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ANALYZING CHANGE IN MEDICATION USE — STATISTICAL APPROACHES

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To my family

ABSTRACT

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Analyzing change in medication use – statistical approaches.

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The objective of this study was to gain an understanding of the effects of population heterogeneity, missing data, and causal relationships on parameter estimates from statistical models when analyzing change in medication use. From a public health perspective, two timely topics were addressed: the use and effects of statins in populations in primary prevention of cardiovascular disease and polypharmacy in older population.

Growth mixture models were applied to characterize the accumulation of cardiovascular and diabetes medications among apparently healthy population of statin initiators. The causal effect of statin adherence on the incidence of acute cardiovascular events was estimated using marginal structural models in comparison with discrete-time hazards models. The impact of missing data on the growth estimates of evolution of polypharmacy was examined comparing statistical models under different assumptions for missing data mechanism. The data came from Finnish administrative registers and from the population-based Geriatric Multidisciplinary Strategy for the Good Care of the Elderly study conducted in Kuopio, Finland, during 2004–07.

Five distinct patterns of accumulating medications emerged among the population of apparently healthy statin initiators during two years after statin initiation. Proper accounting for time-varying dependencies between adherence to statins and confounders using marginal structural models produced comparable estimation results with those from a discrete-time hazards model. Missing data mechanism was shown to be a key component when estimating the evolution of polypharmacy among older persons.

In conclusion, population heterogeneity, missing data and causal relationships are important aspects in longitudinal studies that associate with the study question and should be critically assessed when performing statistical analyses. Analyses should be supplemented with sensitivity analyses towards model assumptions.

Keywords: adherence, cardiovascular disease, trajectory models, longitudinal, marginal structural model, missing data, older persons, polypharmacy, statins

TIIVISTELMÄ

Piia Lavikainen

Lääkkeen käytön muutoksen analysointi – tilastollisia näkökulmia.

Turun yliopisto, Lääketieteellinen tiedekunta, Biolääketieteen laitos, Farmakologia, lääkekehitys ja lääkehoito, Lääketutkimuksen tohtoriohjelma
Itä-Suomen yliopisto, Terveystieteiden tiedekunta, Farmasian laitos, Geriatrisen hoidon tutkimuskeskus
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Väitöskirjatutkimuksen tavoitteena oli lisätä ymmärrystä populaation heterogeenisyyden, puuttuvan tiedon sekä kausaalisuhteiden vaikutuksesta tilastollisten mallien parametrien estimaatteihin analysoitaessa lääkkeiden käytön muutosta. Tutkimus keskittyi kahteen kansanterveyden näkökulmasta ajankohtaiseen aiheeseen: statiinien käyttöön ja vaikutuksiin sydän- ja verisuonisairauksien primaaripreventiossa sekä iäkkäiden monilääkitykseen.

Sydän- ja verisuonisairaus- sekä diabeteslääkkeiden kertymistä kuvailtiin näennäisesti terveillä statiinihoidon aloittajilla latentin kasvukäyrämallin mixture-analyysin avulla. Statiinihoitoon sitoutumisen kausaali vaikutusta akuuttiin sydän- ja verisuonitapahtumaan primaaripreventiossa estimoitiin marginaalisilla rakennemalleilla ja verrattiin diskreetin elinaikamallin tuloksiin. Puuttuvan tiedon vaikutusta kasvufaktoreiden estimaatteihin monilääkityksen kehitystä analysoitaessa tutkittiin vertailemalla tilastollisia menetelmiä jotka erosivat toisistaan oletuksiltaan puuttuvan tiedon mekanismista. Aineistoina käytettiin suomalaisia hallinnollisia rekistereitä sekä Kuopiossa vuosina 2004–07 toteutetun Hyvän Hoidon Strategia-tutkimuksen aineistoa.

Näennäisesti terveillä statiinihoidon aloittajilla havaittiin viisi toisistaan erillistä lääkkeiden kertymisen kehityskaarta kahden vuoden aikana statiinin aloituksesta. Kun marginaalisen rakennemallin avulla huomioitiin statiinihoitoon sitoutumisen ja sekoittavien tekijöiden muutokset, joihin aiempi hoitoon sitoutuminen saattoi vaikuttaa, tuloksena oli diskreetin elinaikamallin kanssa yhteneviä parametriestimaatteja. Puuttuvan tiedon mekanismi osoittautui avaintekijäksi estimoitaessa monilääkityksen kehitystä iäkkäässä väestössä.

Yhteenvedon todetaan, että lääkkeiden käytön muutoksen tilastollisissa analyyseissä on tärkeää ottaa huomioon populaation heterogeenisuus, puuttuvan tiedon mekanismi ja muuttujien väliset kausaalisuhteet. Sovellettavan tilastollisen menetelmän tulisi vastata tutkimuskysymystä ja analyyysien tuloksia tulisi tukea herkkyysanalyyseillä tilastollisten mallien oletuksia kohtaan.

Avainsanat: hoitoon sitoutuminen, iäkkäät, marginaaliset rakennemallit, monilääkitys, pitkittäistutkimus, puuttuva tieto, statiinit, sydän- ja verisuonisairaudet, trajektorimallit

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ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
BIC	Bayesian information criteria
CFI	comparative fit index
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
FCR	Finnish Care Register
FIML	full-information maximum likelihood
FPR	Finnish Prescription Register
GeMS	Geriatric Multidisciplinary Strategy for the Good Care of the Elderly
GMM	growth mixture model
HR	hazard ratio
ICD-10	10 th revision of International Classification of Diseases
IPTW	inverse probability of treatment weight
LDL	low-density lipoprotein
LGCM	latent growth curve model
LMR-LRT	Lo-Mendell-Rubin likelihood ratio test
MAR	missing at random
MCAR	missing completely at random
ML	maximum likelihood
MNAR	missing not at random
MPR	medication possession ratio
MSM	marginal structural model
PDC	proportion of days covered
RCT	randomized controlled trial
RMSEA	root mean square error of approximation
SD	standard deviation
SE	standard error
SII	Social Insurance Institution
SRMR	standardized root mean residual
SRR	Special Reimbursement Register
TLI	Tucker-Lewis index
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by their numbers.

- 1 Lavikainen P, Korhonen MJ, Huupponen R, Helin-Salmivaara A. Accumulation of cardiovascular and diabetes medication among apparently healthy statin initiators. *PLoS One* 2015; 10: e0117182.
- 2 Lavikainen P, Helin-Salmivaara A, Eerola M, Fang G, Hartikainen J, Huupponen R, Korhonen MJ. Statin adherence and risk of acute cardiovascular events among women: accounting for time-dependent confounding affected by previous adherence. *BMJ Open* 2016; 6: e011306.
- 3 Lavikainen P, Leskinen E, Hartikainen S, Möttönen J, Sulkava R, Korhonen MJ. Impact of missing data mechanism on the estimate of change: a case study on cognitive function and polypharmacy among older persons. *Clin Epidemiol* 2015; 7: 169-180.

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1 INTRODUCTION

Medication use and effects of medications in populations are the focus of pharmacoepidemiology (Strom 2006). Medication use is dynamic – medications are initiated and discontinued, dosages are adjusted and a person's medication taking behavior fluctuates over time (Korhonen *et al.* 2011, Slejko *et al.* 2013). For examining the change in medication use and its effects, longitudinal data where multiple measurements are taken on the same person over time are needed (Singer and Willett 2003). Change, in general, may be divided to within-person and between-person change. Change may happen as a natural process or may be forced by an intervention, for example. Although development of new statistical techniques that can be used to investigate change in medication use or its consequences has been rapid during the past three decades, the adoption of sophisticated techniques to pharmacoepidemiology has been slow. Two timely topics of public health importance serve here as motivating examples: the use and effects of statins in population in primary prevention of cardiovascular disease (CVD) and the evolution of polypharmacy in older population.

CVDs are the number one killer in the world (WHO 2014). The efficacy of statins in preventing CVDs has been shown in several randomized controlled trials (RCTs) conducted among both primary and secondary prevention populations (Baigent *et al.* 2005, Brugts *et al.* 2009, Cholesterol Treatment Trialists' Collaboration 2010, Cholesterol Treatment Trialists' Collaborators 2012, Mills *et al.* 2008, Reidenberg 2008, Taylor *et al.* 2013). They are also beneficial for persons at low risk of CVD (Cholesterol Treatment Trialists' Collaborators 2012). Thus, treatment guidelines to statin initiation have widened from secondary prevention to include persons in primary prevention who are at increased risk of experiencing CVD event in the near future or who have a cluster of risk factors for CVD (Perk *et al.* 2012, Stone *et al.* 2014, Tikkanen *et al.* 2013). Consequently, statin initiation seems to have shifted increasingly to primary prevention of CVD, and especially to persons at low risk of CVD (Rikala *et al.* 2013, Wallach Kildemoes *et al.* 2012b). However, the identification of these persons using health care registers may have suffered from lack of data on risk factors needed in estimation of CVD risk leading to a potential for misclassification of risk level. No study has characterized such low-risk population after statin initiation and the evolution of their cardiovascular risk over time. Among persons in primary prevention, statin adherence has been observed to associate with reduced CVD risk (Bouchard *et al.* 2009, Corrao *et al.* 2010, Perreault *et al.* 2009a, Perreault *et al.* 2009b, Shalev *et al.* 2012). However, prior studies have not appropriately adjusted for the time-varying natures of statin adherence and confounding, but may have created bias in their analyses by adjusting for time-dependent confounders measured simultaneously with adherence.

The age structure as well as the size of human population has changed globally during the past 30 years. However, the age structure will undergo the largest changes in the near future as the proportion of persons aged ≥ 60 years will increase to 21% in 2050 (United Nations, Department of Economic and Social Affairs, Population Division 2013).

Increasing use of preventive medications, such as statins, along with aging-related incidence of chronic diseases have led to increasing use of multiple medications or polypharmacy (Hiitola *et al.* 2007, Jyrkkä *et al.* 2006, Upmeier *et al.* 2013). Consequently, problems related to polypharmacy, such as drug-drug interactions or risk of adverse events, are likely to increase. Several studies have investigated aging-related change in the number of medications in use among older persons. However, the majority of the studies have included only survivors of two time points in their analyses and have not accounted for attrition which may have lead to inefficient and possibly biased estimation.

The primary goal of this study was to gain insight into the effects of population heterogeneity, missing data, and causal relationships on parameter estimates from statistical models by comparing and contrasting statistical methods when analyzing change in medication use. The secondary aim was to provide new statistical aspects for estimating change in medication use. The study consists of applications of trajectory models (latent growth curve models and growth mixture models), marginal structural models and Diggle-Kenward selection models. Along with the application of more sophisticated statistical methods, the aforementioned topics of significant public health importance are touched upon.

2 REVIEW OF THE LITERATURE

2.1 Cardiovascular diseases

CVDs consist of coronary heart disease (CHD), cerebrovascular disease (ischemic and haemorrhagic stroke), hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure (World Health Organization [WHO] 2011). The process underlying CHD, ischemic stroke and peripheral artery disease is related to atherosclerosis (Stone *et al.* 2014). Atherosclerosis is a continuous process with hypercholesterolemia being one of its main causes (Perk *et al.* 2012). Atherosclerosis develops gradually during lifetime, starting from early adolescence and is in advanced stage by the time symptoms occur (Perk *et al.* 2012, WHO 2007, WHO 2011). Sometimes, there may not be any symptoms of the underlying CVD before sudden myocardial infarction or stroke occurs (retrieved from www.who.int, accessed 27 October 2015).

CVD is the leading cause of death globally; it accounted for 31% (17.5 million CVD deaths of a total of 56 million deaths) of deaths from any cause in 2012 (WHO 2014). In addition, over 5.9 million CVD deaths in 2012 were premature occurring before age of 70 years (WHO 2014). In particular, the proportion of premature CVD deaths is higher among women than in men (Perk *et al.* 2012). In Europe, CVDs are responsible for over half of deaths (retrieved from WHO available at www.euro.who.int, accessed 1 December 2015). About 80% of CVD deaths in men results from myocardial infarction and strokes while the corresponding proportion for women is 75% (WHO 2011).

In 1972, Finland was a country with the world's highest CVD mortality rate among men (Puska 2010). Annual age-standardized death rates for CHD and cerebrovascular diseases have steadily declined in Finland over the past 30 years (retrieved from the European health for all database, available at www.euro.who.int, accessed 27 October 2015). For CHD, age-standardized death rate declined from 277 to 99 deaths per 100,000 persons between 1980 and 2013. For cerebrovascular diseases, the decrease was from 113 to 41 deaths per 100,000 persons during the same time period. However, diseases of the circulatory system, especially CHD that causes one of five deaths, are still leading causes of death in Finland (Statistics Finland 2013). The crude incidence of CHD has declined during the past decade whereas the crude incidence of stroke has remained stable (CVD Register maintained by the National Institute for Health and Welfare, available at www.thl.fi, accessed 11 November 2015).

In Finland, 1.5 million (27%, Finnish Medicines Agency Fimea and Social Insurance Institution 2015) out of 5.5 million inhabitants (retrieved from Statistics Finland, available at www.tilastokeskus.fi, accessed 1 December 2015) received reimbursement for cardiovascular medications in 2014. At the time, 6% of persons aged 40 years or more were eligible for special reimbursement for CHD medications and 16% for medications used for treatment of hypertension (retrieved from Sotkanet available at www.sotkanet.fi, accessed 1 December 2015).

2.1.1 Risk factors

Major risk factors for atherosclerotic CVD promote the process of atherosclerosis. Major behavioral risk factors are unhealthy diet, physical inactivity, smoking, and harmful use of alcohol (Stamler 2005, WHO 2011). These factors may show later in the form of obesity and overweight, elevated levels of blood pressure (hypertension) and blood glucose (diabetes), and abnormal cholesterol levels (dyslipidemia), which are termed major metabolic risk factors (Stamler 2005, WHO 2011). According to the Finnish guideline, non-smoking, healthy dietary habits, at least 30 minutes moderate physical activity every day, body mass index (weight in relation to height) $<25 \text{ kg/m}^2$, total cholesterol level of $<5 \text{ mmol/L}$, low-density lipoprotein (LDL) cholesterol level $<3 \text{ mmol/L}$, high-density lipoprotein cholesterol level $>1 \text{ mmol/L}$, blood pressure $<140/90 \text{ mmHg}$ and blood glucose $<6 \text{ mmol/L}$ are values that lower the CVD risk (Tikkanen *et al.* 2013). Advancing age, male sex, low socioeconomic status, stress, depression, family history of CVD in first-degree relatives, and genetic factors are also reported to increase the risk of CVD (Perk *et al.* 2012, WHO 2011).

2.1.2 Total cardiovascular disease risk estimation

Typically, several risk factors may exist concurrently multiplying the total CVD risk (Puska 2010, Vartiainen *et al.* 2007, WHO 2007). A cluster of modest risk factors may result in higher risk than the presence of a single risk factor at very high level (Reiner *et al.* 2011). Cardiovascular risk can be estimated with established risk prediction charts or calculators such as SCORE (Systemic Coronary Risk Estimation; Conroy *et al.* 2003) that includes Finnish population among other European populations, the international Framingham chart (D'Agostino *et al.* 2008), or the Finnish FINRISK calculator (Vartiainen *et al.* 2007) for working age population. The total risk is estimated as a probability to experience a CVD event or CVD death during a given time period using information on a person's risk factors; typically these include at least age, sex, blood pressure, smoking status and cholesterol level. Calculators differ because different source populations and factors are used to derive the risk functions. Furthermore, the events they predict are differently defined (Cooney *et al.* 2009, Vartiainen *et al.* 2007). Thus, it is suggested to use the one that is derived from a population most similar to that in question (Cooney *et al.* 2009, Reiner *et al.* 2011). Generally, the risk of CVD events is high when a person has prior CVD, diabetes, familial hypercholesterolemia, or chronic kidney disease implicating that the person automatically needs active risk factor management (Reiner *et al.* 2011, Tikkanen *et al.* 2013). Also persons with very high levels of individual risk factors, such as people with a total cholesterol $\geq 8 \text{ mmol/L}$ or LDL cholesterol $\geq 6 \text{ mmol/L}$, or with hereditary dyslipidemia qualify for that (Reiner *et al.* 2011). Thus, the target group for total risk estimation comprises asymptomatic persons who have no history of CVD or diabetes and do not have individual risk factors at very high levels (Reiner *et al.* 2011, Stamler *et al.* 2005).

As an example, using the FINRISK calculator that is suitable especially for the Finnish population, cardiovascular risk is considered to be increased or high when the estimated 10-year risk of myocardial infarction or stroke is $\geq 10\%$ (Tikkanen *et al.* 2013).

The FINRISK function is based on data of the participants of the national FINRISK study in 1982, 1987 and 1992 and 10-year follow-up of CVD outcomes for them (Vartiainen *et al.* 2007). The effect of elevated cholesterol level as an only established risk factor for CVD is modest and at the same level as smoking, elevated systolic blood pressure or diabetes alone (Vartiainen *et al.* 2007). Largest risk reductions are achieved when more than one risk factors are modified at the same time whereas affecting only one risk factor has only minor effect on the total risk. Although the 10-year risk of CVD may be estimated as low, the lifetime risk of CVD may be substantially higher (Berry *et al.* 2012).

2.1.3 Prevention of cardiovascular disease

Prevention of CVD can be divided into primary and secondary prevention. Persons with cardiovascular risk factors but without established atherosclerotic CVD are considered to be in primary prevention whereas persons with established disease are considered to be in secondary prevention (Tikkanen *et al.* 2013). Primary prevention aims to prevent the disease from occurring while secondary prevention targets preventing worsening or recurrence of already established disease (Tikkanen *et al.* 2013, WHO 2011). Although persons without established CVD are at lower risk of CVD, at least half of the vascular events occur among them (Cholesterol Treatment Trialists' Collaborators 2012), making them an important group when considering the target of lowering the incidence of CVD outcomes.

Generally, CVD prevention actions targets prevention of atherosclerosis by modifying risk factors and includes targeted interventions at population and individual level (Perk *et al.* 2012, WHO 2011), which are recommended to be used in combination (WHO 2011). As an example, the North Karelia Project implemented in Finland in 1972 focused on healthier diet and reducing smoking via population level lifestyle interventions (Borodulin *et al.* 2015). During 1972–77, beneficial changes in risk factor distributions were observed (Puska *et al.* 1995). Thereafter, principles of the Project were applied to new areas, and in the national FINRISK study during a 40-year follow-up, reductions in cholesterol and blood pressure levels as well as prevalence of smoking among 30- to 59-year-old population were observed up to 2007 (Borodulin *et al.* 2015). Since then, cholesterol levels have increased modestly, diastolic blood pressure levels have remained stable while systolic blood pressure levels and the prevalence of smoking have continued declining (Borodulin *et al.* 2015). Successful population level reduction in the CVD mortality is attributable to modification of risk factor distributions among Finnish working-age population that has also transferred events to appear later in life and expanded life expectancy (Puska 2010). In agreement, WHO proposes that 80% of all CVD-related mortality can be prevented through adequate lifestyle changes that reduce body mass index, blood pressure, blood glucose and both total and LDL cholesterol (WHO 2011). The beneficial effect of the total cardiovascular risk reduction on the CVD events is obvious (WHO 2011).

Blood pressure-lowering, lipid-lowering (statins), antiplatelet (acetylsalicylic acid) and diabetes medications as preventive drug therapy reduce the risk of CVD among

persons in primary prevention of CVD (Bartolucci *et al.* 2011, Gueyffier *et al.* 1997, Mazzone 2010, Taylor *et al.* 2013). In secondary prevention of CVD, recommended medications to improve prognosis or to attenuate symptoms include antithrombotic agents (acetylsalicylic acid, clopidogrel, warfarin), cardiac glycosides, antiarrhythmic medications, nitrates, antihypertensives, diuretics, peripheral vasodilators, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diabetes and lipid-lowering (statins, fibrates) medications (Lindsberg *et al.* 2011, Porela *et al.* 2015, Raatikainen *et al.* 2014).

Of the 35- to 75-year-old Finnish population who participated in the FINRISK study in 2012, 21% of male and 15% of female participants used lipid-lowering medications whereas 22% of the total study population used blood pressure-lowering medications and 7% had medication for diabetes (Vartiainen *et al.* 2013). Statins were used by 63% of persons using medications for diabetes and by 44% of users of blood pressure-lowering medications (Vartiainen *et al.* 2013). In an asymptomatic all-age Dutch population in primary prevention of CHD in 2010, 7% used lipid-lowering medications and 15% blood pressure-lowering medications (Koopman *et al.* 2013).

2.2 Statins

Statins and combination products (such as simvastatin and ezetimibe) are lipid modifying medications aimed at reducing cholesterol, especially LDL, levels. They belong to the class of medications affecting the cardiovascular system (Anatomical Therapeutic Chemical [ATC] classification code categories C10AA for statins and C10B for combination products) (WHO Collaborating Centre for Drug Statistics Methodology 2016). Statins are reported to reduce LDL cholesterol by 30–60% depending on the type and dose of the statin (Stone *et al.* 2014). In addition, they increase the beneficial high-density lipoprotein cholesterol and decrease triglyceride, but to a lesser extent than LDL cholesterol (Tikkanen *et al.* 2013).

Statins were introduced on the Finnish market at the end of the 1980s (Finnish Committee on Drug Information and Statistics 1989). Cerivastatin was withdrawn from the Finnish as well as global markets in 2001 due to serious adverse events (Furberg and Pitt 2001). Currently, simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin are available in Finland. In 1996, 65,631 persons redeemed a prescription for statins in Finland (personal communication with Leena Saastamoinen/the Social Insurance Institution (SII) of Finland); in 2014 the corresponding figure was 655,439 (i.e. 12% of the population) (Finnish Medicines Agency Fimea and Social Insurance Institution 2015).

