Understanding therapeutic traditions in a multilevel framework - new methodological approaches

Ohlsson, Henrik

2009

From the Unit for Social Epidemiology, Department of Clinical Sciences, Faculty of Medicine, Lund University

Understanding therapeutic traditions in a multilevel framework - new methodological approaches

Henrik Ohlsson

Abstract

Background: The observation of differences in the way apparently similar patients are treated from one health care setting to another, i.e., practice variation, have been recognized in numerous studies. The variations across the health care settings have been shown to exist for different outcomes. However, any measurement of any system will reveal some form of variation and this normal inevitable variation must be separated from special cause variation. Practice variation might, for example, be an expression of inefficient health care if a pharmacological agent is available in different brands at different prices and certain prescribers chose the more expensive one. In this situation, it is relevant to identify determinants of this variation in order to launch appropriate interventions. Inappropriate practice variation may have different origins. Since the process of drug prescription includes a number of phases it could be influenced at different levels (e.g. the patient, prescriber, health care practice). However, very few studies have so far tried to understand the relative importance of the different levels.

Another aspect that rarely has been investigated when studying practice variation is what we denote as therapeutic traditions. This corresponds to the idea that cultural aspects at the practice level might exert a collective influence on prescribers working within the same practice. It can be expressed by the fact that the prescription behavior among physicians within the same practice may be more similar than the prescription behavior among physicians from different practices. This can be operationalized by investigating variance components in a multilevel framework. Many aspects concerning the analysis of variance components, i.e., quantifying overall practice variation, understanding the importance of different levels, monitoring and distinguishing appropriate from inappropriate practice variation, needs much more development. A further development of applied statistical and epidemiological methods may facilitate a more comprehensive understanding of the differences between health care units and thereby a more accurate measure of healthcare quality.

Aims: Through the application of modern multilevel statistical techniques, we aim in this thesis to propose a model of analysis for investigating practice variation. We investigate therapeutic traditions in general and adherence to prescription guidelines and adoption of new drugs in particular. We also examine social and economic conditions at different levels of analysis and the role they play in this context. We focus on the combined analyses of measures of association and of variance and clustering as this can offer original and valuable information that could be of relevance for planning and evaluating interventions aimed to promote

evidence-based prescription. We mainly study adherence to prescription guidelines for statin prescription as these lipid lowering drugs all have similar indications and efficacy.

Material & Methods: The database LOMAS (Longitudinal Multilevel Analysis in Scania) is used and consists of unidentified information on all individuals living in Skåne region, Sweden during the period 1968 to 2008. One of the registers included is the Swedish Prescribed Drug Register that records information on sales of prescribed pharmaceutical agents by the Swedish Corporation of Pharmacies. We use multilevel regression models and generalized estimation equations, and provide an explanation for the application of these methods when focusing on measures of variance and clustering.

Results: Adherence to guidelines for statin prescription and the early adoption of a new statin seemed to some extent to be conditioned by contextual factors particularly at the Health care practice level (HCP) level. The determinants of the individual behaviour are influenced directly by the contextual environment of the practice. Moreover, HCPs that follow guidelines for one drug type also appear to follow guidelines for other drug types, i.e., therapeutic traditions, acting at the HCP level, seems to influence the prescribing behaviour of individual physicians independently of specific drug type. Moreover, men with a lower income were prescribed the cheaper recommended statins to a higher degree than men with a high income.

Conclusion: We present a model of analysis for investigating practice variation were we focus on the combined analysis of measures of association and measures of variance and clustering. We investigate therapeutic traditions in general and adherence to prescription guidelines and adoption of new drugs in particular. Since very few studies have tried to understand the relative importance of the different levels on the process of prescription, this thesis may eventually lead to a better understanding of the relationship between HCP- and individual level characteristics with respect to the prescription process. In turn, better understanding of the importance of different levels may facilitate for decision makers to focus interventions on the right factors at the right levels. By investigating the role of different health care levels on adherence to guidelines, researchers can more efficiently build and test models that capture factors influencing the prescription process.

Key words: multilevel models, variance components, practice variation, adherence to guidelines, determinants of prescription.

List of publications included in the thesis

(I) **Ohlsson H**, Lindblad U, Lithman T, Ericsson B, Gerdtham UG, Melander A, Råstam L, Merlo, J. Understanding adherence to official guidelines on statin prescribing in primary health care - a multilevel methodological approach. *European Journal of Clinical Pharmacology* 2005; 61(9):657-65.

(II) **Ohlsson H**, Merlo J. Understanding the effects of a decentralized budget on physicians compliance with guidelines for statin prescription; a multilevel methodological approach. *BMC Health Service Research* 2007;7: 68(8 May 2007).

(III) **Ohlsson H**, Chaix B, Merlo J. Therapeutic traditions, patient socio-economic characteristics and physicians' early new drug prescribing – a multilevel analysis of rosuvastatin prescription in South Sweden. *European Journal of Clinical Pharmacology* 2009; 65(2):141-150.

(IV) **Ohlsson H**, Lynch KF, Merlo J. Is physicians´ adherence to prescription guidelines associated with patient socio-economic status? – An analysis of statin prescriptions in South Sweden. *Journal of Epidemiology and Community Health (in press)*

(V) **Ohlsson H**, Merlo J. Is physician adherence to prescription guidelines a general trait of health care practices or dependent on drug type? – A multilevel logistic regression analysis in South Sweden. *Pharmacoepidemiology and Drug Safety (in press)*

(VI) Hjerpe P, **Ohlsson H**, Lindblad U, Bengtsson-Boström K, Merlo J. Understanding adherence to therapeutic guidelines: a multilevel analysis on statin prescription in the Skaraborg Primary care database. *In preparation*

Acknowledgements

I would like to thank everyone who helped and supported me during my Ph.D.-period.

Most of all I would like to pay my gratitude to Juan, my supervisor. Throughout my Ph.D.-period, he provided encouragement, good company, and plenty of good ideas, but in particular he showed an incredible enthusiasm.

I also would like to thank Kristian, who also has been working on his thesis and who has contributed in a variety of ways, but mainly by opening up a new perspective for every question raised.

Contents

Introduction

The existence and importance of practice variation in medicine, i.e., the observation of differences in the way apparently similar patients are treated from one health care setting to another,[1] have been recognized in numerous studies.[2-5] The variations across the health care settings have been shown to exist for different outcomes including drug prescription and adherence to prescription guidelines,[6-10] and beside the medical reason the variations have been attributed to several aspects; characteristics of the physician,[11 12] organizational setting and resources,[13] practice population,[13] patient characteristics as well as patient preferences.[14]

However, any measurement of any system or process will reveal some form of variation and this normal inevitable variation must be separated from special cause variation.[2 15 16] Practice variation might, for example, be an expression of inefficient health care if a pharmacological agent is available in different brands at different prices and certain prescribers chose the more expensive one. In this situation, it is relevant to identify the determinants of the special cause variation in order to launch appropriate interventions. However, little has been done to determine whether higher than randomly expected variability across areas or health care settings is in fact detected, or whether certain procedures are more variable than others.[17-22]

Inappropriate practice variation may have different origins. Since the process of drug prescription includes a number of phases (identification of the health problem, decision to prescribe, choice of medication and decision to cease using specific therapy) it could be influenced at different levels (e.g. the patient, prescriber, health care practice). However, very few studies have so far tried to understand the relative importance of the different levels for the prescription process.[6 10 23] One will then also be able to distinguish if the variation is due to patients or physicians or the health care setting.

Two main hypotheses have been developed to try to explain and understand the medical practice variation. The first hypothesis emphasize the uncertainty of the physician when he/she is required to make a decision in circumstances of clinical

ambiguity, as the key factor behind medical practice variation.[5 24 25] Resolving this uncertainty lead to the development of different practice styles. When the uncertainty of the physician is high, factors other than medically relevant characteristics have a major influence. Some researchers have proposed that this hypothesis based on the uncertainty of the prescriber have several drawbacks.[26] For example, it is difficult to explain why physicians change their behavior when economic incitements change. Therefore, a second hypothesis for explaining practice variation that emphasizes differences in opportunities, incentives and influences as explanatory factors for different practice styles have been proposed. This hypothesis implies that the behavior among well-defined groups of physicians are similar since they share a common work environment and similar constraints.[26] This is related to what we in this thesis denote as "therapeutic traditions". Therapeutic traditions correspond to the idea that cultural aspects at the practice level might exert a collective influence on prescribers working within the same practice. It can be expressed by the fact that the prescription behavior among physicians within the same practice may be more similar than the prescription behavior among physicians from different practices. The more the physicians from a practice are alike, compared to physicians from other practices, the more likely it is that the determinants of the individual behavior are influenced directly by the contextual environment of the practice.[27] This idea is analogous to the idea of "social fact" developed by the French sociologist Emile Durkheim (1858-1917).[28] Investigating social groups, Durkheim identified the existence of a contextual phenomenon that was more than the sum of the actions of the individuals composing the social group.[29] Because of this social fact, the individuals within the same social group (i.e., practice) share a collective conscience that conditions a similar behavior. [30]

Quantifying practice variation has been frequently used in order to assess quality in health care. In Sweden this quality assessment is based on the six dimensions in health care developed by the Swedish Board of Health and Welfare (SoS).[31] The dimensions included are evidence based and appropriate (to provide services that are relevant to clinical needs and founded on evidenced based medicine), safe (to avoid injuring users, providers or the environment), patient-centered (adapted to patient's preferences, needs and values), timely (reducing waiting time), efficient (avoid waste of resources) and equitable (provide care of equal quality regardless of the characteristics of the patient) health care. In addition to this work, the SoS in collaboration with the Swedish Association of Local Authorities and Regions (SKL) have published a series of reports comparing healthcare quality and efficiency in the 21 Swedish county councils and healthcare regions by using a set of national performance indicators.[32] The method used for comparing healthcare

quality and efficiency is mainly based on league tables of crude aggregated rates between hospitals regarding existing national performance indicators.

Many aspects concerning the methodology used for quantifying overall practice variation, as well as monitoring and distinguishing appropriate from inappropriate practice variation, needs much more development. The same is true when it comes to identify the causes of the variation. There is a gap between the development of statistical methods and its application in routine epidemiology. A further development of applied statistical and epidemiological methods may fill this gap and can facilitate a more comprehensive understanding of the differences between health care units and can thereby provide a more accurate measure of healthcare quality.

Prescription data, as well as a lot of other information on health-care utilization, are frequently ordered in a hierarchical structure (e.g., prescriptions clustered within physicians that in turn are clustered within health care practices). Furthermore, the prescription process can be influenced at those different levels and as we are interested in separating out the effects of the different levels on the prescription process, multilevel models appear as an appropriate statistical technique for investigating our research questions. In this thesis we use multilevel/mixed regression models [33 34] as well as the alternating logistic regression approach.[35] Multilevel models have in several studies shown to be a useful epidemiological tool for disentangling the role of the context. [23 33 34 36-39] However, very few studies have recognized the importance of modeling clustering and variance components [23 40-45] and have instead mainly focused on measures of association, such as odds ratios. By simultaneously investigating measures of associations and measures of variance and clustering opens up a dimension that has heretofore been underused in drug utilization studies. This combination can provide a more fine-grained empirical description of the drug prescription process.

In addition to therapeutic tradition, other relevant sociological factors that in several studies have been shown to influence clinical decision-making,[46-49] are the socioeconomic circumstances of both patients and the context where the patients are treated.[46-48 50 51] Knowledge about the social and economical determinants of prescription is relevant in order to assess equity in health care, which is a fundamental quality dimension according the Swedish Board of Health and Welfare. This aspect is particularly relevant in health care systems that, like the Swedish,[52] aim to allocate resources on the basis of needs and not on social constructs without a medical rationale. Studies have shown that insurance status

affect physicians' inclination to prescribe recommended drugs.[53] However in Sweden, the cost of medicines in outpatient care is shared by patients and county councils via a reimbursement system where the individual patient never pays more than 200 Euros per year.[54] Therefore, since the economical barriers are not of major relevance, this thesis can provide additional information about the sociological mechanisms underlying the drug choice and prescribing behaviour.

We mainly study adherence to prescription guidelines for statin prescription. We investigate statins as these lipid lowering drugs all have similar indications and efficacy, and there are no reasons for prescribing recommended statins to some patients rather than others based on patient characteristics. This renders them as an ideal medication group for investigating therapeutic traditions and the role that sociological factors play, as the risk of confounding will be small. [55-58]

In chapter six (*Definitions and explanations*), in order to facilitate the understanding of the thesis, definitions and explanations of some concepts are presented. In the first five chapters references to these explanations and definitions will be introduced when required.

General aim

Through the application of modern multilevel statistical techniques, we aim in this thesis to propose a model of analysis for investigating practice variation. We investigate therapeutic traditions in general and adherence to prescription guidelines and adoption of new drugs in particular. During the investigation, we also examine the social and economic conditions at different levels of analysis and the role they play in this context.

Rather than simply investigating measures of association, we focus instead on the combined analyses of measures of association and of variance and clustering. As few studies have tried to separate the effect of different levels on the prescription process and thereby limit the potential of interpreting differences between health care units, this thesis, with a focus on the combination of measures of association and measures of variance, can offer valuable and original information that could be of relevance for planning and evaluating interventions aimed at promoting efficient and evidence-based prescription.

Specific aims

For developing the thesis we conducted six different studies. The specific goals and hypotheses of the studies are summarized in table 1.

In *study I* (table 1) we aimed to operationalize the concept of therapeutic traditions by the combined use of measures of prevalence and measures of variance. The goal was to develop a model to improve the empirical analysis of the drug prescription process and explore the application of multilevel regression analysis within pharmacoepidemiology.

In *study II* (table 1) we applied the model developed in study I in order to measure the effect of an intervention; the decentralized pharmacological budget introduced in Skåne region in 2004. (For a shorter description of the decentralized drug budget see *Definitions and explanations*).

In *study III* (table 1) we further elaborated the previous theory and applied measures of clustering to quantify therapeutic traditions in relation to the process of early adoption of a new statin. Simultaneously, we aimed to investigate the role that both patient and outpatient health care practice (HCP) characteristics played in this context. For this purpose, we applied alternating logistic regression (ALR) and pair-wise odds ratios (PWORs), an innovative analytical approach based on generalized estimation equations (GEE).

In *study IV* (table 1) we investigated the association between patient and HCP characteristics on the one hand, and adherence to guidelines for statin prescription on the other, with a specific focus on social and economic conditions.

In *study V* (table 1) we analyze whether the clustering of behaviors within HCPs was independent of drug types, i.e. if adherence to prescription guidelines was a common trait within HCP or dependent of drug type.

In *study VI* (table 1) we analyzed the implementation of a decentralized drug budget in Skaraborg, Sweden. (For a shorter description of the decentralized drug budget see *Definitions and explanations*). We replicated previous analysis but on a different database that also contained information on the physician level; a level of analysis that was missing in previous studies. We hypothesized that a part of the variance at the HCP-level should be attributed to the physician level. Therefore this study complements previous findings about the relevance of different levels for understanding practice variation.

Table 1: Aim and hypothesis of the included studies

Paper	Aim & Hypothesis
I	**Aim:** To operationalize the concept of therapeutic traditions by the combined use of measures of prevalence and measures of variance and to monitor the introduction of guidelines on statin prescribing issued in Skåne region, Sweden, during March – Dec 2003. The goal was to develop a model to improve the empirical analysis of the drug prescription process and to explore the application of multi-level regression analysis within pharmacoepidemiology. **Hypothesis:** That the introduction of guidelines would result in increased use of recommended statins and decreased variance between Health care practices (HCPs) and municipalities
II	**Aim:** To apply the model developed in study I in order to measure the effect of an intervention; the decentralized pharmacological budget introduced in Skåne region in 2004. Within this framework we aim to monitor and evaluate the role played by the different organizational levels (HCPs, Health Care Areas (HCAs) and Health Care Districts) when it comes to understand physicians' adherence to prescription guidelines. **Hypothesis:** That the decentralized pharmacologic budget would result in increased use of recommended statins and decreased variance between HCPs and HCAs throughout the 25-month observation period.
III	**Aim:** To elaborate the previous developed theory to quantify therapeutic traditions and the early adoption of a new statin, rosuvastatin. For this purpose, we apply an innovative analytical approach using generalized estimation equations (GEE), alternating logistic regression (ALR) and pair-wise odds ratios (PWORs). Simultaneously, we aim to investigate the role that both patient characteristics and HCP factors play in physicians' propensity to prescribe rosuvastatin after its introduction to the market. **Hypothesis:** Since there are no solid therapeutic reasons for prescribing the new, more expensive brand instead of the cheaper, recommended ones, so we expect no systematically differences between HCP in their adoption of the new drug.
IV	**Aim:** To investigate the association between patient and HCP characteristics on the one hand, and adherence to guidelines for statin prescription on the other, with a focus on social and economic conditions. **Hypothesis:** Even though social roles and expectations related to the gender, age, or socioeconomic position (SEP) of the patient might condition the physician's behavior independently of needs, there are no solid reasons for expecting the prescription of more expensive non-recommended brands to patients of a certain age, gender, or SEP.

Paper	Aim & Hypothesis
V	**Aim:** To analyze whether the clustering of behaviors within HCPs is independent of drug types, i.e. if adherence to prescription guidelines is a common trait within HCP or dependent of drug type. This study focus on adherence to prescription guidelines for different types of drugs. We first investigate the clustering of adherence to prescription guidelines regarding three separate drug types: statins, agents acting on the renin-angiotensin system, and proton pump inhibitors. Then we analyze whether the clustering of behaviors within HCPs was independent of drug types, i.e. if adherence to prescription guidelines is a common trait within HCP or dependent of drug type. **Hypothesis:** That therapeutic tradition would have a general influence on prescription behavior and that adherence to guidelines regardless of drug type would be positively correlated within the HCP.
VI	**Aim:** To replicate previous analysis on a different database containing information on the physician level. This level of analysis was missing in earlier studies and we hypothesize that a part of the variance at the HCP-level should be attributed to the physician level. Therefore this study complements previous information about the relevance of different levels for understanding practice variation. **Hypothesis:** That the decentralized drug budget would result in an increased use of recommended statins and decreased variance between physicians and between HCPs and that the variation at the higher levels would to a higher degree be attributed to the HCP level than to the physician level.

Material & Methods

Lomas

This thesis is included within the research project *"Socioeconomic, geographic and ethnical differences in health and health care utilization: a longitudinal and multilevel analysis in Skåne"* that has been approved by the Regional Ethical Committee in South Sweden. The project includes the database LOMAS (Longitudinal Multilevel Analysis in Scania) that consists of unidentified information on all individuals living in Skåne, Sweden during the period 1968 to 2008. The LOMAS database has been assembled with the allowance and assistance of Statistics Sweden, The National Board of Health and Welfare (Centre for epidemiology), and Region Skåne. The personal identification number assigned to each person in Sweden was used by the Swedish authorities to link information on socioeconomic, demographic and health care variables from different registers. Once the record linkage was done the original personal identification number was encrypted to ensure the anonymity of the individuals.

One of the registers included in the LOMAS database is the Swedish Prescribed Drug Register (SPDR) that is administered by the Centre for Epidemiology at the Swedish National Board of Health and Welfare and records information on sales of prescribed pharmaceutical agents by the Swedish Corporation of Pharmacies. Aggregated statistics on drug utilization have been presented since the 1970s in Sweden. However, in order to achieve more effective utilization of drugs, the SPDR was introduced in 1998 and it was possible to analyze information at the dispensation level.[59] Since July 2005 the SPDR includes the Swedish personal identification number which allows record linkage with other health care registers at the individual level. In addition to other data, the SPDR contains the brand name and anatomical therapeutic chemical classification[60] (ATC) code for both prescribed and dispensed drugs, whether the prescription is repeated or not, and the HCP where the prescription was issued (identifiable by barcodes on the prescriptions). Information on prescribers is, however, not available.

Other registers included in the LOMAS database that are employed in this thesis are the register of the total population (RTB), the register of income and taxation

(IoT) and the Longitudinal integration database for health insurance and labor market studies (LISA). From RTB we retrieved information of the size of the population; gender, age, marital status, country of birth, and number of years in Sweden of the individuals. From IoT we retrieved disposable income at both individual and family level and any use of social allowance. From LISA we retrieved education level at both individual and family level.

Skaraborg Primary Care Database

Since the year 2000 all 24 publicly administrated HCPs in the county of Skaraborg, Sweden has shared the same computerized medical journal. From this computerized medical journal a database, Skaraborg Primary Care Database (SPCD), has been constructed in order to provide data for research and quality assessment. The SPCD forms a unique source of clinical information on the prevalence and management of diagnosed disorders. In particular, SPCD has the advantage of containing longitudinal records and detailed prescribing data. Historically an important limitation of register based studies on drug utilization in Sweden has been the lack of source information on prescribed drugs as only dispensed drugs from the pharmacies have been recorded. Moreover the SPCD includes information at the physician level and not only information at the HCP level as the SPDR does.

The computerized medical journal in Skaraborg records, besides all prescriptions for the patient, several demographical and clinical patient characteristics. This information is extracted to the research database SPCD where the HCP, the physician and the patient can be identified by a unique anonymized identification number. The validity of the information in the database has been recently audited and judged to be appropriate for research.[61]

Study design

Information and definition of the datasets included in the different studies are presented in table 2a and 2b together with registers linked, the time periods used, levels of analysis as well as inclusion criteria. For the studies (*study I, II* and the *first part of study III (IIIa*) where we used data prior to June 2005, the SPDR could not be linked with other registers.

Table 2a: Definition of datasets, registers linked and study period

Paper	Dataset-name	Registers linked for the analysis	Study period
I	I	SPDR	April 2003 to December 2003
II	IIa – public HCPs	SPDR	March 2004 to March 2006
	IIb – private HCPs		
III	IIIa	SPDR	July 2003 to June 2004
	IIIb - men	SPDR RTB IoT	July 2005 to December 2005
	IIIc - women		
IV	IVa – public HCPs - men	SPDR RTB IoT	July 2005 to December 2005
	IVb – public HCPs - women		
	IVc – private HCPs - men		
	IVd – private HCPs - women		
V	Va – C10AA	SPDR RTB IoT LISA	July 2006 to December 2006
	Vb – C09		
	Vc – A02BC		
VI	VIa - 2003	SPDR	May 2002 to October 2003
	VIb -2005		July 2004 to December 2005

SPDR: Swedish Prescribed Drug Register
RTB: the register of the total population
IoT: the register of income and taxation
LISA: the Longitudinal integration database for health insurance and labor market studies
SPDR: Skaraborg Primary Care Database

Table 2b: Inclusion criteria and definition of levels/classifications for the datasets

Dataset-name	Inclusion criteria	Levels/ Classifications
I	All initial prescriptions of statins issued at HCPs in the Skåne region	Municipalities : 33 HCPs : 226 Prescriptions : 34 514
IIa	All initial prescriptions of statins issued at public HCPs in the Skåne region	HCAs: 14 HCPs: 136 Prescriptions: 110 827
IIb	All initial prescriptions of statins issued at private HCPs in the Skåne region	HCPs: 115 Prescriptions: 72 012
IIIa	All initial prescriptions of statins issued at HCPs in the Skåne region	HCPs: 170 Time: 4 Prescriptions: 73 547
IIIb	All men in Skåne region who were issued at least one prescription for statins	HCPs: 159 Individuals: 17 695
IIIc	All women in Skåne region who were issued at least one prescription for statins	HCPs: 159 Individuals: 14 316

Dataset-name	Inclusion criteria	Levels/ Classifications
IVa	All men in Skåne region who were issued at least one prescription for statins at public HCPs	HCPs: 142 Individuals: 13 376
IVb	All women in Skåne region who were issued at least one prescription for statins at public HCPs	HCPs: 142 Individuals: 10 743
IVc	All men in Skåne region who were issued at least one prescription for statins at private HCPs	HCPs: 132 Individuals: 8 424
IVd	All women in Skåne region who were issued at least one prescription for statins at private HCPs	HCPs: 132 Individuals: 6 906
Va	All individuals in Skåne region who were issued at least one prescription for statins	HCPs: 198 Individuals: 6 232
Vb	All individuals in Skåne region who were issued at least one prescription for agents acting on the rennin-angiotensin system	HCPs: 198 Individuals: 7 222
Vc	All individuals in Skåne region who were issued at least one prescription for proton pump inhibitors	HCPs: 198 Individuals: 11 563
VIa	All patients with at least one prescription of statin. Only patients with all his/her cardiovascular drugs issued by the same physician were included.	HCPs: 24 Physicians: 425 Individuals: 6 205
VIb		HCPs: 24 Physicians: 402 Individuals: 7 979

In *study I (dataset I)* we selected all initial prescriptions of statins issued at HCPs in Skåne region during the period April to December 2003. Since, according to the Swedish reimbursement system, a prescription that covers a whole year must be dispensed in three occasions, we only considered first dispensations within the study period.

In *study II* we selected two different dataset. During the 25-month period between March 2004 and March 2006 we selected all prescriptions of statins issued by public physicians (*dataset IIa*) and all prescriptions issued by private physicians (*dataset IIb*) at HCPs in Skåne region. We only considered first dispensation within the study period. For an illustration of the hierarchical structure of the health care system in Skåne region see figure 1.

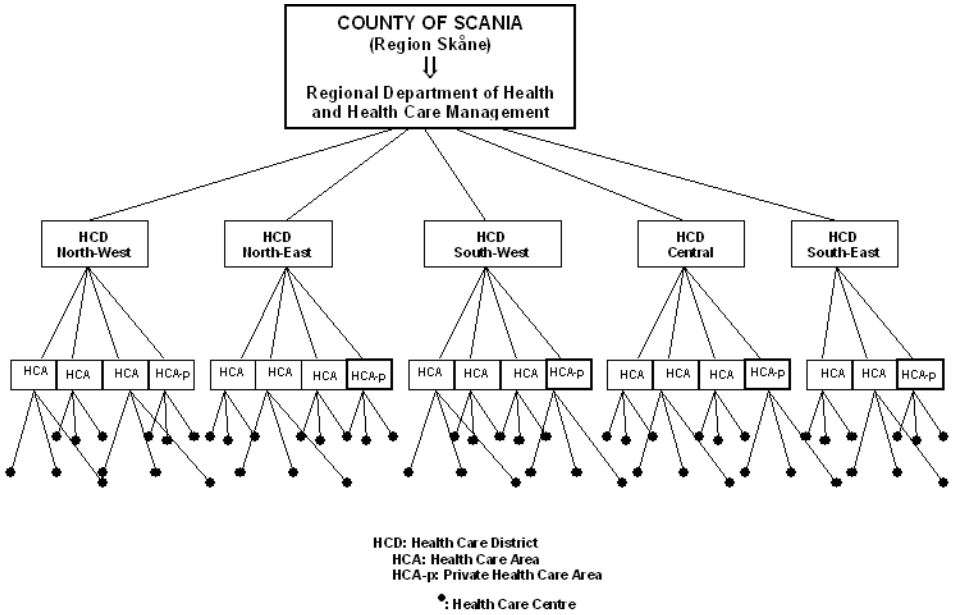


Figure 1: The health care system in Skåne region.

In *study III* we selected three different data sets. The first dataset (*dataset IIIa*) included all initial prescriptions of statins issued at HCPs in Skåne region between July 2003 and June 2004. In the second phase of study III, we included all men (*dataset IIIb*) and women (*dataset IIIc*) in Skåne region who were issued at least one prescription for statins between July and December 2005. These dataset were linked with registers including socioeconomic and demographic characteristics of the individuals.

In *study IV* we selected all patients registered in Skåne who received a statin prescription issued by a physician from one of the region's HCPs between July 2005 and December 2005. This yielded four datasets; *IVa* – men at public HCPS, *IVb* – women at public HCPs, *IVc* men at private HCPs and finally *IVd* – women at private HCPs. These dataset were linked with registers including socioeconomic and demographic characteristics of the individuals.

In *study V* we selected all patients in Skåne region who between July 2006 and December 2006 received a drug from the ATC-categories (i) statins, (ii) agents acting on the renin-angiotensin system, or (iii) proton pump inhibitors. Since there are some occasions where the patient should be prescribed non-

recommended drugs,[62] in order to diminish the risk of confounding, we excluded patients who received a drug from the same ATC-group during the 12 months preceding our study period. Moreover we excluded HCPs without prescriptions from all three ATC-groups. In total we analysed three datasets; *Va* - patients with statin prescriptions, *Vb* - patients with agents acting on the renin-angiotensin system, and *Vc* patients with proton pump inhibitors. These dataset were linked with registers that included socioeconomic and demographic characteristics of the individuals.

Finally, in *study VI* we used the Skaraborg Primary Care Database (SPCD) to identify all patients with at least one prescription of statin. Thereafter we created two datasets, patients with at least one statin prescription during May 2002 to October 2003 (*VIa*), and during July 2004 to December 2005 (*VIb*). If a patient received more than one statin prescription during each time period, the last one was selected.

Outcome variables

The main outcome in this thesis was the prescription of a recommended drug defined according the local drug committee.[63-66] Since 1997 every Swedish county (for a shorter description of the Swedish health care system, see *Definitions and explanations*) has had a drug committee in charge of promoting safe and cost-efficient drug use based on evidence-based medicine.[67-69] Members in the committees mainly include general practitioners (GPs), hospital specialists, pharmacists and clinical pharmacologists. One of their more important responsibilities is to develop guidelines or recommendations for rational drug prescription. Their aim is to recommend medications appropriate to clinical needs, in doses that meet their patients' individual requirements, for an adequate period of time and at the lowest costs to the community. (For a shorter description of guidelines and guidelines implementation, see *Definitions and explanations*).

In all studies we investigate prescription of statins and in *study V* we also analyzed proton pump inhibitors and agents acting on the rennin-angiotensin system. (For a shorter description of statins and statin use in Skåne region see *Definitions and explanations*). In the registers statins were defined according to the Anatomical Therapeutical Chemical (ATC) classification system[60] code C10AA. Agents acting on the renin-angiotensin system were defined according to the ATC-code C09 and Proton pump inhibitors according to the ATC-code A02BC.

In *study I, II, IV and VI* the outcome variable was recommended statins. In *study I* the recommended statins were Simvastatin GEA® (ATC: C10AA01) or Pravachol® (ATC: C10AA03). In *study II and IV* the recommended statin was Simvastatin, regardless of brand, but excluding the original brand ZOCORD® (ATC: C10AA01). In *study VI* the recommended statins were for dataset *VIa* Simvastatin (ATC: C10AA01) and Pravastatin (ATC: C10AA03) and for dataset *VIb* Simvastatin (ATC: C10AA01) alone.

In *study V* the outcome variable was for dataset *Va* recommended statins, i.e. Simvastatin, regardless of brand, but excluding the original brand ZOCORD® (ATC: C10AA01); for dataset *Vb* recommended agents acting on the renin-angiotensin system; i.e. any ACE inhibitor alone (ATC: C09A) or in combination (ATC: C09B) and for dataset *Vc* recommended proton pump inhibitors, i.e. Omeprazol, regardless of brand, but excluding the original brand LOSEC®, (ATC: A02BC01).

In *study III* the outcome variable was rosuvastatin (ATC: C10AA07).

Explanatory variables

Individual variables

Based on the actual evidence there is no patient characteristic that could motivate the preferential prescription of a specific statin before any other statin. This means that differences in care between patients do not originate from differences in indication.[70] Therefore, the included individual-level variables are not considered because of the need for adjustment for confounding, but rather, because we wanted to gain an understanding of the prescribing process. While these variables should not directly affect adherence to prescription guidelines, they may reflect social roles and cultural expectations which in turn might determine prescription of recommended drugs.

The different explanatory variables for each study are included in table 3. All analyses were adjusted for age of the patient. *Study I, II, IIIa, V and VI* were adjusted for gender, while *study IIIb,c and IV* were stratified by gender.

Table 3: Outcome variables, individual level variables, area level variables and statistical method used for the different studies

Dataset-name	Outcome variable	Individual level variables	Area level variables	Statistical method / measure of association / measure of variance and clustering
I	Recommended statins	Age, sex, time (months)	Health care districts, administrative status, physician density	Multilevel logistic regression / odds ratio / median odds ratio
IIa	Recommended statins	Age, sex, time (months)	Proximity to specialized care, own budget management, participation in the information campaign	Multilevel logistic regression / odds ratio / median odds ratio
IIb				
IIIa	Rosuvastatin	Age, sex	Proximity to specialized care, administrative status, rural or urban area, prescribing volume	Generalized estimation equation and Alternating logistic regression / odds ratio / pair wise odds ratio
IIIb		Age, income, marital status, immigrant status, country of birth		
IIIc				
IVa	Recommended statins	Age, income, marital status, immigrant status, country of birth, social allowance	Proximity to specialized care, percentage of high-income patients, rural or urban area	Multilevel logistic regression / prevalence ratio / intra class correlation
IVb				
IVc				
IVd				
Va	Recommended statins	Age, sex, income, marital status, immigrant status, country of birth, social allowance, education	Proximity to specialized care, administrative status	Multilevel logistic regression / odds ratio / median odds ratio
Vb	Recommended C09-drugs			
Vc	Recommended A02BC drugs			
VIa	Recommended statins	Age, sex		Multilevel logistic regression / odds ratio / median odds ratio
VIb			Occupational status, age, sex	

To establish the socioeconomic position of the patients in *study III (dataset IIIb-c), IV and V* we considered each patient's *disposable family income,* s*ocial allowance* (if any), *marital status* and *education* measured at the end of 2004. We also considered the immigrant status of the patients, as we hypothesized that this characteristic could also influence physicians' prescription behavior. *Immigrant status/ethnicity* was measured by the country of birth of the patients and the number of years that every patient had resided in Sweden. The country of birth of the patients was categorized according the World Bank Classification of Country Economies (i.e. low, lower middle, upper middle, and high income).[71] Number of years in Sweden and country of birth, according to the World Bank classification, offered an appropriate alternative for measuring immigrant status/ethnicity as this combination considers the acculturation process of immigrants having resided in Sweden for many years and focuses not on geographic but on economic criteria for classifying country of birth.

Individual socioeconomic position is traditionally measured by the income, education and occupation of a specific individual.[72] The term socioeconomic position (SEP) concerns the social and economic factors that influence the position the individual hold in the society. It is important to understand how these aspects of social stratification are linked to prescription behavior in drug utilization studies. A strong association between SEP and health and the fact that better health is more related to social advantage than with social disadvantage has been shown in several studies. The most commonly used frameworks for studying SEP is based on theories from Max Weber and Karl Marx. Marxian-based social stratification refers to structural relations between groups defined by their relationship to the means of the production. The Weberian approach suggest that the society is hierarchically stratified along many dimensions creating groups that share a common position leading to shared life chances. Individuals create their chances from their ability to benefit from their education, occupation and income.[73] Income is the SEP indicator that most directly measure material circumstances. It is not the actual possession of money that has an effect on health but rather the sense of control and perception of social advantage. For income to be comparable across individuals the measurement of income is transformed to equalized income which is adjusted for family size and reduced associated costs of living.

In *study I and II* we considered time (in months) of a prescription as a continuous variable and in *study I* it was also modeled as a quadratic function.

Area level variables

Because of the structure of the Swedish health care system physicians working at private administrated practices might have a poorer receptivity to the county council policies. From previous studies it is also known that that private care attracts more high-SEP patients than does public care,[74 75] and therefore we took the *administrative status* (private vs. public) of the HCPs into consideration. *Proximity to specialized care* and the particular type of knowledge that it conveys might influence adherence to prescription guidelines. Hence, we also identified those HCPs that employed specialist physicians other than GPs.

Simultaneously to the introduction of the decentralized budget in *study II*, an *information campaign* for supporting appropriate prescription at the HCPs was carried out through the entire observation period. Participation in this campaign was voluntary. Since the campaign could influence prescription patterns independently of any possible effect of the decentralized budget, we included a variable indicating whether the HCP participated in the information campaign or not. In the new compulsory system of decentralized pharmaceutical budget, the responsibility for the administration of the pharmaceutical budget was transferred from the regional Department of Health and Health Care Management to every of the 19 administrative HCAs. However, nine of the 14 publicly-administered HCAs decided to implement a more intense decentralization by transferring the budget responsibility to their HCPs. As this circumstance can influence prescription patterns, these HCPs were identified by a dummy variable, *own budget management.*

Several factors that could influence prescription of newly marketed drugs, such as distribution of information, marketing forces, and patient demands and expectations, may be influenced by the population density of the area. Therefore, in *study III* we considered whether the HCP was located in a *rural or an urban area*, according to the definition provided by the Swedish Association of Local Authorities and Regions. The definition is based on structural characteristics such as population size, commuting patterns and the structure of businesses in the municipality.[76]

HCPs with an elevated number of high income patients may develop therapeutic traditions conditioned by the high income of those patients, and once established these traditions could extend themselves to all patients. In *study IV* we operationalized this possibility by computing *the percentage of high-income patients* at the HCP.

In *study VI* we include information about physician characteristics because previous studies have shown that they might influence the prescription behavior.[13 48 77 78] However, information on physician characteristics was only available for the dataset *VIb*. We included *physician's occupational status* categorized as Intern (IN), Resident (RS), General practitioner (GP) or Locum (LOC). Each category was split into two groups according to the median age of the specific group. Of the eight different groups we used the category of older GPs as reference in the analysis. We also included the *sex of the physician* as a dummy variable (men vs. women) in the analyses.

Methods

As there is no actual evidence that could motivate the preferential prescription of a specific statin before any other statin it appears theoretically plausible to expect no significant variance between HCPs in the prescription of recommended statins. However, if such variance existed, the tendency of prescribing a recommended statin may be more similar among prescribers within the same HCP than among prescribers from different HCPs. This similarity (i.e. residual correlation, in statistical terms) would express itself as a clustering of prescriptions of recommended statins within HCPs and municipalities. That is, a part of the individual propensity of prescribing a recommended statin would be at the HCP. Our rationale was that this phenomenon is an expression of local therapeutic traditions and can be investigated by measures of variance and clustering in hierarchical models.

Prior to hierarchical models there were two options when analyzing data from different levels with ordinary least square regression.[37 79] One could either aggregate the data to the higher level or one could distribute characteristics of higher levels to all individuals. However aggregated analyses cannot distinguish the contextual (the difference a HCP makes) from the compositional (patients within a HCP) effect. This problem has been named the *sociologistic fallacy*.[37] Moreover, aggregating and distributing data pose further problems of interpretation of the results known as the ecological and the atomistic fallacy.[36]
The ecological fallacy[36 80]: identification of a relationship at an area level between an outcome and a contextual characteristic, and attribution of the relationship to individuals when it actually does not exist at the individual level.
The atomistic fallacy[36 80]: Identification of a relationship between an outcome and an individual characteristic, and attribution of the relationship to the contextual level, when it does not exists.

Moreover, distributing data to lower levels is associated with a statistical problem as treating individuals as if they are independent implies that the sample size is dramatically exaggerated. If the outcome varies across higher-level units then individuals cannot be considered to be independent. If the hierarchical structure is ignored too many relationships will be found significant. Violations of standard assumptions of traditional regression (the assumption of homoscedasticity) can be handled within the hierarchical model approach.[33 34]

Multilevel regression models

In order to obtain a model describing the relationship between the response variable and the independent variables as well as considering the clustering of observations within the 2nd and 3rd level units we have in *study I, II, IV, V and VI* used multilevel regression (MLRA). As the outcome variables for all studies in this thesis are dichotomous (yes/no) we have used the binomial distribution function and the logit link function for the relationship between the distribution function and the linear predictor. The regression coefficients associated with the covariates in the logit model estimates the odds ratio (OR).

In a multilevel model the effects, or coefficients, can be defined as constant if they are identical for all groups in a population and varying if the are allowed to differ between groups.[81] The varying between groups can be explained in two sections; random intercept models that represent 2nd level units that differ with respect to the average value of the outcome and random slopes models where the slope of an explanatory variable varies between groups.

The model

Consider a population of N patients. Each patient has a vector of covariates, $\mathbf{x}$, and each patient belongs to one of K clusters. The parameters corresponding to the covariates are in the vector β. It is the variation between the K cluster variables, $u_1 \ldots u_j$ (mutually independent) that are of interest. The u's are assumed to be normally distributed through which inference can be drawn.

In this thesis the outcome variable is dichotomous, which implies that each patient will have the value 1 or 0. The random intercept model (2 levels), with the logit function and with one covariate at the 1st level can be described as follows (equation 1):

$$\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \beta_0 + \beta_1 x_{ij} + u_j$$

$$u_j \sim \text{Normal}(0, \sigma_u^2)$$

The model can straightforwardly be transferred to a three level model.

The relation between an explanatory variable (X_i) and the dependent variable can differ between 2nd level units in many ways. For example, it is possible that the effect of time of the prescription after an intervention on adherence to recommended drugs is stronger within some HCP than in others. In statistical terms this is known as heterogeneity of regressions across groups. Within the multilevel framework this is modelled by random slope by expanding equation 1 to the following equation (equation 2):

$$\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \beta_0 + \beta_1 x_{ij} + u_{0j} + u_{1j} x_{ij}$$

$$u_{0j} \sim \text{Normal}(0, \sigma_{u_0}^2)$$

$$u_{1j} \sim \text{Normal}(0, \sigma_{u_1}^2)$$

With this formulation, the 2nd level variance is now a function of an individual predictor variable X_{ij}.

Variance

The evaluation of the variance is not simply of technical value; rather the variance is of substantive interest in research.[23 39-41 82-84] In multilevel linear regression (where the outcome variable is continuous) the partition of the variance is rather straightforward. The intraclass correlation (ICC) indicates how much of the total variance (($var_{1stlevel}$) + ($var_{2ndlevel}$)) "belongs" to the 2nd level, interpreted as the proportion of the variance explained by the grouping structure in the population[85] or as the degree to which individuals share common experience due to closeness in space and/or time[86]:

Intraclass correlation (ICC): $(var_{2ndlevel}) /((var_{1stlevel}) + (var_{2ndlevel}))$

Statistically the ICC is the correlation between two observations within the same unit of a hierarchical level. A three level model would have two ICCs.

ICC (observations within the same 2nd level unit):

$$((var_{2ndlevel}) + (var_{3rdlevel})) / ((var_{1stlevel}) + (var_{2ndlevel}) + (var_{3rdlevel}))$$

ICC (observations within the same 3rd level unit, but different 2nd level unit):

$$(var_{3rdlevel}) / ((var_{1stlevel}) + (var_{2ndlevel}) + (var_{3rdlevel}))$$

It is also possible to calculate an ICC to describe the similarity of 2nd level units within 3rd level units.

ICC (2nd level units within the same 3rd level unit):

$$(var_{3rdlevel}) / (var_{2ndlevel}) + (var_{3rdlevel})$$

However, in a model with dichotomous outcome the 1st level variance (unlike in the case with a continuous response variable) depends on the expected value, Var $(\Pi_{0j}) = \Pi_{0j} (1- \Pi_{0j})$ as the fixed predictor in the model depends on the outcome. The higher level variance is measured on a different scale than the 1st level variance and hence therefore not comparable.[33 34] Direct epidemiological interpretation of the higher level variance is therefore difficult.[23 87 88] One suitable alternative is calculating the median odds ratio (MOR), as proposed by Larsen and co-authors.[88] The aim of the MOR is to translate the variance in the widely used odds ratio scale, which has a consistent and intuitive interpretation. The MOR is comparable with the odds ratios of individual or area variables and is defined as the median value of the odds ratio between the area at the highest risk and the area at the lowest risk when randomly picking out two areas. In simple terms the MOR could be interpreted as the increased (median) odds of an outcome if one changes to another 2nd level unit with higher risk. In this thesis the MOR shows the extent to which the individual odds of having a recommended drug is determined by the HCP that the patient receives his/her prescription from. The MOR is statistically independent of the prevalence of the outcome and can be computed both in empty models and more complex models.

The MOR quantifies the variation between 2nd level units by comparing to patients from two randomly chosen clusters. By using the 2nd level residuals of the model we compute the odds ratio for each pair of individuals with the same covariates and with the higher odds placed in the numerator. This yields a distribution of the odds ratio (figure 2). The MOR is the median of the odds ratios.

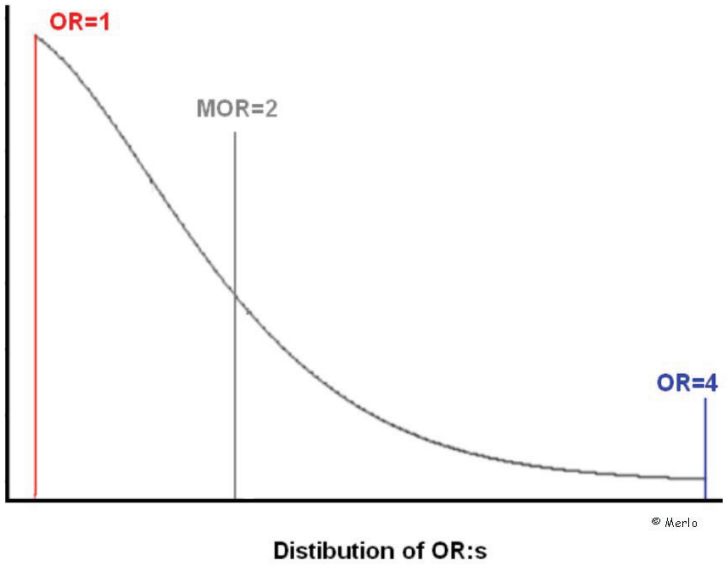


Figure 2: Distribution of odds for each pair of persons with the same covariates with the higher odds placed in the numerator. The MOR is the median of the distribution.

In figure 3 we illustrate scenarios where the MOR is high and the variation between 2nd level units is weak (top), and where the MOR is low and the variation between 2nd level units is strong (bottom).

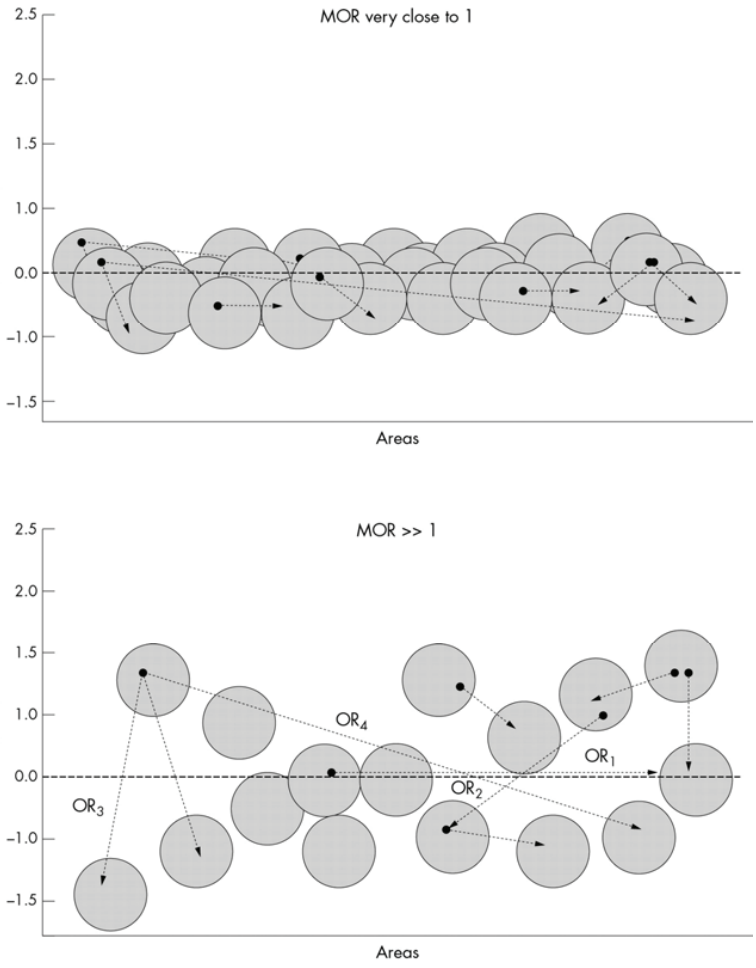


Figure 3: In the top part of the figure we present a situation with very weak variations between areas. In the bottom part of the figure, area level variations were much stronger, which will be reflected in a higher MOR. Considering the area level residuals of the multilevel model, the odds ratio between the person at lowest risk and the person at highest risk is computed for each pair of persons from different areas. Four arbitrary comparisons (R1, R2, R3, R4) are represented in the bottom part of the figure. The MOR is defined as the median value of the distribution of this odds ratio.

In practice, it is not necessary to calculate the OR between all possible pairs. The MOR depends directly on the 2nd level variance and can be computed with the following formula:

$$MOR = \exp\left[(2 \times var_{2ndlevel})^{0.5} \times 0.6745\right] \approx \exp(0.95 \times var_{2ndlevel}^{0.5})$$

where 0.6745 is the 75th percentile of the cumulative distribution function of the normal distribution with mean 0 and variance 1.
If the MOR was equal to 1, there would be no differences between 2nd level units regarding the probability of the outcome (top part of figure 3). However, if there were important 2nd level differences, the MOR would be large (bottom part of figure 3).

Other solutions have been suggested to measure the importance of the variance at higher levels in MLRA by using different methods to calculate the ICC; the simulation method, the binary linear model method, Taylor series linearization and the latent variable method. As each definition arises from different assumptions, each definition may lead to different ICC values.

Simulation: The principle of the simulation method is to translate the 2nd level variance from the logistic to the probability scale. This means that the 1st and 2nd level variances are on the same scale and the ICC can be calculated according to the formula. The consequence of using this method is that different phenomena with similar area variance, but different prevalence, will have different ICCs. Moreover, in models with covariates, the ICC will have a different value for each different type of individual since the ICC depends on the prevalence that in turn depends on the covariates. [39 89] For a given amount of area level variation, the ICC will always be the highest for outcomes with a prevalence of 50%. This aspect needs to be considered when comparing the magnitude of clustering between phenomena with a different prevalence.[89 90]

A binary linear model: This method treats the (0, 1) response as if it were a normally distributed variable. This will generally be acceptable when the probabilities involved are not extreme, but if any of the underlying probabilities are close to 0 or 1, this model would not be expected to fit well, and may predict probabilities outside the (0, 1) range. [39]

Latent variable method: This method converts the individual level variance from the probability scale to the logistic scale. It assumes that the propensity for prescribing a recommended drug (example from our studies) is a continuous latent variable underlying our binary response. Each patient has a propensity to receive a recommended drug, but only individuals whose propensity exceeds a certain limit will receive. The unobserved individual variable follows a logistic

distribution with individual variance equal to 3.29 ($\pi^2/3$). The ICC is, as a result, a function of the area level variance and does not directly depend on the prevalence of the outcome as in the simulation method. [39]

Taylor series linearization: In this approach, the non-linear function used in the multilevel logistic regression is linearized by applying a first-order Taylor series expansion. The expansion gives an approximate transformation of the values estimated from the binomial scale to the logistic scale.

Interval odds ratio and percentage of odds ratios of opposite direction

As explained previously; regression coefficients in multilevel models are adjusted for the dependence of the outcome within areas by including the area level residuals in the models. The regression coefficients for individual variables, in being adjusted for area level residuals, reflect the association between the individual level variables and the outcome within a specific area. Contrary to individual-level variables in MLRA, area variables only take one value in each area and, consequently, it is necessary to compare individuals from different 2nd level units or 3rd level units to quantify area-level associations.[87 88] Therefore we need to incorporate the 2nd level (and 3rd level) variance in the presentation of area-level associations. Consider all possible pairs of individuals with similar covariates, where one individual received his/her prescription at a private administrated HCP and the other from a public administrated HCP. For each pair taking into account the administrative definition and the residuals of these HCPs, one can compute the odds ratio between the individuals within the private HCP and the individuals within the public HCP. All possible pairs give a distribution of odds ratios. The IOR 80% (the choice of 80 % as the interval is arbitrary) is defined as the interval centered on the median of this distribution that comprises 80 % of the values of the odds ratios. The lower and upper bounds of the IOR can be computed with the following equations:

$$IOR_{lower} = \exp\left[\beta + \sqrt{(2 \times var_{2ndlevel})} \times (-1.2816)\right] \approx \exp\left(\beta - 1.81 \sqrt{var_{2ndlevel}}\right)$$

$$IOR_{upper} = \exp\left[\beta + \sqrt{(2 \times var_{2ndlevel})} \times (1.2816)\right] \approx \exp\left(\beta + 1.81 \sqrt{var_{2ndlevel}}\right)$$

where β is the regression coefficient for the 2nd level variable, and the values – 1.2816 and + 1.2816 are the 10th and 90th percentiles of the normal distribution, with mean 0 and variance 1.

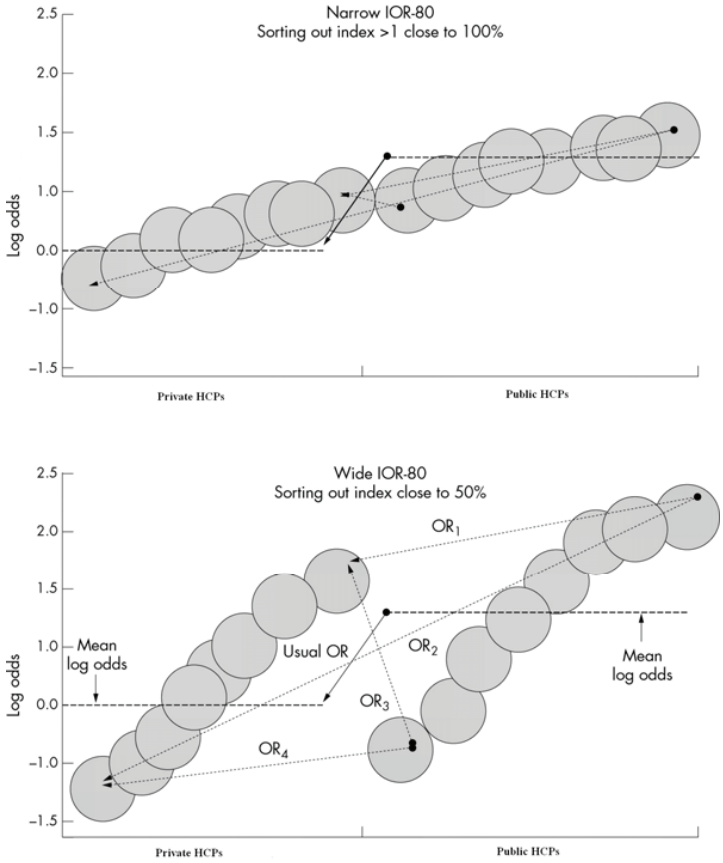


Figure 4 illustrates the rationale of the interval odds ratio (IOR). Private HCPs are grouped on the left and Public HCPs on the right. The thick dotted black lines represent the mean odds of having a recommended drug in private and public HCPs. The log odds of prescribing a recommended drug in each of the areas are function of the administrative (public/private) condition and of the area level residual, and are represented as grey circles over and above the thick dotted black lines. The common OR consists in comparing the thick dotted black lines (see the thick black arrow). By contrast, the IOR also takes into consideration the unexplained area level variation, and therefore compares one person selected from a private HCP and one person from a public HCP (dotted arrows). In the top part we present a situation in which area level residual variations are weak compared with the effect of the area educational level. Therefore, the IOR-80 is narrow. Conversely, in the bottom part, the area level variations are much stronger than the effect of the administrative condition. In that case, the likelihood is high of finding a person in a private HCP who presents higher odds of having a recommended drug than does a person in a public HCP. For this reason the IOR-80 is wide.

