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Characterization of Statin Low-density Lipoprotein Cholesterol Dose-response Utilizing Electronic Health Records in a Large Population-based Cohort

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Abstract

Background: Low-density lipoprotein cholesterol (LDL-C) response to statin therapy has not been fully elucidated in real-world populations. The primary objective of this study was to characterize statin LDL-C dose-response and its heritability in a large, multi-ethnic population of statin users.

Methods: We determined the effect of statin dosing on lipid measures utilizing electronic health records (EHRs) in 33,139 statin users from the Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. The relationship between statin defined daily dose (DDD) and lipid parameter response (percent change) was determined.

Results: DDD and LDL-C response were associated in a log-linear relationship ($\beta = -6.17$, standard error [SE] = 0.09, $P < 10^{-300}$) which remained significant after adjusting for pre-specified covariates (adjusted $\beta = -5.59$, SE = 0.12, $P < 10^{-300}$). Statin type, sex, age, smoking status, diabetes, and East Asian race/ethnicity were significant independent predictors of statin-induced changes in LDL-C. Based on a variance-component method within the subset of statin users who had at least one first-degree relative who was also a statin user (N = 1,036), heritability of statin LDL-C response was estimated at 11.7% (SE = 8.6%, P = 0.087).

Conclusions: Using EHR data, we observed a statin LDL-C dose response consistent with the "rule of 6%" from prior clinical trial data. Clinical and demographic predictors of statin LDL-C response exhibited highly significant, but modest effects. Finally, statin-induced changes in LDL-

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C were not found to be strongly inherited. Ultimately, these findings demonstrate (1) the utility of EHRs as a reliable source to generate robust phenotypes for pharmacogenomic research and (2) the potential role of statin precision medicine in lipid management.

Keywords

pharmacogenetics cholesterol; drug-response phenotype; real-world population; pharmacogenomics; Lipids and Cholesterol; Pharmacology

INTRODUCTION

The prevalence of statin use in the United States has increased to over 35 million patients [1]. Expanded use is a result of extensive evidence suggesting that statin-induced low-density lipoprotein cholesterol (LDL-C) lowering reduces morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD). Lowering LDL-C by even a relatively small magnitude with statin therapy improves outcomes; for example, a statin-induced lowering of LDL-C by only 10 mg/dl is estimated to reduce the risk of major ASCVD events by 5–6% [2]. Furthermore, it has been shown that more intensive LDL-C lowering with statin therapy leads to improved outcomes compared to less intensive therapy, irrespective of pretreatment LDL-C levels [2]. Collectively, these findings demonstrate that statin-induced LDL-C lowering has a major impact on patient outcomes.

Individual LDL-C response to statin therapy can vary substantially. For example, multiple clinical and demographic variables are predictors of LDL-C response [3]. Moreover, it has been observed that genetic polymorphisms play a role in this variation. Although a few genome-wide association studies (GWAS) have identified genetic loci that predict LDL-C response to statin therapy, these studies have small sample size or pool heterogeneous population sources [4–7], thereby having limited statistical power. As a consequence, the genetic basis of low-density lipoprotein cholesterol (LDL-C) response to statin therapy has not been fully elucidated.

In addition, the aforementioned GWAS results were all generated, at least in part, from the data of large randomized controlled trials (RCTs) [8], which may not be representative of what occurs in real-world clinical practice. Fundamental RCT design features such as inclusion/exclusion criteria and the pre-randomization run-in phase select for only subsets of the statin user population [9]. In some large statin RCTs, for example, as many as 30–40% of study participants entering the run-in phase were excluded from randomization into the trial [10, 11]. Furthermore, women, non-White/European race/ethnicity groups, the elderly, and other subpopulations are not adequately represented in the majority of statin trials [8, 12].

Electronic health records (EHRs) have recently been linked to biobank data [13–15], allowing for the completion of GWAS from large cohorts without the need to combine various data sources, which is what has been done to boost the sample size of GWAS results from RCTs. Furthermore, EHR data directly represent clinical practice; results are more generalizable compared to RCTs. Previous work in the past 5–10 years has already validated the utility of EHRs in generating accurate phenotypes of disease status [16–19] and drug response [20–22] by replicating previously discovered genetic associations. It has been predicted that EHR-linked

biobank data will play an important role in the future of cardiovascular precision medicine including discovery of novel genomic markers as well as the implementation of these findings in clinical practice [23].