Recommendations for statin use have widened during the past 20 years from secondary prevention of CVD to high-risk persons in primary prevention along with published new evidence on the beneficial effects of statin therapy in several subpopulations (Perk *et al.* 2012, Wallach Kildemoes *et al.* 2012b). The efficacy of statins in secondary prevention of CVD and among high-risk persons is well established (Baigent *et al.* 2005, Cholesterol Treatment Trialists' Collaborators 2012, Reidenberg

2008). Several meta-analyses of double-blind RCTs have reported beneficial effect of statin therapy on CVD risk among both all and female primary prevention populations (Brugts *et al.* 2009, Bukkapatnam *et al.* 2010, Cholesterol Treatment Trialists' Collaboration 2010, Cholesterol Treatment Trialists' Collaborators 2012, Ijima and Robinson 2015, Mills *et al.* 2008, Taylor *et al.* 2013, Thavendiranathan *et al.* 2006). Moreover, Cholesterol Treatment Trialists' Collaborators' (2012) meta-analysis on 27 trials including 174,149 persons reports statin use to associate with a 43% relative reduction (rate ratio 0.57, 95% confidence interval, CI, 0.36–0.89) in the risk of major coronary events for each 1.0 mmol/L reduction in LDL cholesterol and potential reduction (rate ratio 0.74, 95% CI 0.46–1.19) in the stroke risk among persons with <5% five-year risk of CVD.

Among persons with established CVD, i.e., those in secondary prevention, both American and European as well as Finnish guidelines recommend statin initiation immediately, irrespective of cholesterol levels, in adjunct to lifestyle intervention (Perk *et al.* 2012, Stone *et al.* 2014, Tikkanen *et al.* 2013). Among persons in primary prevention of CVD, the American guideline recommends statin initiation when the risk of atherosclerotic CVD is $\geq 7.5\%$ estimated with Pooled Cohort Equations calculator, which corresponds to a $\geq 2.5\%$ 10-year risk of fatal CVD estimated with the SCORE (Ray *et al.* 2014) and is thus a considerably lower threshold than recommended in the European guideline (Table 2.1). The threshold of risk used in the American guideline to recommend statin initiation is also lower than that in the Finnish guideline, which corresponds to that of the European guideline (risk estimated with the FINRISK is 1.5–3 times that estimated with the SCORE; Kahri and Syväne 2012, Ray *et al.* 2014, Tikkanen *et al.* 2013, Vartiainen *et al.* 2007). Additionally, the American guideline suggests considering statin initiation for a person with 5–7.5% estimated risk of atherosclerotic CVD event (Pooled Cohort Equations) during the next 10 years (Stone *et al.* 2014) whereas the European 2013 guideline advises medical intervention to be considered with a combination of 5–10% estimated 10-year risk of CVD death and LDL cholesterol level ≥ 2.5 mmol/L (Perk *et al.* 2012). Generally, lifestyle intervention should always be put into practice and the initiation of a statin should be guided by total CVD risk, not solely by cholesterol levels (Kahri and Syväne 2012).

Statins are widely used both in primary and secondary prevention of CVD (Rikala *et al.* 2013, Wallach Kildemoes *et al.* 2012b). Broadening of the indications for statin therapy over time as well as a decline in statin prices have resulted in a shift of statin use towards persons at low risk of CVD (Rikala *et al.* 2013, Shalev *et al.* 2014, Wallach Kildemoes *et al.* 2012b).

Table 2.1 Recommendations for when to initiate statin therapy.

	American guideline (Stone <i>et al.</i> 2014)	European guideline (Perk <i>et al.</i> 2012)	Finnish guideline (Tikkanen <i>et al.</i> 2013)
Persons with established CVD (secondary prevention)	Initiate immediately	Initiate immediately	Initiate immediately
Persons without established CVD (primary prevention)	-LDL cholesterol >4.9 mmol/L -Diabetes, age 40–75 years and LDL cholesterol 1.8–4.9 mmol/L -LDL cholesterol 1.8–4.9 mmol/L, age 40–75 years and $\geq 7.5\%$ 10-year risk of atherosclerotic CVD (Pooled Cohort Equations calculator)	-LDL cholesterol ≥ 1.8 mmol/L and $\geq 10\%$ 10-year risk of fatal CVD (SCORE chart) -LDL cholesterol ≥ 2.5 mmol/L and 5–10% 10-year risk of fatal CVD (SCORE chart)	-Diabetes -LDL cholesterol ≥ 6.0 mmol/L -high levels of individual risk factors -moderate to severe chronic kidney disease -hereditary dyslipidemia - $\geq 10\%$ 10-year risk of CVD (FINRISK calculator)

Abbreviations: CVD, cardiovascular disease; LDL, low-density lipoprotein.

In the population-based register studies examining statin use among low-risk persons in the absence of relevant data on indications for statin use, low-risk population has typically been identified as persons without register markers for manifest CVD or major risk factors like diabetes and hypertension (Table 2.2). In this thesis, the term ‘apparently healthy persons’ is used to refer to a population with no register markers for manifest CVD or major risk factors. That is, apparently healthy population seems to be at low CVD risk as estimated based on register data, but due to absence of information on some major risk factors, such as smoking and cholesterol level, the true CVD risk level cannot be assessed. The estimated proportion of low-risk statin initiators of all statin initiators has varied between 12 and 30% (Table 2.2). The length of lookback periods, i.e., periods without register markers for CVD prior to statin initiation, has varied between the studies, which introduces differences between estimated proportions (Table 2.2). Some studies have utilized prescription data solely while the majority have also retrieved information on hospital discharges.

Mismatch in statin use has also been observed: underuse of statins among high-risk and overuse among low-risk persons (Johansen *et al.* 2014, Teeling *et al.* 2005, Upmeier *et al.* 2013, van Staa *et al.* 2013). In Ireland in 1998–2002, about half (40–52%) of all-age population at high risk of CVD, i.e., who had CHD or diabetes, were reported to use statins (Teeling *et al.* 2005). In an American study in 1998–2010, the corresponding proportion was slightly over half (52–58%) of the ≥ 40 -year-old persons (Johansen *et al.* 2014). Among Finns aged >70 years, the prevalence of statin use was 61% among persons who had established CVD, diabetes or familial hypercholesterolemia in 2008 (Upmeier *et al.* 2013). However, of the 35- to 74-year-old population in primary prevention but at high risk (estimated as QRISK2 $\geq 15\%$) of CVD in the United Kingdom between 1993 and 2006, 7% redeemed statins while an increase to 30% was observed in 2007–11 (van Staa *et al.* 2013).

Among Finns aged >70 years in 2008, prevalence of statin use among apparently healthy persons (without established CVD, diabetes or familial hypercholesterolemia) was 13% (Upmeier *et al.* 2013). However, among the low-risk (QRISK2 $< 15\%$) 35–74 year-old primary prevention population in the United Kingdom, the proportion of persons who redeemed statins increased from 2% in 1993–2006 to 5% in 2007–2011 (van Staa *et al.* 2013). The study differed from the study by Upmeier *et al.* (2013) in that it used information on smoking, body mass index, blood pressure and cholesterol levels in risk estimation. The proportion of low-risk statin users may have been overestimated in the studies in Table 2.2 due to absence of information on smoking and cholesterol values and restriction of lookback periods to the time right before statin initiation as several risk factors may be treated simultaneously.

Table 2.2 Register-based studies identifying apparently healthy statin initiators based on register markers for cardiovascular disease.

Reference, country	Data sources	Exclusion criteria	Lookback periods	Proportion of apparently healthy statin initiators
Larsen <i>et al.</i> 2001, Denmark	Odense University Pharmacoepidemiologic Database	Any CVD \ddagger or diabetes medication	Prescriptions within 1 year prior to statin initiation	30% in 1994, 21% in 1998
Raymond <i>et al.</i> 2007, Canada	British Columbia PharmaNet drug information system, Medical Services Plan physician-claims database and hospital discharge abstract database	CHD, atherosclerosis, cerebrovascular disease, PAD, disorders of lipid metabolism, diabetes, diabetes medication or nitrates	Hospital discharges within 3 years and prescriptions within 1 year prior to statin initiation	17% in 1996– 2001
Wallach Kildemoes <i>et al.</i> 2012a, Denmark	Danish National Prescription Registry, Danish National Patient Registry	MI, CHD, stroke, PAD, PAC, diabetes, hypertension, any CVD \ddagger or diabetes medication	Hospital discharges within 29 years and prescriptions within 11 years prior to statin initiation	16% in 2005
Wallach Kildemoes <i>et al.</i> 2012b, Denmark	Danish National Prescription Registry, Danish National Patient Registry	MI, CHD, stroke, PAD, PAC, diabetes, hypertension, any CVD \ddagger or diabetes medication	Hospital discharges within at least 19 years and prescriptions within at least 1 year prior to statin initiation	20% in 1996, 26% in 2009

Table continues

Table 2.2 Continued

Reference, country	Data sources	Exclusion criteria	Lookback periods	Proportion of apparently healthy statin initiators
Rikala <i>et al.</i> 2013, Finland	Finnish Prescription Register, Finnish Special Reimbursement Register	Any CVD [†] or diabetes medication, entitlement to special reimbursement for CVD or diabetes	Entitlements to special reimbursements within 5 years before to 6 months after statin initiation and prescriptions within 1 year prior to or at statin initiation	24% in 1999, 28% in 2008
Upmeier <i>et al.</i> 2013, Finland	Finnish Prescription Register, Finnish Special Reimbursement Register, Finnish Care Register	CHD, ischemic stroke, atherosclerosis, aneurysm, medical procedures related to CHD (CABG, PTCA, vascular surgery of lower extremity arteries or of abdominal aorta), hypertension, diabetes, any CVD [‡] or diabetes medication, entitlement to special reimbursement for diabetes, CHD, hypertension or familial hypercholesterolemia	Hospital discharges, entitlements to special reimbursements and prescriptions during the year of statin initiation and in the previous year	12% in 2000, 12% in 2008

Abbreviations: CABG, coronary artery bypass graft; CHD, chronic heart disease; CVD, cardiovascular disease; MI, myocardial infarction; PAC, other potential atherosclerotic conditions (e.g. heart failure, arrhythmia, aorta aneurysm and nephropathy); PAD, peripheral artery disease; PTCA, percutaneous transluminal coronary angioplasty.

[‡] CVD medications identified as purchases from ATC categories B01, C01, C02, C03, C07, C08 and C09.

[†] CVD medications identified as purchases from ATC categories B01, C01, C02, C03, C04, C07, C08 and C09.

2.2.1 Adherence to statin therapy

Medication adherence describes the degree to which patients follow their prescribed treatment regimens (Vrijens *et al.* 2012). Several methods (reviewed in Andrade *et al.* 2006, Osterberg and Blaschke 2005) have been applied to quantify adherence. Of the methods proposed, typically either proportion of days covered (PDC) or medication possession ratio (MPR) are used (Andrade *et al.* 2006). Both estimate the proportion of days' supply obtained during a specified time-period. However, PDC is calculated using information on medication coverage on a daily basis crediting for overlapping prescriptions which is not accounted for in the calculation of MPR (Leslie *et al.* 2008). Additionally, measures on persistence, i.e., the length of medication use, and discontinuation may be used to quantify adherence (Vrijens *et al.* 2012). In this study, $PDC \geq 80\%$ is used to define adherence versus non-adherence ($PDC < 80\%$) (see Methods for more detailed definition). This cut-off is widely used, although arbitrary (Chowdhury *et al.* 2013).

Despite the widespread use of statins, adherence to statin therapy in real-life setting remains low (Aarnio *et al.* 2014, Chowdhury *et al.* 2013, Lemstra *et al.* 2012, Naderi *et al.* 2012, Perreault *et al.* 2009b) and discontinuing the use is common, especially during the first years of use (Benner *et al.* 2002, Citarella *et al.* 2016, Ellis *et al.* 2004, Helin-Salmivaara *et al.* 2008, Jackevicius *et al.* 2002, Perreault *et al.* 2005a). In addition to the observed low levels of adherence soon after statin initiation, several studies have observed statin adherence to vary, typically to decrease, over time (Jackevicius *et al.* 2002, Korhonen *et al.* 2011, Maningat *et al.* 2013, Perreault *et al.* 2005a, Perreault *et al.* 2005b, Slejko *et al.* 2014).

Suboptimal adherence has been observed in real-world populations, especially in primary prevention of CVD (Table 2.3). During the first year of statin use, 53% of initiators in primary prevention were adherent ($PDC \geq 80\%$) (Rannanheimo *et al.* 2015). During a maximum observation period of 3.5–3.9 years, 62% had $PDC \geq 80\%$ and 37% had $PDC \geq 90\%$ (Bouchard *et al.* 2007, Ellis *et al.* 2004). With a longer adherence assessment period of a maximum of 6 years since statin initiation, 20% had $PDC > 75\%$ (Corrao *et al.* 2010). Mean adherence during a maximum of 9.5 years (median 2.9 years) follow-up was 45% (Chodick *et al.* 2008). The therapy was discontinued by 32–48% of the initiators during the first year after initiation (Citarella *et al.* 2016, Perreault *et al.* 2005a) while 35–83% continued with the therapy two or three years after statin initiation (Chodick *et al.* 2008, Ellis *et al.* 2004, Perreault *et al.* 2005a, Perreault *et al.* 2005b). Among persons aged ≥ 66 years, 75% of new statin users had discontinued the therapy during the two years after statin initiation (Jackevicius *et al.* 2002).

Table 2.3 Statin adherence in populations in primary prevention of cardiovascular disease.

Reference	Study population and sample size	Adherence measure	Proportion of adherent persons	Discontinuation rate
Jackevicius et al. 2002	≥66 y, 61% ♀, n=21,602	Statin purchase at every 4 months	NA	24 months: 75%
Ellis et al. 2004	≥18 y (mean 57 y), 47% ♀, n=2,544	PDC from statin initiation to last purchase or end of 3.9 years of follow-up	62% with PDC ≥80%	36 months: 50%
Perreault et al. 2005a	50–64 y, 61% ♀, n=25,733	Statin purchase at every 2 months	NA	6 months: 33% 1 year: 48% 3 years: 61% 6 months: 35% 3 years: 65% NA
Perreault et al. 2005b	50–64 y, 62% ♀, n=13,642	Statin purchase at every 2 months	NA	NA
Bouchard et al. 2007	50–64 y, 65% ♀, n=12,180	PDC from statin initiation to a maximum of 3.5 years of follow-up for persons followed for >1 year	37% with PDC ≥90% (Mean PDC 65%)	NA
Mann et al. 2007	all age (mean 61 y), 10% ♀, n=71	Self-report with revised Morisky adherence scale since statin initiation	3 months: 45% 6 months: 43%	NA
Chodick et al. 2008	≥18 y (mean 55 y), 55% ♀, n=136,052	PDC from statin initiation to a maximum of 9.5 years	Mean PDC 45%	2 years: ~83%
Corrao et al. 2010	≥18 y (mean 62 y), 59% ♀, n=90,832	PDC from statin initiation to a maximum of 6 years of follow-up	20% with PDC >75% 20% with PDC 51–75% 60% with PDC ≤50%	NA
Rannanheimo et al. 2015	45–75 y, 56% ♀, n=97,575	PDC during the first year after statin initiation	53% with PDC ≥80% 26% with PDC 40–79% 21% with PDC <40%	NA
Citarella et al. 2016	≥20 y, 53% ♀, n=18,972	Statin purchases without gaps of ≥3 months	NA	12 months: 32%

Abbreviations: NA, not available; PDC, proportion of days covered.

Among persons in primary prevention of CVD, non-adherent persons are typically younger (Corrao *et al.* 2010, Mann *et al.* 2007, Perrault *et al.* 2009a, Shalev *et al.* 2012), have less cardiac (Perreault *et al.* 2009a, Perreault *et al.* 2009b, Shalev *et al.* 2012) and non-cardiac (Shalev *et al.* 2012) comorbidities and less other medications, i.e., polypharmacy (Corrao *et al.* 2010, Perreault *et al.* 2009b) than adherent persons. Low perceived risk (Citarella *et al.* 2016, Halava *et al.* 2014, Mann *et al.* 2007, Shalev *et al.* 2012), low socioeconomic level (Shalev *et al.* 2012), and fewer general practitioner visits (Shalev *et al.* 2012) are also associated with non-adherence. For gender, results are mixed (Corrao *et al.* 2010, Shalev *et al.* 2012).

2.2.2 Adherence to statin therapy and the risk of atherosclerotic cardiovascular events in primary prevention

Association between adherence to statin therapy and incidence of atherosclerotic cardiovascular events in general population in primary prevention of CVD has been examined in several studies (Table 2.4). All of the studies reported reduced CVD event risk for adherers in comparison with non-adherers (Table 2.4). Adherence was typically assessed by PDC or MPR as a time-fixed or time-dependent variable except in one study which measured adherence based on prescription refills during the first year since statin initiation. When PDC or MPR was used, adherers were defined using a 76–90% cutoff and the lower than threshold level was further divided into 1–4 subcategories. Slejko *et al.* (2014) focused on initially adherent persons (PDC $\geq 80\%$ during the first year after statin initiation) to allow for a comparison between continuous adherers and those who switched from adherence to non-adherence. In their study, those who remained adherent during the second year had 57% (95% CI 44–65%) reduced risk of non-fatal CVD events compared with those with a steep decline in adherence level (from $\geq 80\%$ to $< 20\%$) during the second year (Slejko *et al.* 2014). For non-fatal CHD events after first year of follow-up, adherers (PDC $\geq 90\%$ or $\geq 80\%$ or $\geq 76\%$ from statin initiation to time of an event or ≥ 2 prescription fills during the first year of statin use) had 19–26% reduced risk compared with non-adherers (PDC $< 90\%$ or $< 40\%$ or $< 26\%$ or 1 prescription fill) (Bouchard *et al.* 2009, Corrao *et al.* 2010, Patrick *et al.* 2011, Rannanheimo *et al.* 2015). When all-cause mortality was combined with non-fatal CHD events after first year of follow-up, the risk reduction was 18% (95% CI 13–23%) for adherers (MPR $\geq 80\%$ from statin initiation to the time of an event) in comparison with non-adherers (MPR $< 20\%$) (Perreault *et al.* 2009a). However, for a composite of non-fatal CHD and stroke emerging after first year of follow-up, 36% risk reduction was reported for adherers (MPR $\geq 80\%$ from statin initiation to the time of an event) compared with non-adherers (MPR $< 20\%$) (Shalev *et al.* 2012). Finally, adherence (MPR $\geq 80\%$ from statin initiation to the time of outcome) reduced the risk of cerebrovascular disease encountered after first year of follow-up by 26% (95% CI 16–35%) when compared with non-adherence (MPR $< 20\%$) (Perreault *et al.* 2009b). However, 35% (95% CI 22–45%) reduction in the incidence of ischemic stroke (Korhonen *et al.* 2016) and 13% (95% CI 4–22%) reduction in the incidence of major cardiovascular events (Ruokoniemi *et al.* 2011) is reported for adherent (PDC $\geq 80\%$) diabetic persons in primary prevention in comparison with non-adherent (PDC $< 80\%$) ones.

Definition for population in primary prevention varies between the studies although all the studies targeted population without manifest CVDs. In all studies, the participants had to be free of hospital discharges for CVD during the 1–5 years prior to study initiation and 5 out of 7 studies included medical procedures in this definition as well. Additionally, studies excluded persons (except the study by Patrick *et al.* 2011) based on prescription records for medications used in the treatment of CHD 1–3 years prior to study initiation. In the Finnish study by Rannanheimo *et al.* (2015), subjects were required not to have special reimbursement for any cardiovascular medication at statin initiation and one year thereafter. Shalev *et al.* (2012) used one-year lookback periods to identify primary prevention persons based on hospital discharges, medical procedures and medication use. Age was restricted to 45–75 or 45–85 years in the majority of the studies (Perreault *et al.* 2009a, Perreault *et al.* 2009b, Rannanheimo *et al.* 2015, Shalev *et al.* 2012). However, one study examined 50- to 64-year-old adults (Bouchard *et al.* 2007), one included all persons aged ≥ 18 years (Corrao *et al.* 2012) whereas one had no age restriction at all (Slejko *et al.* 2014). The proportion of women varied between 50–65% in the studies examined. Four of the studies were designed as cohort studies and three applied nested case-control design within a cohort. Finally, outcomes were assessed using information on hospital discharges and, in some studies, additionally on medical procedures and medication purchases. In the majority of the studies found, estimation results were adjusted both for baseline and time-dependent confounders. However, time-dependent confounders were measured during the adherence assessment period. Thus, the values of these confounders may have been affected by prior adherence which was not accounted for in the statistical analyses.

Generally, adherent persons may differ from non-adherent persons in many respects other than adherence level. Adherers may be generally healthier and more adherent to recommendations concerning health behavior than non-adherent ones which would introduce residual confounding termed healthy-adherer bias (Brookhart *et al.* 2007, Dormuth *et al.* 2009, Patrick *et al.* 2011). For example, Patrick *et al.* (2011) provide evidence on the existence of such bias. They examined the association between statin adherence and use of preventive services and various outcomes potentially attributable to unhealthy lifestyle. They observed that adherers were more likely to use preventive services but less likely to experience clinical outcomes not known to be related to statin use than non-adherers. However, Rannanheimo *et al.* (2015) considered the healthy-adherer effect by adjusting for a few lifestyle factors (body mass index, smoking, alcohol use, physical activity) and self-reported health but found no major effect on the effect estimate.

Table 2.4 Observational studies on the association between statin adherence and cardiovascular events among general primary prevention population.