It should be noted that the IOR-80 is not a common confidence interval. The interval is narrow if the residual variation between different 2nd level units is small,

and wide if this variation is large. If the interval contains the value 1, this indicates that the effect of the higher-level characteristic under scrutiny is not that important when compared with the remaining residual higher-level heterogeneity. The IOR therefore complements the information provided by the normal OR.

Other solutions to incorporate the 2nd level (and 3rd level) variance in the presentation of area-level associations have been suggested.[89] Even if the overall OR for the association between an area variable and the outcome is conclusively higher or lower than one, the distribution of OR for pairwise comparison between exposed and unexposed areas could contain a considerable percentage of ORs of opposed direction. Therefore, one can calculate the percentage of ORs of opposed direction as complementary information to the overall OR of each area-level variable (when always comparing an individual with higher propensity of receiving a recommended drug from a private HCP to a person with a lower propensity from a public HCP). This measure considers the area residual variance in the calculation of the ORs of the area level variables, and indicates the extent to which the area variable under study is of importance as compared with residual area variations. If this measure is 50% the association has no relevance. ORs of opposed direction can be calculated by the following equation:

$$\Phi = (\beta_2 - \beta_1 / (2*\mathrm{var}_{2ndlevel})^{0.5})$$

If the area variable under study is a categorical variable β_1 equals zero. Φ represents the cumulative distribution function for the normal distribution with mean zero and variance one. If $(\beta_2 - \beta_1 / (2*\mathrm{var}_{2ndlevel})^{0.5})$ equals 0, Φ equals 0.5 and the percentage of Ors of opposed direction is 50 %.

Both the IOR 80% and the percentage of ORs of opposed direction can be calculated in models adjusting simultaneously for several contextual covariates. [89]

Ranking of 2nd level units

The ranking of the 2nd level units is performed by following previous recommendations for comparing performance between different health care units.[91] The 2nd level units are ranked according their posterior means (also known as "shrunken residuals") obtained from the MLRA. Each residual corresponds with the OR of adherence with guidelines of the unit, with the whole material as reference in the comparisons. Since the 2nd level units are treated as coming from a population distribution of 2nd level units, the estimation procedure can pool all the information in the data thus allowing the predictions of place-specific

relationships to be based on precision-weighted estimators, which take account of sample sizes. Imprecisely estimated, the posterior means are shrunk towards the overall mean, while reliably estimated, posterior means are largely immune to this shrinkage. Thereby MLRA have the potential to avoid the misestimating problems caused by small numbers and sampling fluctuations in traditional methods based on single-level regressions. There are substantial differences between crude aggregated rates and the MLRA predictions of performance based on residual variation in a null model even though it takes no account of individual composition. These differences arise because of the shrinkage procedure with rates for practices with unreliably small target numbers being shrunk towards the overall performance. Studies have shown that especially when health risk is low and areas are small, random noise can mislead researchers into producing spurious area variability that may appear as significant in standard statistical analyses.[92]

The simple formula for the shrinkage factor is:

$$SF = var_{2ndlevel\ /}\ (var_{2ndlevel} + (var_{1stlevel} / N_n))$$

where N_n is the number of 1st level units within the 2nd level unit. The area shrunken residual is calculated by multiplying SF with the raw area residual. Since the ICC is a function of the first and second level variance the SF formula can be rewritten as:

$$SF = 1 / (1 + (1/ N_n) * ((1/ICC) - 1))$$

This indicate that when N_n and/or ICC getting smaller the shrunken residual will shrink more towards the mean 0. In a dataset with sufficiently large N_n and ICC, the results from multilevel analysis should approach those from single-level analysis.[93]

However, there is no simple formula for shrinkage for either more complex normal models or for MLRA. The simple example given above does however motivate how these shrinkages work so that in a logistic regression the degree of shrinkage will depend on the number of individuals in the cluster and the 2nd level variance.

Estimation procedure

For study I, II, V, and VI we used the MLwiN software.[94] For discrete response multilevel models, maximum likelihood estimation is computationally intensive,

and therefore quasi-likelihood methods are implemented in MLwiN. These procedures use a linearisation method, based on a Taylor series expansion, which transforms a discrete response model to a continuous response model. After applying the linearisation, the model is then estimated using iterative generalised least squares (IGLS) or reweighted IGLS (RIGLS) [33] In study I we used this estimation procedure. For study II, V, VI we used the Markov chain Monte Carlo method (MCMC) using the Metropolis-Hastings algorithm.[95] This method consists of running a chain in which values of the different parameters are simulated until convergence. The MCMC method is a Bayesian approach to the subject of estimation opposite to the more usual frequentist approach. In the Bayesian approach one combines prior beliefs/ideas with the data collected to produce new posterior beliefs/ideas about the problem. Often little is known about the parameters prior to the data collection, and so default prior distributions are required that express this lack of knowledge. Starting point for the Bayesian computation can be adapted from the classical point estimates from the quasilikelihood estimation.[81] After fitting the model, a distribution is produced for the parameters that combine the prior information with the data, and this distribution is known as the posterior distribution. The MCMC methods make a large number of simulated random draws from the posterior distribution of all parameters in the model, and use this information to form a summary of the underlying distribution. The advantages of the MCMC method is that you can calculate the full posterior distribution, which is often leading to more accurate small-sample inferences than those just based on estimates ± 1.96 SE, and the possibility to incorporate prior information.[95]

Simulation studies have shown that the use of quasi-likelihood methods might produce underestimated results, even for reasonable sample sizes and prevalence. The drawback with MCMC is that it requires extended computational time for convergence. [96]

The Deviance Information Criterion (DIC) was used as a measure for model fit. A lower value of the DIC indicates a better fit for the model. The DIC diagnostic is a combination of fit measured by the deviance and complexity measured by pD (the effective number of parameters). The interest in comparing models is in the difference in DIC.[95 97]

Prevalence ratios

When the prevalence of an outcome of interest is rare in the study population (<10%), the odds ratio and the prevalence ratio are equivalent. However as the

prevalence increase the differences between the odds ratio and the prevalence ratio increases.[98-100] Therefore, in study IV we calculated the prevalence ratio (PR) instead of the odds ratio. For this study we estimated the parameters in the WinBugs software[101], and stored the results from each random draw (5000 random draws) from the posterior distribution. For each draw, we calculated, for parameters of interest, the prevalence ratio by dividing the predicted probability for the individuals with the characteristic studied by the predicted probability of the individual without the characteristic studied. This gave us a distribution of prevalence ratios and from this distribution we calculated the median and corresponding 95 % credible interval (95 % CI).

Alternating Logistic Regression and the Pair Wise Odds Ratio

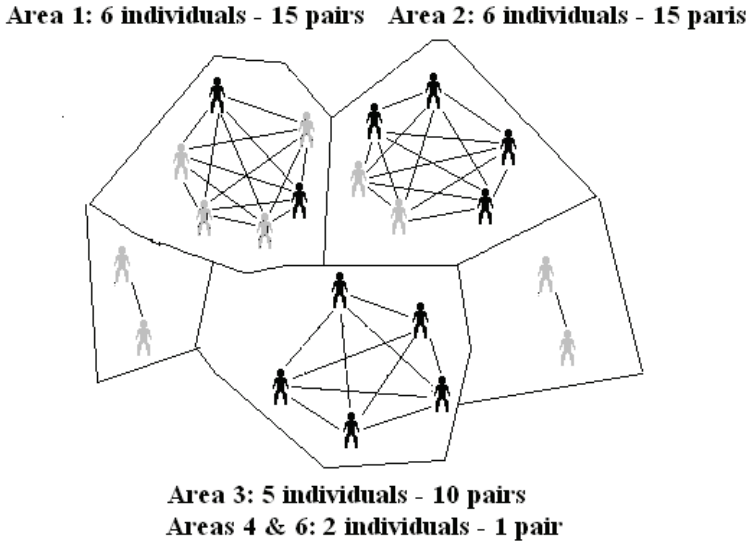
The ALR model accounts for the dependence of the outcome within different levels/categories and thereby allows accurate statistical estimations. Also, the ALR methodology allowed us to quantify the clustering of similar outcome within 2nd level units with an index in the form of an odds ratio, the PWOR.[35] Only a few studies have employed ALR and PWOR when measuring contextual effects within the epidemiological framework. [42 102-111] In *study III* we used the ALR-PWOR approach.

In order to compute PWORs, the model considers all the pairs involving two prescriptions from the same HCP. Using *p11* to denote the probability that both prescriptions in a pair are the measured outcome, *p00* to denote the probability that none of the prescriptions in a pair are the measured outcome, and *p10* and *p01* to denote the probabilities that only one of the prescriptions in a pair is the measured outcome, the PWOR can be calculated as:

$$\mathrm{PWOR} = \frac{p_{00} \times p_{11}}{p_{10} \times p_{01}}$$

The PWOR reflects the increase in the odds of a prescription having the studied outcome given that another prescription randomly selected from the same HCP also has the studied outcome. The PWOR is equal to 1 in the absence of clustering. If the PWOR is larger than one this indicates that the studied outcome within the same HCP is more frequent than what could be expected if prescriptions are distributed randomly across HCPs.

The pairwise odds ratio is calculated as follows. For simplicity we consider only 5 areas, see figure 4. Black individuals represent individuals with recommended drug while grey individuals represent individuals with non-recommended drugs.



Distribution of the 42 pair of individuals: Pairwise odds ratio = 2			
	Individual # 1		
Individual # 2		Recommended drug	Non recommended drug
	Recommended drug	P_{11} = 16 pairs	P_{11} = 8 pairs
	Non recommended drug	P_{11} = 8 pairs	P_{11} = 8 pairs

Figure 4: Top - Black individuals represent individuals with recommended drug while grey individuals represent individuals with non-recommended drugs. The PWOR is calculated as shown in the table.

This can easily be expanded to individuals with the same characteristics or individuals within the same type of areas.

Practically, PWORs are calculated from the ALR model, which simultaneously estimates the following two equations:

$$\log(PWOR_{kl}) = \alpha Z_{kl}$$

$$\text{logit}(p_k) = \beta_0$$

The first equation expresses the logarithm of PWORs as a function of a dummy variable *Z*, which simply indicates whether two patients (or two prescriptions) *k* and *l* in a pair belong to the same category or not (the variable *Z* is equal to 0, and the PWOR to 1, for prescriptions from different HCPs). The ALR model simultaneously estimates a logistic regression by a GEE for the outcome (the second equation): in this equation, p_k refers to the expected probability of prescribing rosuvastatin for the patient *k*.

By quantifying the context dependence of the studied outcome, PWORs can be used as measure of therapeutic traditions. A higher PWOR indicates a stronger effect of therapeutic traditions.

The calculations can be made using the GENMOD procedure in SAS software, version 9.1 (SAS Institute, Cary, NC, USA), to fit the ALR models.

Model building and Proportional change of variance

We follow previous recommendations for model building;[34] (I) an empty model with no explanatory variables in order to separate the variance into different levels, (II) a model including individual covariates in order to understand the individual characteristics influence on the variance and (III) a model including both individual and contextual characteristics in order to understand the individual and contextual influence on the variance.

In the analyses we made some exceptions from the established procedure: *In study I and II* we also included the variable *time* in model A in order to be able to investigate variance at different time periods. We also allowed the regression coefficients of the variables *time* and *sex* to be random at the HCP level (i.e. random slope analysis) in the models in order to investigate whether these individual-level associations varied between different HCPs. In the presence of slope variance, the HCP variance becomes a function of the individual variables.[112] In *study V* we, in order to investigate if the random effects were correlated across

drug types used the HCP residuals from model A and classified them into three categories ("residualgroup"). Thereafter, on each separate drug type we used an interaction of the variable residualgroup between the two other drug types in order to investigate if the adherence to guidelines were dependent of the other drug types. The interaction provided us with 6 different groups (lowest tertile in both groups (1), (reference group), lowest tertile in one group and middle tertile in the other (2), lowest tertile in one group and highest tertile in the other (3), middle tertile in both groups (4), middle tertile in one group and highest tertile in the other (5), highest tertile in both groups (6). Finally, in an extended model (model D), we added the variable residualgroup as a contextual variable.

In *study VI* we considered two empty models, with and without the physician level in order to study the effect the inclusion of the physician level had on the variance at the HCP level.

Applying an established procedure, we also used the variance/PWOR obtained in the empty model as reference ($Var_{reference}$) to calculate the percentage of change in the magnitude of clustering, which was explained by including individual or contextual characteristics in the model with more variables (Var_{more}).

$$\text{Percentage change in variance} = ((Var_{reference} - Var_{more})/(Var_{reference})) \times 100$$

$$\text{Percentage change inPWOR} = ((PWOR_{reference} - PWOR_{more})/(PWOR_{reference}-1)) \times 100$$

We used this percentage for estimating the relevance of patient characteristics (i.e. the patient composition of the HCPs) as well as the relevance of contextual characteristics of the HCPs when understanding a possible clustering of similar behaviour.

Results

Measures of variance and clustering

In *study I* (table 4) the overall prevalence of recommended statins was 20 % and the MOR_{HCP} was 1.96 at the beginning of the study period. However, we found a significant slope variance in the association between prescription of recommended statins and both time and sex, and therefore the HCP variance became a function of these variables. The variance and the MOR decreased over time, but were still high at the end of the study period. For *study I* the PCV indicates that 75% of the differences between municipalities were explained by the individual and contextual characteristics included in model C. However, this percentage was only 3% in relation to variance between HCPs.

In *study II* (table 4) the overall prevalence of guideline adherence was 62% in the public sector and 50% in the private, with a clear increasing trend during the whole study period. In the first month, 48% of the public and 39% of the private HCPs prescribed recommended statins, and this percentage increased to 74% in the public and 62% in the private sector by the end of the study period. These trends were similar in all five health care districts, but adherence was always lowest in the southwest district, and highest in the northeast and southeast districts.

In model A the MOR_{HCA_HCP} in the public sector was 2.28 indicating that a physician's median odds of prescribing a recommended statin would approximately double if this physician moved to an HCP in an HCA with greater adherence to guidelines. However, when decomposing the MOR in specific levels, the propensity of prescribing recommended statins presented a higher degree of clustering at the HCP level than at the HCA level (MOR_{HCP} = 2.18 vs. MOR_{HCA} = 1.31). The MOR_{HCP} in the private sector was 3.47, indicating an even stronger clustering among private HCPs.

There was an increasing temporal trend in prescription of recommended statins. However, this trend differed between HCPs. Because of this slope variance, the MOR_{HCP} became a function of time indicating that even if the MOR_{HCP} decreased throughout the study period, the final variation was still high (MOR_{HCP} = 1.86 in

the public sector and 2.73 in the private). The analysis of the PCV indicates that 50% of the differences between HCAs were explained by the individual and contextual characteristics included in model C. In relation to variance between HCPs, this percentage was only 8% in the public sector and 0% in the private. The ranking of the HCPs and HCAs regarding the prevalence of prescription of recommended statins in each area relative to the overall prevalence in the county at the beginning of the shows that the differences between HCAs disappeared after adjustment, but although many HCPs changed position in the ranking, the HCP dispersion around the mean was not reduced after adjustments.

Table 4: Prevalence and measures of clustering and variance from the different studies

Dataset-name	Prevalence	MOR/PWOR/ ICC – 3rd level	MOR/PWOR/ ICC – 2nd level	PCV – 3rd level*	PCV – 2nd level*
I	20 %	1.41	1.96	75 %	3 %
IIa	62 %	1.31	2.18	50 %	8 %
IIb	50 %	-	3.47		0 %
IIIa	2 %	3.56 (1.95–6.51)		42 %	
IIIb	1.2 %	-	2.99 (1.63–5.49)		37 %
IIIc	1.1 %	-	2.58 (1.79–3.73)		33 %
IVa	79 %	0.7 %	0.9 %	17 %	8 %
IVb	79 %	0.6 %	1.2 %	25 %	+ 7 %
IVc	65 %	-	10.4 %		3 %
IVd	65 %	-	9.3 %		+ 3 %
Va	94 %	-	2.71 (2.23-3.39)		40 %
Vb	72 %	-	4.72 (3.90-5.92)		38 %
Vc	88 %	-	2.16 (1.95-2.45)		29 %
VIa	77 %	1.41	1.39	0 %	0 %
VIb	84 %	1.12	1.22	2 %	0 %

* Compares full model with empty model
MOR: Median odds ratio
PWOR: Pairwise odds ratio
ICC: Intraclass correlation
PCV: Proportional change of variance

In *study III* , *dataset IIIa* (table 4), for the period July 2003 to June 2004, there was a decreasing trend in the prevalence of rosuvastatin prescriptions ranging from 2.6% (410/16,073) in the first trimester to 1.5% (283/18,273) in the last. Model A shows that during the first trimester of the observation period, rosuvastatin prescriptions co-occurred within certain HCPs more frequently than one would expect if prescriptions were distributed randomly, i.e. PWOR = 3.56 (95% CI 1.95–6.51), and the clustering continued to be high in the following

trimesters. The between-time clustering was also high, indicating that those HCPs with a higher level of rosuvastatin prescription during one trimester were also more likely to prescribe rosuvastatin in the other trimesters. When including the contextual variables (model C) the PWOR was reduced by approximately 40% in the first and second trimesters but only by 9% in the third trimester.

For *dataset IIIb-c* the clustering of rosuvastatin prescriptions at the HCP level was high for both men (PWOR = 2.99) and women (PWOR = 2.58). Adjustment for the patient characteristics studied attenuated the magnitude of clustering to a small extent. However, the inclusion of contextual variables decreased the magnitude of clustering by approximately 20%.

For *study IV* (table 4) adherence to guidelines was systematically lower among private HCPs (65 % vs 79 %). Moreover, model A shows that the ICC_{HCP} value for men in the private sector was 10.4 %, which indicate that factors varying between HCPs to a high degree influence the prescription of recommended statins. However, factors at the HCP/HCA level seemed to be less relevant in the public sector, illustrated by a lower ICC. Even though the higher levels seemed to be less relevant the HCP level seemed to be more important than the HCA level. This pattern was similar for women. The ICC for different income groups in model C was approximately 1 % in the public sector and it varied between 7- 9 % in the private sector.

When individual and contextual variables were included, the higher level variance decreased for men by 2% within privately-administered HCPs and 8 % within publicly-administered. For women there seemed to be an increase in variance in model C compared to model A.

In *study V* (table 4) adherence to guidelines was 88 % for proton pump inhibitors (A02BC), 72 % for agents acting on the renin-angiotensin system (C09) and 94 % for statins (C10AA). The adherence at the HCPs ranged for A02BC from 10-100% (25^{th} %: 82 %; 75^{th} %: 94 %), for C09 from 0-100 % (25^{th} %: 46 %; 75^{th} %: 88 %) and for C10AA from 0-100 % (25^{th} %: 90 %; 75^{th} %: 100 %). For model A there was high clustering of similar behavior at HCPs for the different drug types (MOR_{C09} = 4.72 (3.90-5.92), MOR_{C10AA} = 2.71 (2.23-3.39) and MOR_{A02BC} = 2.16 (1.95-2.45)). These results were attenuated only to a small degree when individual characteristics were included in model B. However, when contextual factors were included in model C the clustering was considerably reduced; approximately 30 % for C09 and C10AA and 11 % for A02BC. In

model D the variance decreased, compared to model A, by approximately 40 % for C09 and C10AA and 29 % for A02BC.

In *study VI* (table 4) the overall prevalence of adherence with guidelines for prescription of statins had increased from 77 % in 2003 (*dataset VIa*) to 84 % in 2005 (*dataset VIb*). Model A indicates that $MOR_{HCP2003}$ = 1.41 and $MOR_{HCP2005}$ = 1.15. In model B, when the physician level is included, the $MOR_{HCP2003\text{- }PHYSICIAN2003}$ = 1.61 indicating the existence of inefficient therapeutic traditions acting at the higher levels. The HCP and physician levels accounts for approximately 50 % each of the variation at the higher levels in 2003 ($MOR_{HCP2003}$ = 1.41 vs. $MOR_{PHYSICIAN2003}$ = 1.39). For dataset 2005 the $MOR_{HCP2005\text{-}PHYSICIAN2005}$ = 1.25 indicating that the differences between physicians and HCPs have decreased. In fact, the decrease in variance for HCPs and physicians between the two periods are 89% respectively 65%. The $MOR_{PHYSICIAN2005}$ seems to be higher than the $MOR_{HCP2005}$ but the results are not conclusive.

The PCV shows that the inclusion of individual and contextual variables did not explain the variance at the HCP level or the physician level. The DIC diagnostics shows that ignoring a level (model A) worsens the model fit for both dataset 2003 and 2005 and that Model C (2003) and Model D (2005) have the best model fit.

Individual level variables

For *study I and II* (table 5) there was a significant temporal trend in prescription of recommended statins. However, many specific HCP temporal trends differed from the overall trend in the county, illustrated by the random slopes model.

In *study I, II, and V* (table 5) men had a lower probability than women of being prescribed a recommended statin. However, for the other studies we found no conclusive differences between men and women regarding the prescription of recommended statins.

In *study I, II and VI* (table 5) older age increased the probability of being prescribed a recommended statin, and in *study III* decreased the probability of being prescribed rosuvastatin, though by a very low degree. Compared with the youngest age group in *study IV*, men over 70 had higher odds of being prescribed a recommended statin. However, women aged 70-79 treated at private practices had lower probability of receiving a recommended statin. Regarding *study V*; for C09 older patients had a higher probability than younger of receiving recommended drugs, but for A02BC it was the opposite.

Table 5a: Measures of association for individual covariates for study I and II, odds ratios and 95 % confidence intervals

	Dataset I	Dataset IIa	Dataset IIb
Time	1.25 (1.20–1.31)	1.05 (1.04–1.05)	1.05 (1.04–1.07)
Time^2	0.98 (0.98–0.99)	-	1.00 (1.00–1.00)
Age (one year increase)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Sex (male vs women)	0.89 (0.82–0.95)	0.93 (0.88–0.99)	0.92 (0.85–0.99)

Table 5b: Measures of association for individual covariates for study III, odds ratios and 95 % confidence intervals (selected associations are included)

	Dataset IIIa	Dataset IIIb	Dataset IIIc
Age (one year increase)	0.96 (0.94–0.97)	0.94 (0.92–0.95)	0.96 (0.95–0.98)
Income			
Low	-	Reference	Reference
Middle low	-	1.22 (0.67–2.22)	1.00 (0.58–1.73)
Middle high	-	1.35 (0.87–2.10)	1.66 (0.93–2.95)
High	-	1.74 (1.07–2.85)	1.58 (0.91–2.72)

Table 5c: Measures of association for individual covariates for study IV, prevalence ratios and 95 % credible intervals (selected associations are included)

	Dataset IVa	Dataset IVb	Dataset IVc	Dataset IVd
Income				
Low	1.10 (0.95–1.28)	1.11 (0.93–1.31)	1.18 (1.02–1.35)	1.11 (0.95–1.29)
Middle low	1.07 (0.92–1.25)	1.13 (0.96–1.33)	1.19 (1.04–1.36)	1.15 (1.00–1.34)
Middle high	1.12 (0.96–1.30)	1.07 (0.91–1.25)	1.07 (0.95–1.20)	1.05 (0.92–1.20)
High	Reference	Reference	Reference	Reference

Table 5d: Measures of association for individual covariates for study V, odds ratios and 95 % credible intervals selected associations are included)

	Dataset Va	Dataset Vb	Dataset Vc
Age (one year increase)		1.01 (1.00-1.02)	
Sex (male vs women)	0.73 (0.58-0.92)		
Income			
Low	1.07 (0.77-1.50)	1.23 (1.02-1.49)	1.32 (1.12-1.57
Middle low	1.14 (0.83-1.57)	1.27 (1.06-1.51)	1.20 (1.01-1.41)
Middle high	0.96 (0.72-1.28)	1.17 (0.99-1.38)	1.11 (0.94-1.30)
High	Reference	Reference	Reference

Table 5e: Measures of association for individual covariates for study VI, odds ratios and 95 % confidence intervals (selected associations are included)

	Dataset VIa	Dataset VIb
Sex (male vs women)	1.01 (0.88-1.14)	1.07 (0.95-1.22)
Age groups		
1 (-54 years)	Reference	Reference
2 (55-64 years)	1.05 (0.84-1.29)	0.96 (0.78-1.17)
3 (65-74 years)	1.32 (1.08-1.62)	1.07 (0.88-1.30)
4 75- years)	1.51 (1.20-1.89)	1.09 (0.87-1.35)

Regarding the socioeconomic variables (table 5) we found that for *study III* individuals in the highest income quartile had higher odds of being prescribed rosuvastatin than individuals in the lowest income quartile. In *study IV* we saw that for men with high income and cohabitation were both associated with a lower adherence to guidelines. Moreover, in *study V* we found that compared with low income patients those with high income presented a lower probability of being prescribed a recommended drug, except for C10AA were we found no conclusive differences.

Area level variables

For studies not stratified on administrative condition (*study I, III, V*) we found that the probability of prescribing rosuvastatin or non recommended drugs was higher in private than in public HCPs, expect in study I (table 6). For the studies stratified on administrative condition (*study II and IV)* this was also confirmed by the higher adherence to guidelines among public HCPs. Moreover, the inclusion of this variable (administrative condition) seemed to explain part of the clustering at the HCP level, even though the clustering was still high after the inclusion. Furthermore, in *study III* we illustrate that private HCPs seem to have adopted rosuvastatin faster than public HCPs and a Cox regression model showed that private HCPs had a 1.82 (95% CI 1.16–2.84) times higher hazard of adopting rosuvastatin than public HCPs. In addition, at the end of the observation period almost 70% of private HCPs had given at least one prescription of rosuvastatin compared with only 45% of public HCPs.

Table 6a: Measures of association for contextual covariates for study I and II, odds ratios and 95 % confidence intervals (selected covariates included)

	Dataset I	Dataset IIa	Dataset IIb
Public v. private HCC	1.01 (0.86–1.18)	-	-
IOR-80	0.28–3.63	-	-
Physician density (rate)	-	-	-
1st tertile	2.66 (1.16–6.06)	-	-
IOR-80	0.74–9.53	-	-
2nd tertile	Reference	-	-
3rd tertile	2.36 (1.34–4.16)	-	-
IOR-80	0.66–8.47	-	-
Specialist physician vs GP	-	1.41 (1.18- 2.01)	0.97 (0.66- 1.31)
% opposed ORs	-	38 %	49 %

Table 6b: Measures of association for contextual covariates for study III, odds ratios and 95 % confidence intervals (selected associations are included in the table)

	Dataset IIIa	Dataset IIIb	Dataset IIIc
Private v. public	4.31 (1.93–9.62)	3.41 (1.95–5.95)	3.09 (1.58–6.05)
Specialist physician vs GP	0.97 (0.58–1.62)	1.62 (0.88–3.00)	1.19 (0.62–2.29)

Table 6c: Measures of association for contextual covariates for study IV, prevalence ratios and 95 % credible intervals (selected associations are included in the table)

	Dataset IVa	Dataset IVb	Dataset IVc	Dataset IVd
% of high-income patients				
T1	1.06 (0.99–1.17)	1.02 (0.97–1.09)	0.92 (0.81–1.05)	1.00 (0.89–1.16)
T2	1.10 (1.02–1.22)	1.03 (0.99–1.13)	0.96 (0.85–1.06)	0.97 (0.86–1.07)
T3	Reference	Reference	Reference	Reference

Table 6d: Measures of association for contextual covariates for study V, odds ratios and 95 % credible intervals (selected associations are included)

	Dataset Va	Dataset Vb	Dataset Vc
Private v. public	2.76 (1.85-4.37)	3.86 (2.63-5.53)	1.18 (0.86-1.54)
Residualgroup1	Reference	Reference	Reference
Residualgroup2	1.42 (0.77-2.46)	2.10 (1.13-4.18)	2.38 (1.59-3.48)
Residualgroup3	2.57 (1.19-5.36)	2.47 (1.24-5.13)	2.06 (1.36-3.15)
Residualgroup4	1.66 (0.80-3.30)	2.85 (1.37-6.27)	1.79 (1.08-2.89)
Residualgroup5	1.98 (1.00-3.73)	5.97 (3.01-12.24)	3.02 (2.04-4.41)
Residualgroup6	2.24 (1.08-4.49)	3.53 (1.67-8.32)	3.17 (1.95-5.07)

Table 6e: Measures of association for contextual covariates for study VI, odds ratios and 95 % confidence intervals (selected associations are included)

	Dataset VIa	Dataset VIb
Young Intern	1.67 (0.85-3.46)	1.67 (0.78-3.43)
Old Intern	0.86 (0.48-1.57)	0.85 (0.48-1.58)
Young Resident	0.90 (0.62-1.33)	0.91 (0.62-1.32)
Old Resident	0.81 (0.55-1.19)	0.80 (0.55-1.18)
Young GP	0.87 (0.69-1.09)	0.87 (0.69-1.10)
Old GP	Reference	Reference
Young Locum	0.75 (0.51-1.11)	0.75 (0.51-1.11)
Old Locum	0.56 (0.38-0.82)	0.56 (0.38-0.82)

Other included HCP variables explained only a very small part of the variance at the HCP level and the associations were seldom conclusive. Moreover, the IOR was often very wide or the percentage of ORs of opposite direction was close to 50 % indicating that those variables were not important for explaining the variation among HCPs.

However in *study II* among the public HCPs, prescriptions of recommended statins were more frequently issued at HCPs with specialist physicians other than GPs, but no such association was observed for private HCPs. In *study IV* there was no clear association between adherence to prescription guidelines and the percentage of high-income patients at the HCP, except for men treated at public HCPs where a lower percentage of such patients were associated with higher adherence to guidelines. Moreover, in *study V* model D shows that higher adherence to the other drug types is associated with a higher adherence to guidelines for all drug types. This effect was strongest for drug type C09 and weakest for C10AA.

Moreover, in *study I*, physician density, a municipality characteristic, appeared to play a role in improving adherence, but this association was U-shaped, with the lowest probability in the second tertile group. The IOR-80 was relatively wide but this actually suggests that this variable may have some relevance for the implementation of prescription guidelines.

Discussion

General discussion

In this thesis we present a model of analysis for investigating practice variation where we focus on the combined analysis of measures of association and measures of variance and clustering. We investigate therapeutic traditions in general and adherence to prescription guidelines and adoption of new drugs in particular. (For a conceptual framework for pharmacoepidemiological studies see *Definitions and explanations*).Therapeutic traditions correspond to the idea that cultural aspects at the practice level might exert a collective influence on prescribers working within the same practice, and this can be expressed by the fact that the prescription behavior among physicians within the same practice may be more similar than the prescription behavior among physicians from different practices. In our studies we found that adherence to guidelines for statin prescription and the early adoption of a new statin seemed to be conditioned by contextual factors particularly at the HCP level. Additionally, we observed that physicians from the same HCPs showed a similar propensity to both prescribe recommended statins and adopt a new statin compared to physicians from other practices. These results suggest that, to some degree, the determinants of the individual behavior have directly to do with the contextual environment of the practice. Moreover, HCPs that follow guidelines for one drug type also appear to follow guidelines for other drug types, i.e., therapeutic traditions, acting at the HCP level, seems to influence the prescribing behavior of individual physicians independently of specific drug type.

We mainly focus on statins since they have the same indication and only marginal differences in efficacy and they are therefore an illustrative group of pharmacological agents for measuring inappropriate practice variation. While adherence to guidelines in general is a well-developed research topic,[67 113-115] our analytical approach of focusing on both changes in variance and changes in prevalence is actually an innovative way of investigating practice variation in pharmacoepidemiology. [6 10 116 117] However, this approach has been previously implemented in other research fields.[40 41 44 81 96 118] Since very few studies have tried to understand the relative importance of the different levels on the process of prescription, this thesis may eventually lead to a better understanding of the

relationship between HCP- and individual level characteristics with respect to the prescription process. In turn, this may facilitate for decision makers to focus interventions on the right factors at the right levels. By investigating the role of different health care levels on adherence to guidelines, researchers can more efficiently build and test models that capture factors influencing the prescription process. In addition, we provide a methodological description of multilevel regression models and generalized estimation equations and the alternating logistic regression, and the application of these methods when focusing on measures of association and measures of variance and clustering.

Quantifying practice variation has been frequently used in order to assess quality in health care.[32] In this thesis we quantify practice variation with the median odds ratio, the intra-class correlation and the pair wise odds ratio. By using these measures we found, for example, that after the introduction of the decentralized drug budget the prevalence of recommended statins increased and the variation between practices decreased. Just an increase in prevalence of recommended drugs does not necessarily imply better care since the increase in prevalence could depend on a few physicians/HCPs with a very high prevalence. The desired outcome is obviously not only to increase adherence with guidelines but also to eliminate unnecessary practice variation. By including variance measures as well, we can obtain information if the interventions had an effect on all physicians/HCPs.

In the series of reports, from the National board of Health and Welfare, that compares healthcare quality in the Swedish county councils, the method for comparing different national performance indicators is mainly based on rankings (league tables) of crude aggregated rates between hospitals.[32] By using the posterior means (see Methods) instead of crude aggregated rates, as we do in this thesis, where the 2nd level units are treated as coming from a population distribution of 2nd level units, the MLRA has the potential to avoid the misestimating problems caused by small numbers and sampling fluctuations in traditional methods based on single-level regressions. Nevertheless, several studies have emphasized the uncertainty of these league tables.[91 119] But in combination with an overall measure (MOR, ICC) of the importance of the higher health care levels (e.g., HCPs) it might provide a more comprehensive understanding of the differences between HCPs and thereby a more accurate measure of healthcare quality. This combination might facilitate for decision makers to determine whether the variability is due to chance or is in fact detected. Moreover, this approach can be applied to other procedures as well, and can thereby facilitate our understanding whether certain procedures are more variable than others.

In this thesis we also investigate the role that social and economic conditions at different levels of analysis play for understanding the process of prescription. We illustrate that a physician's decision to prescribe recommended drugs is conditioned, beside the therapeutic traditions acting at the HCP-level, by the socioeconomic (e.g. income, marital status) and demographic (e.g. age) characteristics of the patient. This situation cannot be justified by any medical argument, but may rather reflect the influence of constructed social roles and cultural expectations.

Contextual effects

In all studies the empty model (i.e., the model with no explanatory variables) illustrates that factors related to the HCP level played a relevant role in understating individual prescription of recommended statins and the early adoption of a new statin. In study V were we included agents acting on the renin angiotensin system and proton pump inhibitors, we also observed that factors related to the HCP played a relevant role for understanding the prescription of recommended drugs within these drug types. Since we only included new users in this study, there are no compositional factors that could motivate the preferential prescription of a recommended drug within the group of agents acting on the renin angiotensin system before any other drug within the same group. However, for proton pump inhibitors there could actually be some compositional factors that could motivate a prescription of a non recommended drug which would suggest that the clustering we see for this drug could partly be explained by patient characteristics.

Moreover, it seemed like the third level, whether it was municipality or HCA, played a minor role in the process of prescription. Although, in study VI, where we included information at the physician level, it seemed like the physician level and HCP level had similar relevance. Moreover, adjustment for the patient characteristics studied attenuated the magnitude of clustering only to a small extent, but the inclusion of the area level variable defining administrative status (private vs. public HCP) seemed to decrease the magnitude of clustering to a higher degree.

In *study I*, adherence to recommended statins increased and the variation decreased along the study period (March-December 2003), which suggested that in some way the publication of the official prescription guidelines in January

2003, had a positive influence on statin prescription. However, at the end of the observation period adherence was still low and practice variation high. These results suggest that by some means the publication of the official prescription guidelines reduced the initial practice variation, from MOR ≈ 2 in April to MOR ≈1.5 in September 2003. Thereafter practice variation increased slightly but never reached the heterogeneity observed at the beginning of the observation period. These facts may reflect inefficient therapeutic traditions, and suggest that more intensive interventions may be necessary to promote adherence to prescription guidelines.

In *study II* we evaluated the effect of a decentralized pharmaceutical budget, implemented in January 2004, which intended to promote adherence with prescription guidelines. According to our results, this intervention appeared to considerably improve adherence to guidelines for statin prescription and, promoted efficient pharmacological treatment. In this study we performed separate analyses for publicly and privately administrated HCPs, since we believed that the administrative background could modify the effect of these interventions. However, even though guideline compliance was systematically lower among private facilities, compliance in both the public and the private sector increased progressively from the implementation of the decentralized budget through the observation period. Our results suggest that adherence to guidelines seemed to be conditioned by contextual factors, especially at the HCP levels. Based on the MOR measure, we observed that physicians from the same HCP exhibited a similar propensity to prescribe simvastatin. The variation between public HCAs was very low and could partly be explained by contextual characteristics. Contrarily, the variation between both public and private HCPs was high and remained unexplained throughout the whole observation period.

Study III showed that early adoption of rosuvastatin was highly clustered at certain HCPs, and that this clustering remained considerably high across the whole observation period (July 2003 – Dec 2004). Therefore, this study also suggests the existence of strong therapeutic traditions that, at the HCP level, influence prescribing behavior of individual physicians. However, even if contextual characteristic appeared to be relevant for understanding physicians' motivation to adopt rosuvastatin, it could not completely explain the observed variance in rosuvastatin prescription. In fact, those HCPs that prescribed one prescription of rosuvastatin were almost four times more likely to prescribe one more prescription during the same trimester, and almost three times more likely to prescribe rosuvastatin during the following trimester. This observation suggests

that local therapeutic traditions remain over time, and that prescription of rosuvastatin was not an occasional early phenomenon.

It is important to consider that the context, i.e. the HCP where the physicians worked, seems to have affected both early adoption and the subsequent prescription of rosuvastatin. When analyzing trends in rosuvastatin prescription it is relevant to realize that this drug was subject of safety concerns[120-122] during the observation period. These warnings possibly influenced the patterns of drug utilization, as evidenced by an overall reduction in the prevalence of rosuvastatin prescriptions in the last trimester of observation. However, the clustering of rosuvastatin prescriptions was not substantially affected. Earlier studies also suggest that a high volume of prescribing at an HCP may affect physicians' adoption of new drugs since the likelihood of seeing a patient as a candidate for the new drug would be higher.[123] But, there are no specific indications that should make one patient more suitable than another for receiving a rosuvastatin prescription, and, in fact, the present analysis shows no association between rosuvastatin prescription and prescription volume at the HCP. Previous studies have also shown that medical innovations are more likely to be adopted earlier in urban areas than in rural areas.[123] However, in this study we did not find support for this association.

Adopting a new drug could be appropriate for the health of the patient and cost-effective for the community, but in some cases newly marketed drugs only bring a marginal or insignificant contribution to the conventional therapeutic arsenal. In addition, prescribing decision are made with uncertainty about the risks.[124] Previous studies have shown considerable variation between prescribers regarding early adoption of newly marketed drugs, and this variation has been suggested to reflect differences in information and attitudes among prescribers.[124-133] Early adopters of a new drug have in studies been classified, despite their risk taking attitude, as opinion leaders that influence other prescribers.[134 135] However, no study have found a risk taking group of physicians across different drug types.[127] Research on determinants of early adoption of new drugs is still scarce, and an increased understanding of the mechanisms leading to physicians' early adoption of new drugs is, therefore, highly relevant for promoting evidenced-based prescribing.

Study IV also suggests the existence of different therapeutic traditions, acting at the HCP level, which influences the prescription behavior of individual physicians. Based on the MOR measure we observed that physicians from the same HCP exhibited a similar propensity to prescribe recommended statins.

Moreover, private HCPs had both higher clustering of similar behavior and systematically lower adherence to guidelines, and this pattern remained after the inclusion of individual and contextual characteristics.
In *study V* we show that therapeutic traditions, acting at the HCP level, influence the prescribing behavior of individual physicians for all three studied drug types: statins (ATC: C10AA), agents acting on the renin-angiotensin system (ATC: C09), and proton pump inhibitors (ATC: A02BC). Moreover, the therapeutic traditions seemed to be a general trait of HCPs that affects all kinds of prescriptions independent of drug type. HCPs that follow guidelines for one drug type appear also to follow guidelines for other drug types. Still, regarding therapeutic traditions or practice styles, previous studies have shown contradictory results. While Landon et al[136] found no evidence of a consistent practice style (eg, "aggressive" or "conservative") for 5 different clinical scenarios, O'Neill et al[14] found evidence of physician practice patterns that persist across multiple clinical scenarios which implies that this subject needs further investigation.

In *study VI* we demonstrate that transferring the economical responsibility from the central health care authorities at the County Council to the local HCPs considerably improved adherence to statin prescription guidelines among prescribers. Not only did we observe an increase in the overall prevalence of use of recommended statins from 77 % in 2003 to 84 % in 2005, we also observed that the variance among both HCPs and physicians decreased considerably by 89% and 65% respectively. These results fully agree with the results from *study II*. The current analysis improves the information obtained in *study II* since we had access to physician level information. This information confirmed previous observations on the relevance of the physician level for understanding practice variation, and realize that the physician and the HCP levels shared in 2003 about one half of the variance each.[116] However, in 2005 – after the decentralized budget – the residual variance became almost negligible. Yet, most of the (small) residual variance seemed to be across physicians. This is also illustrated by the fact that none of the HCP and only a few physicians conclusively differed from the overall mean adherence in 2005.

In our study, in 2003, the contextual variance was rather large and approximately equal distributed among HCPs and physicians, indicating the any intervention aimed to improve adherence with guidelines should be focused on both levels simultaneously. In fact the decentralized budget was such an intervention, and it appeared to effectively decrease the variance at both levels. In 2005 the higher level variance was very small which suggests that any further intervention directed to HCPs or physicians would render less effective. In 2005 we observed that older

locum physician had a lower adherence to prescription guidelines than older GPs, which may reflect intrinsic characteristics of this personal category. Locum physicians share the common work environment and the same constraints as other physicians at the HCP but only for a limited period of time and therefore might be less affected by the therapeutic traditions acting at the HCP. However, in spite of the conclusive association between this physician category and low adherence to guidelines, an intervention focusing on locums will possible not be very efficient since the residual variance (and the corresponding MOR) was negligible and inclusion of the physician characteristics did not contribute to the explanation of the variance.

As explained above, factors related to the HCP level seemed to play a relevant role in understating individual prescription of the specific outcomes in each study. However, even though the inclusion of some of the area level variables was associated to adherence to guidelines, only the inclusion of administrative status (private vs. public HCP) seemed to decrease the magnitude of clustering. We also observed for all studies that private HCPs prescribed non-recommended drugs and rosuvastatin to a higher degree than public HCPs.

For other included area level variables we found that for example HCPs with a low percentage of high-income patients tended to prescribe the recommended statins more often than HCPs with an overall higher level of patient income. A similar contextual phenomenon was observed between health care districts; the southwest district displayed a much lower adherence to guidelines than all other districts in the county. These variables did not decrease the magnitude of clustering, and a complementary analysis also show that percentage of OR of opposite direction is close to 50 % (see Methods), strengthening the interpretation that these variables are not important for understanding the clustering of similar behavior.

Framework for studying contextual effects

During the latter years several conceptual framework for investigating contextual effects has been developed (see for example Diez-Roux[137] and O´Campo[138]). The conceptual framework used in this thesis is developed by Merlo.[139] This framework stresses four important parts (I) the appropriate boundaries conditioning contextual effects, (II) their specific characteristics, (III) the mechanisms through which these characteristics operate, and finally (IV) how life-course exposure to different environments affects individual risk. Even though this framework focuses on cardiovascular diseases it can straightforwardly be

applied to pharmacoepidemiology and the investigation of practice variation and specifically contextual determinants of prescription.

Regarding the first step in the framework; i.e. the relevant context, this is rather straightforward in health care utilization research, as health care practices or hospitals are natural boundaries. However, still it is of key importance to consider different levels of analysis in order to attribute the variation to the correct level. In this thesis we have used different levels of the health care organization (physician, HCP, HCA, municipality) as boundaries for the higher level units. Moreover, by using measures of clustering and variance, it was possible to assess the scale on which contextual influences operate. The approach of "components of health variation" is relevant for both examine determinants of prescription and for planning interventions, especially when it comes to deciding on what scale interventions should be directed.

For the second step in the framework; i.e. the specific characteristics of the higher level units, there are two main ways of measuring a variable at the higher levels. One can either aggregate individual-level data and aggregate to give average characteristics of the group (collective or derived variables), or one can directly measure properties of the group (contextual or integral variable).[140] However, it has also been suggested that there are two additional types of higher level characteristics, structural and environmental. The structural variables refer to the social interaction between members of the group while the environmental variables refer to physical or chemical exposure to the group.[36] In health care utilization research this is also relatively straightforward as the higher level characteristics are to a high degree pre-determined; organization form, type of unit (specialist physicians /general practitioners), location and size. In this thesis we have investigated several different contextual variables that could be of relevance for adherence to guidelines (see table 3). Moreover, in study IV we have included a derived variable (share of high income patients).

For the third step in the framework, i.e., to investigate the associations and the mechanism through which the contextual effects operate on the individual, it is possible to conceptualize four ways (figure 5); (a) by directly affecting the outcome, e.g., direct cross level effect, (b) by modifying the relationship between an individual covariates and the outcome, e.g., cross level effect modification, (c) by affecting the individual covariate which in turn affects the outcome, e.g., indirect cross level effect, and (d) by examine whether the higher level environment as a whole (N) modifies the association between individual variables.[141] These different approaches has been investigated in previous studies[141]

but in this thesis we have mainly focused on (d). In multilevel models this is modeled by the random slopes approach. For example in study I and II where we have allowed the regression coefficients of the variables time and sex to be random at the HCP level. This gave us the possibility to investigate whether these individual-level associations varied between different HCPs. In the presence of slope variance, the HCP variance becomes a function of the individual variables.

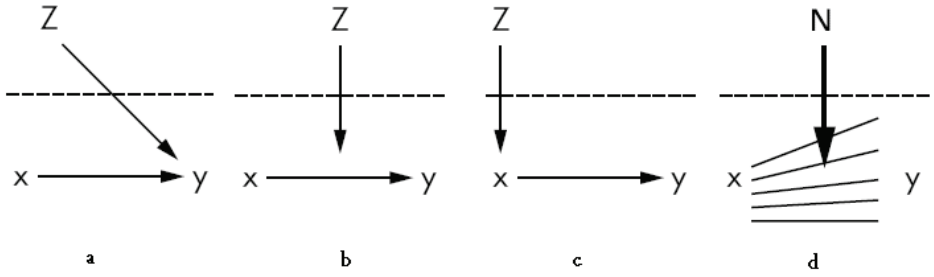


Figure 5: Different ways to conceptualize the associations and the mechanism through which the contextual effects operate on the individual. In this figure Z is a higher level variable, x is an individual level variable, and y is the individual level outcome.

Few studies investigating practice variation have recognized the importance of modeling clustering and variance components and have mainly been focused on measures association, such as odds ratios or prevalence ratios between some practice variable and the outcome under investigation. This thesis emphasizes that without knowledge of the 2nd level random effects (measures of clustering and variance), the fixed-effect parameters (associations) at the 2nd level become "decontextualized".[23 40 44 45 142 143 144] However, as previously discussed;[23 45 141] there is no direct correspondence between the amount of variance at a given level and the extent to which explanatory variables are associated with the studied outcome. In fact a relatively small 2nd level variance may correspond to relatively large standardized mean differences.[23 141 143 145] In examining associations it is sufficient that the 2nd level units show enough contrast of exposure for the contextual variable. The variance can be considered as a local (spatial and temporal) phenomenon while the associations are not temporal and spatial restricted.[83 140 142] By neglecting the variation within 2nd level units may also lead to erroneous conclusions and inefficient interventions.[23 45 141] Therefore it is relevant to understand how both measures of association and measures of variance are influenced by individual and area level variables in the model. By following the

previously explained procedure of model building facilitates this understanding. The first step is an empty model with no explanatory variables in order to separate the variance into different levels, the second step is a model including individual covariates in order to understand the individual characteristics influence on the variance and finally the third step which is a model including both individual and contextual characteristics in order to understand the individual and contextual influence on the variance. A low 2nd level variance in the empty model, suggests that there are small differences in the outcome between 2nd level units. In contrast a high 2nd level variance in the empty model implies that there are large differences between second level units. If the 2nd variance is reduced in the second step (when individual characteristics is included in the model), we can conclude that the included individual characteristics explain the differences between 2nd level units and the variation was due to compositional confounding rather than a contextual effect only.

If a 2nd level characteristic gives rise to a high odds ratio we can conclude that the association between the 2nd level characteristic and the outcome is strong. However, if the 2nd level variance in the empty model was originally low, there are small differences between the 2nd level units and an intervention based on the included 2nd level characteristic will most likely be inefficient. In contrast, if the 2nd level variance was high in the empty model and remains high after including the 2nd level characteristic, this 2nd level characteristic is not that important for explaining differences between 2nd level units, even though the odds ratio is high and the association is strong. In this case an intervention based on the included 2nd level characteristic will most likely be inefficient. Finally if the 2nd level variance is high in the empty model, and decreases when the 2nd level characteristic is included we have an argument to consider an intervention based on this second level characteristic that will have higher potential to be efficient. Figure 6 illustrates the different scenarios. This is, however, a simplified figure, though there could actually occur situations when low clustering and low variance in the empty model increase when individual characteristics are included.

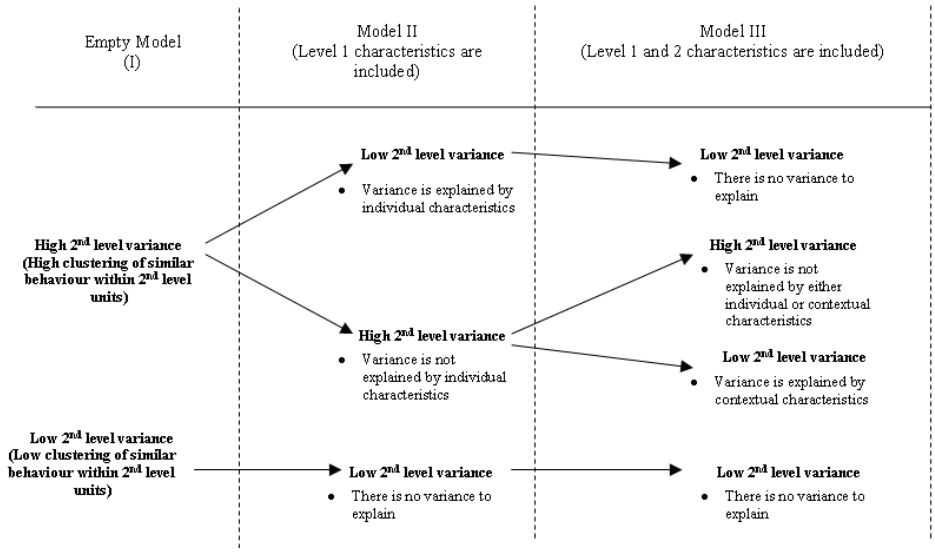


Figure 6 illustrates a simplified figure of the model building for multilevel models and the possible explanations for the 2nd level variance

As an example, imagine two different studies of adherence to guidelines among Health Care Practices (HCPs) in county A and in county B. While the prevalence in county A and B are similar, the empty model shows that the variance (differences) among HCPs is high in county A and low in county B. This implies that if an intervention is supposed to be launched in order to increase adherence to guidelines, specific HCPs might be useful targets in county A while in county B a similar intervention would be less efficient as the differences between HCPs are small. In this example we observe that when including patient characteristics the variances remain the same, so the variance is not confounded by compositional bias. In both studies we also observe that large HCPs are associated with higher adherence to guidelines (same odds ratio in both studies), and the variance among HCPs in county A decreases. This indicates that an effective intervention in county A should focus on large HCPs. We can also imagine a situation where county A *and* county B had high variance in the empty model, but the inclusion of the variable "large vs. small HCP" (same odds ratio) only decreases the variance in county A. This implies that there are other unmeasured contextual characteristics that explain the variance among HCPs in county B and an intervention should be focused only on large HCPs in county A. This example illustrates the reasoning surrounding a multilevel analysis of practice variation, as

it not only focuses on measures of association but also includes measures of variance.

One of the central empirical questions concerning contextual effects is whether the higher-level variations remains significant when a range of appropriate and relevant individual variables are included in the model to allow for the patient composition of particular administrative areas, i.e., the problem for researchers is how to measure the independent effect of workplaces and hospitals.[146] One of the main problem proposed, is the difficulty in fully accounting for unmeasured characteristics related to the sorting of individuals into different context, and that two individuals from two different areas are not exchangeable even after controlling for individual variables.[147] Furthermore, when there is limited data within every cell of the analysis there could be an increased risk of extrapolation.[147] However, these concerns are general for all observational epidemiology, but can to some extent be compensated by appropriate analyses and epidemiological reasoning.[148]

Individual variables

Based on the actual evidence there is no patient characteristic that could motivate the preferential prescription of a non recommended statin before any other recommended statin. Therefore the individual-level variables in the analysis are included, not because of the need for adjustment for confounding, but rather because we wanted to gain an understanding of the prescribing process.

In *study I and II* our empirical analysis found that men were prescribed more statins than women, but women had a slightly higher probability than men of being prescribed the cheaper, recommended, statins. As men have a higher prevalence of ischemic heart disease and are therefore expected to be more represented among statin users. But the gender differences in the prescription of simvastatin did not seem rational and might instead be a reflection a social constructs.

Study III also reveals the existence of inequity in health care as rosuvastatin was prescribed more frequently to younger patients and to those with a high SES than to elderly patients or to those with a low income.

