

Use of statins and other lipid-modifying agents across pregnancy – a nationwide drug utilization study in Norway in 2005-2018

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Short running head: Statin use across pregnancy

Abbreviations: ATC, The World Health Organization's Anatomical Therapeutic Chemical Classification System; DDDs, defined daily doses; ICD-10, The International Classification of Diseases, version 10; ICPC-2, The International Classification of Primary Care-2; KUHR, The Norway Control and Payment of Health Reimbursement Database; LMA, lipid-modifying agents; MBRN, The Medical Birth Registry of Norway; NorPD, The Norwegian Prescription Registry; NPR, The Norwegian Patient Registry

Abstract

Background and aims: Statins are becoming more widely used among women of reproductive age; however, nationwide data on statin use across pregnancy is scarce. We therefore aimed to describe the drug utilization patterns for statins and other lipid-modifying agents (LMAs) before, during, and after pregnancy, for all pregnancies in Norway from 2005 to 2018.

Methods: We linked individual-level data from four nationwide electronic health care registries in Norway and characterized the prescription fills of statins and other LMAs across pregnancy. We also examined trends in pregnancy-related LMA use, and characterized women using statins and other LMAs on parameters of health status and co-morbidity.

Results: In total 822 071 pregnancies for 503 723 women were included. The number of statin prescription fills decreased rapidly during first trimester and returned to pre-pregnancy levels about one year postpartum. Pregnancy-related statin use increased from 2005 (approx. 0.11 % of all pregnancies) to 2018 (approx. 0.29 % of all pregnancies); however, in total, few statin prescriptions were filled within any trimester of pregnancy ($n = 331$, 0.04 % of all pregnancies). Statin use was more common in women with higher age, higher weight, smoking, and comorbidities such as hypertension and diabetes mellitus; also, statin users often had co-medication pertinent to these conditions.

Conclusions: Although statins and other LMAs were increasingly being used around the time of pregnancy among women in Norway, drug use was mostly discontinued during first trimester. Our results suggest that pregnancy-related statin use should be monitored, and that drug safety analyses for maternal and offspring health outcomes are needed.

Keywords: drug utilization, statins, lipid-modifying agents, pregnancy, registry, nationwide

Introduction

Statins (HMG coenzyme A [HMG-CoA] reductase inhibitors) reduce plasma LDL cholesterol (LDL-C) and thereby the risk of atherosclerotic cardiovascular disease (ASCVD) both effectively and safely [1, 2]. Statins therefore constitute the main line of therapy for patients with elevated ASCVD risk [3–5]. In recent years, most clinical guidelines have further lowered the threshold for initiating treatment with statins [3–5]; thus, statins are now more commonly used among the general population [6]. Drug Wholesales Statistics in Norway show that statin use has increased over time also among women of reproductive age [7]. In 2004, 1 in 182 women aged 20–44 years in Norway were prescribed at least one lipid-modifying agent (LMA, ATC [Anatomical Therapeutic Chemical Classification] group C10), the majority of which was statin monotherapy (ATC group C10AA). In 2020, the rate of LMA use had increased to 1 in 126 women aged 20–44 years.

We may expect a further increase in the number of women of reproductive age who use statins in the coming years. The reason is at least two-fold. First, as hypercholesterolemia is being detected more frequently and earlier in life, and the threshold for initiating treatment is generally low, so is the age that statin therapy is started. This is a natural consequence of realizing that *duration of treatment* (number of treatment years) is key to effective risk reduction [8]. Second, the average maternal age at first pregnancy is still increasing, leading to a higher proportion of women of reproductive age with elevated ASCVD risk [9]. Importantly, considering that a proportion of all pregnancies are unplanned, the expected increase in statin use will probably affect the population-wide exposure to statins also in early pregnancy. However, statins have traditionally been *contraindicated* during pregnancy, due to the role of cholesterol in embryonic development, proposed teratogenic effects of statins, and lack of safety data. Most women planning pregnancy are therefore recommended to stop statin therapy [4].

Although important both from a cardioprotective and safety point of view, nationwide data on statin use across pregnancy is scarce. Therefore, in the present study, we aimed to describe the complex drug utilization patterns for statins and other lipid-modifying agents (LMAs) before, during, and after pregnancy, for all pregnancies in Norway in the period 2005 to 2018, using nationwide linked electronic health care registries. A secondary aim was to determine health-related characteristics of women using statins and other LMAs during pregnancy.

Material and methods

Study design, data sources and study population

The present study was a nationwide registry drug utilization study where we described the use of statins and other LMAs across pregnancy for all pregnancies in Norway in the period 2005 to 2018.

Using the unique, personal identity number of Norwegian citizens, we linked individual-level data from four national health registries in Norway up until 2018: The Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Registry (NorPD), the Norwegian Patient Registry (NPR), and the Norway Control and Payment of Health Reimbursement Database (KUHR).

The MBRN has registered pregnancy-related information since 1967, including pregnancy duration, complications, growth of the fetus, and health status of both the mother and the child, for all pregnancies in Norway ending after gestational week 12 [10]. NorPD has recorded all prescribed medications dispensed at Norwegian pharmacies to non-institutionalized individuals since 2004, including the type of drug, the date of prescription filling, and the number of defined daily doses (DDDs) dispensed [11]. Medications in NorPD are classified according to the World Health Organization's Anatomical Therapeutic Chemical Classification (ATC) System (see <https://www.whocc.no/> for details).

NPR includes information on activity in both secondary and tertiary health care settings in Norway. The NPR uses the International Classification of Diseases, version 10 (ICD-10). KUHR stores information on activity in *primary* health care settings in Norway. KUHR records the reason for the utilization of health care services, which includes visits to general practitioners (GPs) and emergency services. KUHR uses both ICD-10 diagnostic codes and the International Classification of Primary Care-2 (ICPC-2) codes.

For the present study, we included all women with a pregnancy recorded in the MBRN in 2005-2018. We excluded pregnancies with missing gestational length, as timing of drug exposure could not be calculated for these pregnancies (**Figure 1**). Pregnancies where women used statins and other LMAs were identified through dispensed prescriptions in NorPD.

To characterize women using LMAs during pregnancy, we classified pregnancies into different subgroups based on different criteria. First, limited to one year before conception to one year after delivery, we classified pregnancies into the following groups:

- Classification no. 1 (statin groups): Pregnancies for women using any statin or specific statins agents.
- Classification no. 2 (non-statin LMA groups): Pregnancies for women using any non-statin LMA, or specific non-statin LMA agents.

Similarly, limited to any time before conception to one year after delivery, we classified pregnancies into the following groups:

- Classification no. 3 ("discontinuation" groups): 1) pregnancies where women discontinued their statin prescription fills at least three months before conception, 2) pregnancies where women discontinued their statin prescription fills within three

months before conception, 3) pregnancies where women filled their statin prescription during pregnancy, and 4) other.

- Classification no. 4 (groups based on history of statin use before pregnancy): 1) pregnancies for long-term, “experienced” statin users (10-148 prescription fills), 2) pregnancies for “intermediate-term” users (4-9 prescription fills), and 3) pregnancies for “short-term users and beginners” (1-3 prescription fills). History of statin use was calculated as the chronological, rolling count of prescription fills per woman and pregnancy. We determined the ranges by binning the number of prescriptions into three groups of approximately equal number of observations.
- Classification no. 5 (dyslipidemia diagnosis groups): 1) pregnancies for women with a dyslipidemia diagnosis (ICPC-2 code T93) not using LMAs, and 2) pregnancies for women with a dyslipidemia diagnosis using LMAs.
- Classification no. 6 (co-morbidity groups based on number of indications for LMA therapy): pregnancies for women using LMA with 1) 0 indications for LMA use, 2) 1 indication for LMA use, 3) 2-3 indications for LMA use, 4) 4-8 indications for LMA use, or 5) ≥ 9 indications for LMA use. Number of LMA indications was defined as the per-pregnancy sum of unique drugs used in diabetes (ATC code A10), antithrombotic agents (B01), and cardiovascular system (C other than C10), and the unique diagnosis codes defined in **Table S1**.

This project was approved by the Regional Committee for Research Ethics in South-Eastern Norway (approval number 2018/140/REK South-East) and by the Data Protection Officer at the University of Oslo (approval number 58033).

Exposure to statins and other LMAs

Exposure to statins and other LMAs was defined based on the date of prescription dispensing and the dispensed amount expressed in number of DDDs. We assumed that all the dispensed statins were consumed as 1 DDD per day. The main exposures of interest were prescription fills of statins, as well as prescription fills of other, non-statin LMAs. After linking the birth registry to the prescription registry, we searched for use of any LMA (statin or non-statin LMA; all codes in the ATC group C10). The ATC codes for statins included C10AA01 (simvastatin), C10AA05 (atorvastatin), and C10AA07 (rosuvastatin). The ATC codes for other LMA included C10AC01 (colestyramine), C10AX06 (omega-3 triglycerides incl. other esters and acids), and C10AX09 (ezetimibe). The number of prescription fills of other statins and non-statin LMAs (and combination use) was generally very low; therefore, we combined these into a group called ‘Other’.

We defined exposure as the presence of at least one prescription fill within each time frame. Time frames of interest were mainly between one year before conception to one year after delivery, including the entire pregnancy and pregnancy trimesters (trimester 1: 1-93 days after time of conception; trimester 2: 94-186 days after conception; trimester 3: > 186 days after conception).

Co-medication

We examined co-medication among women using statins and other LMAs. Among co-medication where LMAs would likely be indicated, we included drugs used in diabetes (ATC code A10), antithrombotic agents (B01), and cardiovascular system (C other than C10). We also had access to a range of other co-medications which we examined using the first ATC level, including alimentary tract and metabolism (A), blood and blood-forming organs (B), genito-urinary system and sex hormones (G), systemic hormonal preparations excl. sex hormones and insulins (H), antiinfectives for systemic use (J), musculo-skeletal system (M), and nervous system (N). Where relevant, we also considered co-medications at the second ATC level. We omitted some ATC codes that had either few observations or were considered less relevant, such as dermatologicals (D), antineoplastic and immunomodulating agents (L), antiparasitic products, insecticides and repellents (P), respiratory system (R), sensory organs (S), and various (V).

Diagnoses

We examined diagnoses among women using statins and other LMAs using ICD-10 codes in NPR and ICD-10 and ICPC-2 codes in KUHR. Among diagnostic codes where LMAs would likely be indicated, we included 28 second level ICD-10 codes from endocrine, nutrition and metabolic (ICD-10 main group E) and circulatory (I) diagnostic groups; we also included 22 second level ICPC-2 codes from the cardiovascular (K) and endocrine, metabolic and nutrition (T) (Table S1). Where relevant, we highlighted aggregated subgroups, such as T9, which cover diabetes type 2 (ICPC-2 code T90) and dyslipidemias (T93). Notably, we did not have access to some relevant diagnosis such as metabolic disorders (E70-E90) which include dyslipidemias (E78) and the subgroup familial hypercholesterolemia (E78.0).

We also had access to a range of other diagnoses, including the following ICD-10 codes: psychiatric and behavior (F), nervous system (G), pregnancy, birth and maternity (O), and miscellaneous (Z); for the ICPC-2 codes, we included musculoskeletal (L), nervous system (N), psychiatric (P), airways (R), urinary tract (U), and pregnancy, birth and family (W). We omitted some diagnosis codes that had either few observations or were considered less relevant, such as skin (L) and respiratory (J) for ICD-10, and social (Z) for ICPC-2.

Maternal characteristics

We derived the following information from the MBRN: maternal age at delivery, marital status, parity, pre-pregnancy body weight, employment, pre-pregnant folate use, smoking, comorbidities (asthma, chronic hypertension, chronic renal disease, pre-existing diabetes, epilepsy, and rheumatoid arthritis), plurality, previous pregnancy loss, and an obstetric comorbidity index (adapted from [12]). Variables were categorized as presented in the tables and figures.

Recurrent pregnancies

Recurrent pregnancy was defined as any record of a pregnancy ending after gestational week 12, including both live and non-live births (that is, elective terminations, late miscarriages after gestational week 12, and stillbirths).

