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VIRVA HYTTINEN

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ABSTRACT

Health care resources should be used and organised efficiently and equitably in such a way that they produce as much health as possible. This dissertation consists of four sub-studies, whose aims were to determine persons' selection for potentially inappropriate medication (PIM) use, and whether initiation of PIM use is associated with health care service use, costs and mortality in older people.

The data used are from two different population-based cohort studies: data on older people with Alzheimer's disease (AD) between 2005 and 2011, and a 10 % random sample of a general community-dwelling, older population between 2000 and 2013. PIMs were defined by the Meds75+ database maintained by the Finnish Medicines Agency (FIMEA).

People with AD initiated PIM less frequently than those without AD. There were age-related differences in the factors associated with PIM initiation, e.g. gender and socioeconomic status, in older community-dwelling persons aged 65–74 and ≥75 years. Overall, PIM initiation was more dependent on patient characteristics, but also on some healthcare system related factors, such as differences in the prescribing of PIM between physicians, and potentially different regional treatment practices.

PIM initiation was statistically significantly associated with hip fractures in people with AD only after restricting the analyses for the first PIM use period. Also, in the general community-dwelling population, the first PIM use period was particularly associated with an increased risk of fracture-specific hospitalisations and mortality after considering selection for PIM use. PIM users also had higher hospital costs compared to non-users during the 12-year follow-up.

In conclusion, this dissertation confirms that PIM use is related to a variety of interrelated patient- and physician-level factors. PIM use is associated with an increased risk of negative health outcomes and a greater risk of hospitalisation, and thus, higher hospital costs.

Keywords: *Older people, Medication error, Health outcomes, Economic outcomes, Survival analysis, Register-based studies*

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Iäkkäillä vältettävien lääkkeiden käytön terveydelliset ja taloudelliset näkökohdat
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TIIVISTELMÄ

Terveydenhuollon voimavarojen tulisi olla käytetty ja organisoitu tehokkaasti ja oikeudenmukaisesti siten, että ne tuottavat mahdollisimman paljon terveyttä. Tämä väitöskirja koostuu neljästä osatutkimuksesta, joissa selvitetään iäkkäillä vältettävien lääkkeiden käyttöön valikoitumista, ja vältettävien lääkkeiden käytön yhteyttä terveyspalvelujen käyttöön, kustannuksiin ja kuolleisuuteen.

Tutkimuksen aineisto koostuu kahdesta eri väestöpohjaisesta kohorttiaineistosta: Alzheimerin tautia sairastavat iäkkäät henkilöt vuosina 2005–2011 ja 10 % satunnaisotos kotona asuvista iäkkäistä vuosina 2000–2013. Iäkkäillä vältettävät lääkkeet on määritelty Fimean ylläpitämän Lääke75+-tietokannan mukaan.

Vältettävien lääkkeiden käytön aloitus oli vähäisempää Alzheimerin tautia sairastavien iäkkäiden keskuudessa verrattuna tautia sairastamattomiin henkilöihin. Potilaan ominaisuuksilla, mm. sukupuoli ja sosioekonominen asema, oli ikäryhmittäisiä eroja vältettävien lääkkeiden käyttöön valikoitumisessa kotona asuvilla 65–74- ja ≥75-vuotiailla iäkkäillä. Vältettävien lääkkeiden käytön aloitus on yhteydessä potilaan ominaisuuksiin, mutta myös terveydenhuoltojärjestelmään liittyviin tekijöihin, kuten lääkäreiden välisiin eroihin vältettävien lääkkeiden määräämisessä ja mahdollisesti erilaisiin alueellisiin hoitokäytäntöihin.

Alzheimerin tautia sairastavilla vältettävien lääkkeiden käyttö oli yhteydessä suurentuneeseen lonkkamurtuman riskiin vain ensimmäisen käyttöjakson aikana. Kotona-asuvilla iäkkäillä erityisesti vältettävien lääkkeiden aloituskäyttöjaksoon liittyi suurentunut sairaalahoitoa vaativien murtumien ja kuolleisuuden riski, myös otettaessa huomioon mahdollinen vältettävien lääkkeiden käyttöön liittyvä valikoitumisharha. Vältettävien lääkkeiden käyttäjillä sairaalakustannukset olivat suuremmat verrattuna niihin henkilöihin, jotka eivät käyttäneet vältettäviä lääkkeitä 12 vuoden seuranta-aikana.

Tämän väitöskirjatutkimuksen perusteella vältettävien lääkkeiden käyttö on yhteydessä moniin potilaasta ja lääkäristä riippuviin tekijöihin. Vältettävien lääkkeiden käyttöön liittyy suurentunut terveysseurausten ja sairaalahoidon riski, ja siten myös suuremmat sairaalakustannukset.

Avainsanat: *Iäkkäät, lääkityspoikkeama, terveysseuraukset, kustannukset, elinaika-analyysi, rekisteritutkimus*

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Kuopio with fall colours, October, 2018

Virva Hyttinen

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ABBREVIATIONS

AD = Alzheimer's disease
ADE = Adverse drug event
ADR = Adverse drug reaction
ATC = Anatomical Therapeutic Chemical
A&E = Accident and emergency department
CI = Confidence Interval
COPD = Chronic Obstructive Pulmonary Disease
DDD = Defined daily dose
ED = Emergency department
FIMEA = Finnish Medicines Agency
GEE = Generalized estimating equations
GP = General practitioner
HILMO = Care Register for Health Care
HR = Hazard ratio
HRQoL = Health-related quality of life
ICC = Intraclass correlation
IV = Instrumental variable
MEDALZ = Medication use and Alzheimer's disease
NSAID = Nonsteroidal anti-inflammatory drug
OR = Odds ratio
PIM = Potentially inappropriate medication
PIP = Potentially inappropriate prescribing
PSM = Propensity score matching
QALY = Quality-adjusted life years
SF = Statistics Finland
SII = Social Insurance Institution
START = Screening Tool to Alert Doctors to Right Treatment
STOPP = Screening Tool of Older Persons' potentially inappropriate Prescriptions
THL = National Institute for Health and Welfare
WHO = World Health Organization

1 INTRODUCTION

Due to limited health care resources, available resources should be optimally allocated, meaning that they produce as much health as possible. In Finland, one of the main objectives in the Medicines Policy 2020 is for *"rational pharmacotherapy and good medication safety* [to] *enhance the wellbeing of the population, improve public health and decrease healthcare expenditures"* (Ministry of Social Affairs and Health 2011). For this purpose, the Ministry of Social Affairs and Health in Finland set up a steering group for the Rational Pharmacotherapy Action Plan in 2016. The action plan was completed at the end of 2017, and one of the main objectives for rational pharmacotherapy up to 2022 is for cost-effective medication to be used, and for care providers to be able to make extensive use of electronic systems and reliable information sources on medications to support their decision-making. Rational pharmacotherapy means that medication treatments are "*safe, effective, cost-effective, equitable and of high quality*". (Ministry of Social Affairs and Health 2018a, p. 10, 23.)

The general aim of this dissertation is to evaluate health and economic aspects of potentially inappropriate medication (PIM) use in older populations. PIMs are defined as those medications that entail more risks than benefits for older people (Beers et al. 1991). Pharmacotherapy in older people is complex due to physiological changes related to ageing. Ageing has effects on distribution, metabolism and excretion of drugs (Kivelä and Räihä 2007, p. 6–7). For example, many anticholinergic medications and medications that impact the central nervous system are defined as PIMs in older people because they can cause e.g. cognitive decline or even delirium and increased fall risk (Kivelä and Räihä 2007, p. 17–18; Woolcott et al. 2009).

In Finland, almost half of all medication costs are accrued by only five percent of the population; those with the highest medication costs. Furthermore, over half of these high-cost medication users are over 65 years old, and almost half of them are using more than ten different medications. (Saastamoinen and Verho 2013.) Simultaneous use of multiple medications, also known as polypharmacy, has increased during the last four decades. Every fourth older person is using at least ten medications (referred to as excessive polypharmacy), and every third, at least 6–9 medications. (Jyrkkä 2011, p. 101.) Polypharmacy is itself a challenge for rational pharmacotherapy, and thus therapeutic equilibrium. Polypharmacy also increases the risk of use of PIMs (Fialová et al. 2005; Ahonen 2011; Vieira de Lima et al. 2013). A Finnish study found that PIMs are more commonly used among high-cost patients with polypharmacy compared to all medication users aged over 65 years (Saastamoinen and Verho 2015).

Despite the risks of PIM being well known, PIM use is prevalent in older people worldwide (Tommelein et al. 2015; Opondo et al. 2012; Vartiainen et al. 2017). In Finland, the Meds75+ database is developed to support clinical decision-making and is intended to improve medication safety for people aged 75 and over (Finnish Medicines Agency 2015). The database divides medications that were used in the older population into four categories (A to D), and PIMs are defined as D medications ("avoid use in older persons"). However, only a few previous studies (e.g. Bell et al. 2013) utilise the Meds75+, so more studies, particularly studies on associated outcomes, are needed for the validation of the Finnish criteria. In addition, there is a need for large nationally representative studies to find out how the health care system itself is treating older patients at the population level.

This dissertation consists of four sub-studies. Works 1 and 2 aimed to identify the associations of demand and supply side factors with PIM use in older people. More specifically, the aim was to identify risk factors for PIM use. Works 3 and 4 aimed to identify the associations of PIM initiation with hospitalisation, hospital costs and mortality in older people. In this dissertation, two different datasets based on Finnish population-based registers gave a unique opportunity to evaluate this phenomenon, in addition to the general community-dwelling older population, also in older people diagnosed with Alzheimer's disease, which can be spesifically vulnerable group.

The dissertation is structured as follows: Chapter 2 describes the conceptual framework of this dissertation; the framework of health care utilisation and the mechanisms of medication errors, in order to understand the interactions between physician and patient that can lead to PIM use. Chapter 3 presents the empirical context of PIM use in older people; the criteria of PIM, prevalence of PIM use, previous studies of factors and health outcomes associated with PIM use, and the associations between PIM use and health care utilisation and costs. Chapter 4 summarizes the previous literature. The aims of the study will be presented in Chapter 5. Chapter 6 describes data sources, study populations and the methods used in this dissertation. Chapter 7 presents the results. The discussion of the results will be presented in Chapter 8, which also presents an assessment of the study and topics for future research. Lastly, Chapter 9 concludes the dissertation.

2 CONCEPTUAL FRAMEWORK

2.1 THE FRAMEWORK OF HEALTH CARE UTILISATION

In health economics, the three main interests are efficiency, organisation and distribution of health care services. In an ideal situation, health care resources are used and organised efficiently and equitably in such a way that they produce as much health as possible. The aim of efficient and equitable health care leads to choices, for example, about the type of services provided and to whom, and how those services are organised. Making a choice always incurs opportunity costs, which are valued according to the benefit provided by the next best alternative.

The use of health care services can be seen as a result of the interaction between demand and supply. Demand in relation to health care services is, in an ideal world, based only on need, and more accurately, the need for health, and needs may be unlimited. In the real world, there are also other factors that have an effect on demand, for example, the patient's ability to pay for and seek care, and other patient characterisctics, e.g. age, gender, socioeconomic status etc.

It is obvious that the use of health care services increases with age due to increasing morbidity. It has been found that health care utilisation increases with age even when long-term care services are not considered. Worsening health status is the main predictor, but health care utilisation can also increase because of different access to or different prices of health care services in older age. (Sheiner 2011, p. 870–873.) This can be more clearly demonstrated in insurance-based countries, but older people may have better access to private health care services in countries with publicly funded systems too, provided their income level is higher than that of younger people.

Gender differences in health care use have been widely studied. Generally, women have a higher life expectancy worldwide (OECD 2018). Studies show that women use more health care services (Suominen-Taipale et al. 2006), and self-report poorer health status than men (e.g. Denton et al. 2004; Gerritsen and Deville 2009). However, gender differences exist between countries and between health care services. For example, men are hospitalised more often than women (Suominen-Taipale et al. 2006). Explanations for differences in health care use include, for example, structural, psychological and behavioural aspects. Between genders, there are differences in e.g. family structure, income level, education, occupation and social support, and these affect health differently. In addition, health behaviour may differ, for example, men are more often smokers and consume more alcohol. (Denton et al. 2004, p. 2597–2598.)

Lower socioeconomic status is associated with poorer subjective health and well-being (Read et al. 2015) as well as higher mortality (Huisman et al. 2004). Income level and education can have an impact on for example health behaviour, and thus health and health care utilisation. On the other hand, people with higher incomes have better access to health care, and thus can use more health care services, even when they are in better health. People with lower incomes are more likely to avoid seeking medical care, because they cannot afford the care (Hannikainen 2018). In Finland, it has been found that there are socioeconomic differences in use of public and private outpatient care services, as people with higher incomes were more likely to use more private

services while those on lower incomes used more public services (Manderbacka et al. 2009, p. 181; Hannikainen 2018). A Norwegian study demonstrated the existence of socioeconomic inequality, especially in special outpatient care, and the authors discussed whether these inequalities may be connected to e.g. the physician-patient relationship, when general practitioners are acting as the gatekeepers of special care (Vikum et al. 2012). It has been found that a patient's socioeconomic status can have an impact on the physician's communication, e.g. they communicate in a less informative way with patients from lower social classes (Willems et al. 2005).

Marital status and living situation may also be associated with health care service use (Joung et al. 1995; Noro et al. 1999). It is obvious that the need for help and social support is different for people living alone, and loneliness itself can be a risk factor for poor health, increasing e.g. mortality (Holt-Lunstad et al. 2015). However, a recent systematic review did not find that weaker social relationships in older people are associated with health care utilisation (Valtorta et al. 2018). Studies have shown that unmarried people may have a higher risk of mortality than married people (Kaplan and Kronick 2006). Possible explanations for the protective effect of marriage on mortality may be that married people have healthier lifestyles and that social relationships can have an impact on perceived health. However, the protective effect decreases at poorer levels of health. (Zheng and Thomas 2013.)

Demand in relation to health care services is obviously associated with the availability of those services. Availability of services differs when comparing rural and urban areas. In addition, studies have shown that people in rural areas may have poorer health than their urban counterparts (Lankila et al. 2012). However, these differences are mostly explained by the different socioeconomic status and health behaviour of people living in urban and rural areas (Fogelholm et al. 2006).

Overall, patient characteristics have an effect on both the demand for and supply of health care services. However, when patients seek care, physicians wield considerable power as health care decision-makers and are traditionally seen as the principal agents of patients. In economics, the traditional perspective is to see people as rational actors, meaning that they maximise their utility functions within a set of constraints. As a benevolent agent, a physician also maximises a patient's utility. However, the markets can fail due to many reasons, for example, because of information asymmetry. Physicians might work under "bounded rationality", which means that a person can have both knowledge limitations and computational capacity as a decision-maker (Simon 1990, p. 15). Information asymmetry between patients and care providers means that the care providers have more information, for example, about the available health care services and the health status of the patient.

It can be assumed that prescribing PIM to a patient is not in the interests of the physician as a benevolent agent for the patient. Thus, ideally, physicians would not prescribe PIMs, if they knew which medications cause more harm than benefits in older people. PIM prescribing still happens quite frequently, it is not totally random, and the patient characteristics that increase the risk of PIM use can be identified (see Chapter 3). In this study, prescribing PIM was seen as an end result of the interaction between patient and physician. Physicians' decision processes were not included in the empirical study, but this study understands that physicians and facilities interact with patients and with each other (Anderson 1973). In addition, as other humans, physians make mistakes, and thus PIM is an unintended consequence of the prescribing process. When PIM is defined as medications that should be avoided in older people, PIM prescribing can be seen as a quality deviation in the medication

process or a medication error, which can cause adverse health outcomes, and thus a potential increase in health care service utilisation and costs.

2.2 MECHANISMS OF MEDICATION ERRORS

A medication error is defined as *"a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient*" (Ferner and Aronson 2006, 1013). A medication error does not always result in harm, but according to Aronson (2009b) it is important to observe all errors because there is a possibility that they will lead to an error of clinical relevance in the future. Medication errors can be related to the prescribing process, medication manufacturing, dispensing or taking, or monitoring therapy (Aronson 2009a).

This study focuses on medication errors that were defined as PIMs in older people. However, it must be borne in mind that PIMs are "potentially" inappropriate, and a physician may at times consider some PIMs appropriate based on the indications. In addition, there is heterogeneity among older people when some are frailer than others of the same age.

PIM use is a consequence of the prescribing process. Medication error may be caused by mistakes or skill-based errors in prescribing. Mistakes can be divided into knowledge-based errors and rule-based errors. A knowledge-based error means that the error happened due to ignorance of general or specific information. (Aronson 2009b.) For example, if a physician is unaware of or ignores the fact that PIM use might cause older patients more harm than good. Rule-based errors can be categorised as "*the misapplication of a good rule or the failure to apply a good rule; and the application of a bad rule"* (Aronson 2009b, 603). For example, misapplication of the PIM criteria can be categorised as a rule-based error. Skill-based errors can be caused by action (a "slip") or memory (a "lapse"). Slips are errors that occur, for example, when a physician prescribes the wrong medication. Lapses are memory-based, and they happen where, for example, the physician forgets that the patient is allergic to certain medications. (Aronson 2009b.)

It is well known that prescribers are making decisions in multifactorial and complex environments (Anderson et al. 2014). There are many interrelated factors that are associated with PIM prescribing. One of the main contributors is the complexity of the prescribing environment, in addition to complexity at the patient and physician level. Complexity at patient level relates to multimorbidity, polypharmacy and patient heterogeneity. This also leads to complexity at physician level, for example, when several physicians are treating patients with several diseases. (Clyne et al. 2016b.)

2.2.1 Physician and health care system related factors

Cullinan et al. (2014b, 631) have synthesized four key concepts that are associated with PIM prescribing from the physician's point of view: "*(1) the need to please the patient, (2) feeling of being forced to prescribe, (3) tension between prescribing experience and prescribing guidelines and (4) prescriber fear"*. The need to please the patient occurs, for example, in a situation where a patient wants medication. That situation also relates to the second concept, where physicians feel that they are "forced" to prescribe medications, but also to e.g. a lack of alternatives. In these situations, physicians often know what

medication would be appropriate but feel unable to follow guidelines. This relates to the third concept, in which physicians feel that the guidelines are not compatible with real life. The fourth concept, prescriber fear, relates to e.g. the fear of causing harm to patient. This arises, for example, where there is reluctance to stopping a medication that is already being taken by the patient. (Cullinan et al. 2014b.)

According to a review by Anderson et al. (2014), physicians have different attitudes towards the initiation or continuation of PIMs. For example, physicians may fear the negative consequences of discontinuing or changing PIMs. These consequences may be related to the prescriber him/herself, the patient or other health professionals. (Anderson et al. 2014.)

More specifically, qualitative studies have shown that physician-related factors in PIM prescribing can be explained by, for example, limited knowledge or experience of PIM use in older people (Ramaswamy et al. 2011; Clyne et al. 2016b; Voigt et al. 2016), lack of specific education or training (Cullinan et al. 2014a), or difficulties in balancing the benefits and harms of PIMs (Anderson et al. 2014). Physicians self-reported that the main barrier to appropriate prescribing in older people is the large number of medications older patients is typically using (Ramaswamy et al. 2011).

Overall, physicians are generally well aware of the problems or risks related to PIM use (Cullinan et al. 2014a; Pohontsch et al. 2017), but there is still a lack of awareness of the PIM criteria (Ramaswamy et al. 2011; Dalleur et al. 2014; Cullinan et al. 2014a; Clyne et al. 2016b; Pohontsch et al. 2017). Physicians emphasise that even when they feel "forced" to prescribe PIMs, they are not putting the patient at risk (Cullinan et al. 2014a). Physicians justify PIM prescribing, for example, with constant monitoring (Pohontsch et al. 2017). Despite the risks, physicians report that the patient's quality of life is more important than the appropriateness of the prescription (Cullinan et al. 2014a). Sometimes, even when prescribers know that the medication is problematic, they want to ease the distress of patients who have several diseases (Pohontsch et al. 2017). Often PIM also meets the needs of the patient (Anderson et al. 2014).

There is interaction between general practitioners (GP) and specialists too. There may be a reluctance to question the prescribing choices of colleagues when GPs do not want to make changes in medication regimen started by a specialist (Anderson et al. 2014; Pohontsch et al. 2017). In addition, difficulties arise where patients have several treating physicians who do not communicate with each other (Pohontsch et al. 2017). Prescriptions are also commonly renewed via computerised systems, so the physician does not meet the patient face to face. Furthermore, reviews of patient's medications may not be systematic if prescriptions are renewed without meeting the patient (Saastamoinen et al. 2008). This may be a problem currently in Finland because prescription validity was recently extended from one year to two years from the date of prescribing, which is a long period without checks.

System-related errors are related to design, organisational or environmental aspects of health care (Flynn et al. 2010, p. 411). For example, studies have shown that system-related factors associated with PIM prescribing include: interruption (Cullinan et al. 2014a), lack of time and effort, increased workload, limited applicability of PIM lists in daily practice, lack of alternatives to PIMs (Anderson et al. 2014; Dalleur et al. 2014; Voigt et al. 2016), or lack of information technology infrastructure (Cullinan et al. 2014a).

2.2.2 Patient-related factors

As prescribing decisions result from the physician-patient relationship, the patient also plays his/her own role in the prescribing process, and thus in producing medication errors. Studies have shown that the physician-patient relationship with older people can be quite paternalistic, which means that patients see physicians as authoritative figures. This paternalism may be emphasised in situations where patients behave more passively with respect to their medication management. (Clyne et al. 2016b.)

However, sometimes patients themselves are not concerned about risks even though the physician has explained the risks related to PIMs (Pohontsch et al. 2017). Patients may be reluctant to stop or change their medications (Anderson et al. 2014; Pohontsch et al. 2017), and may not readily accept alternative medications (Anderson et al. 2014). This can be explained, for example, by a fear of the risks that stopping may entail or the hope that the medication will help at a later point (Reeve et al. 2013). Some patients, especially those using a high number of medications, may demand medications from physicians (Pohontsch et al. 2017). It is obvious that the patient wants relief from his/her symptoms. Pressure to prescribe may also come from the patient's family (Cullinan et al. 2014a).

Increasing the number of medications causes difficulties in the prescribing process also from the patient's point of view. Sometimes patients cannot remember all the medications that they use or forget to mention them. Notably, patients do not necessarily report over-the-counter medications and natural remedies if they think that they are harmless (Pohontsch et al. 2017). It is also typical for patients to fail to report new symptoms they have experienced when taking their medications to the prescriber. They may remain silent, leading the prescriber to believe that there are no problems with the medication. (Britten 2009.)

3 POTENTIALLY INAPPROPRIATE MEDICATION (PIM) USE IN OLDER PERSONS

3.1 CRITERIA OF PIMS

Various explicit (criterion-based) and implicit (judgement-based) criteria have been developed to assess PIMs in order to improve medication use in older people in different countries. Explicit criteria are often medication- or disease-oriented, while implicit criteria are patient-oriented (Spinewine et al. 2007). Explicit criteria can often be applied without clinical judgement, and their implementation to clinical practice is often easier (Spinewine et al. 2007; Chang and Chan 2010).

The first and the most well-known set of explicit criteria is Beers, which was developed in the USA at the beginning of the 1990s. It was first developed to assess the medications of patients in institutional care, but was later updated and extended to include all geriatric care, excluding hospice and palliative care. (Beers et al. 1991, Beers 1997; American Geriatrics Society 2012.) The latest update of Beers was carried out in 2015 (American Geriatrics Society 2015). Other popular explicit criteria are, for example, the Irish Screening Tool of Older Persons potentially inappropriate Prescriptions/Screening Tool to Alert Doctors to Right Treatment (STOPP/START) criteria (O'Mahony et al. 2015), the French Laroche (Laroche et al. 2007), the German PRISCUS (Holt et al. 2010) and FORTA (Kuhn-Thiel et al. 2013). The latest criteria are to be found in the EU(7)-PIM list, which was developed to identify and compare PIM prescribing in older people in Europe (Renom-Guiteras et al. 2015).

Because generalising the criteria developed in other countries can be, to some extent, problematic, national criteria are always the most desirable (Dimitrow et al. 2011). Chang and Chan (2010) reported in their review that differences between the explicit criteria included in the study, were mostly related to differences in medication availability and prescribing practices across countries. For example, one half of the 74 medications listed in the Beers Criteria (2003) did not have marketing authorisation in Finland in 2010 (Hartikainen and Ahonen 2011). In Finland, the Database of Medication for Older Persons (Meds75+ since 2015) was initially developed by the Centre for Pharmacotherapy Development (ROHTO) in 2008. The database, intended for use by health care professionals, was published in 2010, and has since then been maintained by the Finnish Medicines Agency (FIMEA). (Jyrkkä et al. 2017.) In the database, about 500 medications (Anatomical Therapeutic Chemical (ATC) -codes) are divided into four classes from A to D: "*A) suitable for older persons, B) lack of research evidence, clinical experience or efficacy among older persons, C) suitable for older persons, with specific cautions, and D) avoid use in older persons*" (Finnish Medicines Agency 2015; Jyrkkä et al. 2017). The Meds75+ can be considered as explicit PIM criteria, as the database does not take into account e.g. patient's individual characteristics or adherence (Dimitrow et al. 2013). In addition, this study does not take into account drug-drug or drug-disease interactions, indication, dosage, or duration of therapy.

3.2 PREVALENCE OF PIM USE

Despite the risks, PIM use has been found to be common among older people worldwide (Curtis et al. 2004; Fialová et al. 2005; Nyborg et al. 2012; Bradley et al. 2014; Price et al. 2014; Chang et al. 2015; Moriarty et al. 2015; Grina and Briedis 2017). Table 1 presents the studies reporting on the prevalence of PIM use in older people. According to reviews, the prevalence of PIM use varies from 11.5 % to as much as 79 % depending on the criteria used or the study setting (Guaraldo et al. 2011; Hill-Taylor et al. 2013). A review by Opondo et al. (2012) reported that the median prevalence of PIM use was 20 % among older patients in primary care setting. A recent review by Tommelein et al. (2015) concluded also that the prevalence of PIMs is over 20 % among people aged 65 or older in Europe. Differences in prevalences can be explained e.g. by differences in PIM criteria, exposure period and study populations and settings (Jiron et al. 2016). For example, prevalences are often lower if they were estimated cross-sectionally as a point prevalence compared to e.g. a 12-month period prevalence (Mantel-Teeuwisse et al. 2001). In addition, prevalence rates can vary when comparing self-reported PIM use to register-based estimates. Also criteria and their versions differ, for example, the newer Beers Criteria include longer list of drugs and drug-disease interactions than older versions (e.g. 2003) (Jiron et al. 2016).

People living in a long-term care could be at higher risk of PIM use (Morin et al. 2016). The review by Morin et al. (2016) found that almost half of the older people living in nursing homes are using PIMs. A Finnish study showed that almost 35 % of nursing home residents used at least one PIM as defined by the Beers (2003) Criteria (Hosia-Randell et al. 2008). The review by Morin et al. (2016) indicated that prevalence estimates were increasing among nursing home residents.

PIMs are also common in people with dementia or cognitive impairment (Johnell 2015). A recent review found that the prevalence of PIM use varied from 15 % to almost 47 % among people aged ≥65 with dementia (Patel et al. 2017). Renom-Guiteras et al. (2018) studied PIM use among people with dementia in eight European countries and found that almost 60 % of study subjects were prescribed at least one PIM as defined by the EU(7)-PIM list. The authors discussed how the prevalence of PIM use might be higher than in other studies because the study population was frailer, with some subjects already in long-term care. In addition, the development of the EU(7)-PIM list was based on several published PIM criteria (such as the PRISCUS, Laroche, Beers and McLeod criteria) (Renom-Guiteras et al. 2015), so it can take more medications into account.

In Finland, a study by Leikola et al. (2011) found that almost 15 % of people aged 65 or over had been prescribed PIMs as defined by the Beers Criteria (2003) in 2007. In a study using the Meds75+ database, 30 % of people aged ≥75 used PIMs in 2004 (Bell et al. 2013). A recent study, using the data from this dissertation, showed higher prevalence (43 %) when the prevalence was estimated as an one-year period prevalence including persons aged ≥65 used PIMs in 2000 (Vartiainen et al. 2017). PIM use decreased during the study period, so 18 % of older people used PIMs during the last year of the study period (year 2013). It must be noted that the study followed the same population during the 14-year study period, so the real reduction in PIM use within the entire Finnish older population is smaller. (Vartiainen et al. 2017.) However, the recent 4-month prevalence estimates from the Finnish registers showed that PIM use has slightly decreased within the entire Finnish older population: in 2015, PIMs were used by 24.7 % of people aged ≥75, in 2016, by 23.4 % and in 2017 by 20.3 % (Jauhonen et al. 2018). Studies conducted in the general older populations showed that the prevalence of PIM use has decreased in many countries, e.g. in the USA, France and Norway, during the last decade (Bongue et al. 2009; Hovstadius et al. 2014; Price et al. 2014; Jiron et al. 2016).

Table 1. Studies on prevalence of PIM use in persons aged ≥65 years

Study (country)	Study design (study years)	Study setting	n	Age (mean)	Criteria	Prevalence of PIM use
Original studies						
Bell et al. 2013 (Finland)	Cross-sectional (2004)	Community-dwelling people and nursing home residents	781	≥75 years (81.7)	Meds75+	30.0 %
Bongue et al. 2009 (France)	Cross-sectional (1995–2004)	Non-institutionalised people	30,683	≥65 years (70.1)	Beers (1997)	1995: 14.9 % 2004: 9.0 %
					French update criteria of the Beers (1997)	1995: 33.5 % 2004: 19.3 %
Bradley et al. 2014 (The United Kingdom)	Cross-sectional (2007)	Participants in the UK Clinical Practice Research Datalink (CPRD)	1,019,491	≥70 years (NA)	STOPP	29.0 %
Chang et al. 2015 (Taiwan)	Cross-sectional (2009)	Ambulatory patients	1,164,701	≥65 years (NA)	Beers (2012)	86.0 %
					PIM-Taiwan criteria	73.0 %
					PRISCUS	67.0 %
Curtis et al. 2004 (USA)	Cohort (1999)	Outpatients	765,423	≥65 years (73.8)	Beers (1997)	21.2 %
Fialová et al. 2005 (Incl. eight European countries)	Cross-sectional (Sep 2001 – Jan 2002)	Home care patients	2,707	≥65 years (82.2)	Beers (1997)	Czech Republic: 15.7 % Italy: 13.6 % Finland: 17.1 % Norway: 9.8 % Iceland: 5.9 % United Kingdom: 5.9 % The Netherlands: 9.1 % Denmark: 3.3 % **Total in all countries: 9.8 %**

Table 1. (continued)

Study (country)	Study design (study years)	Study setting	n	Age (mean)	Criteria	Prevalence of PIM use
					Beers (2003)	Czech Republic: 25.2 % Italy: 25.7 % Finland: 20.3 % Norway: 14.7 % Iceland: 15.1 % United Kingdom: 13.5 % The Netherlands: 13.1 % Denmark: 5.8 % **Overall in all countries: 16.9 %**
					McLeod (1997)	Czech Republic: 31.8 % Italy: 6.8 % Finland: 14.4 % Norway: 11.3 % Iceland: 4.4 % United Kingdom: 5.2 % The Netherlands: 7.6 % Denmark: 3 % **Overall in all countries: 10.9 %**
Grina and Briedis 2017 (Lithuania)	Cross-sectional (2015)	Population-based	431,625	≥65 years (75.8)	Beers (2003)	25.9 %
					Beers (2015)	24.1 %
					EU(7)-PIM list	57.2 %
Hosia-Randell et al. 2008 (Finland)	Cross-sectional (2003)	Nursing home residents	1,987	≥65 years (83.7)	Beers (2003)	34.9 %
Jiron et al. 2016 (USA)	Cohort (2007–2012)	Medicare patients	38,250	>65 years (77.5)	Beers (2012)	2007: 34.2 % (12-month prevalence 64.9 %) 2012: 34.2 % (12-month prevalence 56.6 %)
Leikola et al. 2011 (Finland)	Cross-sectional (2007)	Non-institutionalised people	841,509	≥65 years (NA)	Beers (2003)	14.7 %

Table 1. (continued)

Study (country)	Study design (study years)	Study setting	n	Age (mean)	Criteria	Prevalence of PIM use
Moriarty et al. 2015 (Ireland)	Cohort (2009–2012)	Community-dwelling people	2,051	≥65 years (74.8)	STOPP	Baseline: 52.7 %; follow-up: 56.1 % 1 PIM: baseline 29.8 %; follow-up: 29.4 % 2 PIMs: baseline 13.2 %; follow-up: 15.0 % ≥3 PIMs: baseline 9.8 %; follow-up: 11.8 %
					Beers (2012)	Baseline: 30.5 %; follow-up: 33.1 % 1 PIM: baseline 15.8 %; follow-up: 17.0 % 2 PIMs: baseline 9.4 %; follow-up: 9.9 % ≥3 PIMs: baseline 5.3 %; follow-up: 6.1 %
					The third iteration of the ACOVE	Baseline: 19.8 %; follow-up: 22.0 % 1 PIM: baseline 16.4 %; follow-up: 18.1 % 2 PIMs: baseline 3.0 %; follow-up: 3.1 % ≥3 PIMs: baseline 0.4 %; follow-up: 0.8 % Defined by any of the criteria: Baseline: 61.4 %; follow-up: 64.8 %
Nyborg et al. 2012 (Norway)	Cross-sectional (2008)	Community-dwelling people	24,450	≥70 years (NA)	NORGEP	1 PIM or more: 34.8 % 2 PIMs or more: 14.0 % 5 PIMs or more: 0.8 %
Price et al. 2014 (Australia)	Cohort (1993–2005)	Population-based	187,616	≥65 years (NA)	Beers (2003)	13-year prevalence: 74.7 %

Table 1. (continued)

Study (country)	Study design (study years)	Study setting	n	Age (mean)	Criteria	Prevalence of PIM use
Renom-Guiteras et al. 2018 (Incl. eight countries)	Cohort (baseline Nov 2010 – Apr 2012, follow-ups: three months)	People with dementia	2,004	≥65 years (83)	EU(7)-PIM list	Sweden: 1 PIM or more 49.6 %; 2 PIMs or more 15.2 % Finland: 1 PIM or more 58.9 %; 2 PIMs or more 25.0 % The Netherlands: 1 PIM or more 66.7 %; 2 PIMs or more 39.2 % Germany: 1 PIM or more 61.6 %; 2 PIMs or more 26.3 % Estonia: 1 PIM or more 47.0 %; 2 PIMs or more 16.0 % France: 1 PIM or more 65.2 %; 2 PIMs or more 24.1 % Spain: 1 PIM or more 67.5 %; 2 PIMs or more 35.7 % England: 1 PIM or more 66.0 %; 2 PIMs or more 28.1 % **Overall in all countries:** 1 PIM or more: 60.0 %; 2 PIMs or more: 26.4 %
Vartiainen et al. 2017 (Finland)	Cohort (2000–2013)	Community-dwelling people	64,250	≥65 years (75)	Meds75+	2000: 43.0 % 2013: 18.0 %
Reviews						
Guaraldo et al. 2011 (Review incl. studies from five countries)	Review incl. 19 studies (Publ. years: 1997–2009)	Community-dwelling people	777–2,133,864	≥60 years (NA)	Beers (1991, 1997 and 2002), Zhan, HEDIS	11.5–62.5 %
Hill-Taylor et al. 2013 (Review incl. studies from nine countries)	Review incl. 12 studies (Publ. years: 2007–2012)	Community-dwelling eople, hospital or long-term care patients	344,957	≥65 years (74.9–86.9)	STOPP/START (eight studies compared to the Beers criteria (2002), MAI index or Australian criteria)	21.4–79.0 %
Johnell 2015 (Review incl. studies from Europe, Asia, USA and Australia)	Review incl. 22 studies (Publ. years: 2002–2013)	People with dementia or cognitive impairment	34–2,665	NA	Beers, Laroche, PRISCUS, STOPP, Holmes, McLeod, HEDIS, Austrian list and the modified Beers criteria	10.2–56.4 %

Table 1. (continued)

Study (country)	Study design (study years)	Study setting	n	Age (mean)	Criteria	Prevalence of PIM use
Morin et al. 2016 (Review incl. studies from 18 countries)	Review incl. 43 studies (26 studies with point prevalence) (Publ. years: 1990–2014)	Nursing home residents	227,534 (50–86,312)	≥60 years (77.7–~87)	Beers (1991, 1997, 2003 and 2012), Laroche, McLeod, STOPP/START, HEDIS, NORGEP, PRISCUS, Zhan, ACOVE, BEDNURS, Stuck, Rancourt, and other country-specific criteria (Swedish, Austrian, Australian) and implicit criteria	5.4–95.0 % Overall PIM prevalence: 43.2 % (95 % CI 37.3–49.1 %)
Opondo et al. 2012 (Review incl. studies from 11 countries)	Review incl. 19 studies (Publ. years: 1997–2012)	Older patients in primary care settings	NA/100–12,513,584	>65 years (NA)	Beers (1991, 1997, 2003), the modified Beers (2003), Zhan, HEDIS HRME, MRPS	Overall median PIM rate: 20.0 %
Patel et al. 2017 (Review incl. studies from three countries)	Review incl. seven studies (Publ. years: 2010–2013)	Community-dwelling people with dementia	342–131,808	≥65 years (77–80.9)	Beers (2003), Laroche, PRISCUS, Lindblad classification	15.0–46.8 %
Tommelein et al. 2015 (Review incl. studies from 23 European countries)	Review incl. 52 studies (Publ. years: 2002–2014)	Community-dwelling people	50–1,019,491	≥65 years (70.1–85.8)	Beers (1997, 2003), STOPP/START (2008), PRISCUS, Laroche, MAI, IPET, NORGEP and other country-specific criteria	Overall PIM prevalence: 22.6 % (95 % CI 19.2–26.7 %)

PIM, potentially inappropriate medication; NA, not available; STOPP, Screening Tool of Older Persons potentially inappropriate Prescriptions; START, Screening Tool to Alert Doctors to Right Treatment; MAI, Medication Appropriateness Index; NORGEP, Norwegian General Practice; HEDIS, Health Plan Employer Data and Information Set; CI, confidence interval

3.3 RISK FACTORS FOR PIM USE

3.3.1 Patient-related factors

A high number of comorbidities, typically operationalized by Charlson comorbidity score, is one of the factors most often associated with PIM use (Stock et al. 2014; Tommelein et al. 2015). A high number of comorbidities is related to polypharmacy, so as expected, the risk of PIM use increases with the number of medications used (Ahonen 2011; Guaraldo et al. 2011). Polypharmacy is one of the major predictors for PIM use (Fialová et al. 2005; Ahonen 2011; Vieira de Lima et al. 2013; Tommelein et al. 2015), which is most commonly defined as the current use of five or more medications (Gnjidic et al. 2012), and the use of ten or more medications is often called excessive polypharmacy (e.g. Jyrkkä 2011, p. 4). A Finnish study of nursing home residents found that PIM users as defined by the Beers Criteria (2003) were more likely to have nine or more medications daily compared to non-users (Hosia-Randell et al. 2008). Also, in people with dementia, the higher number of medications used is associated with a higher risk of PIM use (Patel et al. 2017). Cognitive impairment and dementia alone is associated with a lower risk of PIM use. One reason might be that physicians are more cautious about prescribing PIMs to more vulnerable patients. (Johnell 2015.)