Reference, country	Design, study population	Max follow-up, years	Exposure definition	Exposure classification	Time-dependent confounders	Outcome	Crude effect estimate (95% CI)	Adjusted effect estimate (95% CI)
Bouchard <i>et al.</i> 2007, Canada	NCC (n=12,180), 50–64 y, 65% ♀	3.5	PDC from statin initiation to time of outcome	≥90% <90%	Cardiac comorbidities measured during the follow-up	Non-fatal CHD after 1 st year of follow-up	RR 0.84 (not reported)	RR 0.81 (0.67–0.97) 1.00
Perreault <i>et al.</i> 2009a, Canada	NCC (n=147,601), 45–85 y, 63% ♀	6.5	MPR from statin initiation to time of outcome	≥80% 60–79% 40–59% 20–39% <20%	Cardiac and non-cardiac comorbidities and medication use measured during the follow-up	Non-fatal CHD or all-cause death after 1 st year of follow-up	RR 0.90 (0.85–0.96) 0.92 (0.85–1.00) 0.94 (0.86–1.02) 0.95 (0.87–1.04) 1.00	RR 0.82 (0.77–0.87) 0.85 (0.78–0.92) 0.87 (0.80–1.00) 0.91 (0.84–1.01) 1.00
Perreault <i>et al.</i> 2009b, Canada	NCC (n=41,140), 45–85 y, 63% ♀	6.5	MPR from statin initiation to time of outcome	≥80% 60–79% 40–59% 20–39% <20%	Cardiac and non-cardiac comorbidities measured during the follow-up	Non-fatal cerebrovascular disease after 1 st year of follow-up	RR 0.83 (0.74–0.93) 0.93 (0.80–1.07) 0.90 (0.76–1.06) 1.01 (0.86–1.19) 1.00	RR 0.74 (0.65–0.84) 0.82 (0.71–0.96) 0.83 (0.70–0.98) 0.97 (0.83–1.15) 1.00
Corrao <i>et al.</i> 2010, Italy	Cohort (n=90,832), ≥18 y (mean 62 y), 59% ♀	6	PDC from statin initiation to time of outcome	≥76% 51–75% 26–50% <26%	Concomitant cardiac medication use and switching of statins measured during the follow-up	Non-fatal CHD after 1 st year of follow-up	HR 0.97 (0.85–1.12) 0.90 (0.79–1.04) 0.86 (0.75–0.99) 1.00	HR 0.81 (0.71–0.94) 0.82 (0.71–0.95) 0.85 (0.72–0.98) 1.00
Patrick <i>et al.</i> 2011, US	Cohort (n=29,675), all-age (mean 76 y), 85% ♀	1	Prescription fills during the first year since statin initiation	≥2 1	Not measured	Non-fatal CHD after 1 st year of follow-up	Not reported	RR 0.74 (0.52–1.04)

Table continues

Table 2.4 Continued

Reference, country	Design, study population	Max follow-up, years	Exposure definition	Exposure classification	Time-dependent confounders	Outcome	Crude effect estimate (95% CI)	Adjusted effect estimate (95% CI)
Shalev et al. 2012, Israel	Cohort (n=171,535), 45–75 y, 58% ♀	12	MPR from statin initiation to time of outcome	≥80% 60–79% 40–59% 20–39% <20%	Efficacy of statin therapy measured during the follow-up	Non-fatal CHD or stroke after 1 st year of follow-up	Not reported	HR 0.64 (0.60–0.67) 0.63 (0.59–0.67) 0.71 (0.67–0.75) 0.90 (0.85–0.96) 1.00
Slejko et al. 2014, United States	Cohort (n=11,126), all-age (mean 56 y), 50% ♀	5	Second year PDC	≥80% 20–79% <20%	Not measured	Non-fatal CVD after 1 st year of follow-up	Not reported	HR 0.43 (0.35–0.56) 0.93 (0.79–1.09) 1.00
Rannanheimo et al. 2015, Finland	Cohort (n=97,575), 45–75 y, 56% ♀	3	Cumulative PDC updated in one-year periods after statin initiation	≥80% 40–79% <40%	Not measured	Non-fatal CHD after 1 st year of follow-up	HR 0.77 (0.72–0.82) 0.87 (0.82–0.94) 1.00	HR 0.77 (0.72–0.82) 0.86 (0.80–0.92) 1.00

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MPR, medication possession ratio; NCC, nested case-control; PDC, proportion of days covered; RR, rate ratio.

2.3 Polypharmacy among older persons

Conventionally, older persons are defined as person ≥ 65 years (Taylor *et al.* 2009) and consequently, age structure reports of the total world population use this or ≥ 60 years as a threshold. However, due to increasing years of healthy life experienced after the age of 65 years and the first impacts of the aging process experienced around the age of 75 years, the definition of older person is currently shifting to persons aged 75 and older. In this study, the literature review allows inclusion of persons aged ≥ 60 years whereas the results section considers older persons to be those aged ≥ 75 years.

Polypharmacy describes multiple use of medications by a single person or the use of more medications than is clinically necessary (Clyne *et al.* 2012, Hajjar *et al.* 2007, Maher *et al.* 2014). Several ways to define polypharmacy have been applied (Fulton *et al.* 2005, Maher *et al.* 2014). Qualitative definitions describing the quality of medication are used (Fulton *et al.* 2005). More often, polypharmacy is quantitatively defined as the simultaneous use of two or more, or four to six or more medications (Fulton *et al.* 2005). Also a distinction between polypharmacy and excessive polypharmacy, as use of 10 or more medications concomitantly, has been proposed (Jyrkkä *et al.* 2009). Because of absence of consensus for the definition, polypharmacy may also be defined as a continuous measure of the number of simultaneous medications in use (Lapi *et al.* 2009) which is also applied in this study.

Older persons are the largest consumers of medications – in 2014, persons aged 75 years or more accounted for 22% of the total medicine costs in Finland (Finnish Medicines Agency Fimea and Social Insurance Institution 2015) while their share of the total population was only 9% (retrieved from the Statistics Finland, available at http://www.tilastokeskus.fi/tup/suoluk/suoluk_vaesto.html, accessed 1 December 2015). In a study on medication use among Finns aged 80 years or more in 2003, 98% of participants were using at least one medication; 85% used cardiovascular medications (ATC category C), 70% medications for the nervous system and 65% antithrombotic medications (Jyrkkä *et al.* 2006). More specifically, 12% used lipid-lowering medications, 41% diuretics, 51% beta blockers, 20% calcium channel blockers and 30% used agents acting on the renin-angiotensin system (Jyrkkä *et al.* 2006). The mean number of medications taken regularly and as-needed was 7.5 (Jyrkkä *et al.* 2006).

The use of preventive medications, such as statins, has increased in older populations over time (Upmeier *et al.* 2013). With aging, several chronic diseases may be diagnosed requiring the use of multiple medications (Clyne *et al.* 2012, Hiitola *et al.* 2007, Jyrkkä *et al.* 2006). Consequently, problems related to polypharmacy, such as drug-drug interactions or risk of adverse events, are likely to increase along with persons' increasing medication burdens.

The evolution of polypharmacy can be investigated between cohorts (i.e., between repeated cross-sectional studies) or within a cohort. Comparison of cross-sectional studies describes changes in prescribing practices as well as time-related habits, whereas

longitudinal setting concentrating on evolution in time within a cohort describes the effect of the aging process (Jylhä 1994) and accumulation of the burden of comorbidities. Generally, the majority of the longitudinal cohort studies describing the evolution of the number of medications among older persons report increment in mean number of medications with aging (Table 2.5). Studies differ in terms of medications included in the calculation of total number, age restrictions at the baseline and inclusion of in-hospital persons, which complicates comparison of the results.

In the studies (Table 2.5), change over time has typically been examined by comparing mean numbers of medications between two time points, except in the study by Blumstein *et al.* (2008) that modeled change between three time points using repeated-measures analysis of variance. However, comparing two time points assumes a linear trend for growth, and the results tell nothing about the non-linear shape of evolution between the time points (Singer and Willet 2003). All of the earlier studies focused on investigating change among those examined at every time point, i.e., using complete data where persons with missing data at some time points were discarded. The mean number of medications reported for the three time points (2.2, 2.7 and 2.7 at baseline and on average 3.6 and 11.7 years thereafter, correspondingly) in the study by Blumstein *et al.* (2008) give rise to suspicion of a non-linear change over time. Although change scores and pairwise comparisons are unbiased estimates of linear within-persons change, these methods are not unbiased when averaged over an aged population. In longitudinal studies of older persons, focusing on those for whom data are available or on survivors means making inference on the healthiest group of persons and possibly obtaining overly optimistic estimates for the entire cohort (Diehr *et al.* 2005). Mortality among older persons is high (Jylhä 1994, Steinman *et al.* 2007) and has been reported to associate with the number of medications in use (Jyrkkä *et al.* 2009, Espino *et al.* 2006).

Table 2.5 Studies on the evolution of the number of medications in use within a cohort of older persons.

Reference, country	Study period(s)	Age at baseline, years	Setting and size of study population	Medications included	Result
Stewart <i>et al.</i> 1991, US	1978–79 & 1987–88	≥65	Community dwellers, n=924	Rx, OTC	↑ 1.2 medications in 10 years.
Jylhä 1994, Finland	1979 & 1989	60–79	Population-based, n=393	Rx, OTC	↑ 0.9–1.4 prescribed medications in 10 years
Fillenbaum <i>et al.</i> 1996, US	1986–87 & 1989–90	≥65	Community dwellers, n=3,224	Rx, OTC	↑ 0.4 Rx medications and ↓ 0.1 OTC medications in 3 years.
Veehof <i>et al.</i> 2000, Netherlands	1994 & 1997	≥65	Community dwellers, n=1,544	Rx	↑ 1.0 medications in 4 years.
Jyrkkä <i>et al.</i> 2006, Finland	1998 & 2003	≥75	Population-based, n=339	Rx, OTC	↑ 1.2 medications in 5 years.
Steinman <i>et al.</i> 2007, Israel	1990–91 & 1997–98	70 ± 1	Community dwellers, n=280	Rx, OTC	↑ 3.3 medications in 7 years.
Blumstein <i>et al.</i> 2008, Israel	1989 & 1993–94 & 2001–02	75–94	Community dwellers, n=160	Rx, OTC	Non-significant ↑ 0.4 medications in 12 years
Lapi <i>et al.</i> 2009, Italy	1995 & 1999	≥65	Community dwellers, n=568	Rx, OTC	↑ 0.9 medications in 5 years.
Lu <i>et al.</i> 2015, Taiwan	2002 & 2011	≥65	Population-based, n=59,042	Rx	↑ 2.0–2.1 medications during the 10-year follow-up.

Abbreviations: OTC, over-the-counter medication; Rx, prescription medication.

↑, increase; ↓, decrease.

2.4. Change in medication use

A person's medication use is dynamic: physicians initiate medications, medications may need to be discontinued or dosages changed, which is typical at the initiation phase of medication use. From the patient perspective, persons should adhere to medications to have full benefit from the therapy. However, transitions between adherence and non-adherence are common over time (Korhonen *et al.* 2011, Slejko *et al.* 2013).

2.4.1 Medication use as an outcome

When the aim is to study longitudinal patterns or developmental trajectories of medication use in a population, trajectory models can be applied. However, modeling a single growth trajectory for the entire population may lead to oversimplification of the growth process as the population may consist of several homogeneous subpopulations (Jung and Wickrama 2008). This study focuses on latent growth curve models in relating medication use as an outcome variable to time and on growth mixture models in identifying subpopulations and estimating mean trajectories within subpopulations.

Missing data on medication use may lead to inefficient estimation and biased growth estimates (Enders 2010). Thus, accounting for missing data mechanism in estimation by adjusting for missing data can produce more accurate estimates of growth.

2.4.1.1 Latent growth curve models and growth mixture models

Latent growth curve models (LGCMs; Meredith and Tisak 1990) that belong to structural equation modeling framework can capture heterogeneity in growth trajectories. In addition to individual growth trajectories, LGCM captures differences between individuals at baseline level and slope of change. Generally, LGCM may be presented as follows:

$$\begin{aligned} \mathbf{y}_i &= \mathbf{\Lambda}\boldsymbol{\eta}_i + \boldsymbol{\varepsilon}_i \\ \boldsymbol{\eta}_i &= \boldsymbol{\alpha} + \boldsymbol{\zeta}_i \end{aligned}$$

where \mathbf{y}_i is a $t \times 1$ vector of repeated outcome measurements for a person $i \in \{1, \dots, N\}$ at t time-points. Vector $\boldsymbol{\eta}_i$ represents latent growth factors, such as intercept, linear slope and, in the case of non-linear development, quadratic slope. Matrix $\mathbf{\Lambda}$ represents factor loadings for latent growth factors that describe the functional form of individual trajectories. Vector $\boldsymbol{\varepsilon}_i$ consists of time-specific measurement errors that are assumed to follow normal distribution with zero means. Vector $\boldsymbol{\alpha}$ consists of growth factor means and vector $\boldsymbol{\zeta}_i$ of normally distributed residuals with zero means that describe differences between individual growth factors and population means. Further, all covariances between latent growth factors and measurement errors are assumed to be zero. $\boldsymbol{\Psi} = \text{cov}(\boldsymbol{\eta}_i) = \text{cov}(\boldsymbol{\zeta}_i)$ is a covariance matrix of the growth factors and $\boldsymbol{\Theta} = \text{cov}(\boldsymbol{\varepsilon}_i)$ is that of the measurement errors. Finally, the covariance matrix of the observed outcomes may be presented as

$$\text{cov}(\mathbf{y}) = \mathbf{\Lambda}\boldsymbol{\Psi}\mathbf{\Lambda}^T + \boldsymbol{\Theta}$$

and the mean structure of the observed outcomes as

$$E(\mathbf{y}) = \Lambda\boldsymbol{\alpha}.$$

That is, growth factor means represent the average development of population over time assuming that persons are drawn from a homogeneous population (Reinecke and Seddig 2011). The above LGCM is a formal presentation of growth curve models and also applies to multilevel and random-effects models (Reinecke and Seddig 2011).

Where marginal LGCMs produce information on population means and allow for heterogeneity in intercept and slope in a single population, growth mixture models (GMMs; Laird and Ware 1982, Muthén and Shedden 1999) model heterogeneity in development within subpopulations identified from a larger heterogeneous population (Jung and Wickrama 2008, Reinecke and Seddig 2011). GMMs characterize the shape of trajectories within subpopulations and produce estimates for intercepts and slopes of the identified trajectories. The method assumes that each person's trajectory over time results from a person being a member of a latent (unobserved) subpopulation or class. GMM may be presented as follows:

$$\begin{aligned} \mathbf{y}_{ik} &= \Lambda_k \boldsymbol{\eta}_{ik} + \boldsymbol{\varepsilon}_{ik} \\ \boldsymbol{\eta}_{ik} &= \boldsymbol{\alpha}_k + \boldsymbol{\zeta}_{ik} \end{aligned}$$

where subscript k allows for the estimation of latent classes. Following from the definition of LGCM, class-specific covariance matrix for observed outcomes in GMM is

$$\text{cov}(\mathbf{y}_k) = \Lambda_k \boldsymbol{\Psi}_k \Lambda_k^T + \boldsymbol{\Theta}_k$$

and the class-specific mean structure of the observed outcomes is

$$E(\mathbf{y}_k) = \Lambda_k \boldsymbol{\alpha}_k.$$

Because the number of latent classes (k) is unknown *a priori*, growth mixture modeling is an iterative process. It starts by specifying a single-class growth model, i.e., LGCM, after which alternative models with varying numbers of latent classes are fitted. The model with the appropriate number of unobserved latent classes is typically identified using Bayesian information criteria (BIC; Schwartz 1978) value and Lo-Mendell-Rubin likelihood ratio test (LMR-LRT; Lo *et al.* 2001) statistic comparing the current model against the model with one less class. In addition to these fit indices, convergence, an entropy value (near one, Celeux and Soromenho 1996), size of the latent classes, and posterior probabilities are used. Because GMM parameters are estimated with maximum likelihood method using iterative expectation-maximization algorithm, finding a local maximum instead of global maximum can distort the analysis (Hipp and Bauer 2006). Therefore, estimation results should be replicated when reanalyzing the model using the best two log-likelihood values (Jung and Wickrama 2008).

GMM allows for class-specific random effects, i.e., latent growth factors. However, variances and, thus, covariances of intercept and slope factors may be fixed to zero instead. Such a restricted model is termed latent class growth model (or alternatively, group-based trajectory model; Nagin and Land 1993, Nagin and Odgers 2010), which has recently been used for analyzing longitudinal patterns of medication adherence (Franklin *et al.* 2013, Franklin *et al.* 2015a, Franklin *et al.* 2015b, Li *et al.* 2014).

2.4.1.2 Missing outcome data

Here, missing data are defined as intended measures that were not taken (Lehtonen and Pahkinen 2004). Missing data may result from mortality or disease progression, but also from reasons unrelated to health, such as refusing to participate or to respond in a survey or moving out of the specific study area, or loss of insurance coverage in studies based on administrative data. Death leads to permanent missing data; after leaving the study once the person will no longer participate (Schafer and Graham 2002). This type of missing data produces a monotone missing data pattern, and is termed attrition in longitudinal studies (Little and Rubin 2002, Schafer and Graham 2002). Other reasons for missing data can also introduce a non-monotone missing data pattern, meaning that persons intermittently miss examinations (Schafer and Graham 2002). Unit nonresponse occurs when a person fails to participate in the study, but item nonresponse is also possible; for example, when a person does not provide data on all parts of a questionnaire (Lehtonen and Pahkinen 2004, Schafer and Graham 2002). This study focuses on monotone missing data pattern which is generally a less demanding pattern from a modeling perspective.

Rubin (1976) and Little and Rubin (2002) classify missing data on three categories based on the mechanism that leads to missing data. Let $\mathbf{R}_i = (R_{i1}, \dots, R_{iT})^T$ be the missing data indicator vector for a person $i \in \{1, \dots, N\}$ scored as a binary discrete-time survival indicator. Let r_{it} be a value of a random variable R_{it} at a time point $t \in \{1, \dots, T\}$ with $r_{it} = 0$ indicating observed value for a participant i at time t and $r_{it} = 1$ missing value. Let $\mathbf{Y}_i^{obs} = (Y_{i1}^{obs}, \dots, Y_{i,k-1}^{obs})$ and $\mathbf{Y}_i^{mis} = (Y_{ik}^{mis}, \dots, Y_{iT}^{mis})$ be the observed and missing outcome variable vectors for some $k \in \{1, \dots, T\}$ and, thus, $\mathbf{Y}_i = (\mathbf{Y}_i^{obs}, \mathbf{Y}_i^{mis})$ complete outcome vector. Additionally, let x_i be a fully observed model covariate. When data are missing completely at random (MCAR), the probability of missing data does not depend on observed or unobserved outcomes or other measured variables. That is $P(\mathbf{r}_i | \mathbf{y}_i^{obs}, \mathbf{y}_i^{mis}, x_i) = P(\mathbf{r}_i)$. Later, methodologists have proposed to expand Rubin's (1976) three-class taxonomy to include a weaker assumption of MCAR; a covariate-depending MCAR, where the probability of missing data depends on model covariate but is independent of outcome conditional on the model covariate, $P(\mathbf{r}_i | \mathbf{y}_i^{obs}, \mathbf{y}_i^{mis}, x_i) = P(\mathbf{r}_i | x_i)$ (Diggle and Kenward 1994, Hogan *et al.* 2004). Under the MCAR assumption, data on complete cases are representative of the target population. Missing at random (MAR) mechanism allows the probability of missing data to depend on the observed data but not on the unobserved outcomes; $P(\mathbf{r}_i | \mathbf{y}_i^{obs}, \mathbf{y}_i^{mis}, x_i) = P(\mathbf{r}_i | \mathbf{y}_i^{obs}, x_i)$. If both observed and unobserved outcomes predict the probability of missing data, the data are termed to be missing not at random (MNAR), meaning that missing data mechanism cannot be ignored in statistical analyses because the outcome variable vector $\mathbf{y}_i = (\mathbf{y}_i^{obs}, \mathbf{y}_i^{mis})$ and probability of missingness $P(\mathbf{r}_i)$ are jointly distributed, $P(\mathbf{y}_i, \mathbf{r}_i)$. This is the weakest assumption meaning that, for example, the current, possibly unobserved outcome is associated with the probability of missing data (Enders 2010).

There are no tests available to distinguish between alternative missing data mechanisms (Enders 2010). The only mechanism that can be tested is MCAR (Enders

2010). When the assumption of missing data mechanism is violated, the results obtained are biased (Enders 2010). Neglecting the MNAR mechanism in analysis can lead to attrition bias already with small proportions of attrition (Kristman *et al.* 2004). For this, sensitivity analyses for the impact of MNAR mechanism assumption are warranted (Enders 2010).

In order to explore change among the entire cohort, a variety of methods to deal with missing outcome data have been developed (Hogan *et al.* 2004). During the past decades, literature on missing data methods, especially to account for MNAR mechanism, has been expanding fast and new methods are frequently proposed. This literature review does not provide an exhaustive list of all statistical techniques currently available to account for missing outcome data but is rather demonstrative of the magnitude of possibilities and differences between alternative, classical methods under each of the missing data assumptions. A list of the strategies discussed below is presented in Table 2.6.

Under the MCAR assumption, deletion techniques as well as imputation of values that would have been observed had the value not been missing are used (Table 2.6) (Revicki *et al.* 2001, Schafer and Graham 2002). Deletion methods typically waste data and result in inefficient estimates when dropout rate is high and a variable has a declining or increasing trend (Little and Rubin 2002). Single imputation methods include methods that fill in the data by predicting a single replacement value. In contrast to deletion methods, single imputation methods make use of the data with missing values that deletion methods exclude. However, these methods typically underestimate variance (Enders 2010). Generally, use of the presented simple *ad hoc* methods is not recommended today (Enders 2010, Little and Rubin 2002).

When MAR is a plausible assumption, methods based on maximum likelihood (ML; Anderson 1957, Dempster *et al.* 1977), multiple imputation (Rubin 1978, Rubin 1987) or weighting of generalized estimating equations (Little and Rubin 2002, Robins *et al.* 1995, Rotnitzky *et al.* 1998) can be applied (Table 2.6). Full-information ML estimation (FIML; Arbuckle 1996, Little and Rubin 2002) attempts to identify the most likely parameters that produce a particular sample of data in the presence of missing data. In the FIML estimation, missing values are not imputed but the model is estimated with all available data. To illustrate, let \mathbf{Y}_i be a multivariate normally distributed outcome vector for a person i with a population mean vector $\boldsymbol{\mu}_i$ and covariance matrix $\boldsymbol{\Sigma}_i$ that are functions of model parameters. The objective is to find model parameters that maximize the log-likelihood function and produce population mean vector $\boldsymbol{\mu}_i$ and covariance matrix $\boldsymbol{\Sigma}_i$ that are as close as possible to sample mean vector $\bar{\mathbf{Y}}_i$ and covariance matrix \mathbf{S}_i . The sample log-likelihood is a sum of individual log-likelihoods,

$$\log L = -\frac{1}{2} \sum_{i=1}^N \{k_i \log(2\pi) + \log|\boldsymbol{\Sigma}_i| + (\mathbf{Y}_i - \boldsymbol{\mu}_i)^T \boldsymbol{\Sigma}_i^{-1} (\mathbf{Y}_i - \boldsymbol{\mu}_i)\} \quad (2.1)$$

where k_i is the number of complete observations for a person i (Enders and Bandalos 2001, Enders 2010). As the log-likelihood is calculated for each person using all the available data of that person, the content and size of the matrices can vary between

persons (superscript i in the equation 2.1). Computing FIML estimates usually requires iteration; for example, using the expectation-maximization algorithm, which is another ML algorithm (Dempster *et al.* 1977). Methods based on ML assume large enough sample size to produce unbiased estimates that are normally distributed (Schafer and Graham 2002). In addition, the method used may be vulnerable to departures from model assumptions for complete data. However, standard errors may be produced using robust versions to protect against violations of normality. Generally, ML-based estimates are unbiased under both MCAR and MAR (Enders and Bandalos 2001).