Data analyses

The unit of analysis was the pregnancy, as is common for drug utilization analyses. This means that the analyses were performed irrespective of how many fetuses the women were carrying. We estimated the number of prescription fills for statins and other LMAs from one year before conception, during pregnancy, and up to one year after delivery. We also estimated the time trends of use from 2005 to 2018 as a proportion of total number of pregnancies per year. We used several visualization approaches to display the results, for example using the number of prescription fills per 2-week period as a function of time (using estimated time of conception as time zero). See further details in each figure legend.

Using descriptive statistics, we evaluated the main characteristics, comorbidities, and concomitant medications of women with and without LMA prescription fills. For example, in tables, we present frequencies (%) and medians (interquartile ranges, IQR).

All data analyses were performed in R version 3.6.2 [13] using RStudio (Boston, MA, USA, www.rstudio.com) and the tidyverse framework [14].

Results

We included 822 071 pregnancies for 503 723 unique women (Figure 1). Half of the women contributed with one pregnancy ($n = 250\,664$, 49.8 %), and a sizable proportion contributed with two ($n = 196\,579$, 39.0 %) or three pregnancies ($n = 49\,119$, 9.8 %); few women contributed with four or more pregnancies ($n = 7\,361$, 1.5 %). We counted 13 876 multiple births in the birth registry in 2005-2018, of which 13 661 were twin pregnancies (1.7 % of all 822 071 pregnancies), 209 were triplet pregnancies (0.03 %), and six were quadruplet pregnancies (0.0007 %). The characteristics of the pregnancies is shown in **Table 1**.

Compared to non-statin users, statin users had higher maternal age (47 vs. 31 % above 32 years for any statin use and no statin use, respectively), higher pre-pregnancy maternal weight (70 vs. 65 kg), higher prevalence of smoking (25 vs. 19 %), and comorbidities, such as any chronic illness (24 vs. 6.7 %), chronic hypertension (6.5 vs. 0.5 %), or diabetes (18 vs. 3.5 %) (Table 1). This pattern was consistent from 2005 to 2018 (**Figure S1**).

LMA use across pregnancy

In the period 2005 to 2018, between one year before conception and one year after delivery, 8 255 prescriptions were filled for an LMA, covering 2 772 pregnancies and 2 304 unique women; of these, 6 703 prescription fills (81.2 %) were for a statin, covering 2 439 pregnancies and 2 010 unique women (**Figure 2**). The main statin agents used were simvastatin and atorvastatin. Although the number of prescriptions decreased during the first trimester of pregnancy, statin prescriptions were filled in first trimester for a total of 298 unique pregnancies (0.036 % of all pregnancies), and in any trimester for a total of 331 unique pregnancies (0.04 % of all pregnancies). The reduction in prescription fills started already three months before pregnancy, from almost 150 to about 100 prescription fills per two-week period. The number of prescription fills remained low throughout second and third trimester (less than 10 prescription fills per two-week period), increased steadily following pregnancy, and returned to pre-pregnancy levels after almost one year postpartum. The pattern was similar for all statin agents and doses (**Figure S2**).

Non-statin LMAs were less commonly used across pregnancy compared with statins. In the period 2005 to 2018, between one year before conception and one year after delivery, 1 659 prescriptions were filled for a non-statin LMA, covering 599 pregnancies and 519 unique women (**Figure S3**). While ezetimibe use followed a pattern similar to that of statins, the use of cholestyramine and omega-3 was more stable across pregnancy. Non-statin LMA prescriptions were filled in first trimester for a total of 89 unique pregnancies (0.011 % of all pregnancies), and in any trimester for a total of 121 unique pregnancies (0.015 % of all pregnancies).

Temporal trends in pregnancy-related LMA use

Pregnancy-related LMA use increased from 2005 to 2018, both for statins and other LMAs (**Figure 3**). Within 1 year before pregnancy, any LMA use increased from 0.14 % of all pregnancies in 2006 to 0.29 % of all pregnancies in 2018; similarly, within 1 year after pregnancy, any LMA use increased from 0.11 % of all pregnancies in 2005 to 0.23 % of all pregnancies in 2017. In contrast, any LMA use during pregnancy was approximately 0.05 %

of all pregnancies throughout the whole period. Simvastatin was the most frequently used drug until approximately 2013, when atorvastatin (and rosuvastatin) became more frequently used. Use of ezetimibe and colestyramine also increased over time.

Co-medication across pregnancy

Women using LMAs were using cardiovascular co-medication across pregnancy (**Figure 4**). For example, co-medication with alimentary tract and metabolism drugs (ATC group A) increased in pregnancy, partly resulting from diabetes drugs (A10). Similarly, drugs for blood and blood-forming organs (B) increased during pregnancy, mainly as a result of anti-thrombotic agents (B01). Also, certain subgroups of cardiovascular system drugs (C) increased slightly towards the end of pregnancy and in the immediate time following delivery, such as vasoprotectives (C05), beta-blockers (C07), calcium channel blockers (C08), and renin-angiotensin system (C09).

Approximately 37 % of women who used LMAs in pregnancies also used a cardiovascular system drug *other* than LMAs, including antihypertensives, and 16 % used diabetes drugs (data not shown).

Diagnoses across pregnancy

Women using LMAs were being diagnosed with conditions across pregnancy pertinent to LMA use (**Figure 5**). For example, group E1 in ICD-10, covering endocrine, nutrition and metabolic diseases including diabetes spiked during pregnancy; however, T9 in ICPC-2, which include diabetes mellitus type 2 and dyslipidemia, did not. Group I in ICD-10 (circulatory) increased towards the end of pregnancy and following delivery, while group K in ICPC-2 (cardiovascular) increased following delivery. We counted at least one diagnosis of dyslipidemia (ICPC-2 code T93 in KUHR) for 62 % of all pregnancies where a prescription for an LMA had been filled between one year before conception and one year following delivery (**Figure S4**).

Characteristics of pregnancies based on additional subgroups

In the Supplementary Results and Discussion, we present and discuss the characteristics of pregnancies for LMA users more in-depth, based on several additional subgroups, including use of non-statin LMAs, and discontinuation (**Table S2-S6, Figure S5-S7**).

Discussion

In the present work, we explored the use of statins and other LMAs across pregnancy for all pregnancies in Norway in the period 2005 to 2018. We found that statin use displayed a distinct pattern across pregnancy: The number of statin prescription fills decreased during first trimester, which indicates that women discontinue statins once they know they are pregnant, as recommended by guidelines. Furthermore, we found that pregnancy-related LMA use increased from 2005 to 2018, and that women using statins and other LMAs had different characteristics than other women. Our results highlight the importance of monitoring pregnancy-related statin use and should inform drug safety analyses for maternal and offspring health outcomes.

LMA use displayed a distinct pattern across pregnancy

The number of statin prescription fills decreased during first trimester, indicating that women discontinue statins once they know they are pregnant. In fact, the decrease in statin prescription fills started already three months before pregnancy, likely reflecting pregnancy planning, at least among a subgroup of the population. Also, despite the high number of pregnancies ($n = 822\,071$), in relatively few pregnancies ($n = 298$, 0.036 %), a prescription for a statin had been filled during first trimester. This is largely in line with data from other populations [15–19]. Although reassuring, the low frequency of statin exposure during pregnancy limits the power of drug safety analyses.

The increase in prescription fills occurred slowly and returned to pre-pregnancy levels about one year postpartum. The slow increase could reflect at least two things: statin contraindication during breastfeeding, and leftover pills from before pregnancy. Notably, there was a trend that beginners started using statins earlier than other women; this group likely comprise women that during pregnancy become aware they are at increased ASCVD risk. These data suggest that, in practice, pregnancy is used by the clinicians to assess ASCVD risk and to initiate treatment, at least for some women. Doing this more systematically for all women could be one way to bridge the gap in ASCVD assessment and treatment for women compared to men, which has recently been highlighted [20, 21]. Also, because pregnancy can be considered a physiological test of the pregnant woman and family, pregnancy-related assessment of ASCVD risk may be a primordial prevention strategy worth considering implemented on a more large-scale level [22, 23].

The pregnancy-induced changes in prescription fills for non-statin LMAs were also remarkable. While prescription fills for ezetimibe followed a pattern similar to that of statins, other non-statin LMAs were less affected by pregnancy. Because there is a lack of safety data for *all* LMAs, guidelines generally recommend that *no* LMAs – statin or non-statin – be dispensed during pregnancy or lactation [4]. However, bile acid sequestrants such as cholestyramine may be considered for women with a severe FH phenotype, since these are not absorbed. Therefore, in the present data, cholestyramine use can potentially be seen as a marker of a severe type of FH in the absence of the actual ICD-10 code for FH (E78.0).

Pregnancy-related LMA use increased over time

Pregnancy-related LMA use increased from 2005 to 2018. As expected, monotherapy with simvastatin and atorvastatin were the main groups of LMAs, corresponding well with trends in use of statin agent in clinical trials [4]. Interestingly, the use of combination therapy increased in the past few years, possibly due to the results from the IMPROVE-IT trial, which confirmed clinical benefit of adding ezetimibe on top of statin therapy for ASCVD prevention [24]. Following new reimbursement policies in June 2005, simvastatin was made the drug of choice in Norway [25]. In accordance with these regulations, many low dose atorvastatin users switched to simvastatin instead, and new users were more often put on simvastatin. Over time, atorvastatin again became more widely used, and is now the drug of choice, likely also because of reimbursement rules and introduction of cheap, generic medications [6]. Rosuvastatin monotherapy also became more popular the last decade, which may be related to improved detection and treatment of subjects with familial hypercholesterolemia (FH). In general, these patterns of statin use correspond well with the pattern of statin use in the whole Norwegian population [6].

Women using statins and other LMAs across pregnancy had different characteristics than other women

Women using statins and other LMAs across pregnancy had higher pre-pregnancy age and weight, a larger proportion of smokers, and various co-morbidities, such as hypertension, kidney disease and diabetes mellitus; factors that reflect elevated ASCVD risk and thereby indication for treatment with statins [4]. This is in line with previous observations: pregnant women using statins generally have a more metabolic unhealthy phenotype than those not using statins, for example due to higher prevalence of diabetes mellitus, smoking, or dyslipidemia, depending on the study population [16, 17]. Scientists have long argued that people with high *lifetime* risk of ASCVD events would likely benefit with statin treatment already early in life, even if the *short-term* risk is negligible [26–28]. For dyslipidemia, evidence from FH is the archetypical example in this regard, although contemporary studies using genetics have facilitated a wider recognition across medical sub-disciplines [27]. However, the lifetime ASCVD risk related to *other* risk factors is also highly relevant, as our data here point to. With time, as the concept of lifetime risk is being adopted by clinicians, more people are likely to be treated at a younger age, including women of reproductive age. It is therefore pivotal to keep pregnancy-related statin use under surveillance.

Co-medication and diagnoses were common among women using statins and other LMAs, supporting a more prevalent co-morbidity

Interestingly, each pharmacological group and diagnosis group showed very distinct patterns across pregnancy. The use of both anti-thrombotic and anti-diabetic medication increased in first trimester and decreased after delivery. Concomitant use of non-LMA cardiovascular drugs was also common across pregnancy, and for some pharmacological subgroups even increased slightly in third trimester (vasoprotectives, beta-blockers, calcium channel blockers, and renin-angiotensin system). Note that the use of renin-angiotensin system drugs is not recommended in the first trimester due to conflicting results regarding risk of malformations, and are contraindicated during the second and third trimester due to an increased risk of human fetal and neonatal toxicity [29, 30]. Collectively, these data further

suggest that the pregnancies of women using LMAs can be considered high-risk pregnancies. Also, the pronounced co-medication highlights the importance of considering the concurrent use of *other* potentially teratogenic drugs and interaction of these with statins when evaluating statin safety [19].

The use of ICD-10 diagnoses for diabetes mellitus (group E1) was high already before pregnancy among LMA users, and increased midway through first trimester. Prenatal care in Norway and elsewhere focuses on detecting alterations in glucose homeostasis in pregnant women, and for good reason [31]. The HAPO study found that maternal glucose concentration associated with risk of developing several adverse health outcomes, such as pre-eclampsia, preterm delivery and macrosomia [32]. Importantly, in that study, the association was both linear and had no apparent threshold. In addition, gestational diabetes mellitus is an excellent predictor of future development of insulin resistance and diabetes mellitus in both mother and offspring [22, 23]. In contrast, the use of ICPC-2 diagnoses for both diabetes mellitus and dyslipidemia (group T9) went slightly down in pregnancy. Because pregnancy induces a physiological hyperlipidemia, guidelines for prenatal care do usually not recommend routinely measuring lipids in pregnancy, thereby masking the pattern observed with ICD-10 diagnoses.

