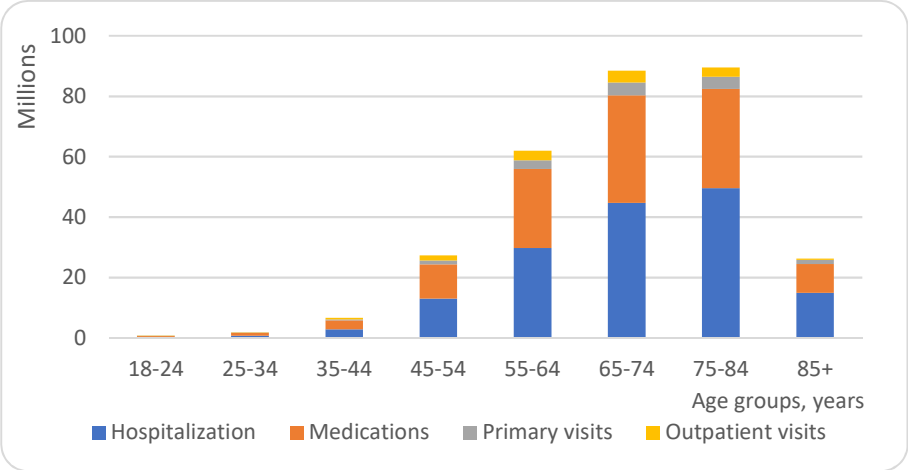


Figure 9. Share of health care costs in different age groups

As the number of patients in each age group differed (ranging from 2,000 in 18–24 years to 116,423 in 65–74 years), we have estimated the average

amount spent in EUR per patient per year for different health care services and plotted it against the proportion of expenses in the age groups. Although there was a gradual steep increase in expenses per patient with the increasing age and proportion of expenses almost in all age groups, this tendency was seen up to the age of 76–84 years. There was a decrease in expenses per patient after age 85+. The only service with expenses per patient stable from 65 years on was primary care. At the same time, there was a decrease in expenses for outpatient services and an increase in hospitalisation, signalling that those elderly patients tend to approach hospital emergency departments rather than outpatient clinics.

5.5 Paper V

The IMCM was implemented in five pilot sites from Spain (the Andalusian Health System and the Aragon Health System), Lithuania (VULSK, Vilnius and Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Kauno Klinikos, Kaunas), and Italy (Università Cattolica del Sacro Cuore (UCSC) Rome). As described in the methods section, a survey was carried out at the start of the project to identify the characteristics of the participating centres before the implementation of the IMCM. Results of the survey revealed some common goals for the five pilot sites, such as to increase multidisciplinary collaboration, promote evidence-based practice, and reduce inequalities in access to care and support services. A summary of some of the characteristics of VULSK is illustrated in Table 10. All five pilot sites included a six-month run-in period (patient recruitment), followed by a 12-month implementation period. Key indicators were measured at the end of the implementation. In all cases, the main care providers were either general practice physicians or nurses (or they were involved in the multidisciplinary meetings). Case managers were appointed in most interventions and social workers were also included as part of the core multidisciplinary team. All five sites reported that their patients would undergo a comprehensive assessment at the start and end of the integrated care process, but a few included a regular periodic assessment in-between. Most of the programmes reported some key common characteristics of the intervention and services, patient education and follow-up visits. Referrals between medical specialities were reported by all five sites and clinical tests in all but one. However, other characteristics of the intervention and services differed to some extent between settings.

Most sites used technologies in their interventions. For example, four of the five sites offered eHealth services and half of the multidisciplinary team

meetings were conducted virtually. All five sites reported using digital health care communication tools; these were mainly e-referrals but there were also other aspects like virtual conferences with patients and online appointment schedules. Three quarters of the sites had electronic systems for registering/ monitoring care processes and all used electronic health records. However, currently none of the programmes used electronic decision support systems. The survey also highlighted some noticeable deficiencies, especially in community and social resources.

Table 10. Characteristics of Vilnius pilot site (modified based on characteristics from all sites)

Patients	Patients with MM (2+ diseases)
Age	45–70
A target number of patients	200
General aim	To improve the quality of life, decrease the number of potentially avoidable hospitalisations/ readmissions and improve the quality of MM patient care by implementing the IMCM
Setting	Different primary health care centres (1 public, 1 private)
Implementation	A six-month run-in period (patient recruitment), followed by a 12-month implementation period

The five sites were required to implement at least one component from the 2018 MM care model proposed by CHRODIS [52], which proposed 16 components. VULSK included components from all five domains (Table 11). Most sites (four out of five) included regular, comprehensive assessments of patients, a multidisciplinary team, a case manager, individualised care plans, and shared decision making between patients and care providers.

Table 11. Components of the IMCM to be applied in Vilnius site of the interventions (modified based on characteristics from all sites)

Components of IMCM	**VULSK**
Delivery of the care model system	
Regular comprehensive assessment of patients	Yes
Multidisciplinary, coordinated team	Yes
Professional appointed as a coordinator of the individualised care plan (“case manager”)	Yes
Individualised care plans	Yes
Decision support	

Implementation of evidence-based practice	No
Training members of the multidisciplinary team	Yes
Developing a consultation system to consult professional experts	Yes
Self-management support	
Training of care providers in self-management support	No
Providing options for patients and families to improve their self-management	Yes
Shared decision making (care provider and patients)	Yes
Information systems and technology	
Electronic patient records and computerised clinical charts	No
Exchange of information between care providers and sectors by clinical information systems	Yes
Uniform coding of patients' health problems where possible	No
Patient-operated technology allowing patients to send information to their care providers	No
Social and community resources	
Supporting access to community and social resources	No
Involvement of social network (informal), including friends, patient associations, family, neighbours	Yes

VULSK implemented the care model in Family Medicine Centre but the implementation was also expanded beyond the primary care setting to include secondary and tertiary care physicians for creating patient management teams. It was aimed at MM patients attending primary care settings. The programme's main objective was to promote evidence-based practice among primary care MM patients to improve their quality of life, decrease the number of potentially avoidable hospitalisations and readmissions, and elaborate economic evaluation of the expenditure for the MM patients. The intervention targeted ten components of the IMCM (see Table 11) from all five domains. In particular, it included all components from the delivery of care model and the decision support components. The specific aims of the intervention included: (1) reducing adverse outcomes related to the presence of multiple diseases and the risk of drug-drug interactions by elaborating individualised integrated care plans; (2) optimising treatment, maintenance, and health care resources by coordinating individualised integrated care plan; (3) maximising outcomes and increasing continuity of care while decreasing fragmentation and optimising access to care and services through a case manager; (4) providing doctor-to-doctor decision support in situations where further clinical support or knowledge is needed outside of the core team through a consultation system of professional experts; (5) improving the patients' access to community resources, formal care, patient associations and support groups,

and psychosocial support by providing multidisciplinary care both in terms of different levels of the health care profession and different disease specialisations.
During the development of action plans, each pilot site defined key performance indicators to measure the success of the respective interventions. A common approach was chosen for assessing the impact of the interventions that consisted both of quantitative and qualitative analysis. The specific key performance indicators at VULSK are described in Table 12.

Table 12. Specific key performance indicators at VULSK: intermediate health-related outcome measures and process indicators (modified based on characteristics from all sites)

Process indicators	Existence of a guideline that describes the role of a case manager
	Percentage of patients with individualised care plan based on a comprehensive assessment
	Number of visits to primary care team per patient in 12 months
	Number of consultations in 12 months
Health-related outcomes	**Immediate**
	ACIC and PACIC+
	Long-term
	Number of unplanned visits in 12 months
	Number and duration of hospitalisations, admissions to emergency units, and avoidable hospitalisations in 12 months
	Number of incompatible drugs combination (drug interaction rate)
	EQ-5D questionnaire is a standardized instrument developed by the EuroQol Group as a measure for the health-related quality of life
	The EQ VAS records patients' self-rated health on a vertical visual analogue scale

PACIC+: The Patient Assessment of Care for Chronic Conditions+, ACIC: Assessment of Chronic Illness Care questionnaire, EQ VAS: EuroQol-visual analogue scales, EQ-5D: EuroQol 5D.

The ACIC [140] questionnaire was chosen as an appropriate quantitative measure of changes that care teams make in their health care systems and correlates well with other measures of productivity and system change. The PACIC+ [139] was also selected for quantitative measuring outcomes of the interventions. This tool measures specific actions or qualities of care that patients report having experienced during the intervention. The actions are congruent with the chronic care model and consist of 26 items. Both instruments will be collected and analysed pre- and post-implementation.

5.6 Paper VI

Paper VI summarises the first implementation results from 5 pilot sites evaluating data from the ACIC and PACIC+ questionnaires. The focus of the thesis was on Vilnius site results and total results from all pilot sites.

5.6.1 ACIC results

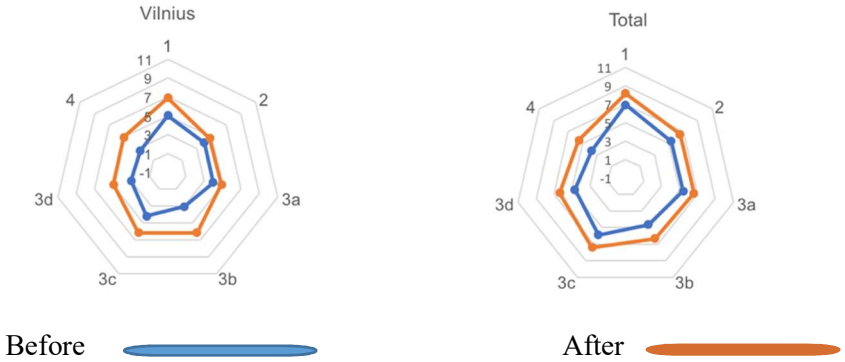
Before the implementation, members of the implementation teams (5 pilot sites) carried out a total of 14 ACIC surveys (5 from Vilnius). After the implementation, 17 ACIC surveys were completed (5 from Vilnius).
The pre-post implementation comparison of ACIC domains and a total score is displayed in Table 13. Pre-implementation ACIC total mean scores ranged from 3.70 in Vilnius to 7.90 in Andalusia. Post-implementation ACIC total mean scores varied from 5.52 in Vilnius to 8.04 in Kaunas. An increase in the ACIC scores was also found across sites except in Andalusia, although they were not statistically significant in general (Figure 10). For the total sample, there was a considerable increase in the ACIC scores at the end of the intervention in Parts 3b to 4 and ACIC total. Effect sizes ranged from 0.58 (Part 1) to 1.10 (Part 4) for ACIC dimensions, and it was 0.83 for the ACIC total score.

Table 13. Mean scores of ACIC survey subscales and total scale, before (pre) and after (post) implementation of the IMCM (modified based on all sites' ACIC scores)

		VULSK			**Total (5 pilot sites)**			
		Mean	**SD**	**p**	**Mean**	**SD**	**p**	**ES**
Part 1	**Pre**	5.01	0.87		6.91	2.16		
	Pos	6.88	1.42		8.16	1.39		
	Diff	1.87		0.066	1.25	1.65	0.072	0.58
Part 2	**Pre**	4.00	1.25		5.33	1.72		
	Pos	4.75	0.63		6.58	1.84		
	Diff	0.75		0.324	1.25	0.86	0.071	0.72
Part 3a	**Pre**	3.94	1.16		5.44	1.98		
	Pos	4.88	1.76		6.61	2.00		
	Diff	0.94		0.408	1.17	1.35	0.128	0.59
Part 3b	**Pre**	3.06	0.43		4.65	2.01		
	Pos	6.13	1.45		6.34	1.92		
	Diff	3.07		0.007	1.69	1.21	0.026	0.84

Part 3c	**Pre**	4.17	0.76		5.86	1.73		
	Pos	6.13	1.74		7.38	1.65		
	Diff	1.96		0.085	1.52	1.74	0.026	0.88
Part 3d	**Pre**	3.00	0.54		4.68	2.28		
	Pos	4.90	1.99		6.34	1.81		
	Diff	1.9		0.115	1.66	3.32	0.035	0.73
Part 4	**Pre**	2.71	0.77		3.74	1.63		
	Pos	4.96	1.81		5.54	1.50		
	Diff	2.25		0.063	1.8	0.976	0.011	1.10
Total	**Pre**	3.70	0.72		5.23	1.78		
	Pos	5.52	1.30		6.71	1.45		
	Diff	1.82		0.051	1.48	1.41	0.022	0.83

Mann-Whitney test. Pre: pre-implementation score; Post: post-implementation score; Diff: difference in scores post-pre implementation; SD: Standard deviation; ES: effect size; ACIC components: Part 1, delivery system organization; Part 2, community linkages; Part 3a, self-management support; Part 3b, decision support; Part 3c, delivery system design; Part 3d, clinical information systems; and Part 4, integration of IMCM components.



1. Delivery system organization; 2. Community linkages; 3a. Self-management support; 3b. Decision support; 3c. Delivery system design; 3d. Clinical information systems; 4. IMCM component integration.

Figure 10. ACIC mean scores before (pre) and after (post) implementation of the IMCM, Vilnius site and total sample (modified based on all sites' ACIC scores)

5.6.2 PACIC+ results

208 patients (45 from Vilnius) completed the PACIC+ survey both pre- and post-implementation. At the Vilnius site patients had a mean age of 61 (SD: 9.1) and 51.1% of patients were women. In general, women accounted for 52.2% of the total sample with a mean age of 62.9 (SD: 17.1; range: 20-93). The mean *change score* for the total sample was 4.91 (SD: 1.14); 58% of the total sample reported better care in the last 12 months. For the Vilnius site, these indicators were 4.7 (SD: 0.8) and 57.1%, respectively.

The baseline PACIC+ summary score ranged from 2.91 (SD: 0.96) in Andalusia to 3.90 (SD: 0.78) in Vilnius. *Arrange* was the domain with the lowest scores across sites, while *advise* had the highest scores. After the intervention, the PACIC+ summary score ranged from 3.46 (SD: 0.97) in Andalusia to 4.55 (SD: 0.35) in Aragon. As at baseline, *arrange* was the domain with the lowest scores in all sites and *advise* was the domain with the highest scores.

At follow-up, the sample was composed of 210 patients. A significant increase was found in the PACIC+ summary score (Table 14), ranging from 3.25 at baseline to 4.03 after the intervention ($p< 0.001$). PACIC+ domains also increased significantly, with *arrange* being the domain with the highest increase (0.99), although *advise* was the domain that reached the highest score (4.16, SD: 0.75). By sites, the lowest increases were observed in Vilnius (0.09 in *assist* to 0.26 in *arrange*). The estimated marginal means in the PACIC+ 5As summary score by pre- and post-implementation in the Vilnius site were 3.89 and 4.06, respectively.

Table 14. Mean scores of PACIC+ survey subscales and total scale, before (pre) and after (post) implementation (modified based on all sites' PACIC+ scores)

		Vilnius (n=40)			**Total (5 pilot sites) (n=210)**			
		Mean	**SD**	**p-value**	**Mean**	**SD**	**p-value**	**Effect size**
Assess	**Pre**	3.95	0.84		3.34	1.03		
	Post	4.05	0.83		4.10	0.88		
	Diff	0.10	0.54	0.226	0.77	0.96	<0.001	0.75
Advise	**Pre**	4.10	0.73		3.42	0.99		

	Post	4.23	0.70		4.16	0.75		
	Diff	0.14	0.62	0.177	0.74	0.97	<0.001	0.75
Agree	**Pre**	3.87	0.90		3.23	1.07		
	Post	4.09	0.77		4.01	0.87		
	Diff	0.21	0.73	0.072	0.78	1.01	<0.001	0.73
Assist	**Pre**	3.78	1.04		3.05	1.08		
	Post	3.87	0.82		3.82	0.90		
	Diff	0.09	0.79	0.475	0.76	0.96	<0.001	0.70
Arrange	**Pre**	3.17	1.09		2.48	1.11		
	Post	3.43	0.88		3.48	1.03		
	Diff	0.26	0.77	0.040	0.99	1.19	<0.001	0.89
5 As Summary	**Pre**	3.90	0.78		3.25	0.95		
	Post	4.07	0.75		4.03	0.82		
	Diff	0.17	0.62	0.093	0.78	0.90	<0.001	0.82

Paired Student's t-test; Diff: difference in scores post-pre-implementation; SD: Standard deviation; Missing data on PACIC+ pre, for Aragon: imputed with a regression model.

The regression models of PACIC+ domains and the summary score showed that a bigger change in PACIC+ was mainly associated with lower scores in corresponding PACIC+ domains at baseline (standardised beta, β= -0.72 in *advice*, to -0.692 in *assess*, p< 0.001) and a greater change (β= 0.24 in *agree* to 0.34 in *assess*, p< 0.001) in ACIC domain 1 (delivery system organisation) (Table 15).