When the MNAR mechanism is assumed for missing data, there are several methods available (Table 2.6), all of which rely on strong, untestable assumptions and are generally advised to be conducted as a sensitivity analysis (Enders 2010). ML-based methods (selection models, shared parameter models and pattern-mixture models) require a model for the missing data mechanism to model the joint distribution of outcome and missing data processes. Selection models present the joint model as $f(\mathbf{y}_i, \mathbf{r}_i) = f(\mathbf{y}_i)P(\mathbf{r}_i|\mathbf{y}_i)$ where $\mathbf{y}_i = (\mathbf{y}_i^{obs}, \mathbf{y}_i^{mis})$ (Heckman 1979). That is, a model for the full data and a model to describe missing data mechanism conditional on the full data are required. As an example, the longitudinal selection model by Diggle and Kenward assumes a well-known distribution for the full data \mathbf{y}_i measured over time and the probability of missing data to follow a logistic regression conditional on previous (observed) and current (potentially missing) outcomes (Diggle and Kenward 1994). By altering the specification of the missing data model, special cases for MAR and MCAR assumptions are obtained. Selection models are vulnerable to departures from normality assumption in the case of continuous outcome and even slight departures may have a substantial effect on parameter estimates (Kenward 1998). However, distributional assumption cannot be verified when outcomes are missing. Shared-parameter models differ from selection models in that they link the full data model and the missing data process through shared parameters; individual intercepts and slopes instead of observed outcomes (Wu and Carroll 1988). Pattern-mixture models (Little 1993, Hogan and Laird 1997) group persons based on their missing data patterns and model the observed data within each group, $f(\mathbf{y}_i, \mathbf{r}_i) = P(\mathbf{r}_i)f(\mathbf{y}_i|\mathbf{r}_i)$. That is, a marginal model for missingness and a model for the full data conditional on missingness are required. However, as the objective is usually to gain information on the marginal estimates over the missing data patterns, estimates retrieved by a pattern-mixture model need to be further analyzed, computing, for example, a weighted average over the patterns and standard errors (Enders 2011). However, identification of parameters of growth (linear, possibly quadratic) for the first and possibly for the second follow-up is restricted (Muthén *et al.* 2011). Additionally, application of pattern-mixture models requires sufficient sample size for each of the missing data patterns. Several extensions which, for example, account for heterogeneity of data have been introduced to these ML-based methods during the past decade (Muthén *et al.* 2011). In sum, all of the presented methods model the same joint distribution but may end up with different results due to the unverifiable model-specific assumptions needed for each model.

Table 2.6 Statistical techniques to account for missing outcome data in longitudinal studies.

Assumption	Group of methods	Example method
MCAR	Deletion methods	<ul style="list-style-type: none"> • Listwise deletion • Pairwise deletion
	Single imputation methods	<ul style="list-style-type: none"> • Last observation carried forward • Arithmetic mean imputation • Regression imputation • Hot-deck imputation
MAR	Maximum likelihood based methods	<ul style="list-style-type: none"> • Mixed models • Generalized linear mixed models • Latent variable framework • Survival analysis
	Imputation methods	<ul style="list-style-type: none"> • Stochastic regression imputation • Multiple imputation • Bayesian multiple imputation
	Weighting methods	<ul style="list-style-type: none"> • Weighted generalized estimating equations
MNAR	Maximum likelihood based methods	<ul style="list-style-type: none"> • Selection models • Shared parameter models • Pattern-mixture models
	Imputation methods	<ul style="list-style-type: none"> • Multiple imputation • Bayesian multiple imputation
	Weighting methods	<ul style="list-style-type: none"> • Weighted generalized estimating equations

Abbreviations: MAR, missing at random; MCAR, missing completely at random; MNAR, missing not at random.

2.4.2 Medication use as an exposure

Several alternative ways exist to measure exposure to a medication over time (see examples in Figure 2.1). Exposure may be assessed at baseline or during a prespecified time-period that is needed, for example, when assessing medication adherence. In the study by Slejko *et al.* (2014) (see Table 2.4) exploring the effect of statin adherence on the incidence of non-fatal CVD events, adherence was assessed during the second year after statin initiation. Time-dependent exposure assessment takes into account changes in exposure status and/or its intensity over time. In the study by Rannanheimo *et al.* (2015) statin adherence was assessed at cumulatively updated one-year time-intervals since statin initiation (see Figure 2.1). However, in the studies in Table 2.4 applying nested case-control design (Bouchard *et al.* 2007, Perreault *et al.* 2009a, Perreault *et al.* 2009b), statin adherence was measured from statin initiation to time of outcome for cases and to time of selection for controls as a time-invariant value. As one person could serve as a control for several cases before possibly turning into a case, adherence could be assessed several times, i.e., at several time points, for a person.

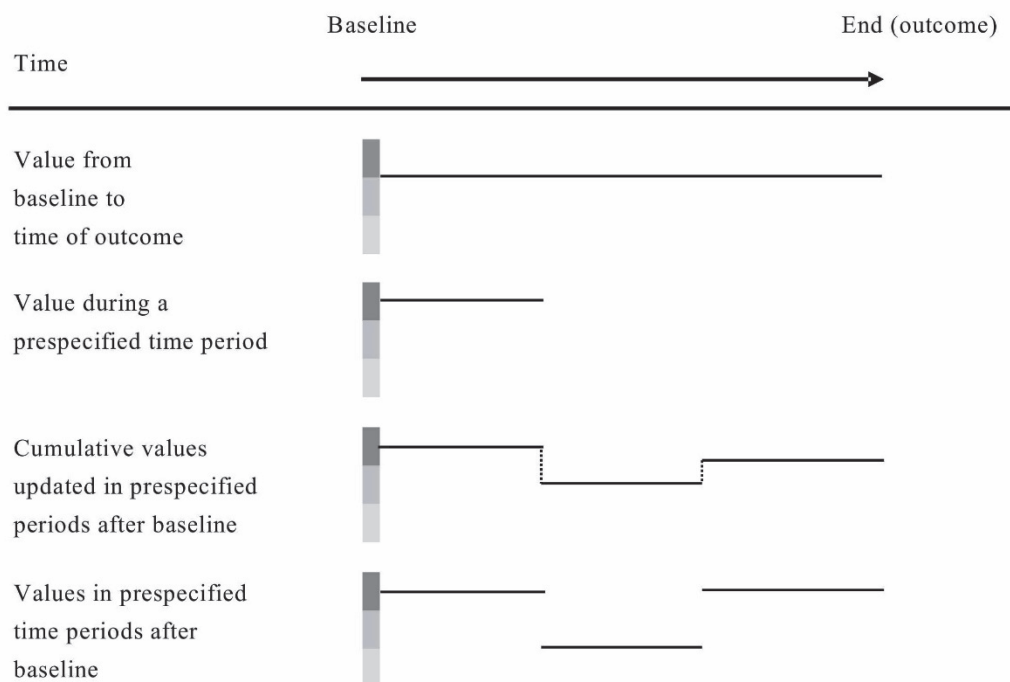


Figure 2.1 Examples of methods to assess exposure to a medication use during a study.

Statistical modeling with time-dependent exposure requires more complex models than modeling with time-fixed exposures. In addition, estimation is even more complicated in the presence of both time-dependent exposure and time-dependent confounding, i.e., when the time-dependent confounder predicts both future medication use and outcome events and is also affected by previous medication use as illustrated in Figure 2.2. In the two directed acyclic graphs (Greenland *et al.* 1999) presented in the

Figure 2.2, L_1 is a risk factor measured most recently to time 1 that confounds the association between medication use A_1 measured at time 1 and outcome Y measured thereafter introducing confounding bias in the analysis if L is not controlled for. On the other hand, adjusting for a set of confounders L_2 measured most recently to time 2 means conditioning on an intermediate variable, resulting in that the apparent effect may be weaker or stronger than the true effect. If there are unmeasured confounders that are common causes for the intermediate confounders L_2 and the outcome Y (Figure 2.2a), adjusting for L_2 may open a non-causal path between medication use and the outcome and create association (Hernán *et al.* 2004, Robins *et al.* 2000). From observational data, it is possible to test whether A_k is associated with L_k , but impossible to determine whether there is unmeasured confounding. Observational studies typically rely on an assumption of no unmeasured confounding – that is, a sufficient set of variables that are not caused by the exposure is measured (Figure 2.2b).

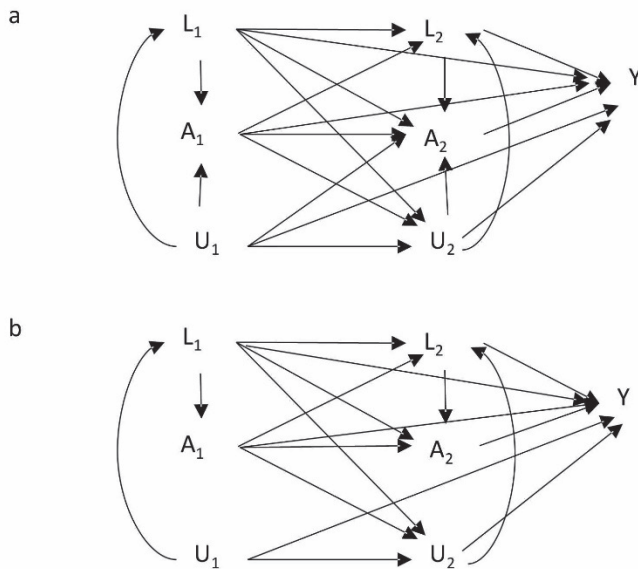


Figure 2.2 Directed acyclic graphs of time-dependent confounding. L_1 and L_2 , time-dependent measured confounders at times 1 and 2; U_1 and U_2 , time-dependent unmeasured confounders at times 1 and 2; A_1 and A_2 , time-dependent medication exposures at times 1 and 2; Y , outcome (modified from Robins *et al.* 2000).

Statistical methods to overcome the problem caused by time-dependent confounding include marginal structural models (MSMs; Robins 1999, Robins *et al.* 2000), g-computation formula (Robins 1986) and g-estimation of nested structural models (Robins *et al.* 1992). Here, the focus is on inverse probability of treatment weighted estimation of MSMs.

2.4.2.1 Inverse probability of treatment weighted estimation of marginal structural models

Inverse probability of treatment weighted estimation of MSM aims to produce a pseudo-population in which confounders are conditionally exchangeable between exposure groups, but in which the causal effect is preserved (Hernán *et al.* 2000). To review MSMs, a causal inference framework is first introduced. The notation used in this section follows the one by Hernán and Robins 2016. A sample of n persons from a larger population of size N is assumed to be selected independently and at random. Let $\bar{\mathbf{A}}_{it} = (A_{i0}, A_{i1}, \dots, A_{it})$ denote exposure history for a person i up to time $t \in \{1, \dots, T\}$. For simplicity, let Y_i denote outcome measured at the end of follow-up at $t+1$. From here on, capitalized letters denote random variables and lowercase letter observations (values) of random variables. Bolded letters denote vectors. Let $Y_i^{\bar{\mathbf{a}}_{it}}$ denote the outcome that would have been observed had the person exposure history $\bar{\mathbf{a}}_{it}$. To conceptualize an observational study as a conditionally randomized experiment, three identifiability conditions are needed to hold: consistency, conditional exchangeability and positivity (Rosenbaum and Rubin 1983). The assumption of consistency requires that $Y_i^{\bar{\mathbf{a}}_{it}} = Y_i^{A_{it}} = Y_i$ when $\bar{\mathbf{A}}_{it} = \bar{\mathbf{a}}_{it}$. That is, the observed outcome is equal to the potential outcome when the exposure history is $\bar{\mathbf{a}}_{it}$. Conditional exchangeability (referred also as no unmeasured confounding) states that $Y_i^{\bar{\mathbf{a}}_{it}} \perp\!\!\!\perp A_{it} | \bar{\mathbf{L}}_{it}, \bar{\mathbf{A}}_{i,t-1}$; for each $\bar{\mathbf{a}}_{it}$, Y_i and A_{it} are statistically independent at time t given the past exposure $\bar{\mathbf{A}}_{i,t-1}$ and measured confounding history $\bar{\mathbf{L}}_{it} = (\mathbf{L}_{i0}, \mathbf{L}_{i1}, \dots, \mathbf{L}_{it})$ measured most recently to time t . Positivity assumption states that $P(A_{it} = a_{it} | \bar{\mathbf{L}}_{it} = \bar{\mathbf{l}}_{it}, \bar{\mathbf{A}}_{i,t-1} = \bar{\mathbf{a}}_{i,t-1}) > 0$ for all $\bar{\mathbf{l}}_{it}$ with $P(\bar{\mathbf{L}}_{it} = \bar{\mathbf{l}}_{it}, \bar{\mathbf{A}}_{i,t-1} = \bar{\mathbf{a}}_{i,t-1}) > 0$. That is, at every stratum of confounders $\bar{\mathbf{l}}_t$ at time point t , there are some exposed and some unexposed persons. Let $Y_i^{\bar{\mathbf{a}}'_{it}}$ denote the outcome that would have been observed had the person, possibly contrary to the fact, exposure pattern $\bar{\mathbf{a}}'_{it}$. Time-dependent exposure $\bar{\mathbf{A}}_{it}$ has a causal effect on outcome Y when $Y_i^{\bar{\mathbf{a}}_{it}} \neq Y_i^{\bar{\mathbf{a}}'_{it}}$ for two exposure patterns $\bar{\mathbf{a}}_{it}$ and $\bar{\mathbf{a}}'_{it}$. Average treatment effect is a difference between expectations at the population level, $E(Y^{\bar{\mathbf{a}}_t}) - E(Y^{\bar{\mathbf{a}}'_t})$. To compare with, association is the difference between conditional expectations, $E(Y | \bar{\mathbf{a}}_t) - E(Y | \bar{\mathbf{a}}'_t)$. However, causal inference is complicated because of nonexistence of counterfactual outcomes in real-world settings.

MSM for average outcome under treatment history $\bar{\mathbf{a}}_t$ is as follows

$$E(Y^{\bar{\mathbf{a}}_t}) = g\{h(\bar{\mathbf{a}}_t), \beta\}$$

where $g\{\cdot\}$ is a suitable function for producing the desired causal effect estimate (risk difference, risk ratio, odds ratio) in the entire source population (Robins *et al.* 2000). However, because of lacking information on potential outcomes, inverse probability of treatment weighting of each person i is needed to estimate a causal effect from an associational model

$$E(Y_{it} | \bar{\mathbf{A}}_t = \bar{\mathbf{a}}_t) = g\{h(\bar{\mathbf{a}}_t), \alpha\}$$

(Robins *et al.* 2000). For this, an assumption of no model misspecification is needed when constructing both inverse probability of treatment weights (IPTWs) and the MSM (Cole and Hernán 2008). In the absence of selection bias, unmeasured confounding and measurement error, true causal parameter β equals inverse probability weighted

parameter α (Robins *et al.* 2000). Functional form of the exposure, $h(\bar{\mathbf{a}}_t)$, in MSM depends on the analysis strategy and design of the study and affects interpretation of the effect of estimate. It may be defined as exposure history (e.g. a value from the most recent measure, an indicator of ever being exposed) or as cumulative exposure, for example (Platt *et al.* 2013). Weighting introduces within-person correlation which must be accounted for using a robust standard error estimator for MSM (Robins *et al.* 2000).

Inverse probability of treatment weights

For a discrete exposure, unstabilized IPTW for a person i in time-point $t \in \{1, \dots, T\}$ is defined as

$$W_{it} = \prod_{k=0}^t 1/P(A_{ik} = a_{ik} | \bar{\mathbf{A}}_{i,k-1} = \bar{\mathbf{a}}_{i,k-1}, \bar{\mathbf{L}}_{ik} = \bar{\mathbf{l}}_{ik}) \quad (2.2)$$

where $A_{i,-1} = 0$ for all (Daniel *et al.* 2013, Hernán and Robins 2016, Robins *et al.* 2000). Thus, the denominator of (2.2) is a person's probability up to time t to receive his/her own observed exposure history conditional on his/her confounder and prior exposure history. IPTW generalizes to include models for dichotomous and non-dichotomous exposures (Cole and Hernán 2008, Hernán and Robins 2016, Robins *et al.* 2000). Unstabilized weights produce a pseudo-population where all the persons have the same probability of being exposed and unexposed, and there is no measured confounding (i.e. no arrows from L to A in Figure 2.2). Typically, weights are stabilized in order to improve precision of the estimator (Cole and Hernán 2008, Hernán *et al.* 2000). For example, marginal probability of the observed exposure may be used to minimally stabilize weights as follows:

$$SW_{it} = \prod_{k=0}^t \frac{P(A_{ik} = a_{ik})}{P(A_{ik} = a_{ik} | \bar{\mathbf{A}}_{i,k-1} = \bar{\mathbf{a}}_{i,k-1}, \bar{\mathbf{L}}_{ik} = \bar{\mathbf{l}}_{ik})}. \quad (2.3)$$

Alternatively, numerator of (2.3) may be defined as $P(A_{it} = a_{it} | \bar{\mathbf{A}}_{i,t-1} = \bar{\mathbf{a}}_{i,t-1})$ or $P(A_{it} = a_{it} | \bar{\mathbf{A}}_{i,t-1} = \bar{\mathbf{a}}_{i,t-1}, \mathbf{B}_i = \mathbf{b}_i)$ at time-point t where \mathbf{B}_i denotes a vector of baseline confounders (Daniel *et al.* 2013, Robins *et al.* 2000, Robins and Hernán 2009). Including baseline confounders \mathbf{B} in the numerator of (2.3) may be desired when they modify the exposure effect (Kaufman 2010). Expected mean of the stabilized weights should be close to 1. Deviations indicate model misspecification or possible violation of positivity assumption (Cole and Hernán 2008). Also extreme weights may be indicative of model misspecification (Cole and Hernán 2008).

With time-dependent exposure, inverse probability of treatment weighting is applied at time-points where the value of exposure changes. When the purpose is to mimic RCT, intention-to-treat analysis strategy is typically used. It assumes that once a person is exposed (initiates medication), he/she remains exposed until the end of follow-up regardless of the true exposure trajectory (Danaei *et al.* 2013). This assumption is suitable when exposure remains stable (Cole and Hernán 2008, Hernán *et al.* 2000, Robins *et al.* 2000), and assumption of conditional exchangeability is not needed after first-time exposure (Cole and Hernán 2008). Another option is as-treated analysis

strategy where exposure levels are modeled as observed (Danaei *et al.* 2013). In this case, assumption of conditional exchangeability is needed also after medication initiation at every time point where exposure levels change. Thus, the study question along with the choice of analysis strategy plays an important role when constructing the IPTWs.

2.4.2.2 Applications of marginal structural models

A literature search of applications of MSMs for time-dependent exposures in studies related to CVD or CVD medications found 11 observational cohort studies and three RCTs with randomized treatments at baseline (Table 2.7). The majority of these applied as-treated analysis strategy.

In studies investigating the effects of medications, consistency is often considered as a reasonable assumption (Hernán and Taubman 2008). Ill-defined intervention (e.g. physiological measures such as LDL cholesterol) leads to difficulty in achieving conditional exchangeability because, for example, genetic factors that affect both LDL cholesterol and outcome are not easily measured (Hernán and Taubman 2008). But for well-defined interventions, as in the majority of the studies found, major confounders do not include complex physiological or genetic processes and are therefore measurable. A critical assessment of consistency assumption provides a good basis to continue constructing a MSM.

All the studies found used inverse probability of treatment weighting in MSMs to achieve conditional exchangeability (Tables 2.7 and 2.8). It is demonstrated that models used to construct IPTWs (here exposure models) should include only risk factors for the outcome and confounders, not variables that are only predictors of exposure, to obtain unbiased and less variable weights (Lefebvre *et al.* 2008). As expected, the studies by Cook *et al.* (2002 & 2012), Ilomäki *et al.* (2011) and Delaney *et al.* (2009) reported inclusion of risk factors for the outcome. Surprisingly, De Keyser *et al.* (2014) reported that they included variables assumed to affect treatment decision in the exposure models. Cook *et al.* (2012) and Danaei *et al.* (2013) constructed separate exposure models by previous exposure, which is recommended for as-treated analysis strategy to capture changes in exposure (Platt *et al.* 2013, Yang *et al.* 2014). Basically, time-dependent confounders were in all studies treated as lagged variables to ensure that they are common causes for exposure and outcome (Cook *et al.* 2002), that is, confounders. However, some studies additionally adjusted for confounders measured simultaneously with the exposure. Cook *et al.* (2002) included non-fatal cardiovascular events measured during the exposure (aspirin) assessment period in their exposure models. These events were assumed to have a strong and immediate effect on both the aspirin use and CVD mortality. If the effect of a time-invariant or time-varying confounder is expected to change over time, exposure models may be fitted separately for each time-point instead of pooling exposure models across time (Platt *et al.* 2009). However, this may lead to increased variation and small loss in efficiency (Platt *et al.* 2009). All studies (Table 2.8)

applied pooled regression models in IPTW construction and did not adjust for time-modified confounding.

Typically, stabilized ITPWs were used; two studies (Hernández *et al.* 2012, Wiesbauer *et al.* 2008) did not report using stabilized weights. Stabilization was achieved either with prevalence of exposure, probability of observed exposure conditional on prior exposure, or with probability of observed exposure conditional on prior exposure and (a subset of) baseline confounders in the numerator of equation (2.3). Every second study using stabilized weights assessed positivity assumption by providing at least a mean of the stabilized IPTWs (Table 2.8). One study (De Keyser *et al.* 2014) explored the effect of extreme weights as a sensitivity analysis with weights truncated at 0.01th and 99.99th percentiles as proposed in the literature (Cole and Hernán 2008). Two additional studies (Cook *et al.* 2012 and Danaei *et al.* 2013) used truncated weights in the primary analyses and reported no estimate from analysis with non-truncated weights. None of the studies examined conditional exchangeability between exposure groups after weighting (in the pseudo-population).