Moreover, in *study IV* we illustrated that the physician's decision to prescribe a recommended statin is conditioned by the socioeconomic (e.g. income, marital status) and demographic (e.g. age) characteristics of the patient. For example, men

with a lower income were prescribed the cheaper recommended statins to a higher degree than men with a high income. Similarly, older men were prescribed the recommended statins less frequently than younger patients with the same need. This socioeconomic and demographic inequity was similar among private and public HCPs, even though private HCPs generally had a lower adherence to guidelines. Interestingly, among men but not among women, low income and living alone were associated with a higher prescription of recommended statins. Moreover, older women had a lower adherence than younger women, while the situation was the reverse among men, though these results were not conclusive.

Furthermore, *study V* also demonstrates the existence of inequity in health care as socioeconomic and demographic factors conditioned the prescription of recommended drugs for the included drug types. For example, it was more common to prescribe more expensive, non-recommended drugs to patients from higher income groups.

These situations cannot be justified by any medical argument, but may rather reflect the influence of constructed social roles and cultural expectations.[46] On the one hand, the prescription of a more expensive brand may reveal a different approach to a specific therapeutic problem that could result from differences in information and knowledge. However, it could also express the belief that more expensive drugs are better than cheaper ones, or could be used for the purpose of displaying income or wealth where this display serves as an instrument of attaining or maintaining social status.[149] This is based on the theory of Thorstein Veblen concerning conspicuous consumption and stating that specialized consumption of goods as an evidence of pecuniary strength and the conversely, the failure to consume becomes a mark of inferiority and demerit. Following this theory the consumption of more expensive goods has also served as the norm to which consumption has tended to conform.

From the perspective of equity in health care, this thesis brings into question physicians´ choice of more expensive, but not more efficient, brands for some groups of patients, given that a large part of this medication expenditure is funded by the public reimbursement system. One rationale for this behavior might be that sociological forces influence physicians' prescription decisions over and above evidence-based knowledge.[47 48 77 78] Patients of higher SEP may be more aware and have better communication skills, making it easier to express their demands and expectations and to be more involved in the treatment decision.[150] This discriminatory prescription pattern cannot lead to any harm for the patient, since all statins have a similar efficacy. However, we believe that our results are , to

some degree, applicable to other medical treatments in primary health care. In some contexts, lack of access to recommended treatments could have more severe consequences for the individual. Prescription of non-recommended drugs is also an inappropriate behavior from a cost-effectiveness perspective. It is inappropriate that high-income patients are prescribed more expensive brands that are no more effective than the cheaper recommended ones. This behavior, perhaps occurring in other primary health medical treatments as well, reduces overall available economic resources that could be used in other areas of the health care sector.

This thesis points out that sociological forces should be considered from a perspective of equity in access to health care in general and when trying to implement prescription guidelines in routine care in particular.

Methods

MLRA and ALR have been successfully employed in a number of previous epidemiological studies, and appear to be a useful epidemiological tool for investigating and quantifying medical practice variation.[6 10 42 103 104 106-111 116 117 151]

In order to truly investigate variation, studies must use reliable methods that are able to detect variability when it exists. These methods must also perform robustly when there are differences in prevalence of the outcome, and when level 2 units vary in size.

Regarding the methods used in this thesis, both methods provide analogue, but not identical, information. While the ALR approach provides information on the magnitude of clustering of similar behavior within different 2nd level units, the MLRA approach measures the heterogeneity between 2nd level units. In MLRA the effect of 2nd level units is modeled as being random, and the objective is to draw conclusions about the population from which the observed units were drawn rather than about these particular units, and valid inferences require correct specification of the distribution of the random effects and the link function. The ALR, however, requires only a correct specification of the link function. Figure 8 illustrates the distribution of the random effects from study III when modeled with the MLRA approach. It shows that the random effects are not normally distributed and therefore inferences based on the assumption of normality, i.e., the median odds ratio, will not be correct. Therefore, in this study we applied the ALR methodology.

Moreover, the fixed effects are interpreted differently for MLRA and ALR. As the ALR model simultaneously estimates a marginal mean model for the fixed parameters they have to be interpreted as population average, i.e the effect of the covariate *x* averaging over clusters. In the MLRA model the interpretation is cluster specific, i.e. the effect of a covariate *x* for a given cluster[87].

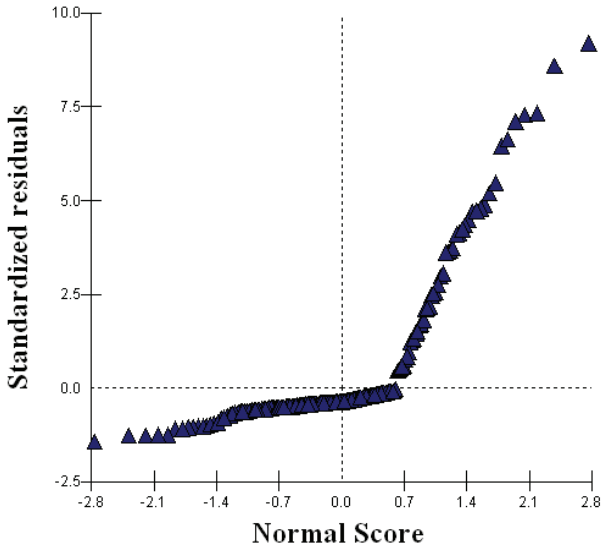


Figure 8: Standardized residuals for study III plotted against normal scores in order to check model assumptions. One such assumption is that the residuals at each level follow Normal distributions. This assumption may be checked using a Normal probability plot, in which the ranked residuals are plotted against corresponding points on a Normal distribution curve. If the Normality assumption is valid, the points on a Normal plot should lie approximately on a straight line.

Measures of variance and clustering

If the main focus is to disentangle the importance of different levels on the studied outcome the ICC obtained from the variance components in the MLRA can give valuable information. However, the ICC has some disadvantages in multilevel logistic models and the interpretations have to be done carefully.[39 90 152 153] Studies have shown that the value of the ICC may vary substantially by calculation method (see methods part for the different ICCs).[90] There are no clear criteria for choosing between the methods. However, it is recommended that a calculation using the different methods should be carried out, and if concordance

is achieved, then one can have more confidence in the results.[94] ICCs computed by the latent-variable method are easy to interpret if the response is derived from a truncation of underlying continuous response.[90] However, prescription of a recommended statin is truly discrete and the interpretations of the ICC calculated from the latent variable method must be done carefully. Analyzing the binary response as a continuous variable (linear model) is especially vulnerable to extreme outcomes.[90 152] The simulation method provides some advantages as it does not involve any approximations, and the results can then be considered as a rather reliable estimate of the ICCs.[39 90 152]

When the researcher is more interested in general information about clustering the MOR/PWOR might be a more suitable approach. But, even if the MOR and PWOR increase as the higher levels becomes more important, the comparison with the importance of the 1st level is not possible. As the MOR is restricted by the assumption of normally distributed second level residuals, as well as the problem of estimating the 2nd level variance among a population of for example socioeconomic groups, the PWOR is a valuable alternative.

In order to compare and evaluate the MOR with the PWOR and the ICC we conducted a simulation study where we with simulated datasets contrasted the MOR-value, the ICC and the PWOR-value for different scenarios. In the simulation approach, following an established procedure[154], we focused on models with no explanatory variables. Since the variance in MLRA and the PWOR in the ALR are not dependent on the prevalence we simulated different scenarios with different cluster sizes and different variances. All simulations were performed in the software packages MLwiN, SAS, and R. We set following conditions for our simulation study: (I) the number of 2nd level units was set to 200 and 30 (II) the number of 1st level units in each 2nd level unit was set to have a normal distribution with mean 30 standard deviation 0 and 40 (III) a supplementary model was included with 15 2nd level units and 500 1st level units (IV) the variances of the random intercept was set to 0.01, 0.1, 0.2, 0.5, 1, 1.5 and 2. To generate the outcome, a Bernoulli distribution was used. The overall prevalence of the outcome was set to 50 %. For practical purposes we generated 1000 data sets for each combination. The SAS procedure NLMIXED with default options was used for estimation of the MLRA. This procedure only allow for maximum likelihood estimation. If convergence was not achieved the estimated parameters were not included in the calculated summary statistics. Distributions for random effects were normal. The SAS procedure GENMOD with default options was used for estimation of the ALR model. The dependency model was specified with

the exchangeable settings, that assumes a common pairwise log-odds ratio for all clusters. We calculate the 5th, 50th and 95th percentiles from the simulations.

Figure 9 show the results from the simulation studies. In general the MOR is approximately 25-30 % higher than the PWOR. For models with small sample size (30 2nd level units and 30 1st level units) the NLMIXED procedure had problems converging (almost 70 % of the models did not converge). The PWOR-estimation produces larger intervals for smaller unbalanced samples than the MOR-estimation. While the different simulation scenarios create rather similar estimates for each method, the intervals are smaller when the number of 2nd level units is high and the number of 1st level units is low compared to when the number of 2nd level units is low and the number of 1st level units is high. Moreover, equal number of 1st level units within the 2nd levels units produces smaller intervals than unbalanced number of 1st level units within the 2nd level units.

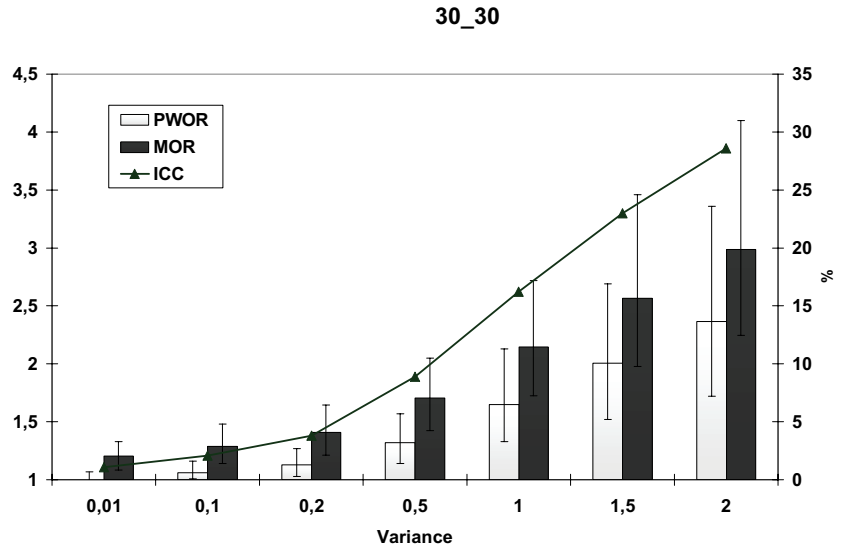


Figure 9a

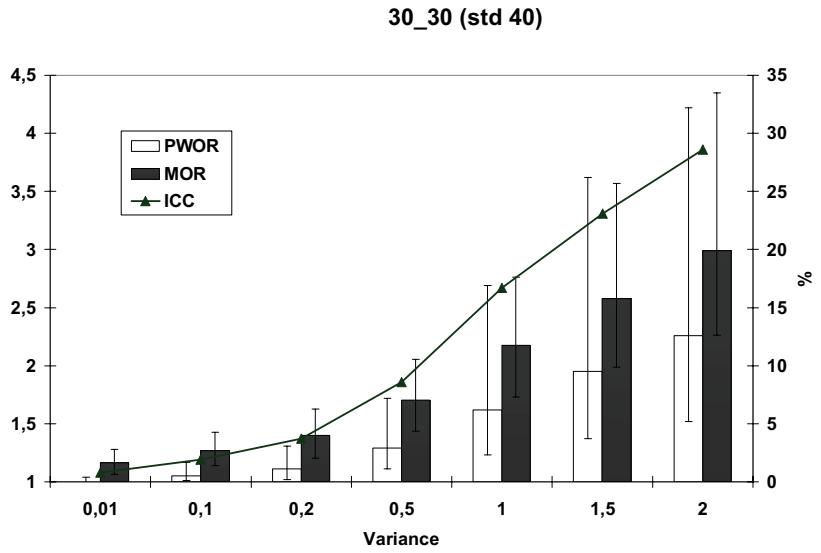


Figure 9b

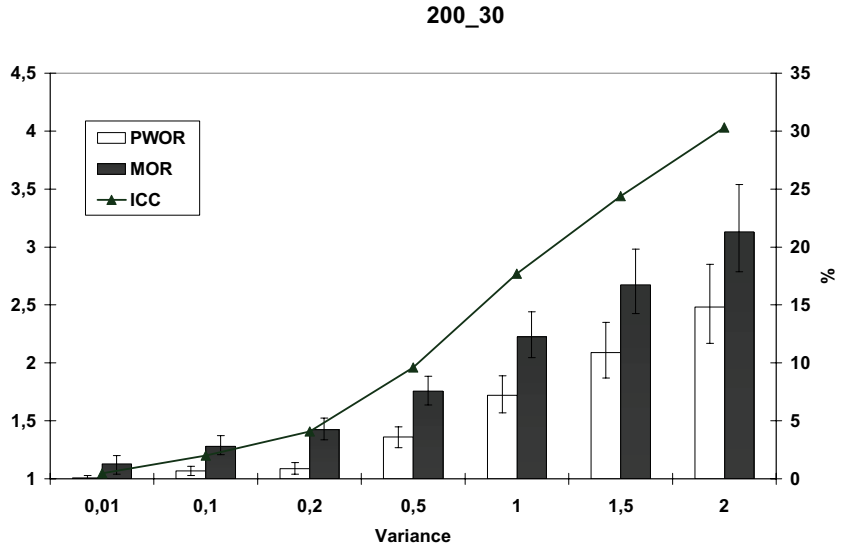


Figure 9c

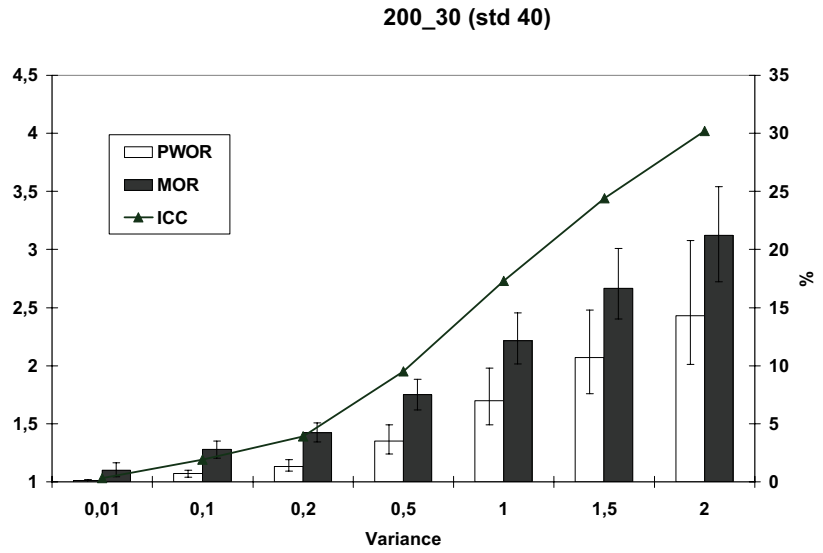


Figure 9d

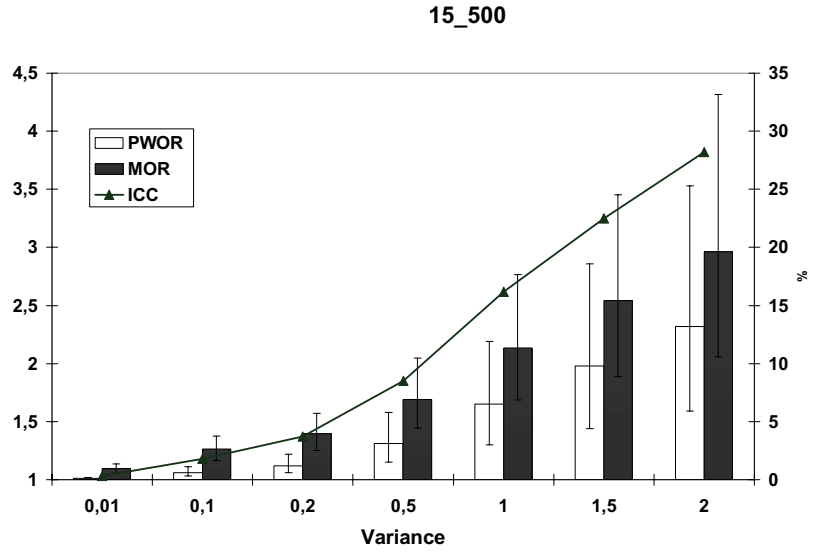


Figure 9e

Figure 9: The figures illustrate the results from the simulation study. The MOR (black) and the PWOR (white) are measured on the left Y-axis. The line represents the ICC and is measured on the right Y-axis. The black lines within each pile represent the 5th and 95th percentile. The X-axis represents the variance for the simulations.
9a shows scenarios with 30 level 2 units with 30 level 1 units in each level 2 units. 9b figure shows scenarios with 30 level 2 units, but the number of level 1 units in each level 2 unit has a normal distribution with mean 30 and standard deviation 40.
9c and 9d represents 200 level 2 units with 30 level 1 units in each level 2 unit (9c) and 200 level 2 units and 30 level 1 units with a standard deviation of 40 (9d).
9e represents scenarios with 15 level 2 units with 500 level units in each level 2 unit.

In table 7 the contextual effects are presented for the first 5 studies (13 datasets) included in this thesis. All models have been, for simplicity, reconstructed as two-level models with prescriptions (individuals) nested within HCPs.

Table 7 Different measures of the importance of the 2nd level

Dataset	2nd level variance	Median Odds ratio	ICC Simulation	ICC Binary method	ICC latent variable	Pairwise odds ratio
I	0.28 (0.22-0.37)	1.66 (1.56-1.79)	4.4 %	4.3 %	7.8 %	1.21 (1.15-1.27)
IIa	0.53 (0.42-0.69)	2.00 (1.86-2.21)	10.8 %	9.5 %	13.9 %	1.29 (1.18-1.41)
IIb	1.18 (0.88-1.59)	2.82 (2.45-3.33)	20.1 %	16.0 %	26.4 %	1.65 (1.27-2.14)
IIIa	3.49 (2.46-5.13)	5.94 (4.46-8.68)	12.9 %	9.5 %	51.5 %	2.60 (1.97–3.44)
IIIb	1.98 (1.26-3.14)	3.83 (2.92-5.42)	5.0 %	0 %	37.6 %	2.99 (1.63–5.49)
IIIc	1.37 (0.82-2.43)	3.05 (2.37-4.42)	2.6 %	0 %	29.3 %	2.58 (1.79–3.73)
IVa	0.31 (0.20-0.49)	1.70 (1.53-1.95)	2.4 %	4.2 %	8.4 %	1.17 (1.05-1.31)
IVb	0.75 (0.56-1.04)	2.28 (2.04-2.65)	10.4 %	12.8 %	18.9 %	1.62 (1.31-2.00)
IVc	0.36 (0.24-0.64)	1.77 (1.60-2.14)	3.1 %	4.8 %	8.9 %	1.19 (1.09-1.29)
IVd	0.70 (0.52-0.97)	2.22 (1.99-2.53)	9.3 %	13.2 %	17.6 %	1.85 (1.38-2.48)
Va	1.09 (0.71-1.64)	2.71 (2.23-3.39)	8.7 %	11.3 %	24.9 %	1.85 (1.23-2.76)
Vb	2.65 (2.04-3.48)	4.72 (3.91-5.93)	31.9 %	31.4 %	44.6 %	2.29 (1.74-3.02)
Vc	0.65 (0.49-0.88)	1.95 (1.56-2.45)	7.8 %	9,8 %	16.5 %	1.52 (1.24-1.87)

The table includes the 2nd level variance estimated in a multilevel logistic regression. From the variance at the 2nd level the MOR has been calculated, as well as the different ICC obtained by the binary linear method, the simulation method

and the latent variable method. In addition, the PWOR have been calculated from the ALR.

If we want to quantify the contextual effect by measuring the heterogeneity among 2nd level units we find in study I, that when changing HCP to a HCP with a higher probability of prescribing a recommended statin (MOR) the individual will increase his/her odds by 1.66 of getting a recommended statin. However, in the same study the PWOR was equal to 1.21 reflecting that there is a 1.21 higher odds of a prescription being a recommended statin given that another prescription randomly selected from the same HCP is a recommended statin. If we consider the ICC, it ranges between 4-8 % indicating the degree to which prescriptions or correlated due to the fact that they were issued at the same HCP.

In study IIa the different measures for ICC are rather similar (10-15 %). However, the MOR-value is 2.00 while the PWOR is only 1.29. For study III the assumptions for inferences on the 2nd level variance are not fulfilled, (i.e., the 2nd level residuals are not normally distributed) and the MOR and ICC are not interpretable. Regarding study IV, the ICC calculated by the latent variable methods gives rise to a higher ICC than the other methods. The relative differences between MOR and PWOR are not as high compared to study II. In study V the different ICC measures give rise to rather different results. The latent variable method indicates that a large part of the variance can be attributed to the higher level. However, for dataset Va and Vc the other methods for calculating the ICC show that less than 10 % can be attributed to higher levels. The difference between MOR and PWOR is large for dataset Vb, were the variance at the 2nd level is high.

When used as a measure of contextual effects, it is of high importance to be aware of the different underlying interpretations. The researcher needs to learn the meaning of the different values. These observations does not lead to any answer to which measure is more proper to use when estimating the contextual effect, it only emphasizes that they are measuring different things. As an example a MOR of 1.5 indicates that when changing a HCP to a HCP with a higher prevalence of recommended drugs your odds of receiving a recommended statin will increase by 1.5 A PWOR of 1.5 indicates that if you are prescribed a recommended statin the odds that another prescription from the same HCP also is a recommended statin is 1.5 higher. While an ICC of 5 % indicates that of the total variance 5 % can be attributed to the HCP level.

Strengths & Limitations

The use of large register databases in drug utilization research is appropriate for evaluating drug prescription, and they are also useful for evaluating the effect of drug policy because they measure actual utilization and economic outcomes accurately, are broadly representative, and are large enough to detect small changes. Moreover, Sweden has a rather homogenous health care system and a long tradition of register-based epidemiology which increases the validity of the information. Also according to the Centre for epidemiology at the National Board of Health and Welfare, the validity of the registers appears appropriate. [155]

Observational epidemiological studies based on health-care utilization register databases are often the only option for investigating questions that for practical reasons, costs, or ethics cannot be analyzed by randomized trials.[156] [157] Such databases are an invaluable source of epidemiological information on health related outcomes as well as drug prescribing. Their representativeness of routine clinical care makes it possible to study real-world effectiveness.[70] On the other hand, critiques of observational epidemiology have highlighted its vulnerability to confounding, reverse causation, measurement error and selection bias that may threaten the validity of observational non-randomized register based studies. But the last decades have witnessed an increase of methodological advances in the design and analysis of epidemiological register based studies in order to bring the non-randomized studies closer to acceptable validity,[158] and rather than to discard observational studies, the main effort is to reduce bias and confounding that constitutes a condition for the progress of epidemiological studies.[148] Moreover, multilevel modeling[33-35] is a very appropriate statistical technique to simultaneously analyze information from different levels (i.e. patient, prescriber, organizational unit). Multilevel models for observational designs are well developed and can be easily applied through commercial software. In this thesis we also follow the standards proposed by the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology)[159] initiative that was established in 2004. This initiative aims to implement standards for reporting observational epidemiological studies.

Because of similar indications and efficacy, statins are an ideal medication group for investigating prescribing behavior and the risk for confounding is low. Prescription of recommended statins is not specifically indicated for certain patients to the exclusion of others. There is therefore no rationale for considering patient characteristics as confounder factors. According to the prescription guidelines in Skåne region there is one patient related condition in which a non-recommended statin has a preferential indication. In fact, when simvastatin does

not reach sufficient effect, a change to atorvastatin 80 mg is officially recommended. However, a complementary analysis indicates that atorvastatin 80 mg was approximately 0.5 % of all the statin prescriptions during 2004, and including this substance in the category of recommended statin had no influence on the results.

In the first five studies we did not have access to information at the physician level. A part of the HCP variation found could therefore in fact be physician variation, [6 10 117] an aspect we observed in study VI from the Skaraborg Primary Health Care Database. Previous studies have also shown that variations at the physician level accounted for about 50% of the variation at the HCP level. [116] However, some studies suggest that the intra-practice variation is rather small in comparison with the inter-practice variation, due to the fact that physicians working in similar settings tend to act alike.[26] Nevertheless, in general the variation attributable to physicians/groups of physicians have been approximately 10 %, [6 10 116 160-164] while some studies have shown that for managerial questions the intra-unit correlation is higher than for prescribing questions. [165]

Specific limitations

Study I

In study I we investigated HCPs nested within municipalities rather than within HCAs as we did in the other studies. However, since HCAs became responsible for the management of the new decentralized budget, we did not consider the municipality as a relevant level in the other studies, and a sensitivity analysis (data not shown) including the municipality level confirmed our assumption. Moreover, for the studies were HCAs or municipalities were included we found very small variation at this level.

Study II

It is known that face-to-face visits such as those performed during the intervention campaign have a documented effect on prescription patterns. But in our analysis participation in the information campaign was not associated to higher adherence with guidelines. Given that participation in this campaign was free, it is probable that other reasons apart from the information campaign itself confound the observed association. For example, HCPs with a very low adherence to guidelines at the start of the intervention may be especially prone to participate in order to improve their prescription patterns. This effort would have only raised adherence to the same level as rest of the HCPs. Due to selection biases interpretation of the effect of the information campaign is limited.

Evaluation of the decentralized budget was less affected by bias since the adoption of the new budget system was mandatory and embraced all the prescribers in the county. Nevertheless, it cannot be ruled out that other external influence besides the decentralized budget could provide an alternative explanation of our results. Nevertheless, it is reasonable to believe that the intense trend of increasing prescription of simvastatin occurring after the implementation of the budget actually reflects the new economic responsibility of the prescribers. Several studies suggest that payment method affects physicians' prescription behavior.[114 166 167] Moreover, even if guideline dissemination alone has a less important effect on prescribing patterns,[114 166 167] it has proved to be effective as part of a multifaceted intervention and as a predisposing foundation for other strategies.

Study VI

Comparing the two data sets in study VI shows an improvement in adherence to guidelines, illustrated by the increase in prevalence and the reduction in variance. Unmeasured factors besides the decentralized budget, like attitudes and contact with the pharmaceutical industry, might affect these circumstances.

Most patients receive statins as a long time therapy. However, according the Swedish rules a prescription can not be issued for a period longer than one year. Therefore, in routine care repeat prescriptions are sometimes issued by phone and eventually by a different physician that the one that initiated the treatment. We have tried to identify homogeneous physician-patient relations by only including patients with all cardiovascular prescriptions by the same physician. However, we can not exclude a delayed effect of the decentralized budget conditioned by the fact that for new users the physicians prescribe recommended drugs, but for continuous users the physicians do not change to recommended drugs but continue with the original non-recommended drug, especially if the repeated prescription is written by another physician. The fact that there are small differences in the total number of patients with non-recommended statins for the different datasets might reflect that for new users the physicians prescribe recommended drugs, but for continuous users the physicians do not change to recommended drugs but continue with non-recommended drugs.

This study investigates statin prescription in primary health care. Therefore, our results are not directly applicable to those drug prescribed for patients at hospital care. Older patients treated in primary care but also in municipal homecare are also excluded since their prescriptions are not registered in the database.

Conclusions

The aim of this thesis was, with a specific focus on multilevel models, to propose a model of analysis for investigating practice variation in general and therapeutic traditions in particular. By using clustering of similar behavior within different HCPs as a measure of therapeutic traditions we found that adherence to guidelines for statin prescribing and the adoption of a new statin seemed, to a significant degree, to be conditioned by contextual factors at the HCP, i.e., therapeutic traditions at the HCP seemed to influence the individual physician in their propensity to follow guidelines.

Moreover, by applying multilevel models we were able to focus on the variability and heterogeneity over and above the focus on average relationships and thereby provide information that can be of relevance when investigating quality in health care and as a foundation for targeting interventions for evidenced based and cost-efficient prescription.

Specific conclusions

Study I

In *study I* we aimed to operationalize the concept of therapeutic traditions by the combined use of measures of prevalence and measures of variance. The goal was to develop a model to improve the empirical analysis of the drug prescription process and explore the application of multilevel regression analysis within pharmacoepidemiology. We studied the introduction of guidelines by investigating variance between different municipalities and outpatient health care practices (HCPs) regarding adherence to guidelines on statin prescribing.

Our hypothesis was that the introduction of guidelines would result in increased use of recommended statins and decreased variance between HCPs and municipalities.

We showed that adherence increased and the variation decreased along the study period, which suggests that in some way the publication of the official

prescription guidelines in the county had a positive influence on statin prescribing. However, at the end of the observation period adherence was still low and practice variation high. These facts may reflect inefficient therapeutic traditions, and suggest that more intensive interventions may be necessary to promote adherence to prescription guidelines. Moreover, we illustrated that multilevel regression analyses are a very suitable methodology for studying practice variation, as it provided us with the possibility to separate the effect of different levels in order to target interventions more efficiently.

Study II

This study aimed to monitor and evaluate the effect of the decentralized pharmacological budget on prescribing behavior and the role played by the different organizational levels (HCPs, Health Care Areas (HCAs) and Health Care Districts) when it comes to understand physicians' adherence to prescription guidelines. Our hypothesis was that the decentralized pharmacologic budget would result in increased use of recommended statins and decreased variance between HCPs and HCAs throughout the 25-month observation period.

We showed that the decentralized pharmaceutical budget seems to considerably influence prescription behavior and increase adherence to guidelines for statin prescription. Though, at the end of the observation period, variation between HCPs was still high, especially among private HCPs. These remaining disparities may reflect inefficient therapeutic traditions, and suggest that more intensive interventions may be necessary to promote adherence to prescription guidelines. Obviously, a decentralized pharmaceutical budget transfer power in management and decision-making from higher to lower levels of the health care organization, which in turn increases economic responsibility among prescribers and creates incentives for efficient drug prescription. Therefore, as a natural consequence, adherence to the drug committee's recommendations increases.

Study III

In this study we aimed to elaborate the previous developed theory that considers measures of clustering to quantify therapeutic traditions and the early adoption of a new statin, rosuvastatin. For this purpose, we applied an innovative analytical approach using generalized estimation equations (GEE), alternating logistic regression (ALR) and pair-wise odds ratios (PWORs). Simultaneously, we aimed to investigate the role that both patient characteristics (i.e. sex, age, socioeconomic position, marital status, country of birth) and outpatient health care practice

(HCP) factors (e.g. public v. private administration, proximity to specialized care, rural vs. urban setting, total prescription volume) played in physicians' propensity to prescribe rosuvastatin after its introduction to the market.

Applying the GEE-ALR and PWOR methodology we observed that contextual factors (e.g. therapeutic traditions) at the HCP may be relevant for understanding physicians' propensity to early adopt and prescribe a new statin (i.e., rosuvastatin), especially in the private sector. Additionally, the age and SES of the patients appeared to influence the prescribing behavior of the physicians, as rosuvastatin was more frequently prescribed to both younger men and younger women with high income.

Our study indicated the existence of inefficient therapeutic traditions, and suggests that interventions may be necessary to promote rational prescription guidelines for pharmacologic treatment in the context of a limited health care budget.

Study IV

In this study we aimed to investigate the association between patient and HCP characteristics on the one hand, and adherence to guidelines for statin prescription on the other, with a focus on social and economic conditions. Our results suggested that the physician's decision to prescribe a recommended statin is conditioned by the socioeconomic (e.g. income, living alone) and demographic (e.g. age) characteristics of the patient. Beyond individual characteristics, the contextual circumstances of the HCPs also showed an independent association with adherence to prescription guidelines. An increased understanding of the connection between the SES of the patient and the decisions made by physicians might be of relevance when planning interventions aimed at promoting efficient and evidence-based prescription.

Study V

Since it is still not known if therapeutic traditions are a general HCP trait that affects all kinds of prescription behavior or if it is dependent on specific outcomes this study focused on adherence to prescription guidelines for different types of drugs. Our hypothesis was that therapeutic traditions would be shown to have a general influence on prescription behavior and that adherence to guidelines regardless of drug type would be positively correlated within the HCP.

Our study suggested that a physician's decision to follow prescription guidelines is associated with contextual circumstances, including therapeutic traditions at the HCP. Moreover, therapeutic traditions seem to be a general trait of HCPs that affects all kinds of prescriptions and is independent of drug type. Prescribing behavior is also conditioned by socioeconomic (e.g., income) and demographic (i.e., age, gender) characteristics of the patient.

Study VI

Using the previously developed theory we replicate previous analysis on a different database containing information on the physician level; a level of analysis was missing in earlier studies. We hypothesized that a part of the variance at the HCP-level should be attributed to the physician level. Therefore this study complements previous findings about the relevance of different levels for understanding practice variation. By combining prevalence and variance measures we can obtain more complete information on the effect of the decentralized budget, introduced in Skaraborg region in 2003, on the adherence to guidelines for statin prescription. Transferring power in management and decision-making to the HCPs, seemed to be a powerful intervention for reducing inefficient therapeutic traditions and to create incentives for efficient drug therapy. As a natural consequence, adherence to the drug committee's recommendations increased and differences between physicians and HCPs decreased.

Moreover, the SPCD seems to be an appropriate database for pharmacoepidemiological studies and showed that the physician level and the HCP level bare the same responsibility for understanding the variations when prescribing recommended statins before the introduction of the decentralized drug budget.

Implications

This thesis reveals that both inefficient therapeutic traditions and socioeconomic position of the patient should be considered when trying to implement prescription guidelines in routine care. In general, our results have implications for the achievement of equity of health service policy, since there is no medical or therapeutic reason that could justify the selective prescription of expensive statins to younger men or to patients of high SEP. Moreover, as the Swedish reimbursement system funds a large part of the cost of medications[168] and there are rather large differences in price between recommended and non recommended

drugs, adherence to guidelines is an essential issue in a system with a limited Health Care budget.

The clustering of prescription behavior was greater at the HCP than at the HCA level, which suggests that interventions directed at the HCP level would in principle be more effective than those directed at the HCA level. As the contextual variable "private vs public HCP" explained a considerable part of the variance at the HCP level, interventions directed at private HCPs could be appropriate. Moreover, except as a measure of quality in health care, one of the contributions of quantifying practice variation is also to be able to identify procedures for which practice style differences are large because they reflect disagreement over the established standards.[169] By combining information of the magnitude of adherence rate to prescription guidelines and the degree of clustering provides novel and useful information that could be used to quantify physicians' acceptance rate of the prescription guidelines. For example, a low MOR-value (small differences in adherence between HCPs) and a low overall adherence rate reflect a widespread resistance to following the guidelines. A high MOR-value and a rather low overall adherence rate, exemplified by C09 in study V, reflect that there are specific HCPs with high adherence, while a large majority shows a low adherence rate. Interestingly, both the overall adherence and the MOR-value for C10AA were higher than for A02BC, indicating that there are more HCPs with relatively low adherence for C10AA than for A02BC. This information is of high relevance and ought to be considered when tailoring interventions aimed to promote rational drug prescription.

The importance of the variation phenomenon is also evident in its effect on the debate over health care reform.[1] The potency of the medical profession's influence derived in part from its claim to scientific legitimacy. The variation phenomenon has emboldened public and private policy makers and managers to challenge professional autonomy and control in new ways and has been used to diminish the responsibility of the profession for decisions regarding patient care.

Further studies

Several different aspects have been raised that requires further research:

1. Many aspects concerning the analysis of variance components across time and space needs much more development. There is also a gap between the development of statistical methods and its application in routine epidemiology.

2. Studies focusing on changes in variance and not only on changes in mean, since it is of main relevance to understand and prevent inappropriate health care variation, as it leads to inefficient resource utilization.
3. Studies to investigate how contextual variables affect the individual outcome
4. Investigate additional contextual variables in order to be able to understand and explain different therapeutic traditions.
5. As studies of variation have foremost been focused on isolated clinical outcomes rather than across treatment decisions, [14] and rarely been investigated over time[170 171] studies investigating these issues are required.

Clarifications

Paper I & II: Since the variable sex is included in the analysis with a random slope, the PCV is comparing the difference between the variance for men (and not the total variance) in the model with more variables (model B and C) and the total variance in model A.

Paper III: It is stated that ”The PWOR is equal to 1 in the absence of clustering, and in this case it indicates that rosuvastatin prescriptions within the same HCP were more frequent than could be expected if prescriptions were distributed randomly across HCPs.” However, it should be stated that “The PWOR is equal to 1 in the absence of clustering. If the PWOR is larger than 1, it indicates that rosuvastatin prescriptions within the same HCP were more frequent than could be expected if prescriptions were distributed randomly across HCPs.

Definitions and explanations

Conceptual framework for pharmacoepidemiological studies

The use of drugs in the population is not an undisclosed phenomenon within health care, but a component of the health care system and must be considered accordingly. Nonetheless, the study of the use and the effects of drugs in the population require certain type of knowledge.

Figure 9 illustrates a conceptual framework for pharmacoepidemiological studies.[172] This model elucidates the different areas that treat drug related questions in different phases of the life cycle of a drug. Prior to a drug is licensed and can be used in routine care, it has been tested in randomized clinical trials (RCT). Within the RCT relevant effects of the drug are determined and adverse effects are registered (Phase I, II and III). This implies that, when it is licensed, the existing knowledge about a drug comes from the RCT. RCTs often are rather small and carried out among a selected number of people within specific geographical areas.[70] This must be taken into account when the drug is implemented in the population. RCT only report the efficacy of the drug; the effect under ideal circumstances.[80] The Medical Products Agency (MPA) is the Swedish national authority responsible for regulation and surveillance of the marketing of drugs and other medicinal products. Their task is to ensure that both the individual patient and healthcare professionals have access to safe and effective medicinal products and that these are used in a rational and cost-effective manner.[173] It is then the Pharmaceutical Benefits Board (TLV) who decides if a new medicine should be granted reimbursement status.[174]

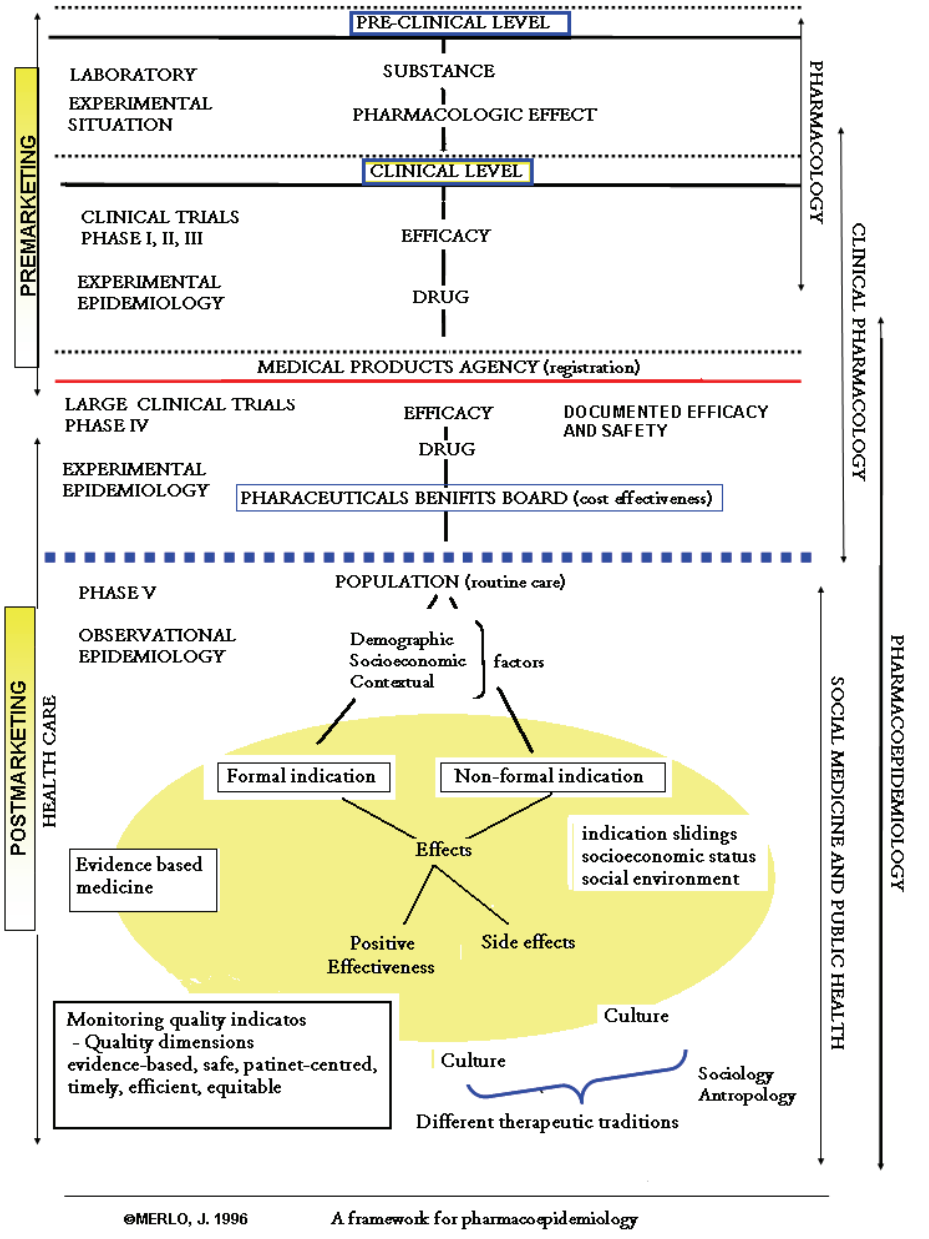


Figure 10: a conceptual framework for pharmacoepidemiology

When a drug is marketed in the population, it is still difficult to decide its effectiveness; if the drug will have the same effects in the population as it hade in RCTs.[80] Contrary to individuals within a RCT, the population is characterized of heterogeneity. Drug users will be different in many senses; demographic, socioeconomic, contextual characteristics can influence the drug use and the effects it will have. Nevertheless, the choices physicians and the drug users make must be based on evidenced medicine; the efficacy of the drug. Drug utilization studies based on large register databases are therefore an invaluable source for information of the effectiveness, appropriateness and equity of drug therapy. This can be used for health system planning and for assessing the quality of prescribing and they are also well suited to help researchers understand the properties and predictors of physicians´ prescribing decision.

The complex nature of drug choice, or prescribing, on an individual physician's level, has not been fully explained by any model. A framework for decision making process have however been proposed. [77 78] Two steps may be distinguished in the drug choice; the generation of a small set of possible treatment options (the evoked set) and the choice of a specific therapy. Whether a specific drug will be part of the evoked set depends on the education and the information received. From the physician's repertoire of treatments (the evoked set) two ways of selecting a drug can be distinguished. One is based on a more active decision while the other is based on a more habitual act. The choice is based on an interaction of expectancies and personal experiences.

Beside the medical factors several studies have documented that non-medical factors influence prescribing decisions. These factors can be divided into three separate categories: (I) Characteristics of the patient – age, gender, socioeconomic position, ethnicity, (II) characteristics of the doctor – medical specialty, level of training, length of clinical experience, age, sex, ethnicity and personality, and (III) features of the practice – organization of the practice, geographical location. Several different studies have emphasized different categories,[6 47-49 150 175-180] while few have distinguished the importance of the different levels.

The Swedish Health Care System

The health services in Sweden are overwhelmingly tax-financed through county taxes. Even if the Swedish Health Care System is rather homogenous all over the country, every one of the 21 county councils in Sweden have a high financial autonomy for managing health care services within their respective areas and are

responsible for supplying their citizens with health care services.[168] A county council tax supplemented by a state grant is the main mean of financing the health care system. Patient fees (out-of-pocket) account for approximately 3% of the total health care costs. Each county council and region is governed by a political assembly, with its representatives elected for a four year period at every general election. Within the framework of national legislation and varying health care policy initiatives from the national government, the county councils and regions have substantial decision-making powers and obligations towards their citizens. The national legislation is based on the principle of equity and aims to allocate resources on the basis of need.

The Swedish health care is delivered in three different levels; primary care, secondary care and tertiary care. The county councils are responsible for all levels. Although the health care is tax-financed the providers can be both publicly and privately organized. The primary care level is mainly organized as primary health care centers covering different geographical areas. The secondary care level provides different forms of specialized health care (e.g. internal medicine, orthopedics). The tertiary care level has a regional level of coverage and serves several counties. This level adds a wider range of sub-specialized medical services.

The cost of medicines in outpatient care is shared by patients and county councils via a reimbursement system where the individual patient never pays more than 200 Euros per year.[54] The total cost for a year of statin treatment varies from approximately 30 Euros (the cheapest recommended statins) to 600 Euros.[181]

Decentralized drug budgets

As drug expenditure during the past decades has increased rapidly in relation to overall health care costs different types of interventions have been proposed and implemented in order to control drug expenditure and to make the clinical decision more and more rationalized and subject to administrative control. In several countries decentralized drug budgets have been introduced at health care facility level in order to control this increase and to promote adherence to prescription guidelines.[182] A decentralized drug budget increases economic responsibility among prescribers by relocating control in management and decision-making from higher to lower levels of the health care organization and, thereby, it creates incentives for efficient drug prescription.[183] Several studies suggest that payment method affects physicians' prescription behavior, even though it has proved to be most effective as part of a multifaceted intervention.[114] [166] [167] [184] [185]

Skåne region – decentralized drug budget

Skåne is situated on the southern part of the Scandinavian Peninsula. The county is geographical divided into 33 municipalities and its area covers less than 3% of Sweden's total area. The population of about 1.2 million represents, however, 13% of Sweden's total population. In January 2004, Skåne region implemented a new system for managing the pharmaceutical budget. In the new compulsory system of decentralized pharmaceutical budget, the responsibility for the administration of the pharmaceutical budget was transferred from the regional Department of Health and Health Care Management to every of the 19 administrative Health Care Areas (HCAs). However, nine of the 14 publicly-administered HCAs decided to implement a more intense decentralization by transferring the budget responsibility to their HCPs. See figure 12 for an explanation of the structure of the health care system in Skåne region. Simultaneously with the introduction of the decentralized drug budget face-to-face visits where specially trained pharmacists visited the HCPs were performed. The pharmacists provided information on current local prescription patterns as a basis for reflection and prescription improvement. This approach has been uses in several countries in order to promote evidence based prescription. While the new economic system was compulsory, participation in the information campaign was voluntary. This kind of intervention have in previous studies shown to have a documented effect on prescription patterns.[167]

Skaraborg – decentralized drug budget

Skaraborg, one of four administrative areas of the region of Västra Götaland in the southwest of Sweden is mostly rural and it is inhabited by approximately 250 000 individuals within 15 municipalities. Primary care is offered by 24 public HCPs, one private HCP and a few private GPs. About 250 000 office visits are registered at the public HCPs every year. Hospital care is offered by 3 hospitals. Approximately, 75% of all drugs were prescribed outside the hospitals and 85% of these prescriptions were made at the public HCPs. In Skaraborg Primary care, the tax-financed part of the pharmaceutical budget was administrated by the regional Department of Health and Health Care Management until 2003 when it was decentralized to the HCP level.

Statins

Statins were introduced about 25 years ago[186] and were first used to treat patients with familial hypercholesterolemia. But not before long their potential in reducing the risks of cardiovascular disease in the general population were

recognized.[187] Several randomized controlled trials proved that statins reduce the risk of first or recurrent myocardial infarction in patients with pre-existing coronary heart disease.[188 189] Treatment with statins reduces the absolute risk with approximately 3-8 %. For primary prevention statins, reduce the risk for cardiovascular disease when there are several risk factors besides hyperlipidemia (an elevation of lipids (fats) in the bloodstream)such as hypertension, obesity, heredity, smoking or/and male gender. However, the benefits for primary prevention are not as high as for secondary prevention.[190] Statins mainly improve blood cholesterol levels primarily by inhibiting the liver enzyme called HMG Co-A reductase, an enzyme that reduces the liver's ability to create cholesterol. Hyperlipidemia consists primarily of high serum cholesterol (total cholesterol level), high LDL-cholesterol, low HDL- cholesterol and high triglycerides. Each of those parts correlates to the risk of heart diseases. An increase of the serum-cholesterol level, a decrease in HDL-cholesterol level and an increase of triglycerides increases the risk of ischemic heart disease. However it is a matter of controversy if there is an optimal cholesterol level and that "the lower the better".[190] There are currently 5 statins on the Swedish market: atorvastatin, fluvastatin, pravastatin, simvastatin and rosuvastatin. A sixth statin, cerivastatin was removed from the market during the summer of 2001 because of potentially serious side effects.[190]

Health economic calculations have mainly been performed regarding effects of treatment with statins and not for other risk factors. Those analyses have shown that treatment with statins for secondary prevention (up till 75 years of age and regardless of gender) is cost effective based on calculations made for each year in perfect health gained. A comparative study between different statins has not been done. For primary prevention acceptable cost effectiveness can be reached with statin treatment for individuals with a high risk of cardiovascular disease, but there are not enough data for general recommendations.

In studies regarding secondary prevention the number of women has been approximately 15 %. Therefore there have been difficulties to prove a significant effect on total mortality. The knowledge from studies regarding primary prevention is restricted and the recommendations are therefore incomplete. For older individuals (> 75 years) there is no documentation for primary prevention treatment.

In patients with stable coronary heart disease, only simvastatin and pravastatin showed a benefit of statin therapy with regard to life-prolonging effect. No such evidence was shown for atorvastatin. Regarding patient-relevant benefits of statins

with acute coronary syndrome no comparative evaluation between different statins was shown. In patients with diabetes mellitus, only simvastatin showed a benefit regarding life-prolonging effect. It cannot be determined from the available long-term intervention studies on different statins that the degree of LDL cholesterol lowering is appropriate to generally demonstrate or quantify benefits with regard to patient-relevant endpoints.[55] Statins are therefore supposed to be used according to those studies that have shown effects on morbidity and mortality rather than according to the surrogate variable cholesterol.

Treatment recommendations from the Medical products agency

For secondary prevention there are indications for lipid lowering treatment if the serum cholesterol exceed 5.0 mmol/L and/ or LDL- cholesterol exceed 3.0 mmol/L.[190] Non-pharmacologic treatment are supposed to be tried primarily and drugs are to be prescribed if non-pharmacologic treatment is insufficient. For secondary prevention lifelong treatment is often required. However, cohort studies of patients who were prescribed statins show variable and often rather high rates of therapy discontinuation.[191] [192] The benefits from lipid lowering treatment for secondary prevention can not be used as an argument for treatment of hyperlipidemia for individuals without coronary disease. Several studies have shown a relative risk reduction at the same level as for secondary prevention but since the incidence among individuals without coronary disease is much lower, the absolute risk is much smaller. Lipid lowering treatment for primary prevention should be reserved to individuals with heredity motives or other risk factors.

Rosuvastatin

There is currently no direct trial evidence of the effect of rosuvastatin on morbidity and mortality. Seven randomized control trials exist with LDL-cholesterol level as an endpoint. The number of patients varied between 141 and 516 and the studies was carried out at least during six weeks and at most during one year. While there is RCT evidence to suggest that rosuvastatin is more effective than the other statins in reducing both total and LDL-cholesterol, it is not possible to prove that these reductions translate into comparable reductions in clinical events. In October 2003, the regional governmental drug advisors in Sweden concluded in a statement that Rosuvastatin were not to be used because it did not meet the criteria of documented safety and cost effectiveness.[122] During the same month Lancet published an editorial that advised against physicians prescribing Rosuvastatin. [120]

Use and cost for statins

The expenditure for statins has fallen since simvastatin became available as a generic during spring 2003. Thereafter a significant fall in prices, approximately 85 % for simvastatin, have been shown. The cost for one year treatment with simvastatin (40 mg) was, in 2004, approximately 260 SEK while for atorvastatin (80mg) the cost was 6 100 SEK.

Figure 11 illustrates the share of the population in Skåne region that during 2006 collected at least one statin prescription from the pharmacies. It illustrates that more men in all age groups used statins. Moreover, of all men between 70-79 years, approximately 30-35 % used statins during 2006; the same number for women was approximately 25 %. As shown in figure 12a and 12b approximately 80 % of the patients receiving a statin prescription received a simvastatin prescription. The expenditure for statins in Skåne region during 2006 was approximately 81 million SEK, of which the patients paid approximately 18 million SEK. The expenditure for the recommended drug, simvastatin, was approximately 15 million SEK (18.5 % of the total cost for statins), of which the patients paid 6.4 million SEK.