Table 15. Linear regression models of PACIC+ domains at post-implementation

Model		**Standar-dised beta**	**t**	**p-value**	**95% CI**		**R^2**
Assess	***(Constant)***		*6.085*	*<0.001*	*1.665*	*3.261*	**0.44**
	Assess pre	-0.604	-10.849	<0.001	-0.667	-0.462	
	ACIC1 diff.	0.335	4.220	<0.001	0.107	0.296	
	ACIC4 diff.	-0.212	-2.767	0.006	-0.359	-0.060	

Advise	***(Constant)***		*8.925*	*<0.001*	*2.488*	*3.899*	**0.55**
	ACIC1 diff.	0.266	3.742	<0.001	0.077	0.248	
	Advise pre	-0.716	-14.543	<0.001	-0.803	-0.611	
Agree	***(Constant)***		*7.247*	*<0.001*	*2.015*	*3.522*	**0.48**
	ACIC1 diff.	0.243	3.172	0.002	0.058	0.250	
	Agree pre	-0.658	-12.304	<0.001	-0.717	-0.519	
Assist	***(Constant)***		*6.940*	*<0.001*	*1.844*	*3.307*	**0.46**
	ACIC1 diff.	0.296	3.737	<0.001	0.085	0.273	
	ACIC4 diff.	-0.225	-3.050	0.003	-0.369	-0.079	
	Assist pre	-0.656	-11.762	<0.001	-0.684	-0.488	
Arrange	***(Constant)***		*6.553*	*<0.001*	*2.023*	*3.765*	**0.46**
	ACIC1 diff.	0.287	3.679	<0.001	0.099	0.328	
	ACIC4 diff.	-0.242	-3.283	0.001	-0.476	-0.119	
	Arrange pre	-0.649	-11.836	<0.001	-0.806	-0.576	
5As summary	***(Constant)***		*6.867*	*<0.001*	*1.802*	*3.254*	**0.45**
	ACIC1 diff.	0.299	3.812	<0.001	0.082	0.258	
	ACIC4 diff.	-0.178	-2.333	0.021	-0.306	-0.026	
	5As summary pre	-0.625	-11.270	<0.001	-0.697	-0.490	

Other variables included in the models: sex, age, civil status, education, activity, ACIC2 diff. Pre: pre-implementation score. Diff.: difference in scores between post- and pre-implementation.

Greater changes in PACIC+ domains *assess*, *assist,* and *arrange* and in summary score scores were consistently associated with a lower change in domain 4 of ACIC (integration). Changes in PACIC+ scores were significantly associated neither with changes in ACIC domain 2 nor with socio-demographic characteristics. The explained variance (R^2) ranged from 0.44 (PACIC+ *assess* model) to 0.55 (*advice*).

6. DISCUSSION

6.1 Paper I

The interactions between COPD and comorbidities have been studied for many years, but mechanisms remain unclear [81], [85], [90]. Airflow limitation, lung parenchyma destruction, and systemic manifestations (systemic inflammation, hypoxia, and hypercapnia) lead to skeletal muscle wasting, osteoporosis, decreased physical activity, depression, etc. Smoking, hypoxia, and systemic inflammation influence the interactions between COPD and comorbidities [67], [68], [70]–[72], [85], [148]. Some pathophysiologic changes in chronic obstructive pulmonary disease can have a direct impact on heart function due to right heart overload [20], [85], [149].

As expected, our cross-sectional analysis pointed out a strong association between the presence of COPD, heart failure and ischemic heart disease. Clustering of comorbidities also confirmed the significance of CVD in COPD patients. This corresponds to other studies of general populations [74], [85]. COPD and CVD share several risk factors, above all smoking and ageing, but the association between COPD and CVD is not thoroughly investigated. However, individuals with COPD have a 2–3-fold increased risk of CVD compared to controls when adjusted to age and tobacco smoking [150]. Therefore, systemic inflammatory changes caused by COPD are also a risk factor for CVD [74], [151], [152]. Studies of the Swedish [149] and German [90] populations showed similar results.

The severity of COPD does not influence the appearance of cardiovascular comorbidities, but the presence of CVD may require a comprehensive therapeutic approach, therefore the consequences of CVD in case of COPD often are underdiagnosed and untreated. The correlation between comorbidities and the severity of bronchoconstriction has not been proven [90]. There were no data on the severity of COPD in the Lithuanian NHIF database, but the enrolment of patients based on the usage of broncholitics for at least six months per year might suggest higher severity of COPD.

Bronchodilators used for the treatment of COPD may cause tachycardia, hypokalemia, QTc prolongation, peripheral vasodilation, etc., less common with long-acting inhaled bronchodilators [153], and therefore the utilisation of cardiovascular-related drugs is higher in COPD. According to extensive population-based analyses, beta-blockers might reduce the risk of mortality in patients with COPD and heart failure [90], [153]. In our COPD cohort, long-

acting or short-acting bronchodilators were not specified and the usage of beta-blockers was not assessed.

A large longitudinal study by Hyun Lee et al. [154] showed the difference in the profile of comorbidities by ethnicity and race in COPD patients in the US and Korea. White non-Hispanic persons had a higher prevalence of dyslipidemia, myocardial infarction, and osteoarthritis [154]. In addition, Westerner's comorbidity profile was reported in Japanese patients [155]. As in the Lithuanian population, white non-Hispanics are predominant, our study showed the highest prevalence of CVD. Cluster analysis revealed the linkage of dyslipidaemia to CVD only in patients without COPD; in the case of COPD, dyslipidaemia was linked to the endocrine-metabolic cluster. The Lithuanian study identified the cardiovascular cluster both in COPD and non-COPD groups, but different clustering trends of dyslipidemia suggest a higher impact of hypoxemia and systemic inflammation in the pathogenesis of CVD in COPD patients rather than of dyslipidaemia.

Substantial evidence was found of an increased risk of lung cancer in patients suffering from COPD compared with those without the disease. A meta-analysis of 21 studies showed pooled 2.79% prevalence and more than six-fold odds of lung cancer in COPD [156]. Lithuanian data demonstrated a higher prevalence of lung cancer but a similar odds ratio. Higher odds of having had lung cancer were found in the German population, but the prevalence was similar to the general population [90].

Epidemiological studies have identified a strong association between COPD and comorbid psychiatric disorders, with the prevalence of depression ranging from 16% to 88.4%. Higher prevalence increasing with the age of ischemic stroke, transient ischemic attack, dementia, Parkinson's disease and sleep disorders have also been reported in different studies [83], [157]–[159]. The prevalence of depression in COPD was not statistically significant, but these patients were more likely to develop depression; a single cluster including depression and other mental diseases was found in COPD males. Declining health status, ageing, frailty, systemic inflammation, smoking, and hypoxemia on brain function might have a substantial effect on the development of reactive depression, but the mechanisms of interactions are not fully understood [74], [85].

Higher prevalence of diabetes mellitus has been reported in COPD patients [81], [85], [90], [160]. Our study revealed increased odds of diabetes and kidney diseases in COPD, but the prevalence of diabetes was not higher. A gout-kidney cluster was found in COPD males.

Previous clustering studies performed in COPD patients used different lists of chronic conditions. Only a few studies were prospective, with a low number of patients having COPD confirmed by spirometry [22], [155]. However, our study was in line with those using individual retrospective data from large registries [23], [24].

In a prospective observational study of 445 Japanese subjects with COPD confirmed by spirometry, Chubachi et al. [155] also used Ward's hierarchical clustering methodology as in our study. But unlike our study, a single metabolic and cardiovascular cluster with a lower prevalence of CVD was revealed in Japanese. A few comorbidities cluster corresponding to Vanfleteren's study [22] was not found in the Lithuanian population. This is probably due to our definition of COPD, as mentioned previously, where more severe patients were included. The musculoskeletal cluster detected in Lithuanian data was not found in the Japanese study [155]. Some similarities were found in psychological (vs. mental) and malignant clusters. An anaemic cluster has been found only in COPD women.

The chronic conditions corresponding to our list of comorbidities were included in Hansen's et al. [24] study based on individual data from different registries in Denmark. This study also showed the importance of the CVD clusters, identifying heavy users of health care systems. The highest rate of hospitalisation was observed in patients with heart disease. Our findings on hospitalisation confirm the importance of CVD in COPD patients. However, Hansen's et al. [24] study has not provided sufficient data to compare other clusters.

Carmona-Pírez et al. [23], [161] in the Spanish EpiChron cohort study showed that MM affects about 75% of patients suffering from chronic obstructive airway diseases; the prevalence of MM was higher than in the general population. The Lithuanian data revealed similar clustering of the most prevalent comorbidities. The stroke-cancer-sensor cluster found in Lithuanian COPD males corresponds to the Spanish neuro-substance use-malignancy cluster leading to high mortality [23]. However, there were some differences in the clustering of less prevalent diseases possibly due to different lists of illnesses included in the study.

Divo and Celli [20] summarised the findings of 11 studies on COPD and comorbidities performed mainly using self-reported data or data from administrative databases. CVD, lung cancer, depression, diabetes, and others were found to lead to decreased functional capacity and increased risk of mortality in COPD patients.

The prevalence of COPD (1.37%) was lower than could be expected from other reports, probably because of the shift of focus towards more active forms of COPD in the current study [10], [162]. A higher male/female ratio (2.3) than that observed in other studies (1.5) could also be partly explained by the sample selection strategy [163], [164]. A relatively sharp increase in both COPD and some of its neurological and psychiatric comorbidities with older age was indicated in our study. Cerebrovascular, neurodegenerative and sleep disorders followed a positive trend when presented both in absolute estimates and in relative measures of prevalence among individuals in selected age groups. Women were more likely to suffer from mood disorders, sleep, anxiety problems, and headaches, and these gender differences were consistent with findings from other studies [163], [164]. Evaluation of the prevalence of neurological and psychiatric disorders in COPD in comparison with a control group fell beyond the scope of this study.

The EFA revealed two possible latent variables that underlie the neurological and psychiatric comorbidities in COPD. One of them grouped dementia, ischemic stroke, transient ischemic attack, Parkinson's disease and epilepsy to the pattern of epilepsy, neurodegenerative and cerebrovascular disease. In this sense, patients with COPD have been shown to age faster because of the earlier onset of COPD comorbidities [26], [165]. It is hypothesised that shared risk or genetic factors, chronic hypoxia, oxidative stress, and systemic inflammation underlie an increased risk of co-occurring pathologies in COPD. The damage to the endothelium probably caused by an increase in molecules related to inflammation or reactive oxygen species might represent the evidence of vascular impairment in COPD. This process promotes atherosclerosis and results in an increased risk of stroke [166], [167]. Systemic inflammation and a dysfunctional reaction to hypoxia might contribute to the more frequent development of Parkinson's disease in COPD [168]. Similar pathological pathways, including systemic inflammation, chronic hypoxia, hypercapnia, oxidative stress and previous cerebrovascular events, could be important in developing dementia [169], [170]. Seizures associated with neurodegeneration or those secondary to cerebrovascular events may occur in epilepsy associated with COPD [171]–[175]. Overall, the relationship between the pathologies grouped under this factor might be highly complex.

Both anxiety and depression are frequent in COPD, often present at the same time and are related to the level of somatic symptoms manifestation [30], [176], [177]. Impaired sleep is also significant comorbidity of COPD [93]. An

obstructive sleep apnea-COPD overlap syndrome can even be recognised as a separate diagnostic entity with increased hypoxia and inflammatory processes [178]. The link between sleep disorders, depression and anxiety in COPD has already been proven earlier and replicated in the EFA during this study [179], [180]. The association of sleep disturbances with cognitive deficits also might occur in COPD [181]. Our study revealed the possibility of such a relationship only among men with COPD. The psychiatric-sleep pattern of COPD comorbidities could be relevant for clinical practice just as targeting poor sleep in COPD might be beneficial in reducing a patient's psychiatric symptoms [182].

6.3 Paper III

Regardless of the methods used, previous studies on the prevalence of MM showed that MM is the "norm" for people aged 65 years or older [35], [110], [111], [115]. Our study revealed that the proportion of subjects with MM related healthcare utilisation starts to increase already by the age of 28-30.

A significantly higher proportion of subjects with MM fall into the 4th quartile of heavy health care resources users compared to those with a single chronic condition. Previously published data about the increasing prevalence of chronic conditions [112] distilled the need for further steps in identifying the profile of chronic diseases in different age groups and further improvement of the preventative programmes.

MM research is mainly focused on older people, and almost every study has noted that additional years of life create an additional opportunity for acquiring other chronic conditions [111], [115]. Though our results are in line with previous analyses, in the case of MM the first age breaking point appeared at 28 years with a proportion of 58%, which is a considerably younger age than previously expected. Also, the significant change in increase continued up to 77 years of age. Navickas R. et al. [59] analysing patients at the age of 45 and older found that over 10% of this population was already diagnosed with 2 or more chronic conditions. Our research analysing patients from 18 years old showed the greatest increase in the proportion of patients with MM in the study population between 28 and 40. McLean et al. [111] already suggested that MM is not just a problem of old age. Adults under 65 with MM also pose a challenge for health and social care systems. In the study by Sauver et al. [110], the number of people with incident MM was substantially greater in people under 65 compared with people aged 65 or older. Our results identifying the age breaking points for the proportion of MM

subjects and the increase in this proportion shed additional light on previously reported data.

The data of this and previous studies imply the need to target preventive efforts at a much younger population and to adjust a more complex, patient-centered view. Single-disease care model nowadays no longer fits the needs of the health care system and patients with MM [2], [41]–[43]. In 2010 the US Department of Health and Human Services highlighted the critical need to identify groups of individuals at higher risk of the first appearance of MM. It is essential to develop effective strategies for the early identification of patients at risk to prevent MM and its adverse health outcomes, such as functional decline and disability, hospitalisations, polypharmacy, worsening quality of life and premature death, which lead to greater use of health services and higher health care costs [2], [35], [37], [41], [59].

We found that by the age of 50, the increase of patients with more than one chronic condition slows down, secondary to a rather large proportion being with MM by the time, which is also in line with MM health care resources usage. This may indicate that the usage of health care resources starts to grow earlier, drawing attention towards more effective prevention of chronic disease onset, potentially with better chances for reduction.

In single disease patients the rate of primary care visits steeply decreases throughout their lifetime. This might be caused by increasing patient expertise or self-management and specialist involvement. However, lack of access as patients get older also could be an important factor not to be missed. Nevertheless, the rate of primary care visits for patients with MM increase throughout the life cycle.

In our study, the increase in the proportion of heavy inpatient care users corresponds to the increase in the proportion of MM starting at the age of 28. Moreover, the proportion of heavy users of primary care and specialist consultations decreases with an increase in the proportion of hospitalisation care users at the age of 85 and above. As we have chosen to analyse patients in 9-year age intervals, further breaking down of the group aged 85+ was not continued due to the very small number of patients aged 94+.

These results are in line with previous studies. Wolff et al. [183] found a strong positive relationship between the risk of avoidable hospital admissions and the number of chronic diseases in individuals aged 65 or older. To summarise, high quality well-coordinated and shared health care approach may not only help to prevent more common outpatient consultations, but also lower the rate of hospitalisations and emergency visits [57].

Our study showed that the proportion of MM patients falling into the 4th quartile of heavy reimbursed medications users starts to increase at the age of 41 and this curve stabilises only at the age of 72. Meanwhile, the proportion of patients with a single chronic condition falling in the same 4th quartile is smaller and decreases gradually at the age of 27. This indicates that each additional chronic disease in MM patients requires higher medication utilisation even at a young age. Moreover, every chronic disease may worsen another one generating the need to intensify the treatment for every chronic condition and thus raising all health care expenditures. Glynn et al. [36] reported increasing costs with the increasing number of chronic diseases. A systematic review by Lehnert et al. [39] revealed the almost exponential rose in total health care expenditures with the number of chronic conditions. Bahler et al. reported 5.5 times higher mean total costs in MM compared with the non-MM sample [35], [109]. These data confirm that patients with MM require much more health care resources with every additional disease.

6.4 Paper IV

About 50 million people live with MM in the EU and they use 70–80% of total health care resources [184]. This study revealed that about 60% of the total health care costs are attributed to the age group of 65–84 years. We have also estimated a steep increase in hospitalisation costs starting at the early age of 45 with the peak at 75–84 years, but the costs for outpatient care decreased in the group aged 75 and older. The number of chronic diseases was increasing with age and was the highest in 75–84 years reaching the mean of 5.25 (SD = 2.08). These results are in line with previous research and can partially explain high health care costs. In 2005, the US average Medicare costs per beneficiary associated with one, two and more than three chronic diseases increased by 7,172, 14,931, and 32,498 US dollars, respectively [185]. In Ireland, the total healthcare costs adjusted per capita increased from EUR 760.20 for 0 to EUR 4096.86 for more than four chronic diseases [36].

The analysis of the structure of expenses in Lithuania showed that the highest proportion of all expenditures was used for hospitalization and medication reimbursement in all age groups and the total cost for patients with MM was EUR 302,843,036.21 per year. More than 50% of all the expenses were allocated for hospitalisation costs and more than 30% for reimbursed medications. Our study revealed different hospitalisation costs in different age groups. The highest proportion of costs was found at the age between 18 and 22 and from 40 years on. It steadily increased until the age of around 79 and

then stabilised again. The impact of MM on hospitalisation costs was investigated in numerous studies. Patients with MM aged 72 years and above used a substantial range of health care resources (25% due to inpatient care, 20% to outpatient care and 20% to medications) in Germany [121]. A Swiss study [35] of MM patients (mean age 74.9) showed that outpatient services accounted for 50.80% of the total costs, inpatient services for 24.10%, and medication costs - for 25.10%.