Thus, we here demonstrate that by leveraging unique features of EHRs, it is possible to generate robust dose-response phenotypes and their correlates that are suitable for pharmacogenetic and pharmcoepidemiologic studies. The primary objective of this study was to characterize statin LDL-C dose-response in a multi-ethnic population of real-world statin users and to estimate heritability of statin LDL-C response as the proportion of phenotypic variation explained by the genome.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. Participants gave informed consent and the study was approved by the Kaiser Foundation Research Institute Institutional Review Board (IRB). The methods are available as supplemental data.

RESULTS

Demographic and clinical characteristics

A total of 33,139 study participants met the criteria for inclusion (Figure 1). Participants were 53% women, had a median age of 64 years at statin initiation (interquartile range [IQR] = 57 to 71), and had a median pretreatment LDL-C of 154 mg/dL (IQR = 130 to 176 mg/dL). These demographics are consistent with previous reports describing statin users [22, 24]. The majority of participants were initiated on lovastatin (63%) or simvastatin (32%) therapy. To account for differences in potency among statin types, we generated a defined daily dose (DDD) value for each type such that 1.0 DDD was equal to 40 mg of lovastatin daily (Supplemental Table 1). The frequency of each statin type varied across DDD (Supplemental Figure 1). Demographic and clinical characteristics are reported in Tables 1 and 2.

Statin LDL-C response

We found that pretreatment and on-treatment LDL-C levels were measured at a median of 20 days (IQR = 8 to 84 days) before and 85 days (IQR = 54 to 178 days) after statin initiation, respectively. On-treatment lipid panels had to have been within a pre-defined window of statin initiation (Supplemental Figure 2).The median on-treatment LDL-C (unadjusted) was 100 mg/dL (81 to 121 mg/dL), corresponding to a median response of −34.1% (IQR = −43.8 to −23.1%) or an absolute change of −51 mg/dl (IQR = −32 to −70 mg/dL).

LDL-C dose-response was found to show a log-linear relationship overall ($\beta = -6.17$, standard error [SE] = 0.09, $P < 10^{-300}$), which remained highly significant after adjustment for pre-specified covariates (adjusted $\beta = -5.59$, SE = 0.12, $P < 10^{-300}$, Table 3, Figure 2). Dose-response slope (i.e., β) was similar for each statin type; the association between DDD and statin LDL-C response remained significant within each statin type stratum (Figure 3).

Dose-response was also similar within each race/ethnicity group (Supplemental Figure 3). Additionally, we observed significant statin LDL-C dose responses within statin-type strata (lovastatin and simvastatin) by sex and race/ethnicity. These data are presented in Supplemental Tables 2 and 3.

Predictors of statin-induced LDL-C changes

Beyond dose-response, multiple covariates were associated with LDL-C response to statin therapy (Table 3). Statin type was a strong predictor of response independent of dose (DDD) and other covariates (Figure 3, Table 3). In particular, simvastatin users had a greater percent reduction in LDL-C response to statin therapy for the same DDD compared to reference lovastatin users ($\beta = -2.14$, SE = 0.244, $P = 1.8*10^{-18}$) while pravastatin users had an attenuated LDL-C response to statin therapy compared to reference lovastatin users ($\beta = 5.47$, SE = 0.707, $P = 9.9*10^{-15}$). In contrast, atorvastatin users did not have a significantly different response for the same DDD compared to lovastatin users after adjusting for covariates (P = 0.210). Women had a greater statin LDL-C response than men after correction for confounding variables ($\beta = -0.89$, SE = 0.18, $P = 1.3*10^{-6}$). Age was also found to be a significant predictor of statin LDL-C response ($\beta = -0.09$, SE = 0.01, $P = 5.8*10^{-21}$) independent of DDD and pre-specified covariates. In contrast to Black/Africans and Hispanic/Latinos, East Asians had a greater percent reduction in LDL-C response to statin therapy compared to reference White/European participants ($\beta = -0.83$, SE = 0.37, P = 0.027, Supplemental Figure 3). Smoking and diabetes were each significantly associated with attenuated LDL-C response to statins ($\beta = 0.96$, SE = 0.19, $P = 2.5*10^{-7}$ and $\beta = 0.96$, SE = 0.24, $P = 8.3*10^{-5}$, respectively). Finally, neither hypertension (P = 0.954) nor body mass index (BMI; P = 0.444) were significant predictors of statin LDL-C response in multivariate analyses. Overall, 13% of the total variance was explained by dose and the pre-specified covariates added to the model. As expected, statin dose and type were the strongest contributors (>12%).