Implications, importance & generalizability

The use of complete data from nationwide registries with mandatory reporting are important strengths of our study. Nationwide data on statin use across pregnancy is scarce, despite the importance both from a cardioprotective and safety point of view. ASCVD is ubiquitous worldwide, and lipid-modification is the primary strategy for ASCVD risk reduction. The present work is therefore likely generalizable to other countries where use of statins and other LMAs is becoming more prevalent also among young people. However, all our results may not be generalizable to all other countries, especially to lower income countries where women experience lower access to education and affordable health care of high quality. For example, although people living in lower income countries likely suffer from statin *undertreatment*, the degree of discontinuation in pregnancy likely differs from higher income countries. Furthermore, one implication of our results is that multi-national collaboration projects may be needed to reliably answer pressing research questions on statin safety, for example related to outcomes such as birth defects in the offspring. Our study covers all pregnant women in Norway from 2005 to 2018, as opposed to a prospective cohort study that includes only a sample of a population. Another strength is that the registry data was collected in standardized forms by health personnel, in contrast to observational studies using differing assessment methods, and self-reporting.

Limitations

This work has some limitations that warrant mention. First, the exposure is 'prescription fill', not *actual* drug use; however, we assume that these associate closely [33]. Note that the impact of primary non-adherence is limited by the fact that only information on drugs actually dispensed from pharmacies to patients is recorded in the NorPD, which is more indicative of use than databases including all drugs prescribed by physicians [34]. Second,

because this study is a sub-study under a larger project regarding medications in pregnancy, we only had access to certain diagnostic codes; for example, we did not have available the ICD-10 code for FH (E78.0). Third, the data is descriptive, and cannot draw any conclusions about the appropriateness of treatment. For example, we did not have access to plasma lipid levels.

Conclusions

In conclusion, the use of statins and other LMAs displayed a distinct pattern across pregnancy. Reassuringly, the number of prescription fills decreased during first trimester. Pregnancy-related statin use increased over time, and women using statins and other LMAs had more co-morbidity compared to other women. These results suggest that pregnancy-related statin use should be monitored and emphasize the need for drug safety analyses for maternal and offspring health outcomes. Finally, our data point to a more widespread use of preconceptional counselling to women of childbearing age that may require statins or other LMAs.

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Conflicts of interest

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Authorship

Authorship overview according to CRediT – Contributor Roles Taxonomy: Conceptualization: JJC, KBH, MPB, HN; Data curation: JJC, HN; Formal analysis: JJC; Funding acquisition: HN, KBH, MPB; Investigation: JJC, HN; Methodology: JJC; Project administration: JJC, KBH, HN; Resources: HN; Software: JJC; Supervision: MPB, KBH, KR, MBV, HN; Validation: JJC; Visualization: JJC; Writing – original draft: JJC; Writing – review & editing: JJC, MPB, KBH, KR, MBV, HN.

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Tables

Table 1

Table 1. Characteristics of the 822 071 pregnancies in 2005-2018, stratified by statin use between one year before conception and one year after delivery (covering 2 439 pregnancies and 2 010 unique women).

	n	No statin use		Any statin use			
		n = 819 632	n = 2 439	Specific statin use			
				Simvastatin, n = 1 235	Atorvastatin, n = 1 144	Rosuvastatin, n = 192	Other statin, n = 81
Age	822 071						
< 28 yrs		322 172 (39)	662 (27)	328 (27)	320 (28)	62 (32)	18 (22)
28 - 32 yrs		240 268 (29)	640 (26)	313 (25)	304 (27)	51 (27)	17 (21)
> 32 yrs		257 192 (31)	1 137 (47)	594 (48)	520 (45)	79 (41)	46 (57)
Employed, yes	656 916	530 164 (81)	1 578 (81)	760 (78)	748 (82)	147 (89)	48 (77)
Civil status	822 071						
Registered partner/cohabitant		760 647 (93)	2 218 (91)	1 112 (90)	1 048 (92)	178 (93)	76 (94)
Other		58 985 (7.2)	221 (9.1)	123 (10.0)	96 (8.4)	14 (7.3)	5 (6.2)
Parity	822 071						
Nulliparous		346 176 (42)	997 (41)	483 (39)	476 (42)	82 (43)	38 (47)
Primiparous		297 202 (36)	832 (34)	436 (35)	383 (33)	66 (34)	21 (26)
Multiparous		176 254 (22)	610 (25)	316 (26)	285 (25)	44 (23)	22 (27)
Previous pregnancy loss, yes	771 869	182 315 (24)	603 (26)	304 (26)	292 (27)	45 (24)	19 (25)
Weight (pre-pregnancy), kg	422 081	65 (58-75)	70 (61-84)	72 (62-87)	70 (61-84)	69 (60-80)	65 (59-73)
Folate use (pre-pregnancy), yes	822 071	232 852 (28)	806 (33)	388 (31)	370 (32)	73 (38)	29 (36)
Smoking, yes	552 527	107 213 (19)	442 (25)	252 (30)	196 (22)	23 (14)	12 (26)
Obstetric comorbidity index	822 071						
0		539 888 (66)	1 058 (43)	486 (39)	527 (46)	113 (59)	25 (31)
1		184 660 (23)	655 (27)	348 (28)	298 (26)	47 (24)	15 (19)
2		66 027 (8.1)	382 (16)	208 (17)	175 (15)	21 (11)	13 (16)
3 or more		29 057 (3.5)	344 (14)	193 (16)	144 (13)	11 (5.7)	28 (35)
Chronic illness, yes	822 071	54 981 (6.7)	596 (24)	329 (27)	264 (23)	22 (11)	35 (43)
Chronic hypertension, yes	822 071	4 286 (0.5)	158 (6.5)	98 (7.9)	66 (5.8)	4 (2.1)	6 (7.4)

Any diabetes mellitus, yes n (%); Median (25%-75%)	822 071	28 717 (3.5)	438 (18)	238 (19)	205 (18)	13 (6.8)	16 (20)
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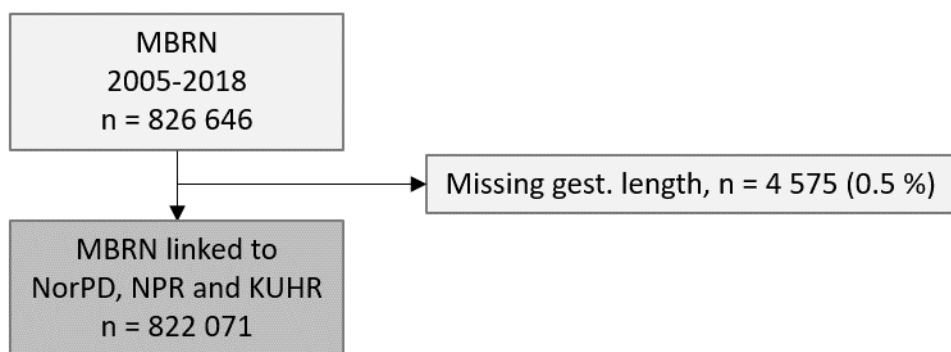
Figures*Figure 1*

Figure 1. *Study flow chart.* Abbreviations: gest, gestational; KUHR, the Norway Control and Payment of Health Reimbursement Database; MBRN, the Medical Birth Registry of Norway; NorPD, the Norwegian Prescription Registry; NPR, the Norwegian Patient Registry.

Figure 2

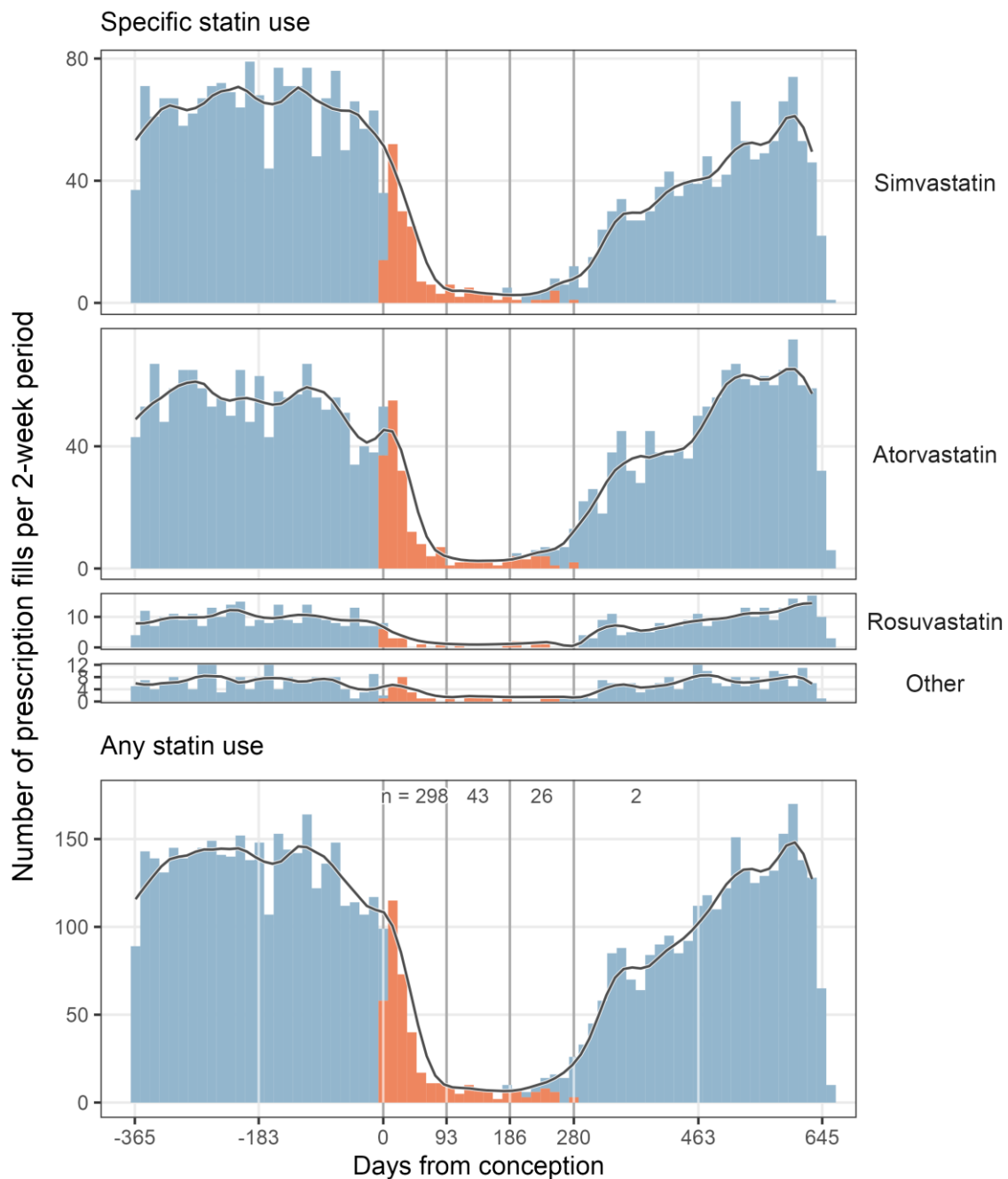


Figure 2. Pattern of prescription fills for statins, one year before, during, and one year after pregnancy. The figure shows the number of prescriptions fills for statins (6 703 prescription fills, 2 439 pregnancies, 2 010 unique women) in 2-week bins, as well as a smoothed 2-month average (one month prior and the subsequent two weeks; local regressions were fit on 10 % of the data points along the line). Blue and red color represents prescription fill of a statin *outside* or *within* any trimester of pregnancy, respectively. Numbers between the vertical lines in the upper part of the lowest panel represent the number of unique pregnancies where a statin prescription had been filled inside pregnancy, per trimester. The vertical lines represent key timepoints in relation to time of conception, including conception and trimester transitions.

