The association between living alone, income and adherence to statin drug therapy

Riikka Sallinen

Väestötiede

Helsingin yliopisto

Maisterintutkielma

Tiivistelmä

Tiedekunta: Valtiotieteellinen tiedekunta

Koulutusohjelma: Sosiaalitieteiden maisteriohjelma

Opintosuunta: Väestötiede

Tekijä: Riikka Sallinen

Työn nimi: The association between living alone, income and adherence to statin drug therapy

Työn laji: maisterintutkielma

Kuukausi ja vuosi: Joulukuu, 2021

Sivumäärä: 45

Avainsanat: Adherence to drug therapy, living alone, socioeconomic position, myocardial infarction

Ohjaaja tai ohjaajat: Pekka Martikainen ja Kaarina Korhonen

Säilytyspaikka: Helda

Muita tietoja:

Tiivistelmä:

Non-adherence to drug therapy is a serious public health problem that increases the risk of disease and mortality. Despite long-term adherence to statins is a key element in preventing cardiovascular disease (CVD) and myocardial infarction (MI), previous studies have shown that the level of adherence drops already within the first six months of treatment. Risk factors for non-adherence are older age, comorbidities, being nonmarried and a lower socioeconomic position. Less is known about the role of living arrangements in non-adherence. The aim of this study is to provide new information on the association between living alone and non-adherence to statin drug therapy after MI, and analyze whether household income mediates or moderates the association.

The analysis utilizes a register-based dataset consisting of an 11 % sample of the Finnish population with an 80 % oversample of people who died between 1988 and 2007. The study population included patients with first hospitalization for MI and at least one purchase of statins. Individuals are followed for five years after MI and censored at the time of emigration, moving to institutional care, a recurring MI or death. General estimating equations (GEE) method, an application of logistic regression for correlated data, is used to analyze the associations. All analyses are conducted separately for men and women and are adjusted for age and year of medicine purchase.

Non-adherence to statin drug therapy increased over the first four years after MI, and a sharp increase occurred after the first three months of follow-up. Among men, the risk of non-adherence was higher for those living alone (odds ratio [OR] =1.24, 95% confidence interval [CI] 1.14–1.36) and those with lower incomes (OR=1.28, 95% CI 1.14-1.42 for lowest quintile). Adjustment for income somewhat attenuated the risk associated with living alone, while adjusting for education and labor market status had a negligible effect. Living alone predicted non-adherence similarly across all income groups among men. No statistically significant associations emerged among women.

In conclusion, men living alone have a higher risk of being non-adherent compared to men living with others. Lack of spousal support and generally poorer health behaviors can be mechanisms behind the observed association. Health care professionals should pay special attention to men living alone to identify patients in high risk of non-adherence. By improving medication adherence, lives and unnecessary healthcare costs can be saved.

Lääkemääräysten noudattamattomuus on vakava kansanterveydellinen ongelma, joka lisää sairastumisen ja kuoleman riskiä. Vaikka pitkäaikainen statiinilääkemääräysten noudattaminen on avainasemassa sydän- ja verisuonisairauksien ennaltaehkäisyssä ja hoidossa, tutkimuksissa on havaittu noudattamisen heikentyvän ensimmäisen puolen vuoden aikana lääkityksen aloittamisesta. Tiedettyjä ennustavia tekijöitä heikolle lääkemääräysten noudattamiselle ovat korkea ikä, oheissairaudet, naimattomuus ja alempi sosioekonominen asema. Asumisjärjestelyiden yhteydestä lääkemääräysten noudattamiseen ja sydänkohtauksen jälkeisestä lääkemääräysten noudattamisesta tiedetään vähemmän. Tässä tutkielmassa tavoitteena on tutkia yksinasumisen yhteyttä statiinilääkemääräysten noudattamiseen sydänkohtauksen saaneilla ja kotitalouden moderoivaa vaikutusta.

Tutkielmassa käytetään rekisteriaineistoa, joka koostuu 11 %:n otoksesta Suomen väestöstä ja 80 %:iin asti lisätyllä otoksella vuosina 1988 – 2007 kuolleista. Tutkimusotokseen sisällytettiin kaikki ensimmäisen sydänkohtauksen saaneet potilaat, joilla oli vähintään yksi statiiniosto. Potilaita seurattiin viisi vuotta mutta seuranta lopetettiin, jos potilas muutti maasta, siirtyi laitoshoitoon, sai uuden sydäninfarktin tai kuoli. Analysoinnissa käytettiin GEE-menetelmää (general estimating equations), joka on logistisen regression sovellus pitkittäisaineistolle. Kaikki analyysit tehtiin erikseen naisille ja miehille ja ikä ja lääkkeen ostovuosi vakioitiin malleissa.

Lääkemääräysten noudattamattomuus yleistyi ensimmäisen neljän seurantavuoden aikana ja erityisesti ensimmäisen kolmen kuukauden jälkeen. Miehillä yksinasuminen (vetosuhde [OR]=1.24, 95%:n luottamusväli [CI] 1.14–1.36) ja alempiin tuloryhmiin kuuluminen (OR=1.28, 95% CI 1.14-1.42 alimmassa tulokvintiilissä) kasvattivat noudattamattomuuden todennäköisyyttä. Tulojen vakiointi heikensi yksinasumisen yhteyttä, mutta koulutuksen ja työmarkkina-aseman vakioinnilla ei ollut huomattavaa vaikutusta. Yksinasuminen ennusti miehillä lääkemääräysten noudattamattomuutta samalla tavalla kaikissa tuloryhmissä. Naisilla tilastollisesti merkitseviä yhteyksiä ei löytynyt.

Johtopäätöksenä yksinasuvilla miehillä on suurempi riski lääkemääräysten noudattamattomuuteen sydänkohtauksen jälkeen verrattuna ei yksin asuviin miehiin. Puolison tuen puuttuminen ja yleisesti huonompi terveyskäyttäytyminen voivat olla selittäviä tekijöitä yhteyden taustalla. Terveydenhuollon työntekijöiden tulisi kiinnittää erityistä huomiota yksinasuvien miesten lääkemääräysten noudattamiseen. Hoitoon sitoutumisen parantamisella voidaan pelastaa henkiä ja säästää terveydenhuoltokuluissa.

Content

1. Introduction

According to World Health Organization's (WHO) estimates, adherence to drug therapies in chronic conditions is approximately 50 % in postindustrial countries. (WHO, 2003) Poor adherence hampers the effectiveness of treatments and increases the risk of serious illnesses and death (Herttua et al., 2013, 2016), which makes it an urgently important topic to study.

Over the recent decades, treatment of chronic illnesses has improved, which has also contributed to the increasing life expectancy. Medication is a key element in the treatment of chronic conditions. In Finland, prevention and care of cardiovascular diseases (CVD) has been successful (Puska et al., 1985; Vartiainen et al., 2010) even though myocardial infarction (MI) remains one of the leading causes of death (Statistics Finland, 2020). Furthermore, due to population ageing and rising prevalence of obesity, the incidence of MI may increase in the future (Lahey & Khan, 2018).

Statins play a central role in the treatment of CVD and the prevention of MI. However, only an estimated 55–73 % adhere to the prescribed statin treatment (Aarnio et al., 2016; Benner et al., 2002; Helin-Salmivaara et al., 2008). Poor adherence to statin drug therapy increases the risk of both the recurrence of MI and death. (Herttua et al., 2013, 2016) However, less is known about adherence to statin drug therapy after MI. Most of the research concerns the medication use of new statin users (Aarnio et al., 2014, 2016; Helin-Salmivaara et al., 2008; Herttua et al., 2016) and only few studies focus on adherence after MI (Benner et al., 2002; Pietrzykowski et al., 2020; Rasmussen et al., 2007)

Previous studies have identified several risk factors for poor adherence to drug therapy, including older age (Mann et al., 2010), being nonmarried (DiMatteo, 2004), lower income, lower level of education (Aarnio et al., 2016) and retirement (Kivimäki et al., 2013). By contrast, people who have comorbidities or acute conditions are more likely to follow the medication recommended by physicians (Jackevicius et al., 2002). However, the effect of living arrangements on adherence to drug therapy remains unknown in the recent literature.

Knowledge on health behavior concerning medication use is needed in order to improve adherence to drug therapy. It is important to study the characteristics of risk groups in

order to direct the support to right places efficiently. In addition to hampering treatment effects among patients, poor adherence to statin drug therapy causes unnecessary costs to society and puts pressure on the health service system. By improving adherence to drug therapy, lives can be saved, unnecessary operations avoided and costs cut.

This study provides new information on statin use after MI in the Finnish context. By using register-based data on medication purchases, the association between living alone, income and adherence to drug therapy is studied. Other social factors including education and labor market status are also considered. Analyses are conducted separately for men and women.

This thesis takes the following structure. First, definition, dimensions and former studies regarding adherence to drug therapy are presented in chapter 2. I will shortly discuss the different factors predicting adherence to drug therapy in the context of cardiovascular diseases in this chapter as well. In chapter 3, risk factors and medications for CVD and MI are discussed. Theoretical framework of health behavior and mechanisms behind living arrangements, socioeconomic position and health behavior are discussed in chapter 4 and the aim of this study and research questions in chapter 5 before moving to data and methods in chapter 6. Chapter 7 is for results and finally, the chapter 8 is for conclusion and discussion.

2. Adhrence to drug therapy

WHO (2003) defines adherence as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." That is, whether people take their medication as prescribed or not and if they continue to take the medication long enough. Adherence to drug therapy thus has two dimensions, adherence and persistence (Ho et al., 2009) and includes initiation, implementation and discontinuation of the treatment (Lam & Fresco, 2015). Commonly, adherence is reported as the proportion of the prescribed doses of medication that is actually taken by the patient in a certain period. (Osterberg & Blaschke, 2005) It has been estimated that only 50 % of patients with chronic conditions adhere to drug therapies in developed countries and in developing countries, the level of adherence is even lower. Poor adherence to drug therapies is thus considered a global public health problem and the impact of poor adherence will grow as the burden of chronic diseases grows. Noncommunicable and chronic diseases are prevalent both in developed and developing countries and the number of cases will increase alongside aging societies. (WHO, 2003)

In addition to adherence to drug therapy in general, adherence has been studied in the context of specific illnesses, such as CVD, diabetes, HIV and AIDS, and many others (WHO, 2003). This study focuses on treatment of CVD and MI, conditions that mostly affect patients of older age, and are thus increasingly important in the ageing populations not only in developed but also in developing countries. MI is an acute and often fatal condition (Duodecim, n.d.), the prevention of which relies both on health behavior modification and medication (Osterberg & Blaschke, 2005; Prochaska & Prochaska, 2011).