Revised dose equivalency table

Based on the discrepancies between our observed relative potencies among statin type and those anticipated from the Food and Drug Administration (FDA) dose equivalency table (involving statin types with adjusted statin response values significantly different from lovastatin reference: simvastatin and pravastatin), we generated a new table with revised DDD designations (Supplemental Table 4). A repeat linear regression analysis using the new DDD designations substantially weakened the association between pravastatin and simvastatin each with statin LDL-C response from lovastatin reference (Supplemental Table 5). The new DDD designations did not have any impact on the association between other covariates and response (Supplemental Table 5).

Heritability and familial phenotypic correlations

Among the 33,139 statin users, we identified 1,036 individuals who had at least one first-degree relative who was also a statin user. A parent-offspring correlation (N = 229 pairs) of statin LDL-C response was 0.060 (SE = 0.067, P = 0.365); a sibling correlation (N = 296 sib pairs) was 0.054 (SE = 0.059, P = 0.357). The heritability estimate derived from all first-

degree relatives was 0.117 (SE = 0.086, P = 0.087), which was below the threshold of statistical significance.

Statin-induced changes in triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C) levels

Statin therapy resulted in a median TG response of −14.3% (IQR = −31.1 to 6.7%) and demonstrated a significant log-linear association with DDD, similar to statin LDL-C dose-response (Figure 4A). Specifically, increasing statin dose was correlated with enhanced TG lowering ($\beta = -2.90$, SE = 0.24, $P = 2.0*10^{-33}$; Supplemental Table 6). HDL-C response to statins showed an overall median response of 0.0% (IQR = −7.4 to 9.0%) and an overall mean response of +1.4% (SE = 0.1%). However, increasing statin DDD was inversely associated with HDL-C elevation after adjusting for potential confounding variables ($\beta = -0.41$, SE = 0.10, $P = 2.4*10^{-5}$, Figure 4B, Supplemental Table 7). Statin therapy was associated with a median overall non-HDL-C change of −30.6% (IQR = −39.7 to −20.7%, Figure 4C). Furthermore, a significant statin dose-response was observed for non-HDL-C after correcting for confounders ($\beta = -5.27$, SE = 0.10, $P < 10^{-300}$, Supplemental Table 8).

DISCUSSION

In this report, we rigorously characterized LDL-C dose response to statin therapy using EHR data from a diverse cohort of over 30,000 patients undergoing routine treatment. We determined the percent reduction of statin-induced LDL-C at various doses, identified covariates associated with statin LDL-C response, and estimated the heritability of this response. To our knowledge, this is the largest single-cohort statin dose-response study.

Statin LDL-C dose response

We observed a significant log-linear dose-response, consistent with previous findings in the literature. Specifically, LDL-C was lowered by an additional 6.2% (5.6% after adjustment for covariates) of the original pretreatment LDL-C for each doubling of the statin dose. This dose-response was consistent with the well-established “rule of 6%”, which describes the additional percent reduction of LDL-C from pretreatment for each statin dose doubling [25].

Predictors of statin LDL-C response beyond dose

To our knowledge, there are only two prior studies with a primary objective to characterize clinical and demographic predictors of LDL-C response to statin therapy. In an open-label clinical trial of 944 participants all receiving simvastatin for 6 weeks, Simon et al. reported that race/ethnicity (only African Americans and Caucasians were included), age, and cigarette smoking were significant predictors of LDL-C response to statin therapy [3]. In a post-hoc study of EXCEL (a RCT investigating lovastatin in 8,245 patients), race (black, white, other), weight change, sex/age combination, exercise/alcohol intake combination, and drug compliance were significant predictors [26]. The presence of these predictors were generally found to be associated with only modest effect sizes (<6% of pretreatment LDL-C difference) compared to the absence of the predictor. As noted, results from these studies were each based on clinical trial populations, examined only one statin type, and had populations of fewer than 10,000 subjects. The current investigation of a real-world

population represents the largest study evaluating the association of phenotypic predictors with statin LDL-C response. Despite the significant associations observed with seven predictors, we only explained 13% of the variance in response (with statin type and dose being the major contributors). The magnitude of these effects were generally consistent with those reported in the prior studies cited above.