A cross-sectional survey in Singapore [186] covering patients aged 60 and above showed that health care costs were three to seven times higher for patients with MM than those with none or one chronic disease. A retrospective cohort study in the province of Ontario [187] demonstrated that among individuals under 65 hospitalisations accounted for 47% of total healthcare costs, outpatient services - 32%, medication - 10% and continuing care costs - 6%. In older adults, the distribution of costs was - 41%, 23%, 19% and 15%, respectively. Our data align with previous research, but the proportion of hospitalisations is very high in our study. This could be due to a clear tendency to reduce outpatient services and regular use of primary care services from the age of 65. Current health policy in Lithuania promotes the active involvement of family doctors in the care of patients with MM and strongly suggests individual consideration of whether the patient needs to be referred to a specialist to avoid unnecessary consultations. However, our data showed that reduced referral to specialists is not an optimal solution. The budget spent on primary and outpatient care was about 11 times lower than the hospital care expenses. This strongly suggests that current outpatient care is insufficient and inappropriately funded for patients with MM. Improvement in outpatient care management and implementation of an IMCM might contribute to optimising the use of health care resources, reducing hospitalisation costs, and improving patients' health.

We estimated that expenses for medication costs account for 39.60%, of which the cost for reimbursed medications is 30.90% and the cost for medications paid out-of-pocket - for 8.70% of the total budget. Previous studies showed a significant increase in spending with each additional chronic disease [188]–[190], but detailed analysis across age groups are lacking in the literature. Patients at 65 and older are at risk of lower income and non-compliance with prescribed treatment. Polypharmacy due to MM, possible drug adverse events and frailty reduce the effectiveness of care in patients with MM despite high spending.

Our study found a tendency to decrease health care expenses per person for all services except primary care in 85+ patients with MM compared with the

age group of 65–84 years. More studies are needed to explain this tendency even though similar results were obtained in the Basque Country study [191]. We found that annual health care expenses in men were almost 20% higher than in women. This might be related to the different clustering of diseases, sociodemographic factors, lifestyle, and the perceived importance of health in men and women or inequality. According to Statistics Lithuania, the average life expectancy is 69.5 years for men and 80.0 years for women [192]. Therefore, we cannot explain lower expenses for women by the age factor. This finding differs from other studies and cannot be explained by the age factor. In the Ontario study [193], expenses for women aged 65 and older were higher and were partially explained by longer life expectancy and a greater risk of MM in older women than men. Other studies reported increased costs of medications and out-of-pocket payments for women [188], [194]. Thus, more research is needed to assess gender differences in the Lithuanian MM population.

There are plenty of other factors influencing health care expenses and we face a challenge in measuring MM costs [194]. Although our study estimated that each additional NCD increased cost by 1.26 times, our aim is further research using a multifactorial approach for a more comprehensive situation analysis.

6.5 Paper V

The article described the methods and critical stages of the pre-implementation phase of five pilot sites implementing an IMCM as part of CHRODIS-PLUS. This common implementation strategy showed the process of adapting care models according to local and national specificities.

The scientific information on such interventions is still lacking [195], [196]. Existing interventions for MM patients often apply different methods and care components, thus challenging a comparison between strategies. Further, as previous interventions have been applied mainly in US counties [195], [196], the application of such models and their components in different settings, including Europe, remains unclear.

The results of this study may bring added value to the knowledge being currently built in two cluster randomised trials in Spain and the United Kingdom [46], [48]. Results from the 3D trial [46], based in the United Kingdom, suggest that an intervention on MM patients in primary care based on a comprehensive assessment every six months does not improve patients' perceived illness burden, treatment burden or quality of life. Instead of disease-focused care a patient-centred care model in the 3D trial was

administered. It focused on improving the coordination, continuity, and efficiency of care via comprehensive multidisciplinary assessments twice per year. However, although patient outcomes were not improved, patient stratification techniques were not applied. Patient stratification might help to identify the most complex-to-treat and demanding groups, who would possibly benefit from the care intervention [137]. The Spanish MULTIPAP project [48] selected patients based on both MM and polypharmacy. The trial aimed to examine the effectiveness of an intervention on improving drug prescriptions and family-physician training on MM, shared decision making and appropriate prescribing. A physician-patient interview was drawn upon the Ariadne principles based on a comprehensive assessment, with consideration being given to the preferences of the patient. The results of the MULTIPAP trial, as well as CHRODIS PLUS intervention, might provide more knowledge on the elements of integrated care that can lead to successful outcomes in MM patients.

6.6 Paper VI

The study aimed to assess the impact of the pilot implementation of the CHRODIS IMCM in five European sites considering the perspective of both patients and health care managers. Despite the differences existing among the sites in the IMCM components implemented and target populations, the intervention had a positive effect across all health care systems tested. The total ACIC score increased from 5.23 at baseline, to 6.71, which means reasonably good support for the care of chronic diseases [106], representing a big change (effect size 0.83). Interventions also resulted in statistically significant positive changes from the patients' perspective in almost all sites. A significant increase in scores was achieved in ACIC domains related to delivery system design, decision support, clinical information systems, and integration of IMCM components. Some increase was observed in all ACIC domains. The study showed that the *delivery system design* component benefited most from the IMCM implementation, as indicated by its greater effect size. This component is included in most comprehensive care programmes for MM [51]; however, the dimension requires well-trained clinical teams capable to support patient self-management and coordinate preventive care [198]. In our study, all implementing sites developed evidence-based practices and a consultation system to support patient decision-making, linked to a clinical information system for providing clinicians with feedback and promoting continuity of care.

All sites except one Spanish site showed an increase in ACIC total and domains scores, but the change in the decision support domain was found to be significant in the Vilnius site only.

PACIC+ results revealed that the interventions were well appreciated by patients in general. All sites included patients with similar sociodemographic characteristics reflecting the population that attended each site. The magnitude of pre-post implementation changes was more remarkable than those reported by previous studies on guided care [199] or goal-setting interventions [200] for older adults with MM. Patients showed the highest degree of satisfaction with care in the *advice* dimension and the lowest one - in the *arrange* domain. Despite the heterogeneity of samples in our intervention, these results were in line with previous studies [201]–[203], indicating the significance of improving actions to arrange patients' follow-ups.

The lower change reported by patients in the Vilnius site might be due to the highest baseline PACIC+ scores, meaning the least room for improvement. The Vilnius pilot site included mainly patients with complex chronic conditions. Therefore, a longer period of the intervention might be required for a significant change in the quality of care. Due to the complexity of MM patients, there is a need for new services and additional funding to adapt to the emergent needs of the IMCM.

About 50% of the variance in the change of PACIC+ scores could be explained by baseline PACIC+ and ACIC scores, independently of patients' characteristics. The lack of association between PACIC+ scores and patients´ characteristics was previously reported in several studies [203]–[205]. Our study revealed that a more considerable change in patients' satisfaction after the intervention was associated with a lower baseline value in the respective PACIC+ dimension. It means that more benefits from the intervention might be achieved by targeting the least satisfied patients.

A more significant change in the ACIC delivery-system design dimension was associated with a greater change in patient satisfaction. The delivery system design component of the IMCM was targeted in every site intervention, including the following dimensions: regular comprehensive assessment of patients; coordinated multidisciplinary teams; case managers; and care plans tailored to suit each patient [52]. The inclusion of case managers in the multidisciplinary team positively affected PACIC+'s total score in heart failure patients [147]. Results from both patients and health care managers conform to the importance of the delivery system design, which should be targeted in public health policies to improve care for patients with MM.

CONCLUSIONS

1-More than two-fold odds of having heart failure and ischemic heart disease, more than six-fold odds of lung cancer and higher hospitalisation rates in COPD patients suggest a target for screening for significant comorbidities and managing multimorbidity. The study showed the highest prevalence of the cardiovascular cluster, lung cancer and renal diseases with an increased hospitalisation rate in COPD. Hospitalisation rates were higher for COPD men (Paper I and II).

2-The prevalence of ischemic stroke, transient ischemic attack, sleep disorders, dementia and Parkinson's disease increases with age in COPD (Paper II).

3-The cardiovascular and endocrine-metabolic clusters are present in COPD patients and MM patients without COPD. The presence of dyslipidaemia in the endocrine-metabolic cluster in COPD, as compared with the cardiovascular cluster in patients without COPD, gives grounds to presume that in the case of COPD the pathogenesis of CVD has some peculiarities caused by hypoxia and systemic inflammation. The betimes identification and treatment of the clusters might positively impact COPD and reduce health care costs (Paper I).

4-Two possible patterns, grouping neurological and psychiatric comorbidities, were found in COPD males. One of them consists of cerebrovascular events, neurodegenerative disorders and epilepsy. The other one includes psychiatric diseases and sleep disorders. (Paper II).

5-Further studies of various databases, standardisation of clustering methodologies and clusters' impact on COPD outcomes may increase the understanding of MM in COPD. Elaborated adjusted multimorbidity case management tools could decrease mortality and reduce health care utilisation. The definition of COPD in administrative databases requires validation (Paper I).

6-The necessity of further studies of different pathological mechanisms, such as inflammatory determinants, reactive oxygen species, vascular damage and others, was highlighted in the co-occurrence of neurological disorders and COPD. Impaired sleep may influence worse psychiatric outcomes in COPD,

although a bidirectional relationship between the two should also be considered. Recognizing the neurological and psychiatric comorbidity patterns could improve the prevention of vascular events and draw attention to the possible need to assess psychiatric disorders in case of impaired sleep (Paper II).

7-MM starts to increase early at the age of 28, and it grows more rapidly in the elderly. Young patients with MM, compared with patients of the same age having only one chronic disease, use more health care resources such as expensive medications and hospitalisations. Current treatment and disease prevention strategies should be reconsidered, focusing on complex approaches in the young, supposedly healthy population at risk of having MM in the future (Paper III).

8-Health care expenses for MM patients in Lithuania gradually increase up to 65 years, remain pretty stable until 84 years and then decrease. Hospitalisation and medication reimbursement costs account for the highest proportion in all age groups. The tendency of the increased use of hospitalisations and the reduced use of outpatient services after the age of 65 years was revealed, also entailing the increase in total health care expenditures. The study identified the need for optimising the care of patients with MM by implementing a complex model in primary health care settings (Paper VI).

9-The IMCM implementation methodology was adjusted to the Lithuanian primary health care system based on the VULSK Family Medicine Centre. Positive primary outcomes suggest that it could be applicable to other health care providers. Some adaptation to local management peculiarities could be necessary. The process indicators for further evaluation (the number of unplanned visits, the number and duration of hospitalisations, admissions to the emergency room, and avoidable hospitalisations, the number of incompatible drug combinations (drug interaction rate), EQ-5D questionnaire, EQ-VAS visual scale) were determined (Paper V).

10-The results of the pilot application of the IMCM in five European settings (including Lithuania) on both primary and specialised care levels consistently showed an improvement in the quality of care from the perspective of the patient and health care managers. Our results underscore the benefits of a comprehensive approach to multimorbidity care, highlighting the need to integrate the IMCM into the National Health Systems to ease the burden that

multimorbidity represents for health care managers, stakeholders, and patients (Paper VI).

FUTURE PERSPECTIVES AND PRACTICAL RECOMMENDATIONS

The thesis demonstrated the importance of a holistic approach to COPD and multiple diseases. The initial positive results of the implementation of DLPM contributed to changes in the Lithuanian health care system.

Based on the findings of CHRODIS, CHRODIS PLUS and this thesis, the Ministry of Health of the Republic of Lithuania initiated the scale-up of the main principles of IMCM implementation. Primary health care centres from different Lithuanian regions selected by tender and financed by EU Structural Funds are implementing components of the IMCM adjusted to the local needs. Comprehensive assessments, multidisciplinary teams, individualised care plans and case managers were selected as the essential obligatory components, and others were optional. Immediate positive results of the projects of the Ministry of Health facilitated preparations for the country-wide inclusion of a case manager in the family doctor's team.

Based on the data used in this thesis, the development of the prediction model for health care costs, supported by the Organization for Economic Cooperation and Development, was started.

Further exploration of the data collected and searching for new data on the models of interactions of chronic diseases, development of better pathways for MM patients, improvement of programmes for primary and secondary prevention, and finding ways for the rational use of limited health care resources could provide an added value for patients suffering from multiple chronic diseases. Examination of clustering might circumvent some of the limitations of prevalence studies by allowing qualitative analysis of the underlying MM profiles.

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ANNEXES

Authorisations provided by the Lithuanian Bioethics Committee.

VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
sui generis darinys prie VILNIAUS UNIVERSITETO

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2020 03 31 Nr.2020/3-1207-692

Tyrimo pavadinimas:

Lėtinių neinfekcinių ligų paplitimo, tarpusavio sąveikos, sveikatos priežiūros paslaugų bei vaistų vartojimo bei klinikinių baigčių vertinimas Lietuvoje

Protokolo Nr.:	LNLP-1
Versija:	1.0
Data:	2020 01 15
Informuoto asmens sutikimo forma:	netaikoma
Pagrindinis tyrėjas:	**Edita Kazėnaitė**
Įstaigos pavadinimas:	VšĮ Vilniaus universiteto ligoninė Santaros klinikos
Adresas:	Santariškių g. 2, Vilnius
Leidimas galioja iki:	2025 01 31

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 2020/3), vykusio 2020 m. kovo 31 d. sprendimu.

Pirmininkas prof. dr. (HP) Saulius Vosylius

Viešoji įstaiga
Universiteto g. 3
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Duomenys kaupiami ir saugomi
Juridinių asmenų registre
Kodas 211950810

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PATVIRTINTA
Lietuvos bioetikos komiteto direktoriaus
2016 m. birželio 10 d. įsakymu Nr. V-14

LIETUVOS BIOETIKOS KOMITETAS
Biudžetinė įstaiga, Algirdo g. 31, LT-03219 Vilnius, tel. (8 5) 212 4565,
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Duomenys kaupiami ir saugomi Juridinių asmenų registre, kodas 188710595

LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2018-09-25 Nr. L-18-3/4

Vilnius

Tyrimo pavadinimas:
„Poliligotų pacientų sveikatos priežiūros stebėjimas ir vertinimas“

Protokolo Nr.: **POL 400**
Versija: **1.1**
Data: **2018 m. rugpjūčio 01 d.**

Tiriamiesiems skirti dokumentai:

Gyvenimo kokybės klausimynas „EQ-5D“ (lietuvių kalba) :
Versija: **EQ-5D-5L** Data: **2009**
Lėtinių sveikatos būklių priežiūros vertinimo klausimynas „PACIC“ (lietuvių kalba) :
Versija: **20 klausimų „PACIC“** Data: **2005**
Hospitalinė nerimo ir depresijos skalė "HAD" (lietuvių kalba) :
Versija: **14 klausimų** Data: **1991**
Trumpasis protinės būklės testas „MMSE“ (lietuvių kalba) :
Versija: **1** Data: **1975**
Savarankiškumo ir galimybės apsitarnauti anketa (lietuvių kalba) :
Versija: **1** Data: **2007**
Informuoto asmens sutikimo forma (lietuvių kalba) :
Versija: **2** Data: **2018 m. rugpjūčio 31 d.**
Asmens informavimo ir asmens sutikimo forma donuoti biologinę medžiagą (lietuvių kalba) :
Versija: **1** Data: **2018 m. rugpjūčio 01 d.**

Pagrindinis tyrėjas: **Gyd., med. m. dr., prof. Vytautas Kasiulevičius**

Tyrimo centro pavadinimas: **Viešoji įstaiga Vilniaus universiteto ligoninės Santaros klinikos (VUL SK)**
Adresas: **Santariškių g. 2, Vilnius**

Leidimas atlikti biomedicininį tyrimą išduotas Lietuvos bioetikos komiteto Biomedicininių tyrimų ekspertų grupės posėdžio, įvykusio **2018 m. rugsėjo 04 d.**, sprendimu.

Vyriausioji specialistė,
laikinai vykdanti direktoriaus funkcijas Asta Čekanauskaitė

SUMMARY IN LITHUANIAN

SANTRAUKA

Santrumpos

ACIC – lėtinių ligų priežiūros vertinimo klausimynas
CHRODIS – Europos Sąjungos šalių bendrų veiksmų dėl lėtinių ligų ir sveiko senėjimo skatinimo per visą gyvenimo ciklą projektas (2014–2016)
CHRODIS PLUS – Europos Sąjungos šalių bendrų veiksmų gerųjų praktikų įgyvendinimui sergant lėtinėmis ligomis projektas (2017–2020)
DLPM – dauginių ligų priežiūros modelis
EFA – tiriamoji faktorių analizė
LOPL – lėtinė obstrukcinė plaučių liga
PACIC+ – pacientams skirtas lėtinių ligų priežiūros vertinimo klausimynas
PI – patikimumo intervalas
SSGG – stiprybės ir silpnybės, galimybės ir grėsmės
ŠS – šansų santykis
TLK-10-AM – Tarptautinė ligų ir susijusių būklių klasifikacija, 10-as leidimas, Australijos modifikacija
VULSK – Vilniaus universiteto ligoninė Santaros klinikos

Įvadas ir literatūros apžvalga

Dauginio ligotumo terminas vartojamas, kuomet nustatytos dvi ar daugiau lėtinių ligų vienu metu tam pačiam asmeniui. Dauginis ligotumas didina bendrą mirtingumą ir reikalauja didelių finansinių ir žmogiškųjų išteklių. Literatūros duomenimis, dauginis ligotumas labai paplitęs, auga didėjant amžiui. Europoje aštuoni iš dešimties 65 metų ir vyresnių žmonių serga lėtinėmis ligomis, daugiau nei 60 proc. jų serga dauginėmis ligomis. Lietuvoje dauginių ligų paplitimas pradeda didėti 45–54 metų amžiaus grupėje, tarp 65 metų asmenų pasiekia 42 proc., o nuo 85 metų – net 62 proc. Dauginis ligotumas siejamas su neigiamais padariniais: didėjančiu mirtingumu, negalia, bloga gyvenimo kokybe ir didelėmis sveikatos priežiūros išteklių sąnaudomis. Pacientai, sergantys keliomis lėtinėmis ligomis, turi kompleksinių sveikatos priežiūros poreikių, todėl jų priežiūrai yra sunaudojama net 74 proc. visų išteklių, skirtų sveikatos apsaugai.
Lėtinė obstrukcinė plaučių liga (LOPL) šiandien yra viena labiausiai paplitusių lėtinių ligų pasaulyje, sukelianti didelį suaugusiųjų sergamumą ir mirtingumą. Tiek mirtingumas, tiek LOPL paplitimas staigiai didėja su

amžiumi. 2015 m. pasaulyje nuo LOPL mirė daugiau nei trys milijonai žmonių. Sergantiesiems LOPL dažniau diagnozuojamos įvairios gretutinės ligos, tokios kaip alerginės, širdies ar smegenų kraujagyslių ligos bei įvairios nervų ir psichikos ligos. Dėl šių priežasčių LOPL sergantiems pacientams reikalinga daugiadalykė priežiūra ir jiems skiriamos didelės išlaidos.