2.1. Measures of adherence

In general, measures of medication adherence can be divided into subjective and objective measures, and into direct and indirect measures. Subjective measures include patient self-reports and healthcare professionals' assessments, for instance. A major limitation of subjective self-reports is that patients often tend to underreport non-

adherence to avoid disapproval of health care providers. Reliable estimates require that patients would report their behavior accurately and without over- or underestimation. Nevertheless, due to simplicity and low costs, self-reports remain popular in medication adherence research field. (Lam & Fresco, 2015)

Objective measures, by contrast, include pill counts, electronic monitoring, secondary database analysis, and biochemical measurements. In secondary database analysis, the data can be collected, for example, from electronic prescription services, where medication purchases are measured in intervals so that refilling is assumed to correspond to the medication-taking behavior (Lam & Fresco, 2015; Grymonpre et al., 2006). Several ways to operationalize adherence to drug therapy has been used: adherence can indicate the total number of medication purchases within a certain period, or patients can be classified as adherent or non-adherent based on certain criteria. Previous studies have also examined the number or length of gaps between consumption, (Lam & Fresco, 2015) or measured the Proportion of Days Covered (PCD). An often used cut-off for adherent vs. non-adherent patients is that the patient is taking 80 % or more of the prescribed medication (Aarnio et al., 2014; Herttua et al., 2013, 2016; Lesén et al., 2011). Compared to objective measures, subjective measures can provide higher level of sensitivity, by giving more detailed information on medication use, but not accuracy into the measurement because of the high risk of over- or underestimation. In an ideal situation, both types of measures could be used in combination and thus objective measures can be used to validate subjective measures. (Lam & Fresco, 2015)

The measures described above are considered as indirect measures of adherence. Direct measures, by contrast, include measuring drug concentration in body fluids by using, for example, blood samples. Direct measures are considered the most accurate measures of medication use but are not very popular due to high costs and sample taking difficulties because it demands many professionals to carry out the tests. Direct measures may also be problematic due to differences in metabolism: For example, some psychiatric medications can be detected in the blood long after stopping the medication use. However, the level of drug plasma can differ by individual characteristics and the quantification can be difficult. (Lam & Fresco, 2015)

2.2. Poor adherence to drug therapy

Poor adherence commonly shows in untimely discontinuation of prescribed medication. The first months are critical as the level of adherence often drops within the first six months, especially in chronic conditions. (Osterberg & Blaschke, 2005) For example, over a 10-year follow-up of older people in the US, adherence to statin drug therapy dropped from 80 % to 56 % during the first six months. (Benner et al. 2002) Helin-Salmivaara et al. (2008) studied new statin users and their long-term persistence to statin therapy between 1995 and 2005. They found that adherence fell after the first year of follow-up to 73 % of patients continuing the drug therapy. In another Finnish paper of new statin users, only approximately 55 % were adherent after the first year of statin therapy (Aarnio et al., 2014). A study from the US focused on secondary prevention and long-term adherence to medication after MI. The researchers followed 292 MI patients for ten years and found that after 3 years less than 50 % of the patients continued medications. (Shah et al., 2009)

In acute conditions, by contrast, the level of adherence appears to remain at a somewhat higher level (Osterberg & Blaschke, 2005). For example, Jackevicius et al. (2002) reported that two-year adherence to statin drug therapy in elderly patients with acute coronary syndrome was 40 %, as compared to patients with chronic coronary artery disease, among whom adherence decreased to 36 %. In addition, patients with comorbidities, such as diabetes or hypertension, were more likely to adhere to statin drug therapy compared to patients with no comorbidities. A systematic review also concluded that the level of adherence is higher among patients with a history of MI or stroke, compared to those without (Mann et al., 2010).

Poor adherence has serious public health implications. Patients with poor adherence are at an increased risk for several adverse health outcomes and death. For example, Herttua et al. (2013) studied antihypertensive drug purchases from the Finnish prescription register between 1995 and 2007, and found that non-adherent patients had over two times higher odds of hospitalization and three times higher odds of fatal stroke compared to adherent patients in a 2-year follow-up.

Kim et al. (2016) found similar results in their study of newly diagnosed hypertensive patients with prescription to antihypertensive medication in South Korea. They found

that patients with intermediate adherence (taking 50–80 % of medication) had a 43 % higher risk and patients with poor adherence (taking less than 50% of medication) had an 81 % higher risk of cardiovascular disease mortality compared to patients with good adherence to their medication. Also, the risk of hospitalization increased alongside of poor adherence. In another study, patients, who failed to adhere to statin or antihypertensive drug therapies, had an increased risk of fatal stroke (Herttua et al., 2016).

There are several factors that may explain poor adherence to drug therapy on individual level. For example, attitudes, lack of knowledge, difficulty to understand or follow the regimes and interaction between patient and doctor may affect medication adherence (Osterberg & Blaschke, 2005). Patients can make intentional or unintentional decisions not to adhere. Intentional non-adherence may relate to assumed side effects or ineffectiveness of the medication. In addition, high price of medicine or difficulties in the interaction between doctor and patient may lead to non-adherence. Asymptomatic diseases, such as diabetes or hypertension, may cause a sense of false security that encourages to reduce medication use (Huupponen & Strandberg, 2020; Kivimäki et al., 2013). Unintentional non-adherence, by contrast, may be due to complicity of treatment, large portions of medication prescribed, or oversight (Huupponen & Strandberg, 2020). These underlying factors are important to acknowledge but typically remain unobserved in research data.

2.2.1. Predictors of poor adherence to drug therapy

Age is a consistent predictor of non-adherence to statins, and the association follows a U-shaped curve. A systematic review concluded that non-adherence to the prescribed statin drug therapy was more likely among patients aged 50 years or less and those aged 70 years or more compared to the middle aged (aged 50-65 years). (Mann et al., 2010) In older adults in particular, non-adherence may relate to mental factors such as poor memory, lower cognitive function, anxiety and sleeping difficulties, as well as physical factors including high body mass index and poor physical or self-rated health. (Yap et al., 2016) Non-adherence in older ages may also relate to retirement. Kivimäki et al. (2013) found that the risk of poor adherence (less than 40 % of days covered by the purchased medication) to hypertensive and type 2 diabetes drug therapy increased after

retirement. It is thus possible that the changes in daily routines following retirement and the shift from occupational health care to public health care can interrupt treatment.

Systematic review of gender differences in statin adherence showed that women were more likely to be non-adherent compared to men. The scholars suggested that mechanisms behind these differences could be attitudes towards and knowledge of the medication and its effects, and a higher risk of side effects among women. In addition, elderly women are most likely group to be prescribe statins but the risk of non-adherence increases in older ages. (Goldstein et al., 2016) However, there is an inconsistency in the former literature on the association between gender and adherence to drug therapy since some studies find no gender differences (Helin-Salmivaara et al., 2008), while others have found higher non-adherence among men (Aarnio et al., 2016).

Consistent evidence, by contrast, exists for that being married increases the probability of medication adherence in general (DiMatteo, 2004). Similar findings have been reported also in the context of antihypertensive (Trivedi et al., 2008) and statin therapies (Pietrzykowski et al., 2020). In a study of 225 patients followed up for a year, married patients were more likely to adhere to the prescribed statin treatment compared to the unmarried and widowed (Pietrzykowski et al., 2020). In addition to being married, living with others was related to better medication adherence in general compared to those living alone (DiMatteo, 2004).

Several studies have also reported an association between lower education (Aarnio et al., 2016; Rasmussen et al., 2007), employment status (Kivimäki et al., 2013; Pietrzykowski et al., 2020) and adherence to drug therapy. For example, Aarnio et al. (2016) found an association between socioeconomic position and medication adherence: a low socioeconomic position in terms of the level of education, occupation and income predicted poorer adherence to drug therapy among new statin users. The association was statistically significant among men but not among women. Another study found that employment and higher education were associated with better adherence to statin drug therapy (Pietrzykowski et al., 2020). A Danish study found that the association between education and adherence disappeared after adjusting for income (Rasmussen et al., 2007) indicating that lower incomes may at least partly explain non-adherence of the lower educated.

Other studies have found the association between income and adherence to drug therapy as well. A meta-analysis by Mann et al. (2010) found that patients with lower income were less likely to adhere to statin treatment. A Finnish study of new statin users measured patient, health and payment related factors as potential predictors of adherence to statin drug therapy. Patient-related factors were age, gender, area of living, number of inpatient days and medical condition. Health-related factors included information about the prescription, such as initiation year and area of specialty of the prescriber. Payment-related variables included information on the costs of the medication for the patient. The main finding of the study was the negative association between high out-of-pocket cost of the medicine and adherence to the medication. Higher out-of-pocket costs were associated with lower odds of good adherence (OR 0.80 and 95 % CI 0.80 to 0.80). (Aarnio et al., 2014)

Lee et al. (2019) studied the combined effect of income and medication adherence on mortality in hypertension. They measured medication adherence by proportion of days the purchases covered and divided adherence to good (at least 80 %), moderate (50 to 80 %) and poor (less than 50 %). Low income predicted 66 % higher risk of poor adherence compared to high income. Patients with low incomes were not only more likely to be non-adherent but had also the highest risk of death if they non-adhere (hazard ratio [HR] 2.46 and 99 % CI 2.38 to 2.54, when poor adherence high income group had HR 1.46 and 99 % CI 1.41 to 1.51, both compared to highest income good-adherence group). Poor medication adherence increased mortality in all income groups but the absolute risk of mortality was higher in lower income groups.

2.3. Summary

Most of the studies concerning adherence to statin drug therapy are conducted on patients in primary prevention, which means that the patients are mainly new statin users with no history of CVD. Only few studies have focused on post-MI adherence on statins (Rasmussen et al., 2007; Shah et al., 2009). The generalizability of these studies, however, remains limited because either the sample size was relatively small for a longitudinal study (Shah et al., 2009) or the focus of the study was not on the level of adherence in the long run but rather on the initiation of treatment (Rasmussen et al., 2007).

Previous studies have identified several predictors of poor medication adherence, such as older age (Mann et al., 2010), female gender (Goldstein et al., 2016), nonmarried status (DiMatteo, 2004; Pietrzykowski et al., 2020; Trivedi et al., 2008), and a lower socioeconomic position (Aarnio et al., 2016; Lee Hokyou et al., 2019; Rasmussen et al., 2007). Less is known about the association between living alone and medication adherence. In particular, it remains unknown whether living alone increases the risk of non-adherence in the context of an acute and potentially fatal condition such as MI. In addition, the evidence of the role gender plays in these associations remains inconclusive as some studies only find and association among men and other studies among both men and women (Aarnio et al., 2016).

3. Cardiovascular disease and statin drug therapy

MI is a serious event where a sudden narrowing or blockage of the coronary artery causes lack of oxygen to the heart muscle, which starts to destroy heart cells. MI in most cases requires hospital care. Every year in Finland approximately 20,000 people suffer from MI and 6,000 people die before reaching the hospital. (Aho & Porola, 2013),

There are several risk factors for MI, many of which relate to health behaviors. For instance, high body mass index (BMI), smoking and dietary factors including high amount of salt and saturated fat are well-established risk factors for MI. Health-related risk factors also include hypertension, diabetes and prior MI. (Laatikainen et al., 2019) In addition, family history of MI and genetic predisposition increase the risk of MI. (Vartiainen et al., 2010) The incidence is higher among men than women and increases with age (Aho & Porola, 2013). Despite the decreasing rates of smoking and hypertension, the strongly increasing obesity rate is a major public health problem and likely contributes to increase the incidence in CVD and MI in Finland (Laatikainen et al., 2019) and in other developed countries (Lahey & Khan, 2018) in the coming decades.