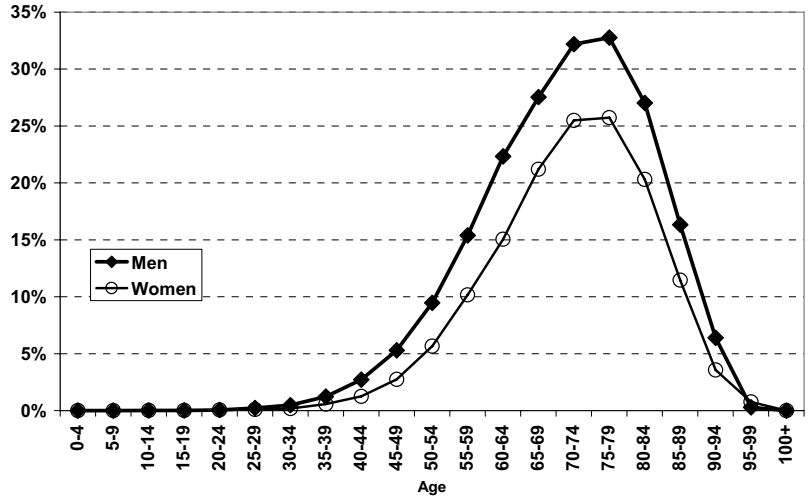


Figure 11: Share of the population (N = 1 169 453) in Skåne region that during 2006 collected at least one statin prescription from the pharmacies. (age on X-axis and percentage of population on Y-axis)

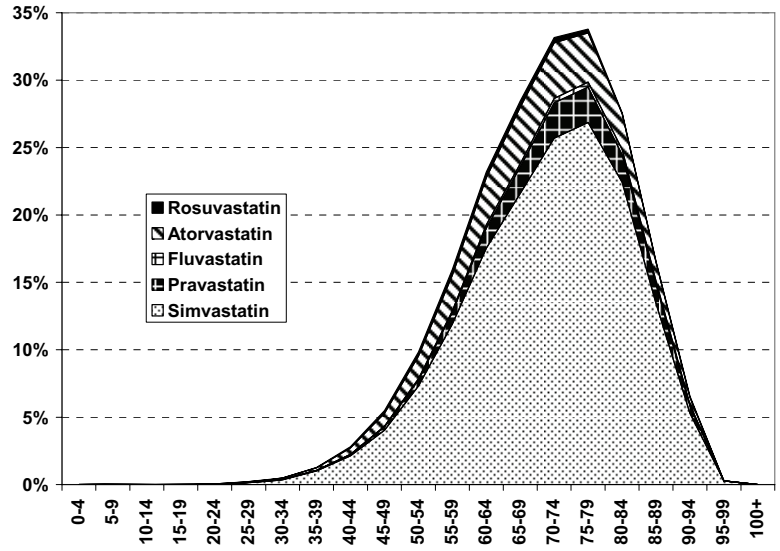


Figure 12a: The different types of statins collected by of the population (men, N=575 889) in Skåne region during 2006 (age on X-axis and percentage of population on Y-axis)

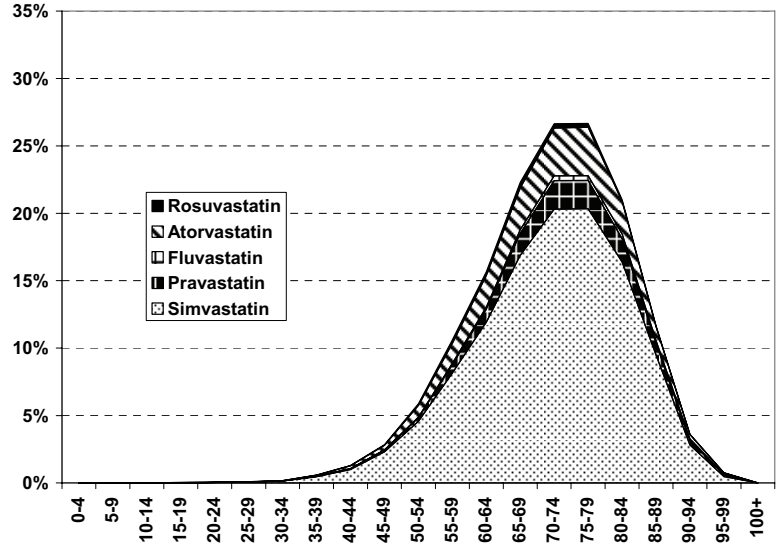


Figure 12b: The different types of statins collected by of the population (women, N=593 546) in Skåne region during 2006 (age on X-axis and percentage of population on Y-axis)

Guidelines

The use of guidelines that aims to implement general standards and thereby diminish the influence of inefficient practice variation have increased during the latter years.[166] Guidelines are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health" [193]. Except as seen as an answer to practice variation, clinical guidelines have been implemented in order to reduce health care cost. The need for guidelines and their effective dissemination arises from a generally perceived need to reduce the variability of medical care and to improve the quality of care as well as a help to physicians that barely are able to be up to date in the increasing volume of new scientific results. [114 193 194]

The spreading of guidelines has been separated into three parts; diffusion, dissemination and implementation. Diffusion is defined as non targeted information spread, while dissemination is defined as targeted or tailored interventions and implementation involves identifying and assisting in overcoming the barriers to the use of the knowledge obtained from a tailored meassage.[114 193] Guideline dissemination alone has in previous studies shown to have a less important effect on the medical decision, however it has proved to be effective as part of a multifaceted intervention and as a predisposing foundation for other strategies.[166 167] The following attributes have been suggested as necessary attributes for acceptance and effective guideline implementation; be compatible with doctors' existing values; (I) not be too controversial, (II) not demand too much changes to existing routines, (III) be defined precisely with specific advice on actions and decisions in different cases, (IV) be supported by an explicit description of the scientific evidence, (V) be straightforward and consistent.[195] Adherence to guidelines have been studied in several articles.[113] When studying adherence one must separate between global adherence, defined as the prescribing of a drug mentioned in the formulary; and specific adherence, defined as prescribing of a drug mentioned in the formulary for which its indication is also mentioned in the formulary.[115]

Studies have shown that effective strategies often have multiple components and that the use of one single strategy, such as reminders or an educational intervention, is less effective.

Moreover characteristics of the guidelines themselves affect actual use. Guidelines that are easy to understand, can easily be tried out, and do not require specific resources, have a greater chance of implementation. Additionally, characteristics of professionals and patients as well as contextual characteristics may influence

guideline implementation. A lack of support from peers or superiors, as well as insufficient staff and time, appear to be the main impediments.[196 197] Moreover, guidelines have shown to be more readily accepted if made and disseminated by the profession.[195 198]

Monitoring adherence to guidelines might be a reasonable way of assessing prescribing patterns. However, guidelines may vary among different regions. Studies have shown that for one specified indication different regions have recommended between 5 to 12 different drugs.[113] Adherence to guidelines has attracted considerable interest in many countries including Sweden.[67 113-115 179 199] However, it is still insufficiently known to what extent guidelines are followed and the factors that at different levels of the health care condition adherence to guidelines.[67 179 199]

Abbreviations

ALR	Alternating logistic regression
ATC	Anatomical therapeutic chemical classification
DDD	Defined daily dose
DIC	Deviance Information Criterion
GEE	Generalized estimation equations
HCA	Health care area
HCP	Health care practice
ICC	Intra class correlation
IOR	Interval odds ratio
IoT	The register of income and taxation
LISA	Longitudinal integration database for health insurance and labor market studies
LOMAS	Longitudinal Multilevel Analysis in Scania
MCMC	Markov chain Monte Carlo
MLRA	Multilevel logistic regression
MOR	Median odds ratio
OR	Odds ratio
PCV	Proportional change of variance
PR	Prevalence ratio
PWOR	Pair wise odds ratio
RCT	Randomized clinical trial
RTB	Register of the total population
SEK	Swedish currency (100 SEK = 8,85 EURO)
SEP	Socioeconomic position
SKL	Swedish Association of Local Authorities and Regions
SPCD	Skaraborg Primary Care Database
SPDR	Swedish Prescribed Drug Register
SoS	National Board of Health and Welfare

Sammanfattning på svenska

Att likartade patienter behandlas olika av olika vårdenheter har uppmärksammats i flertalet studier. Emellertid kommer varje mätning av en process alltid att uppvisa någon form av variation. Därför är det av stor vikt att särskilja på normal oundviklig variation och variation som är omotiverad. Ett exempel på omotiverad variation är när ett och samma läkemedel finns tillgängligt till olika pris, men förskrivaren ändå väljer det dyraste. I denna situation är det av stor vikt att identifiera de bakomliggande orsakerna till denna variation för att kunna genomföra effektiva interventioner. Eftersom förskrivningsprocessen genomgår en mängd olika faser, och den kan påverkas på olika nivåer (patient, förskrivare, vårdenhet), är det av stor vikt att identifiera de olika nivåernas betydelse för val av läkemedel. Emellertid finns det väldigt få studier som har försökt att studera betydelsen av dessa olika nivåer.

En ytterligare aspekt som inte blivit särskilt uppmärksammad inom detta område är vad vi i denna avhandling kallar för ”terapitradtioner”. Med det menar vi att kulturen på en vårdcentral kan påverka förskrivarens val av läkemedel. Det innebär att förskrivare från samma vårdenhet tenderar till att agera likartat jämfört med förskrivare från andra vårdenheter. Desto mer förskrivare från samma vårdenhet agerar likartat desto större är terapitraditionerna.

Att jämföra sjukhus och vårdenheter utifrån nationella kvalitetsindikatorer har de senaste åren blivit väldigt populärt. Sveriges kommuner och Landsting har i samarbete med Socialstyrelsen gett ut ett antal rapporter; ”Öppna Jämförelser” där landsting och sjukhus har jämförts utifrån ett antal nationella kvalitetsindikatorer. Metoden för jämförelserna har framförallt varit rankinglistor där sjukhusen rankats utifrån medelvärdet för den aktuella indikatorn, vilket innebär att möjligheterna för att urskilja oundviklig från omotiverad variation, samtidigt minskar potentialen att förstå om skillnaderna beror på patientsammansättningen eller om sjukhusen/vårdenheterna har någon faktisk betydelse.

Metoderna för att kvantifiera skillnader mellan vårdenheter, men även för att särskilja oundviklig och omotiverad variation behöver därför mer utveckling. Det samma gäller för fastställande av orsakerna till denna variation. Dessutom finns

det en lucka mellan de statistiska metoderna och dess användning i epidemiologiska studier. Utvecklingen och tillämpningen av statistiska metoder för frågor angående jämförelser av vårdenheter kan hjälpa till att fylla denna lucka.

Syftet med denna avhandling är genom att applicera flernivåanalys föreslå en modell för att studera variationen mellan vårdenheter/sjukhus och identifiera vikten av olika nivåer (patient/läkare/vårdenhet/sjukhus). Vi exemplifierar detta genom att studera terapitraditioner och följsamhet till rekommenderade läkemedel. Samtidigt studerar vi vilka sociala och ekonomiska bestämningsfaktorer som kan påverka förskrivningsprocessen på olika nivåer av analysen. Vi fokuserar på en kombinerad analys av variansen (skillnader mellan enheter) och associationer, eftersom detta kan ge mer information som kan användas som underlag till åtgärder för att stimulera evidensbaserad förskrivning. Vi väljer att framförallt studera följsamhet till statiner (blodfettsänkande läkemedel) eftersom statiner har samma indikation och liknande effekt, och därför bör skillnaderna mellan vårdenheter och sjukhus vara liten.

Vi använder oss av databasen LOMAS (Longitudinal Multilevel Analysis in Scania) som innehåller avidentifierad information om alla individer i Skåne under perioden 1968-2008. Ett register i LOMAS är Läkemedelsregistret som innehåller information om alla receptbelagda läkemedel som sålts på apotek i Sverige. För att studera variationen använder vi oss av flernivåanalys (multilevel regression models och generalized estimation equations and the alternating logistic regression). Användningen av dessa metoder innebär att man explicit kan studera och modellera variansen. Vi kvantifierar betydelsen av de olika nivåerna med hjälp av Median odds ratio, Intra Class Correlation och Pairwise odds ratio.

I våra studier fann vi att följsamheten till rekommenderade statiner var till viss del betingat av vilken vårdenhet man tillhörde. Alltså, bestämningsfaktorerna för den individuella läkarens beteende berodde till en viss del på var man arbetade. Dessutom fann vi att de vårdenheter som följde rekommendationerna för en läkemedelsgrupp också följde rekommendationerna för andra läkemedelsgrupper. På vårdcentralsnivå fann vi att privata enheter hade lägre följsamhet än offentliga enheter, denna variabel bidrog också till att förklara en del av skillnaderna mellan vårdenheterna. På patientnivån fann vi att den individuella inkomsten påverkade förskrivarens val av läkemedel framförallt hos män. Det innebar att män med hög inkomst fick i större utsträckning de dyrare icke rekommenderade statinerna jämfört med män med låg inkomst.

I denna avhandling presenterar vi en modell för att jämföra vårdenheter/sjukhus där vi fokuserar på en analys av både variansen och associationer. Vi studerar terapitraditioner och följsamhet till rekommendationer för statiner. Genom att studera betydelsen av olika nivåer för förskrivningsprocessen erhåller vi information som är användbart som underlag till åtgärder och interventioner för en mer rationell läkemedelsförskrivning.

References

1. Blumenthal D. The variation phenomenon in 1994. *N Engl J Med* 1994;331(15):1017-8.
2. Smits HL. Medical practice variations revisited. *Health Aff (Millwood)* 1986;5(3):91-6.
3. de Jong JD. *Explaining medical practice variation - Social organization and institutional mechanisms*, 2008.
4. Wennberg J. Wrestling with variation: an interview with Jack Wennberg [interviewed by Fitzhugh Mullan]. *Health Aff (Millwood)* 2004;Suppl Web Exclusive:VAR73-80.
5. Wennberg JE, Barnes BA, Zubkoff M. Professional uncertainty and the problem of supplier-induced demand. *Soc Sci Med* 1982;16(7):811-24.
6. Davis P, Gribben B. Rational prescribing and interpractitioner variation. A multilevel approach. *Int J Technol Assess Health Care* 1995;11(3):428-42.
7. Davis PB, Yee RL, Millar J. Accounting for medical variation: the case of prescribing activity in a New Zealand general practice sample. *Soc Sci Med* 1994;39(3):367-74.
8. Olesen F, Vedsted P, Norskov Nielsen J. Change in ranking order of prescribing patterns by age and sex standardization of the practice population--audit may be misleading. *Scand J Prim Health Care* 1996;14(3):159-64.
9. Sleator DJ. Towards accurate prescribing analysis in general practice: accounting for the effects of practice demography. *Br J Gen Pract* 1993;43(368):102-6.
10. Davis P, Gribben B, Lay-Yee R, Scott A. How much variation in clinical activity is there between general practitioners? A multi-level analysis of decision-making in primary care. *J Health Serv Res Policy* 2002;7(4):202-8.
11. Geller SE, Burns LR, Brailer DJ. The impact of nonclinical factors on practice variations: the case of hysterectomies. *Health Serv Res* 1996;30(6):729-50.
12. McKinlay JB, Potter DA, Feldman HA. Non-medical influences on medical decision-making. *Soc Sci Med* 1996;42(5):769-76.

13. Epstein AM, McNeil BJ. Physician characteristics and organizational factors influencing use of ambulatory tests. *Med Decis Making* 1985;5(4):401-15.
14. O'Neill L, Kuder J. Explaining variation in physician practice patterns and their propensities to recommend services. *Med Care Res Rev* 2005;62(3):339-57.
15. Crump B. The Good Indicators Guide: Understanding how to use and choose indicators. 2007.
16. Wennberg J. Dealing with Medical Practice Variations: A proposal for action. *Health Affairs* 1984;3(2):6-33.
17. Diehr P, Cain K, Connell F, Volinn E. What is too much variation? The null hypothesis in small-area analysis. *Health Serv Res* 1990;24(6):741-71.
18. Diehr P, Cain KC, Kreuter W, Rosenkranz S. Can small-area analysis detect variation in surgery rates? The power of small-area variation analysis. *Med Care* 1992;30(6):484-502.
19. Diehr P, Grembowski D. A small area simulation approach to determining excess variation in dental procedure rates. *Am J Public Health* 1990;80(11):1343-8.
20. Ibanez B, Librero J, Bernal-Delgado E, Peiro S, Gonzalez Lopez-Valcarcel B, Martinez N, et al. Is there much variation in variation? Revisiting statistics of small area variation in health services research. *BMC Health Serv Res* 2009;9(1):60.
21. Kazandjian VA, Durance PW, Schork MA. The extremal quotient in small-area variation analysis. *Health Serv Res* 1989;24(5):665-84.
22. Shwartz M, Ash AS, Anderson J, Iezzoni LI, Payne SM, Restuccia JD. Small area variations in hospitalization rates: how much you see depends on how you look. *Med Care* 1994;32(3):189-201.
23. Merlo J. Multilevel analytical approaches in social epidemiology: measures of health variation compared with traditional measures of association. *J Epidemiol Community Health* 2003;57(8):550-2.
24. Eddy DM. Variations in physician practice: the role of uncertainty. *Health Aff (Millwood)* 1984;3(2):74-89.
25. Folland S, Stano M. Small area variations: a critical review of propositions, methods, and evidence. *Med Care Rev* 1990;47(4):419-65.
26. Westert GP, Groenewegen PP. Medical practice variations: changing the theoretical approach. *Scand J Public Health* 1999;27(3):173-80.
27. Merlo J, Ohlsson H, Liljeberg A, Lynch K, Lindström M, Rosvall M. Läkemedelsanvändning och effekter i befolkningen (FAS V) - Några exempel på läkemedelsepidemiologisk forskning i Region Skåne. Malmö, 2007.

28. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial of multilevel analysis in social epidemiology -linking the statistical concept of clustering to the idea of contextual phenomenon. *J Epidemiol Commun Health* 2005;59:443-449.
29. Durkheim E. *The rules of sociological method*. 8th ed. New York: Free Press of Glencoe, 1964.
30. Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. *Soc Sci Med* 2000;51(6):843-57.
31. Socialstyrelsen. God vård – om ledningssystem för kvalitet och patientsäkerhet i hälso- och sjukvården, 2006.
32. Asplund K, Sörman H. Öppna jämförelser av hälso- och sjukvårdens kvalitet och effektivitet. Jämförelser mellan landsting 2006. Stockholm: Socialstyrelsen & Sveriges kommuner och Landsting, 2006.
33. Goldstein H. *Multilevel Statistical Models*. 3rd ed. London, UK: Hodder Arnold, 2003.
34. Snijders T, Bokser R. *Multilevel analysis: an introduction to basic and advanced multilevel modeling*. Thousand Oaks, California: Sage Publications, 1999.
35. Carey V, Zeger SL, Diggle P. Modelling multivariate binary data with alternating logistic regression. *Biometrika* 1993;80(3):517-526.
36. Diez Roux AV. A glossary for multilevel analysis. *J Epidemiol Community Health* 2002;56(8):588-94.
37. Diez-Roux AV. Bringing context back into epidemiology: variables and fallacies in multilevel analysis. *Am J Public Health* 1998;88(2):216-22.
38. Duncan C, Jones K, Moon G. Context, composition and heterogeneity: using multilevel models in health research. *Soc Sci Med* 1998;46(1):97-117.
39. Goldstein H, Browne W, Rasbash J. Partitioning variation in generalised linear multilevel models. *Understanding Statistics* 2002;1:223-232.
40. Braumoeller B. Explaining Variance; Or, Stuck in a Moment We Can't Get Out Of. *Political Analysis* 2006;14:268–290.
41. Merlo J, Asplund K, Lynch J, Rastam L, Dobson A. Population effects on individual systolic blood pressure: a multilevel analysis of the World Health Organization MONICA Project. *Am J Epidemiol* 2004;159(12):1168-79.
42. Petronis KR, Anthony JC. A different kind of contextual effect: geographical clustering of cocaine incidence in the USA. *J Epidemiol Community Health* 2003;57(11):893-900.
43. Leyland AH, Boddy FA. League tables and acute myocardial infarction. *Lancet* 1998;351(9102):555-8.

44. Downs G, Rocke D. Interpreting Heteroscedasticity. *American journal of Political Science* 1979;23(4):816-828.
45. Merlo J, Ohlsson H, Lynch K, Chaix B, Subramanian S. Individual and collective bodies: using measures of variance and association in contextual epidemiology. *Submitted* 2009.
46. Clark JA, Potter DA, McKinlay JB. Bringing social structure back into clinical decision making. *Soc Sci Med* 1991;32(8):853-66.
47. Eisenberg JM. Sociologic influences on decision-making by clinicians. *Ann Intern Med* 1979;90(6):957-64.
48. Eisenberg JM. Physician utilization: the state of research about physicians' practice patterns. *Med Care* 2002;40(11):1016-35.
49. Sleath B, Shih YC. Sociological influences on antidepressant prescribing. *Soc Sci Med* 2003;56(6):1335-44.
50. Lynch J, Kaplan G. Socioeconomic position. In: Berkman L, Kawachi I, editors. *Social epidemiology*. New York: Oxford University Press, 2000:13-35.
51. Scott A, Shiell A, King M. Is general practitioner decision making associated with patient socio-economic status? *Soc Sci Med* 1996;42(1):35-46.
52. SFS 1982:763.
53. Wallack SS, Thomas CP, Martin TC, Ryan A. Differences in prescription drug use in HMO and self-insured health plans. *Med Care Res Rev* 2007;64(1):98-116.
54. The Swedish Pharmaceutical Reimbursement System 2007.
55. Evaluation of the effects of statins (with particular consideration of atorvastatin). Cologne: Institut fur Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2006.
56. Greenland S, Morgenstern H. Confounding in health research. *Annu Rev Public Health* 2001;22:189-212.
57. Greenland S, Morgenstern H. Ecological bias, confounding, and effect modification. *Int J Epidemiol* 1989;18(1):269-74.
58. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *J Am Med Assoc* 1999;282(24):2340-6.
59. Merlo J, Liedholm H, Lindblad U, Bjorck-Linne A, Falt J, Lindberg G, et al. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study. *Bmj* 2001;323(7310):427-8.
60. WHO. About the ATC/DDD system (http://www.whocc.no/atcddd/).
61. Hjerpe P, Merlo J, Ohlsson H, Bengtsson-Boström K, Lindblad U. Validity of registration of ICD codes and prescriptions in a research database in

primary care Skaraborg primary care database (SPCD). *Working paper* 2009.
62. Läkemedelsrådet, editor. *Bakgrundsmaterial [in Swedish]*. Lund, 2006.
63. Läkemedelsrådet, editor. *Skånelistan 2004 [in Swedish]*. Lund, 2004.
64. Läkemedelsrådet, editor. *Skånelistan 2006 [in Swedish]*. Lund, 2006.
65. Läkemedelsrådet, editor. *Skånelistan 2005 [in Swedish]*. Lund, 2005.
66. Läkemedelsrådet, editor. *Bakgrundsmaterial*. Lund, 2005.
67. Sjöqvist F, Dahl M-L, Gustafsson L, Hensjö L-O. Drug therapeutics committees: a Swedish experience. *WHO Drug Information.* 2002;16:207-13.
68. Socialdepartementet. Lag (1996:1157) om läkemedelskommittéer. (Law (1996:1157) about drug committees) [in Swedish].
69. Edling AL. Beslut (469/2003), 2003.
70. Schneeweiss S. Developments in post-marketing comparative effectiveness research. *Clin Pharmacol Ther* 2007;82(2):143-56.
71. WorldBankCountryClassification 2005. [http://www.worldbank.org/data/countryclass/countryclass.html]
72. Berkman LF, Kawachi I. *Social Epidemiology*. New York: Oxford University Press, 2000.
73. Oakes JM, Kaufman JS. *Methods in Social Epidemiolgy*. San Fransisco, CA: Jossey-Bass, 2006.
74. Bongers IM, van der Meer JB, van den Bos J, Mackenbach JP. Socio-economic differences in general practitioner and outpatient specialist care in The Netherlands: a matter of health insurance? *Soc Sci Med* 1997;44(8):1161-8.
75. Dunlop S, Coyte PC, McIsaac W. Socio-economic status and the utilisation of physicians' services: results from the Canadian National Population Health Survey. *Soc Sci Med* 2000;51(1):123-33.
76. Bengtsson H. Nuvarnade kommunuppdelning [in Swedish] (Classification of municipalities). In: Kommunförbundet S, editor: Svenska Kommunförbundet, 2003.
77. Denig P, Haaijer-Ruskamp FM. Therapeutic decision making of physicians. *Pharm Weekbl Sci* 1992;14(1):9-15.
78. Denig P, Haaijer-Ruskamp FM, Zijsling DH. How physicians choose drugs. *Soc Sci Med* 1988;27(12):1381-6.
79. Leyland AH, Groenewegen PP. Multilevel modelling and public health policy. *Scand J Public Health* 2003;31(4):267-74.
80. Last J. *A dictionary of epidemiology*. 4th ed. New York: Oxford University Press, 2001.

81. Gelman A. Analysis of variance: Why it is more important than ever. *The annals of statistics* 2005;33(1):1-31.
82. Browne W, Subramanian S, Jones K, Goldstein H. Variance partitioning in multilevel logistic models that exhibit overdispensation. *J. R. Statist. Soc* 2005;168(3):599-613.
83. Lewontin RC. The analysis of variance and the analysis of causes. 1974. *Int J Epidemiol* 2006;35(3):520-5.
84. Merlo J, Ostergren PO, Hagberg O, Lindstrom M, Lindgren A, Melander A, et al. Diastolic blood pressure and area of residence: multilevel versus ecological analysis of social inequity. *J Epidemiol Community Health* 2001;55(11):791-8.
85. Hox J. *Multilevel analysis: Techniques and applications*. Mahway, NJ: Erlbaum, 2002.
86. Kreft I, Leeuw J. *Introducing multilevel modeling*. Thousand Oaks, CA: Sage, 1998.
87. Larsen K, Merlo J. Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. *Am J Epidemiol* 2005;161(1):81-8.
88. Larsen K, Petersen JH, Budtz-Jorgensen E, Endahl L. Interpreting parameters in the logistic regression model with random effects. *Biometrics* 2000;56(3):909-14.
89. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006;60(4):290-7.
90. Vigre H, Dohoo IR, Stryhn H, Busch ME. Intra-unit correlations in seroconversion to Actinobacillus pleuropneumoniae and Mycoplasma hyopneumoniae at different levels in Danish multi-site pig production facilities. *Prev Vet Med* 2004;63(1-2):9-28.
91. Goldstein H, Spiegelhalter D. League tables and their limitations: Statistical issues in comparisions of institutional performance. *J. R. Statist. Soc* 1996;159(Part 3):385-443.
92. Lynch K, Subramanian S, Chaix B, Ohlsson H, Larsen K, Lernamark Å, Merlo, J. Context and health when health risk is low - The case of Type 1 Diabetes in Sweden. *Working paper* 2008.
93. Tan A, Freeman JL, Freeman DH, Jr. Evaluating health care performance: strengths and limitations of multilevel analysis. *Biom J* 2007;49(5):707-18.

94. Rasbash J, Steele F, Browne W. *A User's Guide to MLwiN, Version 2.0. Documentation Version 2.1e.* London, UK: Centre for Multilevel Modelling, Institute of Education, University of London, 2003.
95. Browne W. *MCMC Estrimation in MLwiN (Version 2.0)*. London: Institue of Education University of London, 2003.
96. Wright D, Bobashev GV, Novak SP. Decomposing the total variation in a nested random effects model of neighborhood, household, and individual components when the dependent variable is dichotomous: implications for adolescent marijuana use. *Drug Alcohol Depend* 2005;78(2):195-204.
97. Spiegelhalter D, Best N, Carlin B, van der Linde A. Bayesian measures of model complexity and fit. *J R Statist SocB* 2002;64(Part 4):583–639.
98. Greenland S. Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. *Am J Epidemiol* 2004;160(4):301-5.
99. Katz KA. The (relative) risks of using odds ratios. *Arch Dermatol* 2006;142(6):761-4.
100. Martuzzi M, Elliott P. Estimating the incidence rate ratio in cross-sectional studies using a simple alternative to logistic regression. *Ann Epidemiol* 1998;8(1):52-5.
101. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. . *Statistics and Computing* 2000;10:325--337.
102. Ananth CV, Kantor ML. Modeling multivariate binary responses with multiple levels of nesting based on alternating logistic regressions: an application to caries aggregation. *J Dent Res* 2004;83(10):776-81.
103. Katz J, Carey V, Zeger SL, Sommer A. Estimation of design effects and diarrhea within households and villages. *Am J Epidemiol* 1993;138:994-1006.
104. Katz J, Zeger SL, West Kj, Tielsch J, Sommer A. Clustering of xerophthalmia within households and villages. *Int J Epidemiol* 1993;22:709-15.
105. Vanobbergen J, Lesaffre E, Garcia-Zattera MJ, Jara A, Martens L, Declerck D. Caries patterns in primary dentition in 3-, 5- and 7-year-old children: spatial correlation and preventive consequences. *Caries Res* 2007;41(1):16-25.
106. Petronis KR, Anthony JC. Perceived risk of cocaine use and experience with cocaine: do they cluster within US neighborhoods and cities? *Drug Alcohol Depend* 2000;57(3):183-92.
107. Bobashev GV, Anthony JC. Clusters of marijuana use in the United States. *Am J Epidemiol* 1998;148(12):1168-74.

108. Bobashev GV, Anthony JC. Use of alternating logistic regression in studies of drug-use clustering. *Subst Use Misuse* 2000;35(6-8):1051-73.
109. Chauvin C, Bouvarel I, Beloeil PA, Orand JP, Guillemot D, Sanders P. A pharmaco-epidemiological analysis of factors associated with antimicrobial consumption level in turkey broiler flocks. *Vet Res* 2005;36(2):199-211.
110. Delva J, Bobashev G, Gonzalez G, Cedeno M, Anthony JC. Clusters of drug involvement in Panama: results from Panama's 1996 National Youth Survey. *Drug Alcohol Depend* 2000;60(3):251-7.
111. Preisser JS, Arcury TA, Quandt SA. Detecting patterns of occupational illness clustering with alternating logistic regressions applied to longitudinal data. *Am J Epidemiol* 2003;158(5):495-501.
112. Merlo J, Yang M, Chaix B, Lynch J, Rastam L. A brief conceptual tutorial on multilevel analysis in social epidemiology: investigating contextual phenomena in different groups of people. *J Epidemiol Community Health* 2005;59(9):729-36.
113. Kamps G, Stewart R, van Der Werf G, Schuling J, Jong BM. Adherence to the guidelines of a regional formulary. *Fam Pract* 2000;17(3):254-60.
114. Koutsavlis AT. Disseminating practice guidelines to physicians: Institut national de santé publique du Québec, 2001.
115. Stewart RE, Vroegop S, Kamps GB, van der Werf GT, Meyboom-de Jong B. Factors influencing adherence to guidelines in general practice. *Int J Technol Assess Health Care* 2003;19(3):546-54.
116. Brookhart MA, Solomon DH, Wang P, Glynn RJ, Avorn J, Schneeweiss S. Explained variation in a model of therapeutic decision making is partitioned across patient, physician, and clinic factors. *J Clin Epidemiol* 2006;59(1):18-25.
117. Lopez-Valcarcel B, Ortun-Rubio V, Cabez-Mora A, Lopez-Cabañas A, Diaz-Berenger J, Alamo-Santana F. Evaluation del uso apropiado de medicamentos en atencion primaria. Como se puede mejorar? (Evaluation of the appropriate use of medication in primary care - how do we improve it?) [in Spanish]. *Aten Primaria* 2002;30:467-471.
118. Rasbash J, Browne W, Goldstein H, Yang M, Plewis I, Healy M, et al. Modelling the variance as a function of explanatory variables. *A User's Guide to MLwiN. Version 2.0. Documentation Version 2.1e*. London, UK: Institute of Education, University of London, 2003.
119. Leckie G, Goldstein H. The Limitations of Using School League Tables to Inform School Choice. In: Organisation TCfMaP, editor. Bristol: Department of Economics, University of Bristol, UK, 2009.
120. The statin wars: why AstraZeneca must retreat. *Lancet* 2003;362(9393):1341.

121. Läkemedelsverket. Produktresumén revideras för Crestor (Product resumé for Crestor is revised).
122. Ohlsson O, Kjellström T. Landsomfattande konsensus för behandling av höga blodfetter (För landets läkemedelskommittéordförande LOK) (consensus for treament of high lipids). Lund, Sweden, 2003.
123. Glass H, Rosenthal B. Demographics, practices, and prescribing characteristics of physicians who are early adopters of new drugs. *Pharm and Therapeut* 2004;29(11):699-708.
124. Layton D, Souverein PC, Heerdink ER, Shakir SA, Egberts A. Prescriber adoption of newly approved selective COX-2 inhibitors. *Pharmacoepidemiol Drug Saf* 2008.
125. Coleman J, Menzel H, Katz E. Social processes in physicians´adoption of a new drug. *J of Chronic Dis* 1959;9(1):1-19.
126. Dybdahl T, Andersen M, Kragstrup J, Kristiansen IS, Sondergaard J. General practitioners' adoption of new drugs and previous prescribing of drugs belonging to the same therapeutic class: a pharmacoepidemiological study. *Br J Clin Pharmacol* 2005;60(5):526-33.
127. Dybdahl T, Andersen M, Sondergaard J, Kragstrup J, Kristiansen IS. Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs. *Europ J Clin Pharmacol* 2004;60(9):667-72.
128. Florentinus SR, Nielsen MW, van Dijk L, Leufkens HG, Hansen EH, Heerdink ER. Patient characteristics associated with prescribing of a newly introduced drug: the case of rofecoxib. *Eur J Clin Pharmacol* 2005;61(2):157-9.
129. Greving JP, Denig P, Van der Veen WJ, Beltman FW, Sturkenboom MC, Haaijer-Ruskamp FM. Determinants for the adoption of angiotensin II receptor blockers by general practitioners. *Soc Sci Med* 2006;63(11):2890-8.
130. Jones MI, Greenfield SM, Bradley CP. Prescribing new drugs: qualitative study of influences on consultants and general practitioners. *Brit Med J* 2001;323(7309):378-81.
131. Kozyrskyj A, Raymond C, Racher A. Characterizing early prescribers of newly marketed drugs in Canada: a population-based study. *Eur J Clin Pharmacol* 2007;63(6):597-604.
132. Steffensen FH, Sörensen H, Olesen F. Diffusion of new drugs in Danish general practice. *Fam Prac* 1999;16:407-413.
133. Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J. Physician and practice characteristics associated with the early utilization of new prescription drugs. *Med Care* 2003;41(8):895-908.

134. Rogers E. *Diffusion of Innovation*. New York, NY: New York: Free Press, 1962.
135. Rogers EM. A prospective and retrospective look at the diffusion model. *J Health Commun* 2004;9 Suppl 1:13-9.
136. Landon BE, Reschovsky J, Reed M, Blumenthal D. Personal, organizational, and market level influences on physicians' practice patterns: results of a national survey of primary care physicians. *Med Care* 2001;39(8):889-905.
137. Diez Roux AV. Residential environments and cardiovascular risk. *J Urban Health* 2003;80(4):569-89.
138. O'Campo P. Invited commentary: Advancing theory and methods for multilevel models of residential neighborhoods and health. *Am J Epidemiol* 2003;157(1):9-13.
139. Merlo J. Socioeconomic disparities in cardivascular diseases - a longitudinal multilevel analysis: Swedish Research Council (Vetenskapsrådet) 2005.
140. Blakely T, Woodward A. Ecological effects in mutlilevel studies. *J Epidemiol Comm Health* 2000;54:367-374.
141. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial of multilevel analysis in social epidemiology - Interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. *J Epidemiol Community Health* 2005;59:1022-8.
142. Merlo J, Chaix B, Ohlsson H, Lynch K, Subramanian S. Individual and collective bodies - On the use of measures of varaince and association in contextual epidemiology. *Working paper* 2008.
143. Clarke P, Wheaton B. Addressing data sparseness in contextual population research: Using cluster analysis to create synthetic neighborhoods. *Sociological Methods Research* 2007;35:311.
144. Riva M, Gauvin L, Barnett TA. Toward the next generation of research into small area effects on health: a synthesis of multilevel investigations published since July 1998. *J Epidemiol Community Health* 2007;61(10):853-61.
145. Duncan G, Raudenbush SW. Assesing the effects of context in studies of child and youth development. *Educ Psychol* 1999;34:29-41.
146. Diez Roux AV. Next steps in understanding the multilevel determinants of health. *J Epidemiol Comm Health* 2007;62:957-959.
147. Oakes JM. The (mis)estimation of neighborhood effects: causal inference for a practicable social epidemiology. *Soc Sci Med* 2004;58(10):1929-52.
148. Merlo J, Chaix B. Neighbourhood effects and the real world beyond randomized community trials: a reply to Michael J Oakes. *Int J of epidemiolgy* 2006;35(5):1361-1363.

149. Veblen T. *The Theory of the Leisure Class*, 1899.
150. Willems S, De Maesschalck S, Deveugele M, Derese A, De Maeseneer J. Socio-economic status of the patient and doctor-patient communication: does it make a difference? *Patient Educ Couns* 2005;56(2):139-46.
151. Hjärtinfarkter 1987-2002, samt utskrivna efter vård för akut hjärtinfarkt 1987-2003. *Statistik - Hälsa och sjukdomar 2005:2*.
152. Li J, Gray BR, Bates DM. An empirical study of statisical properties of variance partition coefficients for multilevel logistic regression models. *Communications in statistics - simulation and computation* 2008;37:2010-2026.
153. Roberts JK. Group dependency in the presence of small intraclass correlation coefficients: an argument in favor of not interpreting the ICC. *Annual meeting of the American Educational Research Association*, 2007.
154. Burton A, Altman DG, Royston P, Holder RL. The design of simulation studies in medical statistics. *Stat Med* 2006;25(24):4279-92.
155. Socialstyrelsen. http://www.socialstyrelsen.se/en/about/epc/.
156. Black N. Why we need observational studies to evaluate the effectiveness of health care. *Bmj* 1996;312(7040):1215-8.
157. Sorensen G, Emmons K, Hunt MK, Johnston D. Implications of the results of community intervention trials. *Annu Rev Public Health* 1998;19:379-416.
158. Suissa S. Novel approaches to pharmacoepidemiological study design and statistical analysis. In: Strom BL, editor. *Pharmacoepidemiolgy*. 3rd ed. Chichester, UK: Wiley, 2000:785.
159. STROBE. STrengthening the Reporting of OBservational studies in Epidemiology, 2004.
160. Solomon LS, Zaslavsky AM, Landon BE, Cleary PD. Variation in patient-reported quality among health care organizations. *Health Care Financ Rev* 2002;23(4):85-100.
161. Krein SL, Hofer TP, Kerr EA, Hayward RA. Whom should we profile? Examining diabetes care practice variation among primary care providers, provider groups, and health care facilities. *Health Serv Res* 2002;37(5):1159-80.
162. Sixma HJ, Spreeuwenberg PM, van der Pasch MA. Patient satisfaction with the general practitioner: a two-level analysis. *Med Care* 1998;36(2):212-29.
163. Hofer TP, Hayward RA, Greenfield S, Wagner EH, Kaplan SH, Manning WG. The unreliability of individual physician "report cards" for assessing the costs and quality of care of a chronic disease. *Jama* 1999;281(22):2098-105.

164. Huang IC, Diette GB, Dominici F, Frangakis C, Wu AW. Variations of physician group profiling indicators for asthma care. *Am J Manag Care* 2005;11(1):38-44.
165. Ashworth M, Armstrong D. Partnership effects in general practice: identification of clustering using intra-class correlation coefficients. *Br J Gen Pract* 2003;53(496):863-5.
166. Grimshaw J, Thomas R, Maclennan G, Fraser C, Ramsay C, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8(6).
167. Soumerai S, Majumdar S, Lipton H. Evaluating and Improving Physician Prescribing. In: Strom B, editor. *Pharmacoepidemiolgy*. 3rd ed. Chichester, UK: Wiley, 2000:483-503.
168. Swedish Health Care in an International Context. Stockholm, 2005.
169. Stano M. Evaluating the policy role of the small area variations and physician practice style hypothese. *Health Policy* 1993;24:9-17.
170. Groenewegen P, Westert G. Is there a time trend in medical practice variations?: areview of the litterature and an critical analysis of theoretical approaches. *J Public Health* 2004;12(3):229-36.
171. Westert GP, Groenewegen PP, Boshuizen H, Spreeuwenberg PM, Steultjens MPM. Medical practice variation in hospotal care; time trends of a spatioal phenomenon. *Health & Place* 2004(10):215-220.
172. Merlo J. A framework for Pharmacoepidemiology. Malmö: Samhällsmedicinska institutionen, 1996.
173. Läkemedelsverket, 2008.
174. Act (2002:160) on Pharmaceutical Benefits, 2002.
175. Strom BL. What is pharmacoepidemiology. In: Strom BL, editor. *Pharmacoepidemiology*. 3rd ed. Chichester, UK: Wiley, 2000:3.
176. Fretheim A, Oxman AD. International variation in prescribing antihypertensive drugs: its extent and possible explanations. *BMC Health Serv Res* 2005;5(1):21.
177. Stolk P, Van Wijk BL, Leufkens HG, Heerdink ER. Between-country variation in the utilization of antihypertensive agents: Guidelines and clinical practice. *J Hum Hypertens* 2006;20(12):917-22.
178. Anis AH, Carruthers SG, Carter AO, Kierulf J. Variability in prescription drug utilization: issues for research. *Cmaj* 1996;154(5):635-40.
179. Kasje WN, Denig P, Stewart RE, de Graeff PA, Haaijer-Ruskamp FM. Physician, organisational and patient characteristics explaining the use of angiotensin converting enzyme inhibitors in heart failure treatment: a multilevel study. *Eur J Clin Pharmacol* 2005;61(2):145-51.

180. Thomsen RW, Johnsen SP, Olesen AV, Mortensen JT, Boggild H, Olsen J, et al. Socioeconomic gradient in use of statins among Danish patients: population-based cross-sectional study. *Br J Clin Pharmacol* 2005;60(5):534-42.
181. Martinsson A. IDEAL-studien. http://www.janusinfo.se/imcms/8044, 2005.
182. Jansson S, Anell A. The impact of decentralised drug-budgets in Sweden - a survey of physicians' attitudes towards costs and cost-effectiveness. *Health Policy* 2006;76(3):299-311.
183. Peckham S, Exworthy M, Powell M, Greener I. Decentralisation as an organisational model for health care in England, 2005.
184. Harris CM, Scrivener G. Fundholders' prescribing costs: the first five years. *Bmj* 1996;313(7071):1531-4.
185. Anell A, Jendteg S, Nordling S. *Pharmaceutical prescribing and cost containment - what can Sweden learn from England, Germany and the Netherlands?* Lund: Rahms i Lund, 1999.
186. Aronson JK. Prescribing statins. *Br J Clin Pharmacol* 2005;60(5):457-8.
187. Olsson AG, Molgaard J, von Schenk H. Synvinolin in hypercholesterolaemia. *Lancet* 1986;2(8503):390-1.
188. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344(8934):1383-9.
189. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360(9326):7-22.
190. Behandling med lipidsänkande läkemedel vid prevention av hjärt-kärlsjukdomar. (Treatment with lipid-lowering drugs for prevention of heart diseases) [in Swedish]. *Information från Läkemedelsverket* 2003;14(ISSN 1101-7104):4.
191. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H, et al. Persistence of use of lipid-lowering medications: a cross-national study. *Jama* 1998;279(18):1458-62.
192. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Med J Aust* 1996;164(4):208-11.
193. Thorsen T, Mäkelä M, editors. *Changing professional practice - Theory and practice of clinical guidelines implementation*. Copenhagen, 1999.
194. Brindis RG, Sennett C. Physician adherence to clinical practice guidelines: does it really matter? *Am Heart J* 2003;145(1):13-5.
195. Grol R, Dalhuijsen J, Thomas S, Veld C, Rutten G, Mokkink H. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. *Bmj* 1998;317(7162):858-61.

196. Brand C, Landgren F, Hutchinson A, Jones C, Macgregor L, Campbell D. Clinical practice guidelines: barriers to durability after effective early implementation. *Intern Med J* 2005;35(3):162-9.
197. Francke AL, Smit MC, de Veer AJ, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC Med Inform Decis Mak* 2008;8:38.
198. Langley C, Faulkner A, Watkins C, Gray S, Harvey I. Use of guidelines in primary care--practitioners' perspectives. *Fam Pract* 1998;15(2):105-11.
199. En uppföljning av läkemedelskommitéernas arbete. Hur påverkas läkemedelsanvändningen ? (A follow-up of the effort of the drug committees. How does it affect the drug use?) [in Swedish]. In: Socialstyrelsen, editor.

I

Eur J Clin Pharmacol (2005) 61: 657–665
DOI 10.1007/s00228-005-0975-9

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

H. Ohlsson · U. Lindblad · T. Lithman · B. Ericsson
U.-G. Gerdtham · A. Melander · L. Råstam · J. Merlo

Understanding adherence to official guidelines on statin prescribing in primary health care—a multi-level methodological approach

Received: 22 April 2005 / Accepted: 24 June 2005 / Published online: 25 August 2005

Abstract *Objective*: The aim was to investigate the role that municipalities and out-patient health care centres (HCCs) have in understanding adherence to official guidelines on statin prescribing. Our hypothesis was that after guideline publication, adherence to recommended statin prescription would increase and variance among HCCs and municipalities would decrease. Since multi-level regression analysis (MLRA) is a relatively new methodology in pharmacoepidemiology, we also aimed to explore the application of MLRA in our investigation. *Methods*: We obtained data from the Swedish Corporation of Pharmacies record of sales regarding all initial prescriptions of statins issued between April and December 2003. We applied multi-level analysis on 34,514 individual prescriptions (level 1) nested within 226 HCCs (level 2), which in turn were nested within 33 municipalities (level 3). Temporal trends and gender differences were investigated by means of random slope analysis. Variance was expressed using median odds ratio (MOR) and interval odds ratio. *Results*: HCCs appeared to be more relevant than municipalities for understanding the physicians' propensity to prescribe a recommended statin ($MOR_{HCC} = 1.96$ and MOR Municipality = 1.41). Overall prevalence of adherence was very low (about 20%). After publication of the guidelines, prescription of recommended statins increased, and variance among HCCs decreased but only during the first 4 months of the observation period. *Conclusion*: The publication of official guidelines in the county of Scania exerted a positive influence on statin prescription but, at the end of the observation period, adherence was still low and practice variation high. These facts may reflect inefficient therapeutic traditions and suggest that more intensive interventions may be necessary to promote rational statin prescription.

Keywords Drug utilization studies · Multilevel analysis and adherence to guidelines · Statins

This study has been presented as an abstract at the 20th International Conference of Pharmacoepidemiology and Therapeutic Risk Management, Bordeaux, France, in August 2004; the 3rd Nordic Conference in Epidemiology, Kuopio, Finland, in June 2004; and the first Nordic Social Pharmacy and Health Service Research Conference, Uppsala, Sweden, in October 2004.

H. Ohlsson · T. Lithman · B. Ericsson
Drug Utilization Unit, Scania Region,
Regionhuset, Box 1, 22100 Lund, Sweden

H. Ohlsson (✉) · U. Lindblad · U.-G. Gerdtham
L. Råstam · J. Merlo (✉)
Community Medicine, Department of Medical Science,
Malmö University Hospital, Faculty of Medicine,
Lund University, 20502 Malmö, Sweden
E-mail: henrik.ohlsson@skane.se
E-mail: juan.merlo@med.lu.se

U. Lindblad
The Skaraborg Institute, Skövde, Sweden

A. Melander
The NEPI Foundation, Malmö University Hospital,
Malmö, Sweden

Introduction

The importance of appropriate prescribing for the well-being of the patient and for efficient use of limited health budgets cannot be exaggerated. Since 1997, every Swedish county has had a drug committee charged with promoting safe and cost-efficient drug use based on evidence-based medicine [1]. The committees aim to recommend medications appropriate to clinical needs, in doses that meet their patients' individual requirements, for an adequate period of time and at the lowest costs to the community [2]. The recommendations respect the patients' choices and strive to maximise effectiveness while minimising risks and costs [3]. However, despite the existence of formal committees and guidelines on appropriate prescription, it is still not known to what extent these criteria are being followed and which factors may condition adherence to guidelines [4].

This study aimed to investigate variance among different municipalities and out-patient health care centres (HCCs) regarding adherence to guidelines on statin prescribing issued by the county council of Scania, Sweden, in March 2003. We wanted to investigate prescribing behaviour, and statins are an ideal medication group for this purpose since prescription of recommended statins is indicated for certain patients but not for others and since all statins have a similar efficacy (dependent on the particular dose used). We also analysed prescriptions rather than dispensations by the pharmacies because dispensations are conditioned by the pharmacist (e.g. with dispensation of generic drugs). Our hypothesis was that adherence to guidelines would result in increased prescription of recommended statins and decreased variance among HCCs and municipalities during the observation period.

Moreover, since multi-level regression analysis (MLRA) is a relatively new methodology in pharmacoepidemiology, we also aimed to explore the application of this methodology for investigating practice variation. MLRA allows us to understand not only which patient, HCC and municipality characteristics are associated with adherence to recommended statins, but also the relative role of these different levels for successful adherence to prescription guidelines [5, 6].

Materials and methods

The register of pharmacological agents

Using the Swedish Corporation of Pharmacies record of sales, we selected all 34,514 prescriptions (16,400 for women and 18,114 for men) of statins issued between April and December 2003 at 226 HCCs in the 33 municipalities of Scania. Statins were defined according to the Anatomical Therapeutic Chemical (ATC) classification system code C10AA. The current prescription guidelines in the county were published in March 2003 and we started our evaluation in April in order to allow a run-in period and exclude the initial short-term variation.

In the register, each prescription, regardless of number of drugs, is given a unique serial number. Among other data, the register records information about the brand name and ATC code for both prescribed and dispensed drugs as well as stating whether the prescription is a repeat prescription or not. Moreover, the register records the age and gender of the patient as well as the HCC where the prescription was issued. Prescriptions issued at hospitals, at unidentified places, at places outside Scania and by a prescriber with no agreement with the county council are not recorded in the database.

Though a prescription is valid for 1 year, the reimbursement system accepts a maximum of 3 months' supply per dispensation. Since we evaluated adherence to the prescription guidelines issued in March 2003, we investigated only those prescriptions that were issued after this date. Since dispensations are for 3 months, but prescriptions for 1 year, we selected initial prescriptions only in order to reduce the risk of analysing the same prescription twice. In practical words, a patient may get a prescription of a statin that covers a whole year. However, the rules say that you cannot get the whole year supply on one occasion, but every 3 months. For this reason, we only accounted for the first dispensation within the study period.

Variables

At the individual level, the outcome variable was *prescription* (yes versus no) of Simvastatin GEA or Pravachol, the two *recommended brands* in the county during the period of our analysis. By law, the Swedish Society of Pharmacies dispenses the cheapest alternative of equivalent drugs, if patient and doctor agree. Therefore, since the aim of our study was to investigate determinants of prescription rather than of dispensation, we performed our main analysis on prescribed drugs.

Age was centred on the mean age of 66 years. We created dummy variables to define *sex*, and every one of the five *health care districts* in the county (north-west, north-east, south-west, south-east and central) as well as for the administrative status (private versus public) of the HCC. Private physicians are less restricted by the public health care administration, which could be expressed in a lower adherence to county guidelines.

We considered *time* (in months) as a continuous variable (April = 0, May = 1, ..., December = 8) that was modelled as a quadratic function. At the municipality level, we obtained the variable *physician density*, defined as number of physicians per 10,000 inhabitants in the 33 municipalities in Skåne.

Statistical analysis

Multi-level logistic regression models

Because of the hierarchical structure of the data, with patients (first level) nested within HCCs (second level) which, in turn, were nested within municipalities (third level), we analysed the probability of prescribing a recommended statin by means of MLRA [7, 8].

We applied three consecutive models. The first model (model A) only included the *time* variable. In the second model (model B), we included *age* and *sex*. In the third model (model C), we added the HCC-level variable *private versus public HCC* and the municipality-level variables *physician density* and *health care district*.

To study associations, we calculated odds ratios (ORs) and their 95% confidence interval (95% CI) from the regression coefficients and their standard error (SE) in the fixed-effects part of the multi-level analysis.

Ranking of HCCs

We compared the probability of prescribing a recommended statin in every HCC with the mean probability in the whole county and ranked the HCCs according to this information. To do this comparison, we obtained the posterior means (also called "shrunken residuals") from the multi-level regression. These residuals corresponded to the OR (logarithmic scale), using the whole county as reference [9–11].

Variance, variance function and proportional change in variance

In the random-effects part of the multi-level analysis, we obtained the *variance* (SE) at the HCC and municipality levels. We calculated the *proportional change in variance* (PCV) between two consecutive models as follows:

$$\mathrm{PCV} = (V_0 - V_1)/V_0,$$

where V_0 is the variance in the initial model and V_1 is the variance in the model with more terms.

We allowed the regression coefficients of the variables *time* and *sex* to be random at the HCC level (i.e. random slope analysis). In this way, we were able to investigate whether trends of gender-specific prescribing of recommended statins differed among different HCCs. In the presence of random slopes, the HCC variance becomes a function of the *individual variables*. We used standard applications available in the MLwiN software [12] for the calculation of the variance function. The formulas and an extended explanation are detailed elsewhere [13, 14].

Examining local therapeutic traditions by means of MLRA

Since prescription of recommended statins depends solely on the arbitrary decision of the prescriber, it appears theoretically plausible to expect no significant variance among HCCs and municipalities in the prescription of recommended statins. However, if such variance existed, the tendency of prescribing a recommended statin may be more similar among prescribers within the same HCC and the same municipality than among prescribers from different HCCs and municipalities. This similarity (i.e. residual correlation, in statistical terms) would express itself as a clustering of prescriptions of recommended statins within HCCs and municipalities [10, 15, 16]. That is, a part of the individual propensity of prescribing a recommended statin would be at the HCC or municipality level. Our rationale was that this phenomenon is an expression of *local therapeutic traditions* and can be investigated by measures of variance and clustering in MLRA (see below).

We expected that possible local therapeutic traditions (i.e. unexplained practice variation) would decrease after the official guidelines were published in March 2003 and in this study we aimed to describe this variance.

The median odds ratio

Direct epidemiological interpretation of HCC and municipality variance in the logistic regression is difficult [7, 17]. One suitable alternative is calculating the median odds ratio (MOR), as proposed by Larsen and co-authors [8, 18]. The MOR translates the variance in the widely used OR scale, which has a consistent and intuitive interpretation. The MOR can be directly compared with the ORs of individual or area variables. In very simple terms, the MOR could be interpreted as the increased (median) probability of being prescribed a recommended statin if a patient was to change HCC (or municipality). The MOR depends directly on the HCC-level variance and can be computed using the following formula:

$$\begin{aligned}\mathrm{MOR} &= \exp[\sqrt{(2 \times \mathrm{V_{HCC}})} \times 0.6745] \\ &\approx \exp(0.95\sqrt{\mathrm{V_{HCC}}}),\end{aligned}$$

where V_{HCC} is the HCC-level variance, and 0.6745 is the 75th percentile of the cumulative distribution function of the normal distribution with mean 0 and variance 1.

If the MOR was equal to 1, there would be no differences among HCCs in the probability of prescribing a recommended statin. If there were important HCC-level differences, the MOR would be large.

The accuracy of the variance estimates was evaluated by their SE. We applied an approximate normal test for the calculation of P values. A P value >0.05 was considered non-significant (NS).

The 80% interval OR

Contrary to individual-level variables in multi-level models, area variables only take one value in each area and, consequently, it is necessary to compare individuals from different HCCs or municipalities to quantify area-level associations [19, 20]. Therefore, we need to incorporate the HCC/municipality variance in the presentation of area-level associations. For this purpose, we applied the 80% interval odds ratio (IOR-80), as described in detail elsewhere [8, 18, 20]. The lower and upper bounds of the IOR can be computed using the following equations:

$$\begin{aligned}\mathrm{IOR_{lower}} &= \exp[\beta + \sqrt{(2 \times \mathrm{V_H})} \times (-1.2816)] \\ &\approx \exp(\beta - 1.81\sqrt{\mathrm{V_H}})\end{aligned}$$

$$\begin{aligned}\mathrm{IOR_{upper}} &= \exp[\beta + \sqrt{(2 \times \mathrm{V_H})} \times (1.2816)] \\ &\approx \exp(\beta + 1.81\sqrt{\mathrm{V_H}}),\end{aligned}$$

where β is the regression coefficient for the hospital-level variable, V_{H} is the hospital-level variance, and the values -1.2816 and $+1.2816$ are the 10th and 90th percentiles

of the normal distribution, with mean 0 and variance 1 (see references for further explanation [8, 18, 20]).