Older age is most often found to be associated with PIM use (e.g. Bongue et al. 2009; Guaraldo et al. 2011; Price et al. 2014,). The underlying reasons for the increasing risk of PIM use with age could be greater morbidity and the higher number of medications used. A study by Mo et al. (2015) found that people aged ≥80 have more PIMs than people aged less than 80 years. However, the association between older age and PIM use was barely significant after taking into account the number of diseases and medications in the analysis. Nevertheless, the association between older age and PIM use is still unclear because there are also contradictory or mixed findings. A review by Tommelein et al. (2015) showed that only about half (12/25) of the studies that evaluated age as a risk factor for PIM use found a positive association. According to the findings of a study by Miller et al. (2016), older age is a predictor of lower PIM use as defined by the Beers Criteria (2012). Also a study by Jiron et al. (2016) found a lower risk for PIM use in older age groups after adjusting for individual characteristics and health care utilisation. In addition, Bradley et al. (2014) found that PIMs were less common among people aged over 85 in the United Kingdom. A recent systematic review by Nothelle et al. (2017) found that PIMs were associated with younger age among nursing home residents. The older the patient, the lower the risk of PIM use, which may reflect increasing awareness of the age-related risks of PIMs among physicians (e.g. Fialová et al. 2005).

Generally, studies have shown that women are more likely to use PIMs than men (Guaraldo et al. 2011; Stock et al. 2014; Miller et al. 2016; Morgan et al. 2016). Potential explanations for the higher proportion of PIM users among women include the fact that generally speaking women live longer, use more medications (Manteuffel et al. 2014) and use health care services more frequently than men (Suominen-Taipale et al. 2006). However, there are also contradictory findings depending on, for example, the criteria used. A recent study, using the Beers and the EU(7)-PIM list, found that women had a 30 % higher risk of PIM use, as defined only by the EU(7)-PIM list, but the risk was lower than for men according to the Beers Criteria (versions 2003 and

2015) (Grina and Briedis 2017). Also, a study by Bradley et al. (2014) found that women used slightly fewer PIMs compared to men in the UK.

Studies have mainly shown that there is an association between lower socioeconomic status and PIM use (Bongue et al. 2009; Tommelein et al. 2015; Miller et al. 2016). A recent French study found that those municipalities with high PIM prevalence are more likely to be characterised by low socioeconomic status defined by e.g. unemployment rate, average net taxable and non-taxable income (Beuscart et al. 2017). A Swedish study by Haider et al. (2009) found that a low educational level is associated with PIM after adjusting for age, gender, place of residence and comorbidities.

Previous studies have mainly found that living situation is not associated with PIM use or associations were unclear. A review by Tommelein et al. (2015) reported a positive association between PIM use and living alone in only half of the studies (3/6). On the contrary, Fialová et al. (2005) found that living alone was negatively associated with PIM use. Two recent studies found no association between PIM use and living alone in older primary care patients (Projovic et al. 2016) or older people with dementia (Wucherer et al. 2017).

3.3.2 Physician and health care system related factors

Generally, previous studies have found that the risk of PIM use increases with the number of prescribing physicians (Nyborg et al. 2012; Holmes et al. 2013; Chang et al. 2014; Lim et al. 2016; Projovic et al. 2016). The risk of PIM prescription was found to be higher in visits to family doctors and GPs compared to other specialised physicians (Lai et al. 2009). Rothberg et al. (2008) found that geriatricians have the lowest rate of PIMs compared to internists, family practitioners and hospitalists or cardiologists. Holmes et al. (2013) found that PIM prescribing rates are the highest among primary care, surgery, and pain medicine specialists. They also found variation in PIM prescribing among individual physicians. The study found that 4 % of the variation in PIM use among patients is attributable to physicians (Holmes et al. 2013). A study by Cahir et al. (2014) reported that patient-level characteristics (e.g. number of medications) more significantly explained potentially inappropriate prescribing (PIP), that there was little variation among GPs, and that the variation was not significant after controlling for patient-related factors.

There are mixed findings regarding physicians' demographic characteristics and PIM prescribing. Two studies have not found any association between the physician's age or gender and PIM prescribing (Goulding 2004; Ie et al. 2017). Two Taiwanese studies found that male physicians had a higher risk of PIM prescribing (Lai et al. 2009; Chang et al. 2014). A study by Lai et al. (2009) found that the risk of PIM prescribing was higher among the older physicians. The authors discussed that the differences between younger and older physicians can be explained by a lack of continuum of medical education programs. In a study by Chang et al. (2014), there were diverging results with respect to the association between physician's age and PIM prescribing, depending on the PIM criteria used.

Previous studies have also found regional differences in PIM prescribing (Rothberg et al. 2008; Lund et al. 2013; Jiron et al. 2016; Beuscart et al. 2017). A cross-sectional study reported that older veterans living in rural areas are at higher risk of PIP than those living in urban areas (Lund et al. 2013). A French study evaluated regional differences in PIM prescribing and found that those municipalities with high PIM

prescribing had larger populations and e.g. higher unemployment rates (Beuscart et al. 2017). In that study, there were no considerable differences in health care provision between municipalities with high or low PIM prescribing. One study found that older people living in southern or western parts of the USA were more likely to receive PIMs than their counterparts living in northeastern or north-central parts (Jiron et al. 2016). However, the study did not take into account, for example, socioeconomic differences between regions. Rothberg et al. (2008) found lower rates of PIMs in smaller hospitals and hospitals in urban areas. In addition, there were lower rates of PIMs in those hospitals with geriatricians. In a study by Goulding (2004), there were no associations between PIP and the location of the physician's office or hospital. In addition, Zhan et al. (2001) reported that there was no association between PIM use and urban/rural location or region after controlling for other factors, such as sociodemographic factors and health status.

3.4 PIMS AND HEALTH OUTCOMES

Previous studies have found that PIMs increase the risk of adverse drug reactions and events (ADRs/ADEs) (e.g. Lund et al. 2010; Stockl et al. 2010; Hamilton et al. 2011; Hedna et al. 2015). ADEs are any events that occurred during the medication treatment, while ADRs are reactions or events caused by taking a medication (Nebeker et al. 2004). ADRs include typically, for example, dry mouth, constipation, memory disorder, cognitive decline or even delirium (Kivelä and Räihä, p. 17). However, previous results on the association between PIMs and ADRs/ADEs are contradictory depending on the criteria used or study setting. Hedna et al. (2015) studied the association between PIMs and ADRs within the general older population aged ≥65 in Sweden. The study found that those exposed to PIMs, as defined by the STOPP criteria, had over a twofold increased risk of ADRs. Lund et al. (2010) showed a weak association between PIMs, as defined by implicit MAI criteria, and an increased risk of ADEs in veterans aged ≥65. However, the study did not report any association between PIMs, as defined by the Beers Criteria (2003), and ADEs. A study by Fick et al. (2008) found that medication-related problems are more prevalent among older people taking PIMs, but the results were not adjusted for any covariates. Hamilton et al. (2011) found a significant association between PIMs and ADEs among hospitalised older people when PIMs were defined by the STOPP criteria, but the association was not significant according to the Beers Criteria (2003). Page and Ruscin (2006) did not find any association between PIMs defined by the Beers Criteria (2003) and ADEs after controlling for covariates. Stockl et al. (2010) found that people using sedative hypnotics as defined by the Beers Criteria (2003) are at higher risk of falls and fractures (hazard ratio [HR] 1.22; 95 % CI 1.10–1.35). In addition, a study by Berdot et al. (2009) combined the Beers and Laroche criteria and found that PIMs, especially long-acting benzodiazepines, increase the risk of falling (odds ratio [OR] 1.40; 95 % CI 1.10–1.79). However, when the full PIM list was considered, the association between regular PIM use and falls was not significant, and barely significant with occasional use (OR 1.23; 95 % CI 1.04–1.45).

There are mixed findings regarding the associations between PIM use and functional status. A study by Koyama et al. (2014) found that PIM use was associated with a higher risk of functional impairment among older women. In a study by Fromm et al. (2013), PIM use as defined by the PRISCUS list was not associated with functional

status upon discharge from the hospital. In addition, Lau et al. (2011) did not find any association between PIM use and functional decline among older people with dementia.

Previous studies have mainly not found any association between PIM use and mortality (Hanlon et al. 2002; Klarin et al. 2005; Raivio et al. 2006). In addition, studies of the Finnish general older population showed no significant association between PIM use and mortality (Ahonen 2011, p. 61). A recent review concluded that PIMs are associated with mortality but only in studies which excludes prevalent users (Muhlack et al. 2017). The authors conclude also that all studies with new-user designs were conducted in the USA, so generalisation to other countries should be made with caution. However, the results of new-user design studies can be seen more adequate, because it avoids prevalent user or healthy-user bias. Comparison of prevalent PIM users with non-users can underestimate the connection between PIM exposure and outcomes because prevalent users are those who have survived under treatment (e.g. Danaei et al. 2012)

3.5 PIMS AND HEALTH CARE UTILISATION AND HEALTH CARE COSTS

3.5.1 Cohort and case-control studies

Based on our review (Hyttinen et al. 2016), PIM use is associated with an increased risk of hospitalisation and thus higher health care costs. The systematic review included 39 studies that evaluated PIM use in relation to health care utilisation e.g. hospitalisation, length of stay, and health care visits. The review included only studies with general older populations, so all disease-specific articles were excluded. In accordance with a previous review by Jano and Aparasu (2007), our review indicated that more studies with better data are needed. Most of the studies included in our review included quite short follow-ups (min. 2 months and max. 12 years; median 12 months). Furthermore, in most studies, PIM use was assessed at baseline or in a cross-sectional setting which do not take into account the prevalence user bias or variation in PIM use over time.

Table 2 summarises the studies published after our review (Hyttinen et al. 2016). The studies are mainly in accordance with the previous findings that PIM use is associated with an increased risk of health care utilisation (Endres et al. 2015; Henschel et al. 2015; Narayan and Nishtala 2015; Chen and Cheng 2016; Moriarty et al. 2016; Heider et al. 2017; Varga et al. 2017). However, the connections between PIM use and health care utilisation are quite weak in most studies. In most of the studies that found a positive association between PIM use and increased risk of health care use, the outcome of interest was hospital admissions.

Varga et al. (2017) studied all-cause hospitalisations and reported that PIM use, as defined by Maio criteria, is associated with a 16 % higher risk of hospitalisation over a 10-year period. Narayan and Nishtala (2015) found that PIM use defined by the Beers Criteria (2012) is associated with an increasing risk of fall-related hospitalisation and the use of primary care visits in a large population-based study including almost all New Zealanders. Endres et al. (2015) studied the risk of all-cause hospitalisation associated with PIM use, as defined by the PRISCUS list, and compared this to PIM alternatives in the PRISCUS list, which can be considered to the best possible

comparator. Their results showed that during a 180-day follow-up since cohort entry, PIM use (versus use of PIM alternatives) was associated with a 38 % increased risk for hospitalisation. The PRISCUS list was also used in a study by Heider et al. (2017), which found that the incident PIM users defined by the PRISCUS list have more days in hospital or in rehabilitation clinics compared to those not exposed to PIMs. The advantage of the study was that they matched PIM-users and non-users by entropy balancing to minimize the selection bias. Bias here means that the selection to PIM user and non-user groups is not random (see Chapter 6.5.1). Henschel et al. (2015) matched PIM users and non-users by propensity score matching and they found a positive association between incident PIM use as denifed the PRISCUS and ADE-related hospitalisations. Chen and Cheng (2016) address the selection to the groups by using the instrumental variable (IV) analysis. The IV in the study was a physician's PIM prescription rate as patients may be more likely to receive PIM prescriptions from the physicians with a high PIM rate. The study showed an increasing risk of hospitalisation (excluding non-medical or poisoning events or chemotherapy) for those who used PIMs as defined by the Beers Criteria (2003). They compared also the IV analysis to naïve generalized estimating equation (GEE) model, and found that the likelihood of hospitalization was larger in the IV model compared to the naïve GEE model.

Four studies published after our review (Hyttinen et al. 2016) found mixed findings regarding the criteria used or the level of PIM exposure. A study by van der Stelt (2016) found that PIMs defined by the STOPP criteria were significantly associated with medication-related hospitalisation, but PIM use defined by the Beers Criteria (2012) was associated with hospitalisation only when the subject was using at least two PIMs. Additionally, Wallace et al. (2017) compared two different PIM criteria and found that PIM use defined by the STOPP criteria is associated with emergency department (ED) visits but not with emergency admissions. There was also a significant reduction in health-related quality of life (HRQoL) for patients using at least two PIMs at the baseline. When PIMs were defined by the Beers Criteria (2012), there were no associations between PIM use and ED visits, emergency admissions or HRQoL. The authors discussed that different results depending on the criteria used can be explained by the medication availability, because there were several medications in the Beers Criteria that were not available in the Irish setting. Moriarty et al. (2016) studied ED and GP visits and found that PIMs defined by the STOPP criteria are associated with a higher number of GP and ED visits, but when the number of PIMs was considered, the association with ED visits was statistically significant only where a subject was using at least two different PIMs. Wauters et al. (2016) studied PIM use among the oldest subjects (aged ≥80) and did not find any association between PIM use and higher risk of unplanned hospitalisation after adjusting for covariates.

Our review (Hyttinen et al. 2016) included only seven studies that investigated the association of PIM use on health care costs, and five of those articles found higher medical or total health care costs in PIM users compared to those who did not use PIMs. Our review excluded those studies which only evaluated the medication costs associated with PIM use. The majority (4/7) of the previous studies were conducted in the USA. To our knowledge, only one published study has evaluated PIM use in relation to health care costs after the publication of our review. A German study by Heider et al. (2017) found that PIM users, as defined by the PRISCUS list, had higher mean annual health care costs compared to those who do not use PIMs (6809 euros vs. 4488 euros) (Heider et al. 2017).

3.5.2 Intervention studies

Our review included only four intervention studies, which evaluated the effects of interventions (pharmacist-patient intervention or physician education intervention) on PIM reduction and health care utilisation. The studies did not find any significant results related to PIM reduction and ED visits or hospitalisations (Hyttinen et al. 2016). One study found that physician and nurse visits decreased after an educational intervention targeting PIM-prescribing reduction for physicians in nursing homes (García-Gollarte et al. 2014).

The five recently published intervention studies are mainly in accordance with previous studies included in our review. There were no significant differences between the intervention and control groups in relation to implementig medication reviews in hospitalisations, ED visits, mortality (Campins et al. 2017; Frankenthal et al. 2017; Kiel and Phillips 2017), length of stay (O'Connor et al. 2016) or falls (Frankenthal et al. 2017). A study by Campins et al. (2017) found significant differences in primary care visits at three and six months but not at 12 months. In addition, there were no differences in ED visits or visits to specialists (Campins et al. 2017). A study by O'Connor et al. (2016) found that the STOPP/START intervention reduced ADRs and medication costs, but there were no differences in the median length of stay between intervention and control groups. In addition, another study by Kiel and Phillips (2017) showed significant differences in medication-related problems between intervention and control groups, but no statistically significant differences were reported in hospitalisations or ED visits between the two groups. However, the sample size was small (n=52) and the follow-up only 90 days. Frankenthal et al. (2017) retrospectively evaluated the outcomes of written medication reviews after extending the previous randomised controlled trial (RCT) by an additional 12 months and compared these to orally communicated medication reviews. Their study did not find any significant difference in hospitalisation between intervention and control group, and there were significantly more PIMs in the intervention group between 12 and 24 months but still fewer than in the control group. Authors concluded that the orally communicated medication review, which was implemented at the baseline, was more efficient than the written medication review (Frankenthal et al. 2017). Campins et al. (2017) found that the intervention reduced PIMs compared to the baseline. One recently published economic evaluation also found that a multifaceted intervention significantly reduced the number of PIMs but the intervention was not cost-effective since there were no significant differences in mean quality-adjusted life years (QALYs) between the intervention and control groups (Gillespie et al. 2017). Authors discusses that the study period could be too short to capture effects in longer periods, and the sample size could be too small.

There was one intervention study that was regretfully omitted from our abstract-based review when the systematic review was conducted. The study by Pitkälä et al. (2014) evaluated the effect of nursing training on potentially harmful medication use, which was defined as anticholinergic medication use, use of multiple psychotropic medications, nonsteroidal anti-inflammatory drugs (NSAIDs) and proton-pump inhibitors and PIMs according to the Beers Criteria (2003). The study also investigated the effect of the intervention on the participants' HRQoL, health care service use and mortality during a 12-month follow-up. The results of this study showed that as a whole the intervention reduced potentially harmful medications statistically significantly in the intervention group, but in the control group the mean number

of potentially harmful medications remained constant. There were no differences in the mean number of the Beers (2003) medications between the groups, but the authors mentioned that the updated Beers (2012) Criteria now also included other potentially harmful medications. The results related to health care service use showed that the nursing training intervention reduced hospitalisation after adjusting for age, gender and morbidity, but there were no differences in the use of ambulatory services between the intervention and control groups. In addition, the authors concluded that the intervention maintained HRQoL and that the intervention is not associated with mortality. (Pitkälä et al. 2014.)

There are two recent reviews of RCTs that address PIM use in older people (Clyne et al. 2016a; Hill-Taylor et al. 2016). Clyne et al. (2016a) found that interventions (including pharmacist interventions, computerised clinical decision support systems and multifaceted interventions) reduce the number of PIPs but there was no evidence on improvements in patient outcomes. Health care utilisation was evaluated in only two of twelve studies in the review. One study found that intervention reduces hospitalisations but not ED visits (Clyne et al. 2016a). In the review by Hill-Taylor et al. (2016), three out of four studies evaluated health care utilisation. The authors reported evidence that interventions reduce falls, length of stay in hospital, delirium episodes and primary and ED visits. The review found no evidence on improvements regarding quality of life or mortality, or readmissions (Hill-Taylor 2016). However, the evidence of improvements related to ED visits or length of stay in hospital is still quite weak because only one study investigated ED visits and two length of stay in hospital. Only one study found that the number of ED visits or length of stay in hospital increased in the control group and was unchanged in the intervention group.

Table 2. Characteristics of studies of health care utilisation and costs associated with PIM use published in 2015[a]–2017

Study (country)	Study design (study period)	Washout-period	Study setting	Age (mean)	n	Criteria	Data	Associations with PIM use	Matching analysis or IV approach
Cohort and case-control studies									
Chen and Cheng 2016 (Taiwan)	Panel study (Four years)	None	National Health Insurance-enrollees	≥65 years (73.99)	76,270	The modified Beers Criteria (2003)	Claims data	Hospitalisations (adjusted OR 1.40 95 % CI 1.36–1.44). The likelihood was stronger with IV approach compared to naïve GEE model (adjusted OR 1.99; 95 % CI 1.65–2.40)	IV approach
Endres et al. 2015 (Germany)	Cohort (Jan 2009 – Dec 2010)	Six months (one year in sensitivity analysis)	Ambulatory patients	≥65 years (73.8)	392,337 (PIM group: 79,041; PIM alternatives: 313,296)	PRISCUS	Claims data	Hospitalisation (adjusted HR 1.38; 95 % CI 1.35–1.41) compared to PIM alternatives.	
Heider et al. 2017 (Germany)	Cohort (12 months)	12 months	Insured people	≥65 years (exposed: 75.8; non-exposed: 75.2)	4,475,067 (exposed: 521,644; non-exposed: 3,953,423)	PRISCUS	Claims data	Hospitalisation days (difference 4.48 days [95 % CI 4.39–4.56] p<0.001) and rehabilitation days (0.68 [95 % CI 0.65–0.70] p<0.001). Annual health care costs (mean) (PIM users: 6,809 euros vs. non-users: 4,488 euros [95 % CI 2269–2372]	Entropy balancing
Henschel et al. 2015 (Germany)	Cohort (One year)	Six months	Insured people	≥65 years (NA)	35,696	PRISCUS	Claims data	ADE-related hospitalisation (OR 1.54; 95 % CI 1.23–1.93; Adjusted OR: 1.46; 95 % CI 1.16–1.84)	Propensity score matching

Table 2. (continued)

Study (country)	Study design (study period)	Washout-period	Study setting	Age (mean)	n	Criteria	Data	Associations with PIM use	Matching analysis or IV approach
Narayan and Nishtala 2015 (New Zealand)	Cohort (years 2011–2012)	None	Population-based	≥65 years (74.7)	537,387	Beers (2012)	Claims data	Fall-related hospitalisation (adjusted IRR 1.45; 95 % CI 1.37–1.53) Primary care visits (adjusted IRR 1.15; 95 % CI 1.15–1.16)	
Moriarty et al. 2016 (Ireland)	Cohort (Two years)	None	Community-dwelling people	≥65 years (76.5)	1,753	STOPP/ START	The Irish Longitudinal Study on Ageing (TILDA)	GP visits (IRR 1.14; 95 % CI 1.05–1.25) with at least 1 PIM. ED visits: (Any PIM: adjusted IRR: 1.30; 95 % CI 1.02–1.66; ≥2 PIMs: adjusted IRR 1.42; 95 % CI 1.06–1.91).	
Van der Stelt et al. 2016 (The Nether-lands)	Nested case-control (Sep 2005 – Jun 2006)	None	Hospital patients	≥65 years (case: 79.4; control: 78.5)	338 (cases 169; controls 169)	Beers (2012) and STOPP (2008)	The HARM study	Medication-related hospitalisa-tions: STOPP (1 PIM: adjusted OR 2.30; 95 % CI 1.30–4.07; ≥2 PIMs: adjusted OR 3.08 95 % CI 1.02–9.31) Beers: only with the presence ≥2 PIMs (adjusted OR 4.25; 95 % CI 1.69–10.69)	
Varga et al. 2017 (Italy)	Cohort (11 years)	None	Population-based	≥65 years (NA)	1,480,137	Maio (2007, 2011 and 2014)	The Emilia-Romagna regional database	All-cause hospitalisations: Maio 2014: adjusted HR 1.16; 95 % CI 1.14–1.18 Maio 2011: adjusted HR 1.12; 95 % CI 1.12–1.13 Maio 2007: adjusted HR 1.24; 95 % CI 1.24–1.25	

Table 2. (continued)

Study (country)	Study design (study period)	Washout-period	Study setting	Age (mean)	n	Criteria	Data	Associations with PIM use	Matching analysis or IV approach
Wallace et al. 2017 (Ireland)	Cohort (2 years)	None	Community-dwelling people	≥70 years (77)	904	STOPP and Beers (2012)	Claims data	ED visits: No associations with the Beers (≥2 PIMs: adjusted OR 1.54; 95 % CI 0.88–2.71) STOPP (1 PIM: adjusted OR 1.82; 95 % CI 1.15–2.89; ≥2 PIMs: adjusted OR 1.85; 95 % CI 1.06–3.24) Emergency admissions: No associations with the Beers (≥2 PIMs: adjusted OR 0.72; 95 % CI 0.41–1.28) or STOPP criteria (≥2 PIMs: adjusted OR 1.00; 95 % CI 0.63–1.61) ADEs: No associations with the Beers (≥2 PIMs: adjusted IRR 1.00; 95 % CI 0.78–1.29) STOPP (≥2 PIMs: adjusted IRR 1.29; 95 % CI 1.03–1.60) HRQoL: No associations with the Beers (adjusted coefficient -0.05; 95 % CI -0.11–0.003) STOPP (≥2 PIMs: adjusted coefficient -0.11; 95 % CI -0.16–0.06)	
Wauters et al. 2016 (Belgium)	Cohort (18 months)	None	Community-dwelling people	≥80 years (median 84.4)	503	STOPP/ START	The Belfrail-Med cohort (data collection by patients' own general practitioner)	There was no significant association between PIM use and a higher risk of hospitalisation (1–2 PIMs: adjusted HR 0.96; 95 % CI 0.67–1.38)	

Table 2. (continued)

Study (country)	Study design (study period)	Washout-period	Study setting	Age (mean)	n	Criteria	Data	Associations with PIM use	Matching analysis or IV approach
Frankenthal et al. 2017 (Israel)	Cohort (24 months)	-	Chronic care geriatric facility	≥65 years (NA)	306 (control: 146; intervention: 160)	STOPP/ START	Data from the previously conducted prospective RCT was retrospectively collected including patients' demographic details, functional status, current diagnoses, medications and clinical outcomes (falls and hospitalisations) and mortality.	There was no significant difference in hospitalisations between intervention and control groups after 24-month follow-up (0.6±1.1 vs. 0.4±0.6 p=0.5).	
Interventions									
Campins et al. 2017 (Spain)	RCT (12 months)	-	Community-dwelling people with polypharmacy	≥70 years (control: 78.8; intervention: 79.2)	503 (control: 251; intervention: 252)	STOPP/ START	Patients' prescription medications and electronic primary care clinical visits, EuroQoL-5D and Morisky-Green.	There were no significant differences in mean number of ED visits (1.1 (1.5) vs. 0.9 (1.5) p=0.061) or primary care visits (23.0 (14.1) vs. 24.0 (16.8) p=0.670) or percentage of hospitalised patients (25.2 % vs. 23.3 % p=0.616) between intervention and control groups during 12-month follow-up.	

Table 2. (continued)

Study (country)	Study design (study period)	Washout-period	Study setting	Age (mean)	n	Criteria	Data	Associations with PIM use	Matching analysis or IV approach
Gillespie et al. 2017 (Ireland)	RCT (12 months)	-	Community-dwelling people	≥70 years (control: 76.4; intervention: 77.1)	196 patients (control: 97; intervention: 99) and 21 practices (control: 10; intervention: 11)	Criteria applied in OP-TI-SCRIPT study by the clinical research team	Patients' demographic information, medications, health status, the Euroqol EQ5D-3L, health care resource use (GP visits, practice nurse visits, day-case admissions, inpatient admissions, A&E visits).	Intervention reduced the number of PIPs, but interventions were costlier and there were no statistically significant differences in mean QALYs (0.671; 95 % CI, 0.625–0.716 vs. 0.657; 95 % CI, 0.612–0.703) between intervention and control groups.	
Kiel and Phillips 2017 (USA)	Retrospective post-hoc study (90 days)	-	Ambulatory patients	≥65 years (control: 76.5; intervention: 76.4)	52 (control: 26; intervention: 26)	STOPP/ START	Patients' demographic information, allergies, major chronic conditions, medications, and information on pharmacist interventions and hospitalisations and ED visits.	There were no statistically significant differences in hospitalisations (3 vs. 4 p=0.379 or ED visits 7 vs. 6 p=0.413 between intervention and control groups.	
O'Connor et al. 2016 (Ireland)	Cluster RCT (13 months)	-	Hospital patients	≥65 years (control: median 78; intervention: median 80)	732 (control: 372; intervention: 360)	STOPP/ START	Patients' demographic information, medications, allergies, current and previous diagnoses, information on cognitive status and activities of daily living, and ADRs after hospitalization.	There were no statistically significant differences in median LOS between intervention and control groups (median in both groups 8 days (4–14), but the intervention reduced ADRs and medication costs.	

Table 2. (continued)

Study (country)	Study design (study period)	Washout-period	Study setting	Age (mean)	n	Criteria	Data	Associations with PIM use	Matching analysis or IV approach
Pitkälä et al. 2014 (Finland)	RCT (12 months)	-	Residents of assisted living facilities	≥65 years (control: 83.5; intervention: 82.9)	227 (control: 109; intervention: 118)	Beers (2003)	Residents' demographic data, diagnoses, medication use, cognition, nutritional status, HRQoL, hospitalisations and health and social service use, and mortality.	Intervention reduced the mean number of potentially harmful medications, but not the Beers (2003) medications. The intervention group had fewer hospital days/person/year than participants in the control group (1.4 days (95 % CI 1.2–1.6) vs. 2.3 days (95 % CI 2.1–2.7)). There were no differences in mortality between two groups.	
Reviews									
Hyttinen et al. 2016 (Review incl. studies from 12 countries)	Review incl. 39 cohort, case-time-control and intervention studies (Three months–12 years)	-	All settings	≥65 years (69.8–86.7)	165–1,807,404	Beers (1991/2003/2012/ modified, STOPP/START, MAI, PRISCUS, Zhan, McLeod, HEDIS, DUR and other country-specific criteria	-	In most of the articles, PIMs had a statistically significant association with health care service use, especially hospitalisation, among older people. Findings regarding associations with LOS or readmissions were inconclusive. Five studies found that PIM users had statistically significant higher medical or total health care costs compared to non-users.	

Study (country)	Study design (study period)	Washout-period	Study setting	Age (mean)	n	Criteria	Data	Associations with PIM use	Matching analysis or IV approach
Clyne et al. 2016a (Review incl. studies from eight countries)	Review incl. 12 intervention studies (Six–24 months)	-	Community-dwelling people	≥65 years	81–81,810	Beers (1997 and 2003), MAI, McLeod, STOPP, Swedish criteria, Quebec consensus panel and other own criteria	-	Interventions reduced the number of PIPs, but no evidence on improvements in patient outcomes. One study found that intervention reduced hospitalisations but not ED visits.	
Hill-Taylor et al. 2016 (Review incl. studies from four countries)	Review incl. four intervention studies (until discharge–12 months)	-	Community-dwelling people and long-term care patients	≥65 years	158–1,018	STOPP/ START	-	Interventions can reduce falls, delirium episodes, LOS and primary and emergency care visits. No evidence was found on improvements in quality of life or mortality, or readmissions to hospital.	

[a]A study by Pitkälä et al. was conducted in 2014, which was not included in our review (Hyttinen et al. 2016)
PIM, potentially inappropriate medication; PIP, potentially inappropriate prescription; IV, instrumental variable; GEE, generalised estimating equation; NA, not available; HR, hazard ratio; CI, confidence interval; OR, odds ratio; IRR, incidence rate ratio; ADE, adverse drug event; A&E, accident and emergency department; ED, emergency department; ADR, adverse drug reaction; RCT, randomised controlled trial; MAI, Medication Appropriateness Index; DUR, Drug Utilisation Review; STOPP; Screening Tool of Older Persons' Potentially Inappropriate Prescriptions; START, screening tool to alert doctors to the right treatment; QALY, quality-adjusted life year; HRQoL, health-related quality of life; LOS, length of stay

4 SUMMARY OF THE LITERATURE

PIM prescribing can be seen as a quality deviation in the medication process or a medication error, where PIMs are defined as those medications for which risks outweigh benefits. PIM is a consequence of the prescribing process, which happens in multifactorial and complex environments; there are therefore many interrelated patient and physician factors associated with PIM prescribing. In this study, PIM is defined as an unintended consequence of the prescribing process. In the empirical setting, this study does not discuss motivations, objective functions or information problems of the physician–patient interaction, where a decision regarding a certain prescription is made. Based on the literature, we can assume that there is more variation when interacting with younger and healthier people to find appropriate treatments. As patients age and have more diseases, resulting in multiple medications, the probability of medication error is higher.

Based on previous literature, PIM use is prevalent depending on the criteria used or the study setting, but there is evidence that PIM prevalence is decreasing in many countries. The Beers Criteria are the most widely used, also in Finland, but recent studies show that the use of national criteria in defining PIM use is becoming more common as most of the latest studies have used national criteria e.g. the German PRISCUS, the Italian Maio criteria and the Irish STOPP/START criteria. Only a few previous studies used the Meds75+ database for assessing PIM use in older Finnish people.

Factors associated with PIM use have been extensively studied. The patient groups most affected by PIM use are older, female, have low socioeconomic status, suffer from multimorbidity and polypharmacy, and receive prescriptions from several physicians. Overall, patient-related characteristics have been studied comprehensively while fewer studies have investigated physician-related factors. Most of the studies were conducted in cross-sectional settings and have mainly investigated the risk factors related to prevalent PIM use. Only a few studies have determined the risk of incident PIM use, or initiating PIM use, so there is a clear need for studies that determine the factors related to the selection of persons for PIM use. Also, there are little research on the association between factors related to health care system and PIM use.

As different patients have different probabilities of being prescribed PIMs, so there is a selection process or endogeneity for PIM use. Endogeneity here means that the selection to PIM user and non-user groups is not random, but depends on, e.g. a person's health status, thus making the comparison of health outcomes between the two groups biased. This selection is important to consider, particularly in observational studies (Malmivaara 2015), when assessing outcomes associated with PIM use. Only a few previous studies have taken endogeneity into account (e.g. Chen and Cheng 2016), which may be problematic for observational studies looking at the association between PIM use and health care utilisation.