There is a strong socioeconomic pattern in MI incidence. Lower socioeconomic status, education and income are well-established predicators of MI. (Backholer et al., 2017) In addition, childhood circumstances, such as household crowding and parental socioeconomic position, are associated with higher risk of MI in adulthood (Kilpi, 2017). Marital status is also a known predictor of both MI incidence and mortality, as being nonmarried increases the risk of MI and dying with MI (Wong et al., 2018). Living arrangements are associated with MI incidence and survival: Living with spouse reduces risk of MI incidence and mortality compared to living alone or with other people than spouse (Kilpi et al., 2015).

3.1. Statin drug therapy

High levels of LDL cholesterol increase the risk of acute conditions, including MI and ischemic stroke. In order to lower LDL cholesterol levels and thus prevent CVD and

mortality, statin drug therapy is often initiated. At best, intensive statin treatment can even lower the incidence of MI. Especially after an MI event, patients are prescribed several different medications such as statins, cardiac aspirin, ACE inhibitors, and beta-blockers. Use of statins and cardiac aspirin are usually continued permanently (Duodecim, n.d.).

Statins have been reported to carry some negative side effects. A meta-analysis concerning trials of statin therapy found that statins increased the risk of incident diabetes by 9 %. In addition, there is evidence that statins may cause muscular pain and myopathy. The risk of these side effects increase in long-term use, usually after 12 months. (Molokhia et al., 2008) According to a review article, muscular pain or myalgia is the most common side effect with 1–10 % of patients suffering from them. Up to 1 % of statin users also suffer from problems in liver function. (Ramkumar et al., 2016) These side effects have received publicity more than those of other medicines used in cardiovascular treatment (Kahri & Syvänne, 2012), which may contribute to poor adherence to statin drug therapy.

4. Conceptual framework

Adherence to drug therapy is an important form of health behavior and key factor in preventing serious illnesses (Osterberg & Blaschke, 2005). Health behavior includes a wide range of personal life choices and factors related to lifestyle, such as diet, physical activity, and addictions including smoking and alcohol-related habits. (Prochaska & Prochaska, 2011) Poor health and health behaviors systematically differ across socio-demographic groups: People in low socioeconomic positions and people living alone experience higher rates of morbidity and mortality (Holt-Lunstad et al., 2015; Lahelma et al., 2004; Tabue Teguo et al., 2016; van Raalte et al., 2018). Thus, living alone and socioeconomic position are known indicators of health behavior. In this chapter, I conceptualize how living alone and socioeconomic position may be associated with health behavior and thereby also with medication adherence.

4.1. Living arrangements and health behavior

The association between marital status and mortality is well established and consistent across different diseases, indicating that married people are consistently healthier compared to other groups (Manzoli et al., 2007; Roelfs et al., 2011; Shor et al., 2012). In a meta-analysis by Manzoli et al. (2007), widowed were reported to have 11 %, divorced 16 % and never married 11 % higher risk of death compared to married people. Similar patterns have been discovered in the study of living arrangements and mortality: According to a meta-analysis, people living alone have 32 % increased likelihood of mortality, respectively (Holt-Lunstad et al., 2015).

The association between marital status and mortality has been stronger among men (Hu & Goldman, 1990) and older people (Kiecolt-Glaser & Newton, 2001). However, more recent studies have found the gap between men and women narrowing while the singles' relative risk of death has slightly increased compared to married people. This would suggest that living outside of marriage is becoming equally harmful for men and women. At the same time, increasing number of people never get married and the social pressure of getting married has decreased. This development would challenge the earlier theories suggesting that the damaging effect of remaining nonmarried would be due to

the stress and social pressure of being married. (Manzoli et al., 2007; Roelfs et al., 2011)

It has been argued that the protective effect of social relationships such as marriage is mostly due to social influence and control over the spouse's health behavior. Especially women are believed to control the health behavior of the spouse in their relationships. Therefore, marriage has traditionally been more important to the health of men than women, and marriage dissolution due to divorce or spouse's death has thus been more detrimental to the health of men than women. (Umberson, 1992)

Not only marriage but living together with other people overall may provide social support and social ties that are important for one's well-being. Social support has been found to be a strong positive predictor of health behavior whereas loneliness has been found to be a strong negative predictor of health behavior (Yarcheski et al., 2004) that may increase the risk of death (Tabue Teguo et al., 2016). Social ties to family members living in the same household are often qualitatively different compared to other relationships (Hughes & Waite, 2002) meaning that family members can provide more emotional support and have stronger impact on health when they are living in the same household and sharing the everyday life compared to other relatives and friends.

Social and emotional support is important when dealing with stress. The importance of social support is emphasized especially in dramatic life events, such as MI (Berkman et al., 1992). In addition, social relations support daily routines (Hughes & Waite, 2002) and provide standards on good health practices (Yarcheski et al., 2004), which are important in health behavior and especially in adherence to drug therapy. Loneliness, on the other hand, can weaken the motivation to take care of oneself and to carry out positive health practices. (Yarcheski et al., 2004) However, family relationships can also make more dramatic damage to individuals compared to any other relationships (Hughes & Waite, 2002). For example, health-damaging behaviors, such as alcohol abuse, can be transmitted between family members (Li et al., 2010).

In addition to these causal accounts, other potential mechanisms behind the association between living arrangements and health behavior include direct and indirect selection. Direct selection means that people with poor health behaviors are more likely to remain single, divorce or become widowed. (Martikainen et al., 2005) In other words, people who are not married, may be a select group because of their poor health or unhealthy

behaviors. For example, couples with one heavy drinker have elevated risk of divorce compared to couples where both partners have similar drinking habits (Ostermann et al., 2005). Direct selection is also at play when, for example, older people with poor health and disabilities live in the same household with their children or move to institutionalized care since they cannot manage on their own. Indirect selection, by contrast, refers to mechanisms where a third factor causes both the poor health and living alone. For example, a lower education or socioeconomic status is a strong predictor of both chronic conditions as well as being nonmarried and living alone. (Martikainen et al., 2005)

4.2. Income, socioeconomic position and health behavior

It has been estimated that in Finland there is circa five-year difference in life expectancy between highest and lowest income quintiles (van Raalte et al., 2018). A lower income is associated with higher incidence of (Manrique-Garcia et al., 2011) and mortality in CVD and MI (Avendano et al., 2006) as well as in other diseases (Stringhini et al., 2017).

Differences in health and mortality are evident not only in terms of income but also in terms of any measure of socioeconomic status including education and occupational social class (Kunst et al., 2005; Mackenbach et al., 2008). A higher education gives access to higher positions in the labor market and higher salaries, but it may also provide understanding of health behaviors and their consequences. Occupational characteristics, by contrast, define the workload and autonomy and indicate the social status and position in the society. Income and wealth define material resources, determine purchasing power and resources needed in maintaining good health. (Lahelma et al., 2004) The production of inequalities in health is a complex process and these three measures of socioeconomic position are interdependent but also reflect unique dimensions of socioeconomic position and may thus affect health behaviors independently. (Lahelma et al., 2004) This also means that it is not possible to establish universal causal links between socioeconomic position and health behavior.

However, material, psychosocial and behavioral factors are suggested as pathways between socioeconomic position and health. The materialist explanations suggest that socioeconomic differences in health are mostly due to unequal distribution of resources.

Income and wealth promote better living circumstances and give the possibility to choose healthier options, private health care, and cover the medication costs. (Moor et al., 2017) The materialist explanations also suggest that material and structural conditions, such as crowded housing, neighbourhood conditions, employment status and physical work load, differ across socioeconomic groups and produce health differences (Granström et al., 2015). The psychosocial explanations, on the other hand, suggest that negative life events, chronic stress, low mastery and social support are unequally distributed between socioeconomic groups contributing to the inequalities in health. The behavioral explanations take into account poor health behavior, such as substance abuse, smoking, diet and low physical activity in lower socioeconomic groups. (Granström et al., 2015; Moor et al., 2017) The three pathways operate in relation to each other (Moor et al., 2017). For example, low household income may produce poorer health as it reduces opportunities to choose but may also cause chronic stress in long-term.

5. Aim of the study, relevance and research question

The broad aim of this master's thesis is to enhance our knowledge about the factors associated with adherence to drug therapy. More specifically, the objective is to study the prevalence of non-adherence to statin drug therapy in the five years following MI, and to analyze whether and how living alone and household income predict non-adherence.

There are three key physiological and clinical reasons to study adherence to statin dug therapy after MI. First, MI is considered as a serious attack that carries a high risk of fatal outcomes and in most cases requires hospital care. The prevention of both newly prevalent and recurrent cases is important, and adherence to statin drug therapy is among the most important factors in lowering the risk of recurrence and mortality (Herttua et al., 2013, 2016). Second, compared to other medications after MI, statins are prescribed to all patients and treatment generally is for the rest of the life. (Duodecim, n.d.). This fact gives more confidence and reliability to measuring adherence, since we can expect that patients should be using statins. On the other hand, it means that statins are widely used medications and knowledge of their use is needed both on the individual and population levels. Third, in previous studies statin use has been assessed mainly among newly prescribed statin users, and less is known about the long-term trends of statin use after MI. Since poor adherence hampers the effectiveness of statins, and any untimely discontinuation of statins after MI may have serious health consequences, it is important to identify patients in risk of non-adherence to support long term compliance with treatment.

On the population level, the study of adherence to drug therapy is important for several reasons. Due to ageing populations and rising obesity rates, the prevalence of chronic conditions and particularly the prevalence of risk factors for MI, including hypertension and diabetes mellitus, may rise (Laatikainen et al., 2019; Lahey & Khan, 2018). Accurate information of primary and secondary prevention of these illnesses is needed. Non-adherence to drug therapy causes unnecessary costs for society. By improving adherence to drug therapies, significant cost-saving can be reached because the increased costs of prescribed medications are still lower than the special care interventions that would otherwise be needed (WHO, 2003).

Finally, knowledge about adherence to drug therapy is important for policy makers to direct support to the right places. By investigating predictors of non-adherence to drug therapies, interventions for improving adherence can be made. (WHO, 2003) More detailed knowledge about the risk factors will also help physicians to recognize patients in risk of non-adherence (Osterberg & Blaschke, 2005). More awareness of non-adherence and its risk factors need to be raised to improve treatment and to help patients to better adhere to drug therapy (WHO, 2003).

There is evidence that both living alone and being non-married are associated with poorer health behaviors in general. (Holt-Lunstad et al., 2015; Manzoli et al., 2007; Roelfs et al., 2011; Shor et al., 2012) In addition, marital status is shown to have an association with adherence to drug therapy; being married is associated with better adherence compared to being widowed or non-married (Pietrzykowski et al., 2020). However, little is known about the association between living alone and adherence to statin drug therapy, especially after MI. This knowledge is thus urgently needed.

It has been suggested that a potential mechanism linking living arrangements and health is income. In two-adult families, the household income consists of the incomes of both partners, bringing more stability and financial security. People living alone, by contrast, on average have a lower level of income security. It is thus possible that the poorer health behaviors of people living alone partly relate to their lower household incomes. On the other hand, it could be hypothesized that the presence of other family members is particularly important for the health behaviors of people with low incomes. It is thus important to disentangle whether living alone is most harmful for those in lower socioeconomic position or if it is equally harmful for all.