Figure 3

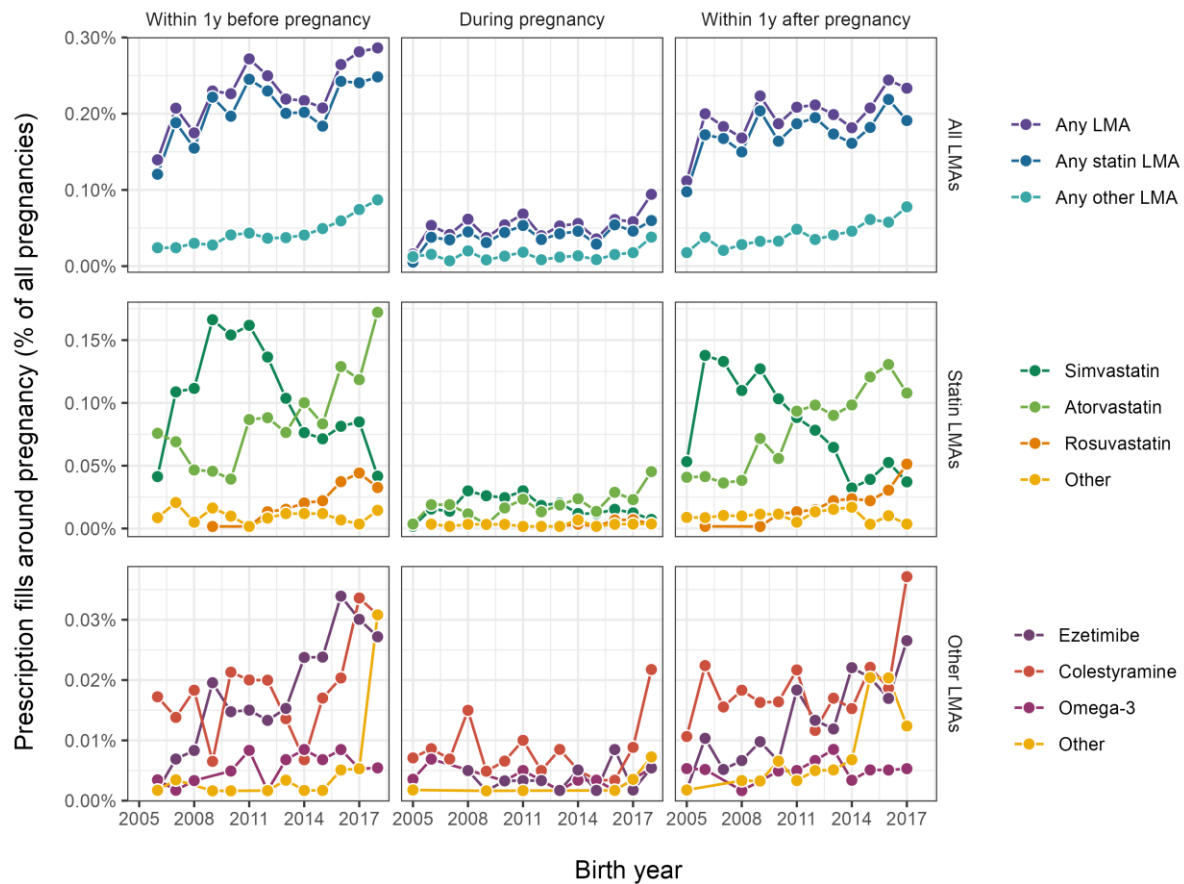


Figure 3. Trends in prescription fills for LMAs, one year before, during, and one year after pregnancy. The figure shows trends in use for groups of LMAs (top row) and individual LMAs (middle and bottom rows), for the periods from 1 year before pregnancy to conception (left column), during pregnancy (middle column), and from delivery until 1 year after delivery (right column). Note that 2005 was excluded for the period within 1 year before pregnancy, as this would largely reflect 2004; similarly, 2018 was excluded for the period within year after pregnancy, as this would largely reflect 2019. Abbreviations: LMA, lipid-modifying agent; y, year.

Figure 4

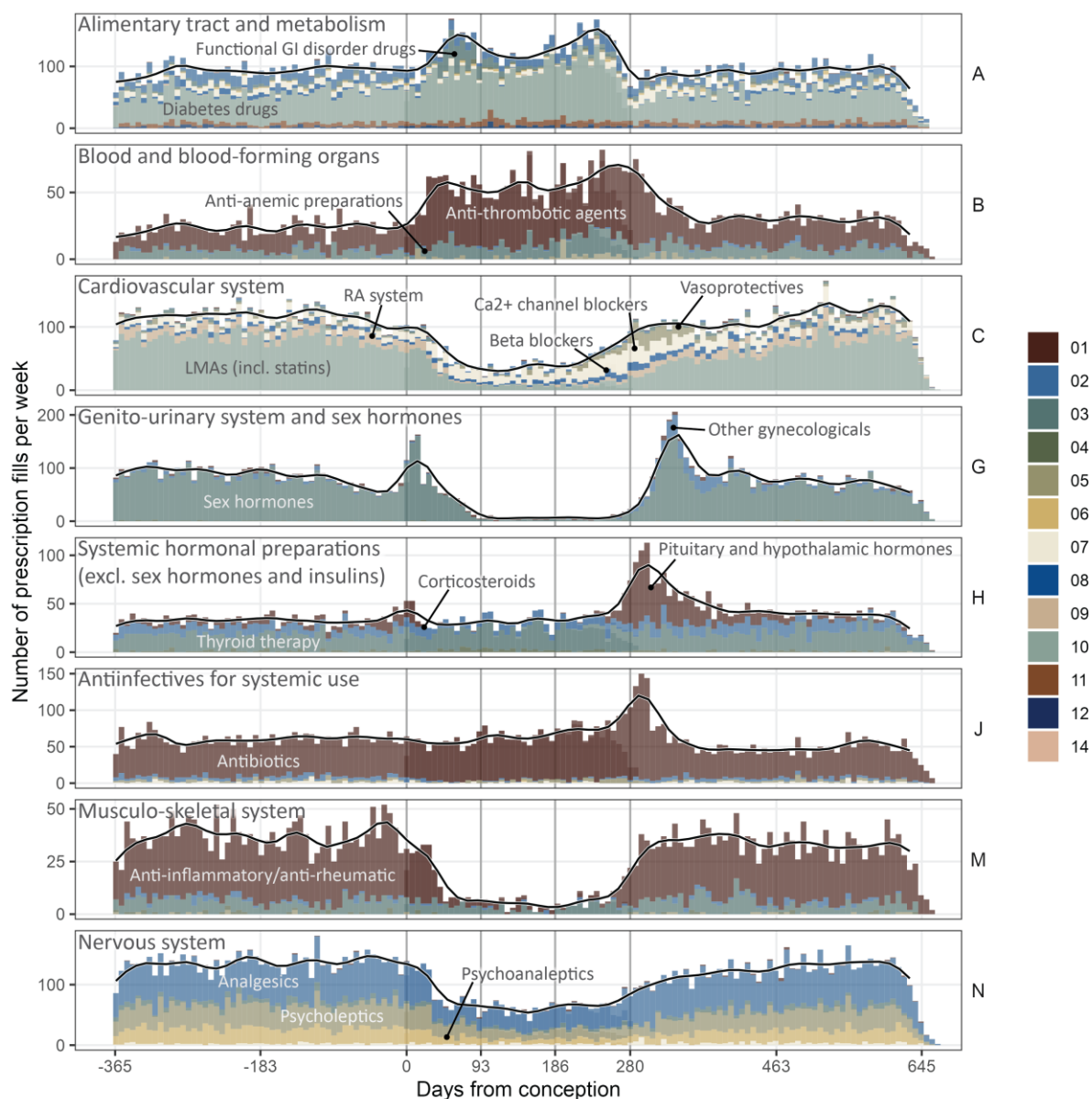


Figure 4. Pattern of co-medication among LMA users one year before, during, and one year after pregnancy. The figure shows the number of prescriptions fills of various medication in 1-week bins for women using statins across pregnancy (those included in Figure 2, covering 2 439 pregnancies and 2 010 unique women), as well as a smoothed 1-month average (two weeks prior and the subsequent week; local regressions were fit on 10 % of the data points along the line). The panels and colors correspond to the first and second level of ATC codes, respectively. Some of the most notable second level ATC codes are annotated by their common names. The vertical lines represent key timepoints in relation to time of conception, including conception and trimester transitions.

Figure 5

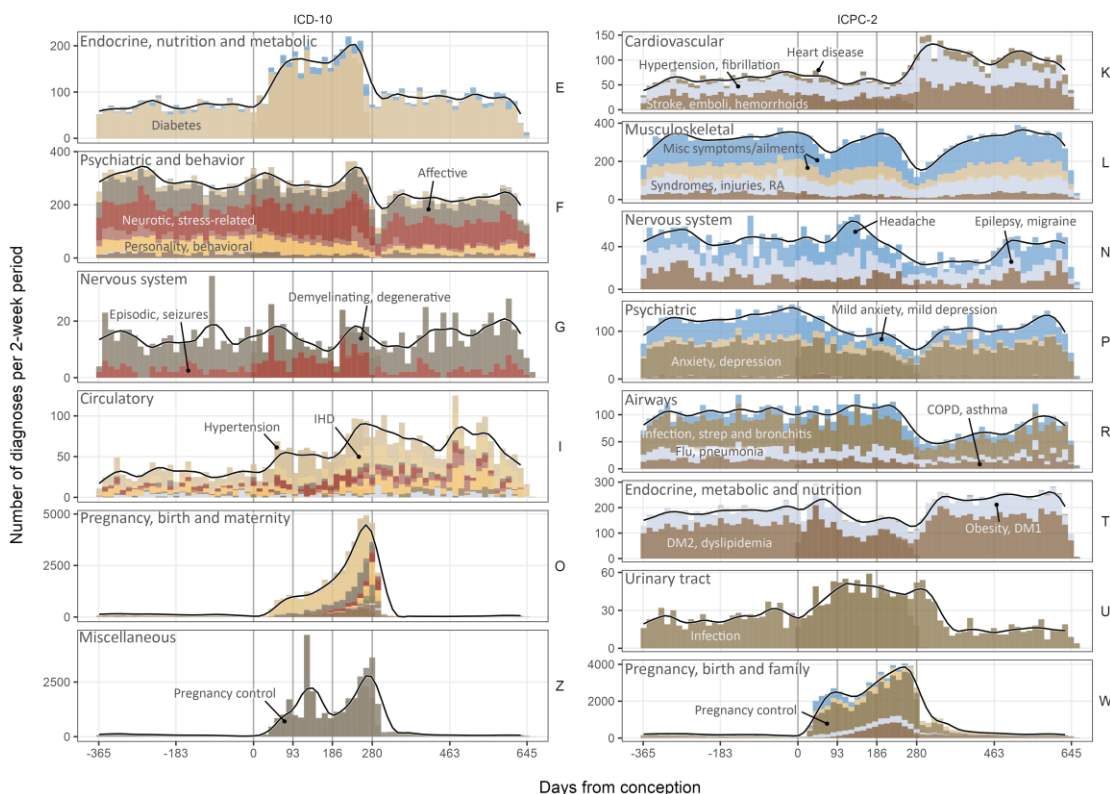


Figure 5. Pattern of the most common diagnoses given among LMA users one year before, during, and one year after pregnancy. The figure shows the number of diagnoses in 2-week bins for women using statins across pregnancy (those included in Figure 2, covering 2 439 pregnancies and 2 010 unique women), as well as a smoothed 2-month average (one month prior and the subsequent two weeks; local regressions were fit on 10 % of the data points along the line). The count for ICD-10 was based on either NPR or KUHR. The data was not restricted to first occurrence of a diagnosis; hence, each woman can be represented by the same diagnosis multiple times. The panels and colors correspond to the first and second level diagnosis codes, respectively. Some of the most notable second level diagnosis codes are annotated by keywords reflecting broad sets of diagnosis terms. The vertical lines represent key timepoints in relation to time of conception, including conception and trimester transitions.