Previous studies have shown that PIM use can increase the risk of hospitalisation, and thus health care costs. However, most previous studies had quite short follow-ups, which do not take e.g. cumulative effects into account. Furthermore, in most studies, PIM use is assessed at baseline or in a cross-sectional setting. Recently published studies investigated mainly incident PIM use or treated PIM use as a time-varying variable, but there is still need for longitudinal studies.

Previous literature regarding RCTs on PIM use in older persons has found that interventions are effective for decreasing the number of PIMs and thus medication costs, but evidence on the effects on health outcomes and health care resource use is scarce.

5 AIMS OF THE STUDY

The aim of this study was to find out whether PIM initiation (defined by the Meds75+ database) is associated with health care service use, health care costs and mortality, by using two different longitudinal study settings. In addition, this study aims to identify risk factors for PIM initiation or the selection for PIM use.

The specific research questions of this dissertation were:

1. How are the demand side (patient characteristics) and supply side (physician, hospital district) factors associated with PIM initiation in older people? (Works 1 and 2)

2. Is PIM initiation associated with an increased risk of hospitalisation and higher costs in older people? (Works 3 and 4)

3. Does initiation of PIM use increase the risk of adverse health outcomes (e.g. mortality) in older people? (Work 4)

6 DATA AND METHODS

6.1 FRAMEWORK

To answer the research questions, Work 1 evaluates incident PIM use and associated factors in a Finnish nationwide cohort of community-dwelling people aged ≥65 with and without Alzheimer's Disease (AD) between 2005 and 2011. Work 2 complements Work 1 in assessing the physician effect on PIM use in addition to other associated factors of incident PIM use in community-dwelling people aged 65–74 and ≥75 during the years 2002–2013. Work 3 evaluates the association between incident PIM use and hip fracture hospitalisations in the Finnish nationwide cohort, which includes all people aged ≥65 diagnosed with AD between 2005 and 2011. Work 4 investigates the association between PIM use and fracture-specific hospitalisations, mortality and hospital costs in community-dwelling older people aged ≥65 during the 12-year study period (2002–2013).

Figure 1 illustrates the conceptual framework of this dissertation and the connections between the sub-studies (Works 1–4) in the dissertation. The studies compare PIM use to non-use in order to evaluate risk factors, health outcomes, health care service use and costs associated with PIM use.

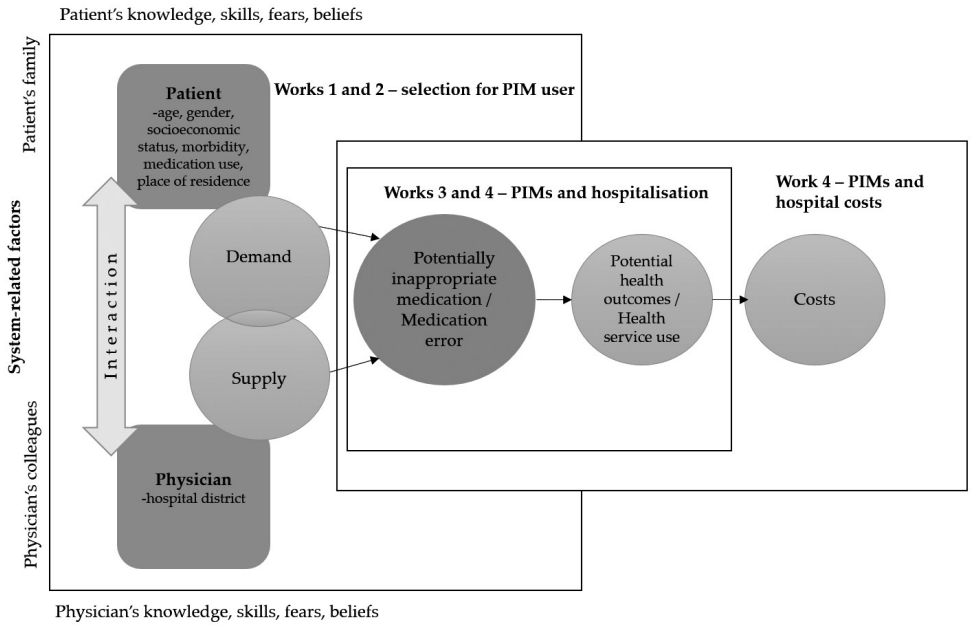

Figure 1. Conceptual framework of the association of PIM use with health and economic outcomes

6.2 DATA SOURCES

Data for Works 1–4 were gathered from the following nationwide registers: the Prescription Register maintained by the Social Insurance Institution (SII), the Care Register for Health Care (HILMO) maintained by the National Institute for Health and Welfare (THL) and the registers of causes of death and socioeconomic factors maintained by Statistics Finland (SF). In addition, the data for Works 1 and 3 included information that was gathered from the Special Reimbursement Register maintained by the SII. Also decisions on long-term institutional care were collected from registers of the SII. All data were linked by using a unique personal identification code.

In Finland, as well as in other Nordic countries, registers offer a valid opportunity to conduct longitudinal pharmacoepidemiological studies (Furu et al. 2010). Based on the systematic review by Sund (2012) the HILMO register has good validity as a whole, but more specifically, hip fractures (for example) are found to be valid outcomes (Sund et al. 2007; Sund et al. 2011). The limitations of the HILMO register are related particularly to subsidiary diagnoses and secondary operations (Sund 2012).

Prescription register

The Prescription register contains information on all reimbursed medication purchases in ambulatory care. In this study, information on the purchases made contains ATC code, the date of purchase, number of packages, strength of the medication, package size, dispensed amount in defined daily doses (DDDs), the identification code of the prescribing physician (or nurse) and information on the residential area of patient. (Social Insurance Institution 2014; Tolppanen et al. 2016.)

Special Reimbursement Register

The Special Reimbursement Register includes information on reimbursement for medication. The register contains information on people who have been entitled to basic or special reimbursement for the medication of diseases diagnosed by a physician. A person is granted entitlement for special reimbursement for medication costs due to certain, severe chronic diseases. The information includes the reimbursement number given to entitlements, the start and end dates of entitlements, and the diagnoses of the diseases for which the entitlement to reimbursement for medication costs were granted. (Social Insurance Institution 2013.)

Care Register for Health Care (HILMO)

The HILMO register includes information on the use of outpatient and inpatient services in special health care, inpatient services in primary health care, inpatient and housing services in social care, and home care services (National Institute for Health and Welfare 2016a). In this dissertation, the data include information on the use of inpatient services, and the use of outpatient services in special health care. The data used contain information on: patient, service provider, arrival and discharge dates for the services, discharge diagnoses and the reason for admission (National Institute for Health and Welfare 2016b, p. 14, 38, 42).

Registers of Statistics Finland (SF)

In this study, data used from the SF registers includes information on the date of birth and gender, date of death, socioeconomic status (the annual disposable income of the household-dwelling unit, occupational social class) and the number of people living in the household.

6.3 STUDY POPULATIONS

6.3.1 Medication use and Alzheimer's disease (MEDALZ) data

Works 1 and 3 are based on the national MEDALZ study, which includes all Finnish community-dwelling patients diagnosed with AD between 2005 and 2011 (N = 70,719), and two comparison individuals without AD matched for age, gender and region of residence (N = 141,436) (Tolppanen et al. 2016). Data were gathered from the nationwide registers, including the Prescription Register, the Special Reimbursement Register, the HILMO, and SF registers (causes of death and socioeconomic information). AD diagnosis was based on the Special Reimbursement Register, which includes all patients entitled to reimbursement for AD medications. This information is comprehensive because the current Finnish care guidelines recommend prescribing anti-dementia medication to everyone with a clinically verified AD diagnosis (Duodecim 2010). Table 3 shows characteristics of the study populations in Works 1 and 3.

Anyone who purchased at least one medication listed in Category D of the Meds75+ database in the 12 months (=wash-out period) preceding the index date was excluded. The index date was the date of AD diagnosis and the corresponding matching date for comparison subjects. Anyone hospitalised for at least 90 days during the wash-out period or at the end of the wash-out period was excluded because the registers do not include information on the medications given to patients at the hospital. Furthermore, those aged under 65 were excluded since the study investigated PIM use in older people and this age limit is in line with other PIM studies. The final study population for Work 1 was 156,800 people, of which 50,494 people had AD.

The study population for Work 3 constituted only those with AD. In addition to the above-mentioned exclusion criteria, those people who had previously been diagnosed with hip fractures prior to AD diagnosis or were hospitalised or in institutional care at the start of the study period were excluded. The final study population for Work 3 included 47,850 people with AD.

Table 3. Characteristics of the study populations of the MEDALZ data

	Work 1						Work 3		
	PIM users with AD (n = 6,165)	**Non-users with AD (n = 44,329)**	**p-value**	**PIM users without AD (n =17,409)**	**Non-users without AD (n = 88,897)**	**p-value**	**PIM users with AD (n = 5,895)**	**Non-users with AD (n = 41,955)**	**p-value**
Age, years[a]			<0.001			<0.001			<0.001
65–74	1,428 (23.2)	7,669 (17.3)		4,177 (24.0)	15,660 (17.6)		1,402 (23.8)	7,489 (17.9)	
75–84	3,619 (58.7)	24,980 (56.4)		10,453 (60.0)	49,466 (55.6)		3,470 (58.9)	23,845 (56.8)	
≥85	1,118 (18.1)	11,680 (26.3)		2,779 (16.0)	23,771 (26.7)		1,023 (17.3)	10,621 (25.3)	
Gender			<0.001			<0.001			<0.001
Male	2,375 (38.5)	15,442 (34.8)		5,774 (33.2)	32,204 (36.2)		2,324 (39.4)	14,991 (35.7)	
Female	3,790 (61.5)	28,887 (65.2)		11,635 (66.8)	56,693 (63.8)		3,571 (60.6)	26,964 (64.3)	
Socioeconomic status (middle age)			0.110			<0.001			0.087
High	2,133 (34.6)	14,780 (33.3)		5,907 (33.9)	29,722 (33.4)		2,042 (34.6)	13,977 (33.3)	
Medium	3,701 (60.0)	27,244 (61.5)		10,555 (60.6)	50,721 (57.1)		3,534 (60.0)	25,822 (61.5)	
Low	191 (3.1)	1,407 (3.2)		559 (3.2)	3,002 (3.4)		183 (3.1)	1,298 (3.1)	
Unknown	140 (2.3)	898 (2.0)		388 (2.2)	5,452 (6.1)		136 (2.3)	858 (2.1)	
Comorbidities									
Asthma or COPD	575 (9.3)	3,235 (7.3)	<0.001	1,690 (9.7)	6,425 (7.2)	<0.001	538 (9.1)	3,053 (7.3)	<0.001
Diabetes	751 (12.2)	5,308 (12.0)	0.638	1,806 (10.4)	8,935 (10.1)	0.196	721 (12.2)	4,998 (11.9)	0.481
Rheumatoid arthritis	286 (4.6)	1,956 (4.4)	0.418	846 (4.9)	3,904 (4.4)	0.006	262 (4.4)	1,805 (4.3)	0.615
Some type of cardiovascular disease	3,182 (51.6)	22,025 (49.7)	0.005	8,915 (51.2)	42,375 (47.6)	<0.001	-	-	-
Epilepsy	92 (1.5)	718 (1.6)	0.456	215 (1.2)	908 (1.0)	0.012	88 (1.5)	670 (1.6)	0.549
Previous stroke	581 (9.4)	4,108 (9.3)	0.690	1,207 (6.9)	7,512 (8.5)	<0.001	544 (9.2)	3,822 (9.1)	0.768
History of cancer	322 (5.2)	2,076 (4.7)	0.062	1,044 (6.0)	4,118 (4.6)	<0.001	396 (6.7)	2,614 (6.2)	0.149
History of psychiatric disorder	191 (3.1)	1,119 (2.5)	0.008	439 (2.5)	1,851 (2.1)	<0.001	231 (3.9)	1,340 (3.2)	0.003
History of substance abuse	171 (2.8)	957 (2.2)	0.002	289 (1.7)	1,378 (1.6)	0.286	162 (2.8)	890 (2.1)	0.002

Table 3. (continued)

	PIM users with AD (n = 6,165)	Non-users with AD (n = 44,329)	p-value	PIM users without AD (n =17,409)	Non-users without AD (n = 88,897)	p-value	PIM users with AD (n = 5,895)	Non-users with AD (n = 41,955)	p-value
Previous hip fracture	266 (4.3)	2,280 (5.1)	0.005	486 (2.8)	3,420 (3.9)	<0.001	-	-	-
Previous other fractures	-	-		-	-		792 (13.4)	6,198 (14.8)	0.006
Medication use[a]									
Opioids	198 (3.2)	1,338 (3.0)	0.408	1,085 (6.2)	2,815 (3.2)	<0.001	181 (3.1)	1,214 (2.9)	0.450
Psychotropic medications[b]	2,147 (34.8)	13,889 (31.3)	<0.001	4,710 (27.1)	17,207 (19.4)	<0.001	2,023 (34.3)	12,940 (30.8)	<0.001
Any antihypertensive medication	-	-		-	-		3,897 (66.1)	28,607 (68.2)	0.001
Bisphosphonates[c]	-	-		-	-		803 (13.6)	5,331 (12.7)	0.049
NSAIDs	-	-		-	-		447 (7.6)	2,209 (5.3)	<0.001
Physicians workplace									
Primary outpatient care	2,705 (43.9)	NA		7,121 (40.9)	NA		-	-	
Hospital	1,229 (19.9)	NA		3,819 (21.9)	NA		-	-	
Other	796 (12.9)	NA		2,093 (12.0)	NA		-	-	
Unknown	1,435 (23.3)	NA		4,376 (25.1)	NA		-	-	
University hospital district			0.003			<0.001			
Oulu	903 (14.7)	6,369 (14.4)		2,362 (13.6)	13,020 (14.7)		-	-	
Kuopio	1,267 (20.6)	9,344 (21.1)		3,486 (20.1)	18,554 (20.9)		-	-	
Tampere	1,458 (23.7)	10,886 (24.6)		4,361 (25.1)	21,859 (24.7)		-	-	
Turku	708 (11.5)	5,535 (12.5)		2,081 (12.0)	11,021 (12.4)		-	-	
Helsinki	1,812 (29.5)	12,074 (27.3)		5,087 (29.3)	24,173 (27.3)		-	-	
Åland[d]/Unknown	17 (0.3)	102 (0.3)		32 (0.2)	270 (0.3)				

AD, Alzheimer's disease; PIM, potentially inappropriate medication; COPD, chronic obstructive pulmonary disease; NA, not available; NSAID, nonsteroidal anti-inflammatory drug
[a]At the start of the follow-up
[b]Excluding PIMs in Appendix 1
[c]Before the diagnosis of AD/start of the follow-up
[d]Not included in the analyses

6.3.2 Potentially inappropriate medication (PIM) use data

The data for Works 2 and 4 were gathered from the Prescription Register as a 10 % random sample of Finnish community-dwelling people aged ≥65 at the beginning of the year 2000 (N = 64,250). The data were linked to the HILMO register and the registers of SF (socioeconomic information and causes of death) using a unique identification code. The study population was followed until the end of 2013. Table 4 shows the characteristics of the study populations in Works 2 and 4.

In both sub-studies, a two-year wash-out period was implemented, which means that those purchasing at least one PIM, as defined by the Meds75+ database, during this period (the years 2000–2001 = wash-out period) were excluded. Also, people who stayed in hospital ≥90 days during the wash-out period or were hospitalised at the beginning of the study period (index date = 1 Jan 2002) were excluded. Those who died during the wash-out period, or for whom the Prescription Register did not include any information on their medication purchases after the index date (incl. e.g. persons living in institutions), were dropped.

In Work 2, the final study population included 28,541 people. In Work 4, those who had earlier fractures were also excluded. As a result, the study population included 27,576 people before matching. In Work 4, propensity score matching (PSM) analysis was used to reduce the bias resulting from a selection process for PIM use (see Chapter 6.5.1). The matched study population included 10,333 PIM users with one matched non-user, totalling 20,666 people. There were 141 people with no matching non-user.

Table 4. Characteristics of the study populations of the PIM use data.

	Work 2			Work 4					
				Before PSM[e]			After PSM		
	PIM users (n = 10,698)	Non-users (n = 17,799)	p-value	PIM users (n = 10,474)	Non-users (n = 17,102)	p-value	PIM users (n = 10,333)	Non-users (n = 10,333)	p-value
Age, years[a]			<0.001			<0.001			0.341
65–74	6,403 (59.9)	8,741 (49.1)		6,288 (60.0)	8,487 (49.6)		6,229 (60.3)	6,131 (59.3)	
75–84	3,744 (35.0)	7,049 (39.6)		3,661 (35.0)	6,729 (39.4)		3,600 (34.8)	3,700 (35.8)	
≥85	551 (5.1)	2,009 (11.3)		525 (5.0)	1,886 (11.0)		504 (4.9)	502 (4.9)	
Gender			<0.001			<0.001			0.863
Male	3,988 (37.3)	7,233 (40.6)		3,929 (37.5)	7,062 (41.3)		3,887 (37.6)	3,899 (37.7)	
Female	6,710 (62.7)	10,566 (59.4)		6,545 (62.5)	10,040 (58.7)		6,446 (62.4)	6,434 (62.3)	
Socioeconomic status (income)[b]			<0.001			<0.001			0.805
<9999€	2,995 (28.0)	5,876 (33.0)		2,933 (28.0)	5,613 (32.8)		2,915 (28.2)	2,921 (28.3)	
10000–19999€	6,322 (59.1)	9,897 (55.6)		6,197 (59.2)	9,544 (55.8)		6,168 (59.7)	6,177 (59.8)	
20000–29999€	893 (8.4)	1,236 (7.0)		879 (8.4)	1,190 (7.0)		864 (8.4)	832 (8.1)	
>30000€	409 (3.8)	522 (2.9)		393 (3.8)	507 (3.0)		386 (3.7)	403 (3.9)	
Unknown	79 (0.7)	268 (1.5)		72 (0.7)	248 (1.5)		-	-	
Living alone[b]	3,776 (35.3)	6,930 (38.9)	<0.001	3,668 (35.0)	6,588 (38.5)	<0.001	3,644 (35.3)	3,799 (36.8)	0.025
Medication use[c]									
Antidiabetics	815 (7.6)	1,341 (7.5)	0.795	803 (7.7)	1,284 (7.5)	0.629	794 (7.7)	830 (8.0)	0.352
Psychotropics	2,375 (22.2)	3,521 (19.8)	<0.001	2,282 (21.8)	3,308 (19.3)	<0.001	2,238 (21.7)	2,190 (21.2)	0.416
Cardiovascular medications	7,426 (69.4)	12,537 (70.4)	0.068	7,291 (69.6)	12,056 (70.5)	0.119	7,195 (69.6)	7,227 (69.9)	0.628
Anti-dementia medications	63 (0.6)	220 (1.2)	<0.001	-	-		-	-	
Opioids	-	-		580 (5.5)	715 (4.2)	<0.001	572 (5.5)	530 (5.1)	0.193
NSAIDs	-	-		4,263 (40.7)	5,579 (32.6)	<0.001	4,211 (40.8)	3,490 (33.8)	<0.001
Excessive polypharmacy	1,455 (13.6)	1,744 (9.8)	<0.001	1,401 (13.4)	1,626 (9.5)	<0.001	1,374 (13.3)	1,302 (12.6)	0.136

Table 4. (continued)

	Work 2			Work 4					
				Before PSM[e]			After PSM		
	PIM users (n = 10,698)	**Non-users (n = 17,799)**	**p-value**	**PIM users (n = 10,474)**	**Non-users (n = 17,102)**	**p-value**	**PIM users (n = 10,333)**	**Non-users (n = 10,333)**	**p-value**
University hospital district			0.026			0.021			0.892
Oulu	1,422 (13.3)	2,296 (12.9)		1,387 (13.2)	2,214 (13.0)		1,376 (13.3)	1,344 (13.0)	
Kuopio	1,885 (17.6)	3,306 (18.6)		1,864 (17.8)	3,203 (18.7)		1,854 (17.9)	1,857 (18.0)	
Tampere	2,316 (21.7)	3,855 (21.7)		2,258 (21.6)	3,699 (21.6)		2,239 (21.7)	2,208 (21.4)	
Turku	1,893 (17.7)	3,291 (18.5)		1,838 (17.6)	3,157 (18.5)		1,829 (17.7)	1,833 (17.7)	
Helsinki	3,109 (29.0)	4,925 (27.6)		3,056 (29.2)	4,704 (27.5)		3,035 (29.4)	3,091 (29.9)	
Åland[d]/Unknown	73 (0.7)	126 (0.7)		71 (0.7)	125 (0.7)		-	-	

AD, Alzheimer's disease; PIM, potentially inappropriate medication; PSM, propensity score matching, COPD, chronic obstructive pulmonary disease; NA, not available; NSAID, nonsteroidal anti-inflammatory drug
[a]At the start of the follow-up
[b]Year 2000
[c]Years 2000–2001
[d]Not included in the analyses
[e]Covariates included in the PSM: age, gender, socioeconomic status, medication use (psychotropics, opioids, excessive polypharmacy), university hospital district

6.4 DEFINITIONS AND MEASURES

6.4.1 PIM use

PIM use was defined as category D medications listed in the Meds75+ database in 2010 (Appendix 1). In Works 1 and 2, PIM use was classified as a dichotomous variable on whether a person initiated or did not initiate at least one PIM during the follow-up. In Work 2, the physician effect models considered a person's new different PIM purchases. In Works 3 and 4, overlapping PIM use periods were taken into account by joining them together and all PIM exposure times were classified as a dichotomous variable of PIM use. In Work 4, exposure times (or risk periods; see Chapter 6.4.2) were one, three and six-month periods, but if there were overlapping PIM use periods calculated from the date of every PIM purchase, the real exposure period varied from person to person. The overlapping PIM use periods meaning that if a person purchased the new PIM before the end of e.g. 1-month exposure period, the calculation continued from that point (Figure 2). In addition, in Works 3 and 4, analyses were also restricted to the first PIM use periods assuming that ADRs occur quite soon after the initiation of the new medication. In the cost model of Work 4, PIM exposure was defined yearly as a dichotomous variable on whether a person purchased or did not purchase at least one PIM in each year of the 12-year follow-up. All medications were classified using the ATC System of the World Health Organization (WHO) (WHO 2011).

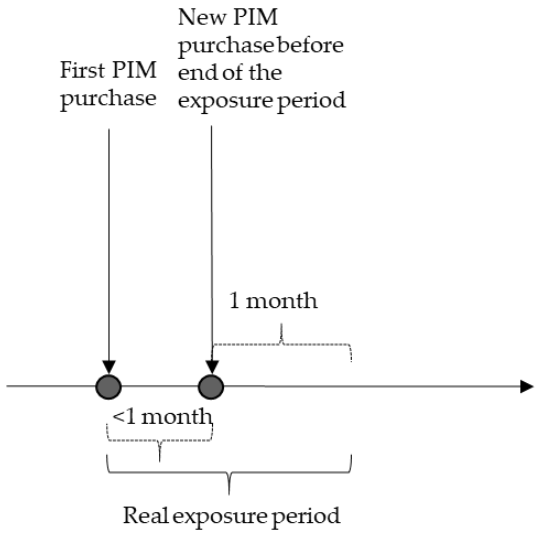

Figure 2. The example of PIM exposure periods in Work 4.

PRE2DUP method

In Work 1 and 3, medication use (in Work 3 also PIM use) periods were calculated using a previously utilised method, called the Prescriptions to Drug Use Periods (PRE2DUP) method. The method calculates medication use periods (continuous use

of a drug) for each person and each medication (ATC code) separately, based on the dispensed medication recorded in the Prescription Register, taking into account the individual purchase pattern: estimated dose over time (based on DDDs), regularity of purchases, and long hospitalisation or nursing home periods. The latter is important, because medications given in hospital are not recorded in the Prescription Register, so the method excludes hospital or nursing home days from medication use periods. The strength of this method is that it yields accurate estimates of medication use over time, and generates reliable estimates of the simultaneous use of medications. (Tanskanen et al. 2015; Taipale et al. 2016.)

New-user design

In all Works, a new-user design was used to investigate incident PIM use. This means that wash-out periods (Works 1 and 3: 12 months; Works 2 and 4: 24 months) were used to exclude prevalent users, who made at least one PIM purchase during the wash-out period. The advantage of new-user design is that it decreases prevalent user bias by restricting data to incident users only (Ray 2003), and excluding those who had survived under the treatment. Including prevalent users can also lead to selection bias, if confounders were measured only after treatment. (e.g. Danaei et al. 2012.)

According to a study by Roberts et al. (2015), wash-out periods longer than 6–12 months are sufficient when controlling for prevalent user bias. However, the sufficient period may be depend on e.g. reimbursement system or for how long a period medications are dispensed, or on whether medications are taken daily or as-needed (Rikala et al. 2010).

6.4.2 Health outcomes/health care utilisation

Health care utilisation was estimated by the risk of fracture-specific hospitalisations, which were classified by using the Finnish version of the WHO's International Classification of Diseases 10th Revision (ICD-10) coding system (National Institute for Health and Welfare 2011), and gathered from the HILMO register. Hospitalisations were considered to be associated with PIM use, if the fracture-spesific hospitalisation occurred during PIM exposure period (or in risk period in Work 4; see Chapter 6.4.1).

In Work 3, the outcome variable was determined as a dichotomous variable of incident hip fractures (the main diagnosis) (ICD-10-codes: S72.0, S72.1, S72.2). In Work 4, the outcome variable included potentially fall-related incident fractures (ICD-10-codes: S22, S32, S42, S52, S62, S72, S82).

In Work 4, the secondary outcome variable was all-cause mortality, which was gathered from the causes of death register. Also, the mean number of total hospital episodes and the mean length of stay of episodes were examined.

6.4.3 Hospital costs

In Work 4, health care costs of all-cause hospitalisations were defined in each hospitalisation episode using the HILMO register. Costs were calculated according to the National Institute for Health and Welfare's estimates of unit costs of social and

health care in Finland in 2011 (Kapiainen et al. 2014). The cost calculation took into account the length of stay of the episode.

6.4.4 Covariates

Patient-related variables

The basic characteristics used in all Works were age, gender, socioeconomic status, morbidity and use of medication. Available information on the most common diseases in older people and factors shown to be associated with the use of PIMs were gathered from the registers. In Works 3 and 4, factors possibly related to a higher probability of falling and fractures were gathered.

Sociodemographic and economic variables

Age was categorised into two (Work 2) or three (Works 1, 3, 4) age groups. In Works 1 and 3, a person's socioeconomic status was based on the information on the person's highest occupational position in the middle age (categorized into four classes: high, medium, low and unknown) (Table 3). In Works 2 and 4, a person's socioeconomic status was based on the information on the household-dwelling unit's disposable income, which was divided by the equivalent number of people living in the household. This was coded into four income classes (Table 4).

In Works 2 and 4, a person's living situation was determined based on information on whether a person was living alone. It was formulated based on the SF register's variable, including the number of people living in a household. All four Works included information on the hospital district where the patient was living based on the person's municipality of residence.

Morbidity and medication use

In Works 1 and 3, information on morbidity was gathered from the Special Reimbursement Register and HILMO register for the years 1972–2012. Information gathered from the Special Reimbursement Register included diagnoses of asthma or chronic obstructive pulmonary disease (COPD), diabetes, rheumatoid arthritis, cardiovascular diseases and epilepsy. Information from the HILMO register included previous strokes, previous fractures (other than hip fracture), depression, bipolar disorders or schizophrenia or other psychiatric disorders. Histories of psychiatric disorders were gathered at least 5 years before the diagnosis of AD (the index date). All diseases from the HILMO register were classified using the Finnish version of the WHO's ICD-10 coding system (National Institute for Health and Welfare 2011).

Information on other medication use was gathered from the Prescription Register. In Works 1, 3 and 4 this information contained the use of opioids and psychotropics (excluding PIMs according to Meds75+). In Work 3 other medication use also included bisphosphonates, antihypertensives and NSAIDs. In Work 4, NSAIDs were also taken into account.

In Works 2 and 4, morbidity was assessed by medication purchases using the Prescription Register. The groups of medication included were antidiabetics, cardiovascular medications, and psychotropics. In Work 2 included also anti-dementia medications. Data on the use of the medications were obtained during the wash-out

period (years 2000–2001). Excessive polypharmacy was defined as annual use of at least ten different medications (ATC codes) during the wash-out period.

Health care related variables

Health care related variables included university hospital district and physician identification codes, which exist for all licensed Finnish physicians. The university hospital area (five areas) was extracted from the information on the person's residential area from the Prescription Register. In Work 2, the analysis included the more specific classification of hospital area (including 21 hospital areas). Physician identification codes were available from the Prescription Register and were included in the analysis in Work 2.

6.5 STATISTICAL METHODS

Table 5 summarises the statistical methods and covariates used in Works 1–4. Differences in baseline characteristics between PIM users and non-users were tested by cross tabulation and chi-square tests. In addition, t-tests and non-parametric tests were used for continuous variables. In Work 4, the correlation between polypharmacy and PIM use was checked by using the Spearman correlation test. The results were reported as hazard ratios (HR), odds ratios (OR) and coefficients with 95 % confidence intervals (CI).

In all four Works, Cox proportional hazard regression (survival analysis) (Cox 1972) was used to analyse the factors associated with PIM use or the association between PIM use and hospitalisation or mortality. The Cox regression is a semiparametric model that compares survival between two groups with a special case of the log-rank test (Harrell 2001, p. 389, 465).

In all Works, the survival time was right-censored, which means that the study ends after a certain period of time or after the failure event has occurred (Harrell 2001, p. 392). In Works 1 and 2, the survival time was censored at the first PIM purchase, at end of study (Work 1: 31 Dec 2012; Work 2: 31 Dec 2013), at death or a long hospitalisation period (≥90 days) - whichever came first. In Work 1, the follow-up also ended if comparison subjects were diagnosed with AD. In Works 3 and 4, the survival time was censored at the first failure (Work 3: hip fracture; Work 4: fracture-specific hospitalisation, and all-cause mortality), end of study (Work 3: 31 Dec 2012; Work 4: 31 Dec 2013), death or long (≥90 days) hospitalisation - whichever came first.

The Proportional hazard assumption is the most important assumption in the Cox regression. It dictates that the hazard curves for the groups should be parallel (Bradburn et al. 2003). In this study, the fulfilment of the proportional hazard assumption was tested with the Schoenfeld residuals, Kaplan-Meier curves and the log-log plot graph.

In Work 1, analyses were performed separately on people with and without AD, because there were interactions between explanatory factors and AD. Also violation of the proportional hazard assumption supported groupwise analysis, which was confirmed by Schoenfeld residuals and Kaplan-Meier curves. In Work 2, analyses were made separately on people aged <75 years and ≥75 years after testing the proportional hazard assumption. In Work 4, the proportional hazard assumption did not hold in mortality analyses. An attempt was made to correct the violation by conducting

separate analyses between genders and age groups, but when the underlying problem related specifically to the hazards between PIM users and non-users, the separate analyses did not fully alter the results of the post-estimation tests.

In Work 2, multilevel mixed-effects logistic regression was used to investigate the physician effect on PIM initiation in both the first (2002) and the last year (2013) of the study period. These models only considered a person's new PIM purchases (different PIM initiations). Two models were formulated; 1) the unconditional (constant-only) model, which estimates the overall probability of a PIM initiation and the variance between physicians, and 2) the random-intercept model, which also includes patient-related fixed predictors: gender, socioeconomic status, the use of antidiabetics, psychotropics or cardiovascular medications, excessive polypharmacy and living situation. A physician identification code was used to define the prescribing physician in each medication purchase.

The proportion of the total variation in PIM purchases explained by the physician effect was calculated by intraclass correlation (ICC). ICC is an index that ranges between 0 and 1 and examines the level of variance of the dependent variable that is explained by study groups. (Xing 2016, p. 351.)

In Work 4, a fixed effects linear model was used to analyse the association between PIM use and hospital costs. The dependent variable was the natural logarithm of hospital costs because the cost distribution was right-skewed. Yearly zero costs were taken into account in the second model, in which the dependent variable was log(x+1) transformation of costs. The models were adjusted for morbidity (defined yearly), time variable (year) and year of death, which was included because health care costs tend to increase near the end of life (e.g. Forma et al. 2009).

The data were analysed using the Stata statistical package (STATA IC 13.1 and IC 14.1, StataCorp, College Station, TX, USA). The significance level was set at p-value 0.05.

Table 5. Research questions and applied statistical methods

Work	Specific research questions in sub-studies	Wash-out period	Statistical methods	Dependent/ outcome variable	Covariates
1	Which risk factors were associated with PIM initiation in people with and without AD?	12 months	Cox proportional hazard regression	PIM initiation	The Prescription Register: age group, gender, other medication use, university hospital district
					SF: socioeconomic status
					HILMO and the Special Reimbursement Register: comorbidities
2	How does PIM initiation accumulate in community-dwelling people aged 65–74 and ≥75 years, and which patient and health care related factors are associated with PIM initiation over time?	24 months	Cox proportional hazard regression Multilevel mixed-effects logistic regression	PIM initiation/ new PIM purchase Levels: Patient and physician	The Prescription Register: gender, morbidity/medication use, excessive polypharmacy, hospital district
					SF: socioeconomic status, living situation
3	Is PIM use associated with an increased risk of hip fractures in people with AD?	12 months	Cox proportional hazard regression	Incident hip fracture	The Prescription Register: PIM use, age groups, gender, other medication use
					SF: socioeconomic status
					The Special Reimbursement Register: comorbidities
					HILMO: previous fractures
4	Is PIM use associated with fracture-specific hospitalisations, mortality, or hospital costs?	24 months	Cox proportional hazard regression Fixed effects linear model	Incident fracture All-cause mortality Health care costs of all-cause hospitalisations during the 12-year follow-up	The Prescription Register: PIM use, age group, gender, morbidity/ medication use, excessive polypharmacy
					SF: socioeconomic status, living situation

6.5.1 Endogeneity in PIM use

As described in Chapter 2, many interrelated factors are associated with PIM use. For this reason, it can be assumed that PIM users and non-users are not two randomly selected homogenous groups that can be directly compared because there may be a selection process for PIM use. Selection may be related to partly known or partly unknown factors, or may be unobservable. This may lead to an endogeneity problem, which arises when at least one of the predictors for PIM use is also associated simultaneously with the dependent outcome variable (Li 2013), so a covariate is

correlated with unobserved error terms. In health economics studies, endogeneity is often caused by unobserved health status. (Deb et al. 2017, p. 201.) In this study, PIM users might have, for example, a higher risk of falls due to these known or non-observable factors. In addition, endogeneity can arise due to differences in prescribing practices among physicians, if the patient had a higher risk of PIM use when visiting a physician with a high PIM prescribing rate (Chen and Cheng 2016).

In this study, PSM analysis was used to remove, or at least reduce, the bias caused by the selection process for PIM use. The PSM analysis with nearest neighbour (1:1) matching searched the PIM user and non-user pairs which were the most similar according to their relevant characteristics before treatment (Caliendo and Kopeinig 2008, p. 32). Available information on those covariates that were related to PIM initiation based on previous studies (e.g. Works 1 and 2) were gathered and the covariates (age, gender, socioeconomic status, use of psychotropics, use of opioids, excessive polypharmacy, university hospital region) were included in the PSM analysis. The advantage of one-to-one matching is that afterwards the groups included the same number of observations. In addition, after nearest neighbour matching there tended to be similarity between the groups increased. (Holmes 2014, p. 107–109.) It should be noted that PSM analysis controls only the potential selection effects of observable variables, but not selection associated with unknown or non-observable factors.