Daugelyje LOPL ir gretutinių ligų tyrimų pasirenkami skirtingi ligų sąrašai, todėl aprašomi įvairios sudėties ligų grupių modeliai, kuriuos sudėtinga palyginti. Vis dėlto LOPL sergančių pacientų gretutinių ligų grupių susidarymas nėra pakankamai ištirtas. Įvairūs įtraukimo kriterijai, naudojamos duomenų bazės, skirtingos grupavimo metodikos ir kitokie gretutinių ligų sąrašai lemia paskelbtų rezultatų įvairovę. Planuojant sveikatos priežiūros intervencijas, skirtas pacientams, sergantiems LOPL ir dauginėmis lėtinėmis ligomis, žinios apie dauginių ligų grupes, jų paplitimą bei poveikį mirtingumui gali būti naudingos. Tolesnis tokio grupavimo tyrimas padėtų išvengti kai kurių paplitimo tyrimų apribojimų, nes leistų atlikti kokybinę pagrindinių dauginių ligų klasterių analizę.

LOPL sergantys pacientai turi psichikos sutrikimų (pvz., depresiją, nerimą), sutrikusį pažinimą, prastai miega bei turi padidėjusią insulto riziką. Tačiau nėra visiškai aišku, ar skirtingos neurologinės ir psichikos gretutinės ligos linkusios pasireikšti kartu ir kokie modeliai išryškėja LOPL sergančių asmenų grupėje. Tokia informacija būtų naudinga neurologams ir psichiatrams, teikiantiems medicinos paslaugas pacientams, sergantiems LOPL.

Esama įrodymų, kad sveikatos priežiūros išlaidos yra susijusios su senėjimu. Kai kurie tyrimai teigia, kad mirties artumas yra svarbesnis sveikatos išlaidų veiksnys nei vien senėjimas. Literatūroje yra daug įrodymų, kad dauginis ligotumas didina sveikatos priežiūros sąnaudas, tačiau Lietuvoje vis dar nėra išsamiai įvertintos sveikatos priežiūros išlaidos skirtingose amžiaus grupėse bei sąsajos su dauginiu ligotumu.

Klinikinėje praktikoje yra taikomas į vieną ligą orientuotas sveikatos priežiūros modelis, todėl dauginėmis ligomis sergantiems pacientams taikoma fragmentuota sveikatos priežiūra, kuri nėra efektyvi, pakankamai veiksminga. Dauginis ligotumas yra susijęs su sveikatos priežiūros kompleksiškumu bei daugelio vaistų vartojimu, todėl didėja galimų nepageidaujamų reakcijų skaičius bei vaistų sąveikos rizika, vaistai gali būti netinkamai vartojami arba paskiriami nederantys vaistai.

Deja, šiuo metu trūksta įrodymais pagrįstų rekomendacijų dėl dauginėmis ligomis sergančių pacientų sveikatos priežiūros. Keli lėtinių ligų priežiūros programų pavyzdžiai buvo įdiegti santykinai mažose populiacijose. Būtina sukurti kompleksinį dauginėmis ligomis sergančių pacientų sveikatos

priežiūros modelį, pagrįstą paciento visapusiško vertinimo ir komandinio darbo principais, kuris pagerintų jų sveikatos priežiūros kokybę.

Ši disertacija paremta šešiais publikuotais moksliniais straipsniais. Jos bendras tikslas buvo ištirti LOPL, dauginio ligotumo ir kitų veiksnių tarpusavio sąveiką bei pasiūlyti galimą sprendimą, kaip pagerinti sveikatos priežiūros kokybę.
I straipsnyje analizuojama LOPL gretutinių ligų epidemiologija, grupių (klasterių) susidarymas ir jų įtaka hospitalizacijoms.
II straipsnyje pagrindinis dėmesys skiriamas neurologinėms ir psichikos ligoms, gretutinėms LOPL, nagrinėjami lyties ir amžiaus skirtumai bei ligų grupių susidarymas.
III straipsnyje buvo apibrėžti amžiaus kritiniai taškai, lemiantys dauginių lėtinių ligų atsiradimą, dažnesnes hospitalizacijas ir didesnį kompensuojamųjų vaistų vartojimą.
IV straipsnyje nagrinėjamas sveikatos priežiūros išlaidų pasiskirstymas, kitimas ir tarpusavio ryšys dauginio ligotumo atveju.
V straipsnyje aprašoma šaliai pritaikyta integruoto daugelio ligų priežiūros modelio (DLPM) įgyvendinimo metodika, sukurta Europos Sąjungos šalių bendrų veiksmų dėl lėtinių ligų ir sveiko senėjimo skatinimo per visą gyvenimo ciklą (CHRODIS) projekte. Šiame darbe nagrinėjama įgyvendinimo metodika, pritaikyta Vilniaus universiteto ligoninės Santaros klinikų (VULSK) Šeimos medicinos centrui.
VI straipsnis atskleidžia pradinius DLPM įgyvendinimo rezultatus. Šie modeliai buvo bandomi penkiuose centruose Italijoje, Lietuvoje ir Ispanijoje Europos Sąjungos bendrų veiksmų gerųjų praktikų įgyvendinimui sergant lėtinėmis ligomis (CHRODIS PLUS) projekte. Baigiamajame darbe buvo siekiama pristatyti pradinę DLPM įtaką sveikatos priežiūros kokybei VULSK Šeimos medicinos centre.

Tyrimo tikslas ir uždaviniai

Darbo tikslas:

- Išnagrinėti lėtinei obstrukcinei plaučių ligai (LOPL) gretutinių ligų paplitimą, dauginio ligotumo sąsajas su LOPL, jo priklausomybę nuo kitų veiksnių, įtaką hospitalizacijoms bei sveikatos priežiūros sąnaudoms;
- Pritaikyti Lietuvos sveikatos priežiūrai, įdiegti ir įvertinti dauginių ligų priežiūros modelį (DLPM).

Uždaviniai:

1. Ištirti atskirų gretutinių ligų dažnį sergant LOPL (I–II straipsniai).
2. Išsiaiškinti gretutinių lėtinių ligų klasterių sąsajas su LOPL (I–II straipsniai).
3. Nustatyti lėtinių ligų klasterių įtaką hospitalizacijoms (I straipsnis).
4. Įvertinti lėtinių ligų didėjimo kritinius taškus (III straipsnis).
5. Ištirti lėtinių ligų didėjimo reikšmę hospitalizacijoms bei vaistų vartojimui (III straipsnis).
6. Išnagrinėti dauginių ligų (įskaitant LOPL) lemiamus sveikatos priežiūros išlaidų struktūros pokyčius, atsižvelgiant į amžių ir ligų skaičių (IV straipsnis).
7. Pritaikyti Lietuvos pirminei sveikatos priežiūros sistemai Europos Sąjungos bendrų veiksmų projekte CHRODIS sukurtą teorinį dauginių ligų priežiūros modelį (V straipsnis).
8. Įdiegti bandomąjį DLPM VULSK Šeimos medicinos centre ir įvertinti pirminį jo poveikį sveikatos priežiūros kokybei (VI straipsnis).

Mokslinis naujumas

Šis doktorantūros tyrimas, kurio metu paskelbti šeši straipsniai, yra pirmasis visapusiškas dauginių ligų tyrimas Lietuvoje, daugiausia dėmesio skiriantis LOPL. Tyrimas buvo pagrįstas realaus gyvenimo duomenimis iš Valstybinės ligonių kasos duomenų bazės. Mūsų žiniomis, tai pirmasis Europoje visos šalies duomenis apimantis tyrimas, kuriame analizuojamas dauginių lėtinių ligų tarpusavio ryšys, senėjimo poveikis ir sveikatos priežiūros išteklių panaudojimas, ieškant geresnių būdų pacientams, sergantiems LOPL ir gretutinėmis ligomis. Ankstesni tyrimai apėmė daugiausia kelis vienos šalies regionus arba buvo orientuoti tik į šio tyrimo apimties dalį.

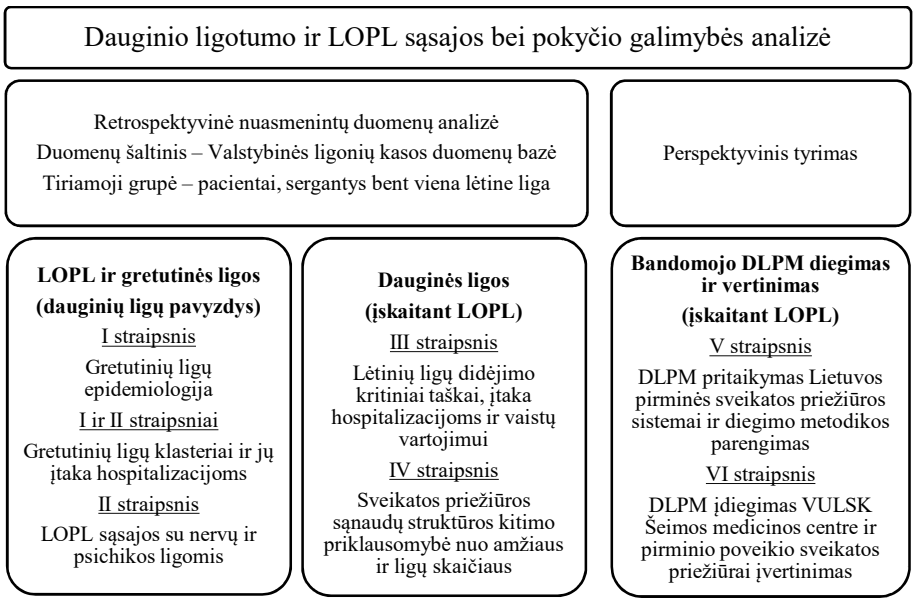
Tarptautinių kvėpavimo takų draugijų forumas Pasaulinio kvėpavimo takų ligų poveikio antrajame leidime paskelbė, kad moksliniai tyrimai turėtų padėti geriau suprasti, kokią įtaką rizikos veiksniai ir gretutinės ligos daro ligos sunkumui ir kaip valdyti LOPL sergant gretutinėmis ligomis, tokiomis kaip miego apnėja, širdies ir kraujagyslių ligos, depresija, osteoporozė, diabetas, plaučių vėžys, senėjimas ir trapumas. Šiam tikslui pasiekti reikalingos žinios apie lėtinių ligų sąveiką ir visapusišką pacientų būklės vertinimą. Šis tyrimas padidino supratimą apie pagrindinių lėtinių ligų tarpusavio ryšį ir pateikė praktinių rekomendacijų, kaip valdyti dauginį ligotumą.

Lietuvoje dar nebuvo atliktas išsamus įvairių amžiaus grupių sveikatos priežiūros kaštų įvertinimas ir netirtos jų sąsajos su dauginiu ligotumu. Šis

tyrimas parodė svarbiausias sritis intervencijai, kuri padėtų sulėtinti išlaidų sveikatos priežiūrai augimą.
CHRODIS projekto metu sukurtas DLPM turėjo būti pritaikytas Lietuvos sveikatos apsaugos sistemai. Bandomasis įgyvendinimas buvo numatytas projekto CHRODIS PLUS metu. Iki šių projektų Lietuvoje nebuvo įgyvendintų dauginių ligų valdymo programų, Europos šalyse taip pat trūko patirties. Padedant tarptautinei komandai, buvo sukurta šaliai pritaikyta metodika, atliktas pirmasis bandomasis DLPM diegimas VULSK Šeimos medicinos centre ir įvertintas pirminis intervencijos poveikis sveikatos priežiūros kokybei.

Tyrimo dizainas ir duomenų šaltiniai

Disertacijoje buvo remiamasi dviem lygiagrečiais tyrimais: retrospektyvia Lietuvos sergančiųjų populiacijos analize ir dauginėmis ligomis sergančių pacientų sveikatos priežiūros valdymo modelio įgyvendinimu. Bendra tyrimo schema pateikta 1 paveiksle.



LOPL – lėtinė obstrukcinė plaučių liga, DLPM – dauginių ligų priežiūros modelis

1 paveikslas. Bendra tyrimo schema

Šio tyrimo duomenys buvo projekto CHRODIS duomenų bazės dalis. Pradinis projektas buvo susijęs su lėtinių ligų prevencijos ir valdymo analize,

naudojant duomenis apie lėtines ligas iš didelių gyventojų duomenų bazių, t. y. nacionalinius elektroninius sveikatos įrašus.

Lietuvos nacionalinė sveikatos priežiūros sistema remiasi privalomuoju sveikatos draudimu ir siekia užtikrinti universalų prieinamumą visiems šalies gyventojams. Ligonių kasų duomenų bazė gauna duomenis apie 98 proc. stacionarinių atvejų ir 90 proc. ambulatorinių apsilankymų (iki 100 proc. pirminės sveikatos priežiūros vizitų) Lietuvoje, apima visą šalies teritoriją ir turi apie 7 000 sistemos vartotojų (sveikatos priežiūros įstaigų). Duomenų bazėje kaupiami demografiniai duomenys, įrašai apie suteiktas pirminės ir antrinės sveikatos priežiūros paslaugas, skubiąją pagalbą ir hospitalizacijas, išrašytus kompensuojamųjų vaistų receptus lėtinėms ligoms gydyti. Kiekvienas apsilankymas ar paslauga šioje duomenų bazėje susieti su ligos kodu pagal Tarptautinės ligų ir susijusių būklių klasifikacijos 10-ą leidimą, Australijos modifikaciją (TLK-10-AM) ir atitinkama standartizuota kaina, kurią nustato valstybė. Atrinkti kintamieji buvo gauti iš Valstybinės ligonių kasos 2012 m. sausio 1 d. – 2014 m. birželio 30 d. laikotarpio elektroninių sveikatos įrašų. Šis laikotarpis pasirinktas dėl duomenų patikimumo, atnaujinus nacionalines ligų kodavimo taisykles ir reglamentus nuo 2012 m.

Perspektyvinis DLPM, sukurto CHRODIS projekto metu, diegimo tyrimas buvo atliktas CHRODIS PLUS projekto metu. Pacientų, sergančių dauginėmis ligomis, priežiūros modelis buvo pritaikytas penkiose bandomosiose vietose (dviejose Ispanijoje, vienoje Italijoje ir dviejose Lietuvoje). Buvo patikrintas DLPM įgyvendinimo efektyvumas klinikiniams ir proceso rezultatams.

Vilniaus tyrimo centre DLPM įdiegtas VULSK Šeimos medicinos centre. Centre teikiama pirminė sveikatos priežiūra daugiau nei 12 000 pacientų, nemaža dalis turi dauginį ligotumą. Duomenys tyrimui gauti naudojant lėtinių ligų priežiūros vertinimo (ACIC) ir pacientams skirtą lėtinių ligų priežiūros vertinimo (PACIC+) klausimynus. Vilniaus tyrimo centro diegimo komanda, sutarusi bendrą kelių komandos narių poziciją, užpildė ACIC klausimynus prieš ir po DLPM diegimo. Demografiniai ir PACIC+ duomenys buvo gauti iš VULSK Šeimos medicinos centro pacientų užpildytų klausimynų, tai buvo tebevykstančio ilgalaikio tyrimo dalis. Duomenys apie PACIC+ ir ACIC klausimynus iš likusių keturių Europos tyrimo vietų buvo gauti CHRODIS PLUS projekto metu.

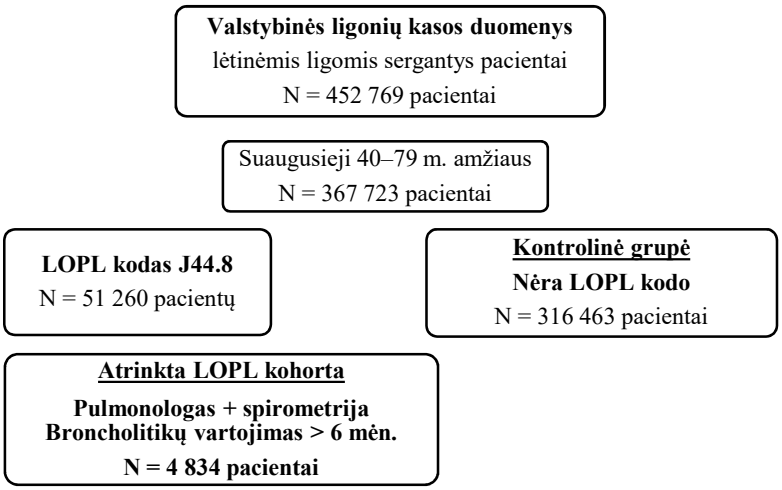
Duomenys

Pradinę pacientų grupę (I–IV straipsniai) sudarė 452 769 pacientai (18 metų ir vyresni), kuriems buvo diagnozuota bent viena lėtinė liga iš 32 lėtinių ligų sąrašo, kurį naudojo Barnettas ir kt. Šį sąrašą sudaro lėtinės ligos, kurių paplitimas yra didžiausias ir kurios turi didžiausią poveikį pacientams (1 lentelė).