ONLINE SUPPLEMENTARY MATERIAL

Use of statins and other lipid-modifying agents across pregnancy – a nationwide drug utilization study in Norway in 2005-2018

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Supplementary Results and Discussion

Main statin agents

From *one year before conception to one year postpartum*, of all dispensations for lipid-modifying agents, one third was simvastatin and one third was atorvastatin (data not shown). For simvastatin, 20 and 40 mg/d were most commonly prescribed, whereas for atorvastatin it was also common to prescribe both 80 mg/d and 10 mg/d. Rosuvastatin was often prescribed in lower doses, including 5 and 10 mg/d. Statins were most widely prescribed in packages of 98 or 100 tablets, thereby covering over three month periods, assuming one tablet per day. Rosuvastatin was also prescribed for shorter periods, such as one month. These results correspond well with use of statin agent and dose in clinical trials [1, 2]. Medium-intensity statins, particularly simvastatin, was the common choice previously; however, in recent years, high-intensity statins, particularly atorvastatin, has become more common (Figure 3). Rosuvastatin can also be considered high-intensity, even at low doses, since its LDL-C-lowering effect at 10-20 mg/d is approximately similar to atorvastatin at 40-80 mg/d [3]. Differences in solubility might also explain trends in popularity: while both simvastatin and atorvastatin are highly lipophilic statins, rosuvastatin is less lipophilic.

The different agents and doses for statin prescription fills were evenly spread out before, during and after pregnancy, and there was no sign that pregnancy induced a shift from one statin agent and dose to another (Figure S2).

Characteristics of LMA users

Non-statin LMA use

Non-statin LMA use across pregnancy varied with several maternal characteristics, including higher age (40 vs. 31 % above 32 years), more frequent use of folate prior to pregnancy (38 vs. 28 %), and more co-morbidities such as chronic hypertension (2.2 vs. 0.5 %) and diabetes mellitus (7.7 vs. 3.5 %) (Table S2). Women using omega-3 had particularly differing characteristics: compared with any non-statin LMA use, they had higher age (51 vs. 40 % above 32 years), had higher pre-pregnancy weight (74 vs. 68 kg), had experienced a previous pregnancy loss (32 vs. 24 %), had more frequent pre-pregnant folate use (41 vs. 38 %), and considerably more co-morbidities (30 vs. 13 % had any chronic illness). These results emphasize that women who use non-statin LMAs generally have poorer health status compared with women who do not use non-statin LMAs.

Discontinuation of statin use

Compared to women who used statins in pregnancy, women who discontinued their statin use earlier (that is, more than three months before conception, or zero to three months before conception) had several characteristics that could reflect *pregnancy planning* (Table S3). They were more often younger (46 and 44 % above 32 years for those discontinuing

more than three months before conception and zero to three months before conception, respectively, vs. 54 % above 32 years for those using statins in pregnancy), employed (84 and 83 % vs. 74 %), had experienced a previous pregnancy loss (29 and 22 % vs. 23 %), had more frequently used folate before pregnancy (37 and 33 % vs. 26 %), lower proportion of smokers (22 and 26 % vs. 26 %), and lower proportion of comorbidities, such as chronic hypertension (5.3 and 5.7 % vs. 10 %) and diabetes (18 and 15 % vs. 24 %). Interestingly, more women discontinued their statin use early for their second pregnancy (primiparous women) compared to other pregnancies (38 and 31 % vs. 30 %). This may possibly be explained by how aware women are they are pregnant, and that they are better informed in their second pregnancy.

Women who filled their first statin prescriptions *after* pregnancy appeared *more similar* to the continuers than the two discontinuer groups (Table S3). For example, they had a more similar age (51 % vs. 54 %), employment status (76 vs. 73 %), and proportion of pre-pregnant folate use (28 vs. 26 %). In drug safety analyses, one common approach to selection of comparator group is using those discontinuing their drug use [4, 5], but these data suggest that comparing continuers with those starting immediately following pregnancy may be viable alternative.

Note also that many women did not start up their statin use immediately after pregnancy. A prescription for a statin was filled within one year before conception but not within one year after delivery for 59 % of all pregnancies (52 % of all women) (data not shown). Pregnancy has therefore induced significant off-statin periods for many women, which has resulted in higher plasma cholesterol and most likely accelerated atherosclerosis.

History of statin use

Before pregnancy, a larger than expected number of women were long-term, experienced statin users (10-148 prescription fills), compared with intermediate-term users (4-9 prescription fills) and short-term users and beginners (1-3 prescription fills) (Figure S5). The drop in prescription fills the last three to six months before pregnancy occurred in all groups; also, all groups were represented as statin users in first trimester. After pregnancy, a larger than expected number of women were beginners. These data indicate that experienced statin users quit before pregnancy but then start up again rapidly, and that a proportion of women discover that they have elevated risk of ASCVD in pregnancy, possibly because of appropriate risk assessment, and then initiate statin therapy.

History of statin use prior to pregnancy also varied with many characteristics (Table S4). At time of conception, compared with short-term users and beginners, long-term, experienced statin users had higher proportion of employment (88 % vs. 81 %), nulliparity (50 vs. 38 %), folate use before pregnancy (40 vs. 32 %), and lower pre-pregnancy body weight (67 vs. 72 kg), lower proportion of smoking (15 vs. 29 %) and less chronic illness (23 vs. 27 %). Importantly, these results suggest that history of statin use may represent another sensitivity analysis in downstream drug safety analyses.

Dyslipidemia diagnoses and LMA use

Among 7 817 pregnancies (covering 5 531 unique women) where the woman was registered with a dyslipidemia diagnosis (ICPC-2 code T93 in KUHR) at any time before pregnancy until one year after delivery, in 1 801 pregnancies (22.7 %, covering 1 254 unique women), the woman used LMA within one year before conception and one year after delivery. Among pregnancies where a dyslipidemia diagnosis was identified, compared with non-LMA users, LMA users generally smoked more frequently (21 vs. 17 %), and had higher proportion of chronic hypertension (4.7 vs. 1.7 %) and diabetes (11 vs. 7.8 %) on top of their dyslipidemia (Table S5). These results suggest that a large proportion of young women with dyslipidemia remain untreated with statins, for unknown reasons. One possibility is that they prefer treatment with diet and lifestyle over medication use.

Indication for treatment with LMAs based on cardiovascular co-medication and diagnoses as a measure of co-morbidity

About 86 % of all LMA users had at least one indication for LMA (Figure S6), based on cardiovascular co-medication (drugs used in diabetes [ATC code A10], antithrombotic agents [B01], and cardiovascular system [C other than C10]) and relevant diagnoses (Table S1). A total of 953 pregnancies had exactly one unique LMA indication, whereas some pregnancies had up to 20 unique LMA indications. The number of unique LMA indications was related to the characteristics of the LMA users, and in general, the more indications, the more co-morbidity (Table S6). This was likely related to the higher age (53 vs. 39 above 32 years for 4-8 vs. zero indications for LMA therapy) and weight (78 vs. 64 kg). The number of LMA indications was also related to the established comorbidity index (26 vs. 3.4 % had a score of three or more). These data indicate that number of LMA indications (here defined as relevant co-medication and diagnoses) adequately capture information about disease severity related to use of statins and other LMAs.

Recurrent pregnancies and statin use

Pregnancy-related statin use in the first pregnancy preceded use of statins in a second, recurrent pregnancy (Figure S7). A total of 245 women (0.052 %) used statin in their first pregnancy. Compared to those who did not use statins in their first pregnancy, fewer women went on to become pregnant again (32.7 % vs. 51.4 %), which may be related to pregnancy complications and perceived risk. Among those who did become pregnant again, almost 1 in 5 used statins also in their second pregnancy. Despite these figures, the absolute number of women using statins in both first and second pregnancy was low, which is reassuring. Recurrent use may generally be of minor importance; still, it seems clear that women who used statins in pregnancy should be provided information regarding pharmacotherapy and pregnancy planning.

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Supplementary Tables

Table S1

Table S1. Overview of diagnosis codes used as indications for lipid-modifying agent (LMA) use, as per Table S6 and Figure S6.

System	Main group	Code	Disease
ICD-10	E Endocrine, nutritional, metabolic	E10	DM type I
ICD-10	E Endocrine, nutritional, metabolic	E11	DM type II
ICD-10	E Endocrine, nutritional, metabolic	E12	DM, undernutrition-based
ICD-10	E Endocrine, nutritional, metabolic	E13	DM, other
ICD-10	E Endocrine, nutritional, metabolic	E14	DM, unspecified
ICD-10	I Circulatory	I10	Essential (primary) hypertension
ICD-10	I Circulatory	I11	Hypertensive heart disease
ICD-10	I Circulatory	I12	Hypertensive kidney disease
ICD-10	I Circulatory	I13	Hypertensive heart-kidney disease
ICD-10	I Circulatory	I15	Secondary hypertension
ICD-10	I Circulatory	I20	Angina pectoris
ICD-10	I Circulatory	I21	Acute myocardial infarction
ICD-10	I Circulatory	I25	Chronic IHD
ICD-10	I Circulatory	I26	Lung embolus
ICD-10	I Circulatory	I47	Paroxysmal tachycardia
ICD-10	I Circulatory	I49	Heart arrhythmia
ICD-10	I Circulatory	I50	Heart failure
ICD-10	I Circulatory	I60	Subarachnoidal bleeding
ICD-10	I Circulatory	I61	Brain bleeding
ICD-10	I Circulatory	I63	Stroke
ICD-10	I Circulatory	I65	Stroke or bleeding, other
ICD-10	I Circulatory	I67	Brain disease, other
ICD-10	I Circulatory	I69	Disease caused by brain disease
ICD-10	I Circulatory	I70	Atherosclerosis
ICD-10	I Circulatory	I72	Aneurism/dissection, other
ICD-10	I Circulatory	I73	Peripheral vessel disease, other
ICD-10	I Circulatory	I74	Arterial embolus/thrombus
ICD-10	I Circulatory	I82	Venous embolus/thrombus
ICPC-2	K Cardiovascular	K74	IHD with angina pectoris
ICPC-2	K Cardiovascular	K75	Acute MI
ICPC-2	K Cardiovascular	K76	Chronic IHD
ICPC-2	K Cardiovascular	K77	Heart failure
ICPC-2	K Cardiovascular	K80	Arrhythmia
ICPC-2	K Cardiovascular	K81	Murmur
ICPC-2	K Cardiovascular	K84	Heart disease
ICPC-2	K Cardiovascular	K85	Hypertension
ICPC-2	K Cardiovascular	K86	Hypertension

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ICPC-2	K Cardiovascular	K89	TIA
ICPC-2	K Cardiovascular	K90	Stroke
ICPC-2	K Cardiovascular	K91	Cerebrovascular disease
ICPC-2	K Cardiovascular	K92	Atherosclerosis
ICPC-2	K Cardiovascular	K93	Lung embolus
ICPC-2	K Cardiovascular	K99	CVD
ICPC-2	T Endocrine, metabolic, nutritional	T82	Obesity
ICPC-2	T Endocrine, metabolic, nutritional	T83	Overweight
ICPC-2	T Endocrine, metabolic, nutritional	T86	Hypothyreosis
ICPC-2	T Endocrine, metabolic, nutritional	T89	DM type I
ICPC-2	T Endocrine, metabolic, nutritional	T90	DM type II
ICPC-2	T Endocrine, metabolic, nutritional	T93	Hyperlipidemia (incl. FH)
ICPC-2	T Endocrine, metabolic, nutritional	T99	Endocrine/metabolic/nutritional disease

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; ICD-10, the International Classification of Diseases, version 10; ICPC-2, the International Classification of Primary Care-2; IHD, ischemic heart disease; MI, myocardial infarction; TIA, transient ischemic attack.