6.6 RESEARCH ETHICS

This research was conducted according to the Responsible Conduct of Research (Finnish Advisory Board on Research Integrity 2012). Pursuant to Finnish legislation there is no need for ethical approval for register-based studies. However, the PIM use data (Works 2 and 4) have been approved by the research ethics committee of the Northern Savo Hospital District (register number 77//2014). Appropriate permissions to access the data have been obtained from each register: SII (71/522/2014), THL (THL/1441/5.05.00/2014) and SF (TK53-1381-14).

According to the Personal Data Act (§ 24) there is no duty to provide information to data subjects in studies where register-based information is collected from sources other than the data subject. In Works 2 and 4, the Data Protection Ombudsman has been notified via submission of a description of the study in accordance with the Personal Data Act (§ 36).

Personal information about the study population was anonymised by creating new study codes for the research purpose during data collection. Researchers had no access to the subjects' real identification codes at any stage of the research. In Works 2 and 4, the registers were merged by the first author.

The data was checked before use and handled carefully. Data in Works 2 and 4 were used via the remote access service provided by SF's Research Services due to the risk of indirect identification from income information (Statistics Finland 2017). All reported analyses were checked by SF's Research Services before they were given to researchers. According to SF's guidelines on preserving the anonymity of study populations, minimum and maximum values were not reported. All studies were conducted within the facilities of the Department of Health and Social Management at the University of Eastern Finland.

7 RESULTS

7.1 SELECTION FOR PIM USER (WORKS 1 AND 2)

Work 1 investigated the risk factors associated with the initiation of PIM use in older people with and without AD. The results showed that people with AD initiated PIMs less often than people without AD. However, the mean duration of PIM use was longer in the AD group than in the non-AD group (203 days vs. 166 days, $p<0.001$). In both, AD and non-AD groups, people aged <75 initiated PIMs more often than people aged ≥75 years. When comparing the risk of PIM initiation by gender, women had a higher risk of PIM initiation in people without AD, whereas men had a higher risk in the AD group. As expected, in both groups, the risk of PIM initiation increased with several diseases, such as asthma or COPD, cardiovascular disease, cancer, and with other medication use, e.g. opioids and psychotropics. In people without AD, diabetes, epilepsy and depression or bipolar disorders also increase the risk of PIM initiation.

Work 2 examined the role of patient characteristics and the physician effect in PIM initiation in older people aged 65–74 and ≥75. Overall, 37.5 % of the study population initiated PIM use during the 12-year follow-up. The mean number of different PIMs was 1.1 per year and 2.8 by the study period. However, 17 % of the PIM initiators purchased ≥5 different PIMs. The study found that women had a higher risk of PIM initiation in the 65–74 age group but in the ≥75 age group gender was no longer significantly associated with PIM initiation. The results also showed that the risk of PIM initiation increased with higher income in the younger age group but not in the older ones (≥75 years). In both age groups, PIM initiation was associated with excessive polypharmacy and psychotropic medication use. Work 2 found that 16 % of the total variance of PIM initiations in people aged 65–74 years was attributable to physicians in the first year of the follow-up (year 2002). The corresponding figure was 11 % among people aged ≥75 years. In the last year of the follow-up (2013), physician-related variance of PIM initiations decreased two percentage points but the study population was also more selected, because the data included only those who had survived. Works 1 and 2 also found statistically significant differences between hospital districts. Table 6 summarises the factors associated with PIM initiation in Works 1 and 2.

Table 6. Factors associated with PIM initiation

Work 1			Work 2		
	People with AD	**People without AD**		**People aged <75 years**	**People aged ≥75 years**
Age					
65–74 years	Reference	Reference			
75–84 years	-***	-***			
≥85 years	-***	-***			
Gender			**Gender**		
Male	Reference	Reference	Male	Reference	Reference
Female	-***	+***	Female	+***	NS
Socioeconomic position (at middle age)			**Socioeconomic position (income)**		
High	Reference	Reference	<9,999€	Reference	Reference
Medium	-*	NS	10,000–19,999€	+*	+***
Low	NS	NS	20,000–29,999€	+**	+*
Unknown	NS	-***	>30,000€	+***	NS
Medication use			**Medication use**		
Opioids	+**	+***	Antidiabetics	NS	NS
Psychotropics	+***	+***	Psychotropics	+***	+***
			Cardiovascular medications	NS	NS
Comorbidities			Anti-dementia medications	NS	NS
Asthma or COPD	+***	+***			
Diabetes	NS	+***	**Excessive polypharmacy**	+***	+***
Rheumatoid arthritis	NS	NS			
Cardiovascular disease	+***	+***	**Living alone**	NS	NS
Epilepsy	NS	+***			
Previous stroke	NS	-**			
Previous hip racture	NS	-*			
History of cancer	+**	+***			
History of depression or bipolar disorders	NS	+*			
History of substance abuse	NS	NS			
Hospital district	-/+***	-/+***	**Hospital district**	**	**
			Prescribing physician	***	***

NS, non-significant; *p<0.05; **<0.01; ***<0.001
AD, Alzheimer's disease; COPD, chronic obstructive pulmonary disease

7.2 HEALTH CARE UTILISATION AND COSTS (WORKS 3 AND 4)

7.2.1 Fracture-specific hospitalisations

Work 3 determined whether PIM initiation is associated with an increased risk of hip fractures in older people with AD. PIM initiation was not associated with hip fractures when all PIM exposure periods were considered (HR 1.21; 95 % CI 1.00–1.48, p=0.056). However, after restricting the analysis to the first PIM use period, the study found that PIM initiation was statistically significantly associated with hip fractures (HR 1.31; 95 % CI 1.06–1.63, p=0.014).

Work 4 analysed whether PIM initiation is associated with potentially fall-related incident fractures in the general older community-dwelling population. Based on results, PIM use is associated with fracture-specific hospitalisations in all PIM exposure periods (one-month: HR 1.20; 95 % CI 1.01–1.44, p=0.039; three-month: HR 1.30; 95 % CI 1.16–1.46, p<0.001; and six months: HR 1.30; 95 % CI 1.17–1.43, p<0.001), but the association was weak in the one-month exposure period (see Kaplan-Meier survival curves in Figure 3). The associations were stronger when the exposure period was restricted to the first PIM use period. The results of PIM use remained quite similar with and without PSM adjusting. Table 7 summarises the main results of Works 3 and 4 on the association between PIM use (Work 4: one-month PIM exposure) and hospitalisations.

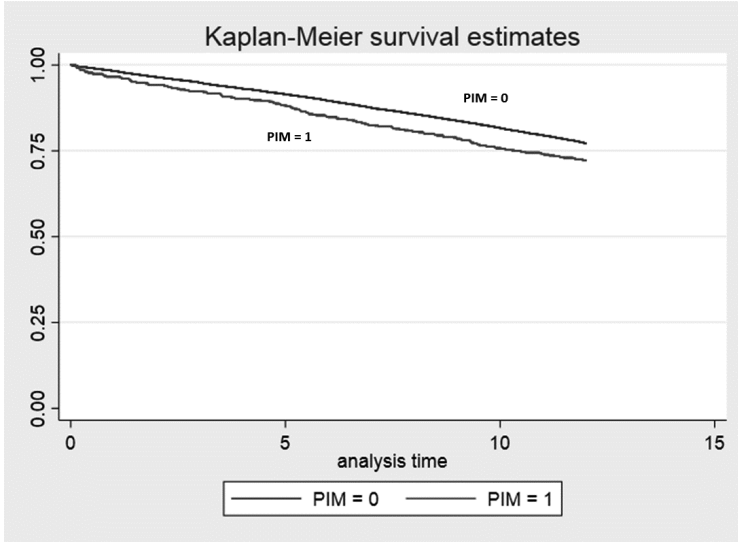

Figure 3. Fracture-specific hospitalisation-free survival curves for PIM users (one-month exposure) and non-users during the 12-year follow-up

Table 7. Cox proportional hazards models of the association between PIM use and fracture-specific hospitalisations

Work 3				Work 4 (One-month PIM exposure)						
	HR	**95 % CI**	**p-value**		**PSM adjusted HR**	**95 % CI**	**p-value**	**HR without PSM**	**95 % CI**	**p-value**
The first PIM use period[a]				**The first PIM use period[b]**						
Non-users	1.00	(reference)		Non-users	1.00	(reference)		1.00	(reference)	
PIM users	1.31	(1.06–1.63)	0.014	PIM users	1.61	(1.11–2.33)	0.013	1.57	(1.08–2.27)	0.018
No. of fractures	2,623			No. of fractures	2,351			3,487		
No. of fractures during PIM use	86			No. of fractures during PIM use	28			28		
PIM use (all exposure periods)				**PIM use (all exposure periods)**						
Non-users	1.00	(reference)		Non-users	1.00	(reference)		1.00	(reference)	
PIM users	1.21	(1.00–1.48)	0.056	PIM users	1.20	(1.01–1.44)	0.039	1.21	(1.02–1.44)	0.032
Age[c]				**Age[c]**						
65–74 years	1.00	(reference)		65–74 years	1.00	(reference)		1.00	(reference)	
75–84 years	1.89	(1.67–2.14)	<0.001	75–84 years	1.85	(1.72–1.98)	<0.001	1.86	(1.75–1.98)	<0.001
≥85 years	3.32	(2.92–3.79)	<0.001	≥85 years	3.35	(2.92–3.85)	<0.001	3.50	(3.17–3.88)	<0.001
Gender				**Gender**						
Male	1.00	(reference)		Male	1.00	(reference)		1.00	(reference)	
Female	1.44	(1.32–1.58)	<0.001	Female	1.77	(1.63–1.92)	<0.001	1.67	(1.56–1.79)	<0.001
Socioeconomic status (at middle age)				**Socioeconomic status (income)[f]**						
High	1.00	(reference)		<9999 €	1.00	(reference)		1.00	(reference)	
Medium	0.99	(0.92–1.07)	0.861	10,000–19,999 €	1.02	(0.94–1.10)	0.600	1.02	(0.95–1.09)	0.549
Low	1.28	(1.06–1.53)	0.010	20,000–29,999 €	1.08	(0.95–1.24)	0.241	1.10	(0.98–1.24)	0.097
Unknown	0.93	(0.70–1.23)	0.606	>30,000 €	1.05	(0.87–1.26)	0.602	1.03	(0.87–1.22)	0.714
Comorbidities				**Medication use[g]**						
Asthma or COPD	1.00	(0.86–1.15)	0.965	Antidiabetics	1.16	(1.03–1.31)	0.014	1.14	(1.02–1.27)	0.017
Diabetes	1.09	(0.97–1.23)	0.156	Psychotropics	1.23	(1.14–1.33)	<0.001	1.21	(1.13–1.30)	<0.001
Rheumatoid arthritis	1.00	(0.83–1.21)	0.970	Cardiovascular medications	0.95	(0.88–1.02)	0.136	0.94	(0.88–1.00)	0.060

Table 7. (continued)

Work 3				Work 4 (One-month PIM exposure)						
	HR	**95 % CI**	**p-value**		**PSM adjusted HR**	**95 % CI**	**p-value**	**HR without PSM**	**95 % CI**	**p-value**
Epilepsy	1.17	(0.86–1.58)	0.324	Opioids	1.16	(1.01–1.34)	0.039	1.17	(1.03–1.34)	0.016
Previous stroke	1.12	(0.99–1.28)	0.075	NSAIDs	0.98	(0.91–1.05)	0.511	0.98	(0.93–1.04)	0.554
Cancer[d]	1.25	(1.07–1.46)	0.004	**Excessive polypharmacy[g]**	1.26	(1.14–1.39)	<0.001	1.27	(1.16–1.40)	<0.001
Previous fractures (excl. hip fracture)	1.38	(1.25–1.51)	<0.001	**Living alone[f]**	1.13	(1.05–1.21)	0.002	1.15	(1.08–1.23)	<0.001
History of psychiatric disorders	0.79	(0.63–0.99)	0.043							
History of substance abuse	1.02	(0.77–1.37)	0.873							
Medication use										
Bisphosphonates[e]	0.90	(0.80–1.00)	0.056							
Opioids[c]	1.29	(1.04–1.60)	0.019							
Psychotropic medications[c]	1.20	(1.11–1.30)	<0.001							
Any antihypertensive medication[c]	0.85	(0.78–0.92)	<0.001							
NSAID[c]	0.87	(0.74–1.03)	0.107							
No. of fractures	2,846			No. of fractures	3,715			4,864		
No. of fractures during PIM use	103			No. of fractures during PIM use	128			132		
No. of subjects	47,850			No. of subjects	20,666			27,255		

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; PIM, potentially inappropriate medication; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug

[a]Adjusted for age, gender, socioeconomic status (at middle age), asthma or COPD, diabetes, rheumatoid arthritis, epilepsy, previous stroke, cancer, previous fractures (excl. hip fracture), history of psychiatric disorders, history of substance abuse and medication use (bisphosphonates, opioids, psychotropics, any antihypertensive medication, NSAIDs)

[b]Adjusted for age, gender, socioeconomic status (income), living situation, morbidity (the use of antidiabetics, psychotropics, cardiovascular medications, opioids and NSAIDs) and excessive polypharmacy

[c]At the start of the follow-up

[d]Active cancer treatment one year before the diagnosis of AD

[e]Before AD diagnosis

[f]Year 2000

[g]At the wash-out period (years 2000–2001)

7.2.2 All-cause hospitalisations

In Work 4 also reported that the unadjusted mean number of all-cause hospital episodes (without zero cost patients) is higher among PIM users (33.9 episodes [95 % CI 32.9–34.9]; median 25 [95 % CI 24–25]) compared to non-users (22.4 episodes [95 % CI 21.8–23.0]; median 16 [95 % CI 15–16]) ($p<0.001$). However, among non-users the mean length of stay per episode is longer (4.7 days; 95 % CI 4.5–4.8) compared to the PIM user group (3.6 days 95 % CI 3.5–3.7) ($p<0.001$) (median 1 day [95 % CI 1–1] in both groups).

There were minor differences in the classifications of hospital episodes ($p<0.001$). Most of the hospital episodes were follow-up appointments (PIM users: 47 % of the episodes; non-users: 44 %) and inpatient care (PIM users: 23 %; non-users: 24.7 %) in both groups. Approximately 11 % of all episodes were appointments and 13 % emergency care visits in both groups. The smallest proportions of visits were in consultation, outpatient surgery, and rehabilitation.

7.2.3 Hospital costs

Work 4 determined the associations between PIM use and unit hospital costs of all-cause hospitalisations during the 12-year follow-up. The results of the fixed linear regression showed that PIM users have 15 % higher hospital costs. There were only 401 people with zero hospital costs during the 12-year follow-up, but when yearly zero costs were taken into account, the results showed that PIM users had 50 % higher hospital costs during the follow-up. Table 8 presents the results related to the association between PIM use and hospital costs.

The unadjusted mean hospital costs (without zero costs) were 60,114 euros [95 % CI 58,434–61,793] (median 35,297 euros [95 % CI 34,404–36,309]) in PIM users and 52,435 euros [95 % CI 50,483–54,388] (median 24,636 euros [95 % CI 23,668–25,493]) in non-users ($p<0.001$).

Table 8. The association between PIM use and all-cause hospital costs in PSM-adjusted fixed effects linear model

	Model without zero costs[a]			Model with zero costs[b]		
	Coef.	**95 % CI**	**p-value**	**Coef.**	**95 % CI**	**p-value**
PIM use						
Non-users	1.00	(reference)		1.00	(reference)	
PIM users	0.15	(0.12–0.18)	<0.001	0.50	(0.44–0.55)	<0.001
Medication use[c]						
Antidiabetics	-0.12	(-0.17–-0.06)	<0.001	-0.01	(-0.11–0.09)	0.820
Psychotropics	0.20	(0.17–0.23)	<0.001	0.40	(0.35–0.46)	<0.001
Cardiovascular medications	0.04	(-0.00–0.07)	0.054	0.33	(0.26–0.39)	<0.001
Excessive polypharmacy[c]	0.76	(0.73–0.79)	<0.001	1.94	(1.89–1.99)	<0.001
Year						
2002	1.00	(reference)		1.00	(reference)	
2003	0.11	(0.07–0.15)	<0.001	0.23	(0.16–0.29)	<0.001
2004	0.17	(0.13–0.21)	<0.001	0.33	(0.26–0.39)	<0.001
2005	0.23	(0.19–0.28)	<0.001	0.62	(0.55–0.69)	<0.001
2006	0.20	(0.16–0.24)	<0.001	0.75	(0.68–0.82)	<0.001
2007	0.24	(0.20–0.28)	<0.001	0.85	(0.78–0.92)	<0.001
2008	0.28	(0.24–0.32)	<0.001	1.00	(0.93–1.07)	<0.001
2009	0.29	(0.25–0.33)	<0.001	1.01	(0.93–1.08)	<0.001
2010	0.35	(0.30–0.39)	<0.001	1.17	(1.09–1.24)	<0.001
2011	0.39	(0.34–0.43)	<0.001	1.33	(1.25–1.41)	<0.001
2012	0.45	(0.40–0.50)	<0.001	1.42	(1.34–1.50)	<0.001
2013	0.45	(0.40–0.50)	<0.001	1.56	(1.48–1.64)	<0.001
Year of death	1.22	(1.18–1.26)	<0.001	2.68	(2.59–2.77)	<0.001
Number of observations	110,577			190,856		
Number of subjects	20,180			20,666		
R-squared						
Within	0.1015			0.1011		
Between	0.1330			0.1705		
Overall	0.1155			0.1252		

PIM, potentially inappropriate medication; CI, confidence interval
[a]Dependent variable: logged hospital costs
[b]Dependent variable: logged(x+1) hospital costs
[c]Defined yearly

7.3 HEALTH OUTCOMES (WORK 4)

7.3.1 All-cause mortality

Work 4 investigated the association between PIM use and all-cause mortality. The results showed that PIM use is associated with mortality in all exposure periods (one-month: HR 1.38; 95 % CI 1.24–1.54, p<0.001; three-month: HR 1.67; 95 % CI 1.56–1.78, p<0.001, and six months). The strongest association was in the six-month exposure period (HR 1.81; 95 % CI 1.71–1.92, p<0.001) (Table 9). The associations were even stronger when follow-up was restricted to the first PIM use period. However, the post-estimation tests showed that the hazards for the PIM user and non-user groups were not parallel so the proportional hazard assumption was violated. The violation was attempted corrected by stratifying the models according to age and gender, which may relate to different hazards of death. However, the models were not corrected by such stratifying, because there were still different and converging hazards between PIM users and non-users.

Table 9. The association between PIM use (six-month PIM exposure period) and mortality in time-varying cox proportional hazards regression in the matched and non-matched populations

	PSM adjusted HR	95 % CI	p-value	HR without PSM	95 % CI	p-value
The first PIM use period[a]						
Non-users	1.00	(reference)		1.00	(reference)	
PIM users	2.22	(2.06–2.39)	<0.001	1.98	(1.84–2.12)	<0.001
Number of deaths	5,066			8,372		
Number of deaths during PIM use	833			847		
PIM use (all exposure periods)						
Non-users	1.00	(reference)		1.00	(reference)	
PIM users	1.81	(1.71–1.92)	<0.001	1.72	(1.62–1.81)	<0.001
Age[b]						
65–74 years	1.00	(reference)		1.00	(reference)	
75–84 years	2.45	(2.34–2.57)	<0.001	2.53	(2.43–2.64)	<0.001
≥85 years	6.57	(6.04–7.14)	<0.001	7.44	(7.01–7.91)	<0.001
Gender						
Male	1.00	(reference)		1.00	(reference)	
Female	0.55	(0.53–0.58)	<0.001	0.56	(0.53–0.58)	<0.001
Socioeconomic status (income)[c]						
<9,999 €	1.00	(reference)		1.00	(reference)	
10,000–19,999 €	0.94	(0.89–0.99)	0.013	0.90	(0.86–0.94)	<0.001
20,000–29,999 €	0.81	(0.73–0.89)	<0.001	0.78	(0.72–0.84)	<0.001
>30,000 €	0.71	(0.62–0.81)	<0.001	0.70	(0.62–0.78)	<0.001
Living alone[c]	1.11	(1.05–1.17)	<0.001	1.09	(1.04–1.14)	<0.001
Medication use[d]						
Antidiabetics	1.53	(1.43–1.64)	<0.001	1.52	(1.43–1.61)	<0.001
Psychotropics	1.17	(1.11–1.24)	<0.001	1.17	(1.12–1.23)	<0.001
Cardiovascular medications	1.30	(1.23–1.37)	<0.001	1.31	(1.25–1.37)	<0.001
Opioids	1.35	(1.24–1.48)	<0.001	1.33	(1.22–1.44)	<0.001
NSAIDs	0.87	(0.83–0.91)	<0.001	0.88	(0.85–0.92)	<0.001
Excessive polypharmacy[d]	1.48	(1.39–1.58)	<0.001	1.43	(1.35–1.52)	<0.001
Number of deaths	8,033			11,361		
Number of deaths during PIM use	1,365			1,390		
Number of subjects	20,666			27,255		

PSM, propensity score matching; PIM, potentially inappropriate medication; HR, hazard ratio; CI, confidence interval, NSAID, nonsteroidal anti-inflammatory drug
[a]Adjusted for age, gender, socioeconomic status (income), living situation, morbidity (the use of antidiabetics, psychotropics, cardiovascular medications, opioids and NSAIDs) and excessive polypharmacy.
[b]At the start of the follow-up (1 Jan 2002)
[c]Year 2000
[d]At the wash-out period (years 2000–2001)

8 DISCUSSION

8.1 INTERPRETATION OF THE RESULTS

This dissertation evaluates the selection for PIM use, and how PIM initiation (defined by the Meds75+ database) is associated with health care service use, health care costs and mortality. PIM use was evaluated in two different older populations, and the results show that PIM use is prevalent. Of those community-dwelling people aged ≥65, 37.5 % initiated PIM use during the 12-year study period. People with AD initiated PIMs less often than the general community-dwelling older population. This is in line with a previous review that reported a lower probability for PIM use among people with cognitive impairment or dementia, which can indicate that physicians are cautious when prescribing PIMs to this specific and more vulnerable patient group (Johnell 2015).

This study found that PIM initiation was mainly dependent on patient characteristics and morbidity, which may be referred to as demand-side factors. Supply-side factors were also associated, because there were differences in PIM prescribing among physicians. In addition, regional differences in PIM initiation were found. Characteristics associated with PIM use are largely studied but previous studies mainly evaluate prevalent PIM use. This dissertation studied incident PIM use, meaning that those already using PIMs were excluded because the focus was on studying the selection for PIM use. In practice, physicians can only decide whether or not to initiate patient on medication or to deprescribe medications (Korhonen et al. 2018). The results of new-user design yield information on factors related to initiation of medications that can be taken into account in e.g. preventing PIM use, and thus can be considered more relevant for supporting decision-making.

PIM initiation was more frequent among people aged <75. The findings of this dissertation are contrary to those of previous studies, which mainly found that older age is one of the main factors associated with PIM use, but mixed findings also exist (Tommelein et al. 2015). A recent study by Miller et al. (2016) also reported that older age is a predictor for lower PIM use as defined by the Beers Criteria (2012). The results indicate that physicians are probably aware of ageing-related changes when prescribing PIMs. The differences from previous studies may be partly explained by different study designs because this study captures only factors associated with PIM initiation, not the factors associated with the continuing of PIMs. According to a previous review by Anderson et al. (2014), physicians have different attitudes towards initiating or continuing PIMs, so this might have an effect on results related to the association between PIM use and age, when comparing prevalent and incident PIM use. In addition, higher age is associated with higher mortality, which may have an effect on the results as a competing risk (e.g. Fialová et al. 2005).

Based on this study, women had a higher risk of PIM initiation among people without AD than those with AD, which is in line with previous studies conducted on general older populations (Guaraldo et al. 2011; Stock et al. 2014; Miller et al. 2016; Morgan et al. 2016). The higher risk for PIM use among women is also reported in other settings, for example, in long-term and acute care settings (Nothelle et al. 2017). Possible reasons for the increased risk of PIM use among women can be that

women use more health care services and medications (e.g. Suominen-Taipale et al. 2006; Manteuffel et al. 2014), and also live longer than men. However, the results of this study showed that men have a higher risk of PIM initiation among people with AD, which is contrary to the results reported in a recent review of PIM use among community-dwelling patients with dementia (Patel et al. 2017). The results might be partly explained by treatment differences for urge incontinence and overactive bladder, as men were more likely to use urinary antispasmodics than women in the data. However, this study also indicates that gender differences in PIM initiation depend on age, while female gender was associated with PIM initiaton only in people aged <75. In people aged ≥75 years, there was no difference in PIM initiation between genders. This finding is consistent with a previous Finnish study, which did not find any association between PIM use as defined by the Meds75+ database and gender among older people aged ≥75 (Ahonen 2011, p. 87–88).

The results related to socioeconomic status are mainly contrary to those of previous studies, which generally reported that a lower socioeconomic status is associated with PIM use (Bongue et al. 2009; Tommelein et al. 2015; Miller et al. 2016). In this study, no association between a low socioeconomic status and PIM use was shown. Higher income was associated with PIM initiation in people aged <75. This might be explained by better access to health care, and thus a higher risk of PIM prescription. In people aged ≥75, the highest income group was no longer associated with PIM initiation. In regard to living situation no association with PIM use was shown in this study. These results are consistent with previous studies which predominantly found that living alone was not associated with PIM use (Projovic et al. 2016; Wucherer et al. 2017). However, living situation is sensitive to time-dependent changes in older people.

As expected, several comorbidities (e.g. asthma or COPD, cardiovascular diseases, cancer) and medication use (opioids, psychotropics, polypharmacy) are associated with PIM initiation, so this study confirms that morbidity and multiple medications are associated with a higher probability of medication error. This finding is in line with previous results on the positive association between PIM use and the use of psychotropic medications or polypharmacy (e.g. Fialová et al. 2005; Vieira de Lima et al. 2013; Tommelein et al. 2015). Based on previous studies, a high number of medications is the main barrier to appropriate prescribing from the physician's point of view (Ramaswamy et al. 2011). This can be explained by the complexity at patient level among patients with multiple diseases or polypharmacy (Clyne et al. 2016b). People with polypharmacy may have a positive attitude to medication so they demand medications from physicians and PIM may meet the needs of patient (Anderson et al. 2014; Pohontsch et al. 2017). In addition, sometimes prescribers only want to ease the distress of patients with multimorbidity even if they know the medication may be problematic (Pohontsch et al. 2017).

Differences in PIM prescribing among physicians were found in this study, which means that some physicians prescribe PIMs more likely than other physicians. Interestingly, the physician effect remained relatively the same even though patient characteristics were controlled. Previous studies have also reported that PIM prescribing varied among physicians (Holmes et al. 2013; Cahir et al. 2014), but in the Irish study by Cahir et al. (2014) physician-related variance remained not significant after adjusting for patient-level variables. In this dissertation, physician-related variance of PIM initiations decreased during the 12-year study period, when comparing the first and the last year of the follow-up. This can indicate that physicians avoid PIM prescribing when people are getting older and, later, they have better knowledge of

the risks related to PIM use, and more information is also available. For example, the Finnish Meds75+ database, which was published in 2010, may have an impact on the prescribing patterns of Finnish physicians. The first published and widely used set of criteria was already available in the 1990's (Beers et al. 1991), but its influence was probably weaker in Finland than in many other countries since it was published in English. However, it should be noted that the population of this study was more selected in the last year of the follow-up. It can be assumed that more people lived at home at the beginning of the follow-up, but the study population was older and frailer in the last year of follow-up, so more people would probably have been living in, for example, sheltered housing. In addition, there are changes in availability and purchasing system of medications during the follow-up. For example, in the last year of the follow-up (2013), opiate-related cough medications were not belonging on the Finnish purchasing system, and the marketing authorisation for e.g. glibenclamide and quinine was no longer valid (Vartiainen et al. 2017). This dissertation cannot control for the physician-related differences (e.g. specialty, unit) from the registers, for example, previous studies have found that the physician's specialty or demographic factors can be associated with PIM prescribing (Rothberg et al. 2008; Lai et al. 2009).

Regional differences in PIM initiation between hospital or university hospital districts were observed, as PIM initiation was the highest in the Helsinki University Hospital area both in patients with and without AD. However, this study did not evaluate the underlying reasons behind this variation. Previous studies have also found regional differences in PIM prescribing (Jiron et al. 2016; Beuscart et al. 2017), but it is difficult to compare these studies because of e.g. different geographical areas and health care systems.

In this study, PIM initiation is associated with fracture-specific hospitalisations. Several previous studies have investigated all-cause hospitalisations (e.g. Reich et al. 2014; Endres et al. 2015; Varga et al. 2017), but in this dissertation, fractures were chosen as outcome measures because PIMs include many fall-risk-increasing medications (e.g. Woolcott et al. 2009). Hip fractures are also costly and cause major harm to patients. PIMs include anticholinergic medications, which can weaken the effect of AD medication, so people with AD can have an even higher risk of adverse-drug events associated with PIMs. This study revealed that PIM initiation is associated with an increased risk of hip fracture in people with AD. However, results were significant only when the analysis was restricted to the first PIM use period, which means that when all exposure periods were taken into account, PIM use was not associated with hip fracture. It has to be noted that AD itself is a risk factor for hip fracture (Baker et al. 2011). Previous studies focused on general older populations have found that PIMs are associated with a higher risk of falls and fractures (e.g. Berdot et al. 2009; Stockl et al. 2010; Lu et al. 2015). Our study shows similar results concerning the association between PIM use and increased risk of fracture-specific hospitalisation in the general older community-dwelling population. However, the association was weak in the one-month exposure period, which might be the most appropriate exposure period for negative outcomes, assuming that ADRs/ADEs occur quite soon after PIM use. Nevertheless, the associations are stronger in the first PIM use period, which indicates a higher risk of a negative outcome when starting PIM. It should be noted that the results are different when all exposure periods are considered because only those who are not hospitalised can survive longer after the first PIM use period. Our studies show also that other patient characteristics, such as older age, female gender and polypharmacy were significant risk factors for fracture-specific hospitalisations,

which is in line with previous studies investigating the association between PIM use and falls/fractures (e.g. Berdot et al. 2009; Narayan and Nishtala 2015).

This study shows that PIM use is weakly associated with an increased risk of mortality, which is in line with a recent review by Muhlack et al. (2017) that reported a higher risk of mortality among PIM users only in studies with a new-user design. Previous studies have mainly not found any associations between PIM use and mortality (e.g. Jano and Aparasu 2007; Lu et al. 2015). However, it should be noted, that modelling cannot correct violation of the proportional hazard assumption, so the results on the association between PIM use and mortality should be construed carefully.

As described earlier in this dissertation, it may be possible that there is a selection effect for PIM use, which means that PIM users had already, for example, a higher risk of fall, due to some observable (e.g. morbidity) or unobservable (e.g. life habits, weight in register-based data) factors, compared to non-users. In this study, the possible selection effect for PIM use was taken into account using PSM analysis. The results of the association between PIM use and hospitalisation or mortality were quite similar both with and without PSM adjustment. However, a register-based study with PSM analysis can only take into account observable heterogeneity.

PIM users had higher hospital costs during the 12-year follow-up, which is consistent with previous studies investigating the association between PIM use and health care costs (e.g. Hyttinen et al. 2016; Heider et al. 2017). Among those hospitalised, PIM users had 15 % higher hospital costs compared to non-users. During the follow-up, only 401 people were not hospitalised (with zero costs). When hospitalisations were observed yearly, about 40 % had yearly zero costs, which indicates that a person was hospitalised e.g. once or a few times during the long follow-up. When yearly zero costs were included in the analysis, PIM users still had 50 % higher hospital costs, which indicates that PIM users had a higher probability of all-cause hospitalisation.

The results of this dissertation confirm the previous literature in that there should be more awareness of the risks related to PIMs since PIM use is associated with a higher risk of negative health outcomes, and thus greater health care utilisation and higher hospital costs. This study offers new information that the risks of negative health outcomes are especially related to starting PIM use and highlights the need to pay attention to PIM initiation. Physicians play a key role in conducting rational pharmacotherapy. In theory, it can be assumed that physicians know that PIMs cause more harm than good and, in an ideal world, they do not prescribe PIMs without careful consideration. This study confirms that the complexity of individual patients, such as people with polypharmacy or multiple diseases, affects PIM prescribing. Based on the results of this dissertation, PIM initiation was mainly explained by patient characteristics or demand-side factors. However, the supply side matters too since differences still exist in PIM prescribing among physicians after controlling for patient-related factors. This confirms that the PIM prescription decision is related to a variety of interrelated patient- and physician-level factors (Clyne et al. 2016b).

In Finland, the Meds75+ database supports clinical decision-making on the medication treatment of people aged ≥75 years and the database is available free of charge at the FIMEA's website (Finnish Medicines Agency 2015). In addition, the MEDS75+ can be found on the Terveysportti health portal (Jyrkkä et al. 2017). However, a little is known how compatible physicians feel the use of the database in clinical practice. According to a recently published national report, the Rational Pharmacotherapy Action Plan by Ministry of Social Affairs and Health (2018a, p.

20), health care organisations should exert more control over how physicians utilise available electronic systems to support their decision-making in prescribing.

Feedback on physicians' prescribing practices is one instrument for improving rational prescribing (Ministry of Social Affairs and Health 2018b, p. 35). In 2018, the Finnish Social Insurance Institution sent feedback to physicians on their prescribing of amitriptyline, nortriptyline and pregabaline, which are categorised as PIMs (D-medications; avoid use in older persons) in the Meds75+ database. The aim of this feedback was to improve rational medication use in people over 75 years of age and increase the awareness of the risks related to these medications in pain management. (Social Insurance Institution 2018.) However, it has to be borne in mind that older people are a very heterogenous group and in some situations PIMs may be needed, for example, in hospice and palliative care (American Geriatrics Society 2015, p. 2228).

A recent review by Clyne et al. (2016a) concluded that interventions (e.g. computerised clinical decision support systems) work differently when comparing PIM initiation and continuation. Better results related to the effectiveness of interventions have most often been reported when decreasing new PIM prescriptions compared to existing PIMs (Clyne et al. 2016a). This can be explained by the different attitudes of physicians towards initiating or continuing PIMs, for example, physicians may be reluctant to discontinue or change PIMs if they have a fear of negative consequences (Anderson et al. 2014).

8.2 METHODOLOGICAL CONSIDERATIONS

The main strength of this dissertation is in its two large, nationally representative longitudinal register-based datasets, which allowed the comparison of PIM use in two different older populations. Several possible biases were taken into account in the analyses. Firstly, prevalent user bias was taken into account by using a wash-out period to restrict the analyses to new PIM users. Secondly, outcome analyses were also restricted to the first PIM use period to decrease possible healthy survivor bias. Thirdly, possible endogeneity bias was decreased by using PSM analysis. Fourthly, PIM exposure was also measured using the PRE2DUP method which, studies have shown, yields the lowest error rates for duration of medication use compared to, for example, time windows (Tanskanen et al. 2017).

There are also some limitations that have to be considered in this dissertation. Firstly, after the exclusion of prevalent PIM users, it could be the case that the study population is healthier and wealthier. Secondly, the Prescription Register includes only reimbursed medication purchases, so there was no information available on non-reimbursed medications, over-the-counter medications, vitamins or herbal products. Thirdly, it is possible that patients were not really taking the medications that were registered as medication purchases in the Prescription Register. Fourthly, the follow-up started in all sub-studies before the Meds75+ database was published, the possibility exists that prescribing practices or the availability of medications changed during the follow-up. In addition, the study population included people aged <75, but Meds75+ supports the medication use of people aged ≥75. However, when the database was developed, the commonly used criteria (e.g. Beers, STOPP/START, Laroche) were taken into account (Finnish Medicines Agency 2015). Furthermore, the mean ages of the study populations were already relatively high at the beginning of the study periods. Fifthly, although PSM analysis was used to decrease the selection

bias, there remains the possibility of unobserved heterogeneity that we cannot capture from register-based data, and also time-dependent confounding. In addition, there is evidence that variables that are strongly associated with the exposure and not associated or only weakly associated with the outcome should not be included in the PSM as this may actually increase the variance and bias of the estimates of the measures of association. However, estimating is not simple, while many variables can be associated both the exposure and outcome. (Patrick et al. 2011.) Sixthly, the modelling in Study 4 cannot correct violation of the proportional hazard assumption. Also, education information accompanied by income information would have been a better measurement of socioeconomic status, but this information was missing for most of the older people. Finally, the data include community-dwelling older people and visits to hospital, so results cannot be generalised to other settings. In addition, PIMs were studied as a group even though they are quite heterogeneous. However, this study's focus was on the phenomenon, not specific classes of medication.