Censoring weights for death (including deaths for other causes than the outcome of interest) (Cook *et al.* 2002, Odden *et al.* 2011), study end (Cook *et al.* 2002, Cook *et al.* 2012, Haukka *et al.* 2012), lost to follow-up (Gerhard *et al.* 2012, Sugihara *et al.* 2009), adverse events (Sugihara *et al.* 2009), artificial censoring (exclusion of persons who discontinued the treatment, Desai *et al.* 2012) and outcome-related censoring (De Keyser *et al.* 2014, Shinozaki *et al.* 2012) were formed. However, in studies where death causes substantial attrition, inverse probability of censoring weighting is regarded inappropriate as causal effect estimate for a population where nobody dies from any other cause than possibly the outcome of interest may not be realistic (Hernán *et al.* 2014). Alternative ways to account for selection bias because of death have been proposed (Egleston *et al.* 2007, Hernán *et al.* 2014) and include, for example, forming a composite outcome where death is incorporated in the primary outcome (Hernán *et al.* 2014).

Most of the studies estimated MSM using a weighted pooled logistic regression model for dichotomous outcomes (Table 2.8). Pooled logistic regression model approximates parameters from Cox's proportional hazards regression model (d'Agostino *et al.* 1990) when hazard of outcome in a time-period is small (<10%) (Westreich *et al.* 2010). However, Ilomäki *et al.* (2011) used pooled binomial regression model with log link function to estimate the relative risk of binge drinking on myocardial infarction. Odden *et al.* (2011), for example, estimated causal risk difference for the effect of antihypertensive medication use on change in kidney function applying pooled linear regression model. Three studies (Desai *et al.* 2012, Haukka *et al.* 2012, Hernández *et al.* 2012) did not provide details of the functional form of exposures in MSMs. All the studies discussed the potential for unmeasured confounding and lack in conditional exchangeability but none of the studies assessed the assumption methodologically (Brumback *et al.* 2004).

In conclusion, in line with the systematic reviews by Yang *et al.* (2014) of 20 pharmacoepidemiological studies using MSMs and published in 2012 and Suarez *et al.* (2011) of 65 papers comparing MSM and conventional models, insufficient reporting of both exposure model and the MSM and lacking details of model constructions was observed in this literature review of applications of MSMs. Assessments of positivity assumption and uncontrolled confounding, details about weight construction, and information on functional form of exposure in MSM are frequently lacking.

Table 2.7 Studies related to cardiovascular disease that apply marginal structural model to account for time-dependent exposure and confounding.

Reference, study design	Max follow-up, years	Exposure definition	Outcome	Analysis strategy	Time-dependent confounder(s)	Time of measurement of time-dependent confounders in weight denominator	Weight numerator specification (stabilization)
Cook <i>et al.</i> 2002, RCT	Mean 5	Aspirin use vs. no use assessed annually	Cardiovascular mortality assessed annually	As-treated	CVD risk factors, non-fatal CVD events	Prior to exposure, nonfatal cardiovascular events also concurrently with exposure	Prior exposure and time
Wiesbauer <i>et al.</i> 2008, cohort	16	Statin use vs. no use assessed in three-month periods	Mortality, assessment periods not reported	Intention-to-treat	CVD risk factors, hemoglobin level, mean arterial pressure	Prior to exposure	Unstabilized weights only
Delaney <i>et al.</i> 2009, cohort	0.75	Beta-blocker use vs. no use in two 90-day periods	Mortality, assessment periods not reported	Intention-to-treat	Blood pressure	Prior to exposure and concurrently with exposure	Marginal probability of observed exposure
Sugihara <i>et al.</i> 2009, cohort	0.25	Combination therapy for OLM+CBB vs. monotherapy for OLM assessed in two-week periods	Change in blood pressure assessed in two-week periods	Intention-to-treat	Blood pressure	Prior to exposure and concurrently with exposure	Marginal probability of OLM+CBB initiation
Ilomäki <i>et al.</i> 2011, cohort	15	Alcohol consumption classified to four levels assessed three times	MI assessed monthly	As-treated	CVD risk factors	Prior to exposure	Prior total alcohol consumption
Odden <i>et al.</i> 2011, cohort	7	Antihypertensive medication use vs. no use assessed annually	Change in kidney function measured in two three- to four-year periods	As-treated	Blood pressure, diabetes, eGFR-creatinine, CVD, heart failure	Prior to exposure	Prior exposure
Cook <i>et al.</i> 2012, RCT	11	Aspirin use vs. no use assessed annually	Major cardiovascular event assessed annually	As-treated	CVD risk factors, cardiovascular conditions, markers of healthy behavior, side effects and other medical factors	Prior to and concurrently with exposure	Prior exposure and a subset of baseline confounders

Table continues

Table 2.7 Continued.

Reference, study design	Max follow-up, years	Exposure definition	Outcome	Analysis strategy	Time-dependent confounders	Time of measurement of time-dependent confounders in weight denominator	Weight numerator specification (stabilization)
Desai <i>et al.</i> 2012, cohort	2	Exposure to some of the four ARBs assessed monthly	Mortality assessed monthly	As-treated	Hospitalization	Concurrently with exposure	Prior exposure and baseline confounders
Gerhard <i>et al.</i> 2012, cohort	5	Aggressive vs. conventional antihypertensive therapy assessed at every six weeks during the first six months and semiannually thereafter	Composite of death, nonfatal MI and nonfatal stroke assessed at every six weeks during the first six months and semiannually thereafter	Intention-to-treat	Blood pressure	Prior to exposure and concurrently with exposure	Not reported but stabilized weights produced
Hauka <i>et al.</i> 2012, cohort	Mean 4.4	Persistence to statins vs. non-persistence assessed in several consecutive periods	Mortality assessed daily	As-treated	Follow-up period	Follow-up time as a sole time-dependent confounder	Baseline confounders
Hernández <i>et al.</i> 2012, cohort	11	ACEI/ARB use vs. no use assessed annually	Mortality assessed monthly	As-treated	Cardioprotective medication use	Not reported	Unstabilized weights only
Shinozaki <i>et al.</i> 2012, RCT	6	Ever treated with atorvastatin vs. never treated assessed annually	Cardiovascular event, assessment periods not reported	Intention-to-treat	Blood pressure, cholesterol and glucose, BMI	Prior to exposure	Prior exposure and baseline confounders
Danaei <i>et al.</i> 2013, cohort	7	Statin initiation vs. non-initiation assessed monthly	CHD assessed monthly	As-treated	CVD risk factors, doctor visits	Prior to exposure	Baseline confounders
De Keyser <i>et al.</i> 2014, cohort	17.7	Ever use of statins vs. never use assessed monthly	Hard CVD event assessed monthly	Intention-to-treat	CVD risk factors	Prior to exposure	Baseline confounders

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CHD, coronary heart disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; OLM, olmesartan medoxomil; RCT, randomized controlled trial.

Table 2.8 Specification of marginal structural model and assessment of assumptions in studies related to cardiovascular disease that apply marginal structural modeling.

Reference	Type of MSM	Functional form of exposure in outcome model	Covariates in outcome model	Estimated causal effect	Positivity assessed	Censoring weights used
<i>Cook et al.</i> 2002	Weighted pooled logistic regression model	Most recent exposure	None	Rate ratio	No	Yes
<i>Wiesbauer et al.</i> 2008	Not reported	Indicator of treatment initiation	Not reported	Hazard ratio	No	No
<i>Delaney et al.</i> 2009	Weighted pooled logistic regression model	Exposure in later 90-day period	None	Rate ratio	No	No
<i>Sugihara et al.</i> 2009	Weighted pooled linear regression model	Indicator of treatment initiation	None	Not reported	No	Yes
<i>Ilomäki et al.</i> 2011	Weighted pooled log-binomial regression model	Most recent exposure	Baseline confounders and time	Relative risk	Yes	No
<i>Odden et al.</i> 2011	Weighted pooled linear regression model	Cumulative use	None	Not reported	Yes	Yes
<i>Cook et al.</i> 2012	Weighted pooled logistic regression model	Most recent exposure	None	Hazard ratio	Yes	Yes
<i>Desai et al.</i> 2012	Weighted pooled logistic regression model	Not reported	Baseline confounders	Odds ratio	Yes	Yes
<i>Gerhard et al.</i> 2012	Weighted pooled logistic regression model	Indicator of treatment initiation	Baseline confounders	Hazard ratio	No	Yes
<i>Haukka et al.</i> 2012	Not reported	Not reported	Not reported	Hazard ratio	No	Yes
<i>Hernández et al.</i> 2012	Weighted Cox's PH regression model	Not reported	Not reported	Hazard ratio	No	No
<i>Shinozaki et al.</i> 2012	Weighted pooled logistic regression model	Indicator of treatment initiation	Baseline confounders	Hazard ratio	No	Yes
<i>Danaei et al.</i> 2013	Weighted pooled logistic regression model	Cumulative use	Baseline confounders	Hazard ratio	No	No
<i>De Keyser et al.</i> 2014	Weighted pooled logistic regression model	Indicator of treatment initiation	Baseline confounders and history of non-skin cancer updated during follow-up	Hazard ratio	Yes	Yes

Abbreviations: MSM, marginal structural model; PH, proportional hazards.

2.5 Rationale of the study

Statin initiation is observed to shift increasingly towards apparently healthy persons in primary prevention of cardiovascular disease (Rikala *et al.* 2013, Wallach Kildemoes *et al.* 2012b). Apparently healthy persons have been identified as those who do not have markers of CVDs, diabetes or medications for these conditions in hospital discharge or prescription registers. However, classification is typically based on time prior to statin initiation and data on smoking and cholesterol levels are unavailable, which complicates risk level assessment at the time of statin initiation and may introduce overestimation of the proportion of apparently healthy persons. No study has characterized apparently healthy population after statin initiation and the evolution of their cardiovascular risk over time.

There are a number of studies examining the effect of adherence to statin therapy on the incidence of CVD in primary prevention of CVD. However, adherence is measured as a fixed value over a prolonged time period resulting in vague estimates of medication adherence. Even when the time-varying nature of adherence has been accounted for, intervening effects of time-varying confounders on the causal pathway have not been properly accounted for and bias may have been introduced in the results. There are no studies accounting simultaneously for both time-varying adherence and time-varying confounding affected by prior adherence, which can be accomplished using MSMs. A review of applications of MSMs related to CVDs discloses a variety of perspectives for model building and reveals lacking reporting of the methods applied that generally prevents evaluation of the success of estimation.

Increasing use of preventive medications, such as statins, and the appearance of chronic diseases with age are increasing the occurrence of polypharmacy among older persons (Hiitola *et al.* 2007, Jyrkkä *et al.* 2006, Upmeier *et al.* 2013). Several studies have investigated the aging-related change in the number of medications in use among older persons. However, the majority of the studies have included only survivors of two time points in their analyses – that is, frail persons who tend to use multiple medications and are at increased risk of death during the follow-up are most likely discarded. As observed in earlier publications, the number of medications in use is associated with mortality indicating MAR or MNAR mechanism for missing data. There are no studies examining the evolution of polypharmacy among older persons with statistical methods that allow for MNAR type of mechanism for the missing data.

3 AIMS OF THE STUDY

The purpose of this study was to gain an understanding of the effects of population heterogeneity, missing data, and causal relationships on parameter estimates from statistical models by comparing and contrasting statistical methods when analyzing change in medication use. The secondary aim was to provide new aspects for estimating change in medication use in order to guide longitudinal studies in analytical choices. The specific aims were:

1. To get insight into the accumulation of cardiovascular and diabetes medications in a population of apparently healthy statin initiators in a *post-hoc* manner applying GMMs.
2. To estimate the causal effect of statin adherence on the risk of acute CVD event in primary prevention of CVD in the presence of time-dependent confounders affected by previous adherence using inverse probability of treatment weighted estimation of MSMs, to examine sensitivity of the effect estimates against different model specifications, and to compare MSM estimation results with those of a conventional discrete-time hazards model.
3. To gain insight into the impact of missing data mechanism on the estimates of change in the mean number of medications in use among older persons.

4 MATERIALS AND METHODS

4.1. Data sources

This study was conducted using data from Finnish health care registers launched for administrative purposes (Studies 1 and 2) and from the population-based Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study (Study 3).

4.1.1 Health care registers

Finnish Prescription Register (FPR) and Special Reimbursement Register (SRR) maintained by the SII of Finland, Finnish Care Register (FCR) maintained by the National Institute for Health and Welfare, and registers maintained by Statistics Finland (Table 4.1) were used. Registers maintained by Statistics Finland include, for example, the Register of Completed Education and Degrees. Statistics Finland compiles information from the Population Information System of the Population Register Center and the Finnish Tax Administration covering all inhabitants of Finland, in addition to other administrative registers and statistics from public officers. Death dates and dates of decisions for long-term institutional care were retrieved from separate registers maintained by the SII. All the registers contain information on all Finnish residents and can be linked using the person identity numbers unique to every resident.

During the study, medications were reimbursed by the SII of Finland according to three reimbursement categories with some limitations depending on the time period. From 2002 until 2006, medications were reimbursed if a purchase exceeded 10 euros deductible in the basic reimbursement category and five euros in the lower and higher special reimbursement categories (National Agency for Medicines and Social Insurance Institution 2003, National Agency for Medicines and Social Insurance Institution 2008). Additionally, a person needed to pay 50% of costs exceeding the 10-euro deductible in the basic reimbursement category and 25% of costs exceeding the five-euro deductible in the lower special reimbursement category. Since 2006, 42% of the medication cost in the basic reimbursement category, 72% of the cost in the lower and 100% of the cost in the upper special reimbursement categories were reimbursed (National Agency for Medicines and Social Insurance Institution 2007). Receiving special reimbursement requires having a certain chronic disease, such as CHD, hypertension or diabetes, and entitlements to special reimbursements are registered in the SRR. The FPR does not contain over-the-counter purchases or purchases made by persons staying in hospitals or public nursing homes. Medications may be purchased for a three-month supply at maximum. For statins, prescription is needed, and all statins have been reimbursable under the basic reimbursement category except for persons who are entitled to lower special reimbursement for dyslipidemia associated with CHD or familial hypercholesterolemia. However, reimbursement of atorvastatin and rosuvastatin was restricted since October 2006 to treatment of severe disorders of lipid metabolism for high-risk persons in cases where other statins were not tolerated or were ineffective (Martikainen *et al.* 2010). In 2004, the FPR covered 97% of all reimbursed purchases

(National Agency for Medicines and Social Insurance Institution 2005) and in 2007, 99% (National Agency for Medicines and Social Insurance Institution 2008).

The nationwide FCR covers all Finnish hospitals. The register includes information on patients discharged from inpatient care, specialized outpatient care, and day surgical procedures. The FCR has been shown to be a valid data source for epidemiologic studies of CVDs (Pajunen *et al.* 2005, Sund 2012, Tolonen *et al.* 2007) covering, for example, 95% of first strokes in 1993–98 (Tolonen *et al.* 2007).

4.1.2 Geriatric Multidisciplinary Strategy for the Good Care of the Elderly study

The GeMS study was designed to evaluate a model for a geriatric assessment, care and rehabilitation. A random sample of 1,000 persons was selected from persons aged 75 years and older (born before 1 November 1928) and living in the city of Kuopio, Finland, using the census data of the city of Kuopio on 1 November 2003. The selected participants were randomly assigned to intervention (n=500) and control (n=500) groups. Of the invited participants, 162 refused to participate, 55 died before baseline examination and two relocated. The remaining 781 persons participated in the baseline examination in 2004. Three annual follow-up examinations were performed at one-year intervals in 2005, 2006, and 2007.

Trained study nurses conducted annual structured interviews with each participant. A structured questionnaire was used to collect information on sociodemographic factors, health status and medication use. If a person was unable to answer the question, the required information was requested from a close relative or caregiver. During the interviews, participants were asked to specify all the medications they had been using during a two-week period using an open-ended question. Medication containers and prescriptions were requested to be brought to the interviews to reduce recall error. Information was collected on prescription and over-the-counter medication use. In addition, medication use was confirmed from participants' medical records from primary and specialized health care. The total number of medications included medications taken regularly and when required.

Table 4.1 Characteristics of the health care registers utilized.

	Finnish Prescription Register	Special Re-imbursment Register	Finnish Care Register	Other registers
Maintained by	SII	SII	NIHW	SF
Established	1994	1964	1969	-
Source population	Finnish home-dwelling residents	Finnish residents	Finnish residents	Finnish residents
Information used	Reimbursed medications: -dispensing date -ATC code -strength -number of tablets dispensed	Entitlements to higher medication reimbursement due to specific chronic diseases with start and end dates.	-primary and secondary discharge diagnoses -medical procedures -admission and discharge dates	-place of residence -marital status -income -educational level -labor market status
Additional	Purchases of non-reimbursable medications are not registered. Persons staying at public nursing homes or hospitalized without interruption for over 90 days are not eligible for reimbursement and are registered in a separate register.	Change in reimbursement regulations in 2006.	The 10th revision of the International Classification of Diseases used since Jan 1 1996.	Information compiled from the Population Register Center and the Finnish Tax Administration, among others.

Abbreviations: ATC, Anatomical Therapeutic Chemical; NIHW, National Institute for Health and Welfare; SII, Social Insurance Institution; SF, Statistics Finland.

4.2 Study populations

Table 4.2 summarizes the study populations used in individual studies. For Study 1, a cohort of statin initiators residing in Finland was extracted from the FPR. Persons who were long-term institutionalized within three years prior to the statin initiation were excluded in order to avoid misclassification of medication use as residents of institutions are not eligible for medication reimbursement. The initiation was defined as not having purchased any statin since 1 January 1994. To identify apparently healthy statin initiators at the time of initiation, persons with established CVD, diabetes or hypertension within the preceding seven years or medication for these conditions during the preceding three years of statin initiation were excluded (Table 4.3). Seven-year lookback period for hospitalizations was chosen because it was applied in previous Finnish register-based studies (Helin-Salmivaara *et al.* 2006, Pajunen *et al.* 2005, Ruokoniemi *et al.* 2011) to identify persons with no prior CHD or cerebrovascular events. Three-year lookback period for prescriptions was applied instead of the conventional one-year period (Larsen *et al.* 2000, Raymond *et al.* 2007) because purchases of some antihypertensive medications may not have been registered if the cost of a purchase was under the deductible in the basic reimbursement category. Thus, application of a longer lookback period increased the likelihood of identifying users of these medications since a purchase would be registered when it was purchased simultaneously with other medications and the total cost of the purchase exceeded the deductible.

Study 2 consisted of a cohort of women who initiated statins in 2001–04 and who had not been dispensed statins since 1 January 1994 as identified from the FPR (Table 4.2). Initially, persons who were long-term institutionalized within three years prior to or at statin initiation were excluded because these persons are not eligible for medication reimbursement. In addition, those whose first purchase was cerivastatin were excluded because of withdrawal of cerivastatin from the markets at 2001. Persons who had evidence of atherosclerotic CVD prior to or at statin initiation in the registers were excluded in order to identify persons in primary prevention of CVD (Table 4.3). Additionally, persons who died, were institutionalized or experienced an outcome event within the first year after statin initiation were excluded. In comparison with Study 1, primary prevention population was based on persons who were free of established CVD at the date of statin initiation.

Study 3 included the GeMS cohort consisting of all the persons who attended the baseline examination in 2004 (Table 4.2).

Table 4.2 Characteristics of Studies.

	Study 1	Study 2	Study 3
Design	Descriptive follow-up study	Retrospective cohort study	Descriptive follow-up study
Study population	Persons aged 45–75 years	Women aged 45–64 years	Persons aged ≥ 75 years
Source population	Finnish residents	Finnish residents	Inhabitants of Kuopio, Finland
Start of follow-up	Apr 1–Dec 31 2006	Jan 1 2002–Dec 31 2005	Nov 1 2003–Jan 26 2005
Length of follow-up	2 years	3 years	3 years
Data sources	FPR FCR	FPR SRR FCR Registers maintained by Statistics Finland	GeMS Study
Exposure	Not applicable	Adherence to statin therapy	Not applicable
Outcome of interest	Accumulated number of cardiovascular and diabetes medications	Acute cardiovascular event	Number of medications in use

Abbreviations: FCR, Finnish Care Register; FPR, Finnish Prescription Register; GeMS, Geriatric Multidisciplinary Strategy for the Good Care of the Elderly; SRR, Special Reimbursement Register.

Table 4.3 Exclusion criteria for Studies 1 and 2.

Criteria	Study 1 (Apparently healthy population)	Study 2 (Population in primary prevention of CVD)
Hospitalizations	Diabetes, hypertension, CHD, cerebrovascular diseases or TIA, atherosclerosis, cardiac insufficiency, or any medical procedure related to CHD (CABG, PTCA) or PAD within 7 years prior to or atrial fibrillation within 1 year prior to statin initiation	CHD, cerebrovascular diseases or TIA, atherosclerosis, aneurysm, or any medical procedure related to CHD (CABG, PTCA), cerebrovascular diseases (carotid endarterectomy or thrombolytic therapy), or PAD within 3 years prior to or at statin initiation
Higher special reimbursements	Not restricted	Chronic CHD at statin initiation
Medication purchases	Cardiovascular‡ or diabetes medications within 3 years prior to statin initiation	Nitrates or other lipid modifying medications within 3 years prior to or at statin initiation

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CVD, cardiovascular disease; PAD, peripheral artery disease; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.

‡ CVD medications identified as purchases from ATC categories B01, C01A, C01B, C01DA, C02, C03, C04, C07, C08, C09A, C09B, C09C and C09D.

4.3 Measures

4.3.1 Adherence to statin therapy

In Study 2, adherence was measured at one-year intervals since statin initiation with the PDC method (Andrade *et al.* 2006). The number of days covered by statin therapy was calculated using a validated dosage assumption of one tablet per day (Romppainen *et al.* 2014) and divided by 365. Persons were assumed to finish the current prescription before starting the refill prescription and thus, in the calculation of PDC, the new prescription started from the day after the end of the prior prescription. Days in hospital were subtracted from the denominators because medication during a hospital stay is offered by the service provider. Switching between statins was considered as a continuation of therapy. Adherence was calculated from the prescription data based on the programming code provided in the paper by Leslie *et al.* (2008). PDC was categorized as adherence or non-adherence using a conventional cut-off value of $\geq 80\%$ for adherence (Andrade *et al.* 2006, Karve *et al.* 2009) that has been widely used (Chowdhury *et al.* 2013).