Table S2

Table S2. Characteristics of the 822 071 pregnancies in 2005-2018, stratified by non-statin lipid-modifying agent (LMA) use between one year before conception and one year after delivery (covering 599 pregnancies and 519 unique women).

	n	No non-statin LMA use	Any non- statin LMA use	Specific non-statin LMA use		
		n = 821 472	n = 599	Ezetimibe, n = 230	Bile acid sequestrants, n = 311	Omega-3, n = 73
Age	822 071					
< 28 yrs		322 639 (39)	195 (33)	86 (37)	98 (32)	18 (25)
28 - 32 yrs		240 746 (29)	162 (27)	62 (27)	84 (27)	18 (25)
> 32 yrs		258 087 (31)	242 (40)	82 (36)	129 (41)	37 (51)
Employed, yes	656 916	531 345 (81)	397 (81)	177 (87)	196 (78)	37 (76)
Civil status	822 071					
Registered partner/cohabitant		762 311 (93)	554 (92)	217 (94)	282 (91)	69 (95)
Other		59 161 (7.2)	45 (7.5)	13 (5.7)	29 (9.3)	4 (5.5)
Parity	822 071					
Nulliparous		346 899 (42)	274 (46)	102 (44)	145 (47)	33 (45)
Primiparous		297 827 (36)	207 (35)	85 (37)	103 (33)	25 (34)
Multiparous		176 746 (22)	118 (20)	43 (19)	63 (20)	15 (21)
Previous pregnancy loss, yes	771 869	182 785 (24)	133 (24)	44 (20)	68 (24)	22 (32)
Weight (pre-pregnancy), kg	422 081	65 (58-75)	68 (59-80)	67 (58-76)	70 (60-84)	74 (60-86)
Folate use (pre-pregnancy), yes	822 071	233 431 (28)	227 (38)	83 (36)	117 (38)	30 (41)
Smoking, yes	552 527	107 568 (19)	87 (20)	25 (14)	55 (24)	7 (16)
Obstetric comorbidity index	822 071					
0		540 618 (66)	328 (55)	143 (62)	171 (55)	26 (36)
1		185 144 (23)	171 (29)	54 (23)	94 (30)	26 (36)
2		66 358 (8.1)	51 (8.5)	16 (7.0)	26 (8.4)	8 (11)

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3 or more		29 352 (3.6)	49 (8.2)	17 (7.4)	20 (6.4)	13 (18)
Chronic illness, yes	822 071	55 497 (6.8)	80 (13)	24 (10)	35 (11)	22 (30)
Chronic hypertension, yes	822 071	4 431 (0.5)	13 (2.2)	5 (2.2)	4 (1.3)	4 (5.5)
Any diabetes mellitus, yes	822 071	29 109 (3.5)	46 (7.7)	17 (7.4)	15 (4.8)	15 (21)

n (%); Median (25%-75%).

Other non-statin LMAs were omitted because of low numbers (a total of n = 9 pregnancies).

Table S3

Table S3. Characteristics of 3 565 pregnancies (covering 2 608 unique women) in 2005-2018 where a statin prescription had been filled at any time before pregnancy until one year after delivery, stratified by discontinuation classification.

	n	Discontinuation ≥ 3 months before conception, n = 2 045	Discontinuation 0-3 months before conception, n = 566	Statin use in pregnancy, n = 331	Statin use initiated after pregnancy, n = 623
Age	3 565				
< 28 yrs		517 (25)	155 (27)	72 (22)	163 (26)
28 - 32 yrs		581 (28)	161 (28)	80 (24)	140 (22)
> 32 yrs		947 (46)	250 (44)	179 (54)	320 (51)
Employed, yes	2 861	1 397 (84)	389 (83)	196 (73)	353 (76)
Civil status	3 565				
Registered partner/cohabitant		1 872 (92)	522 (92)	294 (89)	559 (90)
Other		173 (8.5)	44 (7.8)	37 (11)	64 (10)
Parity	3 565				
Nulliparous		824 (40)	251 (44)	144 (44)	206 (33)
Primiparous		783 (38)	178 (31)	98 (30)	230 (37)
Multiparous		438 (21)	137 (24)	89 (27)	187 (30)
Previous pregnancy loss, yes	3 369	564 (29)	120 (22)	73 (23)	172 (29)
Weight (pre-pregnancy), kg	2 189	70 (61-82)	70 (62-85)	72 (61-85)	73 (62-85)
Folate use (pre-pregnancy), yes	3 565	755 (37)	188 (33)	87 (26)	176 (28)
Smoking, yes	2 675	346 (22)	110 (26)	65 (26)	115 (29)
Obstetric comorbidity index	3 565				
0		895 (44)	265 (47)	128 (39)	224 (36)
1		582 (28)	154 (27)	86 (26)	166 (27)
2		313 (15)	76 (13)	60 (18)	130 (21)
3 or more		255 (12)	71 (13)	57 (17)	103 (17)

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Chronic illness, yes	3 565	505 (25)	117 (21)	109 (33)	156 (25)
Chronic hypertension, yes	3 565	109 (5.3)	32 (5.7)	34 (10)	42 (6.7)
Any diabetes mellitus, yes	3 565	377 (18)	86 (15)	80 (24)	112 (18)
<hr/>					
n (%); Median (25%-75%)					

Table S4

Table S4. Characteristics of 2 890 pregnancies (covering 2 089 unique women) in 2005-2018 where a statin prescription had been filled at any time before pregnancy until conception, stratified by history of statin use at time of the last prescription fill before conception.

	n	1-3 prescription fills, n = 1 370	4-9 prescription fills, n = 781	10-148 prescription fills, n = 739
Year of delivery	2 890			
2005 - 2009		307 (22)	171 (22)	47 (6.4)
2010 - 2014		580 (42)	335 (43)	325 (44)
2015 - 2018		483 (35)	275 (35)	367 (50)
Age	2 890			
< 28 yrs		353 (26)	207 (27)	171 (23)
28 - 32 yrs		359 (26)	223 (29)	226 (31)
> 32 yrs		658 (48)	351 (45)	342 (46)
Employed, yes	2 356	888 (81)	524 (82)	546 (88)
Civil status	2 890			
Registered partner/cohabitant		1 231 (90)	729 (93)	679 (92)
Other		139 (10)	52 (6.7)	60 (8.1)
Parity	2 890			
Nulliparous		515 (38)	322 (41)	366 (50)
Primiparous		504 (37)	295 (38)	245 (33)
Multiparous		351 (26)	164 (21)	128 (17)
Previous pregnancy loss, yes	2 739	370 (29)	204 (27)	165 (23)
Weight (pre-pregnancy), kg	1 874	72 (62-84)	70 (62-82)	67 (60-80)
Folate use (pre-pregnancy), yes	2 890	435 (32)	283 (36)	296 (40)
Smoking, yes	2 237	296 (29)	122 (21)	94 (15)

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Obstetric comorbidity index	2 890			
0		558 (41)	358 (46)	351 (47)
1		388 (28)	206 (26)	212 (29)
2		230 (17)	121 (15)	88 (12)
3 or more		194 (14)	96 (12)	88 (12)
Chronic illness, yes	2 890	369 (27)	177 (23)	169 (23)
Chronic hypertension, yes	2 890	82 (6.0)	45 (5.8)	43 (5.8)
Any diabetes mellitus, yes	2 890	274 (20)	138 (18)	118 (16)

n (%); Median (25%-75%)

Table S5

Table S5. Characteristics of 7 817 pregnancies (covering 5 531 unique women) in 2005-2018 where a diagnosis of dyslipidemia (ICPC-2 code T93) was recorded at any time before pregnancy until one year after delivery, stratified by any lipid-modifying agent (LMA) use (both statin and non-statin agents) between one year before pregnancy and one year after delivery.

	n	Dyslipidemia, but no LMA use across pregnancy, n = 6 016	Dyslipidemia and LMA use across pregnancy, n = 1 801
Age	7 817		
< 28 yrs		1 681 (28)	541 (30)
28 - 32 yrs		1 824 (30)	519 (29)
> 32 yrs		2 511 (42)	741 (41)
Employed, yes	6 420	4 247 (86)	1 248 (84)
Civil status	7 817		
Registered partner/cohabitant		5 641 (94)	1 663 (92)
Other		375 (6.2)	138 (7.7)
Parity	7 817		
Nulliparous		2 429 (40)	724 (40)
Primiparous		2 296 (38)	666 (37)
Multiparous		1 291 (21)	411 (23)
Previous pregnancy loss, yes	7 455	1 502 (26)	441 (26)
Weight (pre-pregnancy), kg	5 070	69 (61-81)	69 (61-82)
Folate use (pre-pregnancy), yes	7 817	2 228 (37)	617 (34)
Smoking, yes	5 969	765 (17)	293 (21)
Obstetric comorbidity index	7 817		
0		3 237 (54)	944 (52)
1		1 651 (27)	480 (27)

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2		728 (12)	217 (12)
3 or more		400 (6.6)	160 (8.9)
Chronic illness, yes	7 817	609 (10)	278 (15)
Chronic hypertension, yes	7 817	100 (1.7)	85 (4.7)
Any diabetes mellitus, yes	7 817	467 (7.8)	207 (11)
<hr/>			
n (%); Median (25%-75%)			

Table S6

Table S6. Characteristics of 2 772 pregnancies (covering 2 304 unique women) in 2005-2018 where a lipid-modifying agent (LMA) prescription had been filled between one year before pregnancy until one year after delivery, stratified by the number of unique drug and diagnosis indications for LMA therapy.

	n	Number of indications for LMA therapy				
		0 n = 384	1 n = 953	2 - 3 n = 664	4 - 8 n = 619	≥ 9 n = 152
Age	2 772					
< 28 yrs		112 (29)	314 (33)	179 (27)	143 (23)	15 (9.9)
28 - 32 yrs		124 (32)	266 (28)	166 (25)	145 (23)	32 (21)
> 32 yrs		148 (39)	373 (39)	319 (48)	331 (53)	105 (69)
Employed, yes	2 211	241 (82)	662 (85)	445 (82)	355 (73)	79 (71)
Civil status	2 772					
Registered partner/cohabitant		354 (92)	883 (93)	607 (91)	550 (89)	129 (85)
Other		30 (7.8)	70 (7.3)	57 (8.6)	69 (11)	23 (15)
Parity	2 772					
Nulliparous		181 (47)	404 (42)	265 (40)	246 (40)	56 (37)
Primiparous		126 (33)	345 (36)	214 (32)	202 (33)	53 (35)
Multiparous		77 (20)	204 (21)	185 (28)	171 (28)	43 (28)
Previous pregnancy loss, yes	2 612	79 (23)	201 (22)	158 (26)	191 (32)	51 (36)
Weight (pre-pregnancy), kg	1 558	64 (58-75)	66 (58-76)	71 (62-85)	78 (63-93)	84 (72-97)
Folate use (pre-pregnancy), yes	2 772	150 (39)	317 (33)	232 (35)	192 (31)	46 (30)
Smoking, yes	2 027	60 (28)	152 (21)	128 (25)	128 (28)	32 (26)
Obstetric comorbidity index	2 772					
0		239 (62)	597 (63)	288 (43)	103 (17)	8 (5.3)
1		109 (28)	231 (24)	207 (31)	193 (31)	23 (15)
2		23 (6.0)	87 (9.1)	93 (14)	159 (26)	45 (30)
3 or more		13 (3.4)	38 (4.0)	76 (11)	164 (26)	76 (50)

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Chronic illness, yes	2 772	26 (6.8)	61 (6.4)	103 (16)	338 (55)	109 (72)
Chronic hypertension, yes	2 772	0 (0)	4 (0.4)	16 (2.4)	84 (14)	60 (39)
Any diabetes mellitus, yes	2 772	3 (0.8)	28 (2.9)	78 (12)	256 (41)	89 (59)
<hr/>						
n (%); Median (25%-75%)						