8.3 FUTURE RESEARCH

The underlying reasons behind the variation in PIM prescribing among physicians and regions should be investigated in future studies. In addition, it would be interesting to identify the effects of the Meds75+ database on prescribing practices after its publication in 2010.

This dissertation includes only the use and costs of hospital visits, so future studies on the association between PIM use and primary care visits are needed. In addition, there is a need for cost-effectiveness studies of physician prescribing practice interventions, e.g. computerised clinical decision support systems, which would improve medication use in older people.

Furthermore, studies using different methods for diminishing the effect of potential selection effects (e.g. instrumental variable methods) are needed.

9 CONCLUSIONS

Based on this dissertation, PIM use is prevalent among older people. PIM initiation was mainly explained by patient-related variables, such as younger age, female gender, excessive polypharmacy and several morbidities, as well as by the use of psychotropics, but there is also variation in PIM prescribing among physicians, and university hospital regions. The findings indicate a decreasing physician-related variance in PIM prescribing during the 12-year follow-up.

According to the findings of this dissertation, the first PIM use period in particular is associated with an increased risk of fracture-specific hospitalisation and mortality. Older people exposed to PIMs had higher hospital costs compared to those who did not use any PIMs over a one decade period.

An implication of this is the importance of conducting interventions and implementing new practices which aim to improve the rationality of medication in older people in different care settings. More support, e.g. electronic systems to support decision-making, is needed for physicians and other health care personnel to aid decisions on the suitability of medication, especially when initiating medication. This is one way to advance the achievement of rational pharmacotherapy in health care and, potentially, to avoid the harmful effects of PIMs at patient and society level.

REFERENCES

Ahonen, J. 2011. Iäkkäiden lääkehoito: vältettävät lääkkeet ja yhteisvaikutukset (Drug use in elderly persons: Inappropriate medication and drug interactions). Publications of the University of Eastern Finland. Dissertations in Health Sciences 66. University of Eastern Finland, Kuopio.

American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society, 60(4): 616–631.

American Geriatrics Society 2015 Beers Criteria Update Expert Panel 2015. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society, 63(11): 2227–2246.

Anderson, K., Stowasser, D., Freeman, C. & Scott, I. 2014. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. BMJ Open, 4(12): e006544.

Aronson, J.K. 2009a. Medication errors: what they are, how they happen, and how to avoid them. QJM: An International Journal of Medicine, 102(8): 513–521.

Aronson, J.K. 2009b. Medication errors: definitions and classification. British Journal of Clinical Pharmacology, 67(6): 599–604.

Baker NL, Cook MN, Arrighi HM, Bullock R. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988–2007. Age Ageing, 40(1): 49–54.

Beers, M.H. 1997. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Archives of Internal Medicine, 157(14): 1531–1536.

Beers, M.H., Ouslander, J.G., Rollingher, I., Reuben, D.B., Brooks, J. & Beck, J.C. 1991. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Archives of Internal Medicine, 151(9): 1825–1832.

Bell, J.S., Ahonen, J., Lavikainen, P. & Hartikainen, S. 2013. Potentially inappropriate drug use among older persons in Finland: application of a new national categorization. European Journal of Clinical Pharmacology, 69(3): 657–664.

Berdot, S., Bertrand, M., Dartigues, J.F., Fourrier, A., Tavernier, B., Ritchie, K. & Alperovitch, A. 2009. Inappropriate medication use and risk of falls--a prospective study in a large community-dwelling elderly cohort. BMC Geriatrics, 9(30), doi: 10.1186/1471-2318-9-30.

Beuscart, J.B., Genin, M., Dupont, C., Verloop, D., Duhamel, A., Defebvre, M.M. & Puisieux, F. 2017. Potentially inappropriate medication prescribing is associated with socioeconomic factors: a spatial analysis in the French Nord-Pas-de-Calais Region. Age and Ageing, 46(4): 607–613.

Bongue, B., Naudin, F., Laroche, M.L., Galteau, M.M., Guy, C., Gueguen, R., Convers, J.P., Colvez, A. & Maarouf, N. 2009. Trends of the potentially inappropriate medication consumption over 10 years in older adults in the East of France. Pharmacoepidemiology and Drug Safety, 18(12): 1125–1133.

Bradburn, M.J., Clark, T.G., Love, S.B. & Altman, D.G. 2003. Survival Analysis Part II: Multivariate data analysis - an introduction to concepts and methods. British Journal of Cancer, 89(3): 431–436.

Bradley, M.C., Motterlini, N., Padmanabhan, S., Cahir, C., Williams, T., Fahey, T. & Hughes, C.M. 2014. Potentially inappropriate prescribing among older people in the United Kingdom. BMC Geriatrics, 14(72), doi: 10.1186/1471-2318-14-72.

Britten, N. 2009. Medication errors: the role of the patient. British Journal of Clinical Pharmacology, 67(6): 646–650.

Cahir, C., Fahey, T., Teljeur, C. & Bennett, K. 2014. Prescriber variation in potentially inappropriate prescribing in older populations in Ireland. BMC Family Practice, 15(59), doi: 10.1186/1471-2296-15-59.

Caliendo, M., Kopeinig, S. 2008. Some Practical Guidance for the Implementation of Propensity Score Matching. Journal of Economic Surveys, 22(1): 31–72.

Campins, L., Serra-Prat, M., Gozalo, I., Lopez, D., Palomera, E., Agusti, C., Cabre, M. & REMEI Group 2017. Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling polymedicated elderly people. Family Practice, 34(1): 36–42.

Chang, C. & Chan, D. 2010. Comparison of Published Explicit Criteria for Potentially Inappropriate Medications in Older Adults. Drugs & Aging, 27(12): 947–957.

Chang, C.B., Lai, H.Y., Yang, S.Y., Wu, R.S., Liu, H.C., Hsu, H.Y., Hwang, S.J. & Chan, D.C. 2014. Patient- and clinic visit-related factors associated with potentially inappropriate medication use among older home healthcare service recipients. PloS One, 9(4): e94350.

Chang, C., Yang, S., Lai, H., Wu, R., Liu, H., Hsu, H., Hwang, S. & Chan, D. 2015. Application of three different sets of explicit criteria for assessing inappropriate prescribing in older patients: a nationwide prevalence study of ambulatory care visits in Taiwan. BMJ Open, 5(11): e008214.

Chen, C.C. & Cheng, S.H. 2016. Potentially Inappropriate Medication and Health Care Outcomes: An Instrumental Variable Approach. Health Services Research, 51(4): 1670–1691.

Clyne, B., Fitzgerald, C., Quinlan, A., Hardy, C., Galvin, R., Fahey, T. & Smith, S.M. 2016a. Interventions to Address Potentially Inappropriate Prescribing in Community-Dwelling Older Adults: A Systematic Review of Randomized Controlled Trials. Journal of the American Geriatrics Society, 64(6): 1210–1222.

Clyne, B., Cooper, J.A., Hughes, C.M., Fahey, T., Smith, S.M. & on behalf of the OPTI-SCRIPT,study team 2016b. Potentially inappropriate or specifically appropriate?' Qualitative evaluation of general practitioners views on prescribing, polypharmacy and potentially inappropriate prescribing in older people. BMC Family Practice, 17(109), doi: 10.1186/s12875-016-0507-y.

Cox, D.R. 1972. Regression Models and Life-Tables. Journal of the Royal Statistical Society. Series B (Methodological), 34(2): 187–220.

Cullinan, S., Fleming, A., O'Mahony, D., Ryan, C., O'Sullivan, D., Gallagher, P. & Byrne, S. 2014a. Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized patients: A qualitative study. British Journal of Clinical Pharmacology, 79(5): 860–869.

Cullinan, S., O'Mahony, D., Fleming, A. & Byrne, S. 2014b. A meta-synthesis of potentially inappropriate prescribing in older patients. Drugs & Aging, 31(8): 631–638.

Curtis, L.H., Ostbye, T., Sendersky, V., Hutchison, S., Dans, P.E., Wright, A., Woosley, R.L. & Schulman, K.A. 2004. Inappropriate prescribing for elderly Americans in a large outpatient population. Archives of Internal Medicine, 164(15): 1621–1625.

Dalleur, O., Feron, J.M. & Spinewine, A. 2014. Views of general practitioners on the use of STOPP&START in primary care: a qualitative study. Acta Clinica Belgica, 69(4): 251–261.

Danaei, G., Tavakkoli, M. & Hernan, M.A. 2012. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. American Journal of Epidemiology, 175(4): 250–262.

Deb, P., Norton, E.C. & Manning, W.G. 2017. Health econometrics using Stata. Stata Press, College Station, TX, 201–219.

Denton, M., Prus, S. & Walters, V. 2004. Gender differences in health: a Canadian study of the psychosocial, structural and behavioural determinants of health. Social Science & Medicine (1982), 58(12): 2585–2600.

Dimitrow, M.S., Airaksinen, M.S., Kivelä, S.L., Lyles, A. & Leikola, S.N. 2011. Comparison of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older: a systematic review. Journal of the American Geriatrics Society, 59(8): 1521–1530.

Dimitrow, M., Leikola, S., Kivelä, S. L., Airaksinen, M., Mykkänen, S., & Puustinen, J. 2013. Iäkkäiden hoidossa vältettävät lääkkeet: katsaus suosituksiin (Inappropriate medication use among the aged. review of the criteria). Duodecim; Lääketieteellinen Aikakauskirja, 129(11): 1159–1166.

Duodecim 2010. Current Care: Memory disorders. In Finnish with English summary. Available at: http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00081 [2016, February 22].

Endres, H.G., Kaufmann-Kolle, P., Steeb, V., Bauer, E., Böttner, C. & Thürmann, P. 2015. Association between Potentially Inappropriate Medication (PIM) Use and Risk of Hospitalization in Older Adults: An Observational Study Based on Routine Data Comparing PIM Use with Use of PIM Alternatives. PLoS ONE, 11(2): e0146811.

Ferner, R.E. & Aronson, J.K. 2006. Clarification of terminology in medication errors: definitions and classification. Drug Safety, 29(11): 1011–1022.

Fialová, D., Topinkova, E., Gambassi, G., Finne-Soveri, H., Jonsson, P.V., Carpenter, I., Schroll, M., Onder, G., Sorbye, L.W., Wagner, C., Reissigova, J., Bernabei, R. & AdHOC Project Research Group 2005. Potentially inappropriate medication use among elderly home care patients in Europe. JAMA: the Journal of the American Medical Association, 293(11): 1348–1358.

Fick, D.M., Mion, L.C., Beers, M.H. & L Waller, J. 2008. Health outcomes associated with potentially inappropriate medication use in older adults. Research in Nursing & Health, 31(1): 42–51.

Finnish Advisory Board on Research Integrity 2012. Responsible conduct of research and procedures for handling allegations of misconduct in Finland. Available at: http://www.tenk.fi/sites/tenk.fi/files/HTK_ohje_2012.pdf [2017, 7/7].

Finnish Medicines Agency. 2015. Meds75+. Available at: http://www.fimea.fi/web/en/databases_and_registeries/medicines_information/database_of_medication_for_the_elderly [2017, 9/5].

Flynn, E., Schell, K.L. & Rickles, J.O. 2010. A Psychosocial Approach to Medication Errors in Rickles, N.M., Rickles, N.M., Wertheimer, A.I. & Smith, M.C. (ed.) Social and behavioral aspects of pharmaceutical care, 2nd edition. Jones and Bartlett Publishers, Sudbury, Mass, 399–426.

Fogelholm, M., Valve, R., Absetz, P., Heinonen, H., Uutela, A., Patja, K., Karisto, A., Konttinen, R., Mäkelä, T., Nissinen, A., Jallinoja, P., Nummela, O. & Talja, M. 2006. Rural-urban differences in health and health behaviour: a baseline description of a community health-promotion programme for the elderly. Scandinavian Journal of Public Health, 34(6): 632–640.

Forma L, Rissanen P, Aaltonen M, Raitanen J & Jylhä M. 2009. Age and closeness of death as determinants of health and social care utilization: a case-control study. European Journal of Public Health, 19(3): 313–318.

Frankenthal, D., Israeli, A., Caraco, Y., Lerman, Y., Kalendaryev, E., Zandman-Goddard, G. & Lerman, Y. 2017. Long-Term Outcomes of Medication Intervention Using the Screening Tool of Older Persons Potentially Inappropriate Prescriptions Screening Tool to Alert Doctors to Right Treatment Criteria. Journal of the American Geriatrics Society, 65(2): e33–e38.

Fromm, M.F., Maas, R., Tumena, T. & Gassmann, K.G. 2013. Potentially inappropriate medications in a large cohort of patients in geriatric units: association with clinical and functional characteristics. European Journal of Clinical Pharmacology, 69(4): 975–984.

Furu, K., Wettermark, B., Andersen, M., Martikainen, J.E., Almarsdottir, A.B. & Sørensen, H.T. 2010. The Nordic countries as a cohort for pharmacoepidemiological research. Basic & Clinical Pharmacology & Toxicology, 106(2): 86–94.

García-Gollarte, F., Baleriola-Júlvez, J., Ferrero-López, I., Cuenllas-Díaz, A. & Cruz-Jentoft, A.J. 2014. An Educational Intervention on Drug Use in Nursing Homes Improves Health Outcomes Resource Utilization and Reduces Inappropriate Drug Prescription. Journal of the American Medical Directors Association, 15(12): 885–891.

Gerritsen, A.A. & Deville, W.L. 2009. Gender differences in health and health care utilisation in various ethnic groups in the Netherlands: a cross-sectional study. BMC Public Health, 9(109), doi: 10.1186/1471-2458-9-109.

Gillespie, P., Clyne, B., Raymakers, A., Fahey, T., Hughes, C.M. & Smith, S.M. 2017. Reducing Potentially Inappropriate Prescribing for Older People in Primary Care: Cost-Effectiveness of the Opti-Script Intervention. International Journal of Technology Assessment in Health Care, 33(4): 494–503.

Gnjidic, D., Hilmer, S.N., Blyth, F.M., Naganathan, V., Waite, L., Seibel, M.J., McLachlan, A.J., Cumming, R.G., Handelsman, D.J. & Le Couteur, D.G. 2012. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. Journal of Clinical Epidemiology, 65(9): 989–995.

Goulding, M.R. 2004. Inappropriate Medication Prescribing for Elderly Ambulatory Care Patients. Archives of Internal Medicine, 164(3): 305–312.

Grina, D. & Briedis, V. 2017. The use of potentially inappropriate medications among the Lithuanian elderly according to Beers and EU(7)-PIM list - a nationwide cross-sectional study on reimbursement claims data. Journal of clinical pharmacy and therapeutics, 42(2): 195–200.

Guaraldo, L., Cano, F.G., Damasceno, G.S. & Rozenfeld, S. 2011. Inappropriate medication use among the elderly: A systematic review of administrative databases. BMC Geriatrics, November 30, 11:79, doi: 10.1186/1471-2318-11-79.

Haider, S.I., Johnell, K., Weitoft, G.R., Thorslund, M. & Fastbom, J. 2009. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. Journal of the American Geriatrics Society, 57(1): 62–69.

Hamilton, H., Gallagher, P., Ryan, C., Byrne, S. & O'Mahony, D. 2011. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Archives of Internal Medicine, 171(11): 1013–1019.

Hanlon, J.T., Fillenbaum, G.G., Kuchibhatla, M., Artz, M.B., Boult, C., Gross, C.R., Garrard, J. & Schmader, K.E. 2002. Impact of inappropriate drug use on mortality and functional status in representative community dwelling elders. Medical Care, 40(2): 166–176.

Hannikainen, K. 2018. Ikääntyneiden sosiaali- ja terveyspalveluiden tarve ja käyttö eroavat tulotason mukaan (The need and use of social- and health care services varies by income level in older people). Suomen sosiaalinen tila 1/2018. Tutkimuksesta tiiviisti 3/2018. Terveyden ja hyvinvoinnin laitos, Helsinki. Available at: http://www.julkari.fi/handle/10024/136061 [2018, 3/28].

Harrell, F.E., Jr. 2001. Regression modeling strategies: with applications to linear models, logistic regression and survival analysis. Springer, New York (NY), pp. 389, 465.

Hartikainen, S. & Ahonen, J. 2011. Iäkkäiden lääkityksen tietokanta tukee lääkevalintoja (Database of medication for elderly supports medication decision-making). Sic! Lääketietoa Fimeasta, no. 1/2011.

Hedna, K., Hakkarainen, K.M., Gyllensten, H., Jonsson, A.K., Petzold, M. & Hagg, S. 2015. Potentially inappropriate prescribing and adverse drug reactions in the elderly: a population-based study. European journal of clinical pharmacology, 71(12): 1525–1533.

Heider, D., Matschinger, H., Meid, A.D., Quinzler, R., Adler, J.B., Günster, C., Haefeli, W.E. & König, H.H. 2017. Health Service Use, Costs, and Adverse Events Associated with Potentially Inappropriate Medication in Old Age in Germany: Retrospective Matched Cohort Study. Drugs & Aging, 34(4): 289–301.

Henschel, F., Redaelli, M., Siegel, M. & Stock, S. 2015. Correlation of Incident Potentially Inappropriate Medication Prescriptions and Hospitalization: An Analysis Based on the PRISCUS List. Drugs - Real World Outcomes, 2(3): 249–259.

Hill-Taylor, B., Sketris, I., Hayden, J., Byrne, S., O'Sullivan, D. & Christie, R. 2013. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. Journal of clinical pharmacy and therapeutics, 38(5): 360–372.

Hill-Taylor, B., Walsh, K.A., Stewart, S., Hayden, J., Byrne, S. & Sketris, I.S. 2016. Effectiveness of the STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment) criteria: systematic review and meta-analysis of randomized controlled studies. Journal of clinical pharmacy and therapeutics, 41(2), 158–169.

Holmes, H.M., Luo, R., Kuo, Y.F., Baillargeon, J. & Goodwin, J.S. 2013. Association of potentially inappropriate medication use with patient and prescriber characteristics in Medicare Part D. Pharmacoepidemiology and drug safety, 22(7): 728–734.

Holmes, W.M. 2014. Using Propensity Scores in Quasi-Experimental Designs. SAGE Publications, Ltd, 55 City Road, London, 107–109.

Holt, S., Schmiedl, S. & Thürmann, P.A. 2010. Potentially inappropriate medications in the elderly: the PRISCUS list. Deutsches Arzteblatt International, 107(31–32): 543–551.

Holt-Lunstad, J., Smith, T.B., Baker, M., Harris, T. & Stephenson, D. 2015. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspectives on psychological science: a Journal of the Association for Psychological Science, 10(2): 227–237.

Hosia-Randell, H.M., Muurinen, S.M. & Pitkälä, K.H. 2008. Exposure to potentially inappropriate drugs and drug-drug interactions in elderly nursing home residents in Helsinki, Finland: a cross-sectional study. Drugs & Aging, 25(8): 683–692.

Hovstadius, B., Petersson, G., Hellstrom, L. & Ericson, L. 2014. Trends in inappropriate drug therapy prescription in the elderly in Sweden from 2006 to 2013: assessment using national indicators. Drugs & Aging, 31(5): 379–386.

Huisman, M., Kunst, A.E., Andersen, O., Bopp, M., Borgan, J.K., Borrell, C., Costa, G., Deboosere, P., Desplanques, G., Donkin, A., Gadeyne, S., Minder, C., Regidor, E., Spadea, T., Valkonen, T. & Mackenbach, J.P. 2004. Socioeconomic inequalities in mortality among elderly people in 11 European populations. Journal of epidemiology and community health, 58(6): 468–475.

Hyttinen, V., Jyrkkä, J. & Valtonen, H. 2016. A Systematic Review of the Impact of Potentially Inappropriate Medication on Health Care Utilization and Costs among Older Adults. Medical Care, 54(10): 950–964.

Ie, K., Felton, M., Springer, S., Wilson, S.A. & Albert, S.M. 2017. Physician Factors Associated with Polypharmacy and Potentially Inappropriate Medication Use. Journal of the American Board of Family Medicine: JABFM, 30(4): 528–536.

Jauhonen H-M., Jyrkkä J. & Koski-Pirilä A. 2018. Lääkkeiden käytön ja kustannusten kehitystä seurataan indikaattoritiedon avulla (The development of medication use and costs are monitored by information on indicators). SIC! Lääketietoa Fimeasta, no. 2/2018.

Jano, E. & Aparasu, R.R. 2007. Healthcare outcomes associated with Beers' criteria: A systematic review. Annals of Pharmacotherapy, 41(3): 438–448.

Jiron, M., Pate, V., Hanson, L.C., Lund, J.L., Jonsson Funk, M. & Sturmer, T. 2016. Trends in Prevalence and Determinants of Potentially Inappropriate Prescribing in the United States: 2007 to 2012. Journal of the American Geriatrics Society, 64(4): 788–797.

Johnell, K. 2015. Inappropriate Drug Use in People with Cognitive Impairment and Dementia: A Systematic Review. Current Clinical Pharmacology, 10(3): 178–184.

Joung, I.M., van der Meer, J.B. & Mackenbach, J.P. 1995. Marital status and health care utilization. International journal of epidemiology, 24(3): 569–575.

Jyrkkä, J., Ahonen, J., Antikainen, R., Hartikainen, S., Hosia, H., Parkkisenniemi-Kinnunen, U. & Huupponen, R. 2017. Lääke75+-tietokanta auttaa vanhusten lääkehoidossa (Meds75+ database helps in planning the drug treatment of older persons). Suomen Lääkärilehti, 72(13): 874–875.

Jyrkkä, J. 2011. Drug use and polypharmacy in elderly persons. Publications of the University of Eastern Finland. Dissertations in Health Sciences 47. University of Eastern Finland, Kuopio.

Kapiainen, S., Väisänen, A. & Haula, T. 2014. Unit costs in social and health care in Finland in 2011. Report 3/2014. National Institute for Health and Welfare. Available at: http://www.julkari.fi/bitstream/handle/10024/114683/THL_RAPO3_2014_web.pdf?sequence=1 [2017, 12/21].

Kaplan, R.M. & Kronick, R.G. 2006. Marital status and longevity in the United States population. Journal of epidemiology and community health, 60(9): 760–765.

Kiel, W.J. & Phillips, S.W. 2017. Impact of Pharmacist-Conducted Comprehensive Medication Reviews for Older Adult Patients to Reduce Medication Related Problems. Pharmacy (Basel, Switzerland), 6(1), doi: 10.3390/pharmacy6010002.

Kivelä, S. and Räihä, I. 2007, Iäkkäiden lääkehoito (Medication use in older people), Kapseli 35.

Klarin, I., Wimo, A. & Fastbom, J. 2005. The association of inappropriate drug use with hospitalisation and mortality: A population-based study of the very old. Drugs and Aging, 22(1): 69–82.

Korhonen, M. J., Ilomäki, J., Sluggett, J. K., Brookhart, M. A., Visvanathan, R., Cooper, T., Bell, J. S. 2018. Selective prescribing of statins and the risk of mortality, hospitalizations, and falls in aged care services. Journal of Clinical Lipidology, 12(3), 652-661. doi:S1933-2874(18)30063-1

Koyama, A., Steinman, M., Ensrud, K., Hillier, T.A. & Yaffe, K. 2014. Long-term cognitive and functional effects of potentially inappropriate medications in older women. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 69(4): 423–429.

Kuhn-Thiel, A., Weiβ, C., Wehling, M. & The FORTA authors/expert panel members. 2013. Consensus Validation of the FORTA (Fit fOR The Aged) List: A Clinical Tool for Increasing the Appropriateness of Pharmacotherapy in the Elderly. Drugs & Aging, 31(2): 131–140.

Lai, H.Y., Hwang, S.J., Chen, Y.C., Chen, T.J., Lin, M.H. & Chen, L.K. 2009. Prevalence of the prescribing of potentially inappropriate medications at ambulatory care visits by elderly patients covered by the Taiwanese National Health Insurance program. Clinical Therapeutics, 31(8): 1859–1870.

Lankila, T., Nayha, S., Rautio, A., Nordstrom, T., Koiranen, M., Taanila, A. & Rusanen, J. 2012. Self-reported health in urban-rural continuum: a grid-based analysis of Northern Finland Birth Cohort 1966. International Journal of Public Health, 57(3): 525–533.

Laroche, M.L., Charmes, J.P. & Merle, L. 2007. Potentially inappropriate medications in the elderly: a French consensus panel list. European Journal of Clinical Pharmacology, 63(8): 725–731.

Lau, D.T., Mercaldo, N.D., Shega, J.W., Rademaker, A. & Weintraub, S. 2011. Functional decline associated with polypharmacy and potentially inappropriate medications in community-dwelling older adults with dementia. American Journal of Alzheimer's disease and Other Dementias, 26(8): 606–615.

Leikola, S., Dimitrow, M., Lyles, A., Pitkälä, K. & Airaksinen, M. 2011. Potentially inappropriate medication use among Finnish non-institutionalized people aged >/=65 years: a register-based, cross-sectional, national study. Drugs & Aging, 28(3): 227–236.

Li, M. 2013. Using the Propensity Score Method to Estimate Causal Effects: A Review and Practical Guide. Organizational Research Methods, 16(2): 188–226.

Lim, Y., Kim, H., Choi, J., Lee, J.S., Ahn, A., Oh, E., Cho, D. & Kweon, H. 2016. Potentially Inappropriate Medications by Beers Criteria in Older Outpatients: Prevalence and Risk Factors. Korean Journal of Family Medicine, 37(6): 329–333.

Lu, W.H., Wen, Y.W., Chen, L.K. & Hsiao, F.Y. 2015. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: A retrospective cohort study. CMAJ, 187(4): E130–E137.

Lund, B.C., Carnahan, R.M., Egge, J.A., Chrischilles, E.A. & Kaboli, P.J. 2010. Inappropriate prescribing predicts adverse drug events in older adults. Annals of Pharmacotherapy, 44(6), 957–963.

Lund, B.C., Charlton, M.E., Steinman, M.A. & Kaboli, P.J. 2013. Regional differences in prescribing quality among elder veterans and the impact of rural residence. The Journal of rural health: official journal of the American Rural Health Association and the National Rural Health Care Association, 29(2): 172–179.

Malmivaara, A. 2015. Benchmarking controlled trial—a novel concept covering all observational effectiveness studies. Annals of Medicine 47(4): 332–340

Manderbacka, K., Häkkinen, U., Nguyen, L., Pirkola, S., Ostamo, A. & Keskimäki, I. 2009. Health care services in Palosuo, H., Koskinen, S., Lahelma, E., Kostiainen, E., Prättälä, R., Martelin, T., Ostamo, A., Keskimäki, I., Sihto, M. & Linnanmäki, E. (ed.) Health inequalities in Finland: Trends in socioeconomic health differences 1980–2005, 9th edition, Ministry of Social Affairs and Health Publications, Helsinki, Finland, 178–194.

Mantel-Teeuwisse, A. K., Klungel, O. H., Verschuren, W. M., Porsius, A., & de Boer, A. 2001. Comparison of different methods to estimate prevalence of drug use by using pharmacy records. Journal of Clinical Epidemiology, 54(11): 1181–1186. doi:S0895-4356(01)00396-1

Manteuffel, M., Williams, S., Chen, W., Verbrugge, R.R., Pittman, D.G. & Steinkellner, A. 2014. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. Journal of Women's Health, 23(2): 112–119.

Miller, G.E., Sarpong, E.M., Davidoff, A.J., Yang, E.Y., Brandt, N.J. & Fick, D.M. 2016. Determinants of Potentially Inappropriate Medication Use among Community-Dwelling Older Adults. Health Services Research, 52(4): 1534–1549.

Ministry of Social Affairs and Health 2011. Medicines Policy 2020. Towards efficient, safe, rational and cost-effective use of medicines [Homepage of Sosiaali- ja terveysministeriö], [Online]. Available at: http://apps.who.int/medicinedocs/documents/s19762en/s19762en.pdf [2018, 4/20].

Ministry of Social Affairs and Health 2018a. In Hämeen-Anttila, K., Närhi, U. & Tahvanainen, H. (ed.) Rational Pharmacotherapy Action Plan. Reports and Memorandums of the Ministry of Social Affairs and Health 15/2018. Helsinki, 2018.

Ministry of Social Affairs and Health 2018b. In Ruokoniemi, P. (ed.) Rational prescribing, dispensing and use of medicines in current and future healthcare and social welfare structures. Reports and Memorandums of the Ministry of Social Affairs and Health 12/2018. Helsinki, 2018.

Mo, L., Ding, D., Pu, S., Liu, Q., Li, H., Dong, B., Yang, X. & He, J. 2015. Patients Aged 80 Years or Older are Encountered More Potentially Inappropriate Medication Use. Chinese Medical Journal, 129(1): 22–27.

Morgan, S.G., Weymann, D., Pratt, B., Smolina, K., Gladstone, E.J., Raymond, C. & Mintzes, B. 2016. Sex differences in the risk of receiving potentially inappropriate prescriptions among older adults. Age and Ageing, 45(4): 535–542.

Moriarty, F., Bennett, K., Cahir, C., Kenny, R.A. & Fahey, T. 2016. Potentially inappropriate prescribing according to STOPP and START and adverse outcomes in community-dwelling older people: a prospective cohort study. British journal of clinical pharmacology, 82(3): 849–857.

Moriarty, F., Bennett, K., Fahey, T., Kenny, R.A. & Cahir, C. 2015. Longitudinal prevalence of potentially inappropriate medicines and potential prescribing omissions in a cohort of community-dwelling older people. European Journal of Clinical Pharmacology, 71(4): 473–482.

Morin, L., Laroche, M., Texier, G. & Johnell, K. 2016. Prevalence of Potentially Inappropriate Medication Use in Older Adults Living in Nursing Homes: A Systematic Review. Journal of the American Medical Directors Association, 17(9): 862.e1–862.e9.

Muhlack, D.C., Hoppe, L.K., Weberpals, J., Brenner, H. & Schottker, B. 2017. The Association of Potentially Inappropriate Medication at Older Age with Cardiovascular Events and Overall Mortality: A Systematic Review and Meta-Analysis of Cohort Studies. Journal of the American Medical Directors Association, 18(3): 211–220.

Narayan, S.W. & Nishtala, P.S. 2015. Associations of Potentially Inappropriate Medicine Use with Fall-Related Hospitalisations and Primary Care Visits in Older New Zealanders: A Population-Level Study Using the Updated 2012 Beers Criteria. Drugs - Real World Outcomes, 2(2): 137–141.

National Institute for Health and Welfare 2016a. Hoitoilmoitusjärjestelmä (Hilmo) (Care Register for Health Care). Available at: https://www.thl.fi/fi/tilastot/tiedonkeruut/hoitoilmoitusjarjestelma-hilmo [2017, 7/13].

National Institute for Health and Welfare 2016b. Hilmo - Sosiaalihuollon ja terveydenhuollon hoitoilmoitus: Määrittelyt ja ohjeistus (Hilmo – Care Register for Social and Health Care: Definitions and Instructions). Available at: https://www.julkari.fi/bitstream/handle/10024/130826/Hilmo-opas_2016_korjattu_WEB_14092016.pdf?sequence=7 [2018, 3/26].

National Institute for Health and Welfare 2011. Third edition of the Finnish version of the International Statistical Classification of Diseases and Related Health Problems. Available at: https://www.julkari.fi/bitstream/handle/10024/80324/15c30d65-2b96-41d7-aca8-1a05aa8a0a19.pdf?sequence=1 [2017, 8/16].

Nebeker JR, Barach P, Samore MH. 2004. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med, 140(10): 795–801.

Noro, A.,M., Häkkinen, U.,T. & Laitinen, O.,J. 1999. Determinants of health service use and expenditure among the elderly Finnish population. European Journal of Public.Health., 9(3): 174–180.

Nothelle, S.K., Sharma, R., Oakes, A.H., Jackson, M. & Segal, J.B. 2017. Determinants of Potentially Inappropriate Medication Use in Long-Term and Acute Care Settings: A Systematic Review. Journal of the American Medical Directors Association, 18(9): 806.e1–806.e17.

Nyborg, G., Straand, J. & Brekke, M. 2012. Inappropriate prescribing for the elderly--a modern epidemic?. European Journal of Clinical Pharmacology, 68(7): 1085–1094.

O'Connor, M.N., O'Sullivan, D., Gallagher, P.F., Eustace, J., Byrne, S. & O'Mahony, D. 2016. Prevention of Hospital-Acquired Adverse Drug Reactions in Older People Using Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment Criteria: A Cluster Randomized Controlled Trial. Journal of the American Geriatrics Society, 64(8): 1558–1566.

OECD 2018. Life expectancy at birth (indicator). doi: 10.1787/27e0fc9d-en. Available at: https://data.oecd.org/healthstat/life-expectancy-at-birth.htm [2018, 3/27].

O'Mahony, D., O'Sullivan, D., Byrne, S., O'Connor, M.N., Ryan, C. & Gallagher, P. 2015. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and Ageing, 44(2): 213–218.

Opondo, D., Eslami, S., Visscher, S., de Rooij, S.E., Verheij, R., Korevaar, J.C., et al. 2012. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. PLoS One, 7(8):e43617.

Page, R.L. & Ruscin, J. 2006. The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. American Journal Geriatric Pharmacotherapy, 4(4): 297–305.

Patel, T., Slonim, K. & Lee, L. 2017. Use of potentially inappropriate medications among ambulatory home-dwelling elderly patients with dementia: A review of the literature. Canadian Pharmacists Journal: CPJ = Revue des pharmaciens du Canada: RPC, 150(3): 169–183.

Patrick, A.R., Schneeweiss, S., Brookhart, M.A., Glynn, R.J., Rothman, K.J., Avorn, J. & Sturmer, T. 2011. The implications of propensity score variable selection strategies in pharmacoepidemiology: an empirical illustration. Pharmacoepidemiology and drug safety, 20(6): 551–559.

Personal Data Act 22.4.1999/523.

Pitkälä, K.H., Juola, A.-L., Kautiainen, H., Soini, H., Finne-Soveri, U.H., Bell, J.S. & Björkman, M. 2014. Education to Reduce Potentially Harmful Medication Use among Residents of Assisted Living Facilities: A Randomized Controlled Trial. Journal of the American Medical Directors Association, 15(12): 892–898.

Pohontsch, N.J., Heser, K., Löffler, A., Haenisch, B., Parker, D., Luck, T., Riedel-Heller, S., Maier, W., Jessen, F. & Scherer, M. 2017. General practitioners' views on (long-term) prescription and use of problematic and potentially inappropriate medication for oldest-old patients - A qualitative interview study with GPs (CIM-TRIAD study). BMC Family Practice, 18(1): 22, doi: 10.1186/s12875-017-0595-3.

Price, S.D., Holman, C.D., Sanfilippo, F.M. & Emery, J.D. 2014. Are older Western Australians exposed to potentially inappropriate medications according to the Beers Criteria? A 13-year prevalence study. Australasian Journal on Ageing, 33(3): E39–E48.

Projovic, I., Vukadinovic, D., Milovanovic, O., Jurisevic, M., Pavlovic, R., Jacovic, S., Jankovic, S. & Stefanovic, S. 2016. Risk factors for potentially inappropriate prescribing to older patients in primary care. European Journal of Clinical Pharmacology, 72(1): 93–107.

Raivio, M.M., Laurila, J.V., Strandberg, T.E., Tilvis, R.S. & Pitkälä, K.H. 2006. Use of inappropriate medications and their prognostic significance among in-hospital and nursing home patients with and without dementia in Finland. Drugs and Aging, 23(4): 333–343.