It should be noted that the IOR-80 is not a common confidence interval. The interval is narrow if the residual variation between different HCCs is small and wide if this variation is large. If the interval contains the value 1, this indicates that the effect of the higher-level characteristic under scrutiny is not that important when compared with the remaining residual higher-level heterogeneity. The IOR therefore complements the information provided by the normal OR.

Parameters were estimated using the restricted iterative generalised least square (RIGLS) method. The analyses were performed using the MLwiN 1.2 software developed by Goldstein research group [12].

Results

Table 1 indicates that the prevalence of adherence with guidelines for prescription of statins was overall 20% and this prevalence was the same for both men and women. The number of private HCCs was similar to the number of public HCCs in the whole county, but this figure was much lower in the north-east and central health care districts. Physician density was lower in the north-west and north-east health care districts than in the other three health care districts.

In Table 2, model A shows that factors related to the HCC and municipality level together played a relevant role in understating individual prescription of recommended statins ($MOR_{Municipality\text{-}HCC} = 2.13$). However, it appears that HCCs are more relevant than are municipalities in this context ($MOR_{HCC} = 1.96$ and $MOR_{Municipality} = 1.41$).

The ranking of the HCCs and municipalities regarding their prevalence of use of recommended statins relative to the overall prevalence in the county at the beginning of the study period (i.e. intercept residuals) is presented in Fig. 1 both before (model A) and after (model C) making adjustments. The differences among the municipalities disappeared after adjustment, but the picture for HCCs is different. Many HCCs changed position in the ranking but the dispersion around the mean was only slightly reduced after adjustments in model C. The PCV indicates that 75% of the differences among municipalities were explained by the individual and contextual characteristics included in model C. However, this percentage was only 3% in relation to variance among HCCs.

Table 2 also shows that there was a significant temporal trend in prescription of recommended statins. Overall, the trends follow a quadratic function that is illustrated in Fig. 2 (thick black line), with a steeper slope at the beginning of the period that levelled off and even decreased at the end of the study period. This figure also shows that many specific HCC temporal trends differed from the overall trend in the county.

The probability of being prescribed a recommended statin increased for every year of age, although by a very low degree. Men demonstrated a lower probability than women of being prescribed a recommended statin but—as in the case of the temporal trend described above—this association differed in different HCCs. Because of the existence of significant slope variance in the association between prescription of recommended statins and both time and sex, the HCC variance became a function of these variables. This phenomenon is illustrated in Fig. 3 where we also show the effect of the adjustments performed in models B and C.

Regarding municipality and HCC-level variables, Table 2 shows that the probability of prescribing recommended statins was similar in private and public HCCs. The IOR-80 was wide, confirming the low

Table 1 Characteristics of the 34,514 prescriptions of statins, issued to 16,400 women and 18,114 men who visited 226 different health care centres (HCCs) in the 33 municipalities of Scania, Sweden. Unless otherwise indicated, values are given as percentages

	Whole Skåne	North-west	North-east	Central	South-west	South-east
Number of statin prescriptions	34,514	11,318	6,264	6,455	9,149	1,328
Men (%)	52	52	54	54	51	53
Mean age (years)	66	66	67	66	66	67
Number of municipalities	33	8	6	10	4	5
Number of HCCs	226	72	43	37	52	22
Number of private HCCs	121	46	19	13	26	17
Physician density[a]		27	23	43	45	40
Recommended statins						
Whole time period	20	18	18	23	20	28
0 (April 2003)	15	14	13	19	15	16
1 (May 2003)	16	12	12	23	16	23
2 (June 2003)	19	17	16	25	17	34
3 (July 2003)	19	18	20	24	14	20
4 (Aug 2003)	21	21	19	26	20	33
5 (Sept 2003)	22	22	19	27	21	22
6 (Oct 2003)	24	23	22	24	25	31
7 (Nov 2003)	20	19	17	21	22	28
8 (Dec 2003)	22	18	21	23	26	33

[a] Number of physicians per 10,000 inhabitants

Table 2 Multi-level logistic regression analysis of adherence to statin prescription guidelines in the county of Scania, Sweden. *HCC* health care centre, *IOR-80* 80% interval odds ratio, *MOR* median odds ratio, *OR* odds ratio, *95% CI* 95% confidence interval, *SE* standard error, *NS* non-significant, *PCV* proportional change in variance in model C using model A as reference

	Model A	Model B	Model C	
Fixed effects		OR (95% CI)	OR (95% CI)	
Time	1.25 (1.20–1.33)	1.25 (1.20–1.33)	1.25 (1.20–1.31)	
Time^2	0.98 (0.98–0.99)	0.98 (0.98–0.99)	0.98 (0.98–0.99)	
Sex		0.88 (0.82–0.95)	0.89 (0.82–0.95)	
Age		1.00 (1.00–1.00)	1.00 (1.00–1.00)	
Public versus private HCC	–	–	1.01 (0.86–1.18)	
IOR-80			0.28–3.63	
Physician density (rate)				
1st tertile			2.66 (1.16–6.06)	
IOR-80			0.74–9.53	
2nd tertile			Reference	
3rd tertile			2.36 (1.34–4.16)	
IOR-80			0.66–8.47	
North-west	–	–	Reference	
North-east	–	–	1.13 (0.77–1.68)	
IOR-80	–	–	0.31–4.07	
South-west	–	–	1.01 (0.60–1.70)	
IOR-80	–	–	0.28–3.64	
South-east	–	–	1.56 (1.01–2.41)	
IOR-80	–	–	0.44–5.61	
Central	–	–	1.29 (0.83–1.99)	
IOR-80	–	–	0.36–4.62	
Random effects	Variance (SE)	Variance (SE)	Variance (SE)	PCV
Municipality (intercept)	0.132 (0.51)	0.119 (0.048)	0.033 (0.022) (NS)	75%
$MOR_{Municipality}$[a]	1.41	1.39	1.18	
HCC (intercept)	0.500 (0.084)	0.495 (0.086)	0.484 (0.084)	3%
MOR_{HCC}[b]	1.96	1.96	1.94	
HCC and municipality (intercept)	0.632	0.615	0.517	18%
$MOR_{Municipality\text{-}HCC}$[c]	2.13	2.11	1.99	
Time (slope)	0.011 (0.002)	0.011 (0.002)	0.011 (0.002)	
Sex (slope)	–	0.067 (0.022)	0.067 (0.022)	
Patient	0.994 (0.008)	0.989 (0.008)	0.989 (0.008)	

[a]When moving to another municipality
[b]When moving to another HCC
[c]When moving to another HCC in another municipality

relevance of this variable for understanding adherence to guidelines on statin prescription.

Compared with the north-west, the south-east health care district exhibited a higher adherence to the county's guidelines on statin prescription. However, in this case, the IOR-80 was also very wide, indicating the low importance of this variable for understanding differences in adherence to guidelines among HCCs.

Physician density—a municipality characteristic—appeared to play a role in improving adherence, but this association was U-shaped, with the lowest probability in the second tertile group. The IOR-80 was relatively wide but this variable may have some relevance for the implementation of prescription guidelines.

Discussion

We present a relatively new analytical approach for drug utilisation studies in pharmacoepidemiology. MLRA reveals the role of different levels for understanding drug prescription and utilisation [5, 6]. Hierarchical structures (e.g. patients nested within physicians in different HCCs nested within counties in different countries) are common in pharmacoepidemiology, and MLRA allows an appropriate analysis of hierarchical structures for both statistical and epidemiological purposes [5, 21]. In the present study, moreover of providing some extended methodological description of MLRA, we have proposed a model of analysis for investigating practice variation in general and adherence to statin prescription guidelines in particular.

We used the month of April 2003 as a starting point in our evaluation since guidelines were published in the middle of March. In April, each HCC and municipality has a specific level of prescription, and our hypothesis was that successful adherence with guidelines would convey increasing prevalence of use of recommended statins and decreasing variance between HCC and municipalities along the observation period. Therefore, adjusting for period of time (e.g. January, February and March) before the publication of the guidelines is less relevant for analysing trends in prevalence and variation during the observation period. Moreover, the

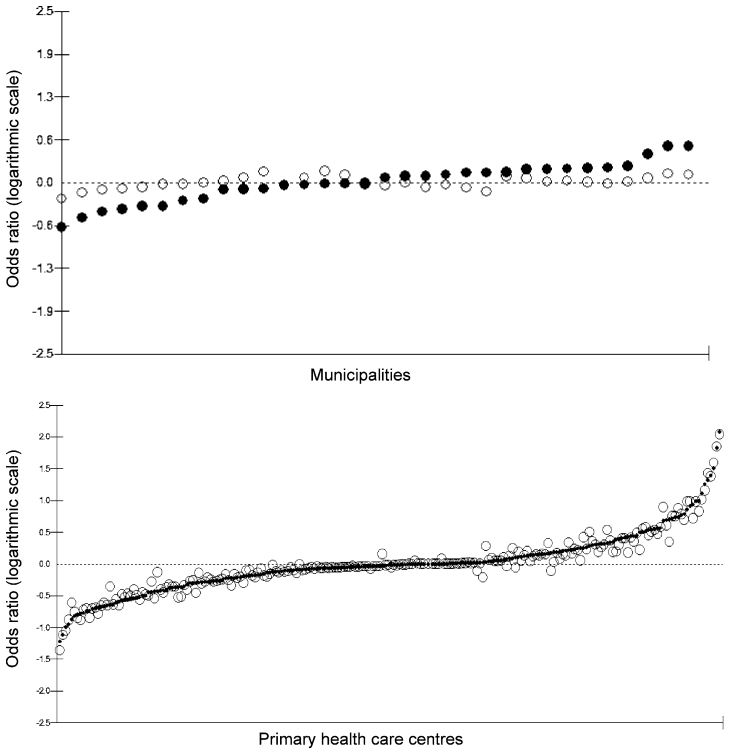


Fig. 1 Differences in adherence to guidelines on statin prescribing among municipalities (*top*) and health care centres (*HCCs*) (*bottom*) before (*filled circles*) and after (*open circles*) adjustments for age, gender, administrative status of the HCC (private versus public), and physician density in the municipality and health care district

investigation of the association between physician density and health care districts and adherence with guidelines can only be done after these guidelines were actually published in the middle of March.

There are few therapeutic reasons for choosing a more expensive drug brand among several brands of similar efficacy. Nevertheless, this practice was fairly common in the county, and the MLRA revealed substantial practice variation that may reflect local therapeutic traditions which hindered prescription of recommended statins.

Adherence to guidelines seemed to a considerable degree to be conditioned by contextual factors at the HCC and municipality levels. Physicians from the same HCCs and from the same municipalities showed a similar propensity to prescribe recommended statins. In other words, HCC and municipality levels appear to bear a significant part of the prescriber's inclination to issue a recommended statin. This relative "responsibility" [6] for successful adherence to prescription guidelines was higher for the HCC than for the municipality level.

These results, illustrated in Fig. 3, suggest that in some way the publication of the official prescription guidelines reduced the initial practice variation, from MOR close to 2 in April to MOR close to 1.5 in September 2003. Thereafter, practice variation increased slightly but never reached the heterogeneity observed at the beginning of the observation period.

It should be noted that some HCCs that showed relatively high adherence in April showed a clear decreasing trend during the study period. The reasons for this behaviour need be investigated in detail. Excluding the outlier with the highest adherence in April (Fig. 2) from the analysis decreased the HCC variance from 0.500 to 0.420 and increased the municipality variance from 0.132 to 0.158 but did not have a major effect on slope variance.

In this study, we did not have access to information at the physician level. A part of the HCC variation found could therefore in fact be physician variation [6, 22, 23], an aspect we observed in the Skaraborg Primary Health Care Database containing information from general practitioners' medical records [24].

Practice variation is a common phenomenon which need not necessarily be inappropriate but, rather, may reflect equivalent therapeutic traditions confronting a

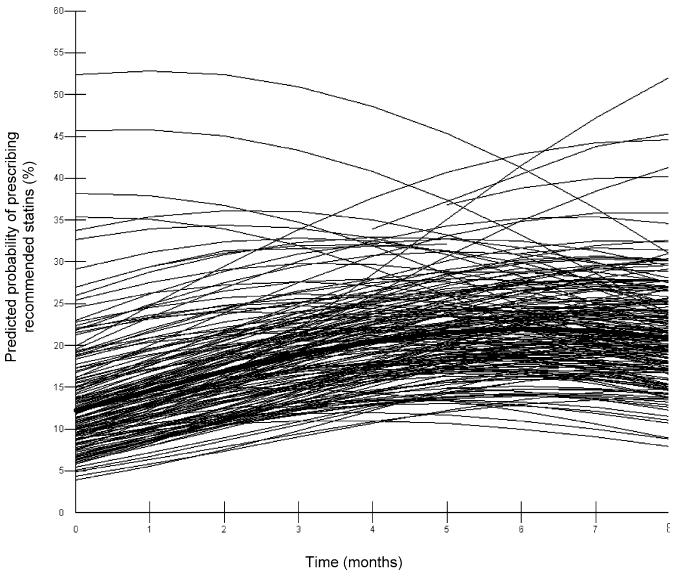


Fig. 2 Temporal trends in adherence to guidelines on statin prescription in the county of Scania (*thick black line*) and in the different health care centres (*HCCs*)

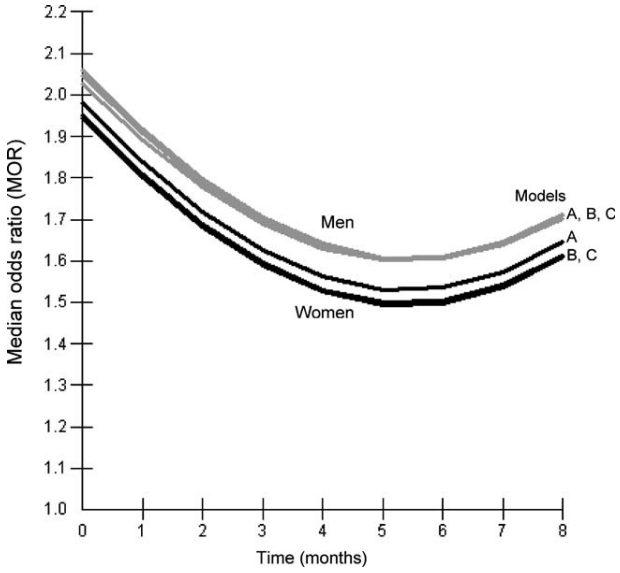


Fig. 3 Median odds ratio (*MOR*) expressing differences in adherence to guidelines on statin prescribing among the different health care centres (*HCCs*) in Scania. Values for men and for women have been adjusted for temporal trends (*model A*), age (*model B*) and characteristics of the HCCs and of the municipalities (*model C*)

similar health problem [25–28]. However, when the same pharmacological agent is available in different brands at very different prices and the prescriber chooses the expensive brand, it is relevant to investigate determinants for these prescription disparities in order to launch interventions promoting appropriate prescription [29]. In this context, statins are an illustrative group of pharmacological agents since they have

concrete indications [30]. They are the first-hand choice for treatment of hyperlipidaemia in adults with a high risk of developing heart disease. Statins have been shown to be effective in primary and, more specifically, secondary prevention of coronary heart disease and ischaemic stroke [31, 32]. Since all statins have the same indication and only marginal differences in efficacy, there are no solid reasons why expensive brands should be prescribed in general and for some patients rather than others in particular.

The process of prescription includes a number of phases (identification of the health problem, decision to prescribe, choice of medication and decision to cease using specific therapy) and could be influenced at different levels (e.g. at the patient, prescriber, HCC or health care district level). However, very few studies have aimed to understand the relative importance of these different levels [6, 22, 23]. Therefore, the present investigation provides valuable and original information that could be of relevance for planning and evaluating interventions aimed to promote efficient and evidence-based prescription.

In this study, we were interested in investigating prescribing behaviour, and statins are an ideal medication group for this analysis. Prescription of recommended statins is not specifically indicated for certain patients to the exclusion of others. There is therefore no rationale for considering patient characteristics as confounder factors. Rather, the interest in these variables resides in understanding reasons for low adherence to prescribing guidelines. In the present investigation, we only considered basic individual variables such as age and gender; however, a study of determinants of adherence to guidelines may require a qualitative research methodology [33].

We found a rather low prevalence of adherence with recommended statins. The main reason for the low use of recommended statins might be that the guidelines were very strict, including only Pravachol and Simvastatin GEA.

It is known that some non-recommended statins such as rosuvastatin have been the subject of safety concerns [34–36]. This fact may promote adherence to use of recommended statins over and above the guidelines. However, this external influence should have affected all the HCCs and municipalities and has therefore less relevance with regard to variance in adherence with guidelines.

Our empirical analysis found that—even if in a small degree—women showed a higher probability than men of being prescribed cheaper recommended statins. The reasons for this behaviour seem irrational but we do think the results raise an interesting question. Our epidemiological study suggests that it may be interesting to perform further investigation, such as a qualitative analysis, in order to obtain more information on the reasons for this prescribing behaviour.

We found that municipality physician density influenced adherence to prescription guidelines. In other words, adherence was lower when the physician density was in the middle tertile group. As far as we know, this subject has been rarely investigated in previous studies and deserves more attention.

MLRA has been successfully employed in a number of previous studies in the field [6, 22, 23, 37] and appears to be a useful epidemiological tool for investigating and quantifying medical practice variation. Consequently, MLRA may prove to be a useful tool for evaluating and planning interventions.

In conclusion, adherence increased and the variation decreased during the study period, which suggests that in some way the publication of the official prescription guidelines in the county had a positive influence on statin prescribing. However, at the end of the observation period, adherence was still low and practice variation high. These facts may reflect inefficient therapeutic traditions and suggest that more intensive interventions may be necessary to promote adherence to prescription guidelines [38].

Acknowledgements This study was supported by grants from the Scania Region's Health Care Research Funds, the Swedish Council for Working Life and Social Research (FAS) (Juan Merlo; Dnr 2003-0580), and the Swedish Research Council (VR) (Juan Merlo; Dnr 2004-6155).

References

1. Sjöqvist F, Dahl M-L, Gustafsson L, Hensjö L-O (2002) Drug therapeutics committees: a Swedish experience. WHO Drug Inf 16:207–213
2. WHO (1987) WHO Conference of Experts on the Rational Use of Drugs, Nairobi, Geneva, Switzerland
3. Barber N (1995) What constitutes good prescribing? BMJ 310(6984):923–925
4. Läkemedelsförsäljningen i Sverige—analys och prognos, Maj 2004 (Drug sales in Sweden—analysis and prognosis, May 2004) [in Swedish]. Socialstyrelsen; Stockholm, Sweden, 2004
5. Merlo J (2003) Multilevel analytical approaches in social epidemiology: measures of health variation compared with traditional measures of association. J Epidemiol Community Health 57(8):550–552
6. Lopez-Valcarcel B, Ortun-Rubio V, Cabez-Mora A, Lopez-Cabañas A, Diaz-Berenger J, Alamo-Santana F (2002) Evaluation del uso apropiado de medicamentos en atencion primaria. Como se puede mejorar? (Evaluation of the appropriate use of medication in primary care—how do we improve it?) [in Spanish]. Aten Primaria 30:467–471
7. Rasbash J, Steele F, Browne W (2003) Logistic models for binary and binomial responses. In: A user's guide to MLwiN. Version 2.0. Documentation Version 2.1e. Centre for Multilevel Modelling, Institute of Education, University of London, London, UK
8. Larsen K, Merlo J (2005) Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. Am J Epidemiol 161(1):81–88
9. Goldstein H (2003) Multilevel statistical models, 3rd edn. Hodder Arnold, London, UK
10. Snijders T, Bokser R (1999) Multilevel analysis: an introduction to basic and advanced multilevel modeling. Sage Publications, Thousand Oaks, CA
11. Burton P, Gurrin L, Sly P (1998) Extending the simple linear regression model to account for correlated responses: an

introduction to generalized estimating equations and multi-level mixed modelling. Stat Med 17(11):1261–1291
12. Rasbash J, Steele F, Browne W (2003) A user's guide to MLwiN. Version 2.0. Documentation Version 2.1e. Centre for Multilevel Modelling, Institute of Education, University of London, London, UK
13. Rasbash J, Browne W, Goldstein H, Yang M, Plewis I, Healy M et al (2003)Modelling the variance as a function of explanatory variables. In: A user's guide to MLwiN. Version 2.0. Documentation Version 2.1e. Institute of Education, University of London, London, UK
14. Merlo J, Yang M, Chaix B, Lynch J (2005) A brief conceptual tutorial of multilevel analysis in social epidemiology—investigating contextual phenomena in different groups of individuals. J Epidemiol Community Health (in press)
15. Merlo J, Chaix B, Yang M, Lynch J, Råstam L (2005) A brief conceptual tutorial of multilevel analysis in social epidemiology—linking the statistical concept of clustering to the idea of contextual phenomenon. J Epidemiol Community Health 59:443–449
16. Merlo J, Chaix B, Yang M, Lynch J, Råstam L (2005) A brief conceptual tutorial of multilevel analysis in social epidemiology—interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. J Epidemiol Community Health, in press
17. Goldstein H, Browne W, Rasbash J (2002) Partitioning variation in generalised linear multilevel models. Understand Stat 1:223–232
18. Larsen K, Petersen JH, Budtz-Jorgensen E, Endahl L (2000) Interpreting parameters in the logistic regression model with random effects. Biometrics 56(3):909–914
19. Zeger SL, Liang KY, Albert PS (1988) Models for longitudinal data: a generalized estimating equation approach. Biometrics 44(4):1049–1060
20. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P et al (2005) A brief con-ceptual tutorial of multilevel analysis in social epidemiology—using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health, in press
21. McMahon AD (2003) Approaches to combat with confounding by indication in observational studies of intended drug effects. Pharmacoepidemiol Drug Saf 12(7):551–558
22. Davis P, Gribben B (1995) Rational prescribing and interpractitioner variation. A multilevel approach. Int J Technol Assess Health Care 11(3):428–442
23. Davis P, Gribben B, Lay-Yee R, Scott A (2002) How much variation in clinical activity is there between general practitioners? A multi-level analysis of decision-making in primary care. J Health Serv Res Policy 7(4):202–208
24. Hjerpe P, Fornwall S, Merlo J (2004) Therapeutic traditions and compliance with local therapeutic guidelines on lipid lowering drugs—a multilevel analysis in the Skaraborg Primary Healthcare Database (SPHD). In: International Society for Pharmacoepidemiology, Bordeaux, 2004
25. Smits HL (1986) Medical practice variations revisited. Health Aff (Millwood) 5(3):91–96
26. Davis P, Gribben B, Scott A, Lay-Yee R (2000) The "supply hypothesis" and medical practice variation in primary care: testing economic and clinical models of inter-practitioner variation. Soc Sci Med 50(3):407–418
27. Wennberg JE, Barnes BA, Zubkoff M (1982) Professional uncertainty and the problem of supplier-induced demand. Soc Sci Med 16(7):811–824
28. Flood AB, Wennberg JE, Nease RF Jr, Fowler FJ Jr, Ding J, Hynes LM (1996) The importance of patient preference in the decision to screen for prostate cancer. Prostate Patient Outcomes Research Team. J Gen Intern Med 11(6):342–349
29. Zara C, Torralba M, Sotoca JM, Prat A, Faixedas MT, Gilabert A (2005) The impact of new drug introduction on drug expenditure in primary health care in Catalunya, Spain. Ann Pharmacother 39(1):177–182
30. Anonymous (2003) Behandling med lipidsänkande läkemedel vid prevention av hjärt-kärlsjukdomar. (Treatment with lipid-lowering drugs for prevention of heart diseases) [in Swedish]. Information från Läkemedelsverket 14:4 (ISSN 1101-7104)
31. LaRosa JC, He J, Vupputuri S (1999) Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 282(24):2340–2346
32. Vrecer M, Turk S, Drinovec J, Mrhar A (2003) Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. Int J Clin Pharmacol Ther 41(12):567–577
33. Jaye C, Tilyard M (2002) A qualitative comparative investigation of variation in general practitioners' prescribing patterns. Br J Gen Pract 52(478):381–386
34. Ohlsson O, Kjellström T (2003) Landsomfattande konsensus för behandling av höga blodfetter (För landets läkemedelskommittéordförande LOK). Lund, Sweden; 1/10 2003
35. Anonymous (2003) The statin wars: why AstraZeneca must retreat. Lancet 362(9393):1341
36. Anonymous (2004) Läkemedelsverket. Produktresumén revideras för Crestor 2004-06-09
37. Merlo J, Liedholm H, Lindblad U, Bjorck-Linne A, Falt J, Lindberg G et al (2001) Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross-sectional study. BMJ 323(7310):427–428
38. Hakansson A, Andersson H, Cars H, Melander A (2001) Prescribing, prescription costs and adherence to formulary committee recommendations: long-term differences between physicians in public and private care. Eur J Clin Pharmacol 57(1):65–70

II

BMC Health Services Research

Research article

Open Access

Understanding the effects of a decentralized budget on physicians' compliance with guidelines for statin prescription – a multilevel methodological approach

Henrik Ohlsson*[1,2] and Juan Merlo[1,2]

Address: [1]Social Epidemiology & HE, Department of Clinical Sciences in Malmö, Faculty of Medicine, Lund University, Sweden and [2]Unit of Health and Health Care Epidemiology, Department of Health and Health Care Management, Region Skåne, Sweden

Email: Henrik Ohlsson* - henrik.ohlsson@skane.se; Juan Merlo - juan.merlo@med.lu.se

* Corresponding author

Published: 8 May 2007

BMC Health Services Research 2007, **7**:68 doi:10.1186/1472-6963-7-68

Received: 14 September 2006
Accepted: 8 May 2007

This article is available from: http://www.biomedcentral.com/1472-6963/7/68

Abstract

Background: Official guidelines that promote evidence-based and cost-effective prescribing are of main relevance for obvious reasons. However, to what extent these guidelines are followed and their conditioning factors at different levels of the health care system are still insufficiently known.

In January 2004, a decentralized drug budget was implemented in the county of Scania, Sweden. Focusing on lipid-lowering drugs (i.e., statins), we evaluated the effect of this intervention across a 25-month period. We expected that increased local economic responsibility would promote prescribing of recommended statins.

Methods: We performed two separate multilevel regression analyses; on 110 827 individual prescriptions issued at 136 *publicly*-administered health care centres (HCCs) nested within 14 administrative areas (HCAs), and on 72 012 individual prescriptions issued by 115 *privately*-administered HCCs. Temporal trends in the prevalence of prescription of recommended statins were investigated by random slope analysis. Differences (i.e., variance) between HCCs and between HCAs were expressed by median odds ratio (MOR).

Results: After the implementation of the decentralized drug budget, adherence to guidelines increased continuously. At the end of the observation period, however, practice variation remained high. Prescription of recommended statins presented a high degree of clustering within both publicly (i.e., MOR_{HCC} = 2.18 and MOR_{HCA} = 1.31 respectively) and privately administered facilities (MOR_{HCC} = 3.47).

Conclusion: A decentralized drug budget seems to promote adherence to guidelines for statin prescription. However, the high practice differences at the end of the observation period may reflect inefficient therapeutic traditions, and indicates that rational statin prescription could be further improved.

Background

Adherence to prescription guidelines

Prescription guidelines that promote evidence-based and cost effective prescribing of drugs are of main relevance for promoting effective and safe pharmacologic treatment as well as for the efficient use of a limited health care budget. Therefore, adherence to prescription guidelines has attracted considerable interest in many countries [1-3], including Sweden [4-6]. However, it is still insufficiently known to what extent guidelines from the drug committees are followed and the factors that at different levels of the health care condition prescription adherence to recommended medication [4,7,8].

In a previous study [9], we investigated the role of municipalities and outpatient Health Care Centres (HCCs) in understanding adherence to official guidelines on statin prescription in the county of Scania, Sweden. Using multilevel regression analysis we developed an epidemiological design suitable for monitoring practice variation and prevalence of adherence to guidelines along time. We noted that HCCs appeared to be more relevant than municipalities for understanding physicians' propensity to prescribe a recommended statin, and that the publication of the guidelines exerted a positive influence. In other words, prescription of recommended statins presented increasing trend and variance between HCCs and municipalities slightly decreased. However, at the end of the observation period the prevalence of adherence to guidelines was inappropriately low and practice variation unsuitably high, suggesting that inefficient therapeutic traditions were still influencing statin prescription. For this reason, it was suggested that more intensive interventions would be necessary to promote rational statin prescription.

The decentralized pharmaceutical budget

The health services in Sweden are overwhelmingly tax-financed through county taxes [10]. Even if the Swedish Health Care System is rather homogenous all over the country, every of the 20 county councils in Sweden (Scania is one of the largest) have a high financial autonomy for managing health care services within their respective areas.

In January 2004, the county council of Scania implemented a new system for managing the pharmaceutical budget. Under the new economic system, responsibility for the administration of the pharmaceutical budget passed from the regional Department of Health and Health Care Management to the 19 administrative Health Care Areas (HCAs) at five Health Care Districts (HCD) of the county [11]. See figure 1 for a short explanation of the structure of the health care system in the County of Scania. Simultaneously to the decentralized pharmacological budget, an information campaign was launched. In this campaign, specially trained pharmacists visited the HCCs and provided information on current local prescription patterns as a basis for reflection and prescription improvement. While the new economic system was compulsory, participation in the information campaign was voluntary.

Aims of the study

In the present study we aimed to monitor and evaluate the effect of the decentralized pharmacological budget on prescribing behaviour and the role played by the different organizational levels (HCCs, HCAs and Health Care Districts) when it comes to understand physicians' adherence to prescription guidelines. Statins are an ideal medication group for this purpose, since they have very homogeneous indications and similar efficacy [12-14], which in principle eliminates the possibility of patient mix when comparing different practices and administrative areas.

A decentralized drug budget increases economic responsibility among prescribers by relocating control in management and decision-making from higher to lower levels of the health care organization and, thereby, it creates incentives for efficient drug prescription [15]. Therefore, our hypothesis was that the decentralized pharmacologic budget and would result in increased use of recommended statins and decreased variance between HCCs and HCAs throughout the 25-month observation period. While increased prevalence of adherence is the more informative parameter of a positive impact of the intervention, only a high prevalence in the area does not necessarily imply better care since it could depend of a few practices with a very high prevalence. Combining prevalence and variance measures we can obtain more complete information.

Due to the hierarchical structure of the data, we applied multilevel regression analysis (MLRA). MLRA accounts for and informs about the dependence of the outcome within organizational levels, and thereby not only produces accurate statistical estimations but also generates information regarding patterns of variation at different levels – an aspect of high relevance for investigating therapeutic traditions [16,17].

Methods

The register of pharmacological agents

We obtained information from the Swedish National Prescription Register [18], administrated by the Swedish Corporation of Pharmacies and based on record of sales. While the decentralized budget started in January 2004, the current recommendations for drug prescription were introduced in March 2004 and so did our observation period. During the 25-month period between March 2004

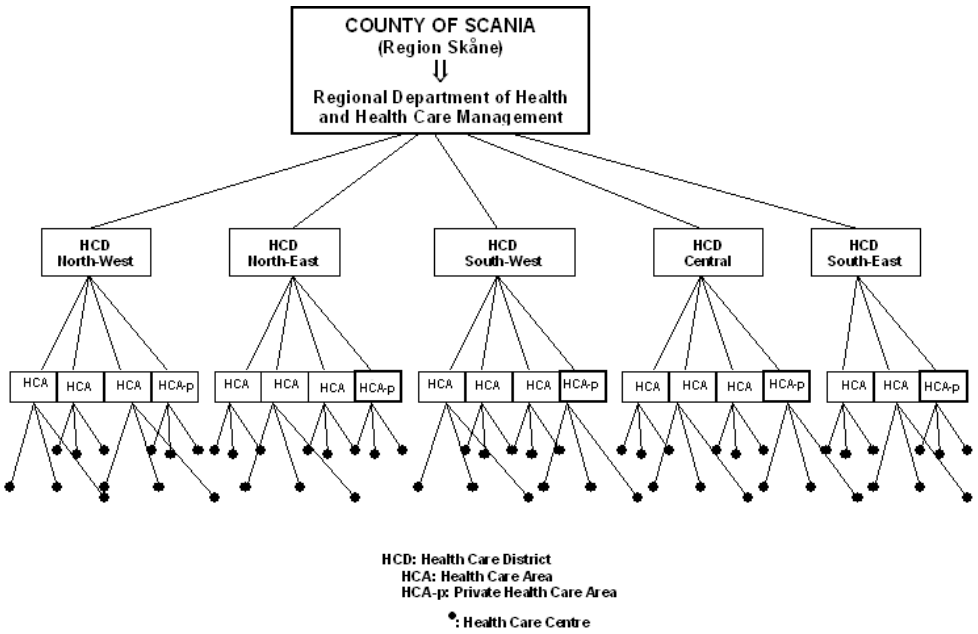


Figure 1
The structure of the health care system in the Scania County council.

and March 2006 we selected all 110827 prescriptions of statins issued by public physicians and all 72012 prescriptions issued by private physicians at 136 public and 115 private HCCs in 14 public and 5 private HCAs in Scania. Statins were defined according to the Anatomical Therapeutical Chemical (ATC) classification system code C10AA [19].

A small percentage (6%; 12 683/195 522) of prescriptions were excluded since they had unidentified origin, they were from places outside Scania, or from HCCs with sporadic statin prescription (i.e., less than 50 prescriptions) during the observation period.

Each prescription, regardless of number of drugs, has a unique serial number in the register. The register data includes information about the age and gender of the patient, the health care facility where the prescription was issued, the brand name and ATC code for both prescribed and dispensed drugs, and whether the prescription was an initial or a repeat prescription.

For descriptive purposes we expressed statin utilization as direct age-standardized number of defined daily doses (DDD)/1000 inhabitants/day obtained by the Equivalent Average Rate methodology [20,21].

This study is a part of the LOMAS project (Longitudinal Multilevel Analysis in Scania) [22] that was reviewed and approved by the Swedish Regional Ethical Review Board in Lund.

Individual-level variables

At the individual level, the outcome variable was *prescription of simvastatin* (yes vs. no). Simvastatin (regardless of brand, but excluding the original brand ZOCORD®) was the recommended statin in Scania during the whole observation period. Simvastatin has proved efficacy [12-14,23] and is the cheapest statin in Sweden. Though a prescription is valid for one year, the reimbursement system accepts a maximum of three months' supply per dispensation, so we selected initial prescriptions only in order to reduce the risk of counting the same prescription more than once.

Individual *age* in years was centred on the mean of 67 for prescriptions issued at public practices, and 66 for those issued at private practices. *Sex* (men vs. women) was defined by a dummy variable. *Time* (in months) was a continuous variable; March 2004 was recoded as 0, April 2004 as 1, and so on to March 2006 that was recorded as 24. Therefore, March 2004 was the intercept value in the regression analysis.

Area-level variables

The structure of the health Care System at the county of Scania

The Region of Scania is situated on the southern part of the Scandinavian Peninsula. The county is geographical divided into 33 municipalities and its area covers less than 3% of Sweden's total area. The population of about 1.2 million represents, however, 13% of Sweden's total population. At the time of this study the health care system at the county of Scania was organized into five health care districts (northwest, northeast, southwest, southeast, and central). These five health care districts managed 19 administrative HCAs which, in turn, controlled 251 HCCs (Figure 1). Of those HCCs, 136 were public administered primary health care centres and hospital outpatient care clinics, and 115 were private primary HCCs assisted by private general practitioners (GPs) and other private specialists. Only five of the 19 HCAs managed private HCCs. The remaining 14 HCAs managed only public HCCs; nine HCAs managed only outpatient clinics at large public hospitals while five administered primary health care centres.

Participation in the information campaign

Simultaneously to the introduction of the decentralized budget, an *information campaign* for supporting appropriate prescription at the HCCs was carried out through the entire observation period. Participation in this campaign was voluntary. Since the campaign could influence prescription patterns independently of any possible effect of the decentralized budget, we included a variable indicating whether the HCC participated in the information campaign or not.

Budget decentralization at the HCA level and HCCs with own budget administration

In the new compulsory system of decentralized pharmaceutical budget, the responsibility for the administration of the pharmaceutical budget was transferred from the regional Department of Health and Health Care Management to every of the 19 administrative HCAs. However, nine of the 14 publicly-administered HCAs decided to implement a more intense decentralization by transferring the budget responsibility to their HCCs. Since this circumstance could influence prescription patterns, such HCCs were identified by a dummy variable. In the analyses, HCCs without their own budget management were used as reference in the comparisons.

Percentage of prescriptions from specialist physician at the HCC level

Since proximity to specialized care and the particular knowledge that it conveys might influence adherence with prescription guidelines, we also identified those HCCs which employed *specialist* physicians other than GPs. In the analyses, HCCs employing GPs alone were used as reference in the comparisons.

Multilevel logistic regression models

We used *multilevel logistic regression analysis* to estimate the probability of prescribing a recommended statin, while accounting for the hierarchical structure of the data (i.e., patients nested within HCCs nested within HCAs) represented in figure 1[16,17].

Since physicians working in private practices may be less receptive to the policies of the county council than those working in public facilities, and because this might modify the effect of the decentralized budget, we performed our analyses separately for physicians under public or private administration

Public HCCs and HCAs were included in the analysis as random terms. However, because there were only five health care districts, which is a low number for including health care districts as a random term, they were included as a dummy variable (i.e., fixed effects), using the southwest district as reference in the comparisons. Since there was only one private HCA in each health care district, in the multilevel analysis of privately administered health care the only random term was HCC.

We developed three consecutive models. Model A included the area (i.e., HCA and HCC) random parameters together with *time*. The intention of this model was to investigate temporal trends of prescription of recommended statins throughout our observation period. Model B included the individual covariates age and sex. Finally, model C added the area-level variables; health care districts, information campaign, presence of specialist physicians other than GPs, and HCC with own budget responsibility. In this way we could investigate whether these contextual characteristics explained residual variation at the HCC and HCA levels.

In the fixed-effects part of the multilevel analysis, we calculated odds ratios (OR) and their 95% confidence intervals (95% CI) from the regression coefficients and their standard errors.

In the random-effects part of the multilevel analysis, we obtained the *variance* (*SE*) at the HCC and HCA levels. We calculated the *proportional change in variance* (PCV) between two consecutive models [24]. We also allowed the regression coefficients of the variables *time* and *sex* to

be random at the HCC level (i.e. random slope analysis) in order to investigate whether these individual-level associations varied between different HCCs. In the presence of slope variance, the HCC variance becomes a function of the *individual variables*. We calculated the variance function as described elsewhere [25].

Theoretically the concept of intraclass correlation (i.e., the percentage of the total variance that is at the area level) is an intuitive measure of therapeutic traditions [9,26,27]. However, in multilevel logistic regression models, the fact that the variances at the area and at the individual levels are measured on different scales makes it difficult to interpret the intraclass correlation. Therefore, we calculated the median odds ratio (MOR) [28,29]. The MOR translates the variance into the widely used OR scale, and can thereby be directly compared with the ORs of individual or area variables. In very simple terms, the MOR could be interpreted as how much a physician's probability of prescribing a recommended statin would (in median) increase if this physician moved to a HCC/HCA with higher adherence to guidelines. A MOR of 1 indicates that there are not differences between HCCs/HCAs in the probability of prescribing a recommended statin. The larger the differences between HCCs (or HCAs) are, the larger the MOR will be.

Even if the overall OR for the association between an area (i.e., HCC or HCA) variable and the outcome is conclusively higher or lower than one, the distribution of OR for pairwise comparison between exposed and unexposed areas could contain a considerable percentage of ORs of opposed direction. Therefore, we calculated the percentage of ORs of opposed direction as complementary information to the overall OR of each area-level variable. This index considers the area residual variance in the calculation of the ORs of the area level variables, and indicates the extent to which the area variable under study is of importance as compared with residual area variations. If the index is 50% the association has no relevance. Details of the formulas and an extended explanation of the statistical analysis can be found elsewhere [30]. An Excel spreadsheet with formulas is available on request.

Ranking of outpatient health care centres and administrative health care areas

Following previous recommendations for comparing performance between different health care units [31], we ranked HCCs and HCAs according their posterior means (also known as "shrunken residuals") obtained from the multilevel regression analyses. Each residual corresponds with the OR of adherence with guidelines (logarithmic scale) of the unit, with the whole county as reference in the comparisons.

Parameters were estimated by MCMC methods [32] and the goodness of fit was evaluated using the deviance information criteria (DIC). We used the MLwiN 2.02 software developed by Goldstein's research group [25].

Results

The age-standardized utilization of statins in the whole county increased from 131 DDD/1000 inhabitants/day in 2004 to 177 in 2006, and a similar increasing trend was observed in all health care districts. Throughout the whole observation period, prescription of statins was highest in the northwest district and lowest in the central district (Table 1).

Table 1 shows that the mean age of the patients receiving a statin prescription was 67 years in the public sector and 66 years in the private. Overall, men were prescribed statins more often than women. More statin prescriptions were issued from public HCCs than from private HCCs. Of all the statin prescriptions issued at public HCCs, 82% originated from a HCC participating in the information campaign, but this figure was only 22% for private HCCs, and varied greatly between districts, being lowest in the southwest district. More statins were prescribed by HCCs composed of GPs alone than by HCCs including other specialists. Of the statin prescriptions issued at public HCCs, 71% originated from HCCs that managed their own pharmacologic budget.

Overall, the prevalence of guideline adherence was 62% in the public sector and 50% in the private, with a clear increasing trend during the whole study period. In the first month, 48% of the public and 39% of the private HCCs prescribed recommended statins, and this percentage increased to 74% in the public and 62% in the private sector by the end of the study period. These trends were similar in all five health care districts, but adherence was always lowest in the southwest district, and highest in the northeast and southeast districts (Figure 2).

In model A (see Table 2), the $MOR_{HCA\text{-}HCC}$ in the public sector was 2.28 indicating that a physician's median probability of prescribing a recommended statin would approximately double if this physician moved to an HCC in an HCA with greater adherence to guidelines. However, when decomposing the MOR in specific levels, the propensity of prescribing recommended statins presented a higher degree of clustering at the HCC level than at the HCA level (MOR_{HCC} = 2.18 vs. MOR_{HCA} = 1.31). The MOR_{HCC} in the private sector was 3.47, indicating an even stronger clustering among private HCCs.

As illustrated in Figure 2, there was an increasing temporal trend in prescription of recommended statins. However, this trend differed between HCCs, and the *time* variable

Table 1: Characteristics of the initial prescriptions of statins issued in Scania, Sweden, between March 2004 and March 2006, by Health Care District and specifying prescription of simvastatin (i.e., recommended drug).

	Whole Scania		North-West		North-East		Central		South-West		South-East	
	All	Simvastatin	All	Simvastatin	All	Simvastatin	All	Simvastatin	All	Simvastatin	All	Simvastatin
Number of prescriptions (Public HCCs)	110,827	68,372 (62%)	27,562	17,138 (62%)	19,145	12,978 (68%)	27,509	15,932 (58%)	28,373	16,264 (57%)	8,328	6,060 (74%)
Number of prescriptions (Private HCCs)	72,082	36,256 (50%)	20,270	9,958 (53%)	7,801	4,656 (64%)	7,922	4,342 (58%)	34,024	13,224 (42%)	7,272	4,076 (60%)
Men Public/private	56/55	55/55	53/55	53/55	55/55	55/56	58/52	57/52	56/55	56/55	57/55	57/54
Mean age in years (Public/private)	67/66	67/65	67/67	67/66	68/68	67/68	67/65	67/65	66/66	66/66	68/67	68/67
Number of HCAs (Public/private)	14/5		3/1		3/1		3/1		3/1		2/1	
Number of HCCs (Public/private)	136/115		29/28		25/13		36/18		39/41		7/15	
Percentage of prescriptions from HCCs that participated in information campaign (Public/private)	82/22	82/28	98/24	97/27	97/80	97/80	100/47	100/50	33/0	31/0	100/34	100/36
Percentage of prescriptions from HCCs with own budget administration (Public)	71	71	83	81	87	86	91	89	38	42	35	36
Percentage of prescriptions from specialist physician (Public/private)	34/37	37/34	29/38	32/33	32/4	35/2	35/41	37/43	38/48	42/46	35/15	36/20
DDD/inhabitants/day for statins												
DDD/inhabitants/day, 2004	131		153		127		110		132		129	
DDD/inhabitants/day, 2005	152		180		147		126		152		154	
DDD/inhabitants/day, 2006	177		207		171		147		178		186	

HCC = outpatient health care centre.

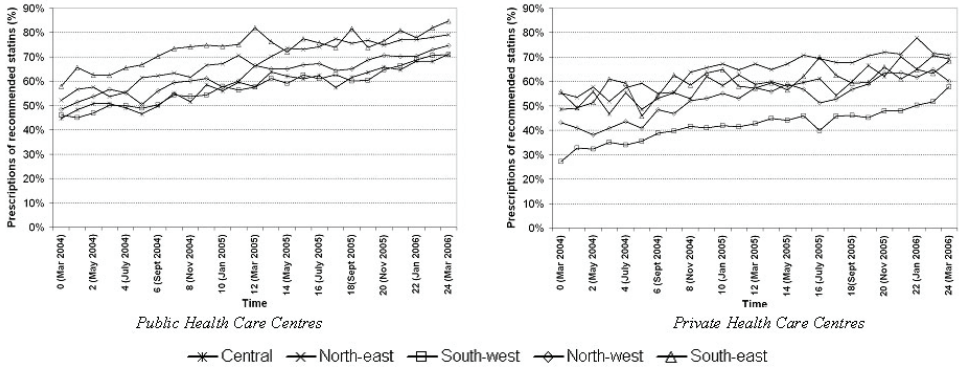


Figure 2
Percentage of recommended statins among initial statin prescription in the health care districts of the county of Scania, public health care centres (right) and private health care centres (left).

presented a significant slope variation between HCCs evidenced by the plot of the predicted values in Figure 3. Because of this slope variance, the MOR_{HCC} became a function of time indicating that even if the MOR_{HCC} decreased throughout the study period, the final variation was still high (MOR_{HCC} = 1.86 in the public sector and 2.73 in the private).

We did not observe any significant slope variation of the time variable at the HCA level.

The analysis of the PCV in Table 2 indicates that 50% of the differences between HCAs were explained by the individual and contextual characteristics included in model C. In relation to variance between HCCs, this percentage was only 8% in the public sector and 0% in the private. The DIC diagnosis suggested that model C represent an improvement over model B in goodness of fit for the public sector, but not for the private.

The ranking of the HCCs and HCAs regarding the prevalence of prescription of recommended statins in each area relative to the overall prevalence in the county at the beginning of the study period is presented in Figure 4 both before (model A) and after (model C) making adjustments. The differences between HCAs disappeared after adjustment, but although many HCCs changed position in the ranking, the HCC dispersion around the mean was not reduced after adjustments.

Overall, men had higher use of statins (Table 1) but lower probability than women of being prescribed a recommended statin (Table 2). The existence of slope variation, however, indicated that this pattern of association was not constant in all HCCs.

Table 2 shows that the probability of prescribing recommended statins was not conditioned by participating in the information campaign. Also, our results suggest that even if adherence to guidelines clearly improved after the implementation of the decentralized budget, this improvement was not more intense among HCCs with own budget administration. Actually – even if the results were not conclusive at the 95% level – comparing to HCC without own budget administration those with own economical responsibility presented a lower, rather than higher, probability of adherence with guidelines, OR = 0.82 (95%CI: 0.68–1.06),

Among the public HCCs, prescriptions of recommended statins were more frequently issued at HCCs with specialist physicians other than GPs, but no such association was observed for private HCCs. Compared with the southwest district, all other districts presented a higher probability of prescribing recommended statins for both public and private HCCs, except public HCCs in the central district.

DiscussionIn this study we evaluated the effect of a decentralized pharmaceutical budget intended to promote

Table 2: Multi-level logistic regression analysis of adherence to statin prescription guidelines in the county of Scania, Sweden

	Model A		Model B		Model C		
	Public	Private	Public	Private	Public	Private	
Fixed effects	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Time	1.05 (1.04–1.05)	1.06 (1.05–1.07)	1.05 (1.04–1.05)	1.06 (1.05–1.07)	1.05 (1.04–1.05)	1.05 (1.04–1.07)	
Time^2		1.00 (1.00–1.00)		1.00 (1.00–1.00)		1.00 (1.00–1.00)	
Sex (women vs men)			0.93 (0.87–0.98)	0.92 (0.84–1.01)	0.93 (0.88–0.99)	0.92 (0.85–0.99)	
Age (one year increase)			1.000 (1.000–1.000)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	
Information campaign (Yes vs No)					1.11 (0.90–1.39)	1.46 (0.73–2.34)	
% opposed ORs					46%	42%	
Specialist physician vs GP					1.41 (1.18–2.01)	0.97 (0.66–1.31)	
% opposed ORs					38%	49%	
HCC with own budget administration (yes vs No)					0.82 (0.68–1.06)		
% opposed ORs					43%		
North-West health care district			–	–	1.37 (1.01–1.93)	1.66 (1.09–2.50)	
% opposed ORs					39%	39%	
North-East health care district			–	–	1.39 (0.84–2.04)	1.78 (1.04–3.89)	
% opposed ORs			–	–	39%	38%	
South-West health care district			–	–	Reference	Reference	
South-East health care district			–	–	2.03 (1.08–3.92)	1.46 (0.84–1.99)	
% opposed ORs			–	–	27%	42%	
Central health care district			–	–	0.85 (0.47–1.15)	1.53 (1.10–2.73)	
% opposed ORs			–	–	45%	41%	
Random effects	Variance (95% CI)	Variance (95% CI)	Variance (95% CI)	Variance (95% CI)	Variance (95% CI)	Variance (95% CI)	**PCV**
HCA (intercept)	0.08 (0.01 – 0.38)		0.15 (0.04 – 0.42)		0.04 (0.00–0.17)		50%
MOR_{HCA}	1.31 (1.11 – 1.80)		1.44 (1.22 – 1.87)		1.21 (1.04 – 1.49)		
HCC (intercept)	0.67 (0.51 – 0.89)	1.70 (1.28 – 2.32)	0.62 (0.46 – 0.84)	1.80 (1.34 – 2.44)	0.62 (0.47 – 0.82)	1.71 (1.26 – 2.34)	8% (Pu)
MOR_{HCC}	2,18 (1.98 – 2.46)	3.47 (2.94 – 4.28)	2,12 (1.92 – 2.39)	3.60 (3.01 – 4.43)	2.12 (1.92 – 2.37)	3.48 (2.92 – 4.31)	0% (Pr)
OHC and HCA (intercept)	0.75		0.77		0.66		12%
$MOR_{HCA\text{-}HCC}$	2.28		2.31		2.17		
Time (slope)	0.000 (0.000 – 0.001)	0.001 (0.001 – 0.002)	0.000 (0.000 – 0.001)	0.001 (0.001 – 0.002)	0.000 (0.000 – 0.001)	0.001 (0.001 – 0.002)	
Sex (slope)	–		0.063 (0.043 – 0.093)	0.149 (0.103 – 0.214)	0.063 (0.043 – 0.094)	0.147 (0.102 – 0.214)	
Deviance information criteria (DIC)	136 649.6	87 811.1	136 114.6	87 421.9	136 113.9	87 422.4	

HCC = outpatient health care centre. MOR = median odds ratio. OR = odds ratio.
95% CI = 95% credible interval. SE = standard error.
PCV = proportional change in variance (PCV) in model C using model A as reference

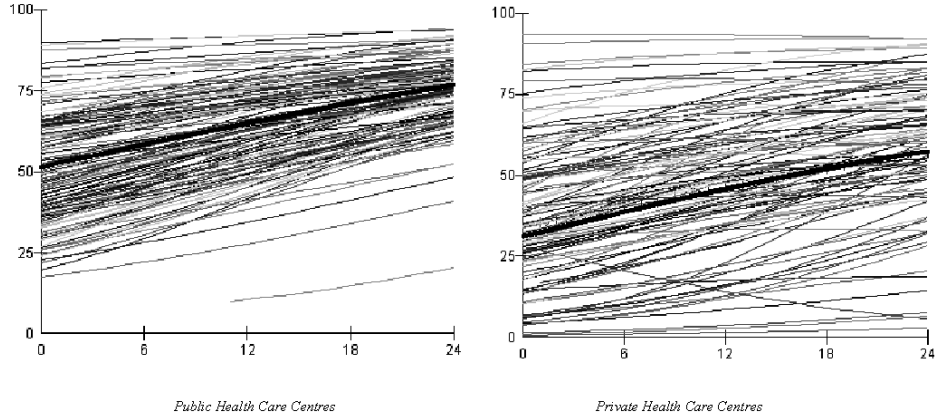


Figure 3
Predicted probabilities for prescribing recommended statins at public (left) and private (right) health care centres in Scania.

adherence with prescription guidelines. According to our results, this intervention appeared to considerably improve adherence to guidelines for statin prescription and, promoted efficient pharmacological treatment.

We performed separate analyses for publicly and privately administrated HCCs, since we believed that the administrative background could modify the effect of these interventions. However, even though guideline compliance was systematically lower among private facilities, compliance in both the public and the private sector increased progressively from the implementation of the decentralized budget through the observation period.

Since our study is observational, several bias and confounding factors need to be considered. While face-to-face visits such as those performed during the intervention campaign have a documented effect on prescription patterns [33], in our analysis participation in the information campaign was not associated to higher adherence with guidelines. Given that participation in this campaign was free, it is probable that other reasons apart from the information campaign itself confound the observed association. For example, HCCs with a very low adherence to guidelines at the start of the intervention may be especially prone to participate in order to improve their prescription patterns. This effort would have only raised adherence to the same level as rest of the HCCs. Due to selection biases interpretation of the effect of the information campaign is limited.

Evaluation of the decentralized budget was less affected by bias since the adoption of the new budget system was obligatory and embraced all the prescribers in the county. Nevertheless, it cannot be ruled out that other external influence besides the decentralized budget could provide an alternative explanation of our results. Also, as we shown in our previous article [9], adherence with guidelines was slightly increasing before the implementation of the decentralized budget. Nevertheless, it is reasonable to believe that the intense trend of increasing prescription of simvastatin occurring after the implementation of the budget actually reflects the new economic responsibility of the prescribers. Several studies suggest that payment method affects physicians' prescription behaviour [2,33,34]. Moreover, even if guideline dissemination alone has a less important effect on prescribing patterns [9,33,34], it has proved to be effective as part of a multifaceted intervention and as a predisposing foundation for other strategies.