1 lentelė. Lėtinių ligų sąrašas, susietas su TLK-10-AM ligų kodais

Piktybiniai navikai C00–C96
Geležies stokos anemija D50
Hipotirozė E02; E03; E89.0
Cukrinis diabetas E10.0–E10.9; E11.01–E11.9
Nutukimas E66
Dislipidemijos E78
Demencija F00.0–F00.9; G30.0–G30.9; F01.0–F01.9; F02.0–F02.8; F03
Psichikos ligos F20.0–F20.9; F30.0–F39; F40.00–F40.9; F41.0–F41.9; F42.0–F42.9; F43.0–F43.9
Parkinsono (Parkinson) liga G20
Išsėtinė sklerozė G35
Epilepsija G40.00–G40.91
Miego apnėja G47.3
Nugaros skausmas G54.1; G54.4; G55.1; M51
Glaukoma H40–H42
Regėjimo sutrikimai ir aklumas H53–H54
Klausos sutrikimai H90.0–H90.8; H91.0–H91.9
Hipertenzinės ligos I10–I15
Širdies išeminės ligos I20–I25
Širdies nepakankamumas I50.0–I50.9
Smegenų kraujotakos sutrikimai I60; I61; I62; I63; I64; I69
LOPL J44.0–J44.9
Astma J45.0–J45.9
Kvėpavimo nepakankamumas J96
Uždegiminės žarnyno ligos K50; K51
Psoriazė L40.0–L40.9
Reumatoidinis artritas M05; M06
Podagra M10.0–M10.99
Artrozė M15–M19
Sisteminė raudonoji vilkligė M32
Osteoporozė M80; M81; M82
Lėtinis inkstų nepakankamumas N18; N19

I ir II straipsniams pirmame pacientų atrankos žingsnyje atrinkta 353 780 pacientų, kurių amžius 40–79 metai. LOPL pacientų atrankai, siekiant įtraukti tik tuos asmenis, kuriems nustatyta patikima LOPL diagnozė, kitame etape buvo naudojami keli kriterijai: pacientui turėjo būti diagnozuota ši liga (kodas J44.8 pagal TLK-10-AM, „Kita patikslinta lėtinė obstrukcinė plaučių liga“), bent vieną kartą konsultuotas gydytojo pulmonologo (konsultacijos metu atlikta spirometrija) bei buvo išrašyti vaistai LOPL gydyti ne mažiau kaip 6 mėnesius per metus. Visi pacientai, neturintys su LOPL susijusių įrašų Valstybinės ligonių kasos duomenų bazėje, buvo priskirti nesergančių LOPL kontrolinei grupei (2 paveikslas).



2 paveikslas. Pacientų atranka retrospektyviniam tyrimui

LOPL atrankos kriterijus atitiko 4 834 asmenys (1,37 proc. pradinės imties nuo 40 iki 79 metų amžiaus), ir tik jų duomenys buvo naudojami tolesnei analizei. Iš neįtrauktų pacientų 316 463 nebuvo diagnozuota LOPL, 46 426 buvo diagnozuota LOPL, tačiau jie neatitiko reikalaujamų kriterijų. Kadangi LOPL dažniausiai pasireiškia sulaukus 40 metų, buvo įtraukti tik 40–79 metų pacientai. Daug nukrypimų buvo nustatyta 80 metų ir vyresniems pacientams, todėl ši grupė nebuvo įtraukta į tolesnę analizę.

Informacija apie širdies ir kraujagyslių ligų (širdies nepakankamumo, išeminės širdies ligos, aritmijos), plaučių vėžio, diabeto, inkstų ligų ir depresijos diagnozes gauta iš lėtinių ligų duomenų rinkinio. Ligos vertintos pagal šiuos kriterijus: trachėjos ar plaučių vėžys (C33–C34), hipertenzija (I10–I15), II tipo cukrinis diabetas (E11.01–E11.9, tik esant paskirtiems

vaistams ir endokrinologo konsultacijos įrašams), išeminė širdies liga (I20–I25, tik esant kardiologo konsultacijos įrašams), aritmijos (I44–I49, tik esant kardiologo konsultacijos išrašams) arba širdies nepakankamumas (I50.0–I50.9, tik esant kardiologo konsultacijos įrašams). Visos neurologinės ir psichikos gretutinės ligos buvo nustatytos tik pagal ligų TLK-10-AM kodus medicinos įrašuose. Sutrikimai, kurie pasireiškė pavieniais atvejais ir (arba) buvo laikomi turinčiais mažą įtaką, buvo neįtraukti. Taip pat buvo pateikta informacija apie hospitalizuotų ligonių skaičių, bendrą buvimą ligoninėje ir paciento neįgalumą.

III ir IV straipsnių analizei buvo atrinkti 18 metų ir vyresni pacientai, kurie per 2,5 metų laikotarpį sirgo bent 2 lėtinėmis ligomis iš 1 lentelėje pateikto sąrašo, kontrolinė grupė buvo viena lėtine liga sergantys pacientai.

V straipsnyje, kuriame pristatoma įgyvendinimo metodika ir aprašomos tyrime dalyvavusių šalių nacionalinės sveikatos priežiūros sistemos ir įgyvendinančios vietos ypatybės, tiriamosios grupės nebuvo.

VI straipsnyje pagrindinis pacientų įtraukimo kriterijus buvo dauginis ligotumas, nors konkretūs įtraukimo kriterijai skyrėsi priklausomai nuo vietos. Dalyvavo 2 centrai Ispanijoje, 1 – Italijoje ir 2 – Lietuvoje. Vilniaus tyrimo centre, pasirašius informuoto paciento sutikimą, įtraukti 195 VULSK Šeimos medicinos centro pacientai, atitinkantys įtraukimo kriterijus (turintys bent dvi lėtines ligas, pažeidžiančias skirtingas sistemas, ir kurių amžius nuo 40 iki 75 metų). Keturiasdešimt penki iš jų užpildė PACIC+ klausimyną prieš ir po DLPM įgyvendinimo. Šioje disertacijoje buvo analizuojami tik PACIC+ duomenys, gauti iš Vilniaus tyrimo centro, kurie buvo lyginti su bendrais visų tyrimo centrų rezultatais.

DLPM diegimo įgyvendinimo planas

V straipsnyje aprašoma diegimo strategija, kurią sukūrė CHRODIS PLUS partneriai ir ekspertai. Jos tikslas buvo pateikti gaires, palengvinančias įprastinės gerosios praktikos, politikos ir priemonių įsisavinimą.

Kiekvienas centras sukūrė įgyvendinimo darbo grupę, kurią sudaro organizatorius, ekspertai, sprendimus priimantys asmenys, pagrindinės suinteresuotosios šalys ir įgyvendintojai. Darbo grupėse buvo periodiškai rengiami tiesioginiai arba internetiniai susitikimai, kiekvienam susitikimui skirtos konkrečios užduotys: diegimo apimties analizė; situacijos analizė – „stiprybės, silpnybės, galimybės, grėsmės“ (SSGG); metodologijos kūrimas ir tobulinimas ir galutinis bandomojo veiksmų plano parengimas.

Apimties analizės metu buvo naudojama struktūrinė grupinė diskusija, išryškinanti planuojamos intervencijos ypatybes, atitinkančias vietos poreikius ir galimybes. Kiekvienas centras atliko penkis veiksmus: nustatė ir apibūdino problemą; iškėlė intervencijos tikslą; aprašė tikslinę populiaciją; išanalizavo intervencijos komponentus, nustatė būtinus veiksmus norimiems rezultatams pasiekti ir pasirinko komponentus iš IMCM vietiniam diegimui.
SSGG analizė buvo naudojama siekiant nustatyti atitinkamų organizacijų vidines stipriąsias ir silpnąsias puses bei išorines galimybes ir grėsmes įgyvendinant intervencijas pagal pasirinktus modelio elementus. SSGG skirta padėti tiek strateginiam planavimui, tiek sprendimų priėmimui, ir tai yra struktūrinis metodas, leidžiantis palyginti skirtingus centrus. Kiekvienas tyrimo centras parengė matricą, kurioje buvo pristatytos svarbiausios jų organizacijos stipriosios, silpnosios pusės, galimybės ir grėsmės penkiais aspektais: tvarumo, organizavimo, įgalinimo, komunikacijos ir stebėjimo bei vertinimo. Diskusijai palengvinti buvo sukurtas šablonas. Metodika buvo sukurta ir patobulinta tiesioginių susitikimų metu, parengtas veiksmų planas, numatantis žingsnius ir veiklas, kuriuos reikia atlikti norint įgyvendinti priežiūros intervencijas.
VI straipsnyje aprašoma intervencija kiekvienoje bandomojoje vietoje. Įgyvendinant DLPM buvo taikoma struktūrizuota metodika, bendra visiems dalyvaujantiems diegimo centrams, tačiau specialiai pritaikyta prie jų specifinių savybių, remiantis pradinės situacijos analize, atlikta prieš intervenciją. Intervencija truko 12 mėnesių, vertinimai buvo atlikti intervencijos pradžioje ir pabaigoje. Visos intervencijos buvo integruotos į įprastą kiekvieno centro praktiką.
Vilniaus centras pasirinko komponentus iš visų penkių modelio domenų bei įtraukė pirminės ir specializuotos sveikatos priežiūros specialistus į DLPM įgyvendinimą. Modelis buvo pritaikytas 195 pacientams, sergantiems dauginėmis ligomis, 40 metų ir vyresniems. Komanda siekė optimizuoti sveikatos priežiūros išteklius ir mažinti priežiūros susiskaidymą, skirdama atvejų vadybininkus ir kurdama individualizuotus priežiūros planus, kurdama specialistų konsultavimo sistemas ir gerindama pacientų prieigą prie bendruomenės išteklių. VULSK pritaikė DLPM, pirmenybę teikdamos dideliems sveikatos priežiūros išteklių vartotojams.
Tiek paciento, tiek sveikatos sistemos perspektyvos dėl teikiamos priežiūros kokybės buvo sutartos kaip pagrindiniai bendri rodikliai visoms įgyvendinančioms vietoms. Savarankiškai suvokiama pacientų priežiūra buvo analizuojama užpildant 26 punktų PACIC+ klausimyną, kuris įvertina konkrečius veiksmus ar priežiūros ypatybes, kurias, pasak pacientų, patyrė

teikiant sveikatos priežiūros paslaugas. Sveikatos sistemos komandos perspektyva buvo įvertinta naudojant ACIC klausimyną – praktinę kokybės gerinimo priemonę, padedančią organizacijoms įvertinti stipriąsias ir silpnąsias lėtinių ligų priežiūros teikimo puses. Abu klausimynai buvo renkami ir analizuojami prieš DLPM įgyvendinimą ir po vienų metų.

Taip pat buvo parengtas klausimynas pagrindiniams demografiniams ir socialiniams pacientų duomenims rinkti (t. y. lyties, amžiaus, civilinės būklės, išsilavinimo ir užimtumo statuso). Įgyvendinus DLPM į klausimyną buvo įtrauktas klausimas apie suvoktą pokytį (pokyčių balas), pacientų buvo klausiama: „Dėl jūsų lėtinių ligų įvertinkite per pastaruosius 12 mėnesių gautos priežiūros pasikeitimo laipsnį.“ Šiame elemente buvo pateiktos septynios Likerto tipo atsakymo parinktys (nuo 1 – labai daug blogiau iki 7 – labai patobulintos).

ACIC (3.5 versija) įvertina lėtinių ligų priežiūros teikimo stipriąsias ir silpnąsias puses septyniose srityse: paslaugų teikimo sistemos organizavimas (1 dalis), bendruomenės ryšiai (2 dalis), parama savipagalbai (3a dalis), sprendimų priėmimo palaikymas (3b dalis), pristatymo sistemos projektavimas (3c dalis), klinikinės informacinės sistemos (3d dalis) ir modelio komponentų integravimas (4 dalis). ACIC buvo taikomas kiekvienoje vietoje prieš ir po įdiegimo. Elementai buvo vertinami nuo 0 (žemiausias paramos lygis) iki 11 (optimalus paramos lygis). Kiekvienos skilties balai buvo gauti susumavus visų skyriuje esančių elementų reikšmes ir padalijus iš elementų skaičiaus toje skiltyje (diapazonas: 0–11). Bendras balas buvo gautas susumavus kiekvieno skyriaus balų vidurkius ir padalijus iš paskirtų skyrių skaičiaus (diapazonas: 0–11). Nustatyti šie priežiūros kokybės lygių diapazonai: 0–2 ribota parama dauginių ligų priežiūrai; 3–5 bazinė parama; 6–8 pakankamai gera parama; ir 9–11 visiškai išplėtota parama. ACIC užpildė įgyvendinimo komandos nariai, gerai išmanantys procesą, taip pat vietos ir sveikatos priežiūros sistemos ypatybes. Po diskusijos ACIC buvo pateikta bendra kelių komandos narių pozicija. Šis klausimynas įvertina atliktus pokyčius ir gerai koreliuoja su kitais proceso vertinimo ir sistemos pokyčių rodikliais. Angliška anketos versija buvo naudojama visuose centruose.

PACIC+ sudaro 26 elementai. Kiekvienas elementas buvo įvertintas nuo 1 (beveik niekada) iki 5 (beveik visada). PACIC+ leidžia taikyti balų metodą ir apibrėžia penkis išmatuojamus rezultatus: įvertinti, patarti, susitarti, padėti ir suorganizuoti. Tai leidžia įvertinti priežiūrą, paramą savipagalbai ir bendruomenės išteklių pasitelkimą. Taip pat buvo apskaičiuotas visuotinis suvestinis balas, remiantis 1–4 ir 6–16 punktų vidurkiu. PACIC+ buvo išverstas į kelias kalbas, buvo naudojamos lietuvių, italų ir ispanų versijos.

Retrospektyvinėje tyrimo dalyje duomenys iš Valstybinės ligonių kasos duomenų bazės gauti naudojant duomenų eksportavimo programinę įrangą. Anoniminė informacija buvo įkelta į saugų serverį, specialiai sukurtą šiam tyrimui. Pagal Lietuvos duomenų apsaugos reglamentą tokio tipo analizei paciento sutikimas nereikalingas.

I straipsnis. Atliktos dvi analizės, siekiant įvertinti ryšį tarp LOPL ir gretutinių ligų. Apskaičiuota asociacijų aprašomoji statistika ir šansų santykiai. Nuolatiniai kintamieji buvo išreikšti kaip vidurkiai ir standartinis nuokrypis (SD), o kategoriniai kintamieji – skaičiais ir procentais. Įvertintas LOPL gretutinių ligų paplitimas tiriamojoje ir kontrolinėje grupėse. Ligos paplitimo skirtumai buvo ištirti naudojant chi kvadrato testus.

Buvo atlikta skerspjūvio analizė, siekiant kiekybiškai įvertinti ryšį tarp LOPL ir kitų lėtinių gretutinių ligų. Mūsų pagrindinis rezultatas buvo ryšys tarp paplitusios LOPL ir kiekvienos tiriamos gretutinės ligos diagnozės. Nekoreguoti šansų santykiai ir 95 % pasikliautinieji intervalai (CI) tarp rezultatų kintamojo ir kiekvieno aiškinamojo kintamojo buvo įvertinti naudojant logistinę regresiją. Kiekvienai ligai buvo sukurti atskiri kelių kintamųjų modeliai, siekiant ieškoti painiavos ar poveikio modifikacijos pagal lytį, amžių ir gyvenamąją vietą.

Visiems pacientams buvo atliktas aglomeracinis hierarchinis klasterizavimas taikant Wardo ryšį skerspjūvio fenotipui nustatyti. Jaccardo koeficientas buvo naudojamas kaip panašumo matas dėl kintamųjų dichotominio pobūdžio. LOPL sergančių pacientų ligų klasterizavimas buvo atliekamas, jei ne mažiau kaip 5 proc. pacientų buvo nustatyta liga, atskirai vyrams ir moterims. Klasteriai buvo pavaizduoti grafiškai, naudojant metodą „iš apačios į viršų“, vieną klasterį pažymint ta pačia spalva.

Visos statistinės analizės buvo atliktos naudojant STATA 11 versiją (StataCorp. 2009. Stata Statistical Software: 11.0 leidimas. College Station, TX, JAV), STATISTICA 10 versiją (StatSoft, Inc. Talsa, OK, JAV.) ir R (versija 3.6.1). R paketai „stat“ (procedūra „hclust“), „vegan“, „dendextend“, „pheatmap“ ir „fpc“ buvo naudojami hierarchiniam grupavimui ir grafiniam vaizdavimui atlikti. Reikšmingumo lygis buvo apibrėžtas kaip $p < 0,05$.