We anticipated that after adjusting for DDD, there would be no association between statin type and response (e.g., we anticipated that lovastatin and atorvastatin would have the same response since lovastatin 40 mg and atorvastatin 10 mg were both given the same DDD value based on the dose equivalency table). However, statin type was a strong predictor of statin LDL-C efficacy even after adjusting for DDD and covariates. Simvastatin use correlated with enhanced LDL-C lowering (2% additional LDL-C lowering relative to lovastatin) and pravastatin use was associated with weaker LDL-C response (5% less LDL-C lowering relative to lovastatin), whereas atorvastatin was not significantly different from lovastatin within a given DDD group. Thus, our data show an 8% statin LDL-C response difference between pravastatin and simvastatin after adjusting for DDD. This is of a magnitude greater than a double-dose shift in potency; for example if we had assigned each pravastatin dose at half the potency from the FDA dose equivalency table that we used to determine the DDD groups (i.e., 80mg pravastatin daily as a DDD = 1.0 instead of DDD = 2.0, etc.) pravastatin LDL-C response would have better matched the other statin types within a given DDD group. We constructed a revised dose equivalency table that account for these observed differences. Discrepancies in LDL-C response between statin types previously recognized to be equivalent have been reported in the literature. In a meta-analysis of 181 RCTs, Naci et al. showed comparisons among statin types and doses that were discrepant from previous dose equivalency charts [27]. Similar to the present study, this also led to the generation of a revised dose equivalency table [27]. Inconsistencies exist between the Naci et al. equivalency table and our revised table, which further underscore the complexity of statin LDL-C response equivalency among statin types. Altogether, these data suggest that current statin dose equivalency tables may not accurately capture potency differences among statins.

Race/ethnicity impacted statin-induced LDL-C changes. Specifically, we found that East Asian participants had an enhanced response to therapy (compared to reference White/Europeans) after correcting for BMI and other covariates. This finding is consistent with substantial data showing that East Asians may be more responsive to statin therapy than other populations [28]. East Asian participants receiving statins have been found to have increased statin plasma levels and enhanced LDL-C lowering compared to white participants [29, 30]. Body weight was found to account for only a small fraction of the difference in statin LDL-C response between East Asians and whites [30]. Consequently, high intensity doses of statins approved in the US are not approved in Japan [28]. Furthermore, manufacturer prescribing information for rosuvastatin recommends initiation at one-eighth of the maximum dose in East Asians [31]. Interethnic variability in genetic polymorphisms of enzymes and transporters involved in statin drug disposition may play a significant role in pharmacokinetic and pharmacodynamic differences observed in East Asians [28]. We did not observe any other race/ethnicity differences in statin LDL-C response. This finding contrasts

with the CAP study in which African-Americans had a weaker statin LDL-C response compared to whites [3].

Heritability of statin LDL-C response

Our heritability analyses provides novel information about the contribution of genetic factors to statin LDL-C response variation. In particular, this estimate provides an assessment of the total proportion of phenotypic variation explained by genetics. To our knowledge, this is the first report that estimates the heritable component of variability in statin LDL-C dose response. Our data indicate that statin LDL-C response is only modestly heritable (12%). In contrast, prior reports suggest that untreated LDL-C levels have much stronger heritability (25–98%) [32]. Our sample size was small; these results require validation in a population with more first-degree relatives for enhanced power. However, the findings are consistent with past statin LDL-C GWAS studies [4–7], which have reported a relatively small number of genetic loci meeting genome-wide significance (compared to GWAS of untreated LDL-C levels [33]). Considering the limitations of previous statin LDL-C GWAS studies (e.g. small sample size, RCT populations with low generalizability), the potential for identifying additional genetic predictors with clinical relevance remains.

Study limitations

A limitation of this study is that half of the study participants initiated therapy with low-intensity statin therapy (DDD < 1.0), an intensity that does not reflect more recent dosing recommendations [8]. This is because the EHR data was extracted from a time-period (1996–2013) when high- and mid- intensity statin regimens were less likely to be prescribed. Indeed, the objective of this study was not only to characterize statin LDL-dose response, but importantly to characterize overall response specifically for doses that are likely to be prescribed in current practice. Thus, the present results may not be completely generalizable to contemporary practice. Nevertheless, the large sample size and diversity of our study population allowed us to determine lipid responses for each intensity range with adequate statistical power while controlling for the effects of multiple covariates.