Observational studies are often the only option for investigating questions that for reasons of feasibility, costs, or ethics cannot be analysed by randomized trials [35,36]. In our observational study we used multilevel regression analysis, which not only produces more correct statistical analysis (i.e., it accounts for residual correlation within areas) but also informs about the role that different health care levels play in understanding drug prescription and utilization [16,17].

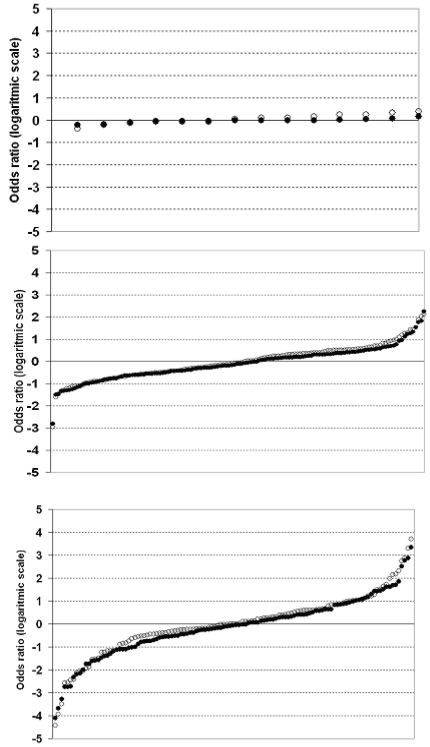


Figure 4
Differences (i.e. residuals) between health care centres obtained from the model including random parameters together with time (unfilled circles) and the model also including age, sex, health care districts, information campaign, presence of specialist physician other than general practitioners, and degree of decentralization (filled circles). Public administrative health care areas (top), public health care centres (middle), and private health care centres (bottom).

Our results suggest that adherence to guidelines seemed to be conditioned by contextual factors, especially at the HCC levels. Based on the MOR measure, we observed that physicians from the same HCC and from the same HCA exhibited a similar propensity to prescribe simvastatin. This clustering of prescription behaviour was greater at the HCC than at the HCA level, which suggest that interventions directed at the HCC level would in principle be more effective than those directed at the HCA level. Also, private HCCs had both greater clustering of prescription behaviour and lower adherence to guidelines, suggesting that interventions directed at private HCCs could be appropriate.

In a previous multilevel analysis [9] we investigated HCCs nested within municipalities rather than within HCAs as in the present study. However, since HCAs are responsible for the management of the new decentralized budget, we did not consider the municipality as a relevant level in this investigation, and a sensitivity analysis (data not shown) including the municipality level confirmed our assumption. In the present study we did not have access to information at the physician level, but two previous studies have shown that variations at the physician level accounted for about 50% of variations at the HCC level [37,38].

The variation between public HCAs was very low and could partly be explained by contextual characteristics such as health care district, participation in the information campaign, the presence of specialist physicians other than GPs, and degree of decentralization. Contrarily, the variation between both public and private HCCs was very high and remained unexplained throughout the whole observation period (i.e., model C in Table 2). Practice variation between HCCs is a common phenomenon that does not necessarily need be inappropriate, but rather may reveal different strategies for confronting a specific therapeutic problem. Practice variation might reflect medical uncertainty resulting from differences in information and knowledge. However, when the same pharmacological therapy is available as different brands at different prices and the prescriber selects the more costly, there are reasons to question the suitability of the observed practice variation [26,27,39-43]. In this context and since all statins have the same indication and only marginal differences in efficacy, there are no solid reasons for justifying the prescription of expensive brands in general and for some patients rather than others in particular [12-14].

The process of prescription includes a number of phases (identification of the health problem, decision to prescribe, choice of medication, decision to cease using a specific therapy) and could be influenced at different levels (e.g. at the level of the patient, prescriber, HCC, HCA, or health care district). However, few studies have aimed to understand the relative importance of these different levels [7,26,27,37,44]. Moreover, even if adherence with guidelines in general is a well-developed research topic [1-3], as far we know only to investigations have been focused on adherence to guidelines of statin prescription, [45,46] and only our current and previous work has applied multilevel regression analyses [9]. The present investigation provides valuable and original information

that could be of relevance for planning and evaluating interventions aimed to promote efficient and evidence-based prescription.

Because of similar indications and efficacy, statins are an ideal medication group for investigating prescribing behaviour. For this reason, there is no rationale for considering patient characteristics as confounding factors when investigating practice variation. Rather, the value of including individual variables resides in the understanding of the factors that condition adherence to prescribing guidelines. In the present investigation we only considered basic individual variables such as age and gender. An extended study of determinants of adherence to guidelines may also require the investigation of the influence of socioeconomic differences of the patients on the process of prescribing as well as applying qualitative research methodology [47].

According to the prescription guidelines in the county of Scania there is one patient related condition in which a non-recommended statin has a preferential indication [14]. In fact, when simvastatin does not reach sufficient effect, a change to atorvastatin 80 mg is officially recommended. However, a complementary analysis indicates that atorvastatin 80 mg was only 0.5% of all the statin prescriptions, and including this substance in the category of recommended statin had no influence on the results.

In a previous study of ours performed in the county of Scania, the basal level of adherence with recommended statins was much lower than in the present investigation. The main reason for this difference is that in the previous study period, guidelines were very strict, including only Pravachol and Simvastatin GEA rather than Simvastatin as in the present investigation. Certainly, the existence of plain guidelines facilitates adherence, but it does not influence the conclusions of the present investigation.

Our empirical analysis found that men were prescribed more statins than women, but women had a slightly higher probability than men of being prescribed the cheaper, recommended, statins. Men have a higher prevalence of ischemic heart disease and they are therefore expected to be more represented among statin users. On the other hand, the gender differences in the prescription of simvastatin did not seem rational. It is possible that qualitative analyses would give more information on the reasons for this prescribing behaviour.

It is known that some non-recommended statins like rosuvastatin have been the subject of safety concerns [48-50], which may have promoted prescription of simvastatin beyond the influence of the guidelines. However, if this is true, this external influence simultaneously affected all the HCCs and HCAs and therefore should have had less relation to variance between HCCs and HCAs.

Multilevel regression analyses are a very suitable methodology for studying practice variation, and are being successfully employed in an increasing number of studies in the field [7,9,26,27,37,44,51]. They are a useful epidemiological tool for investigating and quantifying medical practice variation, and for evaluating and planning interventions.

Conclusion

In conclusion, the decentralized pharmaceutical budget seems to considerably influence prescription behaviour and increase adherence to guidelines for statin prescription. Though, at the end of the observation period, variation between HCCs was still high, especially among private HCCs. These remaining disparities may reflect inefficient therapeutic traditions, and suggest that more intensive interventions may be necessary to promote adherence to prescription guidelines [52]. Obviously, a decentralized pharmaceutical budget [11,15] transfers power in management and decision-making from higher to lower levels of the health care organization, which in turn increases economic responsibility among prescribers and creates incentives for efficient drug prescription. Therefore, as a natural consequence, adherence to the drug committee's recommendations increases.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

HO and JM developed the original idea, participated in the design, analysis and drafted the manuscript. HO carried out the statistical analysis. All authors read and approved the final manuscript.

Acknowledgements

This study was supported by grants from the Scania Region's Health Care Research Funds, the Swedish Council for Working Life and Social Research (FAS) (Juan Merlo; Dnr 2003-0580), and the Swedish Research Council (VR) (Juan Merlo; Dnr 2004-6155)

This study has been presented as an abstract at the IEA-EEF European Congress of Epidemiology 2006, Epidemiology and Health Care Practice, in Utrecht, The Netherlands, June 28 to July 1, 2006.

References

1. Kamps G, Stewart R, van Der Werf G, Schuling J, Jong BM: **Adherence to the guidelines of a regional formulary.** *Fam Pract* 2000, **17(3):**254-260.
2. Koutsavlis AT: **Disseminating practice guidelines to physicians.** Institut national de santé publique du Québec; 2001.
3. Stewart RE, Vroegop S, Kamps GB, van der Werf GT, Meyboom-de Jong B: **Factors influencing adherence to guidelines in general practice.** *Int J Technol Assess Health Care* 2003, **19(3):**546-554.

4. Sjöqvist F, Dahl M-L, Gustafsson L, Hensjö L-O: **Drug therapeutics committees: a Swedish experience.** *WHO Drug Information* 2002, **16:**207-213.
5. Socialdepartementet: **Lag (1996:1157) om läkemedelskommittéer. (Law (1996:1157) about drug committees) [in Swedish].** .
6. Edling AL: **Beslut (469/2003).** 2003.
7. Kasje WN, Denig P, Stewart RE, de Graeff PA, Haaijer-Ruskamp FM: **Physician, organisational and patient characteristics explaining the use of angiotensin converting enzyme inhibitors in heart failure treatment: a multilevel study.** *Eur J Clin Pharmacol* 2005, **61(2):**145-151.
8. **En uppföljning av läkemedelskommitéernas arbete. Hur påverkas läkemedelsanvändningen ? (A follow-up of the effort of the drug committees. How does it affect the drug use?) [in Swedish].** .
9. Ohlsson H, Lindblad U, Lithman T, Ericsson B, Gerdtham UG, Melander A, Rastam L, Merlo J: **Understanding adherence to official guidelines on statin prescribing in primary health care-a multi-level methodological approach.** *Eur J Clin Pharmacol* 2005, **61(9):**657-665.
10. **Swedish Health Care in an International Context.** Regions SAoLAa. Stockholm; 2005.
11. Lithman T, Noréen D: **Decentraliserad läkemedelsbudget 2004 (Decentralized drug budget) [In Swedish].** 2004.
12. **Evaluation of the effects of statins (with particular consideration of atorvastatin).** Cologne: Institut fur Qualität und Wirtschaftlichkeit im Gesundheitswesen; 2006.
13. **Behandling med lipidsänkande läkemedel vid prevention av hjärt-kärlsjukdomar. (Treatment with lipid-lowering drugs for prevention of heart diseases) [in Swedish].** *Information från Läkemedelsverket* 2003, **14(ISSN 1101-7104):**4.
14. Läkemedelsrådet , (ed): **Bakgrundsmaterial (Backgroundmaterial) [in Swedish].** *Lund* 2006.
15. Peckham S, Exworthy M, Powell M, Greener I: **Decentralisation as an organisational model for health care in England.** 2005.
16. Goldstein H: **Multilevel Statistical Models.** 3rd edition. London, UK: Hodder Arnold; 2003.
17. Snijders T, Bokser R: **Multilevel analysis: an introduction to basic and advanced multilevel modeling.** Thousand Oaks, California: Sage Publications; 1999.
18. **Lag om receptregister (1996:1156) Proposition 1996/97:27 om läkemedelsförmåner och läkemedelsförsörjning m.m (Swedish National Prescription Register Law).** 1996.
19. **About the ATC/DDD system** [http://www.whocc.no/atcddd/]
20. Yule Udny G: **On some points relating to vital statistics, more expecially statistics of occupational mortality.** *Journal of the Royal Statistical Society* 1934, **97(1):**1-84.
21. Merlo J, Ranstam J, Rastam L, Wessling A, Melander A: **Age standardisation of drug utilisation: comparisons of different methods using cardiovascular drug data from Sweden and Spain.** *Eur J Clin Pharmacol* 1994, **46(5):**393-398.
22. Chaix B, Rosvall M, Merlo J: **Assessment of the magnitude of geographical variations and socioeconomic contextual effects on ischaemic heart disease mortality: a multilevel survival analysis of a large Swedish cohort.** *J Epidemiol Community Health* 2007, **61(4):**349-355.
23. **Skånelistan 2006 [in Swedish].** *Lund* 2006.
24. Merlo J, Yang M, Chaix B, Lynch J: **A brief conceptual tutorial of multilevel analysis in social epidemiology : investigating contextual phenomena in different groups of individuals.** *J Epidemiol Community Health* 2005, **59(9):**729-36.
25. Rasbash J, Steele F, Browne W: **A User's Guide to MLwiN, Version 2.0. Documentation Version 2.1e.** London, UK: Centre for Multilevel Modelling, Institute of Education, University of London; 2003.
26. Davis P, Gribben B: **Rational prescribing and interpractitioner variation. A multilevel approach.** *Int J Technol Assess Health Care* 1995, **11(3):**428-442.
27. Davis P, Gribben B, Lay-Yee R, Scott A: **How much variation in clinical activity is there between general practitioners? A multi-level analysis of decision-making in primary care.** *J Health Serv Res Policy* 2002, **7(4):**202-208.
28. Larsen K, Merlo J: **Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression.** *Am J Epidemiol* 2005, **161(1):**81-88.
29. Larsen K, Petersen JH, Budtz-Jorgensen E, Endahl L: **Interpreting parameters in the logistic regression model with random effects.** *Biometrics* 2000, **56(3):**909-914.
30. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, Rastam L, Larsen K: **A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena.** *J Epidemiol Community Health* 2006, **60(4):**290-297.
31. Goldstein H, Spiegelhalter D: **League tables and their limitations: Statistical issues in comparisions of institutional performance.** *J R Statist Soc* 1996, **159(Part 3):**385-443.
32. Browne W: **MCMC Estrimation in MLwiN (Version 2.0).** London: Institute of Education University of London; 2003.
33. Soumerai S, Majumdar S, Lipton H: **Evaluating and Improving Physician Prescribing.** In *Pharmacoepidemiolgy* 3rd edition. Edited by: Strom B. Chichester, UK: Wiley; 2000:483-503.
34. Grimshaw J, Thomas R, Maclennan G, Fraser C, Ramsay C, Vale L, Whitty P, Eccles M, Matowe L, Shirran L, *et al.*: **Effectiveness and efficiency of guideline dissemination and implementation strategies.** *Health Technol Assess* 2004, **8(6):**.
35. Sorensen G, Emmons K, Hunt MK, Johnston D: **Implications of the results of community intervention trials.** *Annu Rev Public Health* 1998, **19:**379-416.
36. Black N: **Why we need observational studies to evaluate the effectiveness of health care.** *Bmj* 1996, **312(7040):**1215-1218.
37. Brookhart MA, Solomon DH, Wang P, Glynn RJ, Avorn J, Schneeweiss S: **Explained variation in a model of therapeutic decision making is partitioned across patient, physician, and clinic factors.** *J Clin Epidemiol* 2006, **59(1):**18-25.
38. Hjerpe P, Fornwall S, Merlo J: **Therapeutic traditions and compliance with local therapeutic guidelines on lipid lowering drugs – a multilevel analysis in the Skaraborg Primary Healthcare Database (SPHD).** In *International society for pharmacoepidemiology* Bordeaux; 2004.
39. Wennberg J: **Wrestling with variation: an interview with Jack Wennberg [interviewed by Fitzhugh Mullan].** *Health Aff (Millwood)* 2004:VAR73-80.
40. Wennberg JE, Barnes BA, Zubkoff M: **Professional uncertainty and the problem of supplier-induced demand.** *Soc Sci Med* 1982, **16(7):**811-824.
41. Smits HL: **Medical practice variations revisited.** *Health Aff (Millwood)* 1986, **5(3):**91-96.
42. Folland S, Stano M: **Small area variations: a critical review of propositions, methods, and evidence.** *Med Care Rev* 1990, **47(4):**419-465.
43. Anis AH, Carruthers SG, Carter AO, Kierulf J: **Variability in prescription drug utilization: issues for research.** *Cmaj* 1996, **154(5):**635-640.
44. Lopez-Valcarcel B, Ortun-Rubio V, Cabez-Mora A, Lopez-Cabañas A, Diaz-Berenger J, Alamo-Santana F: **Evaluation del uso apropiado de medicamentos en atencion primaria. Como se puede mejorar? (Evaluation of the appropriate use of medication in primary care – how do we improve it?) [in Spanish].** *Aten Primaria* 2002, **30:**467-471.
45. Walley T, Folino-Gallo P, Stephens P, Van Ganse E: **Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997–2003.** *Br J Clin Pharmacol* 2005, **60(5):**543-551.
46. Teeling M, Bennett K, Feely J: **The influence of guidelines on the use of statins: analysis of prescribing trends 1998–2002.** *Br J Clin Pharmacol* 2005, **59(2):**227-232.
47. Jaye C, Tilyard M: **A qualitative comparative investigation of variation in general practitioners' prescribing patterns.** *Br J Gen Pract* 2002, **52(478):**381-386.
48. Läkemedelsverket : **Produktresumén revideras för Crestor.** .
49. Ohlsson O, Kjellström T: **Landsomfattande konsensus för behandling av höga blodfetter (För landets läkemedelskommittéordförande LOK).** Lund, Sweden; 2003.
50. **The statin wars : why AstraZeneca must retreat.** *Lancet* 2003, **362(9393):**1341.
51. Merlo J, Liedholm H, Lindblad U, Bjorck-Linne A, Falt J, Lindberg G, Melander A: **Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study.** *Bmj* 2001, **323(7310):**427-428.

52. Hakansson A, Andersson H, Cars H, Melander A: **Prescribing, prescription costs and adherence to formulary committee recommendations: long-term differences between physicians in public and private care.** *Eur J Clin Pharmacol* 2001, **57(1):**65-70.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1472-6963/7/68/prepub

III

Eur J Clin Pharmacol
DOI 10.1007/s00228-008-0569-4

SPECIAL ARTICLE

Therapeutic traditions, patient socioeconomic characteristics and physicians' early new drug prescribing–a multilevel analysis of rosuvastatin prescription in south Sweden

Henrik Ohlsson · Basile Chaix · Juan Merlo

Received: 16 July 2008 / Accepted: 3 September 2008

Abstract
Purpose To investigate the role that both patient and outpatient factors related to health care practice (HCP) play in physicians' early adoption of rosuvastatin.
Materials and methods Generalized estimation equations (GEEs) and alternating logistic regression (ALR) with pairwise odds ratios (PWORs) were used to measure similarities in rosuvastatin prescription within HCPs for all individuals with statin prescriptions in Skåne region, Sweden.
Results After 12 months, 53% of the HCPs had adopted the new statin. Rosuvastatin prescriptions co-occured within certain HCPs 3.56 times more often than one would have expected based on a random distribution. Private HCPs had four times higher probability of prescribing rosuvastatin than public HCPs.
Conclusion Contextual characteristics of the HCP seem to be relevant for understanding physicians' motivation to adopt rosuvastatin. Moreover, our study reveals inequity in health care as the socioeconomic status of the patients appears to influence the prescribing behavior of the physicians irrespective of medical reasons.

Keywords Therapeutic traditions · Alternating logistic regression · Early adopter · Rosuvastatin

H. Ohlsson · B. Chaix · J. Merlo
Social Epidemiology, Department of Clinical Sciences in Malmö, Faculty of Medicine, Lund University, Malmö, Sweden

H. Ohlsson · J. Merlo
Department of Social Medicine, Skåne Region, Malmö, Sweden

B. Chaix
UMR-S 707 Inserm, Université Pierre et Marie Curie-Paris 6, Faculté de Médecine, Paris, France

H. Ohlsson (✉)
Social Epidemiology, Department of Clinical Sciences, Faculty of Medicine, Lund University, 205 02 Malmö, Sweden
e-mail: Henrik.Ohlsson@med.lu.se

Background

In many countries drug expenditure is increasing rapidly in relation to overall health care costs, and a greater variety and availability of new, expensive drugs is one of the key factors influencing this phenomenon. Adopting a new drug could be appropriate for the health of the patient and cost-effective for the community, but in some cases newly marketed drugs only bring a marginal or insignificant contribution to the conventional therapeutic arsenal. Previous studies have shown considerable variation among prescribers regarding early adoption of newly marketed drugs [1–9], and it is known that the decision to adopt a new drug reflects differences in information and attitudes among prescribers [10, 11]. However, research on determinants of early adoption of new drugs is still very scarce. Understanding the mechanisms leading to physicians' early adoption of new drugs is, therefore, highly relevant for promoting cost-effective prescription.

Rosuvastatin was marketed as Crestor (AstraZeneca Pharmaceuticals, Wilmington, DE, USA) and incorporated within the Swedish health reimbursement system in July 2003, when it became the fifth available cholesterol-lowering drug from the class of HMG-CoA reductase inhibitors (statins) [12]. However, simultaneously and in concordance with an editorial in *The Lancet* [13], rosuvas-

tatin was not included in the Skåne region guidelines for rational drug prescription because this drug, despite being effective in lowering total and low-density lipoprotein (LDL) cholesterol, has unstipulated effects on morbidity and mortality and only scarce evidence concerning its safety. Moreover, rosuvastatin was approximately 20 times more expensive than the cheapest alternative statin [14].

The introduction of rosuvastatin on the Swedish market and the fact that there are no solid therapeutic reasons for prescribing the new, more expensive brand instead of the cheaper, recommended ones provide a unique opportunity to investigate determinants of (inappropriate) early adoption of new drugs in general, and of rosuvastatin in particular [15–17]. Therefore, we aimed to elaborate a previous theory that considers measures of variance and clustering to quantify therapeutic traditions [18–21]. For this purpose, we developed an innovative analytical approach using generalized estimation equations (GEE), alternating logistic regression (ALR), and pair-wise odds ratios (PWORs) [22]. Simultaneously, we aimed to investigate the role that both patient characteristics[(i.e., sex, age, socioeconomic status (SES), marital status, country of birth] and factors related to outpatient health care practice (HCP) (e.g., public vs. private administration, proximity to specialized care, rural vs. urban setting, total prescription volume) played in physicians' propensity to prescribe rosuvastatin after its introduction to the market.

Materials and methods

The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (SPDR) [23] is administered by the Centre for Epidemiology at the Swedish National Board of Health and Welfare and records information on sales of prescribed pharmaceutical agents by the Swedish Corporation of Pharmacies. The SPDR was launched in January 1999, and since July 2005, it has been using the Swedish personal identification number system rather than an arbitrary number for each prescription, which allows record linkage with other health care registers at the individual level. Among other data, the SPDR contains the brand name and anatomical therapeutic chemical classification (ATC) code for both prescribed and dispensed drugs, whether the prescription is repeated or not, and the HCP where the prescription was issued (identifiable by barcodes on the prescriptions). Information on prescribers is, however, not available.

At the time rosuvastatin was introduced in the Swedish reimbursement system (July 2003) there was not information in the SPDR at the individual level. This information was only available from July 2005, and therefore we used two different data sets. The first data set included all 84,822 initial prescriptions of statins issued at HCPs in the Skåne region between July 2003 and June 2004. We excluded HCPs with sporadic prescription (i.e., <30 statin prescriptions during the entire observation period), as well as those prescriptions issued from unidentified places or places outside Skåne [13% (11,275/84,822)]. Also, since according to the Swedish reimbursement system, a prescription that covers a whole year must be dispensed in three increments, we only considered first dispensations within the study period. In total we analyzed 73,547 prescriptions (32,641 for women and 40,906 for men) from 170 HCPs. In the second data set, we included all 32,011 individuals (14,316 women and 17,695 men) in Skåne region who were issued at least one prescription for statins between July and December 2005 at the same 159 HCPs (eleven HCPs out of the original 170 gave no prescriptions during this period).

Data from the Longitudinal Multilevel Analysis in Skåne (LOMAS) were used to establish demographic variables and the SES of the individuals [24].

This project was performed with the approval of and assistance from Statistics Sweden and the Centre for Epidemiology at the Swedish National Board of Health and Welfare, as well as approval by the Regional Ethical Review Board in Lund. In order to protect the identity of the individuals, the research database does not contain the real personal identification number but rather an arbitrary number. The link between these two numbers is kept at Statistics Sweden.

Individual-level variables

Statins were defined according to the ATC code C10AA [25]. At the individual level, the outcome variable was prescription (yes vs. no) of rosuvastatin (ATC code C10AA07). In the analyses we included the sex (male vs. female) and age (centered on the overall mean of 66 years) of the patients.

As described elsewhere [26], the SES of the patients seemed to influence the prescribing behavior. Therefore, in the second phase of our analyses we also considered each patient's disposable family income, measured at the end of 2004. We divided income into quartiles and used the highest quartile as reference in the comparisons.

Adopting an exploratory approach we also included the marital and immigrant status of the patients as we hypothesized that these characteristics could influence physicians' prescribing behavior. Marital status was dichotomized into married/cohabiting vs. living alone (i.e., single, divorced, or widowed), with married/cohabiting as reference category. Immigrant status/ethnicity was measured by the country of birth of the patients and the number of years that the patient had resided in Sweden. We categorized this

last variable into (1) always lived in Sweden, (2) ≥10 years in Sweden, and (3) 0–9 years in Sweden. The first category was used as a reference in the analysis. The country of birth of the patients was categorized according the World Bank Classification of Country Economies (i.e., low, lower-middle, upper-middle, and high income) [27]. In the analysis, we merged the first two into a single category designated "low-income country", and used the high-income country category as a reference in the comparisons. Number of years in Sweden and country of birth, according to the World Bank classification, offered an appropriate alternative for measuring immigrant status/ethnicity as this combination considers the acculturation process of immigrants who have resided in Sweden for many years and focuses not on geographic but on economic criteria for classifying country of birth.

Area-level variables

Of the 170 (159) HCPs included in the first (and second) data set, 129 (127) were under public administration as public primary health care centers and hospital outpatient care clinics, and 41 (32) were private primary health care centers employing general practitioners (GPs) and other specialists. The health services in Sweden are largely tax-financed, and even private HCPs are primarily funded by contract between the public health care authorities and the private companies [28]. Private physicians are, however, less influenced by the public health care administration, and we have previously shown that privately managed HCPs have a lower adherence to official guidelines for statin prescription than public HCPs [21]. Therefore, we included this variable (private vs. public) in the analyses since it was possible that the administrative condition of the HCP also influenced early adoption of rosuvastatin.

Given that proximity to specialized care may influence prescription patterns, we also identified those HCPs that employed specialist physicians other than GPs. In the analyses, HCPs employing GPs only were used as reference.

It is probable that several factors that could influence prescription of newly marketed drugs, such as distribution of information, marketing forces, and patient demands and expectations, may be influenced by the population density of the area. Therefore, we considered whether the HCP was located in a rural or an urban area, according to the definition provided by the Swedish Association of Local Authorities and Regions. The definition is based on structural characteristics such as population size, commuting patterns, and the structure of businesses in the municipality [29]. Of the 33 municipalities in Skåne region, those municipalities that were classified as a metropolitan area (1), suburban municipality (6), large town (3), or medium-sized town (7) were classified as urban areas. Sixteen municipalities were classified as rural areas and were used as reference in the analysis.

The total prescribing volume of the HCP where the prescriber works has been shown in previous studies to affect the likelihood that a physician will adopt a new drug, where a larger prescribing volume is associated with higher probability of early adoption of a new drug [30]. Consequently, we included a variable where the number of statin prescriptions at the HCPs during the entire observation period was divided into three categories: T1 (≤234 prescriptions), T2 (235–441 prescriptions), and T3 (>441 prescriptions). We used T3 as reference in the comparisons.

Statistical and epidemiological analysis

Our hypothesis was that the HCP environment (i.e., therapeutic traditions) had an independent influence on physicians' prescribing behavior in general and on early adoption of rosuvastatin in particular. To investigate this hypothesis we applied a previous theory [18–21] that considers measures of variance and clustering to quantify therapeutic traditions, and we measured clustering of rosuvastatin prescription at the HCP level across time, categorized into four consecutive trimesters from July 2003 to June 2004.

In previous studies we employed multilevel regression analyses [20, 21], a suitable analytical approach when the data have a hierarchical structure as in the present case (i.e., prescriptions were nested within different time periods, which in turn were nested within HCPs). However, since the distribution of the prevalence of rosuvastatin prescription at the HCP level was skewed, we applied ALR. Similarly to multilevel regression analyses, the ALR model accounts for the dependence of the outcome within different levels/categories and thereby allows accurate statistical estimations. Also, the ALR methodology allowed us to quantify the clustering of prescriptions of rosuvastatin within HCPs with an index in the form of an odds ratio (OR), the PWOR [22].

In order to compute PWORs, the model considers all the pairs involving two prescriptions from the same HCP. Using p_{11} to denote the probability that both prescriptions in a pair are for rosuvastatin, p_{00} to denote the probability that neither of the prescriptions in a pair is for rosuvastatin, and p_{10} and p_{01} to denote the probabilities that only one of the prescriptions in a pair is for rosuvastatin, the PWOR can be calculated as follows:

$$\mathrm{PWOR} = \frac{p_{00} \cdot p_{11}}{p_{10} \cdot p_{01}} \quad (1)$$

The PWOR reflects the increase in the odds of a prescription being for rosuvastatin given that another

prescription randomly selected from the same HCP may also be for rosuvastatin. By quantifying the context dependence of the rosuvastatin prescription, PWORs can be used as a measure of "therapeutic traditions." The higher the PWOR, the stronger the therapeutic traditions. The PWOR is equal to 1 in the absence of clustering, and in this case it indicates that rosuvastatin prescriptions within the same HCP were more frequent than could be expected if prescriptions were distributed randomly across HCPs.

In practice, PWORs are calculated from the ALR model, which simultaneously estimates the following two equations:

$$\log(\mathrm{PWOR}_{kl}) = \alpha Z_{kl} \tag{2}$$

$$\mathrm{logit}(p_k) = \beta_0 \tag{3}$$

Equation 2 expresses the logarithm of PWORs as a function of a dummy variable Z, which simply indicates whether two patients (or two prescriptions), k and l, in a pair belong to the same category or not (the variable Z is equal to 0, and the PWOR to 1, for prescriptions from different HCPs). The ALR model simultaneously estimates a logistic regression by a GEE for the outcome (Eq. 3); in this equation, p_k refers to the expected probability of prescribing rosuvastatin for the patient k.

We specified several different models. Model A was an empty model without any covariates, which only included time as a second level and HCPs as the third level. This model allowed separate PWORs to be calculated within and across different time periods. Models B and C included individual, and individual and contextual variables, respectively.

Applying an established procedure [31], we used the PWORs obtained in the empty model as reference ($\mathrm{PWOR}_{\mathrm{reference}}$) to calculate the percentage of change in the magnitude of clustering, which was explained by including individual or contextual characteristics in the model with more variables ($\mathrm{PWOR}_{\mathrm{more}}$).

$$\text{Percentage of change} = ((\mathrm{PWOR}_{\mathrm{reference}} - \mathrm{PWOR}_{\mathrm{more}})/(\mathrm{PWOR}_{\mathrm{reference}} - 1)) \times 100 \tag{4}$$

We used this percentage for estimating the relevance of patient characteristics (i.e., the patient composition of the HCPs) as well as the relevance of contextual characteristics of the HCPs for understanding a possible clustering of rosuvastatin prescriptions.

In order to investigate the influence of the SES of patients on the prescription of rosuvastatin, we applied GEE-ALR on the data from July to December 2005 (i.e., the second data set). Model D was an empty model without any covariates, which only included HCPs as a second level, while models E and F further included individual and contextual variables that could explain a possible clustering of rosuvastatin prescriptions.

We performed a survival analysis at the HCP level, in which we followed the HCPs from baseline until the first prescription of rosuvastatin or the end of the first observation period, and performed a Cox regression to investigate the association between the administrative condition (private vs. public) of the HCP and early adoption of rosuvastatin.

To study associations we calculated ORs and their 95% confidence intervals (95% CIs) from the regression coefficients [(standard errors (SEs)].

The calculations were made using the GENMOD procedure in SAS software, version 9.1 (SAS Institute, Cary, NC, USA), to fit the ALR models, and SPSS, version 15 (SPSS, Chicago, IL, USA).

Results

For the period July 2003 to June 2004, there was a decreasing trend in the prevalence of rosuvastatin prescriptions ranging from 2.6% (410/16,073) in the first trimester to 1.5% (283/18,273) in the last.

Table 1 shows that, on average, patients receiving rosuvastatin were younger than patients receiving other statins. More men than women received a statin prescription, and the same was true for rosuvastatin. Throughout the whole study period, private HCPs, HCPs employing specialists as well as GPs, and HCPs located in an urban area more frequently prescribed rosuvastatin than public HCPs, HCPs with only GPs, and HCPs located in rural areas. The lower the amount of total statin prescribed at the HCP, the higher the percentage of rosuvastatin prescription. However, this phenomenon was only apparent in the early phase of the observation period.

A descriptive analysis of the HCPs shows that 90 of the 170 HCPs prescribed at least one prescription for rosuvastatin during the entire study period. Moreover, in three HCPs the prescription of rosuvastatin was considerably higher than in the rest of the HCPs (>15%). Those three HCPs accounted for 13% of all rosuvastatin prescriptions but only for 1% of all statin prescriptions throughout the study period.

Figure 1 shows that private HCPs seem to have adopted rosuvastatin faster than public HCPs. In addition, the Cox regression showed that private HCPs had a 1.82 (95% CI 1.16–2.84) times higher hazard of adopting rosuvastatin than public HCPs. Moreover, at the end of the observation

Table 1 Characteristics of the 73,547 prescriptions for statins issued to 32,641 women and 40,906 men at 170 health care practices (HCPs)

	Jul–Sept 2003		Oct–Dec 2003		Jan–Mar 2004		Apr–Jun 2004	
	Other statin	Rosuvastatin	Other statin	Rosuvastatin	Other statin	Rosuvastatin	Other statin	Rosuvastatin
Prescriptions	15,663	410 (2.6%)	20,143	444 (2.2%)	18,270	344 (1.9%)	17,990	283 (1.6%)
Mean age (years)	66	61	66	58	67	61	67	61
Men (%)	57	50	56	56	55	51	56	54
HCP								
Private	5,073	268 (5.3%)	6,079	264 (4.3%)	4,402	161 (3.7%)	4,447	156 (3.5%)
Public	10,590	142 (1.3%)	14,064	180 (1.3%)	13,868	183 (1.3%)	13,543	127 (0.9%)
Only GPs	9,565	236 (2.5%)	12,861	219 (1.7%)	12,656	230 (1.8%)	12,614	199 (1.6%)
Other specialists	6,098	174 (2.9%)	7,282	225 (3.1%)	5,614	114 (2.0%)	5,376	84 (1.6%)
Rural	1,946	27 (1.4%)	2,548	29 (1.1%)	2,456	32 (1.3%)	2,476	41 (1.7%)
Urban	13,717	383 (2.8%)	17,595	415 (2.4%)	15,814	312 (2.0%)	15,514	242 (1.6%)
Size[a]								
≤234	1,621	69 (4.3%)	1,999	44 (2.2%)	1,536	23 (1.5%)	1,650	19 (1.2%)
235–441	3,961	62 (1.6%)	5,359	89 (1.7%)	5,027	56 (1.1%)	4,996	54 (1.1%)
>441	10,081	279 (2.8%)	12,785	311 (2.4%)	11,707	265 (2.3%)	11,344	210 (1.9%)

Unless otherwise indicated, values are *n*

[a] Size of HCP in terms of number of prescriptions during the observation period

period almost 70% of private HCPs had given at least one prescription of rosuvastatin compared with 45% of public HCPs.

Table 2 (model A) shows that, during the first trimester of the observation period, rosuvastatin prescriptions co-occurred within certain HCPs more frequently than one would had expect if prescriptions were distributed randomly, i.e., PWOR=3.56 (95% CI 1.95–6.51), and this clustering continued to be high in the following trimesters. The between-time clustering was also high (values above the diagonal for model A in Table 2), indicating that those HCPs with a higher level of rosuvastatin prescription during one trimester were also more likely to prescribe rosuvastatin in the other trimesters. Accounting for the age and gender composition (model B) of the HCPs did not attenuate the magnitude of clustering. However, age was conclusively associated with the prescription of rosuvastatin, with a lower probability for older people. When including the contextual variables (model C), the PWOR was reduced by approximately 40% in the first and second trimesters but only by 9% in the third trimester.

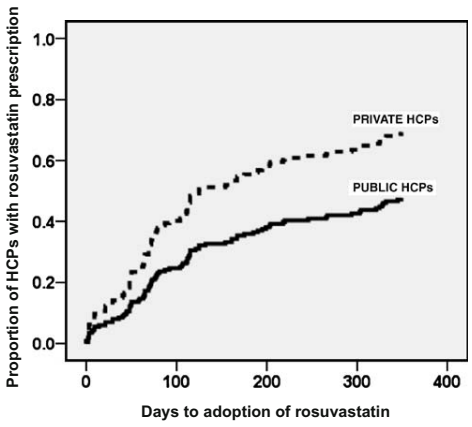


Fig. 1 Prescribing of rosuvastatin in private vs. public health care practices (HCPs) during the observation period July 2003 to June 2004

The probability of prescribing rosuvastatin was approximately four times higher in private than in public HCPs (Table 3). In this model, neither the presence of specialist physicians nor the rural vs. urban location of the HCP was associated with rosuvastatin prescription.

Table 4 shows that from July to December 2005, 366 individuals (1.3% of all individuals with statin prescriptions) were prescribed rosuvastatin. The prevalence of rosuvastatin prescriptions was higher among individuals who were married/cohabiting and also showed a socioeconomic gradient with a higher share of rosuvastatin prescriptions among both men and women with high income. However, there was no association between country of birth of patients and rosuvastatin prescription.

Table 5 shows that individuals in the highest income quartile had higher odds of being prescribed rosuvastatin than individuals in the lowest income quartile. In models D–F we did not find any conclusive association between rosuvastatin prescription and number of years in Sweden, country of birth, or marital status. The clustering of rosuvastatin prescriptions at the HCP level was high for

Table 2 Pair-wise odds ratios and odds ratios (with 95% confidence intervals *in parentheses*) obtained by alternating logistic regression (ALR) analysis of early adoption of rosuvastatin in the county of Skåne, Sweden

Model A	Trimester 1	Trimester 2	Trimester 3	Trimester 4
Trimester 1	3.56 (1.95–6.51)	2.75 (1.87–4.05)	2.18 (1.39–3.43)	2.47 (1.31–4.66)
Trimester 2		2.59 (1.81–3.71)	2.01 (1.42–2.84)	2.41 (1.63–3.58)
Trimester 3			2.71 (1.69–4.35)	2.55 (1.51–4.32)
Trimester 4				3.44 (2.14–5.51)
Model B	Trimester 1	Trimester 2	Trimester 3	Trimester 4
Trimester 1	3.78 (2.08–6.88)	2.88 (1.96–4.25)	2.19 (1.38–3.47)	2.51 (1.30–4.83)
Trimester 2		2.70 (1.86–3.91)	2.00 (1.40–2.86)	2.44 (1.62–3.68)
Trimester 3			2.67 (1.65–4.31)	2.50 (1.47–4.24)
Trimester 4				3.28 (2.01–5.35)
Model C	Trimester 1	Trimester 2	Trimester 3	Trimester 4
Trimester 1	2.05 (1.06–3.93)	1.56 (0.97–2.53)	1.63 (1.11–2.39)	1.61 (1.19–2.17)
Trimester 2		1.59 (0.98–2.58)	1.70 (1.15–2.51)	1.70 (1.14–2.54)
Trimester 3			2.44 (1.51–3.93)	2.08 (1.52–2.85)
Trimester 4				2.47 (1.56–3.92)

both men (PWOR=2.99) and women (PWOR=2.58). Adjustment for the patient characteristics studied attenuated the magnitude of clustering to a small extent. However, the inclusion of contextual variables decreased the magnitude of clustering by approximately 20%.

Discussion

The present study shows that early adoption of rosuvastatin was highly clustered in certain HCPs, and that this clustering remained across the whole observation period. Therefore, our results suggest the existence of strong therapeutic traditions that, at the HCP level, influence prescribing behavior of individual physicians. We also observed that private HCPs prescribed rosuvastatin four times more frequently than public HCPs. However, even if this contextual characteristic appeared to be relevant for understanding physicians' motivation to adopt rosuvastatin, it could not completely explain the observed variance in rosuvastatin prescription. Moreover, our study reveals some inequity in health care as rosuvastatin was prescribed more frequently to younger patients and to those with a high SES than to elderly patients or to those with a low income. In other words, both contextual and patient characteristics seem to have influenced the behavior of the physicians, independently of medical reasons. Our study supports previous findings [6, 7, 32], indicating that a wide range of factors at different levels may influence the diffusion of innovations [33].

It is important to consider that the context, i.e., the HCP where the physicians worked, seems to have affected both early adoption and the subsequent prescription of rosuvastatin. In fact, those HCPs that prescribed one prescription of rosuvastatin were almost four times more likely to prescribe one more prescription during the same trimester, and almost three times more likely to prescribe rosuvastatin during the following trimester. This observation suggests that local therapeutic traditions remain over time, and that prescription of rosuvastatin was not an occasional early phenom-

Table 3 Fixed effects (odds ratios with 95% confidence intervals *in parentheses*) of the generalized estimation equations (GEE)-ALR methodology

	Model A	Model B	Model C
Age (1 year's increase)		0.96 (0.94–0.97)	0.96 (0.94–0.97)
Sex (male vs. female)		0.87 (0.65–1.15)	0.87 (0.67–1.14)
Private vs. public			4.31 (1.93–9.62)
Size[a]			
≤234			0.64 (0.21–1.96)
235–441			0.67 (0.36–1.23)
>441			Reference
Specialist vs. general practitioner[b]			0.97 (0.58–1.62)
Urban vs. rural[b]			0.98 (0.50–1.90)

[a] Size of HCP in terms of number of prescriptions during the observation period
[b] Estimated in a model with the same PWOR for all time periods, and time included as a fixed effect

Table 4 Characteristics of the 32,011 individuals (14,316 women and 17,695 men) who were prescribed at least one statin between July and December 2005

	Total		Men		Women	
	Other statin	Rosuvastatin	Other statin	Rosuvastatin	Other statin	Rosuvastatin
Number of individuals	31,645	366 (1.2%)	17,479	216 (1.2%)	14,166	150 (1.1%)
Mean age (years)	68	61	66	60	69	63
Men	55.2%	59.0%				
Income						
Low	8,248	59 (0.7%)	4,171	32 (0.8%)	4,077	27 (0.7%)
Middle-low	8,101	63 (0.8%)	3,893	35 (0.9%)	4,208	28 (0.7%)
Middle-high	7,788	105(1.3%)	4,553	56(1.2%)	3,235	49(1.5%)
High	7,508	139 (1.9%)	4,862	93 (1.9%)	2,646	46 (1.7%)
Marital status						
Living alone	12,033	105 (0.9%)	5,251	56 (1.1%)	6,782	49 (0.7%)
Married/cohabiting	19,612	261 (1.3%)	12,228	160 (1.3%)	7,384	101 (1.4%)
Country of birth						
High-income country	29,009	335 (1.2%)	16,049	196 (1.2%)	12,960	139 (1.1%)
Middle-income country	1,016	15 (1.5%)	527	10 (1.9%)	489	5 (1.0%)
Low-middle income country	1,486	15 (1.0%)	821	10 (1.2%)	665	5 (0.8%)
Low-income country	134	1 (0.7%)	82	0 (0.0%)	52	1 (1.9%)
Number of years in Sweden						
Always	26,695	301 (1.1%)	14,752	178 (1.2%)	11,943	123 (1.0%)
≥10	4,268	56 (1.3%)	2,316	32 (1.4%)	1,952	24 (1.2%)
0–9	682	6 (1.0%)	411	6 (1.5%)	271	3 (1.1%)

enon. When analyzing trends in rosuvastatin prescription, it is relevant to realize that this drug was the subject of safety concerns [12–14] during the observation period. These warnings possibly influenced the patterns of drug utilization, as evidenced by an overall reduction in the prevalence of rosuvastatin prescriptions in the last trimester of observation. However, the clustering of rosuvastatin prescriptions was not substantially affected.

Earlier studies also suggest that a high volume of prescribing at an HCP may affect physicians' adoption of new drugs since the likelihood of seeing a patient as a candidate for the new drug would be higher [30]. However, there are no specific indications that should make one patient more suitable than another for receiving a rosuvastatin prescription, and, in fact, the present analysis shows no association between rosuvastatin prescription and prescription volume at the HCP. Previous studies have shown that medical innovations are more likely to be adopted earlier in urban areas than in rural areas [30]. However, in this study we did not find support for this association.

Based on the actual evidence there is no patient characteristic that could motivate the preferential prescription of rosuvastatin before any other statin. Therefore the individual-level variables in the analysis are included, not because of the need for adjustment for confounding, but rather because we wanted to gain an understanding of the prescribing process. In the present investigation we observed that women were prescribed less rosuvastatin than men. Also, rosuvastatin was more frequently prescribed to patients with higher SES.

Even though the present analysis confirms previous reports indicating that practice-level factors are relevant for understanding prescribing behavior [18–21, 34, 35], part of the prescribing behavior in the present study could in fact have been due to individual physicians rather than to the characteristics of the HCP. In a previous study [36] we showed that approximately 50% of the variation among practices is in fact due to variations among physicians. However, we did not have access to physician-level information in the current database.

Practice variation is a common phenomenon that is not necessarily inappropriate but rather may reflect different therapeutic approaches to confronting a similar health problem [37, 38]. However, since all statins have homogeneous indication and similar efficacy, statins are an ideal medication group for investigating inappropriate practice variation. At the time of this study, rosuvastatin 40 mg was approximately 20 times more expensive than the cheapest recommended statin. Subsequently, when a pharmacological agent is used in an unsuitable way, which could lead to undesirable inequalities in drug use for the population and have important cost implications, it is relevant to investigate determinants of prescription disparities in order to launch interventions promoting appropriate prescription.

Table 5 Pair-wise odds ratios (PWORs) and odds ratios (ORs) (with 95% confidence intervals *in parentheses*), obtained by alternating logistic regression (ALR) analysis of patients who were prescribed rosuvastatin in the region of Skåne, Sweden, from July to December 2005

	Model D		Model E		Model F	
	Men	Women	Men	Women	Men	Women
PWOR (95% CI)	2.99 (1.63–5.49)	2.58 (1.79–3.73)	2.83 (1.58–5.09)	2.46 (1.73–3.50)	1.89 (1.35–2.63)	1.72 (1.27–2.33)
Individual variables			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (1-year increase)			0.96 (0.94–0.97)	0.96 (0.95–0.98)	0.94 (0.92–0.95)	0.96 (0.95–0.98)
Income						
Low			Reference	Reference	Reference	Reference
Middle-low			1.22 (0.64–2.33)	1.00 (0.58–1.74)	1.22 (0.67–2.22)	1.00 (0.58–1.73)
Middle-high			1.38 (0.85–2.23)	1.68 (0.93–3.03)	1.35 (0.87–2.10)	1.66 (0.93–2.95)
High			1.80 (1.05–3.11)	1.62 (0.93–2.81)	1.74 (1.07–2.85)	1.58 (0.91–2.72)
Marital status						
Living alone			0.78 (0.53–1.13)	0.65 (0.42–1.02)	0.79 (0.56–1.11)	0.66 (0.44–1.01)
Married/cohabiting			Reference	Reference	Reference	Reference
Country of birth						
High-income country			Reference	Reference	Reference	Reference
Middle-income country			1.34 (0.57–3.15)	0.83 (0.25–2.77)	1.33 (0.62–2.83)	0.85 (0.27–2.72)
Low-income country			1.06 (0.38–2.94)	0.54 (0.18–1.65)	1.08 (0.43–2.75)	1.82 (0.63–5.25)
Number of years in Sweden						
Always			Reference	Reference	Reference	Reference
≥10			0.31 (0.05–1.93)	1.46 (0.37–5.86)	0.32 (0.06–1.67)	1.46 (0.40–5.41)
0–9			0.86 (0.19–3.87)	1.31 (0.33–5.86)	0.88 (0.23–3.32)	1.36 (0.36–5.15)
Contextual variables						
Private vs. public HCP					3.41 (1.95–5.95)	3.09 (1.58–6.05)
Size of HCP						
Small					0.86 (0.42–1.79)	0.97 (0.40–2.36)
Medium					0.71 (0.36–1.39)	1.02 (0.51–2.03)
Large					Reference	Reference
Specialist vs. general practitioner					1.62 (0.88–3.00)	1.19 (0.62–2.29)
Urban v. rural					1.14 (0.45–2.84)	0.93 (0.44–1.99)

HCP Health care practice

In previous studies we measured therapeutic traditions using analysis of variance and multilevel logistic regression techniques [20, 21]. In the present investigation we applied the ALR-PWOR approach. Both methods provide analogous, but not identical, information. While the ALR-PWOR approach provides information on the magnitude of clustering of similar behavior within different HCPs, the multilevel logistic regression approach measures the heterogeneity across HCPs. Pair-wise odds ratios appear to be a very suitable measure for interpreting clustering in the well-known OR scale. Also, the ALR-PWOR is appropriate for investigating outcomes with a very skewed distribution [22], as in the present study. The PWOR is also a flexible measure that allows investigation of clustering in arbitrary categories such as different time periods. Alternating logistic regression has been successfully employed in a number of previous epidemiological studies [39–46] and appears to be a relevant measure for investigating and quantifying medical practice variation.

In conclusion, the GEE-ALR and PWOR methodology seems to be a useful tool for investigating determinants of prescription at different levels of analysis. Applying this methodology we observed that contextual factors (e.g., therapeutic traditions) at the HCP may be relevant for understanding physicians' propensity to early adopt and prescribe a new statin (i.e., rosuvastatin), especially in the private sector. Additionally, the age and SES of the patients appeared to influence the prescribing behavior of the physicians, as rosuvastatin was more frequently prescribed to both younger men and younger women with high income. When the same pharmacological therapy is available as different brands at different prices and the prescriber selects the new, more expensive brand based on socioeconomic constructs rather than on medical grounds there are reasons to question the suitability of the observed prescribing process. Our study indicates the existence of inefficient therapeutic traditions and suggests that interventions may be necessary to promote rational prescription guidelines for pharmacologic treatment in the context of a limited health care budget.

References

1. Coleman J, Menzel H, Katz E (1959) Social processes in physicians' adoption of a new drug. J Chronic Dis 9(1):1–19
2. Dybdahl T, Andersen M, Kragstrup J, Kristiansen IS, Sondergaard J (2005) General practitioners' adoption of new drugs and previous prescribing of drugs belonging to the same therapeutic class: a pharmacoepidemiological study. Br J Clin Pharmacol 60 (5):526–533
3. Dybdahl T, Andersen M, Sondergaard J, Kragstrup J, Kristiansen IS (2004) Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs. Eur J Clin Pharmacol 60(9):667–672
4. Greving JP, Denig P, Van der Veen WJ, Beltman FW, Sturkenboom MC, Haaijer-Ruskamp FM (2006) Determinants for the adoption of angiotensin II receptor blockers by general practitioners. Soc Sci Med 63(11):2890–2898
5. Jones MI, Greenfield SM, Bradley CP (2001) Prescribing new drugs: qualitative study of influences on consultants and general practitioners. Brit Med J 323(7309):378–381
6. Steffensen FH, Sörensen H, Olesen F (1999) Diffusion of new drugs in Danish general practice. Fam Prac 16:407–413
7. Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J (2003) Physician and practice characteristics associated with the early utilization of new prescription drugs. Med Care 41(8):895–908
8. Florentinus SR, Nielsen MW, van Dijk L, Leufkens HG, Hansen EH, Heerdink ER (2005) Patient characteristics associated with prescribing of a newly introduced drug: the case of rofecoxib. Eur J Clin Pharmacol 61(2):157–159
9. Kozyrskyj A, Raymond C, Racher A (2007) Characterizing early prescribers of newly marketed drugs in Canada: a population-based study. Eur J Clin Pharmacol 63(6):597–604
10. Haaijer-Ruskamp FM, Hemminki E (1993) The social aspects of drug use. WHO Reg Publ Eur Ser 45:97–124
11. Merlo J, Lynch JW, Yang M, Lindstrom M, Ostergren PO, Rasmusen NK, Rastam L (2003) Effect of neighborhood social participation on individual use of hormone replacement therapy and antihypertensive medication: a multilevel analysis. Am J Epidemiol 157(9):774–783
12. Läkemedelsverket (2004) Produktresumén revideras för Crestor (Product resume for Crestor is revised) (in Swedish). http://www.lakemedelsverket.se/Tpl/NewsPage____1166.aspx. Accessed 18 Sept 2008
13. Editors (2003) The statin wars: why AstraZeneca must retreat. Lancet 362(9393):1341
14. Ohlsson O, Kjellström T (2003) Landsomfattande konsensus för behandling av höga blodfetter (För landets läkemedelskommittéordförande LOK) (Consensus for treament of high lipids) (in Swedish). Lund, Sweden
15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (2006) Evaluation of the effects of statins (with particular consideration of atorvastatin). IQWiG, Cologne
16. LaRosa JC, He J, Vupputuri S (1999) Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. J Am Med Assoc 282(24):2340–2346
17. Vrecer M, Turk S, Drinovec J, Mrhar A (2003) Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. Int J Clin Pharmacol Ther 41(12):567–577
18. Davis P, Gribben B (1995) Rational prescribing and interpractitioner variation. A multilevel approach. Int J Technol Assess Health Care 11(3):428–442
19. Davis P, Gribben B, Lay-Yee R, Scott A (2002) How much variation in clinical activity is there between general practitioners? A multi-level analysis of decision-making in primary care. J Health Serv Res Pol 7(4):202–208
20. Ohlsson H, Lindblad U, Lithman T, Ericsson B, Gerdtham UG, Melander A, Rastam L, Merlo J (2005) Understanding adherence to official guidelines on statin prescribing in primary health care – a multi-level methodological approach. Eur J Clin Pharmacol 61 (9):657–665
21. Ohlsson H, Merlo J (2007) Understanding the effects of a decentralized budget on physicians' compliance with guidelines for statin prescription; a multilevel methodological approach. BMC Health Serv Res 7:68 (8 May 2007)
22. Carey V, Zeger SL, Diggle P (1993) Modelling multivariate binary data with alternating logistic regression. Biometrika 80 (3):517–526
23. Socialstyrelsen (2008) Läkemedelsregistret. http://www.socialstyrelsen.se/Statistik/statistik_amne/lakemedel/Lakemedelsregistret.htm. Accessed 12 May 2008
24. Chaix B, Rosvall M, Merlo J (2007) Assessment of the magnitude of geographical variations and socioeconomic contextual effects on ischaemic heart disease mortality: a multilevel survival analysis of a large Swedish cohort. J Epidemiol Comm Health 61(4):349–355
25. World Health Organisation (2008) About the ATC/DDD system. http://www.whocc.no/atcddd/. Accessed 12 Apr 2008
26. Scott A, Shiell A, King M (1996) Is general practitioner decision making associated with patient socio-economic status? Soc Sci Med 42(1):35–46
27. WorldBank (2008) Country classification. http://www.worldbank.org/data/countryclass/countryclass.html. Accessed 15 Jan 2008
28. Swedish Association of Local Authorities and Regions (2005) Swedish health care in an international context. SAoLAa, Stockholm
29. Bengtsson H (2003) Nuvarnade kommunuppdelning (Classification of municipalities) (in Swedish). Svenska Kommunförbundet http://www.skl.se/artikel.asp?A=11248&C=445. Accessed 22 Jan 2008
30. Glass H, Rosenthal B (2004) Demographics, practices, and prescribing characteristics of physicians who are early adopters of new drugs. Pharm Therapeut 29(11):699–708
31. Wamala SP, Mittleman MA, Schenck-Gustafsson K, Orth-Gomer K (1999) Potential explanations for the educational gradient in coronary heart disease: a population-based case-control study of Swedish women. Am J Public Health 89(3):315–321
32. Jacoby A, Smith M, Eccles M (2003) A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs. Br J Gen Pract 53(487):120–125
33. Rogers E (1962) Diffusion of innovation. Free Press, New York
34. Brookhart MA, Solomon DH, Wang P, Glynn RJ, Avorn J, Schneeweiss S (2006) Explained variation in a model of therapeutic decision making is partitioned across patient, physician, and clinic factors. J Clin Epidemiol 59(1):18–25
35. Lopez-Valcarcel B, Ortun-Rubio V, Cabez-Mora A, Lopez-Cabañas A, Diaz-Berenger J, Alamo-Santana F (2002) Evaluation del uso apropiado de medicamentos en atencion primaria. Como se puede mejorar? (Evaluation of the appropriate use of medication in primary care. How do we improve it?) (in Spanish). Aten Primaria 30:467–471
36. Hjerpe P, Fornwall S, Merlo J (2004) Therapeutic traditions and compliance with local therapeutic guidelines on lipid lowering drugs – a multilevel analysis in the Skaraborg Primary Healthcare Database (SPHD). International Society for Pharmacoepidemiology, Bordeaux, France
37. Smits HL (1986) Medical practice variations revisited. Health Aff (Millwood) 5(3):91–96
38. Wennberg JE, Barnes BA, Zubkoff M (1982) Professional uncertainty and the problem of supplier-induced demand. Soc Sci Med 16(7):811–824

39. Bobashev GV, Anthony JC (1998) Clusters of marijuana use in the United States. Am J Epidemiol 148(12):1168–1174
40. Bobashev GV, Anthony JC (2000) Use of alternating logistic regression in studies of drug-use clustering. Subst Use Misuse 35 (6–8):1051–1073
41. Chauvin C, Bouvarel I, Beloeil PA, Orand JP, Guillemot D, Sanders P (2005) A pharmaco-epidemiological analysis of factors associated with antimicrobial consumption level in turkey broiler flocks. Vet Res 36(2):199–211
42. Delva J, Bobashev G, Gonzalez G, Cedeno M, Anthony JC (2000) Clusters of drug involvement in Panama: results from Panama's 1996 National Youth Survey. Drug Alcohol Depend 60(3):251–257
43. Katz J, Carey V, Zeger SL, Sommer A (1993) Estimation of design effects and diarrhea within households and villages. Am J Epidemiol 138:994–1006
44. Katz J, Zeger SL, West KJ, Tielsch J, Sommer A (1993) Clustering of xerophthalmia within households and villages. Int J Epidemiol 22:709–715
45. Petronis KR, Anthony JC (2003) A different kind of contextual effect: geographical clustering of cocaine incidence in the USA. J Epidemiol Community Health 57(11):893–900
46. Preisser JS, Arcury TA, Quandt SA (2003) Detecting patterns of occupational illness clustering with alternating logistic regressions applied to longitudinal data. Am J Epidemiol 158(5):495–501

IV

Is the physician's adherence to prescription guidelines associated with the patient's socioeconomic position? – An analysis of statin prescription in South Sweden.