II straipsnis. Tiriamoji faktorių analizė (EFA) buvo atlikta ieškant kintamųjų, pagrindžiančių neurologinius ir psichikos dauginio ligotumo modelius sergant LOPL. EFA buvo pagrįsta koreliacijos matrica iš dvejetainių gretutinių ligų duomenų („1“ – sąlyga yra, „0“ – būklės nėra). Įtrauktos tik tos gretutinės ligos, kurių paplitimas buvo daugiau negu 2 proc. pacientų arba atitinkamo jų

pogrupio imties. Diagnozės pagal TLK-10-AM kodus buvo sugrupuotos taikant du principus. Pirma, jei grupėje vyravo viena būklė, vengėme ją sugrupuoti su kitomis, kurių etiologija, mechanizmas ir (arba) pasireiškimas yra nevienalyčiai. Antra, koduotus sutrikimus sujungėme į grupes, jei jie turėjo panašų poveikį paciento sveikatai arba turi panašią etiologiją. Išskirtų faktorių skaičius buvo pagrįstas didesnėmis nei 1,0 savosiomis reikšmėmis ir ploto po kreive įvertinimu. Faktorių apkrovos buvo aiškinamos atlikus įstrižą sukimąsi. Norint nustatyti faktorių apkrovų įtraukimą į gretutinių ligų profilį, buvo naudojama > 0,30 ribinė vertė. Jei pasireiškė Heywoodo reiškinys (faktoriaus apkrova ≥1,00), kintamasis buvo pašalintas ir procedūra buvo pakartota, siekiant pagerinti modelio atitikimą. Norėdami nustatyti gautą atrankos patikimumą, naudojome Kaiserio–Meyerio–Olkino kriterijų (< 0,50 nepriimtina). Vyrų ir moterų pogrupiams buvo atliktas papildomas EFA. *Microsoft Excel* 16.0 buvo naudojama aprašomajai statistikai ir grafikams kurti. IBM SPSS 23.0 buvo naudojamas $\chi 2$ ir Manno–Whitney U bandymams. EFA naudojome STATA 13.0.

III straipsnis. Statistinei analizei naudojome R statistinio skaičiavimo aplinką (3.2.2 versija; R Core Team 2015) (18) ir STATISTICA (StatSoft, 10 versija). Nuolatiniai kintamieji buvo pateikti kaip vidurkiai ± standartinis nuokrypis (SD), o kategoriniai – kaip dažnis ir procentas. Chi kvadrato testas ir Stjudento *t* testas buvo naudojami atitinkamai reikšmingiems ir vidutiniams skirtumams patikrinti. Kritiniams taškams nustatyti naudojome segmentuotą tiesinę regresiją (R paketas „segmentuotas“) [144]. Visos praneštos *p* reikšmės buvo dvipusės, o reikšmingumo lygis buvo nustatytas 0,05.

IV straipsnis. Pacientų amžius buvo apibrėžtas kaip amžius duomenų gavimo metu ir buvo suskirstytas į 8 kategorijas: nuo 18 iki 24 metų, nuo 25 iki 34 metų, nuo 35 iki 44 metų, nuo 45 iki 54 metų, nuo 55 iki 64 metų, nuo 65 iki 74 metų, nuo 75 iki 84 metų ir 85+. Pacientų charakteristikos pateikiamos kaip vidurkiai ± standartinis nuokrypis (SD) nuolatiniams kintamiesiems ir kaip dažniai ir procentai kategoriškiems kintamiesiems. 95 % pasikliautinieji intervalai (PI) buvo apskaičiuoti sveikatos priežiūros paslaugų išlaidoms. Lėtinių ligų ir išlaidų ryšiui įvertinti buvo naudojami apibendrinti tiesiniai modeliai su gama pasiskirstymu ir log ryšio funkcija. Segmentuota tiesinė regresija buvo naudojama lūžio taškams nustatyti (R paketas „segmentuotas“). Statistinei analizei buvo naudojama R statistinio skaičiavimo aplinka (3.4.0 versija; R Core Team 2017) [144] ir STATISTICA (StatSoft, 10 versija). Visos praneštos *p* reikšmės buvo dvipusės, o reikšmingumo lygis buvo nustatytas 0,05.

V straipsnyje buvo aprašyta DLPM įgyvendinimo metodika, todėl jokia statistinė analizė nebuvo taikoma.
VI straipsnis. Dalyviams apibūdinti ir ACIC bei PACIC+ klausimynų rezultatams, bendriesiems ir subskalių balams apibendrinti buvo naudojama aprašomoji statistika (dažniai ir procentai, vidurkiai ir standartiniai nuokrypiai). ACIC balai buvo apskaičiuoti pagal tyrimo centrus ir laiką (prieš arba po intervencijos).
ACIC ir PACIC+ balų skirtumai tarp vertinimų prieš ir po įgyvendinimo kiekvienoje vietoje buvo nustatyti naudojant Manno–Whitney testą ACIC ir Stjudento suporuotą *t* testą PACIC+. Pokyčio dydis buvo įvertintas naudojant Coheno d formulę, skirtą poveikio dydžiui (manant2–meant1)/SDt1) [146], kai 0,50–0,79 rodo vidutinį pokytį, o ≥ 0,80 – didelį pokytį.
Skaičiavimai atlikti naudojant IBM SPSS programinę įrangą, 22.0 versiją.

Apribojimai

Retrospektyvinis tyrimas (I–IV dokumentai) buvo atliktas naudojant realaus gyvenimo duomenis ir fiksuojant bei kiekybiškai įvertinant sveikatos paslaugų naudojimą įvairioms ligoms gydyti. Pirminės ir antrinės sveikatos priežiūros įstaigų įprastų medicininių įrašų naudojimas leidžia išvengti tiriamojo nuomonės pasikeitimo ar pašnekovo išankstinio nusistatymo. LOPL grupė buvo sudaryta tik iš pacientų, kuriems ligą diagnozavo pulmonologas, tai leidžia teigti, kad spirometrija buvo atlikta visiems pacientams, nepaisant to, kad duomenų bazėje nėra spirometrijos duomenų.
Duomenų šaltinį sudarė medicininiai įrašai iš Valstybinės ligonių kasos duomenų bazės, kuri nebuvo kurta stebėjimo tyrimams, ji skirta sveikatos priežiūros įstaigų išlaidų už medicinos paslaugas kompensavimui bei statistikos reikmėms. Gali būti, kad kai kurios ligos buvo įrašytos arba neįrašytos dėl įvairių priežasčių, pavyzdžiui, paslaugų kompensavimo tik nustačius konkrečią diagnozę, numanomo kai kurių būklių stigmatizavimo arba ne visų ligų įrašymo dauginio ligotumo atveju. Vis dėlto, įtraukus pirminės, antrinės ir tretinės sveikatos priežiūros įrašus, taip pat informaciją apie receptus, įvertinus analizuojamo laikotarpio trukmę (daugiau negu 2 metai), buvo padidinta galimybė užfiksuoti visas susijusias diagnozes. Tačiau išlieka tikimybė, kad dalis diagnozių bus praleista.
Kadangi duomenims gauti naudojome ligų sąrašą (1 lentelė), pacientai, sergantys sąraše nepaminėtomis lėtinėmis ligomis, į analizę nebuvo įtraukti. Sąrašas yra diskutuotinas ir galbūt jį būtų galima išplėsti. Įvairūs autoriai gali pasiūlyti skirtingą lėtinių ligų sąrašą, kai kurie jų neįtraukia psichikos ligų, o

būtent jos lemia blogesnius rezultatus ir padidėjusias išlaidas. Nesant sutarimo dėl dauginį ligotumą apibrėžiančio ligų sąrašo, neįmanoma aiškiai apibrėžti, kurios lėtinės ligos turėtų būti neįtrauktos, tai gali turėti įtakos rezultatams, išlaidoms ir pacientų priežiūrai. Nepaisant to, ankstesniame darbe išanalizavome pasirinktų lėtinių ligų paplitimą tarp Lietuvos gyventojų ir patvirtinome, kad į šio tyrimo apibrėžimą įtrauktos lėtinės ligos yra labai paplitusios ir atitinka didžiausią įtaką sveikatos priežiūros paslaugų vartojimui turinčių lėtinių ligų kriterijus.

Mūsų duomenys atspindi kontaktą su sveikatos priežiūros paslaugų teikėju dėl lėtinės ligos nebūtinai tada, kai pirmą kartą buvo nustatyta diagnozė, jei tai buvo iki 2012 m. Be to, yra tikimybė, kad nuo simptomų atsiradimo iki pirmojo kontakto praėjo tam tikras laikas, todėl sunku aiškiai apibrėžti ligos pradžios laiką. Tai, kad buvo tirta visa populiacija ir analizuojamas laikotarpis yra daugiau nei 2 metai, sumažina reikšmingų neatitikimų tikimybę. Be to, išsami duomenų bazės informacija, susijusi su atskirų pacientų diagnozėmis, gydymu, pirminiais ir ambulatoriniais vizitais bei hospitalizacijomis, taip pat jų tendencijomis laikui bėgant, padidina mūsų duomenų patikimumą. Tačiau laikotarpis gali būti nepakankamas, kad apimtų visą kai kurių ligų, kurios labiau linkusios greitai pablogėti, vaizdą. Ribota duomenų bazės trukmė ir apimtis neleidžia toliau analizuoti sąsajos su priežiūra gyvenimo pabaigoje.

Skerspjūvio duomenų analizė galėtų būti laikoma galimu apribojimu, todėl išvadų apie priežastinį ryšį daryti negalima. Kadangi mūsų grupė buvo lėtinių ligų populiacijos tyrimo pavyzdys, lėtinių ligų paplitimas gali būti didesnis nei kituose tyrimuose.

Retrospektyvus mūsų tyrimo pobūdis neleido atrinkti pacientų, sergančių LOPL, pagal klinikinius kriterijus. Todėl kai kurie pacientai, sergantys lengvesnėmis LOPL formomis, galėjo būti pašalinti iš imties. Įvairių LOPL sutrikimų sąsajas reikia vertinti atsargiai, nes jos priklauso nuo *ad hoc* nozologinių subjektų grupavimo ir subjektyvaus galimų paslėptų veiksnių interpretacijos. Tai reiškia, kad naudojami statistiniai metodai nepateikia tiesioginių priežastinių ryšių tarp gretutinių ligų įrodymų.

Klasterizacijos metu stratifikacija pagal amžių nebuvo atlikta, tačiau skirtingų ligų paplitimo analizės rezultatai atitinka klasterinę analizę. Nors LOPL grupėje nustatėme žymiai didesnę ŠKL, širdies nepakankamumo, išeminės širdies ligos, plaučių vėžio, diabeto ir inkstų ligų pasireiškimų riziką, mūsų metodika galėjo nepakankamai įvertinti šių ligų sutapimą. Astmos kodo buvimas LOPL sergantiems pacientams buvo susijęs su vaistų kompensavimo dydžiu. Tačiau LOPL ir astmos sutapimo sindromas gali būti neįvertintas. Duomenų apie rūkymą trūkumas galėtų būti laikomas galimu apribojimu,

tačiau rūkymo epidemiologija Lietuvoje rodo, kad dauguma LOPL sergančių pacientų gali būti daug rūkantys.

Duomenų bazės dydis reiškia, kad trukmę reikėjo riboti. Kai kurie priežiūros pokyčiai galėjo įvykti per pastaruosius kelerius metus ir galėjo turėti įtakos išteklių naudojimui, nors ir labai mažai tikėtina. Paskutinis, bet ne mažiau svarbus dalykas – analizė apsiriboja viena šalimi. Papildoma kitų šalių duomenų bazių analizė galėtų patvirtinti išvadas.

V ir VI straipsniuose yra keletas metodologijos privalumų. Naudojome standartizuotą procedūrą, pritaikytą vietos tyrimo centrų poreikiams, galimybėms ir ypatumams. Buvo sukurtas standartizuotas diegimo paketas, kuris gali būti praktiškai pritaikytas skirtingose Europos šalyse ir sveikatos priežiūros sistemose. Kiekvienas iš penkių centrų dalyvavo reguliariuose bendruose susitikimuose (dažniausiai virtualiai) su projekto koordinatoriais, kad palygintų strategijas ir išsiaiškintų metodologiją. Be to, naudojome SSGG analizę, kuri gali suteikti palyginamos informacijos, leidžiančios nustatyti centrų skirtumus ir panašumus.

Čia aprašytas įgyvendinimo procesas turi galimų apribojimų. Įgyvendinimo procesas truko 18 mėnesių, kad atitiktų trejų metų JA CHRODIS PLUS projekto laikotarpį, pagal tai pasirinkti rodikliai. Ilgesnės intervencijos galėtų įvertinti kitus svarbius su sveikata susijusius rodiklius, tokius kaip mirtingumas, funkcinės būklės pasikeitimas arba trapumas, taip pat ekonominio efektyvumo duomenis. Lietuvoje buvo nuspręsta atidėti pirminės sveikatos priežiūros, specialistų konsultacijų, skubiosios pagalbos skyrių vizitų ir hospitalizacijų skaičiaus matavimus ilgalaikei intervencijai, kurią numato Lietuvos sveikatos apsaugos ministerija. Tikimasi, kad dabartinis bandomasis DLPM diegimas penkiose Europos vietose suteiks pagrindinės svarbios informacijos, kuri turėtų padėti sukurti integruotas dauginėmis ligomis sergančių pacientų priežiūros ir gydymo programas.

Į įgyvendinimo tyrimą buvo įtrauktas pacientų patirties matas (PACIC+), tačiau trūko gyvenimo kokybės vertinimo. Ankstesnės intervencijos, skirtos pagerinti pacientų, sergančių dauginėmis ligomis, priežiūrai, nepakeitė pacientų gyvenimo kokybės. Tačiau buvo pastebėtas pacientų pasitenkinimo pagerėjimas, kuris savaime gali būti laikomas svarbiu teigiamu rezultatu. Metodologija atitiko realaus pasaulio duomenų rinkimą, o tai reiškia tam tikrus apribojimus, pvz., trūkstamus duomenis, nereprezentatyvias imtis arba mažesnį imties dydį. Norint patvirtinti rezultatų pagrįstumą, reikia atlikti daugiau tyrimų. Kadangi kiekvienas centras nustatė savo įtraukimo kriterijus, dalyviai buvo nevienalyčiai pagal savo demografines ir klinikines charakteristikas. Intervencijos turėjo bendrą struktūrizuotą metodiką ir

trukmę, tačiau skyrėsi aplinkybės ir sveikatos priežiūros lygiai. Nors tai galėtų būti laikoma apribojimu, kartu suteikė galimybę parodyti, kad DLPM gali būti pritaikytas skirtingoms sveikatos priežiūros sistemoms. Be to, nepaisant tyrimo centrų skirtumų, visų penkių DLPM domenų komponentai buvo įdiegti ir įvertinti. Galiausiai, norint nustatyti pokyčius, kurie gali atsirasti vėlesniame laikotarpyje, reikalingas ilgesnis stebėjimas.

Rezultatai

I straipsnis

Tyrimo grupę sudarė 321 297 pacientai, kurių amžius 40–79 metai. Iš viso LOPL sirgo 1,5 proc., ligos paplitimas augo didėjant amžiui bei buvo didesnis vyrams (69,1 proc. vs. 34,7 proc.), daugiau LOPL sergančiųjų gyveno kaimo vietovėse (35,4 proc. vs. 27,0 proc.). Žymiai didesnis širdies nepakankamumo, aritmijų, koronarinės širdies ligos, plaučių vėžio ir inkstų ligų paplitimas tarp sergančiųjų LOPL. LOPL ir nesergančių LOPL grupėse diabeto ir depresijos paplitimo skirtumas nebuvo statistiškai reikšmingas. Pakoregavus pagal lytį, amžių ir gyvenamąją vietą, daugiamatė analizė parodė LOPL ryšį su šešis kartus padidėjusia tikimybe susirgti plaučių vėžiu (ŠS 6,66, 95 % PI 5,68–7,82; $p < 0,0001$). Dvigubai didesnė širdies nepakankamumo (ŠS 2,61, 95 % PI 2,46–2,78; $p < 0,0001$) ir apskritai širdies ir kraujagyslių ligų (ŠS 1,83, 95 % PI 1,69–1,97; $p < 0,0001$) tikimybė, palyginti su nesergančiais LOPL. Taip pat nustatyta didesnė aritmijų, diabeto, inkstų ligų ir depresijos rizika.

19 ligų iš 32 ligų (1 lentelė) sąrašo atitiko įtraukimo į klasterius kriterijus. Hierarchinis klasterizacijos algoritmas (Wardo metodas, h = 0,95) LOPL grupėje nustatė šešis klasterius vyrams ir penkis – moterims. Pacientų, nesergančių LOPL, grupėje nustatyti atitinkamai penki ir keturi klasteriai. Šių klasterių struktūra turėjo tam tikrų panašumų, tačiau buvo rasta keletas reikšmingų skirtumų.