A second limitation is that statin dispensing history may not have always correlated with patient statin consumption. Potential examples of this type of discordance may arise from non-adherence (i.e., overestimation of statin consumption) or from incomplete dispensing data (i.e., underestimation of statin consumption) [34]. Poor adherence has been found to be associated with lower rates of adequate statin-induced LDL-C reduction in longitudinal studies [35]. In lieu of closely monitored discontinuation/adherence rates commonly used in prospective clinical trials, we mitigated this limitation by using only the lipid levels for each participant that were most proximal to the date of statin initiation. As a further means to eliminate the potential impact of non-adherence, we only included participants with at least two dispensing records of any statin in the EHR. In terms of potential incomplete dispensing data, the pharmacy database used in the current analysis contained all prescriptions dispensed at Kaiser Permanente Medical Care Plan in Northern California (KPNC) health systems (outpatient and inpatient pharmacies), but does not account for the possibility that some patients may have received statins from outside of KPNC. Nevertheless, the comprehensive nature of health care provided by KPNC to its members (all KPNC health

plan memberships include pharmacy benefits) and our results, which demonstrated a dose-response relationship consistent with RCTs, suggest that this scenario is unlikely to occur in a substantial proportion of patients. Furthermore, KPNC does not reimburse patients for prescriptions dispensed outside of KPNC pharmacies.

A third limitation is that due to the observational nature of this real-world data, unmeasured confounding may occur and possibly bias the observed associations. To reduce the potential of confounding, we harnessed the rich KPNC phenotype data to adjust for a wide range of variables, including those that have been previously found to be associated with statin LDL-C response as well as others that may affect response in theory. Furthermore, given how closely our results conform to those previously reported in RCTs, there is no evidence of confounding.

CONCLUSION

We characterized response of LDL-C to statin therapy using EHRs in a population-based cohort of 33,139 statin users receiving routine clinical care. This is the largest single-cohort statin dose-response study and the first to estimate the heritable component of variability in statin LDL-C dose response. A clear LDL-C statin dose-response was demonstrated. Statin type, race/ethnicity, sex, smoking status, diabetes, and age were identified as significant predictors of statin-induced LDL-C response, independent of dose. These real-world results were generally consistent with what is observed in clinical trial data. Finally, we found that statin-induced changes in LDL-C are modestly inherited. Altogether, these findings provide novel information about the contribution of genetic and non-genetic factors to the phenotypic variation in statin LDL-C response. Further studies are necessary to determine the clinical importance of statin LDL-C precision medicine in practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. Adedinsewo D, et al. Prevalence and Factors Associated With Statin Use Among a Nationally Representative Sample of US Adults: National Health and Nutrition Examination Survey, 2011–2012. Clin Cardiol. 2016;39:491–496. [PubMed: 27505443]
2. Cholesterol Treatment Trialists C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–1681. [PubMed: 21067804]