(Provisionally accepted for publication in Journal of Epidemiology and Community Health)

Henrik Ohlsson[§1, 2], Kristian Lynch[1], Juan Merlo[1, 2]

[1] Social Epidemiology, Dept. Clin. Sci., Faculty of Medicine, Lund University, Sweden

[2] Division of Social Medicine, Skåne County, Sweden

[§] Corresponding author

Henrik Ohlsson

Social Epidemiology
CRC, Malmö University Hospital
205 02 Malmö
Sweden.
Tele: +46 0768871197
Fax: + 46 040491300
Henrik.Ohlsson@med.lu.se

Keywords: Guideline adherence, socio-economic position, decision making, equity, multilevel methods.

Word count: 2 973

Abstract

Background: Knowledge about the social and economical determinants of prescription is relevant in health care systems like the Swedish one, which is based on the principle of equity, and which aims to allocate resources on the basis of need and not on criteria that are based on social constructs. We therefore investigated the association between patient and health care practice (HCP) characteristics on the one hand, and adherence to guidelines for statin prescription on the other, with a focus on social and economic conditions.

Methods: The study included all patients in the Skåne region of Sweden who received a statin prescription between July 2005 and December 2005; 15 581 patients in 139 privately-administered HCPs and 24 593 patients in 142 publicly-administered HCPs. Socioeconomic status was established using data from LOMAS (Longitudinal Multilevel Analysis in Skåne), and stratified multilevel regression analysis was performed.

Results: The proportion of patients receiving recommended statins was lower among privately-administered HCPs than among publicly-administered HCPs (65% vs. 80%). Among men (but not women), low income ($PR_{privateHCP}$ = 1.04 (1.01–1.09) and $PR_{publicHCP}$ = 1.02 (0.99–1.07)) and cohabitation ($PR_{privateHCP}$ = 1.04 (1.04–1.08) and $PR_{publicHCP}$ = 1.03 (1.01–1.07)) were associated with higher adherence to guidelines.

Conclusion: The physician's decision to prescribe a recommended statin is conditioned by the socioeconomic and demographic characteristics of the patient. Beyond individual characteristics, the contextual circumstances of the HCP were also associated with adherence to guidelines. An increased understanding of the connection between the patient's socioeconomic status and the decisions made by the physician might be of relevance when planning interventions aimed at promoting efficient and evidence-based prescription.

Background

Adherence to prescription guidelines is of high relevance not only for ensuring evidence-based pharmacological treatment in routine practice, but also for promoting the efficient use of a limited health care budget in the community.

This subject has therefore attracted substantial attention in many previous studies. [1-5] It is also well documented that sociological factors play a role in clinical decision-making. [6-10] Knowledge about the social and economical determinants of prescription is relevant in health care systems like the Swedish one, which is based on the principle of equity, [11] and which aims to allocate resources on the basis of need and not on criteria that are based on social constructs rather than a medical rationale. Social roles and expectations related to the gender, age, or socioeconomic position (SEP) of the patient might condition the physician's behaviour independently of needs. On the one hand, the prescription of a more expensive brand may reveal a different approach to a specific therapeutic problem that could result from differences in information and knowledge. However, it could also express the belief that more expensive drugs are better than cheaper ones, or could be used for the purpose of displaying income or wealth where this display serves as an instrument of attaining or maintaining social status. [12] Studies have shown that insurance status affect physicians' inclination to prescribe recommended drugs.[13] However, in Sweden, the cost of medicines in outpatient care is shared by patients and county councils via a reimbursement system where the individual patient never pays more than 200 Euros per year.[14] The total cost for a year of statin treatment varies from approximately 30 Euros (the cheapest recommended statins) to 600 Euros.[15] Therefore, this investigation can provide additional information about the mechanisms underlying the drug choice and prescribing behaviour.

Analogously, contextual factors related to the health care practices (HCPs) where the patients are treated might condition prescription patterns that are not necessarily based on evidence. Such practice differences in adherence to prescription guidelines might also express inefficient therapeutic traditions, especially when the brands prescribed are more expensive than the recommended ones. [2, 3, 16]

As in previous studies, we have focused here on cholesterol-lowering drugs from the class of HMG-CoA reductase inhibitors (statins), since different brands have the same indication and

only marginal differences in efficacy, and there are therefore no solid reasons for justifying the prescription of more expensive non-recommended brands to patients of a certain age, gender, or SEP.[17, 18]

In the present study, we performed a multilevel analysis to investigate the association between patient and HCP characteristics on the one hand, and adherence to guidelines for statin prescription on the other, with a focus on social and economic conditions.

Material and Methods

The Skåne region is situated in the southern part of Sweden, and its population of about 1.2 million represents approximately 13% of Sweden's total population. At the time of our study, the health care system in Skåne was organized into 14 publicly administrative health care areas HCAs, which in turn managed 142 primary HCPs and hospital outpatient care clinics assisted respectively by general practitioners (GPs) or other specialists. In addition the health care system included 132 private primary HCPs assisted by GPs or other specialists. Both privately-administered and publicly-administered HCPs were funded through taxes.

We used the record linkage LOMAS (Longitudinal Multilevel Analysis in Skåne) database that among other information includes the socioeconomic characteristics of the patients as well as data from the Swedish Prescribed Drug Register. This last register records information on sales of prescribed pharmaceutical agents dispensed by the Swedish Corporation of Pharmacies, we selected all patients registered in Skåne who received a statin prescription issued by a physician from one of the region’s public or private HCPs between July 2005 and December 2005. The 142 public HCPs yielded 24 119 (13 376 men and 10 743 women) and the 132 private HCPs 15 330 (8 424 men and 6 906 women) patients. A small number of prescriptions (n=1 038) were excluded due to unidentified origin. Statins were defined according to the Anatomical Therapeutical Chemical (ATC) classification system code C10AA. [19]

The project was carried out with the approval of and assistance from Statistics Sweden and the Centre for Epidemiology, and was approved by the Regional Ethical Review Board in Lund. In order to protect the identity of the individuals, the research database used arbitrary identification numbers rather than actual personal identification numbers.

Individual-level variables

The outcome variable at the individual level was prescription of *simvastatin* (yes vs. no), regardless of brand, but excluding the original brand ZOCORD®. Simvastatin was the recommended statin in Skåne during the observation period. [20]

As explained above, the *socioeconomic position* of the patient may influence the decision of the prescriber. We expressed the SEP of the patients as disposable family income along with duration of use of social allowance (if any), both measured at the end of 2004. We divided income into quartiles and used the highest income quartile as reference in the comparisons. Social allowance use was divided into the three categories, (i) more than 9 months, (ii) 0 to 9 months, and (iii) no social allowance, with no social allowance as reference.

Adopting an explorative approach, we also included sex (men vs. women) and marital status in the analysis. Age was divided into five groups; (i) ≤49, (ii) 50-59, (iii) 60-69, (iv) 70-79, and (v) 80-89 years, with the ≤49 age group as reference. Marital status was dichotomized as married/cohabiting versus living alone (i.e., single, divorced, or widowed), with married/cohabiting as reference. We also considered the immigrant status of the patients, as we hypothesized that this characteristic might also influence physicians' prescription behaviour. We measured this by a combination of the number of years spent living in Sweden along with the World Bank classification of the individual's birth country, [21] in order to take into consideration the acculturation undergone during many years of living in Sweden as well as taking an economic rather than geographical perspective on country of birth. We categorized the first variable into (i) always lived in Sweden, (ii) more than 13 years in Sweden, (iii) 5-14 years in Sweden, and (iv) 0-4 years in Sweden. The first category was used as a reference in the analysis. We categorized country of birth into (i) low income, (ii) lower middle income, (iii) upper middle income, and (iv) high income countries. High income countries were used as reference in the analysis. While these variables should not directly affect adherence to prescription guidelines, they may reflect social roles and cultural expectations which in turn might determine prescription of recommended drugs. [6]

Area-level variables

In previous studies, we have shown that physicians working at private practices have a much lower adherence to prescription guidelines; [2, 3] this might stem from poorer receptivity to the county council policies, and these circumstances might modify the effect of the other included variables. It is also known that private care attracts more high-SEP patients than does public care. [22, 23] Hence, our analyses took the administrative status (private vs. public) of the HCPs into consideration.

HCPs with an elevated number of high income patients may develop therapeutic traditions conditioned by the high income of those patients, and once established these traditions could extend themselves to all patients. We operationalized this possibility by computing the percentage of high-income patients at the HCP. This variable was divided into three groups by tertiles, and the group with the highest percentage was used as reference.

Proximity to specialized care and the particular type of knowledge that it conveys might influence adherence to prescription guidelines. Hence, we also identified those HCPs that employed specialist physicians other than GPs. In the analyses, HCPs employing GPs alone were used as reference in the comparisons.

There are several potential influences on drug prescription, such as information diffusion and marketing forces, [24] which may be influenced by the population density of the area. We therefore considered whether the HCP was located in a rural or an urban area according to the definition provided by the Swedish Association of Local Authorities and Regions. [25] Of the 33 municipalities in Skåne, those municipalities that were classified as metropolitan areas (n=1), suburban municipalities (n=6), or large and medium sized towns (n=10) were categorized as urban areas (n=17). The other 16 municipalities were categorized as rural areas, and were used as reference in the analysis.

Statistical analysis

The analyses were stratified by sex and performed for private and public facilities separately. We used *multilevel logistic regression analysis* to estimate the probability of prescribing a recommended statin, while accounting for the hierarchical structure of the data (i.e., patients

nested within HCPs that in turn were nested within HCAs). HCPs and the publicly administrated HCAs were included in the analysis as random terms.

We developed three consecutive models. Model A included the random area parameters only, in order to partition the variance of prescription of recommended statins to different levels. Model B included the individual covariates age, income, social allowance, marital status, country of birth, and number of years in Sweden. Finally, model C added the area-level variables for percentage of prescriptions given to high-income patients, whether the HCP employed a specialist physician or GP, and whether the HCP was situated in a rural or urban area. This allowed us to investigate whether these contextual characteristics explained residual variation at the HCP levels.

For the fixed-effects parameters of the model, we calculated prevalence ratios (PR). We estimated the parameters in the WinBugs software, and stored the results from each step in the iteration procedure (5000 iterations). For each step, we calculated, for parameters of interest, the prevalence ratio. This gave us a distribution of prevalence ratios and from this distribution we calculated the median and corresponding 95 % credible interval (95 % CI). In the random-effects part of the multilevel analysis, we obtained the variance at the HCP and HCA levels. To quantify therapeutic traditions we calculated the intra-class correlation (ICC) using the simulation method. With the simulation method, the values estimated on the logistic scale are transformed to the binary scale. As the ICC depends on the predictors in the model, we calculated the ICC for every income group in model C. [26, 27]
To calculate the percentage of change in the magnitude of clustering that was explained by including individual or contextual characteristics in the model with more variables (Var_{more}), we used the variance obtained in the empty model as reference ($Var_{reference}$) :

$$\text{Percentage of change} = ((Var_{reference} - Var_{more})/(Var_{reference})) \times 100$$

We used this percentage to estimate the relevance of the individual and contextual characteristics for understanding a possible clustering of prescriptions of recommended statins. [2, 3]

Results

More patients visited publicly-administered HCPs (60%) than privately-administered ones (40%), and more men than women received a statin prescription (Table 1). The highest income quartile contained more men than women; and public HCPs catered for more low-income patients than high-income patients, while the situation was reversed for private HCPs (Figure 1). Adherence to guidelines was systematically lower among private HCPs. Women lived alone to a higher degree than men. In terms of immigrant status and SES, 90% of the patients were born in high-income countries and 2% received social allowance.

Table 1: Adherence to guidelines for statin prescription and characteristics of the 34 449 patients on statin prescription during the period July–Dec 2005 in the Skåne region of Sweden.

	WOMEN		**MEN**	
	Private Care	*Public Care*	*Private Care*	*Public Care*
Recommended statins (%)	65	79	65	79
Number of individuals	6 906	10 743	8 424	13 376
Mean age	68	69	66	66
	% recommended statins/ % of individuals		*% recommended statins/ % of individuals*	
Married/Cohabiting	65/55	79/52	67/73	81/69
Living alone	65/45	79/48	65/27	79/31
Disposable family income				
• Low income, Q1	66/26	80/30	67/20	80/25
• Middle low income, Q2	64/27	79/30	67/20	81/24
• Middle high income, Q3	64/25	79/23	65/27	79/26
• High income, Q4	64/22	77/17	64/34	77/25
Use of social allowance				
• None	98/52	98/52	66/99	80/98
• 0-9 months	70/0.8	80/0.8	62/0.5	71/0.9
• 10 –12 months	65/0.8	84/1	50/0.6	74/1
Country of birth				
• High income country	65/92	79/92	66/92	80/92
• High middle income country	62/4	76/3	60/3	70/3
• Low middle income country	59/4	81/5	61/4	78/5
• Low income country	62/0.3	80/0.4	72/0.2	75/0.5
Number of years living in Sweden				
• Always	65/85	79/84	66/86	80/85
• >14 years	61/12	77/12	63/11	77/11
• 5-14 years	66/3	79/4	59/3	78/4
• 1-4 years	81/0.4	87/0.7	69/0.8	72/0.9

Overall, men and women did not differ in terms of being prescribed a recommended statin ($PR_{publicHCP}$ = 1.00 [95% CI: 0.99 – 1.02] and $PR_{privateHCP}$ = 1.02 [95% CI: 0.99-1.04]). Among men, compared with the youngest age group, men over 70 had higher prevalence of recommended statin. However, among women, those aged 70-79 treated at private practices had lower probability of receiving a recommended statin.

Individual high income and cohabitation were both associated with a lower adherence to guidelines for men but not for women (Table 2).

There was no clear association between the percentage of high-income patients at the HCP and adherence to prescription guidelines, except for men treated at public HCPs where a lower percentage of such patients was associated with higher adherence to guidelines (Table 2). Moreover, men treated at private HCPs in urban areas received recommended statins more rarely than those treated at HCPs in rural areas.

In model A, the ICC_{HCP} value for men in the private sector was 10.4 %, which indicate that factors varying between HCPs to a high degree influence the prescription of recommended statins (Table 3). However, factors at the HCP/HCA level seemed to be less relevant in the public sector illustrated by a lower ICC. Even though the higher levels seemed to be less relevant the HCP level seemed to be more important than the HCA level. This pattern was similar for women. The ICC for different income groups in model C was approximately 1 % in the public sector and it varied between 7- 9 % in the private sector.

When individual and contextual variables were included, the higher level variance decreased for men by 2% within privately-administered HCPs and 8 % within publicly-administered. For women there seemed to be an increase in variance in model C compared to model A.

Table 2. Association (prevalence ratios) between patient and health care practice characteristics and adherence to statin prescription guidelines in the Skåne region of Sweden, July–Dec 2005. Values were obtained from the fixed effect part of the multilevel regression.

	Women		**Men**	
	Model C public care	**Model C private care**	**Model C public care**	**Model C private care**
Individual variables				
Age (years)				
• 20-49	REF	REF	REF	REF
• 50-59	0.97 (0.91–1.03)	1.01 (0.95–1.11)	1.02 (0.97–1.07)	1.03 (0.98–1.10)
• 60-69	0.97 (0.92–1.03)	0.96 (0.89–1.04)	1.04 (0.99–1.10)	1.03 (0.99–1.10)
• 70-79	0.96 (0.90–1.01)	0.90 (0.82–0.98)	1.06 (1.01–1.12)	1.06 (1.01–1.14)
• 80-89	0.99 (0.93–1.04)	0.95 (0.87–1.03)	1.07 (1.01–1.14)	1.04 (0.99–1.12)
Disposable family income				
• Low income, Q1	1.01 (0.99–1.04)	1.02 (0.98–1.08)	1.04 (1.01–1.09)	1.02 (0.99–1.07)
• Middle low income, Q2	1.01 (0.99–1.04)	1.03 (0.99–1.08)	1.05 (1.01–1.09)	1.03 (1.00–1.08)
• Middle high income, Q3	1.02 (0.99–1.05)	1.02 (0.98–1.07)	1.02 (0.99–1.05)	1.01 (0.98–1.05)
• High income, Q4	REF	REF	REF	REF
Use of social allowance				
• None	REF	REF	REF	REF
• 0-9 months	1.02 (0.93–1.10)	1.03 (0.81–1.20)	0.91 (0.77–1.03)	0.93 (0.70–1.10)
• 10-12 months	1.05 (0.96–1.12)	0.93 (0.71–1.11)	0.99 (0.79–1.04)	0.95 (0.74–1.09)
Country of birth				
• High income	REF	REF	REF	REF
• High middle income	1.01 (0.96–1.06)	1.00 (0.90–1.09)	0.88 (0.77–0.96)	0.98 (0.89–1.06)
• Low middle income	1.04 (0.99–1.09)	0.99 (0.87–1.08)	1.00 (0.91–1.07)	1.05 (0.98–1.13)
• Low income	1.05 (0.90–1.15)	0.99 (0.68–1.21)	0.97 (0.79–1.12)	1.12 (0.90–1.06)
Number of years living in Sweden				
• Always	REF	REF	REF	REF
• 14 years	0.99 (0.95–1.02)	0.99 (0.92–1.04)	1.00 (0.95–1.05)	0.99 (0.94–1.04)
• 5-14 years	0.97 (0.90–1.03)	1.06 (0.96–1.19)	1.03 (0.95–1.12)	0.95 (0.84–1.03)
• 1-4 years	1.07 (0.97–1.17)	1.15 (0.95–1.36)	0.96 (0.82–1.09)	1.04 (0.90–1.17)
Marital status				
• Married/Cohabiting	REF	REF	REF	REF
• Living alone	1.01 (0.99–1.03)	1.02 (0.99–1.05)	1.04 (1.04–1.08)	1.03 (1.01–1.07)
Contextual variables				
% of high-income patients				
• T1	1.02 (0.97–1.09)	1.00 (0.89–1.16)	1.06 (0.99–1.17)	0.92 (0.81–1.05)
• T2	1.03 (0.99–1.13)	0.97 (0.86–1.07)	1.10 (1.02–1.22)	0.96 (0.85–1.06)
• T3	REF	REF	REF	REF
Specialist physician (yes vs. no)	1.01 (0.92–1.06)	0.91 (0.79–1.02)	1.02 (0.91–1.14)	0.96 (0.85–1.06)
Urban versus rural area	0.95 (0.89–1.00)	0.95 (0.85–1.11)	0.97 (0.89–1.04)	0.84 (0.74–0.95)

Table 3. Random effects part of the multilevel regression analysis of adherence to statin prescription guidelines in Skåne region, Sweden
(numbers within parenthesis are 95 % credible intervals)

	Women		**Men**	
	Public HCPs	**Private HCPs**	**Public HCPs**	**Private HCPs**
Variance				
$HCP_{Model\ A}$	0.27 (0.18-0.41)	0.70 (0.52-0.97)	0.24 (0.16-0.35)	0.75 (0.56-1.04)
$HCA_{Model\ A}$	0.08 (0.00-0.36)	-	0.06 (0.00-0.24)	-
$HCA+HCP_{Model\ A}$	0.36 (0.24-0.64)	-	0.31 (0.20-0.49)	-
$HCP_{Model\ B}$	0.28 (0.19-0.42)	0.72 (0.52-1.00)	0.23 (0.16-0.35)	0.75 (0.55-1.04)
$HCA_{Model\ B}$	0.07 (0.01-0.32)	-	0.05 (0.01-0.22)	-
$HCA+HCP_{Model\ B}$	0.37 (0.24-0.62)	-	0.30 (0.20-0.49)	-
$HCP_{Model\ C}$	0.29 (0.19-0.43)	0.72 (0.52–1.01)	0.22 (0.14-0.35)	0.73 (0.53–1.02)
$HCA_{Model\ C}$	0.06 (0.00-0.37)	-	0.05 (0.00-0.24)	-
$HCA+HCP_{Model\ C}$	0.36 (0.23-0.70)	-	0.28 (0.18-0.49)	-
ICC				
HCP_{ModelA}	1.2 %	9.3 %	0.9 %	10.4 %
$HCA+HCP_{ModelA}$	1.9 %	-	1.5 %	-
$HCP_{Model\ C\ Low\ Income}$	1.1 %	8.6 %	0.9 %	8.5 %
$HCP_{Model\ C\ Middle\ low\ Income}$	1.1 %	8.5 %	0.9 %	8.4 %
$HCP_{Model\ C\ \ Middle\ high\ Income}$	1.1 %	8.7 %	0.9 %	7.3 %
$HCP_{Model\ C\ High\ income}$	1.2 %	8.9 %	1.0 %	8.8 %
HCA= Health care area HCP=Health care practice ICC=Intra class correlation				

Discussion

This study illustrates that the physician's decision to prescribe a recommended statin is conditioned by the socioeconomic (e.g. income, marital status) and demographic (e.g. age) characteristics of the patient. This situation cannot be justified by any medical argument, but may rather reflect the influence of constructed social roles and cultural expectations.[6] For example, men with a lower income were prescribed the cheaper recommended statins to a higher degree than men with a high income. Similarly, older men were prescribed the recommended statins less frequently than younger patients with the same need. This socioeconomic and demographic inequity was similar among private and public HCPs, even though private HCPs generally had a lower adherence to guidelines. From the perspective of equity in health care, our study brings into question physicians´ choice of more expensive, but not more efficient, brands for some groups of patients, given that a large part of this medication expenditure is funded by the public reimbursement system.

Interestingly, in this stratified analysis, we found that among men but not among women, low income and living alone were associated with a higher prescription of recommended statins. Moreover, older women had a lower adherence than younger women, while the situation was the reverse among men, though these results were not conclusive. In general, our results have implications for the achievement of equity of health service policy, since there is no medical or therapeutic reason that could justify the selective prescription of expensive statins to younger men or to patients of high SEP. One rationale for this behaviour might be that sociological forces influence physicians' prescription decisions over and above evidence-based knowledge. [8, 9, 28, 29] Patients of higher SEP may be more aware and have better communication skills, making it easier to express their demands and expectations and to be more involved in the treatment decision. [30]

This discriminatory prescription pattern cannot lead to any harm for the patient, since all statins have a similar efficacy. However, although the current study focuses on statin prescription, we believe that our results are generalizable to other medical treatments in primary health care. In some contexts, lack of access to recommended treatments could have more severe consequences for the individual. Prescription of non-recommended drugs is also an inappropriate behaviour from a cost-effectiveness perspective. Our study points out that these sociological forces should be considered from a perspective of equity in access to health

care in general and when trying to implement prescription guidelines in routine care in particular.

Beyond individual characteristics, the contextual circumstances of the HCPs evidenced an independent association with adherence to prescription guidelines. For example, over and above the characteristics of the patient, HCPs with a low percentage of high-income patients tended to prescribe the recommended statins more often than HCPs with an overall higher level of patient income. However, the inclusion of contextual characteristics did not explain a major part of the variance at the higher level.

Our results also suggest the existence of therapeutic traditions, acting at the HCP level, which influence the prescription behaviour of individual physicians. Based on the ICC measure, we observed that physicians from the same HCP, especially in the private sector, exhibited a similar propensity to prescribe recommended statins. Moreover, private HCPs had both higher clustering of similar behaviour and systematically lower adherence to guidelines, and this pattern remained after the inclusion of individual and contextual characteristics.

Observational studies are often the only option for investigating questions that for reasons of feasibility, costs, or ethics cannot be analyzed by randomized trials. [31, 32] In our study, we used multilevel regression analysis, which not only produces more correct statistical analysis but also provides information about the role that different health care levels play in understanding drug prescription and utilization. Moreover, since the prevalence was rather high in this study we calculated PRs instead of the usual odds ratios. [33] In addition, Sweden has a long tradition of register-based epidemiology, and the registers we used in this study seem to have an acceptable validity as evaluated in previous studies. [34]

Our results suggest that the physician's decision to prescribe a recommended statin is conditioned by the socioeconomic (e.g. income, living alone) and demographic (e.g. age) characteristics of the patient. Beyond individual characteristics, the contextual circumstances of the HCPs, especially in the private sector, also showed an independent association with adherence to prescription guidelines. An increased understanding of the connection between the SES of the patient and the decisions made by physicians might be of relevance when planning interventions aimed at promoting efficient and evidence-based prescription.

Funding

This study was supported by grants from the Scania Region's Health Care Research Funds and the Swedish Research Council (VR) (Juan Merlo; # 2004-6155). The Centre for Economical Demography at the Lund University (Dec 2008), and the Swedish Scientific Council (# 2004-6155)

Competing interests

None

Figure legends

Figure 1: Percentage of patients in different income groups (women to the left and men to the right). The Y-axis shows the percentage of patient and the X-axis the different income groups.

What is already known on this subject?

- Studies have shown that sociological factors influence clinical decision-making; and so the physician's behaviour might be affected by social roles and expectations related to the gender, age, or socioeconomic position of the patient.

What this study adds

- Independently of the patient's needs, the physician's adherence to guidelines for statin prescription is conditioned by the socioeconomic (e.g. income) and demographic (e.g. age) characteristics of the patient; this leads to inequity in the distribution of health care resources.
- Beyond individual characteristics, there is an independent association between the contextual circumstances of the health care practice and its adherence to prescription guidelines.

References

1. Kamps G, Stewart R, van Der Werf G, Schuling J, Jong BM. Adherence to the guidelines of a regional formulary. Fam Pract 2000;17(3):254-60.
2. Ohlsson H, Lindblad U, Lithman T, et al. Understanding adherence to official guidelines on statin prescribing in primary health care-a multi-level methodological approach. Europ J Clin Pharmacol 2005;61(9):657-65.
3. Ohlsson H, Merlo J. Understanding the effects of a decentralized budget on physicians compliance with guidelines for statin prescription; a multilevel methodological approach. BMC Health Serv Res 2007;7:68 (8 May 2007).
4. Koutsavlis AT. Disseminating practice guidelines to physicians: Institut national de santé publique du Québec; 2001.
5. Stewart RE, Vroegop S, Kamps GB, van der Werf GT, Meyboom-de Jong B. Factors influencing adherence to guidelines in general practice. Int J Technol Assess Health Care 2003;19(3):546-54.
6. Clark JA, Potter DA, McKinlay JB. Bringing social structure back into clinical decision making. Soc Sci Med 1991;32(8):853-66.
7. Sleath B, Shih YC. Sociological influences on antidepressant prescribing. Soc Sci Med 2003;56(6):1335-44.
8. Eisenberg JM. Sociologic influences on decision-making by clinicians. Ann Intern Med 1979;90(6):957-64.
9. Eisenberg JM. Physician utilization: the state of research about physicians' practice patterns. Med Care 2002;40(11):1016-35.
10. Scott A, Shiell A, King M. Is general practitioner decision making associated with patient socio-economic status? Soc Sci Med 1996;42(1):35-46.
11. SFS 1982:763.
12. Veblen T. The Theory of the Leisure Class; 1899.
13. Wallack SS, Thomas CP, Martin TC, Ryan A. Differences in prescription drug use in HMO and self-insured health plans. Med Care Res Rev 2007;64(1):98-116.
14. Pharmaceuticals benefits board. The Swedish Pharmaceutical Reimbursement System 2007.
15. Martinsson A. IDEAL-studien. http://www.janusinfo.se/imcms/8044; 2005.
16. Ohlsson H, Chaix B, Merlo J. Therapeutic traditions, patient socio-economic characteristics and physicians' early new drug prescribing – a multilevel analysis of rosuvastatin prescription in South Sweden. Eur J Clin Pharmacol 2009; 65 (2) 141-150
17. Evaluation of the effects of statins (with particular consideration of atorvastatin). Cologne: Institut fur Qualität und Wirtschaftlichkeit im Gesundheitswesen; 2006.
18. Läkemedelsrådet, ed. Bakgrundsmaterial (Backgroundmaterial) [in Swedish]. Lund; 2006.
19. About the ATC/DDD system (http://www.whocc.no/atcddd/). (Accessed at 2008-09-01)
20. Läkemedelsrådet, ed. Skånelistan 2006 [in Swedish]. Lund; 2006.
21. WorldBank. Country Classification [http://www.worldbank.org/data/countryclass/countryclass.html], 2005.
22. Bongers IM, van der Meer JB, van den Bos J, Mackenbach JP. Socio-economic differences in general practitioner and outpatient specialist care in The Netherlands: a matter of health insurance? Soc Sci Med 1997;44(8):1161-8.
23. Dunlop S, Coyte PC, McIsaac W. Socio-economic status and the utilisation of physicians' services: results from the Canadian National Population Health Survey. Soc Sci Med 2000;51(1):123-33.

24. de Laat E, Windmeijer F, Douven R. How does pharmaceutical marketing influence doctors prescribing behaviour? The Hague, the Netherlands; 2002.
25. Bengtsson H. Nuvarnade kommunuppdelning [in Swedish] (Classification of municipalities). Svenska Kommunförbundet; 2003.
26. Goldstein H, Browne W, Rasbash J. Partitioning variation in generalised linear multilevel models. Understanding Statistics 2002;1:223-32.
27. Vigre H, Dohoo IR, Stryhn H, Busch ME. Intra-unit correlations in seroconversion to Actinobacillus pleuropneumoniae and Mycoplasma hyopneumoniae at different levels in Danish multi-site pig production facilities. Preventive veterinary medicine 2004;63(1-2):9-28.
28. Denig P, Haaijer-Ruskamp FM. Therapeutic decision making of physicians. Pharm Weekbl Sci 1992;14(1):9-15.
29. Denig P, Haaijer-Ruskamp FM, Zijsling DH. How physicians choose drugs. Soc Sci Med 1988;27(12):1381-6.
30. Willems S, De Maesschalck S, Deveugele M, Derese A, De Maeseneer J. Socio-economic status of the patient and doctor-patient communication: does it make a difference? Patient Educ Couns 2005;56(2):139-46.
31. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ1996;312(7040):1215-8.
32. Sorensen G, Emmons K, Hunt MK, Johnston D. Implications of the results of community intervention trials. Annu Rev Public Health 1998;19:379-416.
33. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC medical research methodology 2003;3:21.
34. Socialstyrelsen. http://www.socialstyrelsen.se/en/about/epc/.

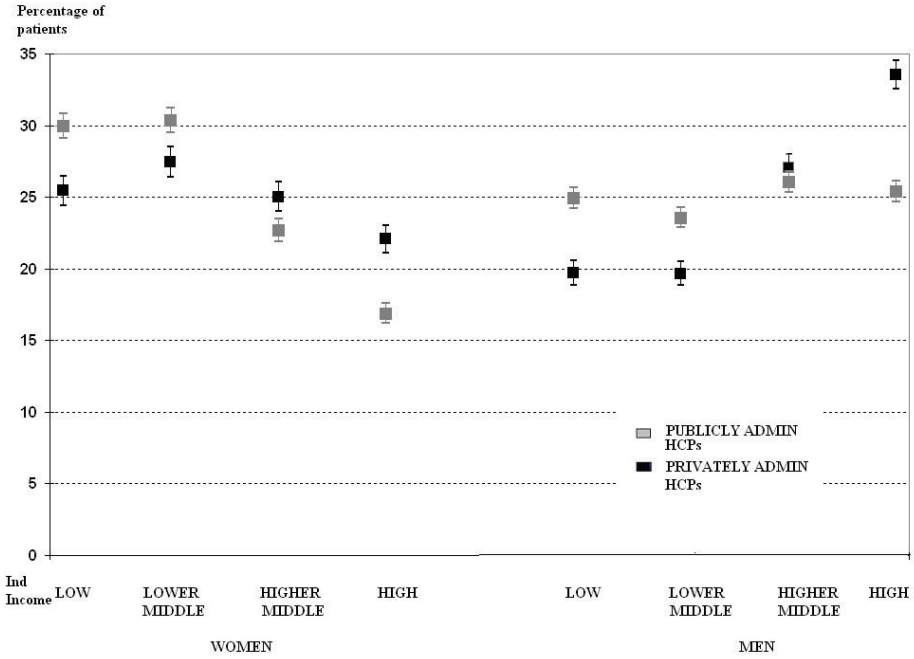


Figure 1: Percentage of patients in different income groups (women to the left and men to the right). The Y-axis shows the percentage of patient and the X-axis the different income groups.

V

Is physician adherence to prescription guidelines a general trait of health care practices or dependent on drug type? – A multilevel logistic regression analysis in South Sweden

(Accepted for publication in Pharmacoepidemiology and Drug Safety)

Henrik Ohlsson,[1,2*] Juan Merlo[1,2]
[1] Social Epidemiology, Department of Clinical Science, Faculty of Medicine, Lund University, Sweden
[2] Division of Social Medicine, Region Skåne, Sweden

[*] Corresponding author:
Henrik Ohlsson
Social Epidemiology
CRC, Malmö University Hospital
205 02 Malmö
Sweden.
Henrik.Ohlsson@med.lu.se
Fax: +46 (0)40 491300
Tel: +46 0768 871197

Running title: Is physician adherence a general trait?

Keywords: Guideline adherence, inequality, decision making, therapeutic traditions, multilevel models.

Take-home messages:
Physicians' decisions to follow prescription guidelines seem to be influenced by therapeutic traditions at specific health care practices, especially in the private sector.

Therapeutic tradition seems to be a general trait of health care practices that affects all kinds of prescriptions.

Prescribing behaviour is also influenced by socioeconomic and demographic characteristics of the patient.

Expensive, non-recommended drugs are more likely to be prescribed to patients from higher income groups. This behaviour can not be justified by any medical argument; however, it may reflect the influence of constructed social roles and cultural expectations.

Inefficient therapeutic traditions reduce available economic resources that could be used in other areas of the health care sector.

Word Count: 2900

Is physician adherence to prescription guidelines a general trait of health care practices or dependent on drug type? – A multilevel logistic regression analysis in South Sweden

Abstract (237 words)

Purpose: Therapeutic traditions at health care practices (HCPs) influence physicians' adherence to prescription guidelines for specific drugs, however, it is not known if such traditions affect all kinds of prescriptions or only specific types of drug. Our goal was to determine whether adherence to prescription guidelines is a common trait of HCPs or dependent on drug type.

Methods: We fitted separate multi-level logistic regression models to all patients in the Skåne region who received a prescription for a statin drug (ATC: C10AA, n = 6232), an agent acting on the renin-angiotensin system (ATC: C09, n = 7222), or a proton pump inhibitor (ATC: A02BC, n = 11 563) at 198 HCPs from July 2006 to December 2006.

Results: There was high clustering of adherence to prescription guidelines at HCPs for the different drug types ($MOR_{\text{agents acting on the renin-angiotensin system}}$ = 4.72 [95 % CI: 3.90-5.92], MOR_{Statins} = 2.71 [95 % CI: 2.23-3.39] and $MOR_{\text{Proton pump inhibitors}}$ = 2.16 [95 % CI: 1.95-2.45]). Compared with HCPs with low adherence to guidelines in two drug types, those HCPs with the highest level of adherence for these two drug types also showed a higher probability of adherence for the third drug type.

Conclusion: Physicians' decisions to follow prescription guidelines seem to be influenced by therapeutic traditions at the HCP. Moreover, these therapeutic traditions seem to affect all kinds of prescriptions. This information can be used as basis for interventions to support rational and cost-effective medication use.

INTRODUCTION

Previous studies have shown that the prescription behaviour among physicians within the same health care practice (HCP) seems to be more similar than among physicians from different HCPs. This phenomenon has been suggested to be an expression of different therapeutic traditions. [1-4] While, this contextual phenomenon has been shown for different isolated outcomes, such as the ordering of specific tests,[5] prescribing rates,[1, 2] early adoption of newly marketed drugs,[6] or adherence to prescription guidelines for specific drugs like statins, [3, 4, 7] it is still not known if this phenomenon is a general HCP trait that affects all kinds of prescription behaviour or if it is dependent on specific outcomes. In the present study we investigate this question by focusing on adherence to prescription guidelines for different types of drugs. Understanding the mechanism behind patterns of adherence to prescription guidelines is important to the promotion of effective and evidenced-based pharmacologic treatment in a health care system based on the principle of equity, such as Sweden's, and to the efficient use of a limited health care budget.

We use multilevel logistic regression analysis (MLRA)[8] within a previously developed framework[1-4, 6, 7] that quantifies therapeutic traditions by means of clustering of similar prescription behaviour within the same HCP. We first investigate the clustering of adherence to prescription guidelines regarding three separate drug types: statins, agents acting on the renin-angiotensin system, and proton pump inhibitors. Then we analyse whether the clustering of similar behaviour within HCPs is independent of drug types, i.e. if adherence to prescription guidelines is a common trait within HCP or dependent of drug type. Our hypothesis was that therapeutic traditions would be shown to have a general influence on prescription behaviour and that adherence to guidelines regardless of drug type would be positively correlated within the HCP.

MATERIAL AND METHODS

Using the Swedish Prescribed Drug Register, which records information on sales of prescribed pharmaceutical agents dispensed by the Swedish Corporation of Pharmacies, we selected all patients in the Skåne region, Sweden who between July 2006 to December 2006 received a drug from the ATC-categories[9] (i) statins (ATC-code: C10AA), (ii) agents acting on the renin-angiotensin system (ATC-code: C09), or (iii) proton pump inhibitors (ATC-code: A02BC). Since there are some occasions where the patient should be prescribed non-recommended drugs,[10] in order to diminish the risk of confounding, we excluded patients who received a drug from the same ATC-group during the 12 months preceding our study period. Moreover we excluded HCPs ($N_{HCP} = 98$) without prescriptions from all three ATC-groups. In total we analysed 198 HCPs that yielded 6232 patients with statin prescriptions, 7222 patients with agents acting on the renin-angiotensin system, and 11 563 patients with proton pump inhibitors.

Individual-level variables

The outcome variable at the individual level was recommended drug according the official guidelines from the Skåne region[11] for any one of the three included drug types. For statins, the recommended drug was Simvastatin (regardless of brand, but excluding the original brand Zocord), for agents acting on the renin-angiotensin system, the recommended drugs were any ACE inhibitor alone (ATC: C09A) or in combination (ATC: C09B); and for proton pump inhibitors, the recommended drug was Omeprazol (regardless of brand, but excluding the original brand Losec).

In the analyses we included the sex, age (mean 65 years), and marital status of the patients. Marital status was dichotomized as married/cohabiting versus living alone (i.e., single, divorced, or widowed), with married/cohabiting as reference.

In previous studies we have shown that the socioeconomic position (SEP) of a patient influences the decision made by the prescriber.[7] To establish the SEP of the patients, expressed as patient's disposable family income, education, and duration of social allowance (if any), we used data from the LOMAS (Longitudinal Multilevel Analysis in Skane) database (see[12] for more information) measured at the end of 2004. We divided income into quartiles and used the highest income quartile as the reference in the comparisons. Education was defined as highest education within the family and was divided into three categories: (i) 0–9 years = low education, (ii) 10–11 years = middle education, and (iii) ≥ 12 years = high education; the highest category was used as reference. Social allowance was divided into three categories: (i) ≥10 months, (ii) 0–9 months, and (iii) no social allowance; no social allowance was used as reference.

We also considered patients' immigration status, as we hypothesized that this characteristic also could influence physicians' prescription behaviour. Looking at both the number of years spent living in Sweden and the World Bank classification[13] of the individual's birth country allowed us to take into consideration the patient's degree of acculturation to Swedish society and to take an economic, rather than geographic, perspective on their country of birth.

We categorized the first variable into (i) always lived in Sweden, (ii) >14 years in Sweden, (iii) 5–14 years in Sweden, and (iv) 0–4 years in Sweden. The first category was used as the reference in the analysis. We categorized country of birth into (i) low income, (ii) lower middle income, (iii) upper middle income, and (iv) high income countries. High income countries were used as reference in the analysis. While these variables should not directly

affect adherence to prescription guidelines, they may reflect social roles and cultural expectations which in turn might determine prescription of recommended drugs.

Area-level variables

Of the 198 HCPs included in the analysis, 114 were public primary health care practices and hospital outpatient care clinics and 84 were private primary health care practices assisted by general practitioners (GPs) and other specialists. The health services in Sweden are largely tax-financed, and even privately managed HCPs are primarily funded by contract between the public health care authorities and private companies.[14] Because private HCPs have shown in previous studies a lower adherence to official guidelines for statin prescription than public HCPs, [3, 4, 7] we also included the variable private versus public in this study.

Proximity to specialized care and the particular type of knowledge that it conveys might influence adherence to prescription guidelines. Hence, we also identified those HCPs that employed specialist physicians other than GPs. In the analyses, HCPs employing GPs alone were used as reference in the comparisons.

Statistical and epidemiological analysis

We performed multilevel logistic regression analysis with patients nested within HCPs, separately for each drug type, and thereby accounted for the hierarchical structure of the data.[8] [15] HCPs were included in the analysis as random terms which allowed us to estimate the variance at the HCP level for each drug type.

We developed four consecutive models for each drug type. Model A included the random area parameters only in order to partition the variance of adherence to guidelines for each drug type.[16] Model B included the individual covariates age, gender, education, income, social allowance, marital status, country of birth, and number of years in Sweden. Model C added the area-level variable, if the HCP employed specialist physicians or GPs only, and if the HCP

was under public or private administration. This allowed us to investigate whether these individual and contextual characteristics explained residual variation at the HCP levels. In order to investigate if the random effects were correlated across drug types, we used the HCP residuals from model A and classified them into three categories of "residualgroup". Thereafter, on each separate drug type we used an interaction of the variable "residualgroup" between the two other drug types in order to investigate if the adherence to guidelines was dependent on adherence with the other drug types. The interaction provided us with 6 different groups (lowest tertile in both groups [1], [reference group], lowest tertile in one group and middle tertile in the other [2], lowest tertile in one group and highest tertile in the other [3], middle tertile in both groups [4], middle tertile in one group and highest tertile in the other [5], and highest tertile in both groups [6]). Finally, in Model D, we added the variable "residualgroup" as a contextual variable. In the fixed-effects part of the multilevel analysis, we calculated odds ratios (OR) and their 95% confidence intervals (95% CI). In the random-effects part of the multilevel analysis, we obtained the variance at the HCP level.

Applying an established procedure,[17] we used the variance obtained in the empty model as reference ($Var_{reference}$), to calculate the percentage of change in the variance that was explained by including individual or contextual characteristics in the model with more variables (Var_{more}). Percentage of change = $([Var_{reference}–Var_{more}]/[Var_{reference}–1])\times 100$. We used this percentage to estimating the relevance of both patient and contextual characteristics for understanding HCP differences in prescribing recommended drugs.

As explained elsewhere,[3 4] in order to quantify therapeutic traditions we calculate the Median Odds Ratio (MOR)[18, 19] based on the second level variance for each drug type. The MOR could be interpreted as how much a physician's odds of prescribing a recommended drug

would (in median) increase if this physician moved to a HCP with higher adherence to guidelines. The larger are the differences between HCPs, the larger is the MOR. Moreover, since the MOR is an odds ratio it can be compared with odds ratios for fixed effect.[19] Parameters were estimated by MCMC methods[20] with MLwiN 2.02[21] and goodness of fit was evaluated using the deviance information criteria (DIC).[22]

This project was carried out with the approval of and assistance from Statistics Sweden and the Centre for Epidemiology, and was approved by the Regional Ethical Review Board in Lund.

RESULTS

Table 1 shows that adherence to guidelines was 94% for statins, 72% for agents acting on the renin-angiotensin system, and 88% for proton pump inhibitors. The adherence at the HCPs ranged for statins from 0% to 100% (25^{th}%: 90%; 75^{th}%: 100%), for agents acting on the renin-angiotensin system from 0% to 100% (25^{th}%: 46%; 75^{th}%: 88%), and for proton pump inhibitors from 10% to 100% (25^{th}%: 82%; 75^{th}%: 94%).

Those who were prescribed proton pump inhibitors were younger than those prescribed agents acting on the renin-angiotensin system or statins. For all drug types the share of low-income patients, patients with low education, patients from high-income countries, and patients who had always lived in Sweden were higher among cheaper but recommended drugs than among more expensive but non-recommended drugs.

Compared with HCPs employing specialist physicians, adherence to guidelines was higher for proton pump inhibitors but lower for agents acting on the renin-angiotensin system at HCPs with only GPs. For all drug types, HCP adherence to guidelines was lower at HCPs under

private administration than at those under public administration, especially for agents acting on the renin-angiotensin system.

Table 2 shows that for agents acting on the renin-angiotensin system men hade a higher probability (odds) of receiving a recommended drug, but for statins this probability was higher for women. For agents acting on the renin-angiotensin system older patients had a higher probability than younger of receiving recommended drugs, but for proton pump inhibitors it was the opposite. Compared with low-income patients, those with high income presented a lower probability of being prescribed a recommended drug, except for statins where we found no conclusive differences. Patients who had lived fewer years in Sweden were less likely to have physicians adhering to guidelines for proton pump inhibitors. Concerning contextual associations, we observed that publicly administrated HCPs had a higher adherence for all drug types. HCPs with only general practitioners had a higher probability of prescribing a recommended agent acting on the renin-angiotensin system. Table 2, model D, shows that for all individual drug types, higher adherence to guidelines is associated with higher adherence to guidelines for the other drug types. This effect was strongest for agents acting on the renin-angiotensin system and weakest for statins.

Table 3 shows that for model A there was high clustering of similar behaviour at HCPs for the different drug types ($MOR_{statins}$ = 2.71 [95 % CI: 2.23-3.39], $MOR_{agents\ acting\ on\ the\ renin\text{-}angiotensin\ system}$ = 4.72 [95 % CI: 3.90-5.92], and $MOR_{proton\ pump\ inhibitors}$ = 2.16 [95 % CI: 1.95-2.45]). These results were attenuated only to a small degree when individual characteristics were included in model B. However, when contextual factors were included in model C the clustering was considerably reduced; approximately 30% for statins and agents acting on the renin-angiotensin system and 11% for proton pump inhibitors. In model D the variance decreased, compared to model A, by approximately 40% for statins and agents acting on the renin-angiotensin system and 29% for proton pump inhibitors.

Figure 1 illustrates that the residuals (standardized) from model A, between the different drug types, are correlated, indicating that HCPs with low adherence to guidelines for, for example, agents acting on the renin-angiotensin system had low adherence for proton pump inhibitors and statins as well. The correlation seemed to be strongest between agents acting on the renin-angiotensin system and proton pump inhibitors.

Table 4 indicates that 11% of the HCPs belonged to the group with lowest adherence for all three drug types; however the proportion of publicly administrated HCP in this group was only 14%. Moreover, 28% of the HCPs belonged to the group with the highest adherence for one drug type and the lowest for another drug type.

For all drug types, Model D was a better model fit than Model A.

DISCUSSION

Our study show that therapeutic traditions, acting at the HCP level, seems to influence the prescribing behaviour of individual physicians for all three studied drug types: statins (ATC: C10AA), agents acting on the renin-angiotensin system (ATC: C09), and proton pump inhibitors (ATC: A02BC). Moreover, the therapeutic traditions seemed to be a general trait of HCPs that affects all kinds of prescriptions independent of drug type. HCPs that follow guidelines for one drug type appear also to follow guidelines for other drug types.

Furthermore, our study demonstrates the existence of inequity in health care as socioeconomic and demographic factors influenced the prescription of recommended drugs for the included drug types. For example, it was more common to prescribe more expensive, non-recommended drugs to patients from higher income groups. While this behaviour can not be justified by any medical argument, it may reflect the influence of constructed social roles and cultural expectations.

Because the Swedish reimbursement system funds a large part of the cost of medications[14] and there are rather large differences in price between recommended and non recommended drugs, adherence to guidelines is an essential issue in a system with a limited healthcare budget.

In this study we confirm previous results indicating that both contextual and patient characteristics, independent of medical reasons, influence physicians' decision making. However, regarding therapeutic traditions or practice styles, previous studies have shown contradictory results. While Landon et al[23] found no evidence of a consistent practice style (eg, "aggressive" or "conservative") for 5 different clinical scenarios, O'Neill et al[24] found evidence of physician practice patterns that persist across multiple clinical scenarios.

Even though our study is focused on adherence to prescription guidelines in only three drug types, we believe our results could be generalised to other drug types as well. Prescription of non-recommended drugs is inappropriate behaviour from a cost-effectiveness point of view. The fact that this behaviour seems to be influenced by the patient's sociodemographic background is also very relevant from the perspective of equity in health care. It is inappropriate that high-income patients are prescribed more expensive brands that are no more effective than the cheaper recommended ones. This behaviour, perhaps occurring in other primary health medical treatments as well, reduces overall available economic resources that could be used in other areas of the health care sector. Our study reveals that both inefficient therapeutic traditions and sociological forces should be considered when trying to implement prescription guidelines in routine care.

Combining information from the magnitude of adherence rate to prescription guidelines and the degree of clustering as expressed by the MOR-value provides novel and useful information that could be used to quantify physicians' acceptance rate of the prescription

guidelines. For example, a low MOR-value (small differences in adherence between HCPs) and a low overall adherence rate reflect a widespread resistance to following the guidelines. A high MOR-value and a rather low overall adherence rate, exemplified by agents acting on the renin-angiotensin system, reflect that there are specific HCPs with high adherence, while a large majority shows a low adherence rate. Interestingly, both the overall adherence and the MOR-value for statins was higher than for proton pump inhibitors, indicating that there are more HCPs with relatively low adherence for statins than for proton pump inhibitors.

The prescription behaviour for the other drug types had the strongest influence on the drug type with the lowest mean adherence and highest MOR (agents acting on the renin-angiotensin system). This could indicate that it is more likely that a low adherence rate at an HCP for therapeutic decisions, where there are rather small overall differences (small MOR-value), leads to low adherence for therapeutic decisions where there are larger differences between HCPs, rather than the opposite. The descriptive analysis of the adherence rate among the HCPs showed that the HCPs with the lowest adherence for all drug types were to a high degree privately administrated. This information is in line with previous findings, [3, 4, 6, 7] where we have seen that prescriptions from private HCPs seem to be influenced by inefficient therapeutic traditions to a greater extent than in the public sector. However, not all practice variation is necessarily inappropriate. Such variation may, in fact, reflect equivalent therapeutic traditions confronting a similar health problem.[25, 26] But when the same pharmacological agents are available in different brands at very different prices and the prescriber chooses the expensive brand, for several different drug groups, it is hard to find a reasonable justification for this behaviour. .

In this observational study the risk for confounding by indication is low, since only new users are included. Prescription of recommended drugs is therefore not specifically indicated for certain patients to the exclusion of others. Consequently, the inclusion of patient

characteristics resides only in understanding reasons for low adherence to prescribing guidelines.

Even after the inclusion of contextual covariates (model D) the clustering, for all three drug types, is still high, indicating that there might be unmeasured factors like for example attitudes and contact with the pharmaceutical industry that affects the clustering of similar prescription behaviour. However, in conclusion our study suggests that a physician's decision to follow prescription guidelines is associated with contextual circumstances, including therapeutic traditions at the HCP. Moreover, therapeutic traditions seem to be a general trait of HCPs that affects all kinds of prescriptions and is independent of drug type. Prescribing behaviour is also influenced by socioeconomic (e.g., income) and demographic (i.e., age, gender) characteristics of the patient. This information can be used as basis for interventions to support rational and cost-effective medication use.