Ramaswamy, R., Maio, V., Diamond, J.J., Talati, A.R., Hartmann, C.W., Arenson, C. & Roehl, B. 2011. Potentially inappropriate prescribing in elderly: assessing doctor knowledge, confidence and barriers. Journal of Evaluation in Clinical Practice, 17(6): 1153–1159.

Ray, W.A. 2003. Evaluating medication effects outside of clinical trials: new-user designs. American Journal of Epidemiology, 158(9): 915–920.

Read, S., Grundy, E. & Foverskov, E. 2015. Socio-economic position and subjective health and well-being among older people in Europe: a systematic narrative review. Aging & Mental Health, 20(5): 529–542.

Reeve, E., To, J., Hendrix, I., Shakib, S., Roberts, M.S. & Wiese, M.D. 2013. Patient barriers to and enablers of deprescribing: a systematic review. Drugs & Aging, 30(10): 793–807.

Renom-Guiteras, A., Meyer, G. & Thürmann, P.A. 2015. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. European Journal of Clinical Pharmacology, 71(7): 861–875.

Renom-Guiteras, A., Thürmann, P.A., Miralles, R., Klaassen-Mielke, R., Thiem, U., Stephan, A., Bleijlevens, M.H.C., Jolley, D., Leino-Kilpi, H., Rahm Hallberg, I., Saks, K., Soto-Martin, M., Zabalegui, A., Meyer, G. & RightTimePlaceCare Consortium 2018. Potentially inappropriate medication among people with dementia in eight European countries. Age and Ageing, 47(1): 68–74.

Rikala, M., Hartikainen, S., Sulkava, R., & Korhonen, M. J. 2010. Validity of the Finnish prescription register for measuring psychotropic drug exposures among elderly Finns: A population-based intervention study. Drugs & Aging, 27(4), 337-349. doi:10.2165/11315960-000000000-00000

Roberts, A.W., Dusetzina, S.B. & Farley, J.F. 2015. Revisiting the washout period in the incident user study design: why 6-12 months may not be sufficient. Journal of Comparative Effectiveness Research, 4(1): 27–35.

Rothberg, M.B., Pekow, P.S., Liu, F., Korc-Grodzicki, B., Brennan, M.J., Bellantonio, S., Heelon, M. & Lindenauer, P.K. 2008. Potentially inappropriate medication use in hospitalized elders. Journal of Hospital Medicine, 3(2): 91–102.

Saastamoinen, L.K. & Verho, J. 2013. Drug expenditure of high-cost patients and their characteristics in Finland. The European journal of health economics: HEPAC: Health Economics in Prevention and Care, 14(3): 495–502.

Saastamoinen, L. K., & Verho, J. 2015. Register-based indicators for potentially inappropriate medication in high-cost patients with excessive polypharmacy. Pharmacoepidemiology and Drug Safety, 24(6): 610–618, doi:10.1002/pds.3764

Saastamoinen, L.K., Hannes, E. & Klaukka, T.J. 2008. Repeat prescribing processes in primary care: a qualitative study. International Journal of Pharmacy Practice, 16(3): 155–167.

Sheiner, L. 2011. Inter-generational aspects of health care in Glied, S. & Smith, P.C. (ed.) The Oxford Handbook of Health Economics, Oxford University Press, New York, the United States, 870–889.

Simon, H.A. 1990. Bounded Rationality in Eatwell, J., Milgate, M. & Newman, P. (ed.) Utility and Probability, Palgrave Macmillan UK, London, 15–18.

Social Insurance Institution. 2014. Information on medication purchases (in Finnish). Available at: http://www.kela.fi/documents/10180/243147/Laakeostotiedot_aineistokuvaus_kela.pdf/025e7fae-b971-4d39-8336-e9e5bca5c793 [2017, 7/13].

Social Insurance Institution 2018. Lääkemääräyspalaute (Prescription feedback). Available at: http://www.kela.fi/reseptit [2018, 5/17].

Social Insurance Institution 2013. Lääkkeiden korvausoikeudet (Permits for medication reimbursement). Available at: http://www.kela.fi/documents/10180/243147/Laakkeiden_korvausoikeudet_aineistokuvaus_kela.pdf/8843d8b8-ef4f-4faa-a637-e0aa716ba31e [2017, 7/13].

Spinewine, A., Schmader, K.E., Barber, N., Hughes, C., Lapane, K.L., Swine, C. & Hanlon, J.T. 2007. Appropriate prescribing in elderly people: how well can it be measured and optimised?. Lancet (London, England), 370(9582): 173–184.

Statistics Finland 2017. Remote access use (Fiona). Available at: https://tilastokeskus.fi/tup/mikroaineistot/etakaytto_en.html [2017, 11/23].

Stock, S., Redaelli, M., Simic, D., Siegel, M. & Henschel, F. 2014. Risk factors for the prescription of potentially inappropriate medication (PIM) in the elderly : an analysis of sickness fund routine claims data from Germany. Wiener Klinische Wochenschrift, 126(19–20): 604–612.

Stockl, K.M., Le, L., Zhang, S. & Harada, A.S. 2010. Clinical and economic outcomes associated with potentially inappropriate prescribing in the elderly. The American Journal of Managed Care, 16(1): e1–e10.

Sund, R. 2012. Quality of the Finnish Hospital Discharge Register: a systematic review. Scandinavian Journal of Public Health, 40(6): 505–515.

Sund, R., Juntunen, M., Luthje, P., Huusko, T. & Häkkinen, U. 2011. Monitoring the performance of hip fracture treatment in Finland. Annals of Medicine, 43(Suppl. 1): S39–46.

Sund, R., Nurmi-Luthje, I., Luthje, P., Tanninen, S., Narinen, A. & Keskimäki, I. 2007. Comparing properties of audit data and routinely collected register data in case of performance assessment of hip fracture treatment in Finland. Methods of Information in Medicine, 46(5): 558–566.

Suominen-Taipale, A., Martelin, T., Koskinen, S., Holmen, J. & Johnsen, R. 2006. Gender differences in health care use among the elderly population in areas of Norway and Finland. A cross-sectional analysis based on the HUNT study and the FINRISK Senior Survey. BMC Health Services Research, September 4, 6: 110.

Taipale, H., Tanskanen, A., Koponen, M., Tolppanen, A., Tiihonen, J. & Hartikainen, S. 2016. Agreement between PRE2DUP register data modeling method and comprehensive drug use interview among older persons. Clinical Epidemiology, October 11, 8: 363–371.

Tanskanen, A., Taipale, H., Koponen, M., Tolppanen, A.M., Hartikainen, S., Ahonen, R. & Tiihonen, J. 2017. Drug exposure in register-based research-An expert-opinion based evaluation of methods. PloS One, 12(9): e0184070.

Tanskanen, A., Taipale, H., Koponen, M., Tolppanen, A.M., Hartikainen, S., Ahonen, R. & Tiihonen, J. 2015. From prescription drug purchases to drug use periods - a second generation method (PRE2DUP). BMC Medical Informatics and Decision Making, 15(21), doi: 10.1186/s12911-015-0140-z.

Tolppanen, A.M., Taipale, H., Koponen, M., Lavikainen, P., Tanskanen, A., Tiihonen, J. & Hartikainen, S. 2016. Cohort profile: the Finnish Medication and Alzheimer's disease (MEDALZ) study. BMJ open, 6(7): e012100.

Tommelein, E., Mehuys, E., Petrovic, M., Somers, A., Colin, P. & Boussery, K. 2015. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. European Journal of Clinical Pharmacology, 71(12): 1415–1427.

Valtorta, N.K., Moore, D.C., Barron, L., Stow, D. & Hanratty, B. 2018. Older Adults' Social Relationships and Health Care Utilization: A Systematic Review, American Journal of Public Health, 108(4):e1–e10.

van der Stelt, C.A., Vermeulen Windsant-van den Tweel, A.M., Egberts, A.C., van den Bemt, P.M., Leendertse, A.J., Hermens, W.A., van Marum, R.J. & Derijks, H.J. 2016. The Association Between Potentially Inappropriate Prescribing and Medication-Related Hospital Admissions in Older Patients: A Nested Case Control Study. Drug Safety, 39(1): 79–87.

Varga, S., Alcusky, M., Keith, S.W., Hegarty, S.E., Del Canale, S., Lombardi, M. & Maio, V. 2017. Hospitalization Rates during Potentially Inappropriate Medication Use in a Large Population-Based Cohort of Older Adults. British Journal of Clinical Pharmacology, 83(11): 2572–2580.

Vartiainen, A., Hyttinen, V., Jyrkkä, J., Saastamoinen, L.K. & Valtonen, H. 2017. Iäkkäät käyttävät vältettäviä lääkkeitä yleisesti (Potentially inappropriate medicine use is common among older adults). Suomen Lääkärilehti, 72(49): 29–35.

Vieira de Lima, T.J., Garbin, C.A., Garbin, A.J., Sumida, D.H. & Saliba, O. 2013. Potentially inappropriate medications used by the elderly: prevalence and risk factors in Brazilian care homes. BMC Geriatrics, 13(52), doi: 10.1186/1471-2318-13-52.

Vikum, E., Krokstad, S. & Westin, S. 2012. Socioeconomic inequalities in health care utilisation in Norway: the population-based HUNT3 survey. International Journal for Equity in Health, 11(48), doi: 10.1186/1475-9276-11-48.

Voigt, K., Gottschall, M., Köberlein-Neu, J., Schübel, J., Quint, N. & Bergmann, A. 2016. Why do family doctors prescribe potentially inappropriate medication to elderly patients?. BMC Family Practice, 17(93), doi: 10.1186/s12875-016-0482-3.

Wallace, E., McDowell, R., Bennett, K., Fahey, T. & Smith, S.M. 2017. Impact of Potentially Inappropriate Prescribing on Adverse Drug Events, Health Related Quality of Life and Emergency Hospital Attendance in Older People Attending General Practice: A Prospective Cohort Study. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 72(2): 271–277.

Wauters, M., Elseviers, M., Vaes, B., Degryse, J., Dalleur, O., Vander Stichele, R., Christiaens, T. & Azermai, M. 2016. Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality, and hospitalization in a cohort of community-dwelling oldest old. British Journal of Clinical Pharmacology, 82(5): 1382–1392.

WHO Collaborating Centre for Drug Statistics Methodology 2011. The Anatomical Therapeutic Chemical Classification System. Structure and principles. Available at: http://www.whocc.no/atc/structure_and_principles/ [2017, 1/20].

Willems, S., De Maesschalck, S., Deveugele, M., Derese, A. & De Maeseneer, J. 2005. Socio-economic status of the patient and doctor-patient communication: does it make a difference?. Patient Education and Counseling, 56(2): 139–146.

Woolcott, J.C., Richardson, K.J., Wiens, M.O., Patel, B., Marin, J., Khan, K.M. & Marra, C.A. 2009. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Archives of Internal Medicine, 169(21): 1952–1960.

Wucherer, D., Eichler, T., Hertel, J., Kilimann, I., Richter, S., Michalowsky, B., Thyrian, J.R., Teipel, S. & Hoffmann, W. 2017. Potentially Inappropriate Medication in Community-Dwelling Primary Care Patients who were Screened Positive for Dementia. Journal of Alzheimer's Disease : JAD, 55(2): 691–701.

Xing, L. 2016. Applied Ordinal Logistic Regression Using Stata®: From Single-Level to Multilevel Modeling. SAGE Publications, United States of America, 351.

Zhan, C., Sangl, J., Bierman, A.S., Miller, M.R., Friedman, B., Wickizer, S.W. & Meyer, G.S. 2001. Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. Jama, 286(22): 2823–2829.

Zheng, H. & Thomas, P.A. 2013. Marital Status, Self-Rated Health, and Mortality: Overestimation of Health or Diminishing Protection of Marriage?. Journal of Health and Social Behavior, 54(1): 128–143.

APPENDICES

APPENDIX 1. PIMS ACCORDING TO THE MEDS75+ DATABASE (YEAR 2010)

ATC code[1]	Medication
A02 Drugs for acid related disorders	
A02AD01	Ordinary salt combinations
A02BX02	Sucralfate
A02BX13	Alginic acid
A03 Drugs for functional gastrointestinal disorders	
A03BB01	Butylscopolamine
A03CA02	Clidinium and psycholeptics
A03DA02	Pitofenone and analgesics
A03FA01	Metoclopramide
A04 Antiemetics and antinauseants	
A04AD01	Scopolamine
A06 Drugs for constipation	
A06AB02 and A06AG02	Bisacodyl
A06AB06	Senna glycosides
A06AB08 and A06AB58	Sodium picosulfate (and combinations)
A06AG10	Docusate sodium, incl. combinations
A06AG11	Sodium lauryl sulfoacetate, incl. combinations
A10 Drugs used in diabetes	
A10BB01	Glibenclamide
C01 Cardiac therapy	
C01BA01	Quinidine
C01BA03	Disopyramide
C01BD01	Amiodarone
C02 Antihypertensives	
C02AC01	Clonidine
C02AC05	Moxonidine
C02CA01	Prazosin
C04 Peripheral vasodilators	
C04AD03	Pentoxifylline
C04AE01	Ergoloid mesylates
C07 Beta blocking agents	
C07AA03	Pindolol

C07AA05	Propranolol
C08 Calcium channel blockers	
C08DA01	Verapamil
C08DB01	Diltiazem
G04 Urologicals	
G04BD04	Oxybutynin
G04BD07	Tolterodine
G04BD08	Solifenacin
G04BD09	Trospium
G04BD10	Darifenacin
G04BD11	Fesoterodine
J01 Antibacterials for systemic use	
J01XE01	Nitrofurantoin
M01 Antiinflammatory and antirheumatic products	
M01AB01 and M01AB51	Indometacin
M03 Muscle relaxants	
M03BC01 and M03BC51	Orphenadrine (citrate) (and combinations)
M03BX01	Baclofen
M03BX02	Tizanidine
M09 Other drugs for disorders of the musculo-skeletal system	
M09AA72	Quinine, combinations with psycholeptics
N02 Analgesics	
N02AC52	Methadone, combinations excl. psycholeptics
N02BA01 and N02BA51	Acetylsalicylic acid (and combinations excl. psycholeptics)
N02CA01	Dihydroergotamine
N02CA52	Ergotamine, combinations excl. psycholeptics
N03 Antiepileptics	
N03AB02	Phenytoin
N03AE01	Clonazepam
N04 Anti-parkinson drugs	
N04AA02	Biperiden
N04BB01	Amantadine
N04BC01	Bromocriptine
N04BC06	Cabergoline
N04BD01	Selegiline
N05 Psycholeptics	
N05AA01	Chlorpromazine
N05AA02	Levomepromazine
N05AB03	Perphenazine
N05AB04	Prochlorperazine

N05AC01	Periciazine
N05AE03	Sertindole
N05AF01	Flupentixol
N05AF03	Chlorprothixene
N05AF05	Zuclopenthixol
N05AH02	Clozapine
N05AN01	Lithium
N05BA01	Diazepam
N05BA02	Chlordiazepoxide
N05BA09	Clobazam
N05BA12	Alprazolam
N05BB01	Hydroxyzine
N05CD02	Nitrazepam
N05CD05	Triazolam
N05CD08	Midazolam
N05CF03	Zaleplon
N06 Psychoanaleptics	
N06AA04	Clomipramine
N06AA06	Trimipramine
N06AA09	Amitriptyline
N06AA10	Nortriptyline
N06AA12	Doxepin
N06AB03	Fluoxetine
N06CA01	Amitriptyline and psycholeptics
R01 Nasal preparations	
R01BA01	Phenylpropanolamine
R01BA51	Phenylpropanolamine, combinations
R03 Drugs for obstructive airway diseases	
R03DA04	Theophylline
R05 Cough and cold preparations	
R05DA01	Ethylmorphine
R05DA09	Dextromethorphan
R05DA20	Dextromethorphan and salbutamol (combinations)
R05FA01	Opium derivatives and mucolytics
R05FA02	Opium derivatives and expectorants
R06 Antihistamines for systemic use	
R06AE03	Cyclizine
R06AE05	Meclizine
R06AE53	Cyclizine, combinations

[1]Classified using the ATC System of the WHO

ARTICLES

ARTICLE I

Hyttinen Virva, Taipale Heidi, Tanskanen Antti, Tiihonen Jari, Tolppanen Anna-Maija, Hartikainen Sirpa & Valtonen Hannu (2017). Risk factors for initiation of potentially inappropriate medications in community-dwelling older patients with and without Alzheimer's disease. Drugs & Aging 34(1), 67–77. Available online DOI: https://doi.org/10.1007/s40266-016-0415-9. Reprinted by permission from Springer International Publishing.

ARTICLE II

Hyttinen Virva, Jyrkkä Johanna, Saastamoinen Leena K, Vartiainen Anna-Kaisa & Valtonen Hannu (2018). Patient and Health Care Related Factors Associated with Initiation of Potentially Inappropriate Medications in Community-Dwelling Older Persons. Basic & Clinical Pharmacology & Toxicology. Available online DOI: https://doi.org/10.1111/bcpt.13096. Reprinted by permission from John Wiley and Sons.

ARTICLE III

Hyttinen Virva, Taipale Heidi, Tolppanen Anna-Maija, Tanskanen Antti, Tiihonen Jari, Hartikainen Sirpa & Valtonen Hannu (2017). Incident use of a potentially inappropriate medication and hip fracture in community-dwelling older persons with Alzheimer's disease. Annals of Pharmacotherapy 51(9), 725–734. Available online DOI: https://doi.org/10.1177/1060028017708394. Reprinted by permission from SAGE Publishing.

ARTICLE IV

Hyttinen Virva, Jyrkkä Johanna, Saastamoinen Leena K, Vartiainen Anna-Kaisa & Valtonen Hannu (2018). The Association of Potentially Inappropriate Medication Use on Health Outcomes and Hospital Costs in Community-Dwelling Older Persons: A Longitudinal 12-year Study. The European Journal of Health Economics. Available online DOI: https://doi.org/10.1007/s10198-018-0992-0. Reprinted by permission from Springer Berlin Heidelberg.

ARTICLE I

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ORIGINAL RESEARCH ARTICLE

Risk Factors for Initiation of Potentially Inappropriate Medications in Community-Dwelling Older Adults with and without Alzheimer's Disease

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Abstract

Background Various criteria have been created to define potentially inappropriate medications (PIMs) to help improve the quality and safety of medicine use in older patients. Individuals with Alzheimer's disease (AD) may be at higher risk of adverse drug events associated with PIMs (such as falls).

Objective Our objective was to determine the risk factors for PIM initiation in a nationwide cohort of community dwellers aged ≥65 years with and without AD.

Methods The Finnish nationwide MEDALZ cohort includes all patients diagnosed with AD in 2005–2011 ($n = 70{,}718$) and two comparison individuals without AD (non-AD) matched for age, sex and region of residence for each person with AD. After a 1-year washout period for PIM use and exclusion of those aged <65 years, we included 50,494 patients with AD and 106,306 comparison subjects. PIM use was defined according to Finnish criteria.

Results Subjects without AD initiated PIMs more frequently than those with AD (16.4 vs. 12.2%, respectively; $p < 0.001$). The most common PIMs were muscle relaxants and urinary antispasmodics. Older individuals (aged ≥75 years) were less likely to initiate PIMs. In the AD group, women were less likely to initiate PIMs than men. More comorbidities were associated with PIM initiation, especially in the non-AD group. The use of opioids or psychotropic medicines was associated with PIM initiation in both cohorts. Regional differences between university hospital districts were observed.

Conclusion PIM initiation was dependent on patient characteristics and possibly also some healthcare system-related factors such as differing regional treatment practices. It is important that medicines prescribed to the older vulnerable population are assessed regularly to avoid adverse effects and ensure safe pharmacotherapy, especially in those with multiple comorbidities.

Electronic supplementary material The online version of this article (doi:10.1007/s40266-016-0415-9) contains supplementary material, which is available to authorized users.

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Key Points

Initiation of potentially inappropriate medications (PIM) was less common in patients with Alzheimer's disease (AD) than in those without AD.

A high number of comorbidities and use of opioids or psychotropic medicines (at baseline) were associated with a higher risk for PIM initiation. Older age (≥75 years) had a negative association with PIM initiation.

The effect of sex on PIM initiation differed between individuals with and without AD. Among those with AD, women were less likely to initiate PIMs than were men; however, among those without AD, women were more likely to initiate PIMs than were men.

1 Introduction

Pharmacotherapy in older patients is often complex because of physiological age-related changes and the increasing number of comorbid conditions and medicines used. Older patients are at higher risk of adverse drug reactions and events associated with potentially inappropriate medications (PIMs) [1, 2]. PIMs are defined as medicines with a greater potential for risks than benefits among older patients [3] and have been associated with greater healthcare service utilization, such as hospitalization [4–7], and thus higher healthcare costs [8, 9].

Both explicit (criterion-based) and implicit (judgement-based) criteria for defining PIMs have been created to improve and ensure the quality and safety of pharmacotherapy in older patients. The first and best-known is the Beers criteria [3, 10–13], which are widely used. However, country-specific criteria are often more applicable to the different healthcare settings and medical products authorized across countries. In Finland, the Database of Medication for the Elderly was published in 2010 by the Finnish Medicines Agency to support clinical decision making and to improve the safety of medicine use among patients aged ≥75 years [14]. A previous cross-sectional study using the Finnish criteria found PIM use to be highly prevalent: 30% of a random sample ($n = 234$) of patients aged ≥75 years used PIMs on a regular or as-needed basis [15].

Various studies have been conducted on the prevalence and predictors of PIM use worldwide [16–19]. For instance, factors more frequently associated with the use of PIMs include polypharmacy and the number of different medicines [16, 17, 19], being female [16, 19], being more elderly [16, 19], having lower socioeconomic status [19] and living in residential care [16]. However, these results are partly inconclusive because other studies have also indicated that PIMs were more commonly used in those aged <85 years and in males [17]. A recent systematic review found that the most important factors generally associated with potentially inappropriate prescribing (PIP) are polypharmacy, poor functional status, depression and a high comorbidity score [20].

Population ageing means the number of patients with dementia will increase worldwide [21]. A recent systematic review concluded that PIM use is very prevalent among patients with cognitive impairment or dementia (varying from approximately 10 to >50%) [22]. A previous French study found that approximately 47% of patients with Alzheimer's disease (AD) living at home had at least one PIM according to the Laroche list [23]. Being female and receiving polypharmacy have also both been associated with PIM use in older patients with AD or dementia [23, 24]. Results were also similar in patients with mild cognitive impairment [25]. A Swedish study by Sköldunger et al. [6] found that PIM use was also associated with hospitalization in patients with dementia.

However, studies on PIM use in patients with AD, particularly longitudinal evidence, are lacking. Patients with AD may be at higher risk of adverse drug events associated with PIMs because, for example, anticholinergic medicines may weaken the effect of AD medicines. It is important to identify risk factors for PIM initiation and outcomes associated with PIM to be able to target interventions such as medication reviews to those at highest risk. The aim of this study was to investigate risk factors associated with the initiation of PIM use, defined according to Finnish criteria of the Database of Medication for the Elderly (hereafter, the 'Finnish criteria') [14], in a Finnish nationwide cohort of community-dwelling people aged ≥65 years with and without AD.

2 Methods

2.1 Study Population

The study population in this retrospective cohort study was based on the MEDALZ (Medication use and Alzheimer's disease) cohort [26], which included all Finnish community-dwelling patients diagnosed with AD between 2005 and 2011 ($n = 70{,}718$). The data also included two comparison individuals without AD matched for age, sex and region of residence ($n = 141{,}436$) for each person with AD. Comparison people without AD (non-AD) were identified from registers of the Social Insurance Institution (SII) of Finland, including those covered under the

National Health Insurance—in practice, the whole population.

Patients with AD were identified from the SII's Special Reimbursement Register, which includes patients entitled to special reimbursement of medicines because of chronic diseases, including AD. The Finnish current care guideline recommends that anti-dementia medicines should be prescribed for all people with clinically verified AD if there are no contraindications for use [27]. For AD medicines to be reimbursed, a predefined protocol for the diagnosis of AD must be fulfilled and sent to the SII, which grants the special reimbursement if the criteria are fulfilled. The AD diagnosis must include clinical examination, exclusion of alternative diagnoses, computed tomography or magnetic resonance imaging (MRI) scan and confirmation of the diagnosis by a neurologist or geriatrician.

Data were extracted from the SII nationwide prescription register (medicine use, 1995–2012), the Special Reimbursement Register (comorbidities, 1972–2012), the National Institute for Health and Welfare Hospital Discharge Register (HILMO; previous stroke, history of hip fracture, depression and bipolar disorder, 1972–2012) and Statistics Finland registers (socioeconomic position).

We used the Finnish criteria [14] to define PIM use in our study because this comprehensive categorization comprises all medicines with marketing authorization in Finland in 2010. Medicines in the database are classified into four categories from A to D: category A medicines are appropriate (e.g. simvastatin, bisoprolol, rivastigmine); category B medicines have limited research evidence of appropriateness or practical experience or efficacy in older patients (e.g. glucosamine, antitussives); medicines in category C are suitable for older patients with certain conditions only (e.g. digoxin, temazepam, duloxetine); and medicines in category D are potentially inappropriate for older individuals. In this study, we considered only medicines in category D (medicines to be avoided in older adults) to assess PIMs (see Table S1 in the Electronic Supplementary Material [ESM]). PIM use was classified as a dichotomous variable if a person had purchased at least one PIM during the follow-up period.

All medicines were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [28]. Patient use of opioids (ATC class N02A) and psychotropic medicines that were not included in the PIM definition was measured at the start of follow-up. Psychotropic medicines included antipsychotics (N05A excluding lithium), antidepressants (N06A) and benzodiazepines and related medicines (N05BA, N05CD, N05CF), and were included as a proxy for dementia-related behavioural symptoms. Medicine use start and end dates were determined from Prescription Register data using a previously utilized Prescriptions to Drug Use Periods (PRE2DUP) method for each person and each medicine (ATC code) [29]. The method takes into account the individual purchase pattern of medicines, i.e. regularity of medicine use, stockpiling and hospitalization periods when medicines are provided by the care unit and not recorded in the Prescription Register data. In the modelling, many restrictions that are placed on medicines (such as minimum dose for each medicine package) and dispensing regulations (maximum of 3 months' supply may be dispensed at once) affect the duration of use.

Figure 1 shows the derivation of the study population. A 1-year washout period for PIM use before the index date (the date of AD diagnosis and the corresponding matching date for comparison subjects) was applied to define incident PIM use. After all exclusions, 156,800 subjects were included in the study, 50,494 of whom had diagnosed AD.

2.2 Comorbidities and Other Covariates

Data on comorbidities, including asthma or chronic obstructive pulmonary disease (COPD), diabetes, rheumatoid arthritis, any cardiovascular disease, epilepsy and history of cancer, were extracted from the Special Reimbursement Register. History of hip fracture (S72.0–72.2), previous stroke (I60–64) and history of depression (F32–39) or bipolar disorders (F30–31) were extracted from the HILMO according to the Finnish version of *International Statistical Classification of Diseases and Related Health Problems* (ICD)-10 codes [30] and corresponding ICD-8 and ICD-9 codes. Socioeconomic position was defined as the highest occupational social class recorded for study participants when they were aged 45–55 years, according to classification by Statistics Finland. Socioeconomic position was categorized into four classes (high, medium, low and unknown). The highest class included entrepreneurs and higher clerical workers, 'medium' included lower clerical workers and employees, the lowest class included unemployed, retired and students, and 'unknown' included people with an unknown position and those for whom data were missing at Statistics Finland (about 5% of the cohort). Information about university hospital districts was extracted from the SII register in terms of a person's residential area at the start of the follow-up. Finland has five university hospital areas: Helsinki and Uusimaa (Helsinki University Hospital), Pirkanmaa (Tampere University Hospital), Southwest Finland (Turku University Hospital), Northern Savo (Kuopio University Hospital) and Northern Ostrobothnia (Oulu University Hospital).

2.3 Statistical Analysis

Baseline characteristics of patients with AD and participants without AD (non-AD) with and without PIM

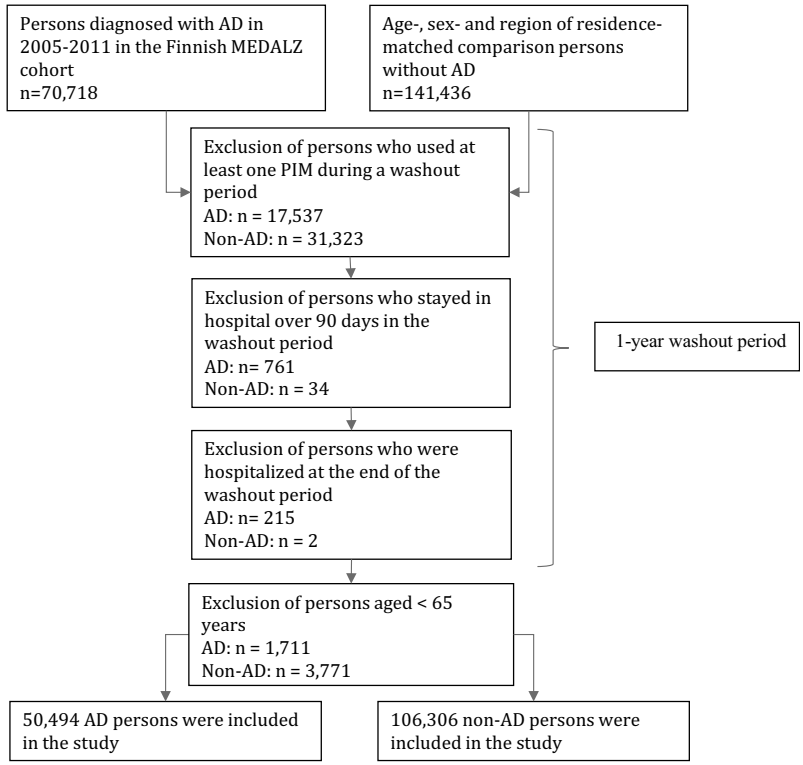

Fig. 1 Flow chart of the study population. *AD* Alzheimer's disease; *MEDALZ* Medication use and Alzheimer's disease; *PIM* potentially inappropriate medication

initiation were compared using a chi-squared test. Cox proportional hazards regression was used to identify risk factors for PIM initiation. Survival time was censored at the first PIM or for any reason at the end of follow-up (follow-up ended on 31 December 2012, at death or at ≥90 days hospitalization, whichever came first). In addition, the follow-up period for the comparison participants ended if they were diagnosed with AD. Associations between predictors (sociodemographic characteristics, comorbidities and medications) and PIM initiation were investigated with Cox regression. Analyses were performed separately in the AD and non-AD cohorts. Group-wise analyses were supported by statistically significant interaction terms between predictors and AD. The proportional hazard assumption was tested using the Schoenfeld residuals and Kaplan–Meier curves. Hazards for PIM initiation differed between people with and without AD according to age, sex, socioeconomic position, epilepsy, previous stroke, history of cancer and other medicine use. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs), and the significance level was set at 0.05. All statistical analyses were performed using Stata statistical package (STATA IC 13.1; StataCorp, College Station, TX, USA). No ethics committee approval was required according to Finnish legislation, because the data were de-identified before being delivered to researchers.

3 Results

3.1 Characteristics of the Study Population

The mean ± standard deviation (SD) age of the study population was 80.7 (±6.14) years, and 64.4% were women. Patients with PIM initiation were more often women and aged <85 years and were more likely to have asthma or COPD, rheumatoid arthritis, any cardiovascular diseases and history of depression or cancer or bipolar disorders than people without PIM initiation. In the AD population, those with PIM initiation were more often slightly younger and male than those without PIM initiation (Table 1). In addition, a higher proportion of people with AD with than without PIM initiation were receiving

Table 1 Baseline characteristics of patients with and without Alzheimer's disease with and without initiation of potentially inappropriate medication

	AD with PIM initiation ($n = 6165$)	AD without PIM initiation ($n = 44,329$)	p Value	Non-AD with PIM initiation ($n = 17,409$)	Non-AD without PIM initiation ($n = 88,897$)	p Value	Difference between AD and non-AD with PIM initiation
Age, years[a]			<0.001			<0.001	<0.001
65–74	1428 (23.2)	7669 (17.3)		4177 (24.0)	15,660 (17.6)		
75–84	3619 (58.7)	24,980 (56.4)		10,453 (60.0)	49,466 (55.6)		
≥85	1118 (18.1)	11,680 (26.3)		2779 (16.0)	23,771 (26.7)		
Sex			<0.001			<0.001	<0.001
Male	2375 (38.5)	15,442 (34.8)		5774 (33.2)	32,204 (36.2)		
Female	3790 (61.5)	28,887 (65.2)		11,635 (66.8)	56,693 (63.8)		
Socioeconomic position (middle age)			0.110			<0.001	0.781
High	2133 (34.6)	14,780 (33.3)		5907 (33.9)	29,722 (33.4)		
Medium	3701 (60.0)	27,244 (61.5)		10,555 (60.6)	50,721 (57.1)		
Low	191 (3.1)	1407 (3.2)		559 (3.2)	3002 (3.4)		
Unknown	140 (2.3)	898 (2.0)		388 (2.2)	5452 (6.1)		
Comorbidities							
Asthma or COPD	575 (9.3)	3235 (7.3)	<0.001	1690 (9.7)	6425 (7.2)	<0.001	0.383
Diabetes	751 (12.2)	5308 (12.0)	0.638	1806 (10.4)	8935 (10.1)	0.196	<0.001
Rheumatoid arthritis	286 (4.6)	1956 (4.4)	0.418	846 (4.9)	3904 (4.4)	0.006	0.487
Any cardiovascular disease	3182 (51.6)	22,025 (49.7)	0.005	8915 (51.2)	42,375 (47.6)	<0.001	0.585
Epilepsy	92 (1.5)	718 (1.6)	0.456	215 (1.2)	908 (1.0)	0.012	0.126
Previous stroke	581 (9.4)	4108 (9.3)	0.690	1207 (6.9)	7512 (8.5)	<0.001	<0.001
Previous hip fracture	266 (4.3)	2280 (5.1)	0.005	486 (2.8)	3420 (3.9)	<0.001	<0.001
History of cancer	322 (5.2)	2076 (4.7)	0.062	1044 (6.0)	4118 (4.6)	<0.001	0.025
History of depression or bipolar disorders	191 (3.1)	1119 (2.5)	0.008	439 (2.5)	1851 (2.1)	<0.001	0.016
History of substance abuse	171 (2.8)	957 (2.2)	0.002	289 (1.7)	1378 (1.6)	0.286	<0.001
Medicine use[a]							
Opioids	198 (3.2)	1338 (3.0)	0.408	1085 (6.2)	2815 (3.2)	<0.001	<0.001
Psychotropic medicines[b]	2147 (34.8)	13,889 (31.3)	<0.001	4710 (27.1)	17,207 (19.4)	<0.001	<0.001
Physician's workplace							<0.001
Primary outpatient care	2705 (43.9)	NA		7121 (40.9)	NA		
Hospital	1229 (19.9)	NA		3819 (21.9)	NA		
Other	796 (12.9)	NA		2093 (12.0)	NA		
Unknown	1435 (23.3)	NA		4376 (25.1)	NA		

Table 1 continued

	AD with PIM initiation ($n = 6165$)	AD without PIM initiation ($n = 44,329$)	p Value	Non-AD with PIM initiation ($n = 17,409$)	Non-AD without PIM initiation ($n = 88,897$)	p Value	Difference between AD and non-AD with PIM initiation
University hospital district			0.003			<0.001	0.062
Oulu	903 (14.7)	6369 (14.4)		2362 (13.6)	13,020 (14.7)		
Kuopio	1267 (20.6)	9344 (21.1)		3486 (20.1)	18,554 (20.9)		
Tampere	1458 (23.7)	10,886 (24.6)		4361 (25.1)	21,859 (24.7)		
Turku	708 (11.5)	5535 (12.5)		2081 (12.0)	11,021 (12.4)		
Helsinki	1812 (29.5)	12,074 (27.3)		5087 (29.3)	24,173 (27.3)		
Reason for end of follow-up							
Hospitalization	1097 (17.8)	9201 (20.8)	<0.001	784 (4.5)	4760 (5.4)	<0.001	<0.001
Death	1618 (26.2)	10,755 (24.3)	0.001	3194 (18.4)	17,023 (19.2)	0.014	<0.001
End of study	3450 (56.0)	24,373 (55.0)	0.148	13,431 (77.2)	67,114 (75.5)	<0.001	<0.001

Data are presented as number of individuals (%) unless otherwise indicated

AD Alzheimer's disease, *COPD* chronic obstructive pulmonary disease, *NA* not applicable, *PIM* potentially inappropriate medication

[a] At time of the diagnosis of AD or at the start of follow-up for comparisons

[b] Excluding PIMs on the list of the Finnish criteria (see Table S1 in the Electronic Supplementary Material)

psychotropic medicines (excluding PIMs on the Finnish criteria list) at the start of follow-up (with PIM initiation: 34.8%; without PIM initiation: 31.3%; $p < 0.001$).