The research questions are:

1. What is the prevalence of non-adherence to statin drug therapy up to five years following MI?
2. How are living alone and household income associated with non-adherence to statin drug therapy?
3. Is the (potential) association between living alone and non-adherence to statin drug therapy mediated by household income?

4. Is the (potential) association between living alone and non-adherence to statin drug therapy moderated by household income, i.e. does the association differ between income groups?

6. Data and Methods

6.1. Data

The data set I am using is a register-based data set from Statistics Finland. It is an 11 % sample from the longitudinal Employment statistics' data between 1987 and 2007, with an 80 % oversample of people who died between 1988 and 2007. In total, the data include 1,274,813 individuals who have turned 15 years on 31.12.2007 at latest. Every individual has a technical identification number by which the information from different data sets is linked together. Statistics Finland provides basic sociodemographic information, such as gender, date of birth and death, employment, education and income measured annually for all individuals in the sample.

There is a linkage to information on medication purchases from the register of Social Insurance Institution of Finland and hospitalization from the register of National Institute for Health and Welfare. The prescription registry includes dates of medication purchases, WHO Anatomical Therapeutic Chemical (ATC) codes and daily doses of drugs, and is available from 1995 onwards. Hospitalization data is available from 1969 onwards including International Classification of Diseases (ICD) 8th, 9th and 10th Revision codes for diagnoses.

6.2. Methods

Design and outcome. All patients who were hospitalized for MI for the first time and had their first purchase of statins between 1995 and 2015 are included in the study. The hospitalization cases and the exact dates of entry to hospital are identified from the register with ICD-8 and ICD-9 code 410 and ICD-10 codes I21 and I22.

The statin purchases are identified from the data with ATC codes C10AA. All statin purchases after the first hospital in-patient care episode are linked to the individuals including the date of purchase and the exact ATC code. Because one purchase of prescribed medicine can cover maximum of three months' dose (*Kerralla korvattava lääkemäärä*, n.d.), the purchases for each patient are measured in 91-day intervals. The patient is considered as non-adherent if she or he does not have any purchases of statins in that interval and adherent if she or he has at least one purchase of statins during the

three-month period. A dummy variable of non-adherence (non-adherent=1, adherent=0) was used for each interval.

The follow-up of patients after the first statin purchase is 5 years and patients are censored from the follow-up if they die, emigrate, move to institutionalized care or get a recurring MI. The exact death and hospitalization dates are known and the timing of moving abroad or to institutionalized care are taken from the end of year's information. From the 62,394 patients, those who had fatal MI (n = 16,279) based on the date of hospitalization and the date of death, moved to institutionalized care during the year of first MI (n = 2,665), were not part of the population at the end of the year of MI (n = 7,040) or did not initiate the treatment, were excluded. Final number of patients is 12,079.

The following sociodemographic factors for each patient are measured: living arrangements, household income, highest completed degree, main type of economic activity, age and gender. All covariates are measured and updated annually and the information is collected from the end of each year.

Main exposures are living alone and household income. Living alone is coded as a dummy variable: living with other people (0) and living alone (1). For measuring material resources of patients, household income is measured and categorized into quintiles. To avoid the problem of inflation over time, annual income quintiles are used. Income quintiles are constructed using the equalized disposable income. It is the total disposable income of all household members, i.e. income after tax and other deductions, divided by the number of household consumption units. The modified OECD equivalence scale is used to weight each member according to their age to obtain these consumption units. As a result, income can be compared between households of varying structures. (*Glossary:Equivalised Disposable Income - Statistics Explained*, n.d.)

Confounding factors are education, labor market status and age. Education is divided into three categories based on the highest completed degree: primary or unknown, secondary and tertiary education. Labor market status is classified into four groups using the information on person's main activity: employed, unemployed, retired and other. Age is measured in years.

Statistical methods. To describe the study population, cross tabulation is used. Since the original data set is not a random sample but contains an oversample of deaths, weights are used to correct for the sampling design.

For the main analyses, binary logistic regression is used to model the relationship between an outcome variable and a set of independent variables. Logistic regression analysis differs from linear regression because the outcome variable is binary, meaning that it can only get values 0 or 1, i.e., the response variable is categorical in two groups. (Hosmer, 2013, 1-2)

Fitting a logistic regression model starts by estimating unknown beta parameters. This is done by using a likelihood function. After fitting the coefficients, the probability of an occurring event can be calculated by the link function, which in the case of logistic regression is the logit transformation. In order to define the logit difference between two values of a covariate and to make the interpretation of the difference more intuitive, odds ratios (OR) are calculated. Odds are calculated as the probability of occurring event divided by its negation. OR is a ratio of odds of two values within a covariate (for example, x=1 and x=0). OR approximates how likely or unlikely it is for the outcome to occur in a given group (x=1) compared to the reference group (x=0). If odds ratio is smaller than 1, the outcome is less likely to occur among the first group compared to reference group and if the odds ratio is greater than 1, the outcome is more likely to occur in the first group compared to reference group. (Hosmer, 2013, 8-10; 49-51)

Since the data are longitudinal repeated data, logistic regression for correlated data is used. In the dataset, there are several observations for each patient. The observations for the same patient are not independent and that is why the model for correlated data is needed. Generalized estimating equations (GEE) method can be used to calculate odd ratios for population average model. Under the population average model the estimates are averages over the patients. The GEE model takes into account the within-patient correlations by using weights. The weights use an approximation of underlying covariance matrix of the correlated within-patient observations with an assumption about the structure of the correlation. (Hosmer, 2013, 318) In this study, auto-regressive correlation structure is used, since it is considered appropriate when there is a time component associated with the observations (Hosmer, 2013, 318).

Three regression models are fitted in order to study the associations. First, separate models for each covariate including living alone and socioeconomic factors are estimated. This model answers the second research question of whether living alone and household income are associated with non-adherence to statins. Living arrangement and income are included to the second model and all covariates to the third model and these models answer the third research question of whether the association between living alone and non-adherence is mediated by household income. Last, moderating effect of income is studied between living alone and non-adherence to statin drug therapy to answer the fourth research question. Moderation is analysed by including an interaction term to model 2 and Wald test is used to test the interaction. Analyses are conducted separately for men and women (interaction between living alone and gender was close to statistical significance: $\chi^2=3.45$, $P=0.06$; and interaction between income and gender was statistically significant: $\chi^2=15.63$, $P<0.00$) using the 95 % confidence level ($\alpha = 0.05$). 95 % confidence intervals (CI) are reported with the estimates. The study design is presented in the Figure 1. All analyses are conducted using Stata version 16.

Figure 1: Study design
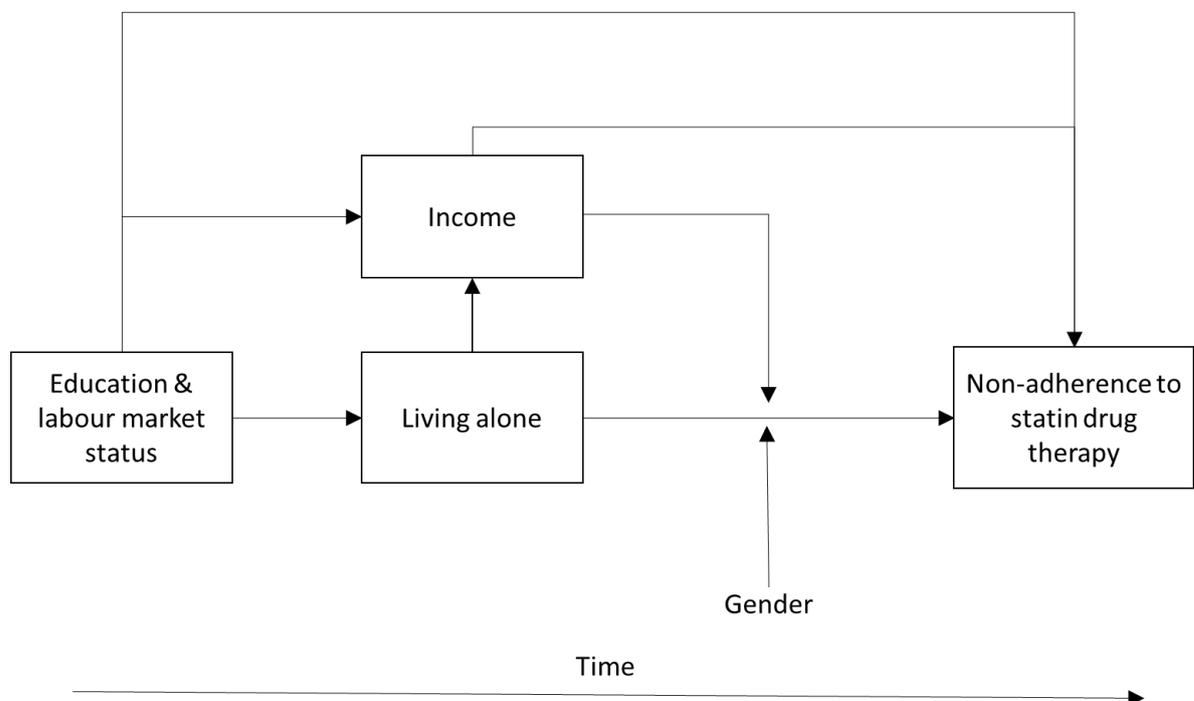
7. Results

Table 1 contains baseline characteristics of the study population with observed frequencies and weighted proportions. Majority of the study population, 65.5 %, were men. The mean age was 64.5 years among men and 71.9 years among women. 20.2 % of men and 47.0 % of women lived alone at baseline. Almost one third of women were in the lowest income quintile whereas largest proportion of men were in the highest quintile. In addition, among both men and women, the majority had only primary level education. Most of the men and women were retired.

Weighted proportions of non-adherent intervals (i.e., 3-month intervals with no statin purchases) in every group are presented in Table 1. 27.0 % of the intervals were non-adherent among men and 25.7 % among women. Both men and women living alone had a higher proportion of non-adherent intervals compared to men and women not living alone. Among men, non-adherence was more frequent in the lower household income quintiles, whereas no such pattern emerged among women. No clear pattern in education was found. Among men, unemployed had higher proportion (31.7 %) of non-adherent intervals compared to other labor market groups.