Supplementary Figures

Figure S1

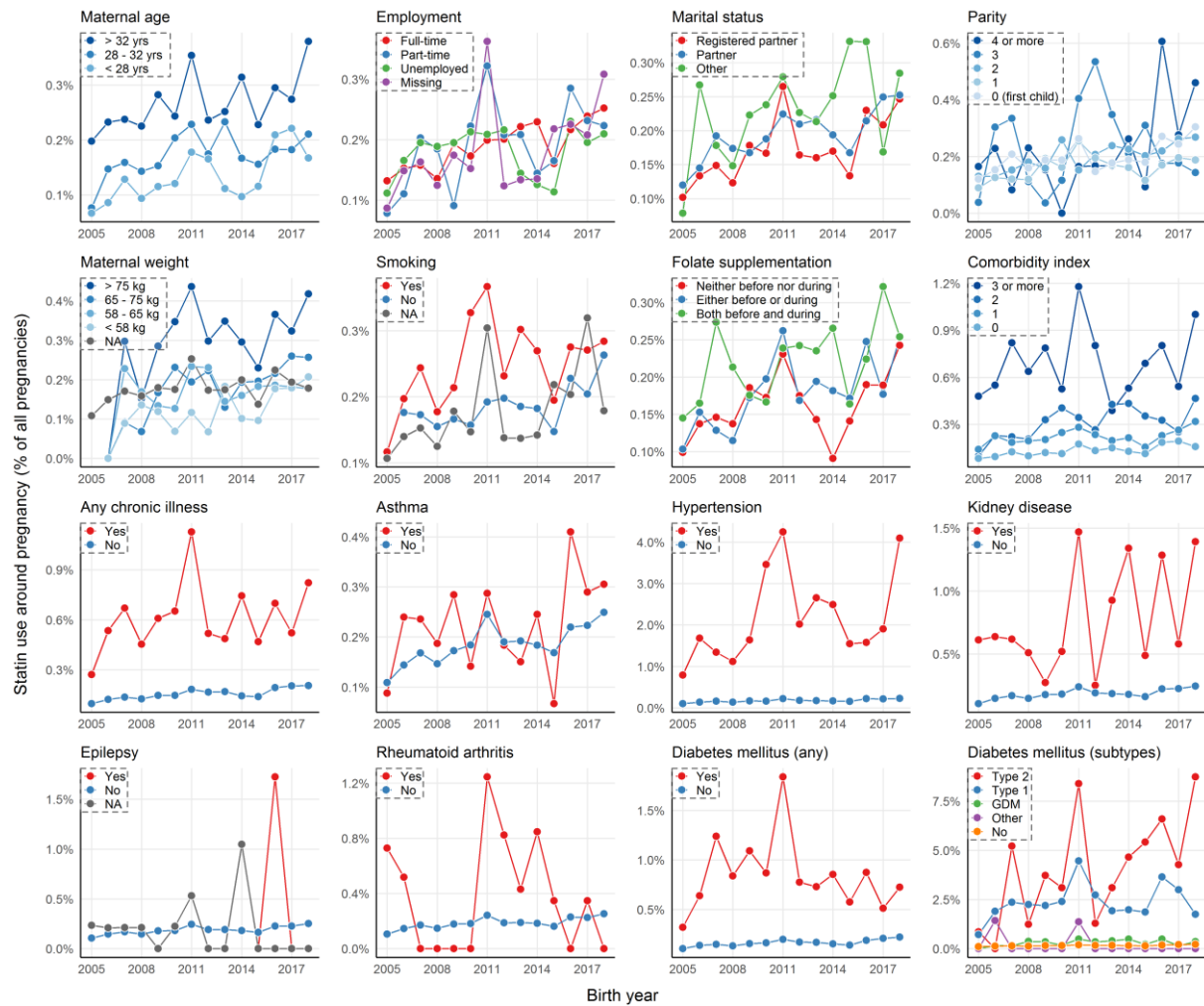


Figure S1. Temporal trends in use of LMAs around pregnancy, stratified by maternal characteristics. The figure contains data on those that filled a prescription for a lipid-modifying agent (LMA) within three months prior to pregnancy or during the entirety of pregnancy (any trimester) in Norway in 2005 to 2018. Maternal characteristics were taken from The Medical Birth Registry of Norway (MBRN).

Figure S2

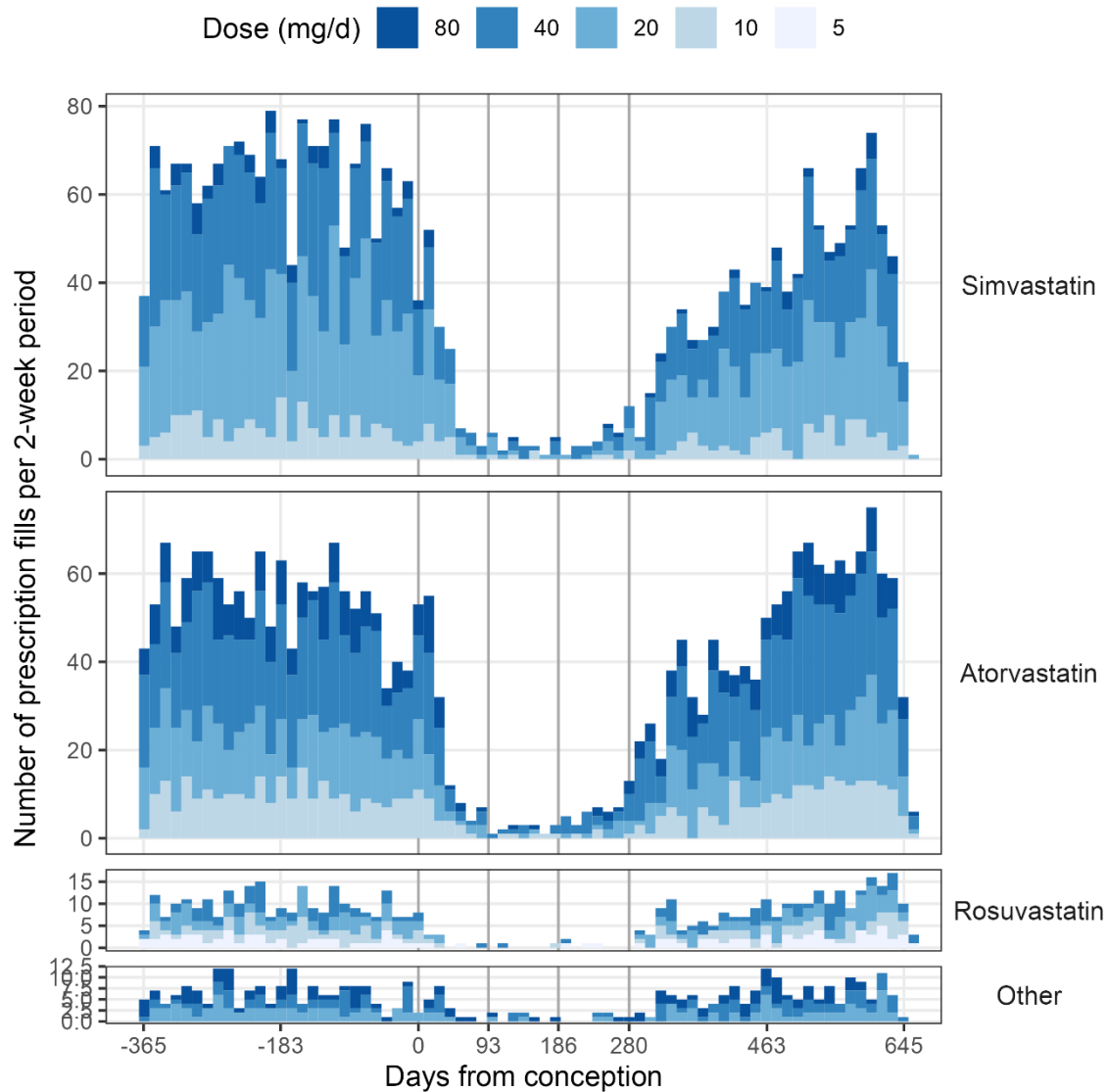


Figure S2. Pattern of statin use one year before, during, and one year after pregnancy: variation in dose. The figure shows 6 703 prescription fills for all women in Norway that were pregnant in the period 2005 to 2018 and that filled a prescription for a statin (ATC groups C10AA and C10B) between one year before conception and one year after delivery (2 439 pregnancies, 2 010 unique women). Data are shown in 2-week bins, stratified by statin agent, and colored by statin dose. The vertical lines represent key timepoints in relation to time of conception, including conception and trimester transitions.

Figure S3

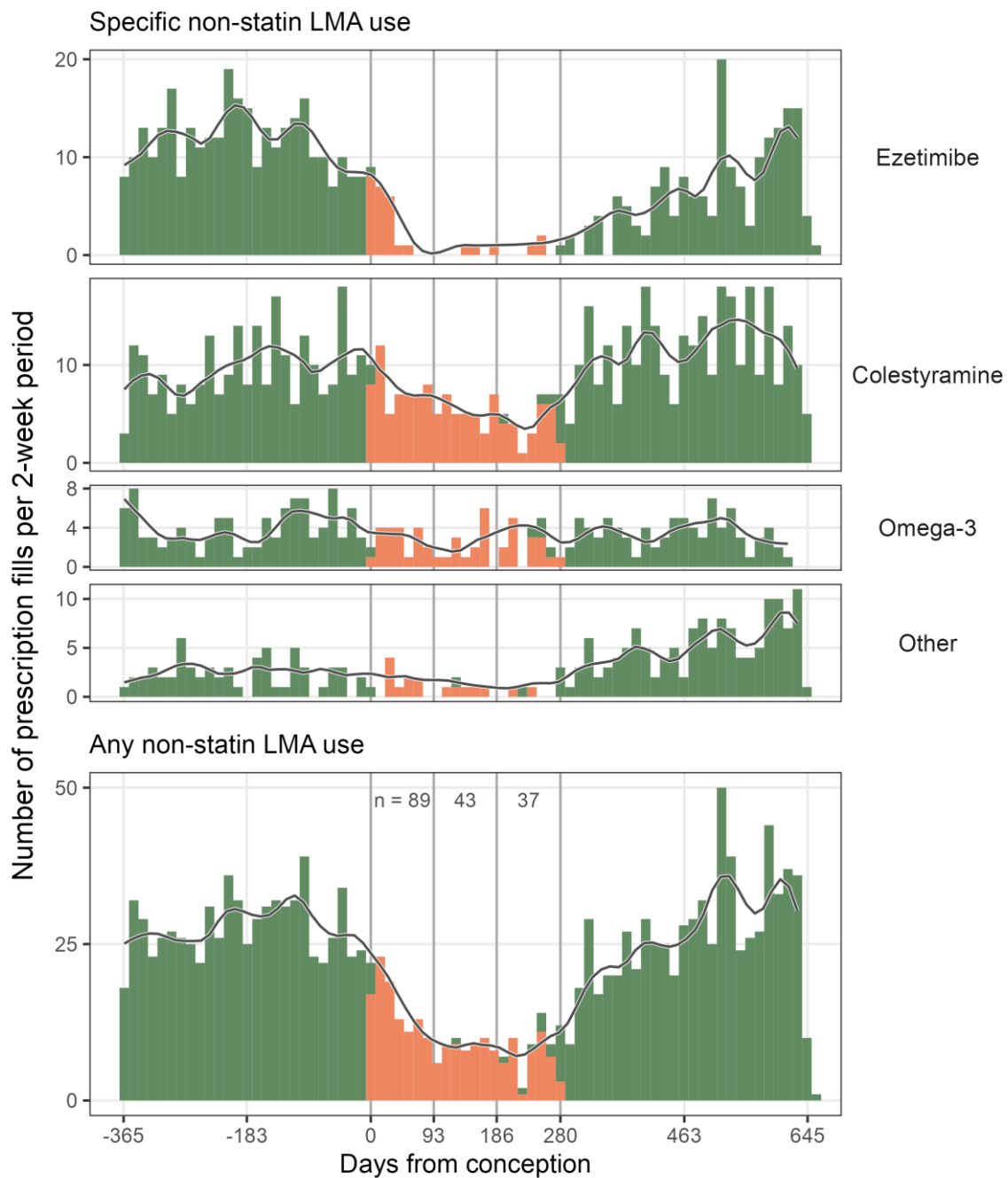


Figure S3. Pattern of prescription fills for non-statin LMAs, one year before, during, and one year after pregnancy. The figure shows 1 689 prescription fills for all women in Norway that were pregnant in the period 2005 to 2018 and that filled a prescription for a non-statin LMA (ATC group C10 except C10AA and C10B) between one year before conception and one year after delivery (610 pregnancies, 526 unique women). The figure shows the number of prescriptions fills of non-statin LMAs in 2-week bins, as well as a smoothed 2-month average (one month prior and the subsequent two weeks; local regressions were fit on 10 % of the data points along the line). Green and red color represents prescription fill of a non-statin LMA *outside* or *within* any trimester of pregnancy, respectively. Numbers between the vertical lines in the upper part of the lowest panel represent the number of unique

pregnancies where a statin prescription had been filled inside pregnancy, per trimester. The vertical lines represent key timepoints in relation to time of conception, including conception and trimester transitions.