4.3.2 Outcomes

In the study of accumulation of cardiovascular and diabetes medications, the outcome of interest was the accumulated number of cardiovascular and diabetes medications quantified as a total number of different ATC codes from ATC categories B01, C01–C09 and A10 at the day of statin initiation and semiannually thereafter. Follow-up started on the day of statin initiation and ended in death, long-term institutionalization, or 24 months after statin initiation, whichever came first.

In Study 2, the primary outcome was acute cardiovascular event that was defined as a composite of acute coronary syndrome (10th revision of International Classification of Diseases (ICD-10) codes: I20.0, I21–I22 as a primary diagnosis in the FCR) and acute ischemic stroke (I63 as a primary diagnosis). Follow-up started one year after statin initiation to exclude early outcomes that occurred before statin therapy could have been assumed to have an effect (Colhoun *et al.* 2004, Downs *et al.* 1998, Mizuno *et al.* 2008, Sever *et al.* 2003) and to allow for stable adherence ascertainment (Andrade *et al.* 2006). Follow-up ended in the occurrence of outcome, death, long-term institutionalization, or when the maximum of three years of follow-up was reached, whichever came first. In a sensitivity analysis towards selection bias due to death and medical procedures that can be viewed as competing risks during the follow-up, a composite outcome of acute cardiovascular events, medical procedures related to CHD (coronary artery bypass graft and percutaneous transluminal coronary angioplasty; medical procedure codes FNA, FNB, FNC, FND, FNE, FN1AT, FN1BT, FN1YT, TFN40, TFN50) and all-cause deaths was formed. In addition, negative control outcome that was expected to be unassociated with the exposure but associated with health behavior was used to examine healthy-adherer effect (Dusetzina *et al.* 2015). For statins, low-energy fractures could reflect unhealthy behavior but are unrelated to statin effect (Peña *et al.* 2015). They were identified as the first hospital visit for a low-energy fracture of hip (ICD-10 codes S32.1–S32.4, S72.0–S72.8 as a primary or secondary diagnosis), wrist (S52.0, S62.4), ankle (S82.1–S82.7, S92.0, S92.3), or forearm (S42.2–S42.4).

In Study 3, the outcome was the number of medications in use measured as the total number of different ATC codes of the medications ascertained in the examination. The number of medications in use was assessed at baseline, and three times at one-year intervals thereafter.

4.3.3 Confounders

No confounders were considered in Studies 1 and 3. In Study 2, sociodemographic and socioeconomic factors, cardiac comorbidity and non-cardiac comorbidity factors were considered as potential confounders when studying the effect of adherence to statin therapy on the risk of acute cardiovascular events (see Table 4.4 for baseline confounders and Table 4.5 for time-dependent confounders). In addition, factors describing statin therapy were considered as confounders. Confounders describing comorbidities and medication use were based on information combined from the FPR, the SRR and the FCR. Information on sociodemographic and socioeconomic factors was retrieved from

various registers maintained by Statistics Finland. Confounders were measured at baseline and at one-year intervals after statin initiation. Charlson Comorbidity Index measured at baseline and annually thereafter was quantified as in Quan *et al.* 2005. The variable for intensity of statin therapy was modified from Stone *et al.* 2014.

Table 4.4 Potential baseline confounders for the effect of statin adherence on the risk of acute cardiovascular events.

Sociodemographic and socioeconomic factors	Factors related to statin therapy	Cardiac comorbidity factors	Non-cardiac comorbidity factors
Age	Intensity of statin therapy	Cardiac arrhythmia	Alcohol-related diseases
Educational level		Diabetes	Cancer
Income	Type of initiating statin	Dysfunctions of lipid metabolism	Charlson Comorbidity Index
Labor market status		Heart failure or chronic cardiac insufficiency	Depression
Marital status	Year of initiation	Hypertensive diseases	Hormone therapy
University hospital catchment area		Insulin use	Mental disorder
		Number of concurrent CVD medications	Number of in-hospital days
			Respiratory diseases
			Rheumatoid arthritis
			Number of concurrent medications
			Use of anxiolytics, hypnotics or sedatives
			Use of corticosteroids for systemic use
			Use of nonsteroidal anti-inflammatory medications

Abbreviations: CVD, cardiovascular disease.

Table 4.5 Potential time-dependent confounders for the effect of statin adherence on the risk of acute cardiovascular events.

Sociodemographic and socioeconomic factors	Factors related to statin therapy	Cardiac comorbidity factors	Non-cardiac comorbidity factors
Income	Increase in intensity of statin therapy	Atherosclerosis	Alcohol-related diseases
Labor market status		Cardiac arrhythmia	Cancer
Marital status		Chronic cerebrovascular diseases or TIA	Charlson Comorbidity Index
		Chronic CHD	Depression
		Chronic CHD hospitalizations	Hormone therapy
		Diabetes	Mental disorder
		Dysfunctions of lipid metabolism	Number of in-hospital days
		Heart failure or chronic cardiac insufficiency	Respiratory diseases
		Hypertensive diseases	Rheumatoid arthritis
		Insulin use	Number of concurrent medications
Medical procedures related to CHD (CABG or PTCA)	Use of anxiolytics, hypnotics or sedatives		
Number of concurrent CVD medications	Use of corticosteroids for systemic use		
Use of nitrates	Use of nonsteroidal anti-inflammatory medications		

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CVD, cardiovascular disease; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.

4.4 Statistical analyses

4.4.1 Accumulation of cardiovascular and diabetes medications

Growth mixture modeling was used in Study 1 to analyze accumulation of cardiovascular and diabetes medications among statin initiators who initiated these medications during the follow-up. Based on numerical exploration of the data, the accumulated number of medications was assumed to follow Poisson distribution as semiannual means and variances of the accumulated number of medications were

approximately equal (see Table 5.1 later). Linear and quadratic GMMs with one to five latent classes were fitted. Quadratic GMM with random intercept for the present study was of the form

$$\ln(\lambda_{it|c_j=k}) = \eta_{0ki} + \eta_{1k}(t-1) + \eta_{2k}(t-1)^2 + \varepsilon_{it},$$

$$t = 1, 2, 3, 4, 5, k = 1, 2, 3, 4, 5$$

$$\eta_{0ki} = \alpha_{0k} + \zeta_{0ki},$$

where $\lambda_{it|c_j=k}$ is a Poisson rate parameter for a count outcome variable for each person i at time point t belonging to a latent class k . Coefficient η_{0ki} is a latent class specific random intercept with a normal distribution. It captures the heterogeneity in intercepts within latent classes. Coefficient η_{1k} is a class-specific linear slope parameter for a time-related variable t and η_{2k} is a class-specific quadratic slope. In the present model specification, variances for latent slope parameters η_{1k} and η_{2k} were fixed to zero to aid in model convergence. Thus, the adopted GMM considered every person within a latent class to show the same development but starting from different values. Residuals ζ and ε are assumed to be independent and identically distributed and to follow normal distribution with zero means.

During the follow-up, of the population of initiators of cardiovascular or diabetes medications, 31 died and 16 were long-term institutionalized and they were followed until death or institutionalization. The Mplus Version 7 program (Muthén and Muthén 1998–2012) with FIML estimation method that assumes MAR mechanism for missing data due to death or long-term institutionalization and provides robust standard errors using a numerical integration algorithm was used to conduct the analyses.

4.4.2 Estimating a causal effect using marginal structural model

In Study 2, MSMs were used to account for time-dependent confounding affected by previous adherence when evaluating the effect of adherence to statins on the risk of acute cardiovascular events. Here, adherence and time-dependent confounders were assessed at one-year intervals since statin initiation whereas acute cardiovascular events were assessed at monthly intervals starting after the first adherence assessment year (Figure 4.1). Hence, data were structured so that each observation represented one person-month.

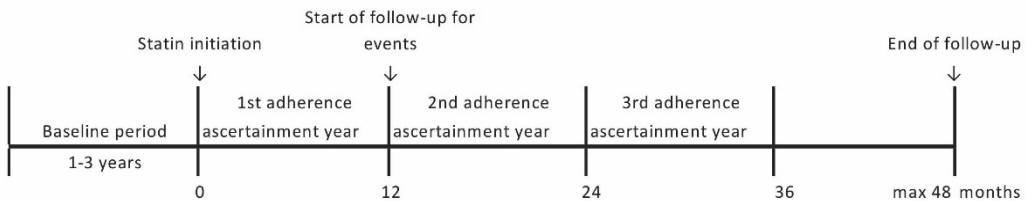


Figure 4.1 Study time line.

In the present study, logistic regression models were used as exposure models in estimation of IPTWs. Potential confounders were measured from the 12-month period preceding the adherence ascertainment period in question. Exposure models included all

the confounders listed in the Tables 4.4 and 4.5. Year-specific stabilized IPTWs were constructed as follows:

$$SW_{it} = \prod_{k=12}^t \frac{P(A_{ik} = a_{ik} | \bar{A}_{i,k-12} = \bar{a}_{i,k-12})}{P(A_{ik} = a_{ik} | \bar{A}_{i,k-12} = \bar{a}_{i,k-12}, \bar{L}_{i,k-12} = \bar{l}_{i,k-12}, \mathbf{B}_i)}, t = 12, 24, 36.$$

In the equation, A_{ik} refers to observed adherence level for person i measured at 12, 24 or 36 months after statin initiation from the previous 12-month period, $\bar{A}_{i,k-12}$ to observed adherence history prior to A_{ik} , \mathbf{B} to baseline confounders, and $\bar{L}_{i,k-12}$ to lagged time-dependent confounders measured prior to A_{ik} at months 12 or 24. At $t = 12$, $\bar{L}_{i0} = \bar{\mathbf{0}}$ was assumed for every person i . As-treated analysis strategy was used and separate models for each time point fitted. The ability of the estimated IPTWs to balance adherence groups was checked comparing distributions of potential confounders between the groups by standardized difference (Austin 2008, Austin 2009). Values $>10\%$ were considered indicative of a meaningful difference between the groups.

In the second phase, MSM was estimated applying inverse probability of treatment weighting for discrete-time hazards model which was estimated using a pooled log-binomial regression model for person-month data as follows:

$$\log[P(y_{im} = 1 | y_{i,m-1} = 0, \bar{C}_{im} = 0, A_{i,m-1})] = \beta_0 + \beta_1 A_{i,m-1}$$

where $m=13, \dots, 48$ and β_0 is intercept. In the equation, $P(\cdot)$ refers to the probability of person i having the outcome of interest at month m , conditional on not being censored at or prior to month m (C_{im} is an indicator of being censored at month m), not having the outcome prior to m and prior adherence. $A_{i,m-1}$ refers to the adherence level measured in the preceding adherence assessment period prior to the month m for person i . For weighted data, exponential function of coefficient β_1 can be interpreted as an average causal effect of adherence on incidence of acute cardiovascular events when everybody maintains adherence during the previous adherence ascertainment year compared with maintaining non-adherence. Robust standard errors for coefficients were obtained. To obtain a MSM, stabilized IPTWs were used to weight the discrete-time hazards model. Estimated hazard ratios (HRs) from MSMs were compared with a HR obtained by fitting a discrete-time hazards model without adjusting for time-dependent confounding (i.e., without weighting) but adjusting for baseline confounders.

Analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Last observation carried forward technique was used to impute missing values in confounders (12 persons had missing data on marital status and labor market status).

4.4.3 Impact of missing data on growth estimates

The impact of missing data on the estimates of change in mean number of medications in use (Study 3) was investigated comparing estimation results from a conventional LGCM assuming MAR with a Diggle-Kenward selection model under MNAR mechanism for missing data (Diggle and Kenward 1994). Additionally, crude sample means were calculated using listwise and pairwise deletion procedures to provide inferences under MCAR assumption.

LGCM was used as a conventional model under MAR assumption and as a measurement model for full data in the Diggle-Kenward selection model assuming MNAR. It was adopted as follows:

$$y_{it} = \eta_{0i} + \lambda_t \eta_{1i} + \varepsilon_{it}, t = 1, 2, 3, 4$$

$$\eta_{0i} = \alpha_0 + \zeta_{0i}$$

$$\eta_{1i} = \alpha_1 + \zeta_{1i}.$$

Restrictions $\lambda_1 = 0$ and $\lambda_4 = 1$ were applied to obtain an identifiable model. Parameters α_0 and α_1 represent the means of the latent intercept and slope components, respectively.

Goodness of fit of the estimated LGCMs was evaluated using five indicators. First, χ^2 test was applied with a non-significant p-value ($p \geq 0.05$) indicating that the model provides a good fit with the data. Second, comparative fit index (CFI) was used to evaluate the adequacy of the specified model in relation to the baseline model (Browne and Cudeck 1993, Marsh *et al.* 1996). CFI varies between 0 and 1, with values greater than 0.95 reflecting an excellent fit of the model to the data. Third, a normed-fit Tucker-Lewis index (TLI) with similar interpretation as CFI was used (Browne and Cudeck 1993, Marsh *et al.* 1996). Fourth, approximation error in the model was evaluated using root mean square error of approximation (RMSEA) with values below 0.05 indicating an excellent fit (Browne and Cudeck 1993, Marsh *et al.* 1996). Finally, standardized root mean residual (SRMR) that measures the average of the residual correlations was used, with values less than 0.03 indicating excellent fit of the model (Browne and Cudeck 1993, Marsh *et al.* 1996).

In the second step, binary logistic regression models were jointly modeled with LGCM to produce Diggle-Kenward selection model. Logistic regression models were specified as follows:

$$\text{logit}[P(r_{it} = 1 | \bar{r}_{i,t-1} = 0)] = \beta_0 + \beta_1 y_{i,t-1} + \beta_2 y_{it}, t = 2, 3, 4.$$

Here, missing data indicator vector r_i was scored as presented in the section 2.4.1.2 and deaths and dropout were combined. Regression coefficient $\beta_2 \neq 0$ indicates MNAR mechanism for missing data and MAR mechanism otherwise (Diggle and Kenward 1994). Similarly, $\beta_2 = \beta_1 = 0$ is indicative of MCAR. Estimates from the LGCM part of the joint model have an interpretation similar to those of the traditional LGCM but under MNAR assumption.

The Mplus Version 6.12 program (Muthén & Muthén, 1998-2010) was used to conduct the analyses. Robust ML estimation was used to calculate non-normality robust standard errors as the number of medications in use outcome was not normally distributed.

4.5 Relation between the studies

Figure 4.2 illustrates relation between Studies. Modeling change in medication use is a key factor that combines the individual studies.

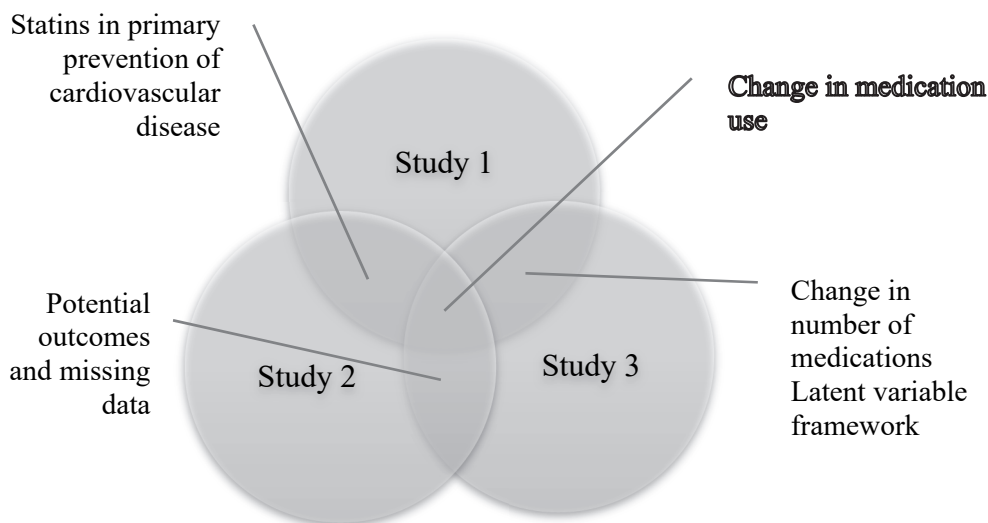


Figure 4.2 Relation between Studies 1, 2 and 3.

4.6 Approvals and ethical considerations

The protocols for Studies 1 and 2 were approved by the institutions keeping the registers. The SII performed the register data linkages for Study 1 and Statistics Finland for Study 2 using identification numbers unique to every Finnish resident. There was no legal requirement for an ethics committee approval because only de-identified register data were used and the persons in the registers were not contacted. No written consent from the persons was required nor sought.

The study protocol for the GeMS study (Study 3) was approved by the Research Ethics Committee of the Hospital District of Northern Savo. Written informed consent was obtained by the study participants or their caregivers or family members.

5 RESULTS

5.1 Accumulation of cardiovascular and diabetes medications

A total of 11,948 persons initiating statin therapy during the last three quarters of 2006 without evidence of prior CVD, diabetes, or medications indicated for these conditions were extracted from the registers. During the subsequent 24 months, every third (4,097 or 34%) purchased cardiovascular or diabetes medications (ATC categories B01, C01–C09 and A10) in addition to statins. Typically, other cardiovascular or diabetes medications were initiated on the day of the statin initiation (1,719 or 42%, Table 5.1) or within the first six months of the follow-up (2,699 or 66%). The semiannually measured mean of the accumulated number of cardiovascular and diabetes medications (mean of the total number of different ATC codes) among the initiators of additional medications increased steadily during the follow-up with increasing variance (Table 5.1).

Table 5.1 Distributions of the semiannual accumulated number of cardiovascular and diabetes medications in use at statin initiation and thereafter for the population with purchases of cardiovascular and diabetes medications during the 24-month follow-up (n=4,097).

	At statin initiation	6 months since statin initiation	12 months since statin initiation	18 months since statin initiation	24 months since statin initiation
Mean	0.54	1.05	1.36	1.65	1.94
Median	0.00	1.00	1.00	1.00	1.00
SD	0.77	1.11	1.23	1.28	1.32
Var	0.59	1.23	1.51	1.64	1.74
Min	0	0	0	0	1
Max	7	8	9	9	9
% with cardiovascular or diabetes medication	42	66	78	90	100

Abbreviations: SD, standard deviation.

Of the alternative linear and quadratic GMMs with one to five latent classes for the group of initiators of additional cardiovascular and diabetes medications, four-class quadratic GMM was selected to be the best fitting model based on the lowest BIC value, estimability and interpretation of the model (Table 5.2). The model was replicated twice using the two best log-likelihood values. The LMR-LRT proposed that a five-class quadratic GMM would describe the data even better than the chosen model but because of the small proportion of patients (0.1%) in the fifth class, the model was rejected.

Table 5.2 Estimation results of linear and quadratic growth mixture models with 1 to 5 latent classes.

Model	Log-likelihood	N of parameters	BIC	Entropy	LMR-LRT	
					Value	P-value
Linear						
1-class	-26,136.3	3	52,298	NA	NA	NA
2-class	-25,916.7	6	51,883	0.718	422.27	<0.001
3-class	-25,766.4	9	51,608	0.723	289.03	<0.001
4-class	-25,720.7	12	51,541	0.715	87.91	<0.001
5-class	-25,720.7	15	51,566	0.755	89.28	<0.001
Quadratic						
1-class	-25,995.1	4	52,023	NA	NA	NA
2-class	-25,664.1	8	51,395	0.754	642.70	<0.001
3-class	-25,511.7	12	51,123	0.749	296.05	<0.001
4-class	-25,467.2	16	51,068	0.737	82.30	<0.001
5-class	-25,462.5	20	51,091	0.762	9.17	0.001

Abbreviations: BIC, Bayesian information criteria; LMR-LRT, Lo-Mendell-Rubin likelihood ratio Test; NA, not available.

The chosen GMM indicated that four distinct subpopulations or classes of persons with common patterns of growth in the accumulated number of medications over the follow-up time could be identified from the group of initiators of additional medications. Means of the random intercepts were statistically significant in all of the classes, as were the linear and quadratic slopes (Table 5.3). Variance of the random intercept component was statistically significant for all the classes, indicating significant between-person differences within classes in this component. Due to fixing of variances of slope components to zero, between-person differences in slopes of changes within classes were not expected.

Table 5.3 Estimation results and semiannual expected means for quadratic growth mixture model with four latent classes.

		Class 1	Class 2	Class 3	Class 4
		Low and slow accumulation	Low accumulation	Moderate accumulation	High accumulation
Class count	n	882	2,431	655	129
Proportion	%	22	59	16	3
Posterior probability	%	20	59	17	4
η_{0k}	Est (SE)	-9.52 (0.68)	-0.65 (0.03)	0.15 (0.04)	0.82 (0.07)
η_{1k}	Est (SE)	4.70 (0.36)	0.57 (0.02)	0.58 (0.02)	0.60 (0.04)
η_{2k}	Est (SE)	-0.56 (0.05)	-0.08 (0.00)	-0.08 (0.00)	-0.10 (0.01)
$Var(\eta_{0k})$	Est (SE)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Factor loadings:					
λ_1	Est	0.00	0.50	1.16	2.26
λ_2	Est	0.01	0.83	1.91	3.74
λ_3	Est	0.09	1.23	2.66	5.10
λ_4	Est	0.62	1.41	3.15	5.75
λ_5	Est	1.34	1.53	3.17	5.34

Abbreviations: Est, estimate; SE, standard error; Var, variance.

Class 1 was viewed to represent low and slow accumulation of cardiovascular and diabetes medications, i.e. no additional medications were redeemed at statin initiation but they started to accumulate after 1.5 years of follow-up. The majority of the persons had the highest probability to belong to class 2 of low accumulation in which persons typically redeemed one additional medication during the first 0.5 year since statin initiation and the count remained low during the follow-up, being an average 1.5 medications at the end of follow-up. Class 3 was considered to represent moderate accumulation group that redeemed one additional medication at statin initiation and a total of three medications by the end of follow-up. Class 4 represented high accumulation group that redeemed two additional medications simultaneously with statin initiation and 3.5 additional medications during the follow-up, having up to 5.3 medications by the end of follow-up.