Table 1: Descriptive statistics and proportion of statin non-adherent intervals, N=12,079

	N (%)	Men Proportion of non-adherent intervals	N (%)	Women Proportion of non-adherent intervals
In the follow-up	7,632 (65.5)	27.0	4,447 (34.5)	25.7
Mean age (SD)	64.5 (11.3)		71.9 (10.8)	
Mean time of follow-up in 91-day periods (SD)	14.3 (6.9)		13.2 (7.2)	
Living arrangements				
Living alone	1,613 (20.2)	30.0	2,128 (47.0)	25.5
Not living alone	6,019 (79.8)	26.3	2,319 (53.0)	25.0
Household income quintiles				
Lowest	1,247 (15.8)	29.6	1,312 (30.6)	24.8
Second	1,463 (17.9)	28.0	944 (22.3)	24.3
Third	1,468 (20.4)	27.2	732 (18.7)	24.5
Fourth	1,407 (21.1)	25.3	600 (15.6)	25.6
Highest	1,485 (24.7)	25.3	424 (12.8)	26.8
Education				
Primary	4,752 (54.3)	27.0	3,327 (69.3)	24.8
Secondary	1,709 (27.7)	28.2	786 (20.8)	26.5
Tertiary	1,171 (17.9)	24.7	334 (9.8)	26.0
Labour market status				
Employed	729 (12.2)	26.9	104 (3.8)	23.0
Unemployed	276 (4.8)	31.7	49 (1.9)	22.4
Retired	5,309 (64.2)	26.5	3,731 (83.5)	24.6
Other	1,318 (18.8)	27.6	563 (10.8)	32.3

Figure 2 presents unadjusted weighted proportions of statin non-adherent patients in the 20 intervals by baseline living arrangements among men. Figure 3 shows same setting as figure 2 but for women. Visual inspection of the differences suggests that men living alone had the highest level of non-adherence over time, and are the only group clearly standing out. Among women, the lines are crossing and no clear pattern can be seen.

No major gender differences in non-adherence emerged either in table 1 or in figures 2 and 3. According to figures 2 and 3, the level of non-adherence increased in the first four years of the follow-up reaching approximately 33 to 37 % among men and 30 to 33 % among women after three and a half years of follow-up. The major increase emerged during the first period of follow-up both among men and women.

Figure 2: Proportion of statin non-adherent patients by baseline living arrangements, men
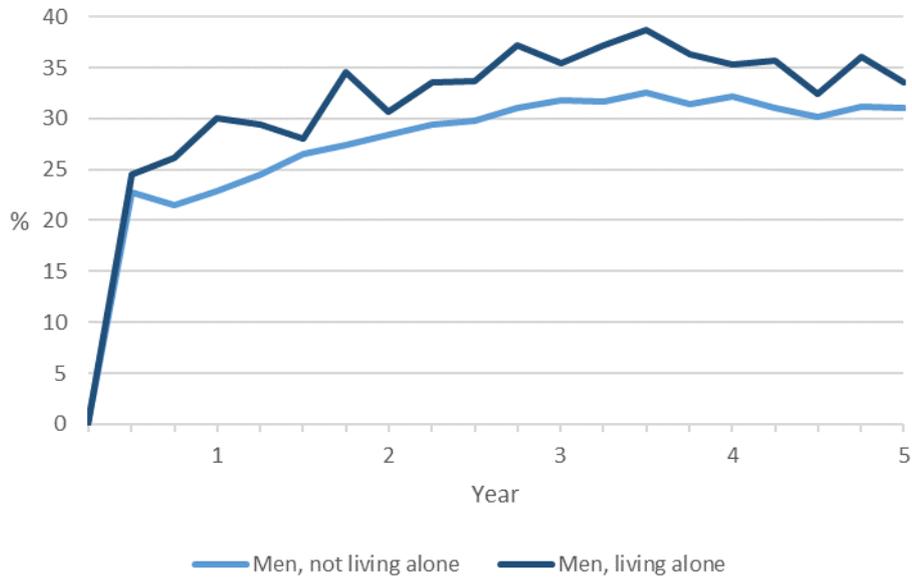

Figure 3: Proportion of statin non-adherent patients by baseline living arrangements, women
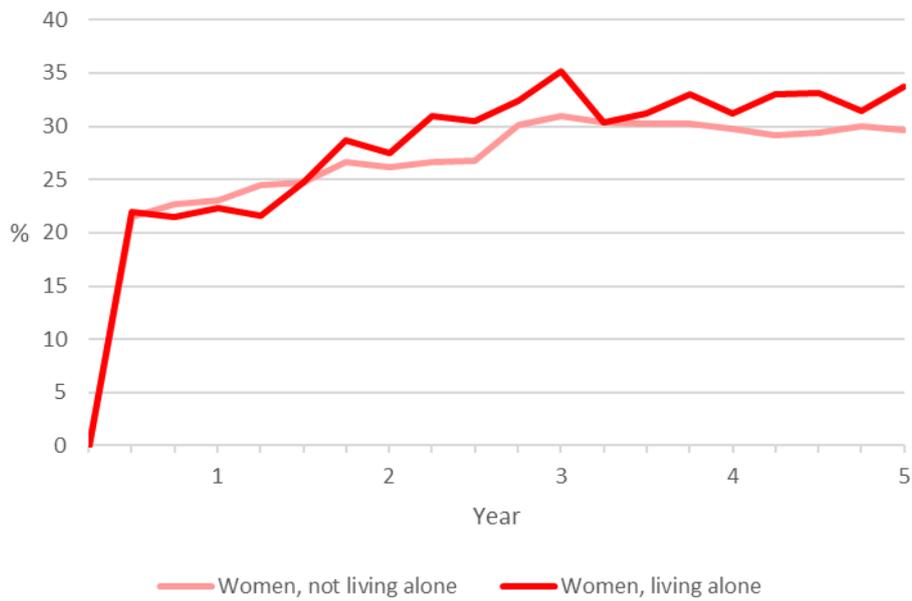
Table 2 presents ORs from the fitted logistic regression models for statin non-adherence among men. All models are adjusted for age and calendar year. Model 1 contains the ORs of fitted logistic regression separately for each covariate. Men living alone had higher odds (OR 1.24, 95 % CI 1.14 – 1.36) of statin non-adherence compared to men who live with others. A gradient in the association with income can be seen: the lower the level of income the higher the odds of being non-adherent to statin drug therapy; only the odds ratio of the fourth income quintile did not differ from the reference category. The lowest income quintile had an OR of 1.28 (95 % CI 1.14 – 1.42) when the reference category was the highest income quintile. Education was also associated with non-adherence to statins. Patients with secondary education had 20 % higher odds and primary education 14 % higher odds of being non-adherent compared to patients with tertiary level education. In addition, male patients who were unemployed, had higher odds (OR 1.22, 95 % CI 1.01–1.46) to be non-adherent compared to employed patients.

Model 2 presents mutually adjusted ORs for living alone and the level of income. Men living alone had 20 % higher odds (OR 1.20, 95 % CI 1.09–1.31) of being non-adherent compared to men who live with others. Men in the lowest income quintile had 20 % higher odds (OR 1.20, 95 % CI 1.08–1.34) of being non-adherent compared the highest income quintile. Men in second quintile had 15 % higher odds (OR 1.15, 95 % CI 1.04–1.27) and males in third quintile had 14 % higher odds (OR 1.14, 95 % CI 1.04–1.25) compared to men in the highest quintile.

Further adjustment for education and labor market status (model 3) only slightly attenuated the association between living alone and non-adherence to statin drug therapy (OR 1.19, 95 % CI 1.09 – 1.30). In addition, the three lowest income quintiles were statistically significantly associated with non-adherence to statins.

Table 2: Logistic regression for non-adherence to statin drug therapy, men

	MODEL 1[†]		MODEL 2		MODEL 3	
	OR	*95 % CI*	*OR*	*95 % CI*	*OR*	*95 % CI*
Living arrangements						
Not living alone	1		1		1	
Living alone	**1.24**	1.14-1.36	**1.20**	1.09-1.31	**1.19**	1.09-1.30
Household income quintile						
Highest	1		1		1	
Fourth	1.00	0.91-1.09	1.03	0.95-1.12	1.02	0.94-1.11
Third	**1.15**	1.05-1.26	**1.14**	1.04-1.25	**1.12**	1.02-1.23
Second	**1.18**	1.07-1.30	**1.15**	1.04-1.27	**1.13**	1.01-1.26
Lowest	**1.28**	1.14-1.42	**1.20**	1.08-1.34	**1.17**	1.04-1.32
Education						
Tertiary	1				1	
Secondary	**1.20**	1.07-1.34			**1.14**	1.02-1.29
Primary	**1.14**	1.02-1.26			1.07	0.97-1.19
Labour market status						
Employed	1				1	
Unemployed	**1.22**	1.01-1.46			1.10	0.92-1.32
Retired	1.00	0.87-1.15			0.95	0.83-1.09
Other	1.05	0.92-1.21			1.02	0.89-1.17

0=adherent, 1=non-adherent

[†]separate analysis for each covariate

Table 3 shows the corresponding associations for women. In model 1, the OR of living alone was 1.07 (95% CI 0.96–1.20). ORs for household income indicated a reversed association as compared to men; the odds of statin non-adherence was lower for lower income quintiles. Only the second lowest quintile, however, was statistically significant (OR=0.84, 95% CI 0.71– 0.99). For education and labor market status, no consistent pattern emerged either. These associations did not substantially change following adjustments in model 2 and model 3. In the full model 2, living alone was associated with an OR of 1.09 (95% CI 0.97–1.23) for statin non-adherence among women.

Table 3: Logistic regression for non-adherence to statin drug therapy, women

	MODEL 1[1]		MODEL 2		MODEL 3	
	OR	*95 % CI*	*OR*	*95 % CI*	*OR*	*95 % CI*
Living arrangements						
Not living alone	1		1		1	
Living alone	1.07	0.96-1.20	1.10	0.98-1.24	1.09	0.97-1.23
Household income quintile						
Highest	1		1		1	
Fourth	0.96	0.82-1.12	0.95	0.82-1.11	0.91	0.76-1.09
Third	0.93	0.79-1.10	0.92	0.78-1.09	0.84	0.71-1.00
Second	**0.84**	0.71-0.99	**0.82**	0.70-0.97	0.94	0.80-1.11
Lowest	0.92	0.78-1.10	0.88	0.74-1.05	0.91	0.76-1.09
Education						
Tertiary	1				1	
Secondary	0.96	0.80-1.15			1.11	0.90-1.37
Primary	1.06	0.86-1.30			1.00	0.83-1.21
Labour market status						
Employed	1				1	
Unemployed	0.90	0.61-1.32			0.92	0.63-1.36
Retired	0.83	0.63-1.07			0.85	0.65-1.10
Other	1.10	0.85-1.44			1.12	0.86-1.47

0=adherent, 1=non-adherent

[1]separate analysis for each covariate

Interaction analysis was conducted for the model 2 in order to find out whether the association bewteen living alone and non-adherence to statin drug therapy is different between income groups. No statistically significant interactions were found either in men (χ^2=1.88, *P*=0.76) or women (χ^2=0.70, *P*=0.95) indicating that the association between living alone and non-adherence to statins is similar across all income groups. The result implies that, in all income groups, men living alone have a higher probability of being non-adherent to statins compared to men who do not live alone, while among women, living alone is not assoicated with non-adherence to statin drug threrapy.

8. Discussion

Adherence to drug therapy is an important part of health behavior and has a major role in preventing illness and recurrence. The first aim of this study was to describe the prevalence of non-adherence to statins up to five years after MI to capture the temporal dimension of non-adherence. For both men and women, non-adherence increased over the first four years. About one in three patients were non-adherent four years after MI. The temporal patterns of non-adherence were similar for men and women.