Figure S4

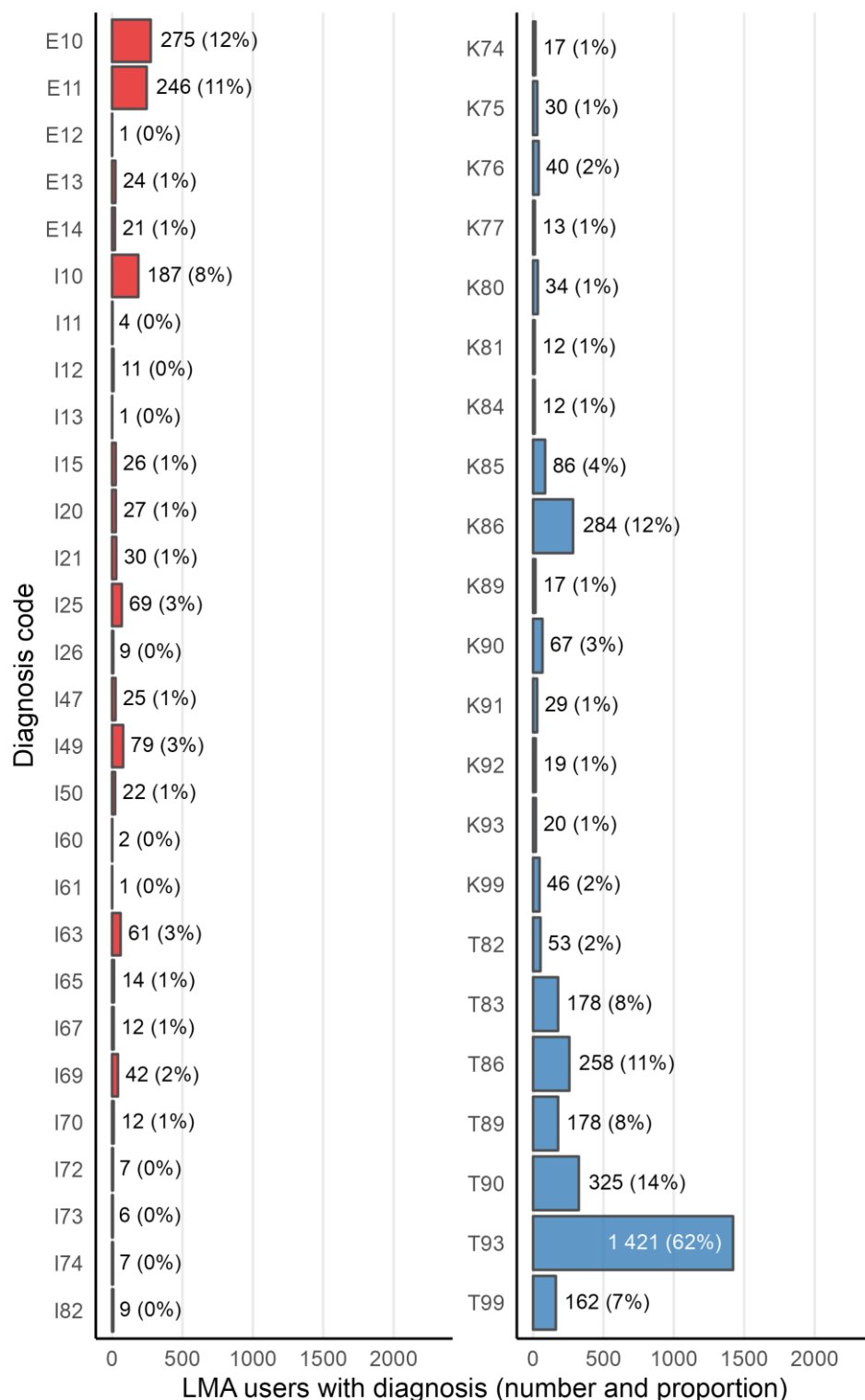


Figure S4. Presence of relevant diagnoses among pregnancies where a prescription for an LMA had been filled. The figure shows the number of pregnancies where a prescription for any LMA had been filled between one year before and one year after pregnancy, and where the woman had a diagnosis pertinent to LMA use at any timepoint before one year after delivery. Red is ICD-10 codes (either NPR or KUHR), and blue is ICPC-2 codes (KUHR only).

The diagnosis groups are in alphabetical order. The x axis has been scaled to the total number of unique pregnancies (n = 2 439), and the percentages reflect the proportion of all unique pregnancies where the particular diagnosis was identified. Diagnosis codes are annotated in Table S1; also, see <https://finnkode.ehelse.no/> for more information about the codes (website in Norwegian). Abbreviations: ICD-10, The International Classification of Diseases, version 10; ICPC-2, The International Classification of Primary Care-2; KUHR, The Norway Control and Payment of Health Reimbursement Database; LMA, lipid-modifying agents; NPR, The Norwegian Patient Registry.

Figure S5

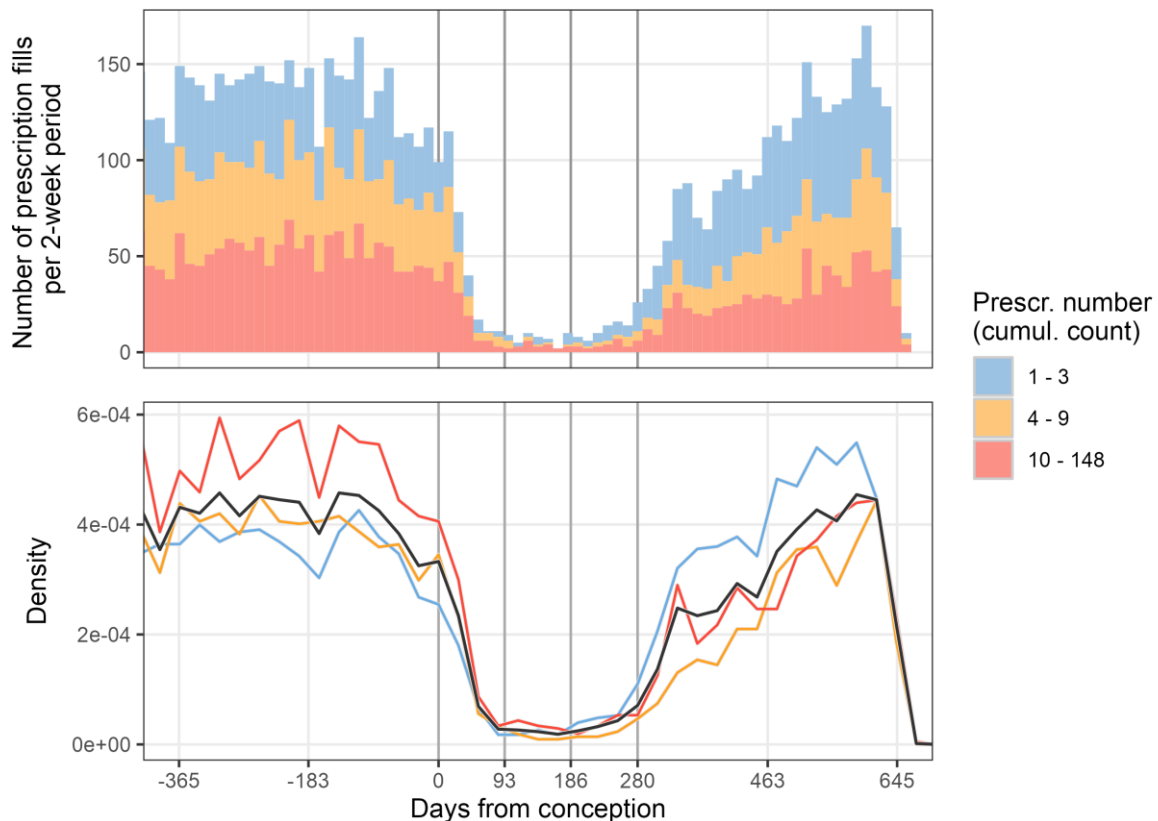


Figure S5. Pattern of history of statin use one year before, during, and one year after pregnancy, stratified by history of statin use at a given point in time. The figure shows history of statin use across pregnancy; history of statin use was calculated as the chronological, rolling count of prescription fills per woman and pregnancy. We determined the ranges by binning the number of prescriptions into three groups of approximately equal number of observations. The histogram shows 2-week bins, and the frequency polygons shows 1-month bins. While the colors denote groups of prescription fill numbers (per woman and pregnancy), the black line represents the average ("expected") numbers. The numbers for the frequency polygons are on *density* scale, the values of which are uninterpretable; interpret the colored groups *in relation to the black line*. The vertical lines represent key timepoints in relation to time of conception, including conception and trimester transitions. Note that this figure shows the *running* history of statin use, while Table S4 shows the last history of statin use before conception.

Figure S6

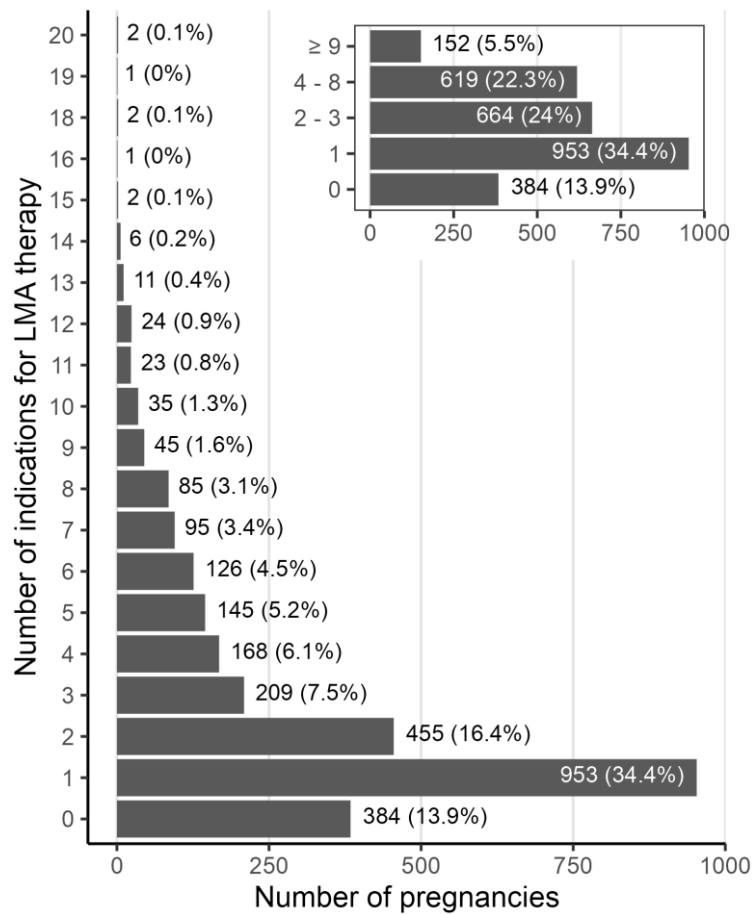


Figure S6. *Co-medication and diagnoses as indications for LMA use.* The figure shows the number of unique indications for LMA use per woman and pregnancy. Indications were defined as the sum of drugs used in diabetes (ATC code A10), antithrombotic agents (B01), and cardiovascular system (C other than C10), and all diagnosis codes defined in Table S1, per woman and pregnancy. The inset is a binned representative of the main panel, which show the actual values. Abbreviations: ATC, The World Health Organization's Anatomical Therapeutic Chemical Classification System; LMA, lipid-modifying agents.

Figure S7

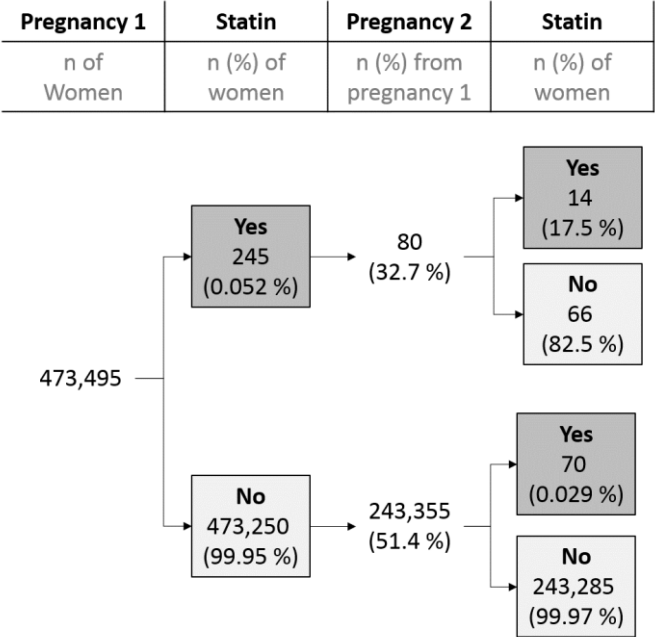


Figure S7. *Statin use in a recurrent pregnancy.* The figure shows statin prescription fills in a given pregnancy, split by pregnancy order and statin prescription fills. Only the first two pregnancies are shown due to low counts in subsequent pregnancies.