3. Simon JA, et al. Phenotypic predictors of response to simvastatin therapy among African-Americans and Caucasians: the Cholesterol and Pharmacogenetics (CAP) Study. Am J Cardiol. 2006;97:843–850. [PubMed: 16516587]
4. Postmus I, et al. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. Nat Commun. 2014;5:5068. [PubMed: 25350695]
5. Chasman DI, et al. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Circ Cardiovasc Genet. 2012;5:257–264. [PubMed: 22331829]
6. Deshmukh HA, et al. Genome-wide association study of genetic determinants of LDL-c response to atorvastatin therapy: importance of Lp(a). J Lipid Res. 2012;53:1000–1011. [PubMed: 22368281]
7. Barber MJ, et al. Genome-wide association of lipid-lowering response to statins in combined study populations. PLoS One. 2010;5:e9763. [PubMed: 20339536]
8. Stone NJ, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889–2934. [PubMed: 24239923]
9. Rothwell PM. Factors that can affect the external validity of randomised controlled trials. PLoS Clin Trials. 2006;1:e9. [PubMed: 16871331]
10. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7–22. doiI: 10.1016/S0140-6736(02)09327-3 [PubMed: 12114036]
11. LaRosa JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–1435. [PubMed: 15755765]
12. Bays HE, et al. National Lipid Association Annual Summary of Clinical Lipidology 2015. J Clin Lipidol. 2014;8:S1–36.
13. Kohane IS. Using electronic health records to drive discovery in disease genomics. Nat Rev Genet. 2011;12:417–428. [PubMed: 21587298]
14. Gaziano JM, et al. Million Veteran Program: A mega-biobank to study genetic influences on health and disease. J Clin Epidemiol. 2016;70:214–223. [PubMed: 26441289]
15. Carey DJ, et al. The Geisinger MyCode community health initiative: an electronic health record-linked biobank for precision medicine research. Genet Med. 2016;18:906–913. [PubMed: 26866580]
16. Wood GC, et al. Association of chromosome 9p21 SNPs with cardiovascular phenotypes in morbid obesity using electronic health record data. Genomic Med. 2008;2:33–43. [PubMed: 18716918]
17. Denny JC, et al. Identification of genomic predictors of atrioventricular conduction: using electronic medical records as a tool for genome science. Circulation. 2010;122:2016–2021. [PubMed: 21041692]
18. Ritchie MD, et al. Robust replication of genotype-phenotype associations across multiple diseases in an electronic medical record. Am J Hum Genet. 2010;86:560–572. [PubMed: 20362271]
19. Kho AN, et al. Use of diverse electronic medical record systems to identify genetic risk for type 2 diabetes within a genome-wide association study. J Am Med Inform Assoc. 2012;19:212–218. [PubMed: 22101970]
20. Delaney JT, et al. Predicting clopidogrel response using DNA samples linked to an electronic health record. Clin Pharmacol Ther. 2012;91:257–263. [PubMed: 22190063]
21. Xu H, et al. Facilitating pharmacogenetic studies using electronic health records and natural-language processing: a case study of warfarin. J Am Med Inform Assoc. 2011;18:387–391. [PubMed: 21672908]
22. Wei WQ, et al. Characterization of statin dose response in electronic medical records. Clin Pharmacol Ther. 2014;95:331–338. [PubMed: 24096969]
23. Hall JL, et al. Merging Electronic Health Record Data and Genomics for Cardiovascular Research: A Science Advisory From the American Heart Association. Circ Cardiovasc Genet. 2016;9:193–202. [PubMed: 26976545]

24. Svensson E, et al. Statin prescription patterns, adherence, and attainment of cholesterol treatment goals in routine clinical care: a Danish population-based study. Clin Epidemiol. 2015;7:213–223. [PubMed: 25759601]
25. Leitersdorf E Cholesterol absorption inhibition: filling an unmet need in lipid-lowering management. European Heart Journal Supplements. 2001;3:E17–E23.
26. Shear CL, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. Effect of patient characteristics on lovastatin-induced changes in plasma concentrations of lipids and lipoproteins. Circulation. 1992;85:1293–1303. [PubMed: 1555273]
27. Naci H, et al. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. Eur J Prev Cardiol. 2013;20:658–670. [PubMed: 23529608]
28. Liao JK. Safety and efficacy of statins in Asians. Am J Cardiol. 2007;99:410–414. [PubMed: 17261409]
29. Matsuzawa Y, et al. Sustained reduction of serum cholesterol in low-dose 6-year simvastatin treatment with minimum side effects in 51,321 Japanese hypercholesterolemic patients. Circ J. 2003;67:287–294. [PubMed: 12655157]
30. Lee E, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther. 2005;78:330–341. [PubMed: 16198652]
31. Tirona RG, et al. Ethnic differences in statin disposition. Clin Pharmacol Ther. 2005;78:311–316. doi: 10.1016/j.clpt.2005.07.006 [PubMed: 16198649]
32. van Dongen J, et al. Heritability of metabolic syndrome traits in a large population-based sample. J Lipid Res. 2013;54:2914–2923. [PubMed: 23918046]
33. Hoffmann TJ, et al. A large electronic-health-record-based genome-wide study of serum lipids. Nat Genet. 2018;50:401–413. [PubMed: 29507422]
34. Young JC, et al. Predictors of prevalent statin use among older adults identified as statin initiators based on Medicare claims data. Pharmacoepidemiol Drug Saf. 2016;25:836–843. [PubMed: 26991151]
35. Vupputuri S, et al. LDL cholesterol response and statin adherence among high-risk patients initiating treatment. Am J Manag Care. 2016;22:e106–115. [PubMed: 26978237]