In the non-AD population, those with PIM initiation were more often younger and female than were those without PIM initiation (Table 1). They were also more likely to use opioids and psychotropic medicines (with PIM initiation: 27.1%; without PIM initiation: 19.4%; $p < 0.001$). Moreover, patients without PIM initiation were more likely to have had a previous stroke or history of hip fracture than those with PIM initiation.

In the AD population, those with PIM initiation were more often slightly older and likely to be male than patients without AD with PIM initiation. Furthermore, patients with AD with PIM initiation were more likely to have diabetes or a previous stroke or history of hip fracture than were patients without AD with PIM initiation. In contrast, those without AD with PIM initiation were more likely to have a history of cancer and to have used opioids more frequently than were patients with AD with PIM initiation.

Most of the PIMs were prescribed by physicians who worked in primary outpatient care, followed by those in hospitals, but information about physicians' workplace was missing for approximately one-fourth of subjects.

The mean follow-up time for all participants was 1120 days (median 975 days). In patients with AD, the mean follow-up time was 987 days (median 850 days); in the comparison population, it was 1183 days (median 1036 days) ($p < 0.001$).

3.2 Initiation of Potentially Inappropriate Medications (PIMs)

Overall, 23,574 (15.0%) patients initiated PIMs during the study period. Of those, 6165 had AD (12.2% of the AD population) and 17,409 did not (16.4% of the non-AD population) ($p < 0.001$). The mean length of PIM use was 203 days (median 79 days) in patients with AD and 166 days (median 52 days) in those without AD ($p < 0.001$).

In the AD group, there were more differences between males and females, as men used more urinary antispasmodics (33.3% among men and 26.1% among women with AD). Overall, the study population purchased 60 different PIMs (see Table S1 in the ESM). In both groups, the most common purchased PIMs were tizanidine, metoclopramide, solifenacin, orphenadrine combinations, diazepam and propranolol (Table 2). The ten most frequent medicines also included tolterodine, trospium and fesoterodine in the AD group and orphenadrine, moxonidine and amitriptyline in the non-AD group. Comparing the use of medicines by sex, the ten most commonly purchased PIMs included oxybutynin and moxonidine in women and theophylline and fesoterodine in men.

Table 2 Most commonly initiated potentially inappropriate medications in subjects with and without Alzheimer's disease

ATC code	Medicine	Subjects with AD			ATC code	Medicine	Subjects without AD		
		Total	Female	Male			Total	Female	Male
A03FA01	Metoclopramide	**794** (**12.9**)	**595** (**15.7**)	**199** (**8.4**)	M03BX02	Tizanidine	**2892** (**16.6**)	**1948** (**16.7**)	**944** (**16.3**)
G04BD08	Solifenacin	**616** (**10.0**)	**313** (**8.3**)	**303** (**12.8**)	A03FA01	Metoclopramide	**2196** (**12.6**)	**1494** (**12.8**)	**702** (**12.2**)
M03BX02	Tizanidine	**593** (**9.6**)	**368** (**9.7**)	**225** (**9.5**)	M03BC51	Orphenadrine, combinations	**1751** (**10.1**)	**1212** (**10.4**)	**539** (**9.3**)
N05BA01	Diazepam	**383** (**6.2**)	**235** (**6.2**)	**148** (**6.2**)	G04BD08	Solifenacin	**1491** (**8.6**)	**970** (**8.3**)	**521** (**9.0**)
M03BC51	Orphenadrine, combinations	**344** (**5.6**)	**211** (**5.6**)	**133** (**5.6**)	C07AA05	Propranolol	**824** (**4.7**)	**534** (**4.6**)	**290** (**5.0**)
G04BD07	Tolterodine	**330** (**5.4**)	**194** (**5.1**)	**136** (**5.7**)	M03BC01	Orphenadrine (citrate)	**757** (**4.3**)	**498** (**4.3**)	**259** (**4.5**)
G04BD04	Oxybutynin	**262** (**4.2**)	**174** (**4.6**)	**88** (**3.7**)	N05BA01	Diazepam	**698** (**4.0**)	**457** (**3.9**)	**241** (**4.2**)
C07AA05	Propranolol	**221** (**3.6**)	**152** (**4.0**)	69 (2.9)	C02AC05	Moxonidine	**676** (**3.9**)	**480** (**4.1**)	**196** (**3.4**)
G04BD09	Trospium	**204** (**3.3**)	95 (2.5)	**109** (**4.6**)	N06AA09	Amitriptyline	**621** (**3.6**)	**411** (**3.5**)	**210** (**3.6**)
G04BD11	Fesoterodine	**196** (**3.2**)	97 (2.6)	**99** (**4.2**)	G04BD04	Oxybutynin	**549** (**3.2**)	**424** (**3.6**)	125 (2.2)
N05BA12	Alprazolam	180 (2.9)	**127** (**3.4**)	53 (2.2)	R03DA04	Theophylline	376 (2.2)	178 (1.5)	**198** (**3.4**)
G04BD10	Darifenacin	175 (2.9)	**118** (**3.1**)	57 (2.4)					
R03DA04	Theophylline	193 (3.1)	101 (2.7)	**92** (**3.9**)					

Data are presented as *n* (%) unless otherwise indicated. The ten most commonly purchased medicines are in bold, and the single most commonly purchased medicines are underlined

ATC Anatomical Therapeutic Chemical classification

3.3 Risk Factors for PIM Initiation

In the Cox proportional hazards regression, women in the non-AD group had a higher risk of PIM initiation, whereas being female decreased the risk of PIM initiation in the AD group (HR 0.85, 95% CI 0.80–0.89; $p < 0.001$) (Table 3). In both groups, younger people—aged 65–74 years—were more likely to initiate PIM use than those aged ≥75 years.

Several comorbidities—asthma or COPD, diabetes, any cardiovascular disease, epilepsy, history of cancer or history of depression or bipolar disorders—significantly increased the risk of PIM initiation in the non-AD group whereas previous stroke or hip fracture decreased the risk. In the AD group, the risk of PIM initiation was higher among those with asthma or COPD, any cardiovascular disease or history of cancer. In both groups, the risk of PIM initiation increased with the use of opioids (AD: HR 1.25, 95% CI 1.09–1.45; non-AD: HR 1.70, 95% CI 1.60–1.81) or psychotropic medicines (AD: HR 1.24, 95% CI 1.17–1.30; non-AD: HR 1.51, 95% CI 1.46–1.57).

All university hospital districts were associated with the initiation of PIMs in the non-AD group. The highest risk of PIM initiation was associated with Helsinki (HR 1.29, 95% CI 1.23–1.35) compared with Oulu. In the AD group, only Helsinki was associated statistically significantly with PIM initiation (HR 1.23, 95% CI 1.14–1.34).

4 Discussion

To our knowledge, this is the first study to determine the initiation of PIMs in community-dwelling older people with and without AD. In both groups, the most commonly purchased PIMs were tizanidine, metoclopramide, solifenacin, orphenadrine combinations, diazepam and propranolol. PIM initiation was more frequent among people without AD. The higher proportion of PIMs among those without AD might be explained by their longer follow-up time and that prescribing practices differed between participants with and without AD. The latter is supported by a finding from a recent review that patients with cognitive impairment and dementia had a lower risk of PIMs, as physicians might be more cautious in prescribing PIMs to more vulnerable patients [22]. In addition, patients with AD often have more contact with geriatricians or neurologists because of their diagnostic process, so their medicines might also be assessed more carefully. PIM criteria were first developed to improve pharmacotherapy in frail nursing home residents [3]. It seems that recommendations for avoiding PIMs have been taken into account in clinical practice. However, it should be noted that the duration of PIM use was longer in the AD group despite the shorter follow-up time.

Our study is one of few studies, e.g. Bradley et al. [17], to find that older age had a negative association with PIM use. This finding is in contrast to that of a recent systematic

Table 3 Cox proportional hazards regression of risk factors for initiation of potentially inappropriate medications

	Subjects with AD	*p* Value	Subjects without AD	*p* Value
Age, years[a]				
65–74	1.00 (reference)		1.00 (reference)	
75–84	0.87 (0.82–0.93)	<0.001	0.85 (0.82–0.88)	<0.001
≥85	0.71 (0.66–0.77)	<0.001	0.62 (0.59–0.65)	<0.001
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	0.85 (0.80–0.89)	<0.001	1.11 (1.08–1.15)	<0.001
Socioeconomic position (middle age)				
High	1.00 (reference)		1.00 (reference)	
Medium	0.94 (0.89–0.99)	0.019	1.01 (0.98–1.05)	0.437
Low	1.04 (0.89–1.20)	0.638	1.00 (0.92–1.09)	0.963
Unknown	1.10 (0.93–1.31)	0.257	0.42 (0.38–0.46)	<0.001
Comorbidities				
Asthma or COPD	1.29 (1.18–1.41)	<0.001	1.31 (1.25–1.38)	<0.001
Diabetes	1.05 (0.98–1.14)	0.189	1.10 (1.04–1.15)	<0.001
Rheumatoid arthritis	1.10 (0.97–1.24)	0.124	1.07 (1.00–1.15)	0.046
Any cardiovascular disease	1.12 (1.06–1.18)	<0.001	1.14 (1.11–1.18)	<0.001
Epilepsy	0.92 (0.74–1.13)	0.407	1.28 (1.12–1.47)	<0.001
Previous stroke	1.04 (0.95–1.13)	0.410	0.92 (0.86–0.97)	0.005
Previous hip fracture	0.99 (0.88–1.12)	0.886	0.89 (0.81–0.98)	0.014
History of cancer	1.18 (1.05–1.32)	0.004	1.43 (1.34–1.53)	<0.001
History of depression or bipolar disorders	1.15 (1.00–1.33)	0.057	1.12 (1.02–1.24)	0.019
History of substance abuse	1.13 (0.97–1.32)	0.115	1.10 (0.98–1.24)	0.113
Medicine use[a]				
Opioids	1.25 (1.09–1.45)	0.002	1.70 (1.60–1.81)	<0.001
Psychotropic medicines[b]	1.24 (1.17–1.30)	<0.001	1.51 (1.46–1.57)	<0.001
University hospital district				
Oulu	1.00 (reference)		1.00 (reference)	
Kuopio	1.06 (0.97–1.15)	0.203	1.08 (1.03–1.14)	0.004
Tampere	1.05 (0.97–1.14)	0.225	1.14 (1.09–1.20)	<0.001
Turku	1.02 (0.93–1.13)	0.660	1.10 (1.03–1.16)	0.002
Helsinki	1.23 (1.14–1.34)	<0.001	1.29 (1.23–1.35)	<0.001
Number of subjects	50,356		106,004	
Number of failures	6148		17,377	

Data are presented as hazard ration (95% confidence interval) unless otherwise indicated

AD Alzheimer's disease, *COPD* chronic obstructive pulmonary disease, *PIM* potentially inappropriate medication

[a] At the time of the diagnosis of AD, or at the start of follow-up for comparisons

[b] Excluding PIMs on the list of the Finnish criteria (see Electronic Supplementary Material Table S1)

review, which found that older age is an important risk factor for PIP [20]. However, we studied PIM initiation, whereas other studies have mainly investigated the prevalence of PIMs. Nevertheless, our results indicate that prescribers may have been aware of aging-related changes and adverse events associated with PIMs among their oldest patients.

In the non-AD group, several comorbidities increased the risk of PIM initiation. This finding is consistent with an earlier study in the general aged population [31]. There were differences in the AD group, where only asthma or COPD, any cardiovascular disease or history of cancer were associated with PIM initiation. In the non-AD group, previous stroke or hip fracture decreased the risk of PIM initiation. This may be because prescribing is more careful in those with a history of serious health events. Many PIMs, especially long-acting benzodiazepines and anticholinergic medicines, might increase the risk of falls [32].

In addition, our results indicated people receiving opioids or psychotropic medicines at baseline had a high risk

of PIM initiation. Previous studies of this same cohort reported that a higher proportion of patients with than without AD used antipsychotics and antidepressants [33]. In addition, the incidence of benzodiazepine use was three to four times higher in the AD population [34]. Some PIMs may be used to treat adverse effects from psychotropic medicines (e.g. urinary anticholinergics, anticholinergic antiparkinson medicines). Alternatively, in an AD population, users of psychotropic medicines may have more comorbidities or more severe disease with neuropsychiatric symptoms of dementia, and these lead to more frequent PIM initiation. As PIM initiation was strongly correlated with psychotropic medicine use, it may be considered a marker for increased PIM initiation risk.

In the non-AD group, women were more likely to initiate PIMs, while the opposite association was observed in the AD group. The higher risk of PIM initiation in men with AD contrasts with the findings of a previous study conducted by Montastruc et al. [23] who found women with AD were more likely to initiate PIMs than men with AD. However, they analysed the overall risk for PIM use according to the Laroche list, which affects study comparability. In our study, men more often used urinary antispasmodics, which can be one explanation for the higher risk of PIM initiations among men. An earlier study by Torvinen-Kiiskinen et al. [35] also found that men with AD had a higher prevalence of concomitant use of urinary antispasmodics and acetylcholine esterase inhibitors than women with AD. Our subgroup analyses on sex and PIM categories showed that men were more likely to use urinary antispasmodics than women. This might be explained by different treatment traditions between males and females. For example, women with incontinence may be offered pads while men are treated with urinary antispasmodics [35].

In this study, socioeconomic position had no association with PIM initiation or the results were inconclusive. Previous studies conducted in the general aged population found that low education level is associated with higher risk of PIM consumption [19]. However, our measure was occupational social class, so the difference can be explained by differences in definitions.

Our study revealed regional differences between university hospital districts that was not explained by any specific PIM medicine (data not shown). Previous studies have also found regional differences in PIM prescribing [36, 37], but they were not comparable with our study because of different study designs, populations and healthcare systems. One study included only inpatients, but also found lower rates of PIMs in smaller hospitals and urban areas [36]. In contrast, another cross-sectional study found that older veterans living in rural areas might be at higher risk of PIP [37]. The underlying reasons and healthcare system-related factors behind the regional differences in PIM initiation should be assessed in future studies.

We found only one earlier study that predicted incident PIM use by the same method, the Cox proportional hazards model [38]. The study did not find any associated characteristics with incident PIM use, but the authors stated that this finding might be explained by the small sample size ($n = 217$). Assessment of risk factors for PIM initiation is important; various studies have identified the challenges of discontinuing and deprescribing medicine use [39], and there is a need to provide additional motivation for patients and slowly decrease the dose.

A strength of this study is its large nationally representative data, which included all people diagnosed with AD between 2005 and 2011, so there is very low selection bias. In addition, we implemented a 1-year washout period for PIM use to restrict our analyses to incident PIM users. However, it is possible that the cohort was healthier because these patients were excluded after the washout period, and the cohort may not have included all AD cases if they were not considered to benefit from or tolerate anti-dementia medicines, although actual use of anti-dementia medicines was not an inclusion criterion. Register-based data avoid the possible recall bias present in interview-based studies. Furthermore, other limitations should also be considered. First, registers include only reimbursed, not all prescribed, medicines. In addition, registers do not include over-the-counter medicines. Second, we do not know whether PIM purchases reflect the real consumption of medicines. However, data on medicine purchases are considered a more reliable estimate of medicine use than prescribing data [40]. Third, the Finnish criteria were developed to support clinical decision making among patients aged $\geq$75 years. Our study also included people aged 65–74 years. However, patients with AD can be considered older than their actual age, and the age of 65 years was most often also used in other studies using explicit criteria (e.g. Beers, Screening Tool of Older People's Prescriptions [STOPP]/Screening Tool to Alert to Right Treatment [START]) [13, 41] for assessing PIMs. Finally, the Finnish criteria were published in 2010, and our follow-up started at earliest in 2005, so the availability of medicines and prescribing practices may have changed in the interim [15]. However, the first Beers criteria were published in 1991 [3]. Although the Finnish criteria are consistent with Beers, we did not use Beers because several of the medicines it lists do not have marketing authorization in Finland.

It should be noted that, by definition, PIMs are 'potentially' inappropriate, and are sometimes necessary. Pharmacotherapy in older patients is often complex, especially for those with many comorbidities and multiple medicines.

Moreover, explicit criteria do not take into account individual patient characteristics and the heterogeneity between older patients. Heterogeneity also relates to comorbidities as risk factors for PIM initiation as no particular disease was strongly associated with PIM initiation. In addition, the clinical picture and progress of disease differs between patients with the same disease. However, it is important that clinicians address risk factors to prevent adverse effects or events. The risks and benefits of initiating PIMs should always be considered for each individual patient.

5 Conclusion

PIM initiation depended on both patient characteristics and morbidities and possibly also some healthcare system-related factors such as differing regional treatment practices. In future, evaluation of the continuation as well as of the initiation of PIMs will be important. Overall, it is important to assess the medicines being prescribed to older vulnerable populations regularly to avoid adverse effects and to ensure safe pharmacotherapy, especially in those with multiple comorbidities.

Compliance with Ethical Standards

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References

1. Hedna K, Hakkarainen KM, Gyllensten H, et al. Potentially inappropriate prescribing and adverse drug reactions in the elderly: a population-based study. Eur J Clin Pharmacol. 2015;71(12):1525–33.
2. Lund BC, Carnahan RM, Egge JA, et al. Inappropriate prescribing predicts adverse drug events in older adults. Ann Pharmacother. 2010;44(6):957–63.
3. Beers MH, Ouslander JG, Rollingher I, et al. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med. 1991;151(9):1825–32.
4. Lu W-H, Wen Y-W, Chen L-K, et al. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. CMAJ. 2015;187(4):E130–7.
5. Reich O, Rosemann T, Rapold R, et al. Potentially inappropriate medication use in older patients in Swiss managed care plans: prevalence, determinants and association with hospitalization. PLoS One. 2014;9(8):e105425.
6. Sköldunger A, Fastbom J, Wimo A, et al. Impact of inappropriate drug use on hospitalizations, mortality, and costs in older persons and persons with dementia: findings from the SNAC study. Drugs Aging. 2015;32(8):671–8.
7. Henschel F, Redaelli M, Siegel M, et al. Correlation of incident potentially inappropriate medication prescriptions and hospitalization: an analysis based on the PRISCUS list. Drugs Real World Outcomes. 2015;2(3):249–59.
8. Akazawa M, Imai H, Igarashi A, et al. Potentially inappropriate medication use in elderly Japanese patients. Am J Geriatr Pharmacother. 2010;8(2):146–60.
9. Fu AZ, Jiang JZ, Reeves JH, et al. Potentially inappropriate medication use and healthcare expenditures in the US community-dwelling elderly. Med Care. 2007;45(5):472–6.
10. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med. 1997;157(14):1531–6.
11. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163(22):2716–24.
12. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60(4):616–31.
13. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227–46.
14. The Finnish Medicines Agency. Database of medication for the elderly. 2015. http://www.fimea.fi/web/en/databases_and_registeries/medicines_information/database_of_medication_for_the_elderly. Accessed 18 Nov 2015.
15. Bell JS, Ahonen J, Lavikainen P, et al. Potentially inappropriate drug use among older persons in Finland: application of a new national categorization. Eur J Clin Pharmacol. 2013;69(3):657–64.
16. Price SD, Holman CD, Sanfilippo FM, et al. Are older Western Australians exposed to potentially inappropriate medications according to the Beers Criteria? A 13-year prevalence study. Australas J Ageing. 2014;33(3):E39–48.
17. Bradley MC, Motterlini N, Padmanabhan S, et al. Potentially inappropriate prescribing among older people in the United Kingdom. BMC Geriatr. 2014;14:72. doi:10.1186/1471-2318-14-72.
18. Moriarty F, Bennett K, Fahey T, et al. Longitudinal prevalence of potentially inappropriate medicines and potential prescribing omissions in a cohort of community-dwelling older people. Eur J Clin Pharmacol. 2015;71(4):473–82.
19. Bongue B, Naudin F, Laroche ML, et al. Trends of the potentially inappropriate medication consumption over 10 years in older adults in the East of France. Pharmacoepidemiol Drug Saf. 2009;18(12):1125–33.
20. Tommelein E, Mehuys E, Petrovic M, et al. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. Eur J Clin Pharmacol. 2015;71(12):1415–27.
21. Prince M, Wimo A, Guerchet M, et al. World Alzheimer Report 2015. The global impact of dementia: an analysis of prevalence, incidence, cost and trends. London: Alzheimer's Disease International; 2015.
22. Johnell K. Inappropriate drug use in people with cognitive impairment and dementia: a systematic review. Curr Clin Pharmacol. 2015;10(3):178–84.
23. Montastruc F, Gardette V, Cantet C, et al. Potentially inappropriate medication use among patients with Alzheimer disease in

the REAL.FR cohort: be aware of atropinic and benzodiazepine drugs! Eur J Clin Pharmacol. 2013;69(8):1589–97.
24. Lau DT, Mercaldo ND, Harris AT, et al. Polypharmacy and potentially inappropriate medication use among community-dwelling elders with dementia. Alzheimer Dis Assoc Disord. 2010;24(1):56–63.
25. Weston AL, Weinstein AM, Barton C, et al. Potentially inappropriate medication use in older adults with mild cognitive impairment. J Gerontol A Biol Sci Med Sci. 2010;65(3):318–21.
26. Tolppanen AM, Taipale H, Koponen M, et al. Cohort profile: the Finnish Medication and Alzheimer's disease (MEDALZ) study. BMJ Open. 2016;6:e012100. doi:10.1136/bmjopen-2016-012100.
27. Finnish Medical Society Duodecim, Helsinki. Current Care: Memory disorders. In Finnish with English summary. 2010. http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00081. Accessed 22 Feb 2016.
28. World Health Organization. WHO Collaborating Centre for Drug Statistics Methodology. The Anatomical Therapeutic Chemical Classification System. Structure and principles. 2011. http://www.whocc.no/atc/structure_and_principles/. Accessed 15 Jan 2016.
29. Tanskanen A, Taipale H, Koponen M, et al. From prescription drug purchases to drug use periods—a second generation method (PRE2DUP). BMC Med Inform Decis Mak. 2015;15:21. doi:10.1186/s12911-015-0140-z.
30. Third edition of the Finnish version of the International Statistical Classification of Diseases and Related Health Problems. 2011. http://www.julkari.fi/bitstream/handle/10024/80324/15c30d65-2b96-41d7-aca8-1a05aa8a0a19.pdf?sequence=1. Accessed 20 Sep 2016.
31. Stock S, Redaelli M, Simic D, et al. Risk factors for the prescription of potentially inappropriate medication (PIM) in the elderly: an analysis of sickness fund routine claims data from Germany. Wien Klin Wochenschr. 2014;126(19–20):604–12.
32. Berdot S, Bertrand M, Dartigues JF, et al. Inappropriate medication use and risk of falls—a prospective study in a large community-dwelling elderly cohort. BMC Geriatr. 2009;9:30. doi:10.1186/1471-2318-9-3.
33. Taipale H, Koponen M, Tanskanen A, et al. High prevalence of psychotropic drug use among persons with and without Alzheimer's disease in Finnish nationwide cohort. Eur Neuropsychopharmacol. 2014;24(11):1729–37.
34. Saarelainen L, Taipale H, Koponen M, et al. The incidence of benzodiazepine and related drug use in persons with and without Alzheimer's disease. J Alzheimer's Dis. 2015;49(3):809–18.
35. Torvinen-Kiiskinen S, Taipale H, Tanskanen A, et al. Concomitant use of acetylcholine esterase inhibitors and urinary antispasmodics among Finnish community-dwelling persons with Alzheimer disease. J Clin Psychopharmacol. 2014;34(6):722–7.
36. Rothberg MB, Pekow PS, Liu F, et al. Potentially inappropriate medication use in hospitalized elders. J Hosp Med. 2008;3(2):91–102.
37. Lund BC, Charlton ME, Steinman MA, et al. Regional differences in prescribing quality among elder veterans and the impact of rural residence. J Rural Health. 2013 Spring;29(2):172–179.
38. Gray SL, Hedrick SC, Rhinard EE, et al. Potentially inappropriate medication use in community residential care facilities. Ann Pharmacother. 2003;37(7–8):988–93.
39. Reeve E, To J, Hendrix I, et al. Patient barriers to and enablers of deprescribing: a systematic review. Drugs Aging. 2013;30(10):793–807.
40. Beardon PH, McGilchrist MM, McKendrick AD, et al. Primary non-compliance with prescribed medication in primary care. BMJ. 1993;307(6908):846–8.
41. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213–8.

ARTICLE II

Hyttinen Virva, Jyrkkä Johanna, Saastamoinen Leena K, Vartiainen Anna-Kaisa & Valtonen Hannu (2018). Patient and Health Care Related Factors Associated with Initiation of Potentially Inappropriate Medications in Community-Dwelling Older Persons. Basic & Clinical Pharmacology & Toxicology. Available online DOI: https://doi.org/10.1111/bcpt.13096. Reprinted by permission from John Wiley and Sons.

ARTICLE III

Hyttinen Virva, Taipale Heidi, Tolppanen Anna-Maija, Tanskanen Antti, Tiihonen Jari, Hartikainen Sirpa & Valtonen Hannu (2017). Incident use of a potentially inappropriate medication and hip fracture in community-dwelling older persons with Alzheimer's disease. Annals of Pharmacotherapy 51(9), 725–734. Available online DOI: https://doi.org/10.1177/1060028017708394. Reprinted by permission from SAGE Publishing.

ARTICLE IV

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ORIGINAL PAPER

The association of potentially inappropriate medication use on health outcomes and hospital costs in community-dwelling older persons: a longitudinal 12-year study

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Abstract

Aims To determine (1) whether potentially inappropriate medication (PIM) use defined by the Meds75 + database is associated with fracture-specific hospitalisations and all-cause mortality, and (2) the association between PIM use and all-cause hospitalisation costs in a 12-year follow-up of a nationwide sample of people aged ≥ 65 years in Finland.

Methods This is a longitudinal study of 20,666 community-dwelling older persons with no prior purchases of PIMs within a 2-year period preceding the index date (1 Jan 2002), who were followed until the end of 2013. Data were obtained from the Finnish Prescription Register, and it was accompanied by information on inpatient care, causes of deaths and socio-economic status from other national registers. Propensity score matching (PSM) analysis was used to account for potential selection effect in PIM use. Cox proportional hazards regression was used to identify the time to the first fracture or death by comparing PIM-users ($n = 10{,}333$) with non-users ($n = 10{,}333$). The association between PIM use and hospital costs was analysed with a fixed effects linear model.

Results PIM use was weakly associated with an increased risk of fractures and death. The association was stronger in the first PIM-use periods. Hospitalised PIM-users had 15% higher hospital costs compared to non-users during the 12-year follow-up.

Conclusion PIM initiation was associated with an increased risk of fracture-specific hospitalisation and mortality and PIM-users had higher hospital costs than non-users. Health care providers should carefully consider these issues when prescribing PIM for older persons.

Keywords Potentially inappropriate medications · Older persons · Register-based study · Health outcomes · Hospital costs

JEL Classification J14 Economics of the Elderly

Introduction

Potentially inappropriate medications (PIMs) are defined as medications whose potential harms outweigh their benefits [1]. Despite risks, the use of PIMs is widely recognised to be quite common among older persons. A previous review estimated that in Europe, overall PIM use prevalence is over 20% in persons aged ≥ 65 years [2]. Finnish studies found that the prevalence of PIM use varied between 15 and 30% in the older population, depending on the study setting and criteria used [3, 4].

Several criteria have been formulated to define PIM use to support and improve the safety of medication use in older persons. The first, and well-known is the Beers Criteria, which were developed in the United States at the beginning of the 1990s and the latest update of this criteria

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was published in 2015 [1, 5]. Other commonly known criteria are, for example, the STOPP/START [6] and PRISCUS criteria [7]. One of the latest sets of criteria is the EU(7)-PIM-list, which was developed to identify and compare PIM prescribing in older people in a European context [8]. However, many national criteria have been developed, because all commonly used criteria cannot be applied in every country due to differences in treatment practices and selection of medications. In Finland, the database of medication for the elderly (Meds75+) maintained by the Finnish Medicines Agency (FIMEA) was published in 2010 [9], but only a few studies have used the Meds75+ criteria up to date.

Previous studies on PIM use and health outcomes have found that there is an association between PIM use and higher risk of adverse drug events [10], falls and fall-related hospitalisations [11, 12] or all-cause hospitalisations [13, 14], and thus higher health care costs [15]. However, there are few studies examining the association of PIM use on health care costs in Europe, but studies indicate that PIM use is associated with higher health care costs [16]. Most of the previous studies used quite short follow-ups, so there is a clear need for longitudinal evidence in nationwide representative data in the European context [15]. In addition, the association between PIM use and mortality is controversial [17, 18], and only a few studies have taken into account possible endogeneity between PIM use and health outcomes [19]. The selection of patients—in this study for PIM use—is important to consider particularly in observational studies [20].

Finnish registers provide a valuable opportunity to gain evidence on PIM use and health outcomes, e.g. health care utilisation. To our knowledge, this is the first study investigating the association between PIM use and fracture-specific hospitalisations with a matched cohort in terms of factors that were related to PIM initiation, which decreases the selection bias by controlling for potential confounders associated with PIM use.

The aims of this study were to determine (1) the association between PIM use and potentially fall-related fractures and all-cause mortality, and (2) the association between PIM use all-cause hospitalisation costs in a 12-year follow-up of a nationwide sample of people aged ≥ 65 years in Finland, taking into account the potential selection effect in PIM use.

Methods

Data sources

This study was conducted using the Finnish nationwide register data from the years 2000–2013. The Prescription Register that is maintained by the Social Insurance Institution (SII) includes all Finnish persons who have received reimbursement of their prescription medication purchases. This means practically the whole noninstitutionalised population, since in Finland, all residents are covered by National Health Insurance and the medicines reimbursement scheme covers most medication purchases in outpatient care. All medications in the Prescription Register were classified based on the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system [21]. The Prescription Register was linked using a unique personal identity code to the Care Register for Health Care (the use of inpatient care) maintained by the National Institute for Health and Welfare, and causes of deaths and socioeconomic information of the study population maintained by Statistics Finland.

Study design and participants

The study population was a 10% random sample of people aged ≥ 65 years from the Prescription Register in the beginning of the year 2000 ($n = 64{,}250$) (Fig. 1). An incident PIM-user was defined as a person who did not have any prescription PIM purchases during 2 years (washout period) preceding the index date (1 January 2002). Persons who purchased at least one PIM during the preceding 2-year period (years 2000–2001) before the index date were excluded ($n = 32{,}087$). In addition, we excluded those persons who suffered a fracture during the washout period. Those persons who were hospitalised for ≥ 90 days during the washout period or were at the hospital at the beginning of the study period were also excluded. This was because the prescription data do not include information on the medications given at hospital. After all exclusions, the study cohort included 27,576 persons. After propensity score matching (PSM) (see statistical analysis), there were 10,333 PIM initiators with one matched non-user, which totalled 20,666 persons in the matched study population. Figure 1 shows the flow chart of the study population.

PIM exposure

PIMs were defined according to the Finnish Meds75+ database (information on medications from the year 2010) [9]. In the database, medications are divided into four categories: A (suitable for older persons), B (lack of research evidence, clinical experience or efficacy among older persons), C (suitable for older persons, with specific cautions) and D (avoid use in older persons). In the current study, a PIM-user was a person purchasing at least one prescription medication in category D during the follow-up period.

PIM exposure was a time-varying variable, which means that a person was defined as PIM exposed for a 31-day (1 month) period (for sensitivity also 90-day (3 months) and 6-month periods) from the date of every PIM purchase, so

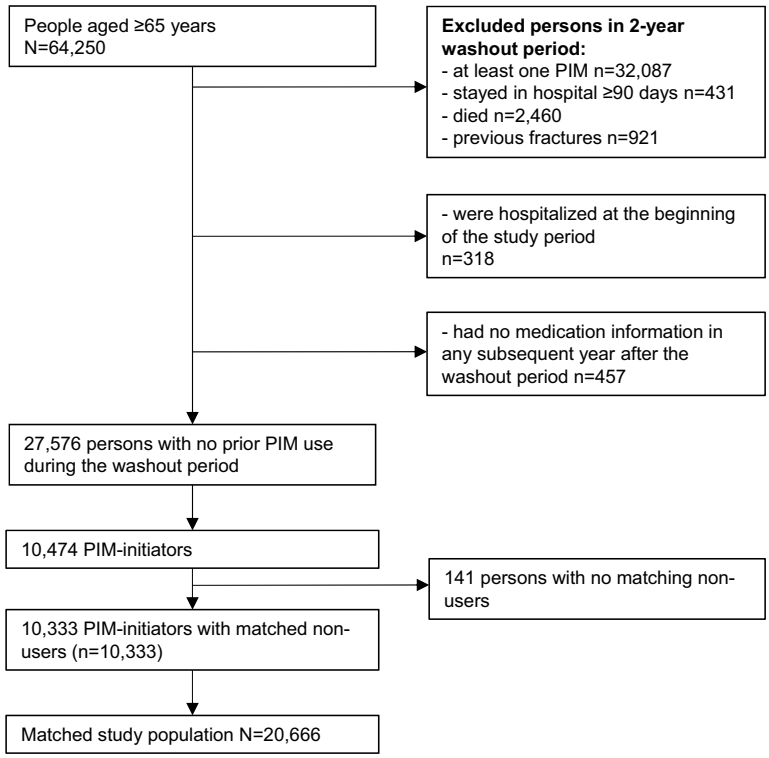

Fig. 1 Flow chart of the study population

the real exposure period can vary between persons if there were overlapping periods. In addition, the analyses were restricted for the first PIM-use period to analyse the risk of fracture after the start of a new medication. The first PIM-use period was defined as the period starting when a person purchased the first PIM and ending after the above-mentioned exposure periods. If there were overlapping periods, the end of the first PIM-use period was calculated from the last PIM purchase date where the exposure period did not include the purchase of other PIMs.

Patient outcome is considered to be associated with PIM exposure, if the fracture-based hospitalisation occurred during PIM exposure period. In the hospital cost model, PIM exposure was defined yearly as a dichotomous variable, whether or not a person had purchased at least one PIM in each year of the follow-up.

Outcome variables

Our primary outcome was a potentially fall-related incident fracture gathered from the Care Register for Health Care based on the Finnish version of International Classification of Diseases (ICD) version ten codes [22]: S22, S32, S42, S52, S62, S72 and S82. The secondary outcome was all-cause mortality obtained from the register of causes of deaths.

Hospital costs of all-cause hospitalisations were defined in each hospital episode according to the National Institute for Health and Welfare's estimates of unit costs of social and health care in Finland in 2011 [23]. The length of stay of each hospital episode was taken into account in cost calculation. In addition, the number of hospital episodes were calculated for each year and the total number of hospital episodes during the follow-up.