5.2 Estimating a causal effect using marginal structural model

A cohort of 42,807 women aged 45–65 years who initiated statins in 2001–04 for primary prevention of CVD was identified from the health care registers. The study population included diabetic persons (11%) and every second person (50%) had purchased other cardiovascular medications during the year preceding statin initiation. Of the population, 53% adhered to statin therapy (PDC \geq 80%) during the first year after statin initiation. Furthermore, 76% remained adherent for two years and 64% for three years since statin initiation. To compare with, 85% remained non-adherent (PDC $<$ 80%) for two years since statin initiation and 74% three years consecutively. The cohort produced 753,796 person-months of adherence and 770,826 person-months of non-adherence with 211 and 263 acute cardiovascular events, respectively.

Stabilized IPTWs had a mean of 1 at each yearly time point (Table 5.4) indicating correct model specifications. Standardized differences were calculated for original data and for the weighted pseudo-population to check exchangeability between adherers and non-adherers. Baseline characteristics were well balanced (standardized difference $<$ 10%) between adherers and non-adherers prior to weighting, with the exception of the proportion of pravastatin initiations and the proportion of initiations at 2004 at 12 months since statin initiation (Figure 5.1). Weighting produced very good balance. Greater unbalance was observed for time-dependent confounders in unweighted data, especially for the classes of the number of concurrent medications at the year prior to the adherence assessment period in question as well as for prevalences of hypertensive disease and diabetes (Figure 5.2). However, increase in the intensity of statin therapy was borderline unbalanced in the weighted data (standardized difference 11%) at 36 months after statin initiation but not in the unweighted data (Figure 5.2). Adding interactions or squared terms had no effect on the mean and standard deviation of the weights or, finally, on the effect estimate.

MSM accounting for time-dependent confounding affected by previous adherence resulted in a HR of 0.77 (95% CI 0.64–0.93) indicating a 23% relative reduction in the hazard of acute cardiovascular events for adherers in comparison with non-adherers (Table 5.5). To account for the impact of large estimated weights on the effect estimate, a sensitivity analysis with weights truncated at 1st and 99th percentiles was conducted, but it did not alter the results. Compared with that of MSMs, HR remained unchanged when estimated with discrete-time hazards model that included time-dependent adherence and baseline characteristics (Table 5.5). However, interpretation of the HR estimated with discrete-time hazards model was conditional on the baseline characteristics. Sensitivity analysis using the composite outcome of acute cardiovascular events, medical procedures related to CHD and death resulted in HR of 0.79 (95% CI 0.69–0.90). The result indicated that medical procedures related to CHD and death as competing risks for acute cardiovascular events did not appreciably bias the effect estimates. During the follow-up, 557 out of 42,301 women without low-energy fractures within three years prior to statin initiation experienced the negative control outcome of a low-energy fracture. Statin adherence potentially reduced the hazard of low-energy

fractures by 10% (HR 0.90, 95% CI 0.76–1.07) compared with non-adherence (Table 5.5). That is, part of the estimated reduction in the hazard of acute cardiovascular events for adherence in comparison with non-adherence may be due to the healthy adherer effect.

Table 5.4 Yearly distributions of stabilized inverse probability of treatment weights.

	At 12 months	At 24 months	At 36 months
Mean	1.00	1.00	1.00
Standard deviation	0.16	0.18	0.21
Minimum	0.57	0.17	0.15
1 st percentile	0.72	0.68	0.62
5 th percentile	0.79	0.76	0.72
Median	0.98	0.98	0.97
95 th percentile	1.28	1.32	1.38
99 th percentile	1.47	1.57	1.66
Maximum	3.02	10.47	11.25

Table 5.5 Estimates from marginal structural models and a conventional discrete-time hazards model adjusted with baseline characteristics on the effects of adherence to statin therapy.

Model	Hazard ratio	95% Confidence interval
Non-adherence	1.00	
Adherence		
1) MSM for acute cardiovascular event	0.77	0.65–0.94
2) MSM for acute cardiovascular event with weights truncated at 1 st and 99 th percentiles	0.78	0.65–0.94
3) Baseline adjusted discrete-time hazards model for acute cardiovascular event	0.76	0.63–0.91
4) MSM for composite outcome	0.79	0.69–0.90
5) MSM for negative control outcome	0.90	0.76–1.07

Abbreviations: MSM, marginal structural model.

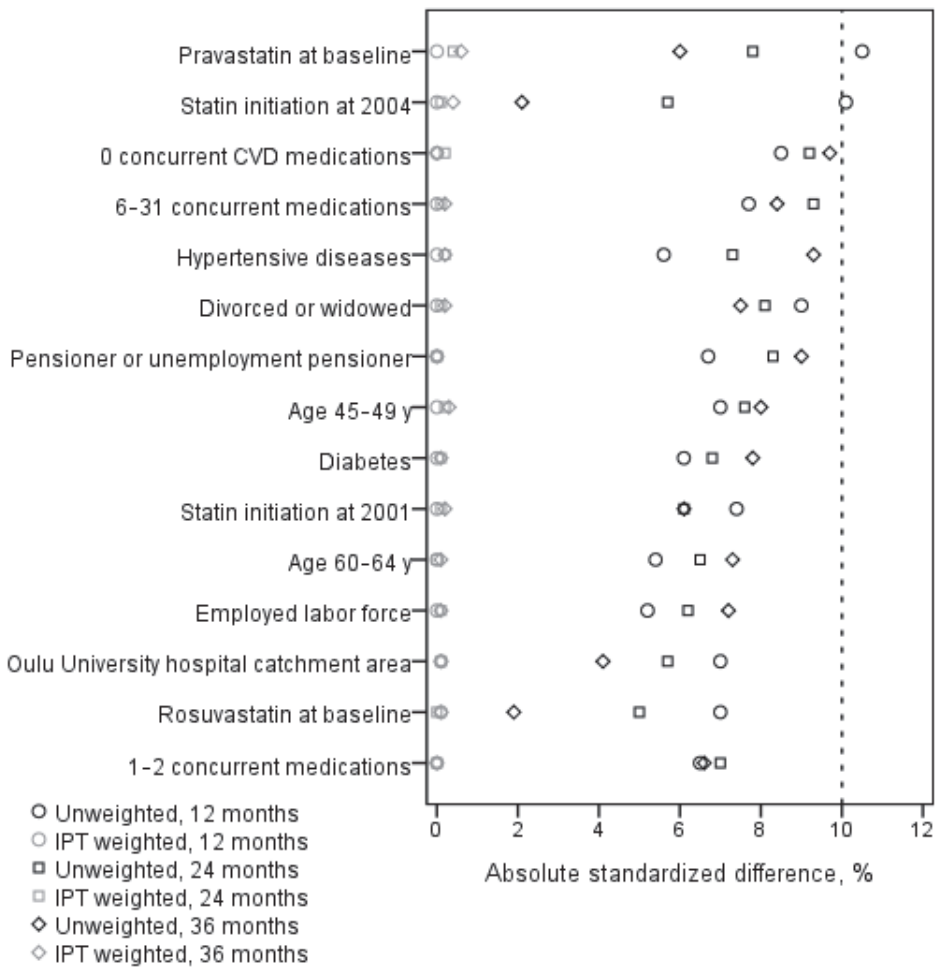


Figure 5.1 Standardized differences $\geq 7\%$ for a comparison of baseline characteristic distributions between adherers and non-adherers to statin therapy. CVD, cardiovascular disease; IPT, inverse probability of treatment.

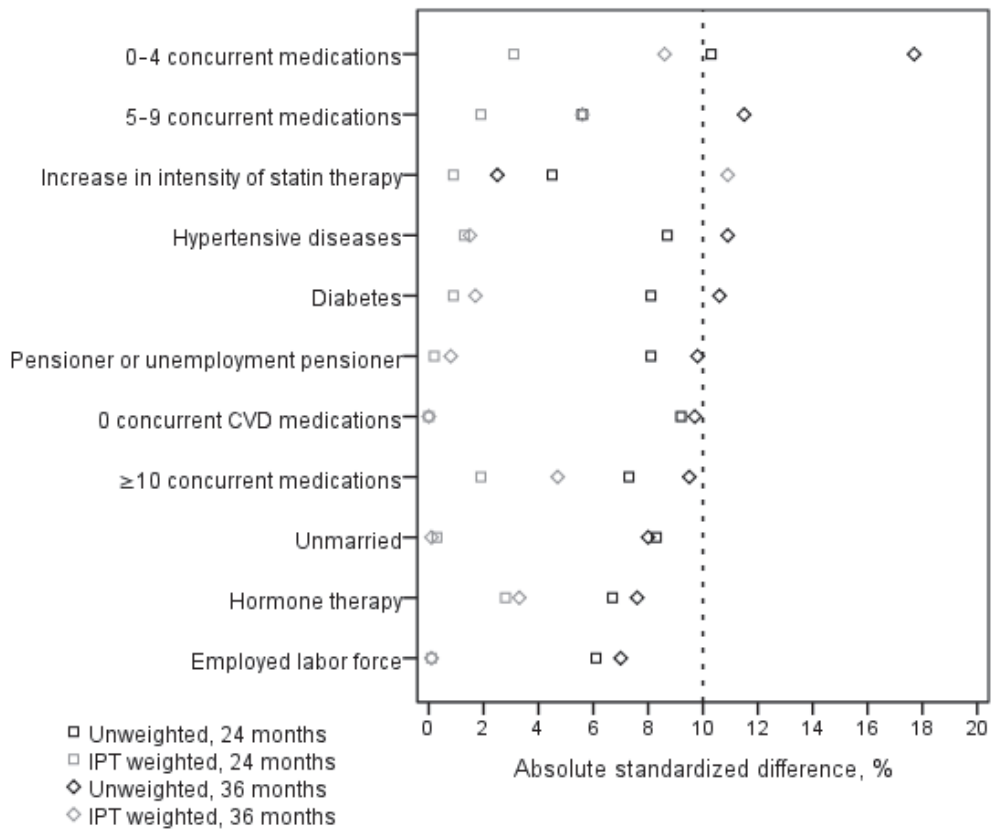


Figure 5.2 Standardized differences $\geq 7\%$ for a comparison of potential time-dependent confounder distributions between adherers and non-adherers to statin therapy for unweighted and inverse probability of treatment weighted data. CVD, cardiovascular disease; IPT, inverse probability of treatment.

5.3 Impact of missing data mechanism on the estimates of change in polypharmacy

During the three-year follow-up, 172 persons (22%) of the baseline population left the study prematurely, primarily because of death (Table 5.6). Response rates at one, two and three years after the baseline were 0.92, 0.84 and 0.78, respectively. The mean number of medications in use was associated with a person's time in study; persons who left the study after baseline examination had an average higher number of medications in use than those who participated in all of the four examinations (i.e., had complete data) (Figure 5.3). Annual distributions of the number of medications in use among year-specific study attendees (available-case analysis) are presented in Table 5.7, showing an increasing trend. Additionally, consecutive measures of the number of medications in use correlated strongly; correlation coefficients varied between 0.89 and 0.93.

Table 5.6 Flow of persons in the GeMS study.

Study year	Participated		Left the study	
	n	%	Death	Other reasons
			n	n
2004	781	100	0	0
2005	717	92	52	12
2006	657	84	55	5
2007	609	78	46	2

Table 5.7 Distributions of the annual observed number of medications in use among year-specific attendees.

	At baseline in 2004	At 1st follow- up examination in 2005	At 2nd follow- up examination in 2006	At 3rd follow- up examination in 2007
n	781	717	657	609
Mean	6.40	6.85	7.07	7.14
Median	6.00	6.00	7.00	7.00
SD	3.84	3.77	3.73	3.72
Min	0	0	0	0
Max	23	23	20	20

Abbreviations: SD, standard deviation

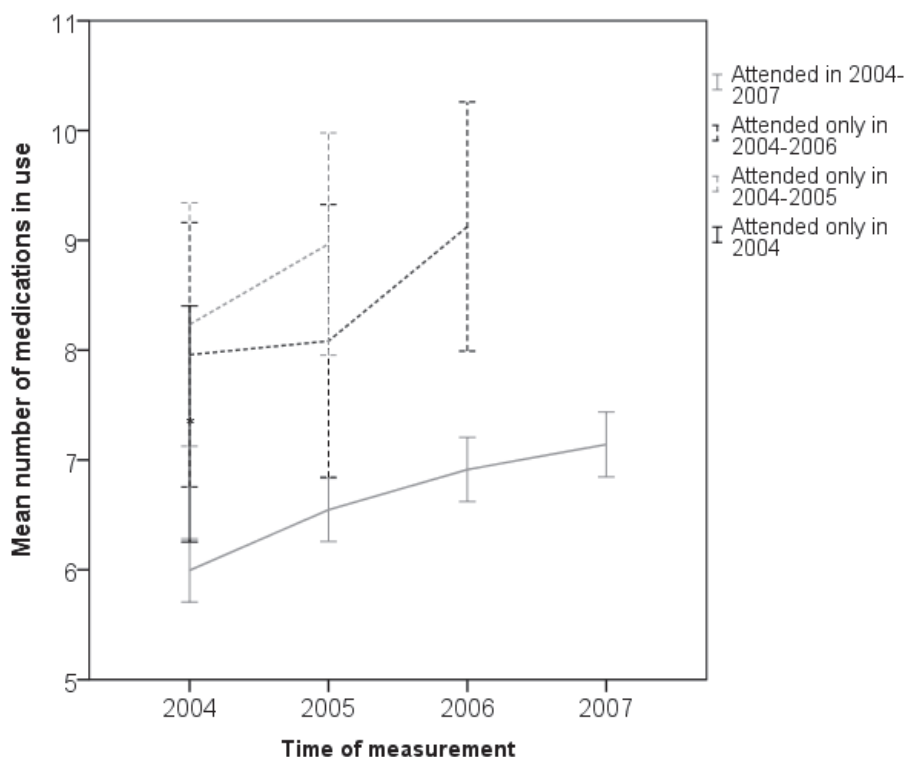


Figure 5.3 Mean number of medications in use stratified by the attending patterns. Error bars represent 95% confidence intervals.

First, LGCMs under MAR assumption were fitted and the shape of growth investigated. A model with a latent baseline level, a linear latent slope component and correlated error terms fitted the data well; $\chi^2(4, N = 781) = 7.74, p = 0.10, CFI = 1.00, TLI = 1.00, RMSEA = 0.04$ and $SRMR = 0.01$. The estimated average number of medications in use at baseline was 6.46 (standard error, SE, 0.14) and the estimated linear slope of change was 0.36 (SE 0.04) medications per year, meaning that it would take approximately three years to receive one additional medication (Table 5.8). Variances of the latent baseline and slope components indicated that there were significant between-person differences in these factors (Table 5.8). Covariance between the latent components was fixed to zero because of statistically insignificant estimated covariance, meaning that the baseline number of medications in use did not correlate with the slope of change.

Second, previously estimated LGCM was fitted together with explicit logistic regression models for missing data process to produce the Diggle-Kenward selection model under the MNAR assumption. Compared with the estimation results produced by the LGCM, estimates of the average baseline level and the slope of change and their variances remained at their level (Table 5.8). Logistic regression models investigated how current and previous numbers of medications affected the probability of missing data and suggested effects of opposite directions (Table 5.9). A high number of

medications at baseline tended to increase the risk of missing data at the first follow-up whereas a high current, potentially unobserved, number of medications decreased the risk. Statistically significant coefficients thus indicated MNAR mechanism for the missing data at first follow-up examination. However, at the second and the third follow-up examination missing data may be regarded to have MCAR mechanism due to statistically insignificant regression coefficients. Altogether, estimates were considered to suffer from collinearity problems as the 95% CIs were broad and estimates of opposite directions. Therefore, the CIs were not interpreted further.

Table 5.8 Estimation results from models to investigate the impact of missing data mechanism.

	Latent growth curve model		Diggle-Kenward selection model	
	Est	SE	Est	SE
η_0 (baseline level)	6.46	0.14	6.41	0.14
η_1 (slope of change)	0.36	0.04	0.32	0.04
$Var(\eta_0)$	10.66	0.67	10.45	0.65
$Var(\eta_1)$	0.36	0.07	0.38	0.07
$Cov(\eta_0, \eta_1)$	0*		0*	
Factor loadings:				
λ_1	0*		0*	
λ_2	0.33*		0.33*	
λ_3	0.66*		0.66*	
λ_4	1*		1*	

Abbreviations: Cov, covariance; Est, estimate; SE, standard error; Var, variance.
*, fixed.

Table 5.9 Estimation results for missing data models from the Diggle-Kenward selection model.

	Odds ratio	95% Confidence interval
Missing in 2005:		
N of medications in 2004	2.23	1.31–3.77
N of medications in 2005	0.39	0.21–0.74
Missing in 2006:		
N of medications in 2005	1.20	1.00–1.45
N of medications in 2006	0.96	0.77–1.19
Missing in 2007:		
N of medications in 2006	1.03	0.82–1.28
N of medications in 2007	1.15	0.91–1.46

Figure 5.4 presents average growth trajectories estimated with LGCM and Diggle-Kenward selection model as well as based on crude sample means among the attendees (available-case analysis assuming MCAR) and crude sample means among the study survivors (complete-case analysis assuming MCAR). Crude sample means calculated among study survivors gave overly optimistic results for population means. However, the slope of change corresponds visually to that estimated with LGCM and Diggle-Kenward selection model. Crude baseline sample mean among year-specific study attendees was naturally in line with the estimates of the average baseline level of sophisticated models, but at the third examination crude sample mean clearly underestimated the means estimated with sophisticated methods. Diggle-Kenward selection model assuming MNAR mechanism proposed a slightly slower accumulation of medications since the baseline than LGCM under MAR. The estimated mean at the third follow-up examination from the Diggle-Kenward selection model lay in between the crude sample means and the one estimated with LGCM.

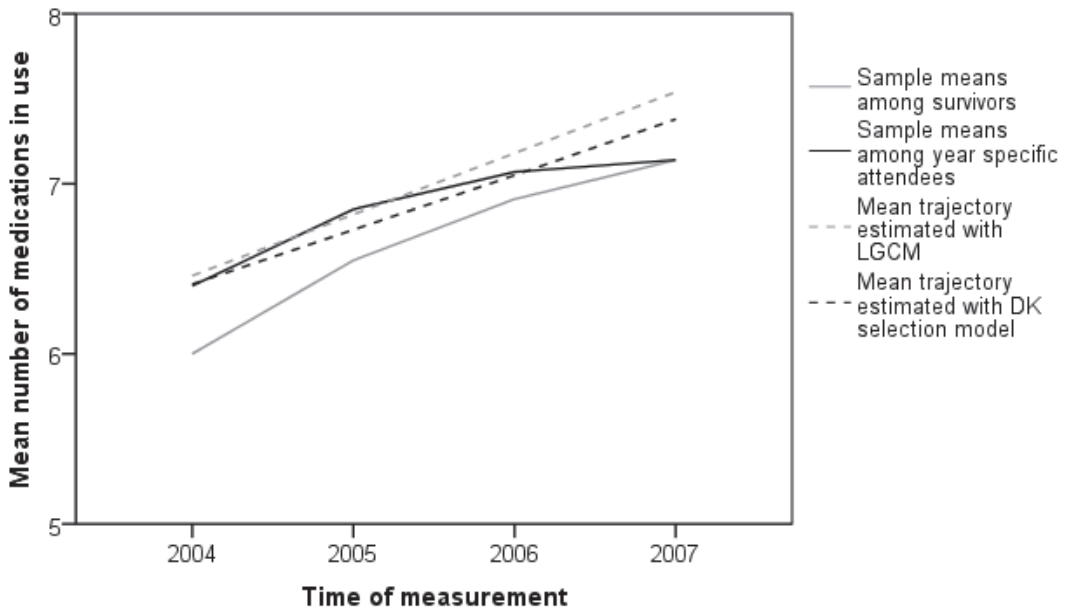


Figure 5.4 Estimated growth trajectories and sample means of number of medications in use. Abbreviations: DK, Diggle-Kenward; LGCM, latent growth curve model.

6 DISCUSSION

6.1 Accumulation of cardiovascular and diabetes medications among apparently healthy statin initiators

In Study 1, accumulating cardiovascular and diabetes medications were considered as proxies for medication-modifiable risk factors for CVD. It was observed that two thirds of the persons initially free of atherosclerotic cardiovascular disease or diabetes or medications for these conditions remained free of medication-modifiable risk factors for two years since statin initiation at 2006. However, every seventh (14%) initiated other cardiovascular or diabetes medications concurrently with statins. It was found that 66% of the apparently healthy statin initiators were correctly classified as such throughout the follow-up, 7% were misclassified as low-risk persons already at the time of statin initiation, and the rest switched from low-risk of CVD at baseline to higher-risk by the end of the 24-month follow-up. Today, the proportion of patients initiating statins and remaining free of additional cardiovascular or diabetes medications may be higher than observed in the present study due to updated guideline recommendations (Tikkanen *et al.* 2013, Perk *et al.* 2012, Stone *et al.* 2014) to initiate statins for persons with lower CVD risk.

To my knowledge, there is scarce literature on the evolution of risk level of apparently healthy statin initiators soon after statin initiation to compare with the current study. Prior studies that have reported increasing proportions of persons at low risk of CVD among all statin initiators over time (Wallach Kildemoes *et al.* 2012b, Rikala *et al.* 2013) have often defined low-risk population as persons free of cardiovascular risk factors at the time just prior to statin initiation. This is also assumed in the Danish method of indication hierarchy (Wallach Kildemoes *et al.* 2012a) which was applied in the current study to identify the cohort of apparently healthy statin initiators. In their study, Danish researchers found that about a quarter of new statin initiators were apparently healthy (Wallach Kildemoes *et al.* 2012a), which is comparable to the proportion observed (34%) in the current study. However, based on the results observed in this study, indication hierarchy may result in overestimation of low-risk statin initiators. There are also prior studies that have considered time after statin initiation when classifying risk level (Upmeier *et al.* 2013). Typically, a maximum of one year after statin initiation is allowed for to capture, for example, entitlements to special reimbursements which may be registered with a few months' delay in the Finnish SRR (Virta *et al.* 2008). After one year of follow-up in the current study, the rate of initiators of other cardiovascular and diabetes medications (and potential for miss-classification) was considerably decreased; 78% of the initiators of additional medications initiated cardiovascular or diabetes medication during the first year of statin use while 12% initiated additional medications 1–1.5 years after statin initiation and 10% after 1.5 years of follow-up.