The increasing level of non-adherence over time has been found in previous studies as well. It is widely known that adherence usually drops after six months of treatment (Osterberg & Blaschke, 2005). However, the estimated level of adherence differs between studies, partly depending on the study design as well as measurement of adherence and possibly depending on the study context. Shah et al. (2009) estimated that 66 % were non-adherent in a three-year follow-up after MI in US. They only had 292 participants in their follow-up which raises concerns of the coverage of the study. On the other hand, it is possible that there are differences between countries and in US non-adherence would be more common. However, more research on country level differences is needed to be confident. Register-based study of new statin users in Finland found 45 % of the patients being non-adherent after first year of treatment. (Aarnio et al., 2014). Another register-based study of long-term adherence to statins found that 27 % of the new statin users were non-adherent already after the first year of follow-up (Helin-Salmivaara et al., 2008). In this study, non-adherence was slightly lower (i.e. adherence was higher) compared to the study of Aarnio et al. (2014) but very close to the study of Helin-Salmivaara et al. (2008). This small difference can also be partly due the fact that adherence is usually higher in acute conditions compared to chronic (Jackevicius et al., 2002).

The second research question was whether living alone is associated with non-adherence to statin drug therapy. Logistic regression model was fitted to study the association. Living alone was statistically significantly associated with non-adherence to statins among men: men who lived alone had a 24 % higher odds of being non-adherent compared to men who did not live alone. The result is in line with a meta-analysis concerning adherence to drug therapy in different conditions: Living with other people was associated with better adherence to drug therapies in general (DiMatteo,

2004). Also married patients are more likely to be adherent compared to never married, widowed or divorced (Pietrzykowski et al., 2020; Trivedi et al., 2008). No similar patterns were found among women as the associations remained statistically nonsignificant. This means that women living alone had similar risk of being non-adherent as women living with other people. The mortality differences by marital have traditionally been weaker among women as well (Hu & Goldman, 1990) which would suggest that women have better health behavior in general independently of their living arrangements. In addition, relatively small sample size in this study may weaken the statistical power of the estimates among women.

The third question was whether the association between living alone and non-adherence is mediated through household income. Among men, adjustment for household income somewhat attenuated the association between living alone and non-adherence indicating that a small part of the association was mediated though income. Further adjustment for education and labor market status as confounders had only minor effect on the estimates. Among women, the association between living alone and statin non-adherence remained statistically nonsignificant in all adjustment models. This founding is consistent with Aarnio et al. (2016) who found a statistically significant association between socioeconomic position and adherence to statin drug therapy among men but not women, meaning that adherence is poorer among men in lower socioeconomic positions but not among women.

Low household income was strongly associated with higher probability of non-adherence among men. The association between income and adherence has been found in previous studies as well (Lee Hokyou et al., 2019; Mann et al., 2010; Rasmussen et al., 2007). Meta-analysis of statin non-adherence found high income patients being systematically more adherent compared to low income patients (odds of non-adherence 0.85 for high income, 95 % CI 0.78 to 0.91) (Mann et al., 2010). Rasmussen et al. (2007) got similar results in their study of statin and beta blocker use after MI in Denmark. They found a clear gradient between income and initiation of the treatment. After adjusting for income, the effect of education disappeared and the scholars suggested that income could be mediating the effect of education. In this study, education was not strongly associated with adherence to statins and the association similarly disappeared after adjusting for income and labor market status.

Finally, moderation between living alone and household income was not observed. No statistically significant interaction either among men or women emerged, which implies that the association between living alone and non-adherence to statin drug therapy is similar in all income groups. This means that living alone predicts non-adherence to statins despite the level of household income among men. The household income could rather have a mediating effect between living alone and non-adherence than moderating since adjusting for income attenuated the association between living alone and non-adherence. However, the mediating effect seems relatively small, which implies that there are different mechanisms behind the living alone and the income. This founding is new as no previous studies have studied the moderating effect of income in the association between living alone and non-adherence to drug therapy.

8.1. Mechanisms and further research topics

Further discussing the mechanisms behind the associations, there could be two possible theoretical explanations behind the association between living alone and non-adherence: a lack of spousal support and control (Hughes & Waite, 2002) and selection (Martikainen et al., 2005). First, medication taking is based on routines and long-term persistence to following the prescription. Control and support of the spouse (Hughes & Waite, 2002) or other family member can be an important factor to ensure adherence. Forgetting, lack of knowledge or difficulties to understand the regimes are common reasons for non-adherence to drug therapy (Osterberg & Blaschke, 2005). Comorbidities, such as dementia, as well as other mental state factors can make it more difficult to adhere to statins (Yap et al., 2016). In these situations the spousal control and support are especially important to help statin users to remain adherent.

On the other hand, MI is a serious and shocking event and spousal support can be an emotionally important factor after hospitalization (Berkman et al., 1992). Support of family members could give better motivation to keep oneself in good health. Men in single households can suffer from loneliness and have less motivation to keep themselves in good health compared to men who live with their family members. (Yarcheski et al., 2004)

Men living alone can be a select group with a higher likelihood of unhealthy behaviors and (Martikainen et al., 2005) of poor health. Statin non-adherence may also reflect one dimension of such unhealthy behaviors that are more prevalent among men living alone. The association between living alone and non-adherence to statins could be thus partly explained by selection mechanisms; men living alone may be a select groups in terms of poorer health behaviors and greater morbidity, in which case the unhealthy behaviors are not because of a lack of a spouse but the spouse is lacking because of poor health. In addition, unhealthy behaviors may also cause lower incomes though, for example, unemployment or disability pension. Such selection mechanisms could be hypothesized considering that medication non-adherence is one of many dimensions of health behavior.

Mechanism behind the association between income and non-adherence to statin drug therapy can be lack of resources, according to the materialist explanations (Moor et al., 2017). The theory would suggest that differences in adherence to drug therapy by income level are mainly due to medicines being too expensive to people with lower incomes. In addition, it is possible that the feeling or fear of poverty and economic deprivation affect people so that they start to cut all the costs no matter of their impact. This explanation could refer more to psychosocial explanation that argues chronic stress being unequally distributed between socioeconomic groups (Lahelma et al., 2004; Moor et al., 2017). The lack of resources and the fear of poverty and economic deprivation could explain why patients with lower household income are more likely to non-adhere.

Other given explanations for socioeconomic differences are related to willingness to treatment. For instance, due to negative publicity of statins and their side effects, many patients might have prejudice against statins (Kahri & Syvänne, 2012). Rasmussen et al. (2007) suggested that one reason for socioeconomic differences in adherence might be that patients in lower socioeconomic positions are less willing to treat an asymptomatic condition. Kivimäki et al. (2013) made the same suggestion when studying retirement and adherence to hypertensive and type 2 diabetes treatment. Asymptomatic conditions may give a false sense of security and lower the barrier to stop the treatment. Education could be in major role and affect adherence to statins by giving better understanding of healthy behavior, affecting one's attitudes and giving more mental resources (Lahelma et al., 2004). The idea of willingness to treatment could also support the behavioral explanation (Moor et al., 2017).

Since household income and living arrangements independently predicted non-adherence and the differences between men living alone and men living with others is not due to the economic contribution of cohabitants, the results support the idea that the mechanisms behind the associations are different as well. The lack of spousal support and control seems plausible mechanism behind the association between living alone and non-adherence whereas the lack of resources could explain the association between household income and non-adherence. However, these mechanisms cannot be directly measured from register-based data and thus remain on hypothetical level. For further research, additional survey data would be useful to study the pathways between living arrangements, income and non-adherence to statin drug therapy.

There are several interesting topics for future research. First, an interesting topic would be to further analyze the association between living alone and non-adherence after MI and continue to analyze how it is associated with MI fatality and overall mortality. Since it is known that poor adherence increases the risk of MI recurrence and fatality (Herttua et al., 2013, 2016), the observed differences in non-adherence could partly explain the social differences in MI mortality in general.

Another topic would be to focus research on living arrangements by dividing it to more specific groups, with the assumption that living only with spouse is qualitatively different compared to living with other family members. This would give more information on how the observed association between living arrangements and adherence comes about. Is the difference in non-adherence mainly between single men and married men living with their spouses or are there other high or low risk groups that were not identified in this study? It would be interesting to compare married people to those who live with someone else, for example only with children. This would give more information on the mechanisms as well: Is spousal support the main mechanism behind healthier behavior or are the other factors affecting health behaviors?

8.2. Methodological considerations

In this study, high quality register-based data was used for all analyses. By using register-based data, accurate information on medication purchases and socioeconomic factors can be reached. Similar information both on medication purchases and

sociodemographic factors would be difficult to obtain from other sources. Another strength of register-based data is that it enables follow-up over years and relatively large sample sizes. What remains unknown is, whether patients take the medication in the end. However, secondary database information on medication purchases is widely considered as a reliable measure of medication intake (Grymonpre et al., 2006). Statins are prescribed to all patients after MI and usually for the rest of their lives (Duodecim, n.d.), which gives more confidence for measuring adherence. The non-adherence should not be due to not needing the medication any more.

One limitation of this study is the loss of observations at baseline due to low level of first purchases compared to number of patients suffering from MI. The sample included only those patients who initiated the statin treatment after their first MI and initiation of treatment differs significantly over time. Because of this, calendar year was adjusted for in all analyses to account for the timing of treatment. Low level of first purchases has also been observed in previous literature. For instance, a previous study of statin use after MI found that in 1995 approximately 16 % and in 2002 approximately 68 % claimed the statin prescription at the pharmacy within 6 months (Rasmussen et al., 2007).

The loss of observations has two possible implications. First, including only those who initiated the treatment excludes the group of patients who remain non-adherent from the beginning and thus gives smaller estimates for the level of non-adherence. In other words, the level of non-adherence is at least 30 % after four years of follow-up but could be even higher if all patients surviving MI were included. Second, the loss of observations hampers the statistical power of the analyses which possibly reduces the size of estimates and enlarges the confidence intervals. Larger sample size could enable more accurate estimates for the predicting factors and increase the representativeness of the sample.

Another limitation of this study is related to measuring non-adherence. In this study, non-adherence was measured as a dichotomous variable based on whether patients had a purchase in a three-month interval. This is different from the majority of the studies where the cut-off for adherence is 80 % of the days covered (proportion of the days covered, PDC) (Aarnio et al., 2014; Herttua et al., 2013, 2016; Lesén et al., 2011). Some studies have used three-level scale for adherence (Kim Soyeun et al., 2016; Lee

Hokyou et al., 2019). Dichotomous scale was chosen to make the results simpler to interpret and to increase the sensitivity of the outcome measure, but it might affect the observed level of non-adherence. An interesting topic for further research would indeed be to measure adherence to drug therapy using a more sensitive scale. For example, Aarnio et al. (2016) presented six different trajectories estimating long-term statin use in their study of new statin users in Finland. They identified near perfect adherence, mild non-adherence, slowly declining adherence, rapidly declining adherence, varying adherence and very rapidly declining adherence. A scale like this gives more information on the temporal dimension of adherence compared to observed proportions in dichotomous scale adherent – non-adherent.

In this study, change in non-adherence was modelled as observed proportions of non-adherent patients in each three-month interval. The decline of adherent patients stopped after four years. This can be due to relatively long follow-up time considering the patients' age and health: The number of patients in the follow-up starts to decline after three years, and the proportion of those who still are in the follow-up after the average follow-up time, have a higher probability of being adherent. This could explain the smoothing or mild U-shape of the curve. Using Kaplan-Meier curves instead of observed proportions shows that a change of non-adherence in time could have been modelled in more detail. However, non-adherence was understood as a changing state rather than once occurring event and for that reason Kaplan-Meier method was not suitable. Another way could have been to estimate adjusted means from the logistic regression model, which would allow adjusting for age and year of follow-up, for instance. In addition, a larger sample size would give more reliable estimates of the change in adherence over time.