Study covariates

In addition to basic patient characteristics, such as age and gender, information on morbidity and socioeconomic status was included for study covariates in the models. Baseline medication use of different ATC groups was obtained as a proxy for morbidity such as metabolic syndrome (medications used in diabetes: A10), psychiatric disorders (psycholeptics, N05; and antidepressants, N06A) and cardiovascular disease (cardiovascular system, C01–04 and C07–C10). Other medication use also included opioids (N02A) and non-steroidal anti-inflammatory drugs (NSAIDs; M01A excluding glucosamine M01AX05). Medication use was defined

during the washout period (years 2000–2001). Excessive polypharmacy was defined as the annual purchase of ten or more different medications (ATC codes) during the washout period.

Income information was used to measure socioeconomic status. In the Finnish population, the variation of education (as measured by the number of school years) is quite small in our age cohort people aged ≥ 65 years. Thus, the socioeconomic status was described by dividing spending money of a household-dwelling unit by the equivalent number of persons (number of equivalent consumers) living in a household and this was coded into four different income classes. The variable recording whether a person was living alone was based on the information on the number of persons living in a household in the registers of Statistics Finland.

Statistical analysis

It can be assumed that there is a selection process in PIM use, so that users and non-users are not homogenous groups that can be directly compared. Some observable or non-observable factors may explain both the PIM use and the outcomes, i.e. the PIM-users might have a higher probability of a fall due to these observable or non-observable factors. The effect of these factors should be controlled to find the genuine association of PIM with the outcomes. The variables in this selection can be partly known (such as age and income) and partly unknown or unobservable. This can lead to an endogeneity problem when, for example, at least one of the predictors for PIM use is also associated simultaneously with the dependent outcome variable [24]. To remove or at least diminish the bias caused by the selection process, PSM analysis was used before the regression models, for matching PIM-users and non-users. PSM analysis with nearest neighbour (1:1) matching identified from the non-users group those persons who are the most closely similar to PIM-users based on their relevant characteristics before treatment [25]. Using PSM, the potential selection effects of known variables can be controlled, but not selection associated with unobserved or non-observable factors. Covariates included in the PSM analyses were those that were related to PIM initiation based on previous studies [26]: age, gender, socioeconomic status psychotropic medications, opioids, excessive polypharmacy and hospital area.

Cox proportional hazards regression was used to investigate the time to the first failure (fall-related fracture or death) by comparing PIM-users with non-users. Survival time was censored at the first failure or for any reason for the end of follow-up (death, ≥ 90 days hospitalisation or end of the study on 31 Dec 2013), whichever came first. Schoenfeld residuals were used to test the fulfilment of the proportional hazard assumption. It is important to consider that the assumption holds, which means that the hazard curves for the groups should be parallel [27]. Cox models included those variables that were considered to be related to falls and fractures: age, gender, socioeconomic status, other medication use (psychotropics, antidiabetics, cardiovascular medications, opioids, NSAIDs and excessive polypharmacy) and living situation.

The association between PIM use and hospital costs were analysed with a fixed effects linear model. The distribution of hospital costs was right skewed, so the natural logarithm of hospital costs was used for the dependent variable. Hospital costs amounting to zero were excluded in the log transformation, so the model took into account only those years when a person was hospitalised. During 12-year follow-up, there were 401 persons with zero costs. Yearly zero costs were taken into account using log $(x+1)$ transformation of costs for the dependent variable. The cost models were adjusted for time variable (year) and year of death, because health care service use, and thus costs, tend to increase near the end of life [28]. Morbidity covariates were defined yearly in the model, because only variables that vary over time can be included in the fixed effects model.

In addition, mean differences of the total hospital costs and total number of hospital episodes and length of stay per episode during the follow-up between PIM-users and non-users were analysed using the Wilcoxon rank-sum test.

Baseline characteristics of PIM-users and non-users were analysed using cross-tabulation and chi-square tests. Other results were reported as hazard ratios (HR) or coefficients with 95% confidence intervals (CI). Results were considered significant with p values < 0.05. All analyses were performed using the Stata statistical package (STATA IC14.1. StataCorp, College Station, TX, USA). Ethical approval of the study was granted by the Research Ethics Committee of the Northern Savo Hospital District.

Results

Descriptives

The mean age of the study population was 74.6 years (SD 5.5, median 73.5) and 62.3% were women. After PSM analysis, there were no differences between PIM-users and non-users according to the covariates included in the PSM (Table 1).

Overall, the study population used 69 different PIMs (see Online Resource 1). The most commonly used PIM was tizanidine, which was used by 19.7% of persons, followed by metoclopramide (14.4%), tolterodine (9.6%), opiate-related cough medications (8.9%) and orphenadrine combinations (8.8%) (Online Resource 2). The ten most commonly used PIMs were otherwise the same between genders, but men

Table 1 Characteristics of the study population

	Before PSM			After PSM		
	PIM-users ($n=10,474$) n (%)	Non-users ($n=17,102$) n (%)	p value	PIM-users ($n=10,333$) n (%)	Non-users ($n=10,333$) n (%)	p value
PSM covariates						
Age[a]			<0.001			0.341
65–74 years	6288 (60.0)	8487 (49.6)		6229 (60.3)	6131 (59.3)	
75–84 years	3661 (35.0)	6729 (39.4)		3600 (34.8)	3700 (35.8)	
≥85 years	525 (5.0)	1886 (11.0)		504 (4.9)	502 (4.9)	
Gender			<0.001			0.863
Male	3929 (37.5)	7062 (41.3)		3887 (37.6)	3899 (37.7)	
Female	6545 (62.5)	10,040 (58.7)		6446 (62.4)	6434 (62.3)	
Socioeconomic status (income)[b]			<0.001			0.805
<9999€	2933 (28.0)	5613 (32.8)		2915 (28.2)	2921 (28.3)	
10,000–19,999€	6197 (59.2)	9544 (55.8)		6168 (59.7)	6177 (59.8)	
20,000–29,999€	879 (8.4)	1190 (7.0)		864 (8.4)	832 (8.1)	
>30,000€	393 (3.8)	507 (3.0)		386 (3.7)	403 (3.9)	
NA	72 (0.7)	248 (1.5)		–	–	
Use of psychotropics[c]	2282 (21.8)	3308 (19.3)	<0.001	2238 (21.7)	2190 (21.2)	0.416
Use of opioids[c]	580 (5.5)	715 (4.2)	<0.001	572 (5.5)	530 (5.1)	0.193
Excessive polypharmacy[c]	1401 (13.4)	1626 (9.5)	<0.001	1374 (13.3)	1302 (12.6)	0.136
University hospital district			0.021			0.892
Oulu	1387 (13.2)	2214 (13.0)		1376 (13.3)	1344 (13.0)	
Kuopio	1864 (17.8)	3203 (18.7)		1854 (17.9)	1857 (18.0)	
Tampere	2258 (21.6)	3699 (21.6)		2239 (21.7)	2208 (21.4)	
Turku	1838 (17.6)	3157 (18.5)		1829 (17.7)	1833 (17.7)	
Helsinki	3056 (29.2)	4704 (27.5)		3035 (29.4)	3091 (29.9)	
Åland[d]/NA	71 (0.7)	125 (0.7)		–	–	
Other covariates included in the analysis						
Medication use[c]						
Antidiabetics	803 (7.7)	1284 (7.5)	0.629	794 (7.7)	830 (8.0)	0.352
Cardiovascular medications	7291 (69.6)	12,056 (70.5)	0.119	7195 (69.6)	7227 (69.9)	0.628
NSAIDs	4263 (40.7)	5579 (32.6)	<0.001	4211 (40.8)	3490 (33.8)	<0.001
Living alone[b]	3668 (35.0)	6588 (38.5)	<0.001	3644 (35.3)	3799 (36.8)	0.025
NA	73 (0.7)	245 (1.4)		–	–	

PSM propensity score matching, *PIM* potentially inappropriate medication, *NA* not available, *NSAID* nonsteroidal anti-inflammatory drug

[a]At the start of follow-up (1 Jan 2002)

[b]Year 2000

[c]At the washout period (years 2000–2001)

[d]Not included in the analyses

used theophylline instead of propranolol, which was used more often by women.

PIM use and associated risk of fractures

Overall, there were 128 (of which 28 occurred in the first PIM-use period) fractures during the 1-month PIM exposure period in the sample of 20,666 individuals. Over the 3-month period, there were 322 (94) fractures and with the 6-month period, 443 (252) fractures. PIM use was associated with an increased risk of fracture for all exposure periods, but the association was weak in the 1-month PIM exposure period (PSM-adjusted HR 1.20, 95% CI 1.01–1.44, $p=0.039$) (Table 2). After restricting our analyses to the first

Table 2 Associated risk of fracture within 1, 3 and 6 months PIM exposure periods in time-varying cox proportional hazards regression

	1 month			3 months			6 months		
	PSM-adjusted HR	95% CI	*p* value	PSM-adjusted HR	95% CI	*p* value	PSM-adjusted HR	95% CI	*p* value
The first PIM-use period[a]									
Non-users	1.00 (reference)			1.00 (reference)			1.00 (reference)		
PIM-users	1.61	(1.11–2.33)	0.013	1.50	(1.22–1.84)	< 0.001	1.38	(1.21–1.57)	< 0.001
Number of fractures	2351			2417			2575		
Number of fractures during PIM use	28			94			252		
PIM use (all exposure periods)									
Non-users	1.00 (reference)			1.00 (reference)			1.00 (reference)		
PIM-users	1.20	(1.01–1.44)	0.039	1.30	(1.16–1.46)	< 0.001	1.30	(1.17–1.43)	< 0.001
Age[b]									
65–74 years	1.00 (reference)			1.00 (reference)			1.00 (reference)		
75–84 years	1.85	(1.72–1.98)	< 0.001	1.85	(1.72–1.98)	< 0.001	1.85	(1.72–1.98)	< 0.001
≥ 85 years	3.35	(2.92–3.85)	< 0.001	3.34	(2.91–3.84)	< 0.001	3.34	(2.90–3.83)	< 0.001
Gender									
Male	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Female	1.77	(1.63–1.92)	< 0.001	1.77	(1.64–1.92)	< 0.001	1.77	(1.64–1.92)	< 0.001
Socioeconomic status (income)[c]									
< 9999 €	1.00 (reference)			1.00 (reference)			1.00 (reference)		
10,000–19,999 €	1.02	(0.94–1.10)	0.600	1.02	(0.95–1.10)	0.581	1.02	(0.95–1.10)	0.583
20,000–29,999 €	1.08	(0.95–1.24)	0.241	1.08	(0.95–1.24)	0.234	1.08	(0.95–1.24)	0.236
> 30,000 €	1.05	(0.87–1.26)	0.602	1.05	(0.88–1.26)	0.586	1.05	(0.88–1.26)	0.589
Living alone[c]	1.13	(1.05–1.21)	0.002	1.13	(1.05–1.21)	0.002	1.13	(1.05–1.21)	0.002
Medication use[d]									
Antidiabetics	1.16	(1.03–1.31)	0.014	1.16	(1.03–1.31)	0.017	1.16	(1.03–1.31)	0.017
Psychotropics	1.23	(1.14–1.33)	< 0.001	1.22	(1.13–1.32)	< 0.001	1.22	(1.13–1.32)	< 0.001
Cardiovascular medications	0.95	(0.88–1.02)	0.136	0.95	(0.88–1.02)	0.130	0.95	(0.88–1.02)	0.129
Opioids	1.16	(1.01–1.34)	0.039	1.16	(1.01–1.34)	0.042	1.16	(1.00–1.33)	0.043
NSAIDs	0.98	(0.91–1.05)	0.511	0.98	(0.91–1.04)	0.470	0.97	(0.91–1.04)	0.448
Excessive polypharmacy[d]	1.26	(1.14–1.39)	< 0.001	1.26	(1.14–1.38)	< 0.001	1.25	(1.14–1.38)	< 0.001
Number of fractures	3715			3715			3715		
Number of fractures during PIM use	128			322			443		
Number of subjects	20,666			20,666			20,666		

PSM propensity score matching, *PIM* potentially inappropriate medication, *HR* hazard ratio, *CI* confidence interval, *NSAID* nonsteroidal anti-inflammatory drug

[a]Adjusted for age, gender, socioeconomic status (income), living situation, morbidity (the use of antidiabetics, psychotropics, cardiovascular medications, opioids and nonsteroidal anti-inflammatory drugs) and excessive polypharmacy

[b]At the start of the follow-up (1 Jan 2002)

[c]Year 2000

[d]At the washout period (years 2000–2001)

PIM-use period, the associations between PIM use and the risk of fractures were stronger in all PIM exposure periods (1, 3 and 6 months).

PIM use and mortality

In total, there were 339 (of which 114 occurred in the first PIM-use period) deaths during PIM use in the 1-month exposure period, 940 (385) deaths in the 3-month exposure period, and 1365 (833) deaths in the 6-month exposure period (Table 3). PIM use was associated with an increased risk of death for all PIM exposure periods. The association was the strongest in the 6-month exposure period (PSM-adjusted HR 1.81, 95% CI 1.71–1.92, $p < 0.001$). When the follow-up was restricted to the first PIM-use periods, the results showed that the association with an increased risk of death was stronger in all first PIM-use periods. However, according to post-estimation tests, the assumption of proportionality was violated between PIM use and mortality, which means that the hazards for the groups were not constant over time. Figure 2 shows that the hazard curves for the PIM-users (with the 6-month exposure period) and non-users converge, and thus were not parallel.

PIM use and hospital costs

Hospital costs were 15% higher in those persons exposed to PIMs (Table 4). After hospital episodes, the main cost drivers in the model were excessive polypharmacy and the last year of life. When yearly zero costs were included in the analyses, meaning persons without hospitalisations, PIM-users had 50% higher hospital costs during the 12-year follow-up.

The unadjusted mean hospital costs were 60,114 euros (95% CI 58,434–61,793) in those PIM-users who were hospitalised and 52,435 euros (95% CI 50,483–54,388) in hospitalised non-users ($p < 0.001$) during the 12-year follow-up. Comparing the number of hospital episodes during the follow-up between PIM-users and non-users, the mean number of total hospital episodes was higher among PIM-users [33.9 (95% CI 32.9–34.9) vs. 22.4 (95% CI 21.8–23.0), $p < 0.001$], whereas the mean length of stay per episode was longer among non-users [4.7 days (95% CI 4.5–4.8) vs. 3.6 days (95% CI 3.5–3.7), $p < 0.001$]. In both groups, most of the hospital episodes were follow-up appointments (about 45–47% of the episodes) and inpatient care (almost 25%). The proportion of emergency care visits were approximately 13% of all episodes in both groups.

Discussion

In this longitudinal 12-year study, we found that PIM use was associated with an increased risk of fracture-specific hospitalisations and mortality in older people. In addition, our study indicated that PIM-users had higher hospital costs compared to non-users during the follow-up period.

Earlier studies have mainly analysed the association between PIM use and all-cause hospitalisation [13, 29, 30], and found that PIM use was associated with an increased risk of hospitalisation [13, 29–31]. We wanted to investigate fracture-specific hospitalisations, because there can be more uncertainty in causality between PIM use and all-cause hospitalisation. In addition, we investigated incident PIM use and treated PIM use as a time-varying variable. In most of the previous studies, PIM use was defined cross-sectionally [15]. Our results are in line with a study by Lu et al. [31], which found that PIM-users defined by the Beers criteria had a greater risk of fracture-specific hospitalisation. However, our results showed that the association was weak with the 1-month exposure period, and the risk increased with longer exposure periods. Nevertheless, our findings indicated that the risk of fracture-specific hospitalisation was greater, particularly in the first PIM-use periods. This result is consistent with a previous study that evaluated the association between PIM use (defined by Meds75+) and hip fracture in older persons with Alzheimer's disease in Finland [32]. Also, Henschel et al. [14] used the 1-month exposure period after taking a new PIM when studying the association between PIM use and adverse drug event-related hospitalisations, and found that PIM-users had over 50% higher risk of hospitalisation.

This study is one of the few studies [14, 16, 19] that takes into account endogeneity with PIM use to draw causal associations between PIM use and health outcomes or costs. Heider et al. [16] used entropy balancing and they found that PIM-users defined by the PRISCUS criteria had a greater use of health care services (measured by days in hospital and rehabilitation) and higher health care costs. A study by Chen and Cheng [19] used the instrumental variable (IV) approach and found that PIM use defined by the Beers criteria increased the risk of hospitalisation in older people in Taiwan. In the study, the likelihood of hospitalisation was even greater in the IV model compared to the model without IV.

Previous results of the association between PIM use and mortality were inconclusive. Most studies have not found significant associations between PIM use and mortality among community-dwelling older people [31, 33]. A recent review concluded that PIMs were associated with an increased risk of mortality only in studies with a new user design (which excluded prevalent users) [34]. Our findings

Table 3 Associated risk of mortality within 1, 3 and 6 months PIM exposure periods in time-varying cox proportional hazards regression

	1 month			3 months			6 months		
	PSM-adjusted HR	95% CI	*p* value	PSM-adjusted HR	95% CI	*p* value	PSM-adjusted HR	95% CI	*p* value
The first PIM-use period[a]									
Non-users	1.00 (reference)			1.00 (reference)			1.00 (reference)		
PIM-users	3.54	(2.94–4.26)	< 0.001	3.19	(2.88–3.55)	< 0.001	2.22	(2.06–2.39)	< 0.001
Number of deaths	4347			4618			5066		
Number of deaths during PIM use	114			385			833		
PIM use (all exposure periods)									
Non-users	1.00 (reference)			1.00 (reference)			1.00 (reference)		
PIM-users	1.38	(1.24–1.54)	< 0.001	1.67	(1.56–1.78)	< 0.001	1.81	(1.71–1.92)	< 0.001
Age[b]									
65–74 years	1.00 (reference)			1.00 (reference)			1.00 (reference)		
75–84 years	2.46	(2.34–2.58)	< 0.001	2.45	(2.34–2.57)	< 0.001	2.45	(2.34–2.57)	< 0.001
≥ 85 years	6.66	(6.13–7.24)	< 0.001	6.61	(6.08–7.18)	< 0.001	6.57	(6.04–7.14)	< 0.001
Gender									
Male	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Female	0.55	(0.52–0.58)	< 0.001	0.55	(0.53–0.58)	< 0.001	0.55	(0.53–0.58)	< 0.001
Socioeconomic status (income)[c]									
< 9999 €	1.00 (reference)			1.00 (reference)			1.00 (reference)		
10,000–19,999 €	0.93	(0.88–0.98)	0.009	0.93	(0.89–0.99)	0.012	0.94	(0.89–0.99)	0.013
20,000–29,999 €	0.81	(0.73–0.88)	< 0.001	0.81	(0.74–0.89)	< 0.001	0.81	(0.73–0.89)	< 0.001
> 30,000 €	0.71	(0.62–0.81)	< 0.001	0.71	(0.62–0.81)	< 0.001	0.71	(0.62–0.81)	< 0.001
Living alone[c]	1.11	(1.05–1.17)	< 0.001	1.11	(1.05–1.17)	< 0.001	1.11	(1.05–1.17)	< 0.001
Medication use[d]									
Antidiabetics	1.55	(1.45–1.67)	< 0.001	1.54	(1.43–1.65)	< 0.001	1.53	(1.43–1.64)	< 0.001
Psychotropics	1.19	(1.13–1.25)	< 0.001	1.18	(1.12–1.24)	< 0.001	1.17	(1.11–1.24)	< 0.001
Cardiovascular medications	1.30	(1.24–1.37)	< 0.001	1.30	(1.23–1.37)	< 0.001	1.30	(1.23–1.37)	< 0.001
Opioids	1.36	(1.24–1.48)	< 0.001	1.35	(1.24–1.48)	< 0.001	1.35	(1.24–1.48)	< 0.001
NSAIDs	0.87	(0.83–0.91)	< 0.001	0.87	(0.83–0.91)	< 0.001	0.87	(0.83–0.91)	< 0.001
Excessive polypharmacy[d]	1.49	(1.40–1.59)	< 0.001	1.49	(1.40–1.58)	< 0.001	1.48	(1.39–1.58)	< 0.001
Number of deaths	8033			8033			8033		
Number of deaths during PIM use	339			940			1365		
Number of subjects	20,666			20,666			20,666		

PSM propensity score matching, *PIM* potentially inappropriate medication, *HR* hazard ratio, *CI* confidence interval, *NSAID* nonsteroidal anti-inflammatory drug

[a]Adjusted for age, gender, socioeconomic status (income), living situation, morbidity (the use of antidiabetics, psychotropics, cardiovascular medications, opioids and nonsteroidal anti-inflammatory drugs) and excessive polypharmacy

[b]At the start of the follow-up (1 Jan 2002)

[c]Year 2000

[d]At the washout period (years 2000–2001)

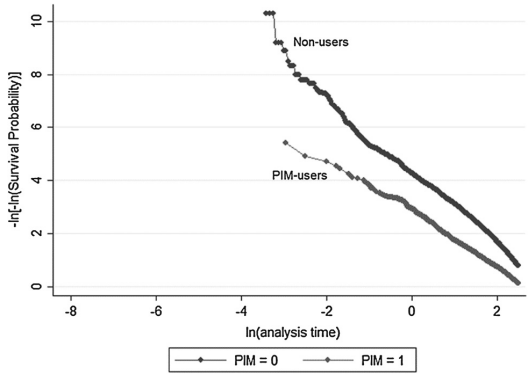

Fig. 2 Proportional hazard assumption test for PIM use (6-month exposure) in mortality analysis

of the increased risk of mortality with those exposed PIMs were consistent with the review. However, it seems that the association between PIM use and mortality is not simple, and there is something unobservable that our modelling cannot capture based on the proportionality assumption tests. Stratifying can be one solution for correction of the proportional hazard assumption, but we noticed that the underlying problem related the hazards between PIM-users and non-users, so the separate analyses between genders and age groups did not change the results of post-estimation tests (see Online Resource 3).

To our knowledge, this is the first study investigating health care cost associated with PIM use in Europe over a one-decade period. Our finding of higher hospital costs among PIM-users during the 12-year follow-up is in line with previous studies [16, 35]. Our results are explained by

Table 4 PIM use and associated all-cause hospital costs in PSM-adjusted fixed effects linear model

	Model without zero costs Dependent variable: logged hospital costs			Model with zero costs Dependent variable: logged $(x+1)$ hospital costs		
	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value
PIM use						
Non-users	1.00 (reference)			1.00 (reference)		
PIM-users	0.15	(0.12–0.18)	< 0.001	0.50	(0.44–0.55)	< 0.001
Medication use[a]						
Antidiabetics	− 0.12	(− 0.17–−0.06)	< 0.001	− 0.01	(− 0.11–0.09)	0.820
Psychotropics	0.20	(0.17–0.23)	< 0.001	0.40	(0.35–0.46)	< 0.001
Cardiovascular medications	0.04	(− 0.00–0.07)	0.054	0.33	(0.26–0.39)	< 0.001
Excessive polypharmacy[a]	0.76	(0.73–0.79)	< 0.001	1.94	(1.89–1.99)	< 0.001
Year						
2002	1.00 (reference)			1.00 (reference)		
2003	0.11	(0.07–0.15)	< 0.001	0.23	(0.16–0.29)	< 0.001
2004	0.17	(0.13–0.21)	< 0.001	0.33	(0.26–0.39)	< 0.001
2005	0.23	(0.19–0.28)	< 0.001	0.62	(0.55–0.69)	< 0.001
2006	0.20	(0.16–0.24)	< 0.001	0.75	(0.68–0.82)	< 0.001
2007	0.24	(0.20–0.28)	< 0.001	0.85	(0.78–0.92)	< 0.001
2008	0.28	(0.24–0.32)	< 0.001	1.00	(0.93–1.07)	< 0.001
2009	0.29	(0.25–0.33)	< 0.001	1.01	(0.93–1.08)	< 0.001
2010	0.35	(0.30–0.39)	< 0.001	1.17	(1.09–1.24)	< 0.001
2011	0.39	(0.34–0.43)	< 0.001	1.33	(1.25–1.41)	< 0.001
2012	0.45	(0.40–0.50)	< 0.001	1.42	(1.34–1.50)	< 0.001
2013	0.45	(0.40–0.50)	< 0.001	1.56	(1.48–1.64)	< 0.001
Year of death	1.22	(1.18–1.26)	< 0.001	2.68	(2.59–2.77)	< 0.001
Number of observations	110,577			190,856		
Number of subjects	20,180			20,666		
R-squared						
Within	0.1015			0.1011		
Between	0.1330			0.1705		
Overall	0.1155			0.1252		

PSM propensity score matching, *PIM* potentially inappropriate medication, *CI* confidence interval

[a]Defined yearly

the higher total number of hospital episodes among PIM-users during the study period. A study by Heider et al. [16] investigated total health care costs in a 12-month period, including also outpatient, rehabilitation and medication costs, and found that the biggest difference between PIM-users and non-users was caused by the mean hospitalisation costs. However, comparing the results with previous studies is problematic, for example, regarding different health care settings.

The main strength of this study is the large, nationally representative longitudinal 12-year register-based data. In Finland, as well as in other Nordic countries, the health registers are quite comprehensive and thus offer a valid opportunity to study medication use in the longitudinal setting [36]. We used a 2-year washout period to restrict our analyses to new PIM-users to avoid prevalent user bias [37]. One strength is that we decreased the possible endogeneity bias using propensity score matching. In addition, we restricted our analyses to the first PIM-use period, which decreases possible healthy survivor bias.

This study has some limitations that have to be considered. First, the Prescription Register includes data only from reimbursed medication purchases, so there was no information available on non-reimbursed medications, over-the-counter medications, vitamins or herbal products. Second, register-based information on medication purchases may not necessarily indicate that those medications were really taken by a patient. However, information on medication exposures is more valid based on registers than self-reported data [38]. Third, the Finnish criteria were published in 2010, and our follow-up started already in 2002, so there might be changes in prescribing practices and availability of medications. Fourth, our study evaluates only fracture-specific hospitalisations, but there are also other causes of hospitalisation that can be associated with PIM use. Fifth, our modelling cannot correct the violation of the proportional hazard assumption; thus our results on the association between PIM use and mortality should be interpreted carefully. Last, even though we used PSM analysis for controlling potential confounders associated with PIM use, there still is a possibility for unobserved heterogeneity that we cannot capture in register-based data (e.g. life style habits, quality of life, physician's knowledge and specialities).

Conclusion

We investigated the association between PIM use and health outcomes and costs in a longitudinal nationally representative data set with a matched cohort of PIM-users and non-users, which decreases the selection bias for PIM use. Our study indicated that particularly PIM initiation defined by the Finnish Meds75+ criteria is associated with an increased risk of fracture-specific hospitalisations and weakly associated with all-cause mortality. In addition, PIM-users had a higher number of hospital visits and thus, higher hospital costs, compared to non-users. Overall, health care providers should carefully consider these findings when prescribing PIM for older persons.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Beers, M.H., Ouslander, J.G., Rollingher, I., Reuben, D.B., Brooks, J., Beck, J.C.: Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch. Intern. Med. **151**(9), 1825–1832 (1991)
2. Tommelein, E., Mehuys, E., Petrovic, M., Somers, A., Colin, P., Boussery, K.: Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. Eur. J. Clin. Pharmacol. **71**(12), 1415–1427 (2015)
3. Leikola, S., Dimitrow, M., Lyles, A., Pitkälä, K., Airaksinen, M.: Potentially inappropriate medication use among Finnish non-institutionalized people aged ≥65 years: a register-based, cross-sectional, national study. Drugs Aging **28**(3), 227–236 (2011)
4. Bell, J.S., Ahonen, J., Lavikainen, P., Hartikainen, S.: Potentially inappropriate drug use among older persons in Finland: application of a new national categorization. Eur. J. Clin. Pharmacol. **69**(3), 657–664 (2013)
5. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel: American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J. Am. Geriatr. Soc. **63**(11), 2227–2246 (2015)
6. O'Mahony, D., O'Sullivan, D., Byrne, S., O'Connor, M.N., Ryan, C., Gallagher, P.: STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing **44**(2), 213–218 (2015)
7. Holt, S., Schmiedl, S., Thürmann, P.A.: Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch. Arztebl. Int. **107**(31–32), 543–551 (2010)
8. Renom-Guiteras, A., Meyer, G., Thürmann, P.A.: The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur. J. Clin. Pharmacol. **71**(7), 861–875 (2015)
9. The Finnish Medicines Agency.: Meds75+. (2015). http://www.fimea.fi/web/en/databases_and_registeries/medicines_information/database_of_medication_for_the_elderly. Accessed 5 Sept 2017
10. Hedna, K., Hakkarainen, K.M., Gyllensten, H., Jonsson, A.K., Petzold, M., Hagg, S.: Potentially inappropriate prescribing and

adverse drug reactions in the elderly: a population-based study. Eur. J. Clin. Pharmacol. **71**, 1525–1533 (2015)
11. Berdot, S., Bertrand, M., Dartigues, J., Fourrier, A., Tavernier, B., Ritchie, K., Alpérovitch, A.: Inappropriate medication use and risk of falls—a prospective study in a large community-dwelling elderly cohort. BMC Geriatr. **9**, 30–30 (2009)
12. Narayan, S.W., Nishtala, P.S.: Associations of potentially inappropriate medicine use with fall-related hospitalisations and primary care visits in older New Zealanders: a population-level study using the updated 2012 beers criteria. Drugs Real World Outcomes **2**(2), 137–141 (2015)
13. Endres, H.G., Kaufmann-Kolle, P., Steeb, V., Bauer, E., Böttner, C., Thürmann, P.: Association between potentially inappropriate medication (PIM) use and risk of hospitalization in older adults: an observational study based on routine data comparing PIM use with use of PIM alternatives. PLoS One **12**(2), e0146811 (2015)
14. Henschel, F., Redaelli, M., Siegel, M., Stock, S.: Correlation of incident potentially inappropriate medication prescriptions and hospitalization: an analysis based on the PRISCUS list. Drugs Real World Outcomes **2**(3), 249–259 (2015)
15. Hyttinen, V., Jyrkkä, J., Valtonen, H.: A systematic review of the impact of potentially inappropriate medication on health care utilization and costs among older adults. Med Care **54**(10), 950–964 (2016)
16. Heider, D., Matschinger, H., Meid, A.D., Quinzler, R., Adler, J.B., Günster, C., Haefeli, W.E., König, H.H.: Health service use, costs, and adverse events associated with potentially inappropriate medication in old age in Germany: Retrospective Matched Cohort Study. Drugs Aging **34**(4), 289–301 (2017)
17. do Nascimento, M.,M., Mambrini, J.V., Lima-Costa, M.F., Firmo, J.O., Peixoto, S.W., de Loyola Filho, A.I.: Potentially inappropriate medications: predictor for mortality in a cohort of community-dwelling older adults. Eur. J. Clin. Pharmacol. **73**(5), 615–621 (2017)
18. Klarin, I., Wimo, A., Fastbom, J.: The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. Drugs Aging **22**(1), 69–82 (2005)
19. Chen, C.C., Cheng, S.H.: Potentially inappropriate medication and health care outcomes: an instrumental variable approach. Health Serv. Res. **51**(4), 1670–1691 (2016)
20. Malmivaara, A.: Benchmarking controlled trial—a novel concept covering all observational effectiveness studies. Ann. Med. **47**(4), 332–340 (2015)
21. WHO Collaborating Centre for Drug Statistics Methodology.: The Anatomical Therapeutic Chemical Classification System. Structure and principles. 2011. http://www.whocc.no/atc/structure_and_principles/. Accessed 20 Jan 2017
22. Third edition of the Finnish version of the International Statistical Classification of Diseases and Related Health Problems.: 2011. https://www.julkari.fi/bitstream/handle/10024/80324/15c30d65-2b96-41d7-aca8-1a05aa8a0a19.pdf?sequence=1. Accessed 16 Aug 2017
23. Kapiainen, S., Väisänen, A., Haula, T.: Unit costs in social and health care in Finland in: 2011. Report 3/2014. National Institute for Health and Welfare. 2014. http://www.julkari.fi/bitstream/handle/10024/114683/THL_RAPO3_2014_web.pdf?sequence=1. Accessed 21 Dec 2017
24. Li, M.: Using the propensity score method to estimate causal effects: a review and practical guide. Organ. Res. Methods **16**(2), 188–226 (2013)
25. Caliendo, M., Kopeinig, S.: Some practical guidance for the implementation of propensity score matching. J. Econ. Surv. **22**(1), 31–72 (2008)
26. Hyttinen, V., Taipale, H., Tanskanen, A., Tiihonen, J., Tolppanen, A.M., Hartikainen, S., Valtonen, H.: Risk factors for initiation of potentially inappropriate medications in community-dwelling older adults with and without Alzheimer's disease. Drugs Aging **34**(1), 67–77 (2017)
27. Bradburn, M.J., Clark, T.G., Love, S.B., Altman, D.G.: Survival analysis Part II: multivariate data analysis—an introduction to concepts and methods. Br. J. Cancer **89**(3), 431–436 (2003)
28. Forma, L., Rissanen, P., Aaltonen, M., Raitanen, J., Jylha, M.: Age and closeness of death as determinants of health and social care utilization: a case-control study. Eur. J. Pub. Health **19**(3), 313–318 (2009)
29. Reich, O., Rosemann, T., Rapold, R., Blozik, E., Senn, O.: Potentially inappropriate medication use in older patients in Swiss managed care plans: prevalence, determinants and association with hospitalization. PLoS One **9**(8), e105425 (2014)
30. Varga, S., Alcusky, M., Keith, S.W., Hegarty, S.E., Canale, D., Lombardi, S., Maio, M.V.: Hospitalization rates during potentially inappropriate medication use in a large population-based cohort of older adults. Br J Clin Pharmacol **83**, 2572–2580 (2017)
31. Lu, W.H., Wen, Y.W., Chen, L.K., Hsiao, F.Y.: Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. CMAJ **187**(4), E130–E137 (2015)
32. Hyttinen, V., Taipale, H., Tolppanen, A.M., Tanskanen, A., Tiihonen, J., Hartikainen, S., Valtonen, H.: Incident use of a potentially inappropriate medication and hip fracture in community-dwelling older persons with Alzheimer's Disease. Ann. Pharmacother. **51**(9), 725–734 (2017)
33. Jano, E., Aparasu, R.R.: Healthcare outcomes associated with Beers' criteria: a systematic review. Ann. Pharmacother. **41**(3), 438–448 (2007)
34. Muhlack, D.C., Hoppe, L.K., Weberpals, J., Brenner, H., Schottker, B.: The association of potentially inappropriate medication at older age with cardiovascular events and overall mortality: a systematic review and meta-analysis of cohort studies. J. Am. Med. Dir. Assoc. **18**(3), 211–220 (2017)
35. Fu, A.Z., Jiang, J.Z., Reeves, J.H., Fincham, J.E., Liu, G.G., Perri, M.: Potentially inappropriate medication use and healthcare expenditures in the US community-dwelling elderly. Med Care **45**(5), 472–476 (2007)
36. Furu, K., Wettermark, B., Andersen, M., Martikainen, J.E., Almarsdottir, A.B., Sorensen, H.T.: The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin. Pharmacol. Toxicol. **106**(2), 86–94 (2010)
37. Ray, W.A.: Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol **158**(9), 915–920 (2003)
38. Rikala, M., Hartikainen, S., Sulkava, R., Korhonen, M.J.: Validity of the finnish prescription register for measuring psychotropic drug exposures among elderly Finns: a population-based intervention study. Drugs Aging **27**(4), 337–349 (2010)

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Potentially inappropriate medications (PIMs) are defined as medications that entail more risks than benefits for older people. Despite the risks of PIM being well known, PIM use is prevalent in older people. This dissertation examines demand and supply factors associated with the initiation of PIM use, and whether PIM initiation is associated with health care service use, costs and mortality by using nationwide register-based data.

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