Trajectories estimated with GMMs revealed that a small proportion (3%) of initiators of other cardiovascular or diabetes medication belonged to “high accumulation” class where persons received on average 2.3 additional medications simultaneously with

statin, with a peak of on average 5.8 medications 1.5 years after statin initiation. In addition, persons in the class of “moderate accumulation” redeemed on average 1.2 additional medications at statin initiation and ended up with 3.2 medications by the end of the two-year follow-up. These two classes of statin initiators accounted for 7% of all the apparently healthy statin initiators. Clearly, persons belonging to these classes were at higher cardiovascular risk already at the time of statin initiation. This kind of information has not been provided prior to this study and it is concluded that persons initiating other cardiovascular or diabetes medications simultaneously with statins should be identified in future register-based studies that aim to identify low-risk persons. However, the remaining population may still include persons with familial hypercholesterolemia or high cholesterol values as well as smokers.

Population of apparently healthy statin initiators was identified based on data on hospital discharges seven years prior and medication purchases three years prior to half a year after statin initiation. Entitlements to special reimbursements were not used to identify prior CVDs. The lengths of the lookback periods were in between those applied in prior studies where the lookback periods varied between one and 29 years for hospital discharges and between one to 11 years for medication purchases (Table 2.2). The current study investigated only accumulation of medication-modifiable risk factors. Information on other major risk factors for CVD, such as cholesterol level, blood pressure, smoking or family history of CVD, was not available, which made it impossible to estimate the overall CVD risk level. In conclusion, the medication-modifiable risk level at statin initiation estimated in this study may underestimate the overall CVD risk level.

Low-dose acetylsalicylic acid was not reimbursable implying a potential underestimation of the accumulated number of medications. However, there may also be overestimation of the accumulated number due to switching of medications (e.g. between alternative blood pressure-lowering medications).

Mixture modeling and structural equation modeling in general have been popular in psychology and social science (Nagin and Odgers 2010, Twisk and Hoekstra 2012) but not in pharmacoepidemiology until recently (Franklin *et al.* 2013, Franklin *et al.* 2015a, Franklin *et al.* 2015b, Li *et al.* 2014). An advantage of the GMMs is the ability to cluster persons according to similarities in growth trajectories and to examine the extent of random variation and to separate it from real differences. Instead of exploring the average number of accumulated medications in the population of initiators of additional medications, GMMs proposed four latent, distinct subpopulations with different patterns of accumulation. However, GMMs and other trajectory models like latent class growth analysis and LGCMs are fully parametric models that are vulnerable to model misspecification. These models are criticized for leading to problems when choosing the final model (Nylund *et al.* 2007). As seen in this study, model fit indices may disagree between alternative models, i.e., in the number of distinct classes, and substantive meaningfulness should play a role when choosing the final model. Additionally, latent classes identified may not correspond to “real” subpopulations but rather to subgroups

that may arise due to other similar characteristics (for example, sample fluctuation) within the groups (Twisk and Hoekstra 2012). This shortcoming may be seen as an overestimate of the number of classes. At their best, the identified latent classes are just an approximation (oversimplification) of reality. Finally, to ensure appropriateness of the four trajectories of accumulation found in this study, the study should be replicated with other datasets on the subject in similar populations.

The GMM analysis used FIML in estimation and thus, allowed for MAR mechanism. It may be possible that the rate of attrition due to deaths and long-term institutionalizations correlates with the number of cardiovascular and diabetes medications accumulated since statin initiation. However, as the rate of attrition was small, 1% for the apparently healthy population with cardiovascular or diabetes medication purchases during the two-year follow-up, this may not considerably bias the estimates. In the present study, GMMs were applied to persons who initiated additional cardiovascular or diabetes medications during the follow-up. However, it could have been possible to analyze GMM with a zero-inflated Poisson model, which accounts for the accumulation of zero medications that introduces additional skewness for a Poisson distribution, for the complete population of apparently healthy statin initiators. Such a model was fitted initially but it did not converge (data not shown) and, thus, the current analysis strategy was chosen.

6.2 Adherence to statin therapy and risk of acute cardiovascular events in primary prevention of cardiovascular disease

The relative reduction of about one fifth in the hazard of acute cardiovascular events for adherence compared with non-adherence observed in this study among women in primary prevention of CVD is in line with the results of the earlier publications for both sexes (see Table 2.4). However, earlier studies applied different definitions for population, adherence and outcome events, which complicates direct comparison between previous studies and the current study. In line with the prior studies, adherence level was observed to fluctuate between adherence and non-adherence, typically decreasing over time. Today, the clinical effect of adhering to statin therapy may be stronger as statin initiation has been estimated to shift to more intensive statins (Tran *et al.* 2014) than at the time of the current study. However, for a person at low risk of CVD, reducing the already low risk of CVD by statin therapy is debatable (Aarnio *et al.* 2015, Greving *et al.* 2011, Ridker and Cook 2013) although some studies have concluded it to be cost-effective (Lazar *et al.* 2011). Acute cardiovascular events were rare in the studied population of 45- to 64-year-old females. Statins are not expensive from the user perspective and benefits may thus be gained at low cost. However, optimal adherence to statin use is required to gain the full benefit of the therapy both in terms of health outcomes and society's health care costs (Aarnio *et al.* 2015, Baroletti and Dell'Orfano 2010). Persons with low perceived risk may not have enough motivation to adhere to the medication; they may not understand the severity of the risk of the disease or the benefit the therapy may provide, or they may fear adverse events (Baroletti and Dell'Orfano 2010). Over time, along with increasing statin intensities, the probability of adverse

events may increase. Enhancing adherence through interventions has not led to improved adherence (Maningat *et al.* 2013, Osterberg and Blaschke 2005, Reese *et al.* 2015).

The objective of an epidemiologic study is to provide valid and precise inference that is generalizable to the target population (Rothman *et al.* 2008). The validity of a study is separated into internal and external validity; furthermore, internal validity may be violated due to confounding, selection bias, or information bias (Rothman *et al.* 2008). Confounding arises when an effect measure is distorted by the presence of a common cause for exposure and outcome – exchangeability of the exposed and unexposed does not hold (Hernán and Robins 2016, Rothman *et al.* 2008). Generally, RCT is considered as a gold standard to evaluate efficacy of a treatment and exchangeability at the baseline is guaranteed by randomization. However, constructing an RCT to examine the efficacy of statin adherence is problematic as participants cannot be directly assigned to various adherence levels, which is why observational studies are preferred. To protect against confounding and selection biases at cohort entry, a new-user design, generally agreed as the default design for studies of comparative effectiveness, was applied (Ray 2003). Confounding is generally divided into measured and unmeasured confounding depending on the availability of measured variables in the analysis phase (Brookhart *et al.* 2010, Hernán and Robins 2016). Observed from the results, exchangeability between the groups regarding the measured potential confounders was quite good at the baseline and at consecutive one-year time points already prior to inverse probability of treatment weighting, and, as expected, especially thereafter. However, the effect of unmeasured confounding on the estimation results was not ascertained and the level of residual confounding remains unknown. After all, it is possible to account for unmeasured confounding only by RCT. However, negative control outcome model was used to assess the potential for healthy-adherer bias emerging from different health seeking behaviors between adherers and non-adherers. On the contrary to the results of external adjustment in the study by Rannanheimo *et al.* (2015), the result observed in the current study gave a reason to believe that the healthy-adherer bias modestly distorted the effect estimates of the main analyses. That is, the true effect of statin adherence on acute cardiovascular events is likely to be weaker than observed here.

Population in primary prevention of CVD was identified from the administrative health care registers as free of established CVD at the day of statin initiation. The lookback period to identify established CVD both from hospital discharges and medication purchases was the preceding three years to statin initiation (and including the date of initiation). Although hospital discharges were identified from a shorter period than in Study 1, entitlements to special reimbursement for chronic CHD at the time of statin initiation were used to identify former CVD more comprehensively. Diabetic persons were included in the primary prevention population as their relative risk reduction of CVD achieved with statin adherence is reported to be of the same magnitude as for non-diabetic persons (Korhonen *et al.* 2016, Ruokoniemi *et al.* 2011). Generally, the results are well generalizable to female Finnish population of this age in primary prevention of CVD.

Selection bias emerges when the association between exposure and outcome differs between those selected to the study and those eligible to the study (Hernán *et al.* 2004). For example, differential loss to follow-up may introduce selection bias if one conditions on the reason for missing data that is a common effect of exposure and outcome (Hernán *et al.* 2004). To start with, persons who experienced the outcome, died or were long-term institutionalized during the first adherence assessment year were excluded from the analyses. However, as statin therapy is not likely to affect the risk of CVD or mortality during the first year of use (Bukkapatnam *et al.* 2010, Colhoun *et al.* 2004, Downs *et al.* 1998, Mizuno *et al.* 2008, Sever *et al.* 2003), excluding persons is not likely to introduce selection bias. Second, censoring due to institutionalization or deaths occurring during the follow-up was not accounted for by using inverse probability of censoring weighting. Theoretically, this may introduce selection bias as the risk of outcome may not be equal among those censored and those left in the cohort. The effect of deaths and medical procedures that may be regarded as competing risks during the follow-up was examined in a sensitivity analysis where a composite outcome of acute cardiovascular events, medical procedures related to CHD and all-cause deaths was formed. Comparable results with the main analysis were obtained. The proportion of persons institutionalized during the follow-up was small (0.3%) which complicated formulation of inverse probability of censoring weights and, further, led to omission of weighting.

Information bias occurs when measurement or classification of a variable (exposure, outcome or confounder) is erroneous (Rothman *et al.* 2008). At the time of the study, some packages of simvastatin cost under €10 in 2005. However, when the cost of a purchase was under €10 in the basic reimbursement category, the purchase was not registered, leading to a potential underestimation of statin use at that time. Additionally, since October 2006, atorvastatin and rosuvastatin purchases were not reimbursed and, thus, not registered. As a shortcoming of using prescription data to quantify adherence, it was impossible to assess whether the medications dispensed were consumed, which may have led to overestimation of the true adherence level. More generally, all the confounders that were based on estimated medication use (number of concurrent medication or concurrent CVD medications, for example) suffered from this uncertainty as well. As depicted by Parienti (2015), averaging adherence to one value over time and, further, dichotomizing it, prevents researchers from observing the dynamic patterns of adherence with different “shapes and shades”. The current study provided a more flexible time-dependent estimation of adherence but was not able to smoothly estimate the shapes and shades of adherence in time due to limitations in model building resulting from the chosen MSM technique and as-treated analysis strategy. The validity of the FCR in identification of myocardial infarction (positive predictive value 69% among women aged 35–74 during 1998–2002; Pajunen *et al.* 2005) and ischemic stroke (positive predictive value 80% among women aged 25 and older during the years 1993–1998; Tolonen *et al.* 2007) is at good level when compared with Finnish population-based myocardial infarction and stroke registers. There were missing data in confounders concerning marital status (0.03%) and labor market status (0.03%). Due to very small proportions of missing data, last-observation-carried-forward imputation method was applied.

In the current study, estimation results from MSMs and from a conventional discrete-time hazards model were comparable and very similar although MSM produced a marginal effect whereas conventional model produced a conditional effect. According to systematic reviews of papers comparing estimates from a MSM with conventional model, this result is common and was also observed in half of the studies included in the reviews (Suarez *et al.* 2011, Yang *et al.* 2014). The reason for lacking difference between the estimates may be absence of strong measured time-dependent confounding affected by prior exposure. For example, in the current study, the intensity of statin therapy may act as an intermediate variable that is associated with the severity of the disease (i.e., cholesterol values). Hypothetically, suboptimal adherence may lead to an increase in intensity of the therapy which, in turn, may lower the risk of CVD event. In addition, compared to low-intense therapy, high intensity statin therapy may more often lead to discontinuation due to adverse events and to a reduction in the need of medical procedures. However, the associations may not be so strong in a real-life setting. More generally, the ability of register-based variables to predict adherence has been shown to be poor (Aarnio *et al.* 2014).

MSM estimates the average treatment effect in the entire study population over time (Robins *et al.* 2000) and, thus, answered the study question “What would be the effect if every woman in primary prevention of CVD would adhere to statins”. For this, the method is sensitive for a non-uniform treatment effect across covariate levels (Kurth *et al.* 2006). Contraindications for treatment should be accounted for when forming the study population.

There are four assumptions for MSMs needed for producing valid estimates (consistency, positivity, exchangeability and correct models both for the exposure and the outcome) that must be considered in every MSM application. Here, adherence to statin therapy was considered as a well-defined intervention similarly to medical therapies generally (Hernán and Taubman 2008). However, there may be psychosocial and behavioral factors that define a person’s medication-taking behavior (Mann *et al.* 2007, Rannanheimo *et al.* 2015) and that cannot be measured directly. But there are some proxies (such as depression, mental disorder, alcohol-related diseases) that relate to these factors and are partly measurable from the registers. To produce exchangeability, an effort was made to identify potential confounders to be included in the exposure models; the selection of variables was guided by expert knowledge and existing literature on risk factors (Downs *et al.* 1998). Exposure models that were produced to balance the two adherence groups at every time point of follow-up were robust to different model specifications, which may be due to large sample size (Lefebvre *et al.* 2008). Because of an excessive number of confounders in the exposure models, random violations of positivity assumption were inherent, but structural violations were not. All the weights had a mean of 1 at every time point, which indicates correct model specifications and non-violations of positivity assumption. Talbot *et al.* 2015 reported that estimates from MSMs are prone to errors in model specifications for the weights as well as functional form of exposure used in MSM. Creating stabilized weights by including prior exposure in the numerator of exposure model (equation 2.3) cancels out some of the confounding

property of prior exposure (consecutive exposures are not mutually independent in a pseudo-population created by weighting the population with stabilized weights).

6.3 Impact of missing data on the estimates of change in medication use

The present study observed differences in estimates of the evolution of polypharmacy during the study period derived under MCAR, MAR and MNAR assumptions for missing data mechanism. Estimates under MCAR assumption underestimated the evolution when compared with estimates under MAR and MNAR. Although estimation results under MAR and MNAR were quite similar, the results achieved indicate that during longer follow-up times than in the current study, differences between MAR and MNAR models may increase and become clinically significant as well. Thus, it will be important in future studies to account for missing data mechanism in longitudinal studies of older persons. The current study supports the notion that statistical methods assuming MCAR pattern for missing data should be avoided, especially in longitudinal studies of older persons, unless the target of inference is to describe evolution among survivors. A model assuming the MAR mechanism is a good starting point with a model under MNAR serving as a sensitivity analysis.

The data for this study came from the longitudinal GeMS study where the validity of the information on the total number of medications in use can be considered good. An effort was made to avoid recall bias in the data collection phase: information on medication use was gathered from prescriptions and medication containers that the subjects brought to the interviews and was ascertained by checking their medical records. The cohort was formed as a random sample of older persons residing in the municipality of Kuopio in 2003, which allows for generalization of the results to older people residing in Kuopio, and likely to a high extent, to older people in Finland due to a national framework used for organization of health care in municipalities (Ministry of Social Affairs and Health 2013).

The Diggle-Kenward selection model to account for MNAR mechanism was chosen because of its attractive property to straightforwardly model the marginal distribution of the outcome as well as its comparability with the LGCM. The selected method has been criticized for the demanding assumptions that need to be assumed; the distribution for the full data as well as a correct model for missing data mechanism (Diggle and Kenward 1994). The Diggle-Kenward selection model is very sensitive against departures of the distribution assumed for the outcome (Kenward 1998). However, robust ML estimation method was applied in the current study to provide protection towards violations of the assumption of normality distribution. The number of medications in use could have been assumed to alternatively follow Poisson or negative binomial distribution. Further, applying a Diggle-Kenward selection model with these distributional assumptions is straightforward in Mplus today (Muthén and Muthén 1998–2012). Interestingly, as interpreted from the logistic regression models for missing data, the models suggested missing data to have MNAR mechanism at the first follow-up examination but MCAR mechanism at the second and the third follow-up examination. This may be explained by the highly correlated consecutive measures of the number of medications in use.

In the current study, deaths and dropouts due to other reasons were combined and the missing data indicator described whether the intended measure was taken or not irrespective of the reasons for missing data. Deaths accounted for 89% of the missing outcome data. However, the current analyses were for illustrative purposes only. To continue, several researchers have proposed treating deaths and dropouts separately (Frangakis and Rubin 2002, Harel and Schafer 2009, Harel *et al.* 2007, Kurland and Heagerty 2005, Kurland *et al.* 2009). Indeed, data missing for a person at examination t due to death means that the person has died at some time point after the prior examination at time $t-1$. Considering the number of medications in use at time t to predict probability of death at t is somewhat strange and unreasonable (Diehr *et al.* 2005, Schafer and Graham 2002). On the contrary, it makes more sense to consider the current, unobserved number of medications for a person lost-to-follow-up from non-mortality reasons. Semiparametric cause-specific selection model to account for multiple causes of MNAR data is introduced in the study by Rotnitzky *et al.* (2001) but was not, however, applied in this study.

LGCM, and thus the Diggle-Kenward selection model applied in this study, assume that persons are drawn from the same population and that development over time can be mapped using one set of parameters. The time axis in this study was defined as time since baseline examination at 2004. However, the population of older persons is very heterogeneous and persons aged 75 years are very different from persons aged 90 years. The estimated trajectory for the mean number of medications in use does not necessarily correspond to the one observed for any of the persons of this population. The time origin of the analyses could be more rationally considered as the age of 75, and differential growth trajectories between age cohorts could be modeled. In addition, as health characteristics are likely to vary greatly also within the proposed age cohorts, modeling latent subgroups within the age cohorts may provide deeper insight to the older persons than seen with the traditional models.

6.4 Future aspects

As reflected in the findings of this study, population heterogeneity is an important aspect to consider in future studies. For example, estimating average treatment effect in a heterogeneous population means assuming that the effect is similar across persons. Clearly, trajectory modeling (LGCM, GMM, latent class growth analysis) and latent variable modeling framework in general are becoming more popular methods in pharmacoepidemiology to model change in medication use and to group persons according to the similarities in their trajectories. Flexibility of the latent variable modeling framework allows for joint modeling of continuous and discrete processes, such as Diggle-Kenward selection models and GMMs. Another example is survival mixture analysis (Asparouhov *et al.* 2006, Muthén and Masyn 2005) where growth mixture and (continuous or discrete-time) survival processes are jointly modeled. In a recent study by Franklin *et al.* (2015b) 12-month statin adherence trajectories were shown to predict cardiovascular events better than PDC classifications. Adherence trajectories were identified using latent class growth models and were used in Cox proportional hazards models as predictors. In future studies focusing on primary

prevention population, adherence trajectories from time periods longer than 12 months could be estimated with GMMs to allow for random growth factors and use the identified classifications to predict cardiovascular events in a similar manner as in the study by Franklin *et al.* (2015b). However, how possible time-dependent confounding affected by previous adherence is to be accounted for in these kind of models remains an open question.

As noticed in the contexts of MSMs and Diggle-Kenward selection model, non-mortality outcomes are not defined after the death of a person. Especially among older persons where attrition because of death is frequent, this may pose a challenge for meaningful analysis (Diehr *et al.* 2005, Schafer and Graham 2002). In causal inference, considering deaths to be independent of risk factors may create selection bias whereas using inverse probability weighting to adjust for selection bias may produce estimates without meaningful interpretation. Forming a composite outcome, however, eliminates selection bias but, consequently, the study question has to be re-formulated. In addition, one option is to apply principal stratification where the inference is restricted to a stratum of persons who would not die regardless of the exposure they received (Rubin 2006). However, identification of these persons may be problematic. For studies exploring medication use as an outcome, Kurland *et al.* 2009 demonstrate modeling data truncated by death by formulating a joint distribution for the outcome and the time to death, providing a comprehensive view of the possible strategies for estimation.

7 CONCLUSIONS

First, two out of three statin initiators without established CVD, diabetes or hypertension remained free of additional cardiovascular and diabetes medications during the two-year follow-up since statin initiation. Four additional subpopulations with different trajectories on the accumulated number of cardiovascular and diabetes medications emerged during the follow-up. Of these, two subpopulations including 7% of apparently healthy statin initiators were identified to have trajectories indicative of higher baseline cardiovascular risk based on appearance of medication-modifiable CVD risk factors concurrently with statin initiation. That is, 66% of the apparently healthy statin initiators were correctly classified as apparently healthy persons throughout the follow-up, 7% were misclassified as apparently healthy persons already at the time of statin initiation, and a cluster of CVD risk factors indicating high CVD risk was observed for the rest of the population by the end of the two-year follow-up. In future studies targeting to define apparently healthy population of new statin users, persons initiating statin simultaneously with cardiovascular or diabetes medications should be identified to avoid misclassification.

Second, adherence to statin therapy decreased the hazard of acute cardiovascular events among persons in primary prevention of CVD after accounting for the time-dependent nature of adherence and confounding factors as well as the relationship between them using inverse probability of treatment weighted marginal structural modeling. The result was robust against selection bias caused by deaths and medical procedures related to CHD during the follow-up. However, another sensitivity analysis proposed the results to possibly suffer from healthy-adherer bias, but only to a moderate extent. In conclusion, time-dependent confounding affected by previous adherence was not considered to be strong as the result was comparable to the one produced with a standard discrete-time hazards model.

Third, assumption of the missing data mechanism in an illustrative study on the evolution of polypharmacy in a longitudinal study of older persons was shown to have a considerable effect on the estimates of evolution over time. Comparison of two time points among survivors, as done in the earlier publications investigating the evolution, gives a misleading result of the overall population. Hence, assuming MAR mechanism for missing outcome data provides a good starting point for statistical analyses. However, in circumstances where deviations from the MAR assumption are likely, sensitivity analyses should be conducted to assess the effect.

Population heterogeneity, missing data and causal relationships are important aspects in longitudinal studies that should be critically assessed. Although the methods applied in this study are not without problems and call for strong assumptions, they are a step towards more valid assumptions of the real-world dependencies. The sensitivity of estimates to alternative modeling assumptions should be routinely tested applying several techniques under different assumptions.

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