When measuring living alone on dichotomous scale only, interesting information on those who do not live alone is lost and the reference group includes different subgroups, such as married couples as well as parents living with their children. However, the focus of this study was more on those who live alone and therefore the classification is justified.

Finally, it is important to consider the role of selection. Previous studies show that patients suffering from MI are a selected group by socioeconomic status (Backholer et al., 2017) and living arrangements (Kilpi et al., 2015). Furthermore, patients surviving

the MI are selected group as well. This means that people suffering from MI are more likely to be in lower socioeconomic positions and to have had poorer health behavior before hospitalization. MI is a serious and often fatal condition (Duodecim, n.d.), but patients in this sample have survived and are thus in better health compared to people with fatal MI. Therefore, the sample in this study is selected already by suffering from MI and surviving. More research would be needed to estimate the effect of this selection, but one could assume that patients in this sample could be in lower socioeconomic position and have poorer health compared to the general Finnish population but in better condition compared to all patients suffering from acute MI. The settings and sample are still very interesting and the results valuable, since knowledge of adherence to drug therapy particularly after MI is needed.

8.3. Conclusion

The aim of this master's thesis was to study the association between living alone, socioeconomic position and adherence to statin drug therapy in the Finnish population using register-based data. This study contributes to the former literature of medication adherence by showing that male patients who live alone have a higher risk of non-adherence to statin drug therapy after MI compared to men not living alone. Furthermore, the analysis show that socioeconomic position, especially income, is associated with adherence to statin drug therapy after MI. The results are important in understanding the mechanisms behind socioeconomic differences in MI recurrence and mortality where non-adherence to statins can have an important mediating effect.

This study gives more information on the health behaviors of those living alone and shows that particularly men in single households need more support to remain adherent to treatment guidelines and highlights the importance of social support in everyday life. Individual level support after MI is needed to help the patients follow their prescriptions and more attention and awareness among healthcare workers is needed in order to improve post-MI care. Support and attention on societal level is needed as well. By improving adherence to drug therapies, both years of life lost and unnecessary healthcare costs can be saved.

Clear income gradient in non-adherence raises questions of accessibility of statins and the functioning of the reimbursement system: Is it possible that the price of statins –

although relatively inexpensive – is preventing the use of these medications? More research is however needed to understand better the mechanisms behind the association between income and non-adherence and to determine whether the current reimbursement system is failing to secure all patients' equal access to medication.

Due to population ageing and rising obesity rates, prevalence of chronic conditions and especially CVD may increase in the future. Alongside ageing, living alone is becoming more common living arrangement. Meanwhile ageing already increases the burden on healthcare system, the number of people at elevated risk of non-adherence may rise. Thus, more efficient treatment of CVD and MI is needed and finding new tools to improve adherence to drug therapy plays a major role in it.

References

Aarnio, E., Martikainen J., Winn A. N., Huupponen R., Vahtera J., & Korhonen M. J. (2016). Socioeconomic Inequalities in Statin Adherence Under Universal Coverage. *Circulation: Cardiovascular Quality and Outcomes*, *9*(6), 704–713. https://doi.org/10.1161/CIRCOUTCOMES.116.002728

Aarnio, E., Martikainen, J. A., Helin-Salmivaara, A., Huupponen, R. K., Hartikainen, J. E. K., Peura, P. K., & Korhonen, M. J. (2014). Register-based predictors of adherence among new statin users in Finland. *Journal of Clinical Lipidology*, *8*(1), 117–125. https://doi.org/10.1016/j.jacl.2013.09.008

Aho, T., & Porola, P. (2013, November 1). *Sydäninfarktin toteaminen*. https://www.kaypahoito.fi/khp00033

Avendano, M., Kunst, A. E., Huisman, M., Lenthe, F. V., Bopp, M., Regidor, E., Glickman, M., Costa, G., Spadea, T., Deboosere, P., Borrell, C., Valkonen, T., Gisser, R., Borgan, J.-K., Gadeyne, S., & Mackenbach, J. P. (2006). Socioeconomic status and ischaemic heart disease mortality in 10 western European populations during the 1990s. *Heart*, *92*(4), 461–467. https://doi.org/10.1136/hrt.2005.065532

Backholer, K., Peters, S. A. E., Bots, S. H., Peeters, A., Huxley, R. R., & Woodward, M. (2017). Sex differences in the relationship between socioeconomic status and cardiovascular disease: A systematic review and meta-analysis. *J Epidemiol Community Health*, *71*(6), 550–557. https://doi.org/10.1136/jech-2016-207890

Benner, J. S., Glynn, R. J., Mogun, H., Neumann, P. J., Weinstein, M. C., & Avorn, J. (2002). Long-term Persistence in Use of Statin Therapy in Elderly Patients. *JAMA*, *288*(4), 455–461. https://doi.org/10.1001/jama.288.4.455

Berkman, L. F., Leo-Summers, L., & Horwitz, R. I. (1992). Emotional Support and Survival after Myocardial Infarction. *Annals of Internal Medicine*, *117*(12), 1003–1009. https://doi.org/10.7326/0003-4819-117-12-1003

DiMatteo, M. R. (2004). Social Support and Patient Adherence to Medical Treatment: A Meta-Analysis. *Health Psychology*, *23*(2), 207–218. https://doi.org/10.1037/0278-6133.23.2.207

Duodecim, K. O. (n.d.). *Sepelvaltimotautikohtaus (epästabiili angina pectoris ja sydäninfarkti ilman ST-nousuja)*. Duodecim - Terveyskirjasto. Retrieved October 2, 2020, from https://www.terveyskirjasto.fi/terveyskirjasto/tk.koti?p_artikkeli=khp00029

Glossary:Equivalised disposable income—Statistics Explained. (n.d.). Retrieved December 2, 2020, from https://ec.europa.eu/eurostat/statistics-explained/index.php/Glossary:Equivalised_disposable_income

Goldstein, K. M., Zullig, L. L., Bastian, L. A., & Bosworth, H. B. (2016). Statin Adherence: Does Gender Matter? *Current Atherosclerosis Reports*, *18*(11), 63. https://doi.org/10.1007/s11883-016-0619-9

Granström, F., Molarius, A., Garvin, P., Elo, S., Feldman, I., & Kristenson, M. (2015). Exploring trends in and determinants of educational inequalities in self-rated health. *Scandinavian Journal of Public Health*, *43*(7), 677–686. https://doi.org/10.1177/1403494815592271

Grymonpre, R., Cheang, M., Fraser, M., Metge, C., & Sitar, D. S. (2006). Validity of a Prescription Claims Database to Estimate Medication Adherence in Older Persons. *Medical Care*, *44*(5), 471–477. https://doi.org/10.1097/01.mlr.0000207817.32496.cb

Helin-Salmivaara, A., Lavikainen, P., Korhonen, M. J., Halava, H., Junnila, S. Y. T., Kettunen, R., Neuvonen, P. J., Martikainen, J. E., Ruokoniemi, P., Saastamoinen, L. K., Virta, L., & Huupponen, R. (2008). Long-term persistence with statin therapy: A nationwide register study in Finland. *Clinical Therapeutics*, *30*, 2228–2240. https://doi.org/10.1016/j.clinthera.2008.12.003

Herttua, K., Martikainen, P., Batty, G. D., & Kivimäki, M. (2016). Poor Adherence to Statin and Antihypertensive Therapies as Risk Factors for Fatal Stroke. *Journal of the American College of Cardiology*, *67*(13), 1507–1515. https://doi.org/10.1016/j.jacc.2016.01.044

Herttua, K., Tabák, A. G., Martikainen, P., Vahtera, J., & Kivimäki, M. (2013). Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: Population-based study. *European Heart Journal*, *34*(38), 2933–2939. https://doi.org/10.1093/eurheartj/eht219

Ho, P. M., Bryson Chris L., & Rumsfeld John S. (2009). Medication Adherence. *Circulation*, *119*(23), 3028–3035. https://doi.org/10.1161/CIRCULATIONAHA.108.768986

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*, *10*(2), 227–237. https://doi.org/10.1177/1745691614568352

Hosmer, D. W. (2013). *Applied logistic regression.* (3rd ed. / David W. Hosmer, Stanley Lemeshow, Rodney X. Sturdivant.). Wiley.

Hu, Y., & Goldman, N. (1990). Mortality Differentials by Marital Status: An International Comparison. *Demography*, *27*(2), 233–250. https://doi.org/10.2307/2061451

Hughes, M. E., & Waite, L. J. (2002). Health in Household Context: Living Arrangements and Health in Late Middle Age. *Journal of Health and Social Behavior*, *43*(1), 1–21.

Huupponen, R., & Strandberg, T. (2020). *Miten auttaa potilasta sitoutumaan lääkehoitoonsa?*

Jackevicius, C. A., Mamdani, M., & Tu, J. V. (2002). Adherence With Statin Therapy in Elderly Patients With and Without Acute Coronary Syndromes. *JAMA : The Journal of the American Medical Association*, *288*(4), 462–467. https://doi.org/10.1001/jama.288.4.462

Kahri, J., & Syvänne, M. (2012). Kenelle aloitan statiinilääkityksen? *Duodecim*, *128*(28), 811–818.

Kerralla korvattava lääkemäärä. (n.d.). kela.fi. Retrieved October 2, 2020, from https://www.kela.fi/tarpeelliset-kustannukset_kerralla-korvattava-laakemaara

Kiecolt-Glaser, J. K., & Newton, T. L. (2001). Marriage and health: His and hers. *Psychological Bulletin*, *127*(4), 472.