Vyrų LOPL grupėje labiausiai paplitęs buvo širdies ir kraujagyslių sistemos klasteris, kuriame dažniausiai buvo hipertenzija ir išeminė širdies liga. Daugiau nei pusė jų buvo hospitalizuoti bent kartą per tyrimo laikotarpį. Panašus dažnis nustatytas endokrininiame-metaboliniame bei astmos, raumenų ir kaulų ligų klasteriuose. Podagros ir inkstų bei psichikos sutrikimų klasterių paplitimas buvo mažiausias, tačiau 70 proc. šių pacientų buvo hospitalizuoti. Taip pat buvo rastas insulto, vėžio ir jutimų klasteris. LOPL sergančioms moterims kai kurių dauginių ligų grupių dažnis buvo panašus,

tačiau buvo nustatyta, kad grupavimosi modeliai skiriasi. Nepaisant to, labiausiai paplitęs buvo širdies ir kraujagyslių sistemos klasteris, kaip ir vyrams. LOPL sergantiems vyrams rasti atskiri astmos, raumenų ir kaulų ligų bei endokrininis-metabolinis klasteriai moterų atveju sudaro vieną klasterį, papildomai prijungiama glaukoma ir psichikos sutrikimai. Moterims, sergančioms LOPL, buvo rastas demencijos ir insulto klasteris, tačiau vėžys buvo susijęs su hipotiroze, osteoporoze ir klausos praradimu. Anemijos klasteris buvo nustatytas tik moterims, sergančioms LOPL. Iš viso 70 proc. moterų, sergančių bent viena liga iš anemijos bei demencijos ir insulto klasterių, buvo hospitalizuotos.

Analizuojant vyrų, nesergančių LOPL, dauginį ligotumą, nustatyta, kad dislipidemija buvo susijusi su labiausiai paplitusiu širdies ir kraujagyslių klasteriu. Insulto, vėžio ir jutimų bei psichikos sutrikimų klasteriai atitiko LOPL sergančių vyrų. Buvo nustatyta, kad podagra prijungiama prie endokrininio-metabolinio klasterio. Atskiras raumenų ir kaulų sistemos klasteris buvo plačiai paplitęs tarp vyrų, nesergančių LOPL. Tarp nesergančių LOPL moterų dislipidemija bei raumenų ir kaulų sistemos buvo susijusios su širdies ir kraujagyslių klasteriu. Nepriklausomai nuo LOPL buvimo moterims buvo nustatyta demencijos ir insulto klasteris. Endokrininį-metabolinį klasterį sudarė tik diabetas ir nutukimas.

Širdies ir kraujagyslių sistemos klasteris (širdies nepakankamumas, išeminė širdies liga, arterinė hipertenzija ir aritmija) buvo labiausiai paplitęs, be reikšmingo skirtumo dėl lyties ar LOPL buvimo. Vis dėlto hospitalizavimo dažnis buvo didesnis LOPL atveju. Tačiau dislipidemija yra susijusi su širdies ir kraujagyslių ligomis tik pacientams, nesergantiems lėtine obstrukcine plaučių liga. LOPL atveju nustatyta dislipidemijos sąsaja su endokrininėmis-metabolinėmis ligomis. Šis atradimas leidžia iškelti hipotezę apie didesnę hipoksemijos ir sisteminio uždegimo įtaką LOPL sergančių pacientų širdies ir kraujagyslių ligų patogenezei.

Osteoporozė ir hipotirozė atitiko grupavimo kriterijus tik moterims, nepaisant LOPL. Astma nepateko į nesergančių LOPL pacientų klasterius. Tik vyrų inkstų nepakankamumas ir podagra atitiko įtraukimo į klasterius kriterijus, tačiau LOPL buvo reikšminga tik inkstų nepakankamumui.

II straipsnis

Buvo ištirta 4 834 LOPL pacientų grupė. 2 767 (57,2 proc.) pacientams buvo diagnozuotas bent vienas neurologinis ar psichikos sutrikimas. Tarp neurologinių ir psichikos sutrikimų dažniausiai buvo nervų, nervų šaknelių ir

rezginio sutrikimai (n = 1 439, 29,8 proc.), miego sutrikimai (n = 666, 13,8 proc.), praeinantis smegenų išemijos priepuolis (n = 545, 11,3 proc.), depresija (n = 364, 7,5 proc.) ir išeminis insultas (n = 349, 7,2 proc.). Laikinojo išemijos priepuolio diagnozė buvo susijusi su hipertenzija (AR = 2,218, 95 % PI nuo 1,429 iki 3,443). Užregistruoti išeminio insulto epizodai buvo susiję ir su hipertenzija (OR = 2,117, 95 % PI nuo 1,262 iki 3,754), ir su aritmija (OR = 1,343, 95 % PI nuo 1,030 iki 1,752).

Skirtingų neurologinių ir psichikos sutrikimų dažnis skyrėsi priklausomai nuo lyties. Vyrai turėjo daugiau su alkoholio vartojimu susijusių sutrikimų (p < 0,0001) ir dažniau sirgo išeminiu insultu (p = 0,001), moterys – depresija, nerimo, somatoforminiais ir miego sutrikimais, galvos skausmais, nervų, nervų šaknelių ir rezginių sutrikimais, praeinamuoju išemijos priepuoliu (p < 0,0001 visiems).

Gretutinių ligų modelių EFA Kaiserio–Meyerio–Olkino (KMO) matas buvo 0,6738 (vidutiniškas). Remiantis savybėmis, buvo išgauti du veiksniai. Pirmas veiksnys grupuoja sutrikimus, kurių paplitimas didėja su amžiumi (išskyrus epilepsiją), taip sudarytas neurodegeneracinių-smegenų kraujagyslių ligų modelis. Antrasis modelis apėmė psichikos ir miego sutrikimus. Siekiant geriau kiekybiškai įvertinti ryšį tarp neurodegeneracinių-cerebrovaskulinių sutrikimų ir epilepsijos (pirmojo faktoriaus kintamieji), buvo apskaičiuoti šansų santykiai. Tikimybių, kad bus diagnozuota epilepsija, reikšmingai padidėjo sergant kartu ir Parkinsono liga (ŠS = 3,624, 95 % PI nuo 1,903 iki 6,903), demencija (ŠS = 4,130, 95 % PI nuo 2,352 iki 7,253), praeinančiu išeminiu priepuoliu (ŠS = 2,440, 95 % PI nuo 1,606 iki 3,707) ir išeminiu insultu (ŠS = 3,051, 95 % PI nuo 1,931 iki 4,819).

Atliekant EFA su vyrų pacientų duomenimis, buvo gautas Heywoodo atvejis dėl Parkinsono ligos. Praleidus šį kintamąjį, demencijos, miego ir psichikos gretutinių ligų ir demencijos, epilepsijos ir smegenų kraujagyslių ligų modeliai išryškėjo, kai KMO matas buvo 0,5923 ir buvo panašus į gautus iš visų pacientų duomenų EFA. Tarp moterų aiškių modelių nepavyko nustatyti.

III straipsnis

Tiriamąją grupę sudarė 452 578 pacientai, sergantys bent viena lėtine liga iš 32 lėtinių ligų sąrašo (1 lentelė). Pacientų, sergančių dauginėmis lėtinėmis ligomis, imtį sudarė 428 252 (94,63 %) tiriamieji. Moterų dalis buvo didesnė nei vyrų (atitinkamai 60,29 % vs. 39,71 %) ir vyrai buvo beveik 5 metais jaunesni už moteris (amžiaus vidurkis buvo atitinkamai 63,9 ± 14,2 vs. 68,8 ± 14,0, p < 0,001).

Amžius turi didžiausią įtaką dauginėms ligoms, kai asmenys yra tarp 28 ir 39,8 metų amžiaus, o tiriamųjų, sergančių viena ar keliomis lėtinėmis ligomis, dalis yra atitinkamai 58 proc. ir 78 proc.. Vis dar reikšmingas, nors ir ne toks ryškus poveikis buvo stebimas iki 50 metų amžiaus, o pacientų, kuriems diagnozuojamos bent dvi lėtinės ligos, dalis nuo 50 metų amžiaus siekia 91 proc. Sulaukus 58 metų, kiekvieni metai iš eilės yra panašūs savo rizika susirgti papildoma liga, todėl pacientų, sergančių dauginėmis ligomis, dalis padidėjo nuo 96 proc. sulaukus 58 metų amžiaus iki 98 proc. sulaukus 80 metų ir daugiau.

Pacientai, kuriems diagnozuota daugiau nei viena lėtinė liga, naudoja daug pirminės sveikatos priežiūros ir ambulatorinių paslaugų, skirtumai per visą gyvenimo ciklą nedideli.

Viena ir daugiau nei viena liga sergančių pacientų hospitalizacijų skaičius šioje amžiaus grupėje smarkiai didėja ir siekia atitinkamai 20 proc. ir 34 proc. Pacientų, patenkančių į ligoninę, dalis gerokai didėja su amžiumi tiek sergant keliomis lėtinėmis ligomis, tiek viena lėtine liga. Kritinis amžiaus taškas sparčiam hospitalizacijų skaičiaus didėjimui abiejose grupėse yra apie 29 metus, staigus skaičiaus didėjimas tunka iki 57 metų.

Pacientų, sergančių dauginėmis ligomis ir patenkančių į 4-ąjį kvartilį (≥ 312,56 Eur per metus), išlaidų kompensuojamiesiems vaistams dalis pradeda didėti nuo 15 proc. sulaukus 41 metų iki 17 proc. sulaukus 51 metų ir 23 proc. sulaukus 57 metų. Sulaukus 72 metų amžiaus, tolesnio augimo nepastebėta.

Pacientų, sergančių viena lėtine liga ir patenkančių į tą patį 4-ąjį kvartilį, dalis nuo 18 metų prasideda nuo 12 proc., o sulaukus 27 metų palaipsniui mažėja ir sulaukus 52 metų pasiekia 5 proc. Po 56 metų ši dalis išlieka beveik stabili be žymaus padidėjimo vėlesniame etape.

IV straipsnis

Pacientų, sergančių bent viena lėtine liga, imtį sudarė 452 769 pacientai – 273 016 (60,3 proc.) moterų ir 179 753 (39,7 proc.) vyrai. Iš jų 428 430 sirgo dviem ir daugiau lėtinių ligų, todėl buvo įtraukti į tolesnę analizę. Vidutinis visų įtrauktų pacientų amžius buvo 67,83 (SD = 13,34) metų, moterų – 69,71 (SD = 13,00) metų, vyrų – 64,91 (SD = 13,33) metų. Dauginėmis ligomis sergantys pacientai vidutiniškai sirgo 4,79 ± 2,05 lėtinėmis ligomis, didžiausias vidutinis lėtinių susirgimų skaičius – 5,25 ± 2,08 75–84 metų amžiaus grupėje. Pastebėtina, kad net ir jauniausioje amžiaus grupėje (18–24 m.) lėtinių ligų vidurkis siekė 2,52 ± 0,84, palaipsniui didėjo su amžiumi ir beveik dvigubai padidėjo sulaukus 65–74 metų.

Bendros visų pacientų, sergančių dauginėmis ligomis išlaidas per metus buvo 302 843 036,21 Eur,, iš jų 14 194 613,70 Eur (4,69 proc.) sudarė pirminės sveikatos priežiūros išlaidos–, 13 017 573,87 Eur (4,30 proc.) –ambulatorinės išlaidos–, 156,078,078.78 (51.54 proc.) – hospitalizavimo išlaidos ir 119 552 769,86 Eur (39,48 proc.) – išlaidos medikamentams, iš kurių 93 590 567,02 Eur (78,28 proc.) išleista kompensuojamiesiems, 26 834 777,81 Eur (22,46 proc.) – pačių apmokėtiems vaistams. Daugiau nei pusė visų išlaidų (51,54 proc.) buvo skirta hospitalizacijos išlaidoms, kita didelė dalis (30,90 proc.) – kompensuojamiesiems vaistams.

Bendra sveikatos priežiūros paslaugų kaina pacientui, sergančiam dauginėmis ligomis, kasmet vidutiniškai siekė 707,15 Eur (95 % PI 703,37–710,93 Eur). Nors kohortoje buvo didesnė moterų dalis, vyrų pacientų metinės išlaidos buvo žymiai didesnės – atitinkamai 756,52 Eur (95 % PI 749,95–763,09 Eur), palyginti su 631,28 Eur (95 % PI 627,13–635,42 Eur) ($p < 0,001$), o pacientams, gyvenantiems mieste, palyginti su kaimo vietovėmis – atitinkamai 688,79 Eur (95 % PI 683,90–693,68 Eur) vs. 674,59 Eur (95 % PI 668,0–681,18 Eur) ($p < 0,001$).

Įvertinus paciento, sergančio dauginėmis ligomis, metines išlaidas, nustatyta, kad skirtingose amžiaus grupėse konkrečioms sveikatos priežiūros paslaugoms skiriamos skirtingos išlaidos. Didžiausia vidutinė bendra suma – 797,59 Eur ir didžiausios hospitalizacijos išlaidos – 443,00 Eur buvo išleista 75–84 metų, didžiausia vaistų kaina – 304,64 Eur – 65–74 metų, didžiausia pirminės sveikatos priežiūros kaina – 36,12 Eur – 65–85+ metų, o didžiausia ambulatorinės pagalbos kaina – 34,76 Eur – 45–54 metų amžiaus grupėje.

Tolesnė bendrų vidutinių išlaidų ir visų išlaidų pirminiams ir ambulatoriniams apsilankymams, hospitalizavimui ir išrašytiems vaistams dalies, skaičiuojant pagal amžių, analizė parodė skirtingą didėjimo tendenciją amžiaus grupėse ir skirtingose sveikatos priežiūros paslaugose. Vidutinės bendros išlaidos didėjo tiesiškai ir pastoviai nuo 18 iki 75 metų, buvo iš dalies stabilios vyresnio amžiaus, o vėliau sumažėjo vyriausioje 85 metų ir vyresnių amžiaus grupėje. Paslaugos, sudarančios didžiausią vidutinės kainos dalį, skyrėsi priklausomai nuo amžiaus grupės.

Didžiausios hospitalizacijos išlaidos siekė 18–22 metų ir 40 metų amžiaus (minimalios išlaidos buvo pasiektos sulaukus maždaug 25 metų), vėliau nuolat didėjo iki maždaug 79 metų ir vėl stabilizavosi. Vidutinė vaistų kaina panašiai stabiliai didėjo iki maždaug 72 metų amžiaus, o vėliau stabilizavosi. Paties paciento apmokamų vaistų kaina išaugo ryškiau nei kompensuojama nuo 28 iki 53 metų amžiaus. Svarbu tai, kad nors vaistų ir hospitalizavimo kainos buvo panašios amžiaus grupėse iki maždaug 50 metų, hospitalizavimo

išlaidos didėjo staigiau, todėl 85 metų ir vyresnių žmonių vidutinės išlaidos buvo maždaug 1,6 karto didesnės. Vidutinės ambulatorinės išlaidos buvo gana stabilios amžiaus grupėse nuo 18 iki 75 metų ir sumažėjo nuo 75 metų.

Be sveikatos priežiūros išlaidų tendencijų, įvertinome amžiaus kritinius taškus, siekdami nustatyti amžių, kada įvairios sveikatos priežiūros paslaugų išlaidos pradeda didėti, mažėti arba stabilizuotis. Tik vienas amžiaus lūžio taškas rodė sveikatos priežiūros išlaidų už hospitalizavimą sumažėjimą – 22,09 m. Visi kiti amžiaus lūžio taškai rodė arba stabilias, arba padidėjusias išlaidas, o pokyčių pradžią pastebėjo gana jauni pacientai – išaugo ambulatorinės išlaidos nuo 26,53 metų, paties paciento išlaidos nuo 27,82 metų, hospitalizacijos išlaidos nuo 38,64 metų. Kiekviename amžiaus lūžio kritiniame taške kiekviena nauja liga padidino išlaidas 1,26 karto.

Amžiaus grupių dalių pasiskirstymas pagal bendras pacientų, sergančių dauginėmis ligomis, sveikatos priežiūros išlaidas buvo panašus visoms analizuotoms paslaugoms. Visų paslaugų kategorijų santykinė dalis, skirta amžiaus grupėms nuo 18 iki 44 metų, buvo nereikšminga – sudarė 3,10 proc. visų išlaidų ir svyravo nuo 0,13 proc. pirminės sveikatos priežiūros, 0,23 proc. ambulatorinės pagalbos, 1,33 proc. hospitalizacijos iki 1,40 proc. vaistų išlaidoms. Dalis visų išlaidų palaipsniui didėjo vyresnio amžiaus grupėms ir pasiekė aukščiausią tašką 65–74 metų amžiaus grupėje bei sudarė 29,19 proc. (1,39 proc. pirminės sveikatos priežiūros, 1,30 proc. ambulatorinės pagalbos, 14,77 proc. hospitalizacijos ir 11,73 proc. vaistų išlaidų).

Kadangi pacientų skaičius kiekvienoje amžiaus grupėje skyrėsi (nuo 2 000 pacientų 18–24 metų grupėje iki 116 423 pacientų 65–74 metų grupėje), įvertinome vidutinę vienam pacientui per metus išleidžiamą sumą eurais skirtingoms sveikatos priežiūros paslaugoms ir sudarėme išlaidų proporcijų amžiaus grupėse grafiką. Nors, didėjant amžiui ir išlaidų daliai beveik visose amžiaus grupėse, išlaidos vienam pacientui palaipsniui staigiai didėjo, tokia tendencija buvo pastebima iki 76–84 metų amžiaus. Išlaidos vienam pacientui po 85 metų amžiaus sumažėjo. Vienintelė paslauga, kurios išlaidos vienam pacientui stabilios nuo 65 metų, buvo pirminė sveikatos priežiūra. Kartu mažėjo išlaidos ambulatorinėms paslaugoms ir padaugėjo hospitalizacijų, o tai rodo, kad vyresnio amžiaus pacientai linkę kreiptis į ligoninių skubiosios pagalbos skyrius, o ne į poliklinikas.