ACKNOWLEDGEMENTS

This study was supported by grants from the Scania Region's Health Care Research Funds, the Swedish Council for Working Life and Social Research (FAS) (Juan Merlo; Dnr 2003-0580), and the Swedish Research Council (VR) (Juan Merlo; Dnr 2004-6155). The funding source has no involvement. There are no conflicts of interest

REFERENCES

1. Davis P, Gribben B. Rational prescribing and interparctitioner variation. A multilevel approach. *Int J Technol Assess Health Care* 1995;11(3):428-42.
2. Davis P, Gribben B, Lay-Yee R, et al. How much variation in clinical activity is there between general practitioners? A multi-level analysis of decision-making in primary care. *J Health Serv Res Policy* 2002;7(4):202-8.
3. Ohlsson H, Lindblad U, Lithman T, et al. Understanding adherence to official guidelines on statin prescribing in primary health care-a multi-level methodological approach. *Europ J Clin Pharmacol* 2005;61(9):657-65.

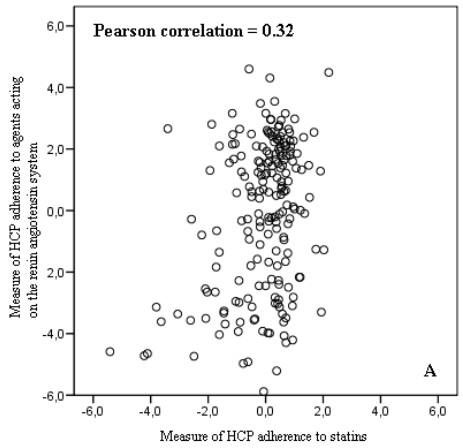
4. Ohlsson H, Merlo J. Understanding the effects of a decentralized budget on physicians compliance with guidelines for statin prescription; a multilevel methodological approach. *BMC Health Serv Res* 2007;7:68 (8 May 2007).
5. Brookhart MA, Solomon DH, Wang P, et al. Explained variation in a model of therapeutic decision making is partitioned across patient, physician, and clinic factors. *J Clin Epidemiol* 2006;59(1):18-25.
6. Ohlsson H, Chaix B, Merlo J. Therapeutic traditions, patient socio-economic characteristics and physicians' early new drug prescribing – a multilevel analysis of rosuvastatin prescription in South Sweden. *Submitted* 2008.
7. Ohlsson H, Merlo J. Is physicians´ adherence to prescription guidelines associated with patient socio-economic status? – An analysis of statin prescriptions in South Sweden. *Submitted* 2008.
8. Goldstein H. *Multilevel Statistical Models*. 3rd ed. London, UK: Hodder Arnold, 2003.
9. WHO. About the ATC/DDD system (http://www.whocc.no/atcddd/).
10. Läkemedelsrådet, editor. *Bakgrundsmaterial (Backgroundmaterial) [in Swedish]*. Lund, 2006.
11. Läkemedelsrådet, editor. *Skånelistan 2006 [in Swedish]*. Lund, 2006.
12. Chaix B, Rosvall M, Merlo J. Assessment of the magnitude of geographical variations and socioeconomic contextual effects on ischemic heart disease mortality: a multilevel survival analysis of a large Swedish cohort. *J Epidemiol Comm Health* 2007;61(4):349-55.
13. WorldBank. Country Classification [http://www.worldbank.org/data/countryclass/countryclass.html] 2005.
14. Swedish Health Care in an International Context. Regions SAoLAa, editor. Stockholm, 2005.
15. Snijders T, Bokser R. *Multilevel analysis: an introduction to basic and advanced multilevel modeling*. Thousand Oaks, California: Sage Publications, 1999.
16. Goldstein H, Browne W, Rasbash J. Partitioning variation in generalised linear multilevel models. *Understanding Statistics* 2002;1:223-232.
17. Wamala SP, Mittleman MA, Schenck-Gustafsson K, et al. Potential explanations for the educational gradient in coronary heart disease: a population-based case-control study of Swedish women. *Am J Public Health* 1999; 89(3):315-21.
18. Larsen K, Merlo J. Appropriate assessment of neighbourhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. *Am J Epidemiol* 2005; 161(1):81-8.
19. Larsen K, Petersen JH, Budtz-Jorgensen E, et al. Interpreting parameters in the logistic regression model with random effects. *Biometrics* 2000; 56(3):909-14.
20. Browne W. *MCMC Estimation in MLwiN (Version 2.0)*. London: Institute of Education University of London, 2003.
21. Rasbash J, Steele F, Browne W. *A User's Guide to MLwiN, Version 2.0. Documentation Version 2.* London, UK: Centre for Multilevel Modelling, Institute of Education, University of London, 2003.
22. Spiegelhalter D, Best N, Carlin B, et al. Bayesian measures of model complexity and fit. *J R Statist SocB* 2002;64(Part 4):583–639.
23. Landon BE, Reschovsky J, Reed M, et al. Personal, organizational, and market level influences on physicians' practice patterns: results of a national survey of primary care physicians. *Med Care* 2001;39(8):889-905.

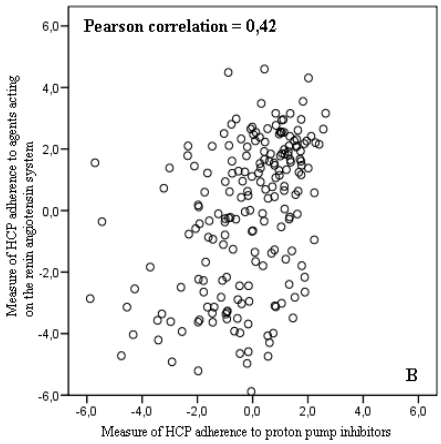
24. O'Neill L, Kuder J. Explaining variation in physician practice patterns and their propensities to recommend services. *Med Care Res Rev* 2005;62(3):339-57.
25. Wennberg J. Wrestling with variation: an interview with Jack Wennberg [interviewed by Fitzhugh Mullan]. *Health Aff (Millwood)* 2004;Suppl Web Exclusive:VAR73-80.
26. Wennberg JE, Barnes BA, Zubkoff M. Professional uncertainty and the problem of supplier-induced demand. *Soc Sci Med* 1982;16(7):811-24.

FIGURE LEGENDS

Figure 1

Scatter plots of standardized residuals for each health care practice from the empty multilevel models for each drug type. Figure 1a shows the correlation between agents acting on the renin-angiotensin system and statins, figure 1b shows the correlation between agents acting on the renin-angiotensin system and proton pump inhibitors and figure 1c shows the correlation between proton pump inhibitors and statins


Pearson correlation = 0.32
Measure of HCP adherence to agents acting on the renin angiotensin system
Measure of HCP adherence to statins
A


Pearson correlation = 0,42
Measure of HCP adherence to agents acting on the renin angiotensin system
Measure of HCP adherence to proton pump inhibitors
B

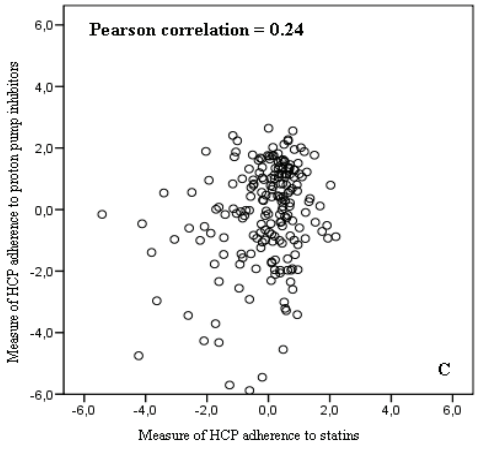

Pearson correlation = 0.24
Measure of HCP adherence to proton pump inhibitors
Measure of HCP adherence to statins
C

Table 1: Adherence with guidelines for prescription of Proton pump inhibitors (ATC: A02BC), Agents acting on the renin-Angiotensin system (ATC: C09) and Statins (ATC C10AA) and characteristics of the patients during the period July 2006-Dec 2006 in Skåne region, Sweden, Values are percentages if not other indicated

	Statins (C10AA)		Agents acting on the renin-angiotensin system (C09)		Proton pump inhibitors (A02BC)	
	Not recom-mended	Recom-mended	Not recom-mended	Recom-mended	Not recom-mended	Recom-mended
Number of individuals	398 (6.4%)	5834 (93.6%)	2012 (27.9%)	5210 (72.1%)	1439 (12.4%)	10124 (87.6%)
Gender (% men)	60.8	51.7	48.5	51.9	40.3	38.7
Mean Age	63.0	64.8	64.4	66.7	56.5	56.5
Marital status						
Married/Cohabited	63.6	61.7	62.4	58.0	58.5	58.2
Living Alone	36.4	38.3	37.6	42.0	41.5	41.9
Disposable income						
Low income (Q1)	21.4	22.5	22.0	25.9	26.4	28.9
Low mid income (Q2)	19.6	23.6	22.4	25.3	24.4	26.1
High mid income (Q3)	26.1	24.7	25.4	25.0	25.0	24.1
High income (Q4)	32.9	29.3	30.2	23.8	24.2	21.0
Social Allowance						
No	96.7	97.5	98.1	97.6	95.0	95.5
0-9 months	1.3	1.2	1.0	1.3	2.8	2.7
10 –12 months	2.0	1.3	.9	1.1	2.2	1.8
Country of Birth						
High income country	84.7	90.1	90.3	91.2	82.3	86.0
High mid income country	7.5	3.7	4.5	3.6	7.1	4.6
Low mi income country	7.5	5.7	4.9	4.9	8.5	8.1
Low income country	.3	.4	.3	.4	1.4	1.2
Education						
Low education	27.6	34.6	35.4	42.8	29.9	33.1
Middle education	23.9	26.1	22.1	23.4	25.5	22.6
High Education	48.5	39.2	42.5	33.8	44.6	44.3
Number of years in Sweden						
Always	76.4	81.9	82.5	84.6	74.1	79.5
>14 years	1.8	1.4	1.4	1.2	2.8	2.7
5-14 years	3.5	3.8	3.1	3.2	8.3	6.8
1-4 years	18.3	12.9	13.0	11.0	14.7	11.1
HCC variables						
General practitioner	213 (6,2%)	3244 (93,8%)	1333 (28,1%)	3412 (71,9%)	1125 (12,2%)	8076 (87.2%)
Specialist Physician	185 (6,7%)	2590 (93.3%)	679 (27,4%)	1798 (72,6%)	314 (13,3%)	2048 (82.1%)
Administrative condition						
Public	200 (4,5%)	6844 (89,1%)	1025 (20,4%)	3997 (79,6%)	839 (10,9%)	6844 (89,1%)
Private	198 (11,3%)	3280 (84,5%)	987 (44,9 %)	1213 (55,1%)	600 (15,5%)	3280 (84,5%)

Table 2: Multi-level logistic regression analysis of adherence to prescription guidelines in the county of Scania, Sweden - fixed effects for model C, D						
	Model C			**Model D**		
	Statins	*Agents acting on the renin-angiotensin system*	*Proton pump inhibitors*	*Statins*	*Agents acting on the renin-angiotensin system*	*Proton pump inhibitors*
Fixed effects	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	1.00 (0.99-1.01)	1.01 (1.00-1.02)	1.00 (0.99-1.00)	1.00 (0.99-1.01)	1.01 (1.00-1.02)	1.00 (0.99-1.00)
Men vs Women	0.73 (0.58-0.93)	1.30 (1.15-1.47)	0.96 (0.86-1.08)	0.73 (0.58-0.92)	1.30 (1.15-1.48)	1.00 (0.85-1.10)
Living Alone	0.94 (0.75-1.19)	1.05 (0.92-1.20)	0.96 (0.86-1.10)	0.94 (0.74-1.20)	1.05 (0.91-1.19)	0.97 (0.85-1.09)
Income						
-Low	1.05 (0.76-1.48)	1.23 (1.02-1.49)	1.31 (1.10-1.59)	1.07 (0.77-1.50)	1.23 (1.02-1.49)	1.32 (1.12-1.57)
-Low middle	1.13 (0.83-1.55)	1.27 (1.06-1.54)	1.21 (1.02-1.42)	1.14 (0.83-1.57)	1.27 (1.06-1.51)	1.20 (1.01-1.41)
-High middle	0.94 (0.71-1.26)	1.17 (0.99-1.39)	1.11 (0.94-1.31)	0.96 (0.72-1.28)	1.17 (0.99-1.38)	1.11 (0.94-1.30)
-High	Ref	Ref	Ref	Ref	Ref	Ref
Education						
Low	1.19 (0.89-1.60)	1.11 (0.93-1.33)	1.08 (0.90-1.27)	1.20 (0.90-1.60)	1.13 (0.94-1.34)	1.07 (0.89-1.27)
Middle	1.14 (0.88-1.51)	1.19 (1.01-1.41)	0.88 (0.76-1.02)	1.15 (0.88-1.51)	1.20 (1.02-1.40)	0.88 (0.76-1.03)
High	Ref	Ref	Ref	Ref	Ref	Ref
Number of years in Sweden						
Always	Ref	Ref	Ref	Ref	Ref	Ref
>14	1.05 (0.45-2.62)	0.76 (0.45-1.30)	0.80 (0.54-1.21)	1.03 (0.46-2.87)	0.75 (0.44-1.32)	0.81 (0.54-1.22)
5-14	1.69 (0.80-3.65)	1.01 (0.65-1.54)	0.71 (0.52-0.98)	1.70 (0.81-3.81)	1.00 (0.65-1.53)	0.72 (0.52-1.00)
0-4	0.88 (0.60-1.31)	0.89 (0.70-1.13)	0.79 (0.63-0.98)	0.89 (0.60-1.32)	0.89 (0.71-1.13)	0.80 (0.63-1.01)
Country of Birth						
High	Ref	Ref	Ref	Ref	Ref	Ref
Low	2.08 (0.36-52.35)	1.08 (0.41-3.14)	1.13 (0.66-2.01)	2.16 (0.35-59.98)	1.08 (0.39-3.19)	1.12 (0.65-1.97)
Lower-middle	0.71 (0.41-1.31)	1.14 (0.78-1.68)	1.29 (0.96-1.75)	0.73 (0.40-1.33)	1.17 (0.79-1.71)	1.27 (0.93-1.71)
Upper-middle	0.50 (0.29-0.86)	0.93 (0.66-1.32)	0.77 (0.57-1.05)	0.50 (0.28-0.84)	0.94 (0.65-1.37)	0.76 (0.57-1.04)
Social allowance						
No	Ref	Ref	Ref	0.94 (0.38-2.78)	Ref	Ref
0-9 months	0.98 (0.40-3.07)	1.24 (0.73-2.30)	0.98 (0.68-1.43)	0.58 (0.25-1.42)	1.26 (0.71-2.27)	0.97 (0.68-1.41)
10-12 months	0.57 (0.26-1.51)	1.10 (0.58-2.13)	1.07 (0.71-1.69)	0.94 (0.38-2.78)	1.11 (0.59-2.17)	1.03 (0.67-1.63)
HCC variables						
Private vs Public	3.23 (2.33-4.65)	5.20 (3.46-8.25)	1.60 (1.28-2.10)	2.76 (1.85-4.37)	3.86 (2.63-5.53)	1.18 (0.86-1.54)
Specialist vs GP	1.34 (0.51-1.94)	1.83 (1.03-2.96)	1.21 (0.84-1.67)	1.23 (0.80-1.93)	1.75 (1.11-2.54)	1.15 (0.87-1.51)
Residualgroup1				Ref	Ref	Ref
Residualgroup2				1.42 (0.77-2.46)	2.10 (1.13-4.18)	2.38 (1.59-3.48)
Residualgroup3				2.57 (1.19-5.36)	2.47 (1.24-5.13)	2.06 (1.36-3.15)
Residualgroup4				1.66 (0.80-3.30)	2.85 (1.37-6.27)	1.79 (1.08-2.89)
Residualgroup5				1.98 (1.00-3.73)	5.97 (3.01-12.24)	3.02 (2.04-4.41)
Residualgroup6				2.24 (1.08-4.49)	3.53 (1.67-8.32)	3.17 (1.95-5.07)

Table 3: Multi-level logistic regression analysis of adherence to prescription guidelines in Skåne region, Sweden - Random effects for model A, B ,C ,D.				
Random effects	HCC (intercept)	MOR_{HCP}	Deviance information criteria (DIC)	Variance explained (compared with model A)
Model A				
Statins	1.09 (0.71-1.64)	2.71 (2.23-3.39)	2746.26	
Agents acting on the renin-angiotensin system	2.65 (2.04-3.48)	4.72 (3.90-5.92)	7058.78	
Proton pump inhibitors	0.65 (0.49-0.88)	2.16 (1.95-2.45)	8174.89	
Model B				
Statins	1.05 (0.67-1.59)	2.65 (2.19-3.33)	2749.13	3.7 %
Agents acting on the renin-angiotensin system	2.63 (2.02-3.48)	4.70 (2.02-3.48)	7038.33	0.7 %
Proton pump inhibitors	0.64 (0.47-0.87)	2.14 (1.92-2.43)	8170.58	1.5 %
Model C				
Statins	0.68 (0.41-1.08)	2.20 (1.85-2.70)	2734.64	37.6 %
Agents acting on the renin-angiotensin system	1.84 (1.40-2.43)	3.64 (1.74-2.15)	7034.85	30.6 %
Proton pump inhibitors	0.58 (0.42-0.78)	2.07 (1.86-2.33)	8167.30	10.7 %
Model D				
Statins	0.65 (0.38-1.08)	2.16 (1.80-2.69)	2734.31	40.3 %
Agents acting on the renin-angiotensin system	1.64 (1.24-2.19)	3.39 (2.89-4.11)	7032.43	38.1 %
Proton pump inhibitors	0.46 (0.34-0.63)	1.91 (1.74-2.13)	8163.58	29.2 %

Table 4: Frequencies of different residual groups from the multilevel regression analysis.								
			Total		**Public**		**Private**	
Adherence agents acting on the renin-angiotensin system	*Adherence statins*	*Adherence proton pump inhibitors*	*Number of HCPs*	*%*	*Number of HCPs*	*%*	*Number of HCPs*	*%*
Low	Low	Low	22	11.1	3	2.6	19	22.6
Low	Low	Middle	8	4.0	1	0.9	7	8.3
Low	Low	High	4	2.0	0	0.0	4	4.8
Low	Middle	Low	4	2.0	2	1.8	2	2.4
Low	Middle	Middle	8	4.0	3	2.6	5	6.0
Low	Middle	High	4	2.0	1	0.9	3	3.6
Low	High	Low	9	4.5	2	1.8	7	8.3
Low	High	Middle	3	1.5	2	1.8	1	1.2
Low	High	High	4	2.0	2	1.8	2	2.4
Middle	Low	Low	6	3.0	4	3.5	2	2.4
Middle	Low	Middle	7	3.5	3	2.6	4	4.8
Middle	Low	High	8	4.0	5	4.4	3	3.6
Middle	Middle	Low	11	5.6	9	7.9	2	2.4
Middle	Middle	Middle	8	4.0	6	5.3	2	2.4
Middle	Middle	High	2	1.0	1	0.9	1	1.2
Middle	High	Low	6	3.0	4	3.5	2	2.4
Middle	High	Middle	9	4.5	7	6.1	2	2.4
Middle	High	High	9	4.5	9	7.9	0	0.0
High	Low	Low	2	1.0	1	0.9	1	1.2
High	Low	Middle	5	2.5	3	2.6	2	2.4
High	Low	High	4	2.0	2	1.8	2	2.4
High	Middle	Low	3	1.5	2	1.8	1	1.2
High	Middle	Middle	8	4.0	6	5.3	2	2.4
High	Middle	High	18	9.1	14	12.3	4	4.8
High	High	Low	3	1.5	2	1.8	1	1.2
High	High	Middle	10	5.1	8	7.0	2	2.4
High	High	High	13	6.6	12	10.5	1	1.2
Total			198		114		84	

VI

Understanding adherence to therapeutic guidelines: a multilevel analysis on statin prescription in the Skaraborg Primary care database

Per Hjerpe, MD [1,2], Henrik Ohlsson [2], Ulf Lindblad, MD, PhD [3], Kristina Bengtsson Boström, MD, PhD [1], Juan Merlo, MD, PhD [2]

1) R&D Centre, Skaraborg Primary Care, Skövde, Sweden

2) Social Epidemiology, Department of Clinical Science, Faculty of Medicine, Lund University, Sweden

3) Department of Public Health and Community Medicine/Primary Health Care, The Sahlgrenska Academy at Gothenburg University, Sweden

Reprint requests and correspondence to

Per Hjerpe, MD

FoU-centrum Primärvården Skaraborg

Storgatan 18

S-541 30 Skövde, Sweden

E-mail per.hjerpe@vgregion.se

INTRODUCTION

The use of prescription guidelines aiming to implement general therapeutic standards is today a common feature in many health care systems.[1] The need for guidelines arises from a general understanding that promoting evidence based and efficient medical care may reduce unnecessary medical practice variation[2] and improve quality.[3] Moreover guidelines may also be an aid for prescribers that are hardly able to assimilate the increasing volume of new scientific information.[1 4-6] However, even though the investigation of adherence to guidelines is attracting increasing interest, it is still not sufficiently understood what and how factors at different levels of the health care organization condition adherence to guidelines.[7-11] In Sweden, every county council has a therapeutic committee responsible of the issuing of evidence-based guidelines.[12] Despite these recommendations several studies have demonstrated substantial and unexplained differences in the adherence with guidelines among physicians and among Health Care Practices (HCP).[9 10 13-15] These differences express themselves as a clustering of similar prescription behavior among physicians at the same HCP and suggest the existence of local therapeutic traditions. Quantifying and understanding this variation is relevant for the planning of interventions aimed to improve the quality of drug prescription.

We have previously shown[10] that in the Region of Skåne, Sweden, the implementation of a decentralised drug budget increased adherence to guidelines and promotes efficient drug therapy. Similarly, in Skaraborg, Sweden the economical responsibility of tax-financed drug cost was transferred from the regional administration to the local HCP in the year 2003. However, the effects of this intervention are still unknown. In the present study, using multilevel regression analyses, and data from the Skaraborg Primary Care Database (SPCD)[16] we evaluate the effect of this decentralised drug budget. We focus on adherence to statin (HMG-CoA reductase inhibitors) prescription since this group of cholesterol lowering drugs has very homogeneous indications and similar efficacy which nearly eliminates the possibility of confounding by indication and patient mix when comparing different practices and physicians. We also aimed to disentangle the relevance of different levels (i.e. patients, physicians, HCPs) for understanding adherence with guidelines. Based on previous studies[10] our hypothesis was that the decentralized budget

would result in an increased prevalence and a decreased variance between physicians and between HCPs, concerning prescription of recommended statins.

MATERIALS AND METHODS

The Skaraborg Primary Care Database (SPCD)

Skaraborg, one of four administrative areas of the region of Västra Götaland in the southwest of Sweden is mostly rural and it is inhabited by approximately 250 000 individuals within 15 municipalities. Inpatient care is offered by three public hospitals and primary care by 24 public and one private HCPs, as well as by a few private solo practitioners. About 250 000 office visits are registered at the public HCPs every year. Approximately 75% of all drug prescriptions are issued outside the hospitals and 85% of them at public HCPs.

The SPCD started in 2000 and is based on a common computerized medical journal used by all the 24 publicly administrated HCPs in the area. Among other information all drug prescriptions, laboratory tests, and current diagnosis at every consultation are recorded. The SPCD allows the identification of the HCP, the physician and the patient by a unique anonymized identification number.

Study population

From the SPCD, we identified all patients with at least one prescription of statin defined according to the Anatomical Therapeutical Chemical (ATC) classification system code C10AA.[17] Thereafter we selected two datasets, (i) patients with at least one statin prescription during May 2002 to October 2003 (i.e., 2003 dataset), and (ii) during July 2004 to December 2005 (i.e., 2005 dataset). If a patient received more than one statin prescription during each time period, the last one was selected. Prescriptions for other cardiovascular drugs, Long-acting nitrates (ATC: C01DA08, C01DA14), Loop diuretics (C03C), Potassium-sparing diuretics (C03D), Diuretic combinations (C03E),Thiazides (C03A, C03B),Beta blockers (C07), Calcium channel blockers (C08), ACE-inhibitors (C09A, C09B), Angiotensin receptor blockers (C09C, C09D), Fibrates (C10AB), and Resins (C10AC) were also extracted. Only patients where all his/her cardiovascular drugs

were issued by the same physician were included. The 2003 dataset included 6205 patients, treated by 425 physicians at 24 HCPs and in the 2005 dataset, 7979 patients treated by 402 physicians at 24 HCPs.

Individual level variables

The outcome variable was prescription of recommended statin (yes v. no). In the 2003 dataset, these drugs were Simvastatin (Zocord® or generic simvastatin) and Pravastatin (Pravachol®) and in the 2005 dataset only Simvastatin (Zocord® or generic simvastatin). We categorized the age of the patients into four groups: -54 years, 55-64, 65-74, and 75-, and used the youngest group as reference in the comparisons. We included the sex of the patients as a dummy variable using women as reference in the analysis. Based on the actual evidence neither age nor sex or any other patient characteristic should motivate the preferential prescription of a specific statin before any other. Therefore, the inclusion of individual-level variables in the analysis was not motivated by the need of adjustment for confounding but rather, because we wanted to gain an understanding of the prescribing process.

Physician level variables

Previous studies have shown that prescription behaviour is influenced by prescriber characteristics. We, therefore, included physician's occupational status categorized as Intern (IN), Resident (RS), General practitioner (GP) or Locum (LOC). Each category was split into two groups according to the median age of the specific group. Of the eight different groups older GPs were used as reference in the analysis. We included the sex of the physician as a dummy variable using women as reference in the analyses. However, information on physician's characteristics was only available for the 2005 dataset.

Multi-level regression models

We used multilevel generalized regression models analysis.[18 19] to estimate the probability of prescribing a recommended statin, while accounting for the hierarchical structure of the data (i.e., patients nested within physicians nested within HCPs). We developed three consecutive models (A, B, C) for data set 2003 and 4 models (A, B, C and D) for data set 2005. Model A was an empty two level model including only patients

and HCPs as random effects. Model B was a three-level model in which patients were nested within physicians that were in turn nested within HCPs. Model C and Model D added the patient characteristics respectively patient and physician characteristics. In this way we aimed to investigate if the individual and contextual characteristics could explain the residual variation between physicians and between HCPs. We estimated odds ratios and 95 % credible intervals (95 % CI) from the models. Model fit was evaluated by comparing change in the deviance information criteria (DIC).

In the random-effects part of the multilevel analysis, we obtained the variance and 95% credible intervals at the physician and the HCP levels and used this information to calculate the median odds ratio (MOR) and 95% credible intervals.[18-21] The MOR translates the variance into the odds ratio (OR) scale, and is thereby comparable with OR of individual or area variables. The MOR can be interpreted as the amount by which a patients odds of receiving a recommended statin would increase (in median) if this patient moved to a physician/HCP with higher adherence to guidelines. If the MOR was equal to 1, there would be no differences between physicians or HCPs in the odds of prescribing a recommended statin. If there were important physician-level or HCP differences, the MOR would be large on this level.

We calculated the percentage of change in magnitude of variance (PCV) that was explained between the intial (references) model ($Var_{initial}$) when including more variables in an extended model (Var_{more}):

Percentage of change (PCV) = $((Var_{initial}–Var_{more})/(Var_{initial}))x100$

We used this percentage to estimate the relevance of the individual and contextual characteristics for understanding a possible clustering of prescriptions of recommended statins. Parameters were estimated by MCMC methods with the MLwiN 2.00 software.[22]

RESULTS

Table 1 indicates that overall the prevalence of adherence with guidelines for prescription of statins increased from 77 % in 2003 to 84 % in 2005. In 2003 older patients had higher adherence to guidelines, but these age differences disappeared in 2005. Men were

prescribed statins more of the than women, but there were not sex related differences in the prescription of recommended ones. In 2005, 68% of all the statins were prescribed by male doctors that also showed a slightly lower percentage of prescription of recommended statins than female colleagues. There were no differences among physician categories except for young interns that showed the highest (90%) and older locums the lowest (77%) adherence with guidelines.

Figure 1 illustrates that while there were some HCPs with rather low adherence to guidelines in 2003 all HCPs had approximately 80 % adherence in 2005. It is also obvious that the HCPs with the poorest adherence in 2003 showed the largest improvement in 2005.

Table 2 shows the association between on the one hand patient and physician characteristics and on the other prescription of recommended statins according the multilevel regression analysis. In 2003 adherence to guidelines increased with age of the patients, but in 2005 there were no differences between age groups. Older locum physicians presented a conclusively lower probability of prescribing a recommended statin than older GPs.

Model A in table 3, only includes two levels (i.e., patients and HCPs) and informs that in median a patient's odds of receiving a recommended statin would increase 2.14 times in 2003 ($MOR_{HCP2003}$ = 2.14) and 1.37 times in 2005 ($MOR_{HCP2005}$ = 1.37) if he/she moved to an HCP with higher adherence to guidelines.

Model B in table 3 includes three levels (i.e., patients, physicians and HCPs) and shows that the HCP and physician levels accounted each for approximately 50 % each of the variation at the higher levels in 2003 ($MOR_{HCC2003}$ = 1.89 vs. $MOR_{PHYSICIAN2003}$ = 1.88). In 2005 the variance among HCPs and physicians was lower ($MOR_{HCC2005}$ = 1.30 vs. $MOR_{PHYSICIAN2003}$ = 1.52). The differences between physicians (-55%) and HCPs (-82%) decreased considerably between 2003 and 2005.

Model C in table 3 expands model B by including individual level variables and model D accounts moreover for the characteristics of the physicians. Neither of them had a mayor influence on the observed variance in model B.

Figure 2 illustrates that in 2003 about 30% of the HCPs and approximately 4% of the physicians presented and level of adherence that was conclusively different from the overall mean adherence. However, in 2005 none of the HCPs and only a few physicians differed conclusively from the overall mean.

The DIC diagnostics shows that the inclusion of both HCPs and physicians improves the model fit compared with including only the HCP level for both 2003 and 2005 datasets. Nevertheless, Model C (2003) and Model D (2005) have the best model fit.

DISCUSSION

Our investigation demonstrates that transferring the economical responsibility from the central health care authorities at the County Council to the local HCCs considerably improved adherence to statin prescription guidelines among prescribers. We not only observed that the overall prevalence of use of recommended statins increased from 77 % in 2003 to 84 % in 2005, but also that the variance among both HCCs and physicians decreased considerably by 89% and 65% respectively. Our results fully agree with a previous analysis of ours[10] performed in the county of Scania.

We have previously discussed that therapeutic traditions can be operationalized and investigated by measures of variance and clustering in multilevel regression analyses.[9 10] The idea is that the more the prescriptions from a physician/HCP are alike, compared to prescriptions from other physicians/HCPs, the more likely it is that the determinants of the individual prescription have to do directly with the physician/HCP. On this background, our study indicates that the therapeutic traditions existing among both physicians and HCPs in 2003 before the implementation of the decentralized budget were counteracted by the implementation of the decentralized budget.

The current analysis improves the information obtained by our previous investigation in the county of Scania[10] since we had access to physician level information. Using this information we could confirm previous observations.[23] on the relevance of the physician level for understanding practice variation, and realize that the physician and the HCP levels shared in 2003 about one half of the variance each. However, in 2005 – after the

decentralized budget – the residual variance became almost negligible. Yet, it appeared that most of the (small) residual variance was among physicians. This is also illustrated in figure 2 by the fact that none of the HCP and only a few physicians conclusively differed from the overall mean adherence in 2005.

Our analytical approach of focusing on both changes in variance and changes in prevalence is actually an innovative way of investigating practice variation in pharmacoepidemiology. However, this approach has been previously implemented in other research fields.[24-27] In fact, observing an increasing in the prevalence of prescription of recommended stating does not necessarily imply an improvement since the variation around the prevalence could be very high. The desired outcome is obviously not only to increase adherence with guidelines but also to eliminate unnecessary practice variation.

An advantage of the multilevel regression analysis is that it allows disentangling the variance in the outcome among the different levels of analysis and using this information for identifying which level could be most relevant for a possible intervention. In our study, as example, in 2003 the contextual variance was rather large and approximately equal distributed among HCPs and physicians, indicating the any intervention aimed to improve adherence with guidelines should be focused on both levels simultaneously. In fact the decentralized budget was such a kind of intervention, and it appeared to effectively decrease the variance at both levels. In 2005 the higher level variance was very small and information which suggests that any further intervention directed to HCPs or physicians would render less effective.

In 2005 we observed that older locum physician had a lower adherence to prescription guidelines than older GPs, which may reflect intrinsic characteristics of this personal category. Locum physicians share the common work environment and the same constraints as other physicians at the HCP but only for a limited period of time and therefore might be less affected by the therapeutic traditions acting at the HCP. However, in spite of the conclusive association between this physician category and low adherence to guidelines an intervention focusing on locums will possible not be very efficient,[28] since the residual variance (and the corresponding the MOR) was negligible and inclusion of the physician characteristics did not contribute to explain the variance.

Observational epidemiological studies are often the only option for investigating questions that for practical, economical, or ethical reasons cannot be analysed by randomized trials.[29-32] Nevertheless, confounding and selection bias may threaten the validity of the studies. However, because of similar indications and efficacy, statins are an ideal medication group for investigating prescribing behaviour,[33] and there is no rationale for considering patient characteristics as confounding factors when investigating practice variation.

While confounding by indication was not a threat for investigating prescription of recommended statins, the value of including individual and physician covariates resides in the understanding of the prescription process. In the present investigation we only considered basic individual variables such as age and gender of the patient, and our results showed that for dataset 2003 younger patients had a lower propensity to receive recommended statins. This circumstance cannot be justified by any medical argument, but may rather reflect the influence of constructed social roles and expectations. From the perspective of equity in health care, it is relevant to question the physicians´ choice of more expensive, but not more efficient, brands for some groups of patients, given that a large part of this medication expenditure is funded by the public reimbursement system. We can not exclude that unmeasured factors besides the decentralized budget might have influenced the observed results (i.e., increase in prevalence and reduction in variance). In addition, the expiration of the Zocord patent in 2003, with the following decline in price for generic simvastatin and increase in cost difference with other statins, might have contributed in choosing the recommended statin.

Most patients receive statins as a long time therapy. However, according the Swedish rules a prescription can not be issued for a period longer than one year. Therefore, in routine care repeat prescriptions are sometimes issued by phone and eventually by a different physician that the one that initiated the treatment. We have tried to identify homogeneous physician-patient relations by only including patients with all cardiovascular prescriptions by the same physician. However, we can not exclude a delayed effect of the decentralized budget conditioned by the fact that for new users the physicians prescribe recommended drugs, but for continuous users the physicians do not

change to recommended drugs but continue with the original non-recommended drug, especially if the repeated prescription is written by another physician.

Our study investigates statin prescription in primary health care. Therefore, our results are not directly applicable to those drug prescribed for patients at hospital care. Older patients treated in primary care but also in municipal homecare are also excluded since their prescriptions are not registered in the database.

Practice variation is a common phenomenon that is not necessarily inappropriate but rather may reflect different therapeutic approaches confronting a similar health problem.[34] However, when the same pharmacological therapy is available as different brands at different prices and the prescriber selects the more costly, there are reasons to question the suitability of the observed practice variation.

In conclusion, applying an innovative methodology for investigating practice variation, our study shows that decentralization of the drug budget to the HCPs, i.e., transferring the economical responsibility and the power in management and decision-making to the HCPs, seemed to be an appropriate intervention for reducing inefficient therapeutic traditions. As a natural consequence, adherence to the drug committee's recommendations increased and differences between physicians and HCPs decreased.

Acknowledgements

This research was funded by the Skaraborg research and development council, Skaraborg primary care research and development council, and the Skaraborg Institute, Skövde, Sweden. The Swedish Research Council (Juan Merlo, Dnr 2004-6155 and The Centre for Economic Geography), the Swedish council for working life and social research (Juan Merlo, Dnr: 2007-1772), by an ALF Government Grant Research program (Juan Merlo, Dnr M: B 39 977)

Figure legends

Figure 1: Illustrates, for the 24 HCPs included in the analysis, on the X-axis the percentage of recommended statins 2003, and on the Y-axis recomemmended statins 2005 (top). The bottom figure illustrates, for the 24 HCPs included in the analysis, on the

X-axis percentage of recommended statins in 2003 and on the Y-axis the differences (percentage) between 2003 and 2005.

Figure 2a: Illustrates the residuals from the MLRA for the different levels (physicians/HCPs) for the analysis regarding 2003

Figure 2b: Illustrates the residuals from the MLRA for the different levels (physicians/HCPs) for the analysis regarding 2005 2003

REFERENCES

1. Grimshaw J, Thomas R, Maclennan G, Fraser C, Ramsay C, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8(6).
2. Westert GP, Groenewegen PP. Medical practice variations: changing the theoretical approach. *Scand J Public Health* 1999;27(3):173-80.
3. Socialstyrelsen. God vård – om ledningssystem för kvalitet och patientsäkerhet i hälso- och sjukvården, 2006.
4. Brindis RG, Sennett C. Physician adherence to clinical practice guidelines: does it really matter? *Am Heart J* 2003;145(1):13-5.
5. Koutsavlis AT. Disseminating practice guidelines to physicians: Institut national de santé publique du Québec, 2001.
6. Thorsen T, Mäkelä M, editors. *Changing professional practice - Theory and practice of clinical guidelines implementation*. Copenhagen, 1999.
7. En uppföljning av läkemedelskommitéernas arbete. Hur påverkas läkemedelsanvändningen ? (A follow-up of the effort of the drug committees. How does it affect the drug use?) [in Swedish]. In: Socialstyrelsen, editor.
8. Kasje WN, Denig P, Stewart RE, de Graeff PA, Haaijer-Ruskamp FM. Physician, organisational and patient characteristics explaining the use of angiotensin converting enzyme inhibitors in heart failure treatment: a multilevel study. *Eur J Clin Pharmacol* 2005;61(2):145-51.
9. Ohlsson H, Lindblad U, Lithman T, Ericsson B, Gerdtham UG, Melander A, et al. Understanding adherence to official guidelines on statin prescribing in primary health care-a multi-level methodological approach. *Europ J Clin Pharmacol* 2005;61(9):657-65.
10. Ohlsson H, Merlo J. Understanding the effects of a decentralized budget on physicians compliance with guidelines for statin prescription; a multilevel methodological approach. *BMC Health Serv Res* 2007;7:68 (8 May 2007).
11. Sjöqvist F, Dahl M-L, Gustafsson L, Hensjö L-O. Drug therapeutics committees: a Swedish experience. *WHO Drug Information.* 2002;16:207-13.

12. Socialdepartementet. Lag (1996:1157) om läkemedelskommittéer. (Law (1996:1157) about drug committees) [in Swedish].
13. Ohlsson H, Chaix B, Merlo J. Therapeutic traditions, patient socio-economic characteristics and physicians' early new drug prescribing – a multilevel analysis of rosuvastatin prescription in South Sweden. *Eur J Clin Pharmacol* 2009;65(2):141-150.
14. Ohlsson H, Lynch K, Merlo J. Is physicians´ adherence to prescription guidelines associated with patient socio-economic status? – An analysis of statin prescriptions in South Sweden. *Submitted* 2008.
15. Ohlsson H, Merlo J. Is physician adherence to prescription guidelines a general trait of health care practices or dependent on drug type? – A multilevel logistic regression analysis in South Sweden. *Submitted* 2009.
16. Hjerpe P, Merlo J, Ohlsson H, Bengtsson-Boström K, Lindblad U. Validity of registration of ICD codes and prescriptions in a research database in primary care Skaraborg primary care database (SPCD). *Working paper* 2009.
17. WHO. About the ATC/DDD system (http://www.whocc.no/atcddd/).
18. Goldstein H. *Multilevel Statistical Models*. 3rd ed. London, UK: Hodder Arnold, 2003.
19. Snijders T, Bokser R. *Multilevel analysis: an introduction to basic and advanced multilevel modeling*. Thousand Oaks, California: Sage Publications, 1999.
20. Larsen K, Merlo J. Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. *Am J Epidemiol* 2005;161(1):81-8.
21. Larsen K, Petersen JH, Budtz-Jorgensen E, Endahl L. Interpreting parameters in the logistic regression model with random effects. *Biometrics* 2000;56(3):909-14.
22. Rasbash J, Steele F, Browne W. *A User's Guide to MLwiN, Version 2.0. Documentation Version 2.1e.* London, UK: Centre for Multilevel Modelling, Institute of Education, University of London, 2003.
23. Brookhart MA, Solomon DH, Wang P, Glynn RJ, Avorn J, Schneeweiss S. Explained variation in a model of therapeutic decision making is partitioned across patient, physician, and clinic factors. *J Clin Epidemiol* 2006;59(1):18-25.
24. Braumoeller B. Explaining Variance; Or, Stuck in a Moment We Can't Get Out Of. *Political Analysis* 2006;14:268–290.
25. Downs G, Rocke D. Interpreting Heteroscedasticity. *American journal of Political Science* 1979;23(4):816-828.
26. Merlo J. Multilevel analytical approaches in social epidemiology: measures of health variation compared with traditional measures of association. *J Epidemiol Community Health* 2003;57(8):550-2.
27. Rasbash J, Browne W, Goldstein H, Yang M, Plewis I, Healy M, et al. Modelling the variance as a function of explanatory variables. *A User's Guide to MLwiN. Version 2.0. Documentation Version 2.1e*. London, UK: Institute of Education, University of London, 2003.
28. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial of multilevel analysis in social epidemiology - Interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. *J Epidemiol Community Health* 2005;59:1022-8.

29. Black N. Why we need observational studies to evaluate the effectiveness of health care. *Bmj* 1996;312(7040):1215-8.
30. Merlo J, Chaix B. Neighbourhood effects and the real world beyond randomized community trials: a reply to Michael J Oakes. *Int J of epidemiolgy* 2006;35(5):1361-1363.
31. Schneeweiss S. Developments in post-marketing comparative effectiveness research. *Clin Pharmacol Ther* 2007;82(2):143-56.
32. Sorensen G, Emmons K, Hunt MK, Johnston D. Implications of the results of community intervention trials. *Annu Rev Public Health* 1998;19:379-416.
33. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *J Am Med Assoc* 1999;282(24):2340-6.
34. Crump B. The Good Indicators Guide: Understanding how to use and choose indicators. In: improvement NIfIa, editor, 2007.

Table 1. Characteristics of the prescriptions of statins for patients with one prescriber in 24 HCC in Skaraborg, number (%) if not indicated.

	2003		**2005**	
	Total: (N=6205)		Total: (N=7979)	
	Recommended statin			
	Yes	No	Yes	No
Number (%)	4772 (77)	1433 (23)	6719 (84)	1260 (16)
Patient				
Age (min-max, mean years)	30-89 66	31-89 64	18-93 66	25-104 66
1 -54	637 (73)	233 (27)	855 (84)	166 (16)
2 55-64	1465 (75)	497 (25)	2009 (83)	404 (17)
3 65-74	1710 (78)	471 (22)	2354 (85)	424 (15)
4 75-	960 (81)	232 (19)	1501 (85)	266 (15)
Male	2498 (76)	779 (24)	3603 (84)	660 (16)
Female	2274 (78)	654 (22)	3116 (84)	600 (16)
Doctor				
IN1 -29 (N=21)	-	-	113 (90)	12 (10)
IN2 30- (N=22)	-	-	91 (82)	20 (18)
RS1 -34 (N=32)	-	-	420 (85)	72 (15)
RS2 35- (N=29)	-	-	306 (83)	64 (17)
GP1 -49 (N=65)	-	-	2419 (84)	459 (16)
GP2 50- (N=64)	-	-	2910 (85)	513 (15)
LOC1 -46 (N=89)	-	-	243 (82)	54 (18)
LOC2 47- (N=80)	-	-	217 (77)	66 (23)
Male	-	-	4568 (84)	895 (16)
Female	-	-	2151 (86)	365 (14)

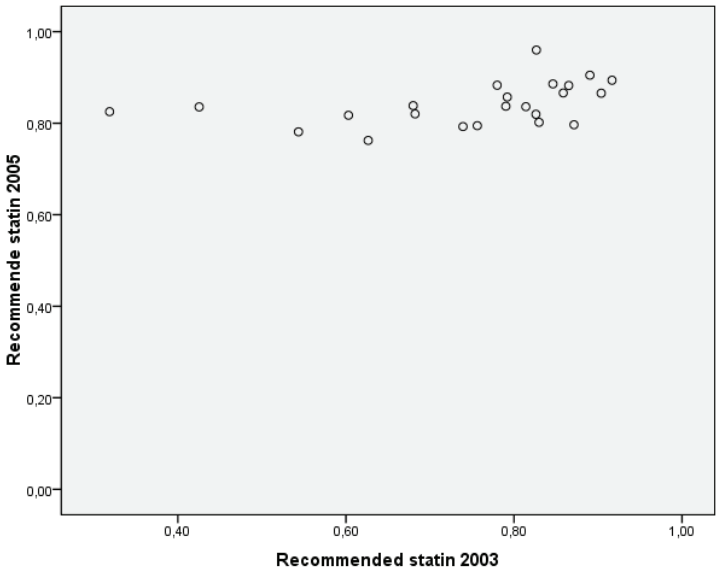
IN=Intern
RS=Resident
GP=Genral practitioner
LOC=Locum

Table 2. Multilevel logistic regression analysis of prescription of recommended statins 2003 and 2005, model A and B

	Model A		**Model B**		**Model C**	
	2003	2005	2003	2005	2003	2005
Fixed effects					OR (95%CI)	OR (95%CI)
PatientAge						
1 -54	-	-	-	-	Reference	Reference
2 55-64	-	-	-	-	1.05 (0.84-1.29)	0.96 (0.78-1.17)
3 65-74	-	-	-	-	1.32 (1.08-1.62)	1.07 (0.88-1.30)
4 75-	-	-	-	-	1.51 (1.20-1.89)	1.09 (0.87-1.35)
Female	-	-	-	-	Reference	Reference
Male	-	-	-	-	1.01 (0.88-1.14)	1.07 (0.95-1.22)
Random effects						
Variance-HCP (95 % CI)	0.64 (0.33-1.16)	0.11 (0.04-0.23)	0.44 (0.20-0.88)	0.08 (0.02-0.20)	0.46 (0.20-0.91)	0.07 (0.01-0.19)
MOR (95 % CI)	2.14 (1.73-2.80)	1.37 (1.22-1.58)	1.89 (1.53-2.44)	1.30 (1.12-1.52)	1.92 (1.54-2.49)	1.29 (1.10-1.51)
Variance-Phys (95 % CI)	-	-	0.44 (0.30-0.60)	0.20 (0.12-0.30)	0.44 (0.31-0.62)	0.20 (0.12-0.30)
MOR (95 % CI)	-	-	1.88 (1.68-2.10)	1.52 (1.40-1.68)	1.89 (1.70-2.12)	1.53 (1.39-1.69)
			Change in variance model A and B			
HCC	-	-	-31%	-27%	-	-
	Change in variance 2003 - 2005		Change in variance 2003 - 2005		Change in variance 2003 - 2005	
HCC	-83%		-82%		-85%	
Physician	-		-55%		-55%	
Deviance Information Criteria (DIC)	6157.85	6898.25	5947.56	6803.07	5936.96	6806.3

Table 3. Multilevel logistic regression analysis of prescription of recommended statins 2005, model C and D

	Model D	**Model E**
Fixed effects	OR (95% CI)	OR (95% CI)
Patient		
Age group		
1 -54	-	REF
2 55-64	-	0.95 (0.77-1.16)
3 65-74	-	1.06 (0.86-1.29)
4 75-	-	1.07 (0.86-1.33)
Female	-	REF
Male	-	1.08 (0.95-1.23)
Doctor		
IN1 -29 (N=21)	1.67 (0.85-3.46)	1.67 (0.78-3.43)
IN2 30- (N=22)	0.86 (0.48-1.57)	0.85 (0.48-1.58)
RS1 -34 (N=32)	0.90 (0.62-1.33)	0.91 (0.62-1.32)
RS2 35- (N=29)	0.81 (0.55-1.19)	0.80 (0.55-1.18)
GP1 -49 (N=65)	0.87 (0.69-1.09)	0.87 (0.69-1.10)
GP2 50- (N=64)	REF	REF
LOC1 -46 (N=89)	0.75 (0.51-1.11)	0.75 (0.51-1.11)
LOC2 47- (N=80)	0.56 (0.38-0.82)	0.56 (0.38-0.82)
Female	REF	REF
Male	0.88 (0.71-1.08)	0.87 (0.71-1.07)
Random effects	Variance (95 % CI)	Variance (95 % CI)
HCC (Intercept)	0.06 (0.00-0.16)	0.06 (0.00-0.16)
MOR	1.26 (1.06-1.47)	1.26 (1.07-1.47)
Physician (Intercept)	0.20 (0.12-0.30)	0.21 (0.13-0.31)
MOR	1.53 (1.39-1.69)	1.54 (1.40-1.70)
DIC (MCMC)	6801.53	6805.55


Recommende statin 2005
1,00
0,80
0,60
0,40
0,20
0,00
0,40
0,60
0,80
1,00
Recommended statin 2003

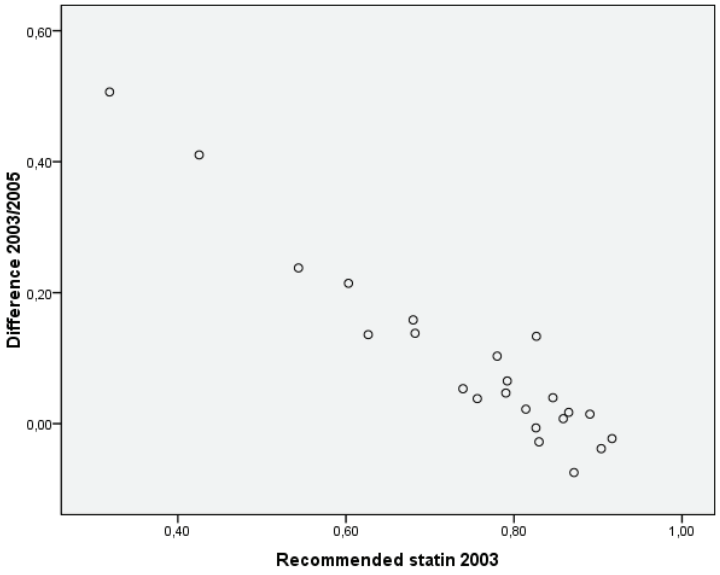

Difference 2003/2005
0,60
0,40
0,20
0,00
0,40
0,60
0,80
1,00
Recommended statin 2003

Figure 1

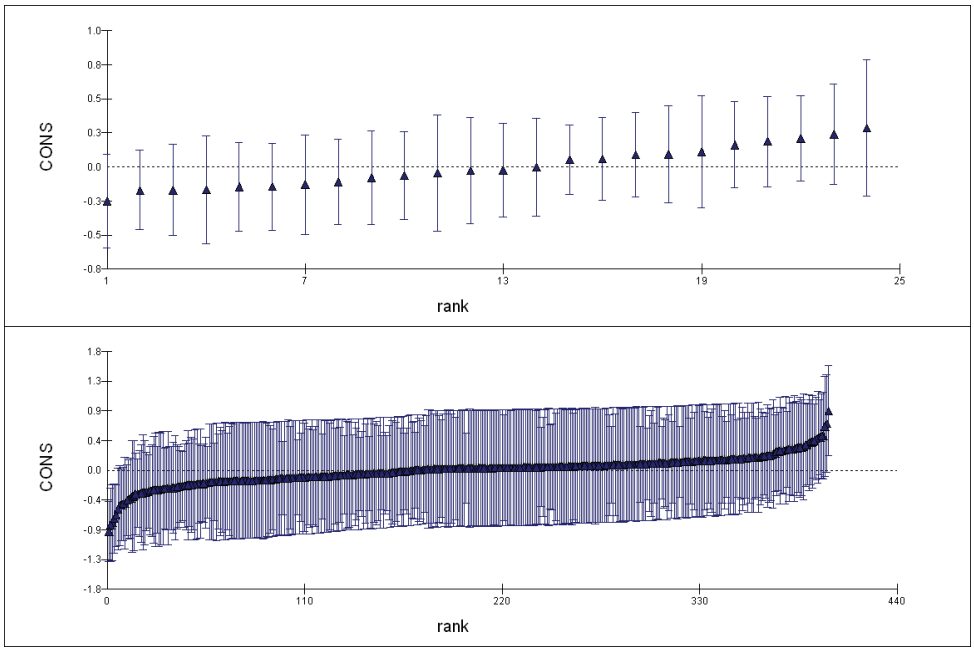


Figure 2a (Residuals for HCP (top) and Physicians (bottom)

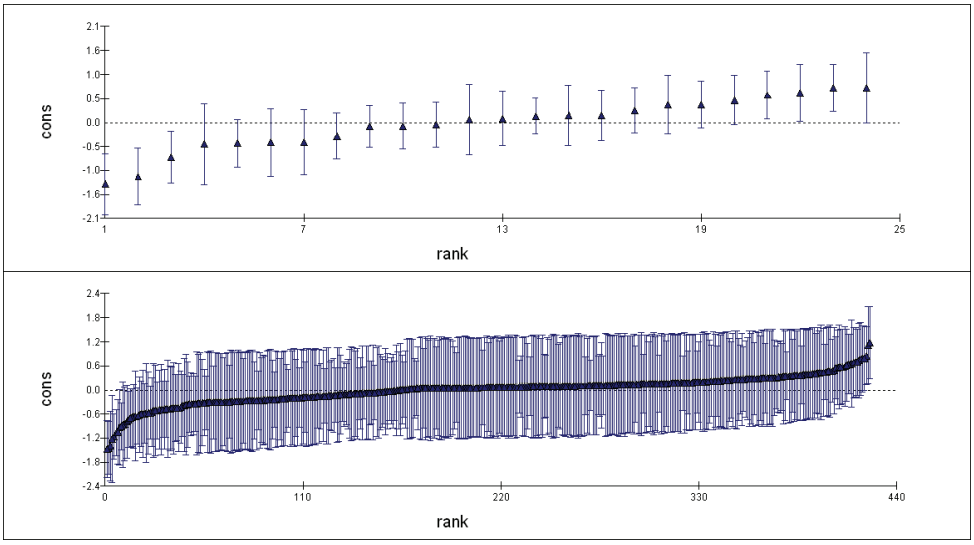


Figure 2b (Residuals for HCP (top) and Physicians (bottom)