Kilpi, F., Konttinen, H., Silventoinen, K., & Martikainen, P. (2015). Living arrangements as determinants of myocardial infarction incidence and survival: A prospective register study of over 300,000 Finnish men and women. *Social Science & Medicine*, *133*, 93–100. https://doi.org/10.1016/j.socscimed.2015.03.054

Kim Soyeun, Shin Dong Wook, Yun Jae Moon, Hwang Yunji, Park Sue K., Ko Young-Jin, & Cho BeLong. (2016). Medication Adherence and the Risk of Cardiovascular Mortality and Hospitalization Among Patients With Newly Prescribed Antihypertensive Medications. *Hypertension*, *67*(3), 506–512. https://doi.org/10.1161/HYPERTENSIONAHA.115.06731

Kivimäki, M., Batty, G. D., Hamer, M., Nabi, H., Korhonen, M., Huupponen, R., Pentti, J., Oksanen, T., Kawachi, I., Virtanen, M., Westerlund, H., & Vahtera, J. (2013). Influence of retirement on nonadherence to medication for hypertension and diabetes. *CMAJ*, *185*(17), E784–E790. https://doi.org/10.1503/cmaj.122010

Kunst, A. E., Bos, V., Lahelma, E., Bartley, M., Lissau, I., Regidor, E., Mielck, A., Cardano, M., Dalstra, J. A., Geurts, J. J., Helmert, U., Lennartsson, C., Ramm, J., Spadea, T., Stronegger, W. J., & Mackenbach, J. P. (2005). Trends in socioeconomic inequalities in self-assessed health in 10 European countries. *International Journal of Epidemiology*, *34*(2), 295–305. https://doi.org/10.1093/ije/dyh342

Laatikainen, T., Härkänen, T., Borodulin, K., Harald, K., Koskinen, S., Männistö, S., Peltonen, M., Sundvall, J., Valsta, L., Vartiainen, E., & Jousilahti, P. (2019). *Sydän- ja verisuonitautien riskitekijät 1992–2017: Laskusuunta jatkunut, mutta hidastunut*. https://www.julkari.fi/handle/10024/139213

Lahelma, E., Martikainen, P., Laaksonen, M., & Aittomäki, A. (2004). Pathways between socioeconomic determinants of health. *Journal of Epidemiology & Community Health*, *58*(4), 327–332. https://doi.org/10.1136/jech.2003.011148

Lahey, R., & Khan, S. S. (2018). Trends in Obesity and Risk of Cardiovascular Disease. *Current Epidemiology Reports*, *5*(3), 243–251. https://doi.org/10.1007/s40471-018-0160-1

Lam, W. Y., & Fresco, P. (2015, October 11). *Medication Adherence Measures: An Overview* [Review Article]. BioMed Research International; Hindawi. https://doi.org/10.1155/2015/217047

Lee Hokyou, Park Jong Heon, Floyd James S., Park Sungha, & Kim Hyeon Chang. (2019). Combined Effect of Income and Medication Adherence on Mortality in Newly Treated Hypertension: Nationwide Study of 16 Million Person-Years. *Journal of the American Heart Association*, *8*(16), e013148. https://doi.org/10.1161/JAHA.119.013148

Lesén, E., Sandström, T. Z., Carlsten, A., Jönsson, A. K., Mårdby, A.-C., & Sundell, K. A. (2011). A comparison of two methods for estimating refill adherence to statins in Sweden: The RARE project. *Pharmacoepidemiology and Drug Safety*, *20*(10), 1073–1079. https://doi.org/10.1002/pds.2204

Li, Q., Wilsnack, R., Wilsnack, S., & Kristjanson, A. (2010). Cohabitation, Gender, and Alcohol Consumption in 19 Countries: A Multilevel Analysis. *Substance Use & Misuse*, *45*(14), 2481–2502. https://doi.org/10.3109/10826081003692106

Mackenbach, J. P., Stirbu, I., Roskam, A.-J. R., Schaap, M. M., Menvielle, G., Leinsalu, M., Kunst, A. E., & European Union Working Group on Socioeconomic Inequalities in Health. (2008). Socioeconomic inequalities in health in 22

European countries. *The New England Journal of Medicine*, *358*(23), 2468–2481. https://doi.org/10.1056/NEJMsa0707519

Mann, D. M., Woodward, M., Muntner, P., Falzon, L., & Kronish, I. (2010). Predictors of Nonadherence to Statins: A Systematic Review and Meta-Analysis. *Annals of Pharmacotherapy*, *44*(9), 1410–1421. https://doi.org/10.1345/aph.1P150

Manrique-Garcia, E., Sidorchuk, A., Hallqvist, J., & Moradi, T. (2011). Socioeconomic position and incidence of acute myocardial infarction: A meta-analysis. *Journal of Epidemiology & Community Health*, *65*(4), 301–309. https://doi.org/10.1136/jech.2009.104075

Manzoli, L., Villari, P., M Pirone, G., & Boccia, A. (2007). Marital status and mortality in the elderly: A systematic review and meta-analysis. *Social Science & Medicine*, *64*(1), 77–94. https://doi.org/10.1016/j.socscimed.2006.08.031

Martikainen, P., Martelin, T., Nihtilä, E., Majamaa, K., & Koskinen, S. (2005). Differences in mortality by marital status in Finland from 1976 to 2000: Analyses of changes in marital-status distributions, socio-demographic and household composition, and cause of death. *Population Studies*, *59*(1), 99–115. https://doi.org/10.1080/0032472052000332737

Molokhia, M., McKeigue, P., Curcin, V., & Majeed, A. (2008). Statin induced myopathy and myalgia: Time trend analysis and comparison of risk associated with statin class from 1991-2006. *PloS One*, *3*(6), e2522. https://doi.org/10.1371/journal.pone.0002522

Moor, I., Spallek, J., & Richter, M. (2017). Explaining socioeconomic inequalities in self-rated health: A systematic review of the relative contribution of material, psychosocial and behavioural factors. *J Epidemiol Community Health*, *71*(6), 565–575. https://doi.org/10.1136/jech-2016-207589

Osterberg, L., & Blaschke, T. (2005). Adherence to Medication. *The New England Journal of Medicine*, *353*(5), 487–497. https://doi.org/10.1056/nejmra050100

Ostermann, J., Sloan, F. A., & Taylor, D. H. (2005). Heavy alcohol use and marital dissolution in the USA. *Social Science & Medicine*, *61*(11), 2304–2316. https://doi.org/10.1016/j.socscimed.2005.07.021

Pajunen, A. (n.d.). *Tilastokeskus—1. Kuolemansyyt 2019*. Tilastokeskus. Retrieved February 24, 2021, from https://www.stat.fi/til/ksyyt/2019/ksyyt_2019_2020-12-14_kat_001_fi.html

Pietrzykowski, Ł., Michalski, P., Kosobucka, A., Kasprzak, M., Fabiszak, T., Stolarek, W., Siller-Matula, J. M., & Kubica, A. (2020). Medication adherence and its determinants in patients after myocardial infarction. *Scientific Reports*, *10*(1), 12028. https://doi.org/10.1038/s41598-020-68915-1

Prochaska, J. J., & Prochaska, J. O. (2011). A Review of Multiple Health Behavior Change Interventions for Primary Prevention. *American Journal of Lifestyle Medicine*, *5*(3), 208–221. https://doi.org/10.1177/1559827610391883

Puska, P., Nissinen, A., Tuomilehto, J., Salonen, J. T., Koskela, K., McAlister, A., Kottke, T. E., Maccoby, N., & Farquhar, J. W. (1985). *The Community-Based Strategy to Prevent Coronary Heart Disease: Conclusions from the Ten Years of the North Karelia Project*. 47.

Ramkumar, S., Raghunath, A., & Raghunath, S. (2016). Statin Therapy: Review of Safety and Potential Side Effects. *Acta Cardiologica Sinica*, *32*(6), 631–639. https://doi.org/10.6515/ACS20160611A

Rasmussen, J. N., Gislason, G. H., Rasmussen, S., Abildstrom, S. Z., Schramm, T. K., Køber, L., Diderichsen, F., Osler, M., Torp-Pedersen, C., & Madsen, M. (2007). Use of statins and beta-blockers after acute myocardial infarction according to income and education. *Journal of Epidemiology & Community Health*, *61*(12), 1091–1097. https://doi.org/10.1136/jech.2006.055525

Roelfs, D. J., Shor, E., Kalish, R., & Yogev, T. (2011). The Rising Relative Risk of Mortality for Singles: Meta-Analysis and Meta-Regression. *American Journal of Epidemiology*, *174*(4), 379–389. https://doi.org/10.1093/aje/kwr111

Shah, N. D., Dunlay, S. M., Ting, H. H., Montori, V. M., Thomas, R. J., Wagie, A. E., & Roger, V. L. (2009). Long-term Medication Adherence after Myocardial Infarction: Experience of a Community. *The American Journal of Medicine*, *122*(10), 961.e7-961.e13. https://doi.org/10.1016/j.amjmed.2008.12.021

Shor, E., Roelfs, D. J., Bugyi, P., & Schwartz, J. E. (2012). Meta-analysis of marital dissolution and mortality: Reevaluating the intersection of gender and age. *Social Science & Medicine*, *75*(1), 46–59. https://doi.org/10.1016/j.socscimed.2012.03.010

Stringhini, S., Carmeli, C., Jokela, M., Avendaño, M., Muennig, P., Guida, F., Ricceri, F., d'Errico, A., Barros, H., Bochud, M., Chadeau-Hyam, M., Clavel-Chapelon, F., Costa, G., Delpierre, C., Fraga, S., Goldberg, M., Giles, G. G., Krogh, V., Kelly-Irving, M., … Zins, M. (2017). Socioeconomic status and the 25 × 25 risk

factors as determinants of premature mortality: A multicohort study and meta-analysis of 1·7 million men and women. *The Lancet*, *389*(10075), 1229–1237. https://doi.org/10.1016/S0140-6736(16)32380-7

Tabue Teguo, M., Simo-Tabue, N., Stoykova, R., Meillon, C., Cogne, M., Amiéva, H., & Dartigues, J.-F. (2016). Feelings of Loneliness and Living Alone as Predictors of Mortality in the Elderly: The PAQUID Study. *Psychosomatic Medicine*, *78*(8), 904–909. https://doi.org/10.1097/PSY.0000000000000386

Trivedi, R. B., Ayotte, B., Edelman, D., & Bosworth, H. B. (2008). The association of emotional well-being and marital status with treatment adherence among patients with hypertension. *Journal of Behavioral Medicine*, *31*(6), 489.

Umberson, D. (1992). Gender, marital status and the social control of health behavior. *Social Science & Medicine*, *34*(8), 907–917. https://doi.org/10.1016/0277-9536(92)90259-S

van Raalte, A. A., Sasson, I., & Martikainen, P. (2018). The case for monitoring life-span inequality. *Science*, *362*(6418), 1002–1004. https://doi.org/10.1126/science.aau5811

Vartiainen, E., Laatikainen, T., Peltonen, M., Juolevi, A., Männistö, S., Sundvall, J., Jousilahti, P., Salomaa, V., Valsta, L., & Puska, P. (2010). Thirty-five-year trends in cardiovascular risk factors in Finland. *International Journal of Epidemiology*, *39*(2), 504–518. https://doi.org/10.1093/ije/dyp330

WHO | ADHERENCE TO LONG-TERM THERAPIES: EVIDENCE FOR ACTION. (2003). WHO; World Health Organization. http://www.who.int/chp/knowledge/publications/adherence_report/en/

Wong, C. W., Kwok, C. S., Narain, A., Gulati, M., Mihalidou, A. S., Wu, P., Alasnag, M., Myint, P. K., & Mamas, M. A. (2018). Marital status and risk of cardiovascular diseases: A systematic review and meta-analysis. *Heart*, *104*(23), 1937–1948. https://doi.org/10.1136/heartjnl-2018-313005

Yap, A. F., Thirumoorthy, T., & Kwan, Y. H. (2016). Systematic review of the barriers affecting medication adherence in older adults. *Geriatrics & Gerontology International*, *16*(10), 1093–1101. https://doi.org/10.1111/ggi.12616

Yarcheski, A., Mahon, N. E., Yarcheski, T. J., & Cannella, B. L. (2004). A Meta-Analysis of Predictors of Positive Health Practices. *Journal of Nursing Scholarship*, *36*(2), 102–108. https://doi.org/10.1111/j.1547-5069.2004.04021.x