V straipsnis

DLPM buvo įgyvendintas bandomojo diegimo centruose: dviejuose Ispanijoje, dviejuose Lietuvoje ir viename Italijoje. Projekto pradžioje buvo

atlikta apklausa, siekiant nustatyti dalyvaujančių centrų charakteristikas. Apklausos rezultatai atskleidė kai kuriuos bendrus penkių bandomųjų vietų tikslus, pvz., didinti daugiadalykį bendradarbiavimą, skatinti įrodymais pagrįstą praktiką ir sumažinti nelygybę, susijusią su priežiūros ir paramos paslaugų prieinamumu. Visuose penkiuose centruose buvo numatytas šešių mėnesių pradinis laikotarpis (pacientų įtraukimas), po kurio sekė 12 mėnesių įgyvendinimo laikotarpis. Pagrindiniai rodikliai buvo įvertinti įgyvendinimo pabaigoje. JA CHRODIS PLUS buvo trejų metų projektas, o intervencijų laikas buvo pasirinktas taip, kad būtų pakankamai laiko pasiruošti, intervencijai taikyti ir rezultatams apibendrinti. Dauguma įgyvendintojų manė, kad svarbu įtraukti bendrosios praktikos gydytojus ir slaugytojus teikiant pagalbą pacientams. Iš tiesų, dauguma pacientų buvo įtraukti pirminės sveikatos priežiūros įstaigose. Visais atvejais pagrindiniai priežiūros paslaugų teikėjai buvo bendrosios praktikos gydytojai arba slaugytojai (arba jie dalyvavo daugiadalykiuose susitikimuose). Daugelyje intervencijų buvo paskirti atvejo vadybininkai, o daugelis jų taip pat įtraukė socialinį darbuotoją į daugiadalykę komandą. Visi penki centrai numatė, kad pacientai bus visapusiškai vertinami integruotos priežiūros proceso pradžioje ir pabaigoje, tačiau kai kurie iš jų įtraukė reguliarų periodinį vertinimą tarp jų. Daugelyje programų buvo suplanuotas pacientų švietimas, tolesni apsilankymai ir siuntimai pas specialistus, klinikiniai (diagnostikos / stebėjimo) tyrimai. Tačiau kitos intervencijos ir paslaugų ypatybės šiek tiek skyrėsi.

Dauguma centrų savo intervencijoms naudojo technologijas. Pavyzdžiui, keturiuose iš penkių centrų buvo teikiamos e. sveikatos paslaugos, o pusė daugiadalykės komandos susitikimų vyko virtualiai. Visi penki centrai naudojo skaitmenines sveikatos priežiūros komunikacijos priemones; dažniausiai elektroninį siuntimą, virtualias konferencijas su pacientais ir internetinius susitikimų tvarkaraščius. Trys ketvirtadaliai centrų turėjo elektronines priežiūros procesų registravimo / stebėjimo sistemas ir naudojo elektroninius sveikatos įrašus. Tačiau nė vienas centras nenaudojo elektroninių sprendimų paramos sistemų. Apklausa taip pat atskleidė kai kuriuos trūkumus, ypač bendruomenės ir socialinių išteklių atžvilgiu. Tiesą sakant, tik vienas centras tiesiogiai padėjo pacientams gauti prieigą prie bendruomenės ir socialinių išteklių.

Penkiuose centruose reikėjo įdiegti bent vieną komponentą iš CHRODIS projekte sukurto DLPM, kuriame buvo pasiūlyta 16 komponentų. VULSK įtraukė komponentus iš visų penkių domenų. Daugelyje vietų (keturiose iš penkių) buvo numatytas reguliarus, išsamus pacientų vertinimas,

daugiadisciplinė komanda, atvejų vadybininkas, individualūs priežiūros planai ir pacientų bei priežiūros paslaugų teikėjų bendri sprendimai.
VULSK įgyvendino priežiūros modelį Šeimos medicinos centre, bet įtraukė ir antrinės bei tretinės sveikatos priežiūros gydytojus, siekdamos sukurti komandas, kurios prižiūrėtų pacientą. DLPM skirtas daugeliu ligų sergantiems pacientams, lankantiems pirminės sveikatos priežiūros įstaigas. Pagrindinis programos tikslas buvo skatinti įrodymais pagrįstą praktiką pirminės sveikatos priežiūros pacientams, sergantiems įvairiomis ligomis, siekiant pagerinti jų gyvenimo kokybę, sumažinti galimai išvengiamų hospitalizacijų ir readmisijos atvejų skaičių bei parengti ekonominį išlaidų multimorbidiniams pacientams vertinimą. Intervencijos metu buvo diegiama 10 DLPM komponentų iš visų penkių domenų. Visų pirma, jis apėmė visus komponentus iš priežiūros modelio ir sprendimų paramos komponentų. Konkretūs intervencijos tikslai apėmė: (1) sumažinti nepageidaujamų pasekmių, susijusių su dauginėmis ligomis ir vaistų ir vaistų sąveikos rizika, rengiant individualizuotus integruotus priežiūros planus; (2) optimizuoti gydymo, priežiūros ir sveikatos priežiūros išteklius derinant individualizuotą integruotos priežiūros planą; (3) maksimaliai padidinti rezultatus ir užtikrinti priežiūros tęstinumą, kartu mažinant susiskaidymą ir pagerinant priežiūros ir paslaugų prieinamumą paskyrus atvejo vadybininką; (4) teikti pagalbą gydytojui priimant sprendimus tais atvejais, kai reikia papildomos klinikinės pagalbos arba žinių, kurių pagrindinė komanda neturi, pasitelkiant profesionalių ekspertų konsultacijų sistemą; (5) gerinti paciento galimybes naudotis bendruomenės ištekliais, formalia priežiūra ir pacientų asociacijomis, paramos grupėmis ir psichosocialine pagalba, teikiant daugiadalykę priežiūrą.
Kurdamas veiksmų planus, kiekvienas tyrimo centras apibrėžė pagrindinius veiklos rodiklius DLPM diegimo vertinimui. Intervencijų poveikiui įvertinti buvo pasirinktas bendras metodas, kurį sudarė ir kiekybinė, ir kokybinė analizė.
Vertinimui parinkti ACIC ir PACIC+ klausimynai, pildomi ir analizuojami prieš ir po įgyvendinimo (aprašyti įgyvendinimo dalyje).

VI straipsnis

Straipsnyje apibendrinami pirmieji įgyvendinimo 5 bandomųjų centrų rezultatai pagal ACIC ir PACIC+ klausimynų duomenis. Disertacijoje daugiausia dėmesio buvo skiriama Vilniaus centro rezultatams, lyginant su visų centrų rezultatais.

Prieš įgyvendinimą įgyvendinimo grupių nariai (5 centrai) iš viso atliko 14 ACIC tyrimų (5 iš Vilniaus). Įgyvendinus atlikta 17 ACIC tyrimų (5 iš Vilniaus).

ACIC bendrieji vidutiniai balai prieš įgyvendinimą svyravo nuo 3,70 Vilniuje iki 7,90 Andalūzijoje. ACIC bendrųjų balų vidurkis po įgyvendinimo svyravo nuo 5,52 Vilniuje iki 8,04 Kaune. ACIC balų padidėjimas taip pat buvo nustatytas visose vietose, išskyrus Andalūziją, nors apskritai jie nebuvo statistiškai reikšmingi. Visos imties ACIC balai labai padidėjo intervencijos pabaigoje 3b–4 dalyse ir ACIC bendras skaičius. Efekto dydžiai svyravo nuo 0,58 (1 dalis) iki 1,10 (4 dalis) ACIC matmenims, o bendras ACIC balas buvo 0,83.

208 pacientai (45 jų iš Vilniaus tyrimo centro) atliko PACIC+ apklausą tiek prieš intervenciją, tiek po jos. Vilniuje pacientų amžiaus vidurkis buvo 61 metai (standartinis nuokrypis, SD: 9,1), iš jų 51,1 proc. buvo moterys. Apskritai moterys sudarė 52,2 proc. visos imties, jų amžiaus vidurkis buvo 62,9 (standartinis nuokrypis, SD: 17,1; diapazonas: 20–93) metų. Vidutinis visos imties pokyčio balas buvo 4,91 (SD: 1,14); 58 proc. visos imties nurodė, kad per pastaruosius 12 mėnesių buvo geresnė priežiūra, Vilniaus centre – 4,7 (SD: 0,8); 57,1 proc.

Pradinis PACIC+ suvestinis balas svyravo nuo 2,91 (SD: 0,96) Andalūzijoje iki 3,90 (SD: 0,78) Vilniuje. „Suorganizuoti (arrange)“ buvo domenas, kurio balai buvo žemiausi visose svetainėse, o „Patarti (advice)“ – aukščiausi. Po intervencijos PACIC+ suvestinis balas svyravo nuo 3,46 (SD: 0,97) Andalūzijoje iki 4,55 (SD: 0,35) Aragone. Kaip ir pradiniame etape, „Suorganizuoti (arrange)“ domeno balai buvo žemiausi visuose centruose, o „Patarti (advice)“ domeno – aukščiausi.

Stebėjimo metu imtį sudarė 210 pacientų. Buvo nustatytas reikšmingas PACIC+ suvestinio balo padidėjimas, svyruojant nuo 3,25 pradiniame etape iki 4,03 po intervencijos ($p < 0,001$). PACIC+ domenų vertės taip pat labai padidėjo, iš jų „Suorganizuoti (arrange)“ padidėjo labiausiai (0,99), o „Patarti (advice)“ pasiekė aukščiausią balą (4,16, SD: 0,75). Pagal centrus mažiausias padidėjimas pastebėtas Vilniuje (nuo 0,09 asist iki 0,26 sutvarkymo). Įvertintas ribinis vidurkis PACIC+ suvestinis balas prieš ir po įdiegimo Vilniaus centre buvo atitinkamai 3,89 ir 4,06.

Išvados

1. LOPL sergantys pacientai turi daugiau kaip 2 kartus didesnę tikimybę sirgti širdies nepakankamumu ir koronarine širdies liga, 6 kartus didesnį šansą sirgti

plaučių vėžiu bei didesnę hospitalizacijos riziką, todėl tikslingas ištyrimas dėl reikšmingų lėtinių ligų bei dauginių ligų valdymas. Tyrimas parodė didžiausią kardiovaskulinio klasterio, plaučių vėžio bei inkstų ligų paplitimą bei didesnį hospitalizacijų skaičių tarp LOPL pacientų. LOPL sergantys vyrai hospitalizuojami dažniau.

2. Išeminio insulto, praeinančio smegenų išemijos priepuolio, miego sutrikimų, demencijos ir Parkinsono ligos paplitimas tarp LOPL pacientų auga didėjant amžiui.

3. Kardiovaskulinis ir endokrininis-metabolinis klasteriai randami tiek LOPL pacientams, tiek nesergantiems šia liga. Tačiau LOPL pacientams dislipidemija patenka į endokrininį-metabolinį klasterį, o nesergantiems LOPL – į kardiovaskulinį klasterį. Tai leidžia daryti prielaidą, kad LOPL atveju širdies ir kraujagyslių ligų patogenezė turi ypatumų, kuriuos lemia hipoksija ir sisteminis uždegimas. Savalaikis klasterinių ligų atpažinimas ir gydymas pagerintų LOPL ligos eigą ir sumažintų sveikatos priežiūros sąnaudas.

4. LOPL pacientams vyrams nustatyti du gretutinių nervų ir psichikos ligų grupių modeliai. Pirmas modelis – smegenų kraujotakos sutrikimai, neurodegeneracinės ligos ir epilepsija, antras modelis – psichikos ligos bei miego sutrikimai.

5. Reikalingi tolesni įvairių duomenų bazių tyrimai siekiant standartizuoti gretutinių ligų klasterių formavimo metodologiją, įvertinti klasterių įtaką LOPL baigtims bei suprasti dauginių ligų sąveiką. Naujų tikslinių dauginių ligų valdymo modelių sukūrimas galimai galėtų sumažinti mirtingumą bei sveikatos priežiūros sąnaudas. LOPL apibrėžimo, naudojant administracines duomenų bazes, validacija galėtų atnešti papildomą naudą tolesniems tyrimams.

6. Šio tyrimo duomenys iškelia poreikį įvertinti, ar uždegiminiai žymenys, reaktyviosios deguonies rūšys, kraujagyslių pažeidimas bei kai kurie kiti patologiniai mechanizmai gali būti esminiai neurologinių sutrikimų atsiradimui LOPL atveju. Pažeistas LOPL pacientų miegas gali turėti įtakos psichikos ligoms, ryšys gali būti abipusis. Neurologinių ir psichikos ligų modelių atpažinimas praktikoje galėtų pagerinti insultų prevenciją bei psichikos sutrikimų įvertinimą esant sutrikusiam miegui.

7. Ligos dažnėja nuo 28 metų amžiaus ir jų dažnis didėja greičiau negu vyresnio amžiaus žmonių grupėje. Santykinai jauniems pacientams, sergantiems dauginėmis ligomis, sveikatos priežiūros sąnaudos didesnės, palyginti su to paties amžiaus pacientais, sergančiais viena liga. Reikia

peržiūrėti rekomendacijas, atkreipiant dėmesį į jaunus, tariamai sveikus žmones, ateityje turėsiančius dauginį ligotumą.
8. Sveikatos priežiūros išlaidos dauginėmis ligomis sergantiems pacientams laipsniškai didėja iki 65 metų amžiaus, lieka stabilios iki 84 metų amžiaus ir vėliau mažėja. Visose grupėse hospitalizacijos kaštai ir išlaidos kompensuojamiesiems vaistams sudarė didžiausią dalį. Nustatyta aiški hospitalizacijų skaičiaus didėjimo bei ambulatorinių konsultacijų mažėjimo tendencija nuo 65 metų, tai atsispindėjo ir visose sveikatos priežiūros išlaidose.
9. Tyrimas patvirtino dauginėmis ligomis sergančių pacientų priežiūros optimizavimo poreikį įdiegiant kompleksinį priežiūros modelį pirminėje sveikatos priežiūroje. Šio tyrimo metu DLPM diegimo metodika buvo pritaikyta Lietuvos sveikatos sistemos pirminės asmens sveikatos priežiūros įstaigai (PASPĮ) VULSK Šeimos medicinos centro pavyzdžiu. Pradiniai geri rezultatai leidžia teigti, kad ši metodika gali būti toliau taikoma kitoms PASPĮ. Gali būti reikalingas tam tikras adaptavimas konkrečios įstaigos vadybos ypatumams.
Numatyti rodikliai ilgalaikiam lėtinių ligų priežiūros vertinimui (neplaninių vizitų skaičius, hospitalizacijų skaičius ir trukmė, vizitų į skubiosios pagalbos skyrių skaičius, išvengiamų hospitalizacijų skaičius, netinkamos vaistų sąveikos dažnis, gyvenimo kokybės EQ-5D ir EQ-VAS paciento klausimyno vertinimas).
10. DLPM bandomojo diegimo rezultatai penkiuose Europos centruose (įskaitant Lietuvą) pirminiame ir specializuotos priežiūros lygmenyse parodė pagerėjusią sveikatos priežiūros kokybę tiek pacientų, tiek sveikatos priežiūros paslaugų teikėjų požiūriu. Šio tyrimo rezultatai pabrėžia visapusiško požiūrio į dauginių ligų valdymą naudą ir DLPM įdiegimo į nacionalinę sveikatos sistemą poreikį siekiant sumažinti dauginio ligotumo keliamus iššūkius sveikatos priežiūros vadybininkams bei pacientams.

Praktinis pritaikymas

Disertacijoje parodyta holistinio požiūrio į LOPL ir dauginį ligotumą svarba, pradiniai teigiami DLPM diegimo rezultatai prisidėjo prie pokyčių Lietuvos sveikatos sistemoje.
Šiuo metu vyksta SAM inicijuotas struktūrinių fondų finansuojamas projektas pirminės sveikatos priežiūros įstaigose – diegiamas dauginių ligų priežiūros modelis, paremtas ES šalių bendrųjų veiksmų projektų CHRODIS, CHRODIS PLUS bei šios disertacijos rezultatais.

SAM planuoja papildyti šeimos gydytojo komandą atvejo vadybininku.
Ekonominio bendradarbiavimo ir plėtros organizacija (EBPO), remdamasi ES projekto CHRODIS PLUS, šios disertacijos bei papildomais Valstybinės ligonių kasos duomenimis, šiuo metu kuria Lietuvai pritaikytą sveikatos priežiūros išlaidų prognozavimo modelį.
Ilgalaikiai moksliniai tyrimai dauginių ligų ir LOPL srityje, apimantys tiek retrospektyvinius, tiek operspektyvinius duomenis, pagilintų žinias apie lėtinių ligų sąveiką bei patogenezę, padėtų tiksliau suformuluoti pacientų priežiūros gaires.

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Elena Jurevičienė obtained a Medical Doctor qualification from Vilnius University in 1992. She became a specialist in Pulmonology in 1998 and acquired a Master‘s degree in management and business administration from Vilnius University in 2004. She has been working as a pulmonologist for more than 20 years, since 2010 in Vilnius University Hospital Santaros Klinikos, and has been in various management positions for about ten years. Also, since 2010 she has worked as a lecturer and later junior assistant at Vilnius University, Faculty of Medicine. Since 2014 she has been involved in EU funded projects and biomedical research on multimorbidity and rare diseases. She joined the Vilnius University doctoral study program in 2015. She co-authored several publications on multimorbidity and pulmonary hypertension and presented at international conferences of the European Respiratory Society, International Foundation for Integrated Care, etc.

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