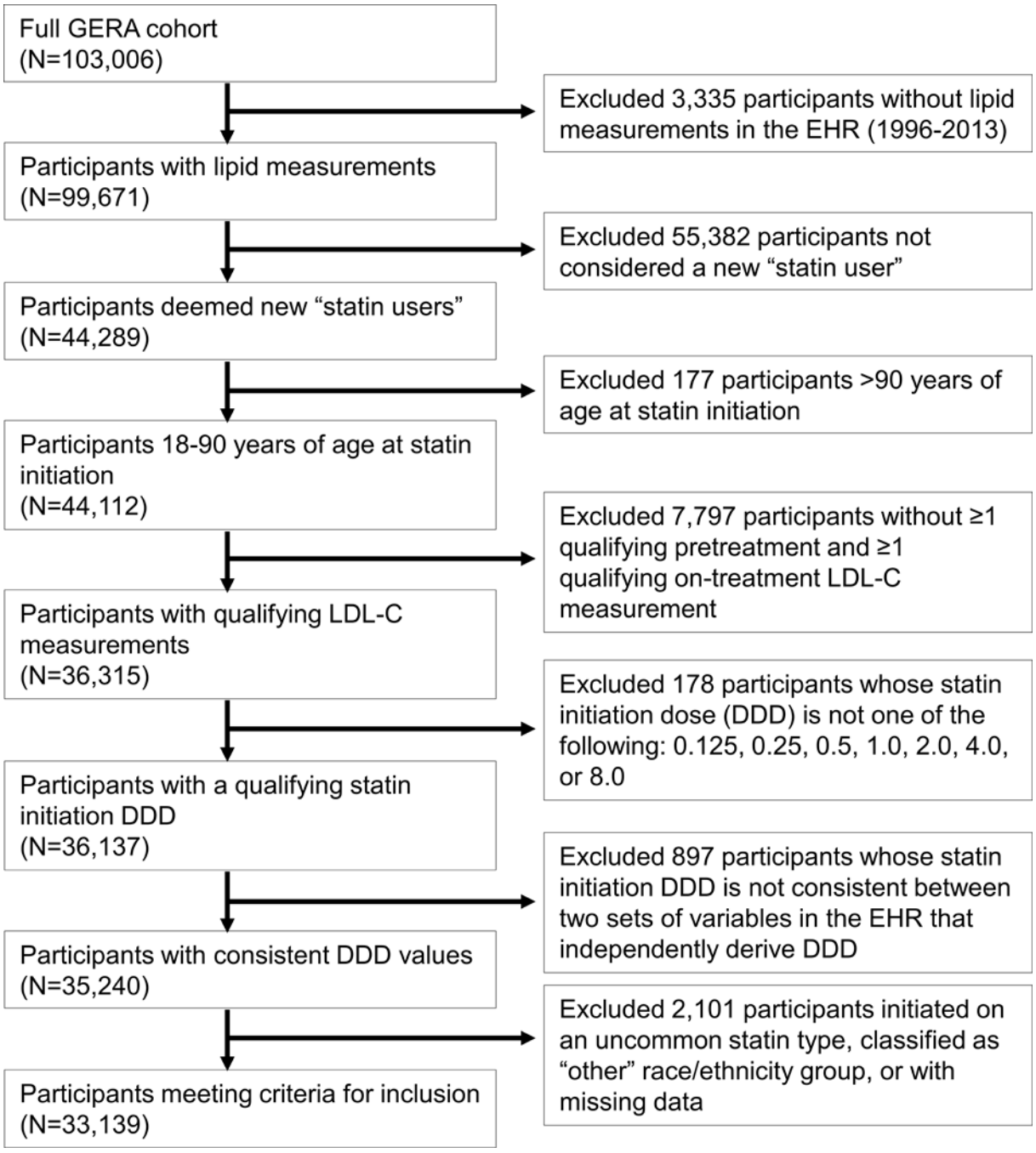

Figure 1:

Flow diagram of study inclusion and exclusion criteria. A “statin user” is defined as an individual who has at least two dispensing records of any statin prescription (e.g., he or she refilled the initial statin prescription; he or she was dispensed a new statin prescription after the initial statin). In order to protect patient privacy for participants >90 years of age (i.e. individuals that could be identified due to low frequency in the population), data including timing of statin initiation was not provided in this subgroup. Thus, it was not possible to

determine if these participants met the criteria for inclusion. Consequently, these participants were excluded from the study.

DDD, defined daily dose; EHR, electronic health records; GERA, Genetic Epidemiology Research on Adult Health and Aging; LDL-C, low-density lipoprotein cholesterol.

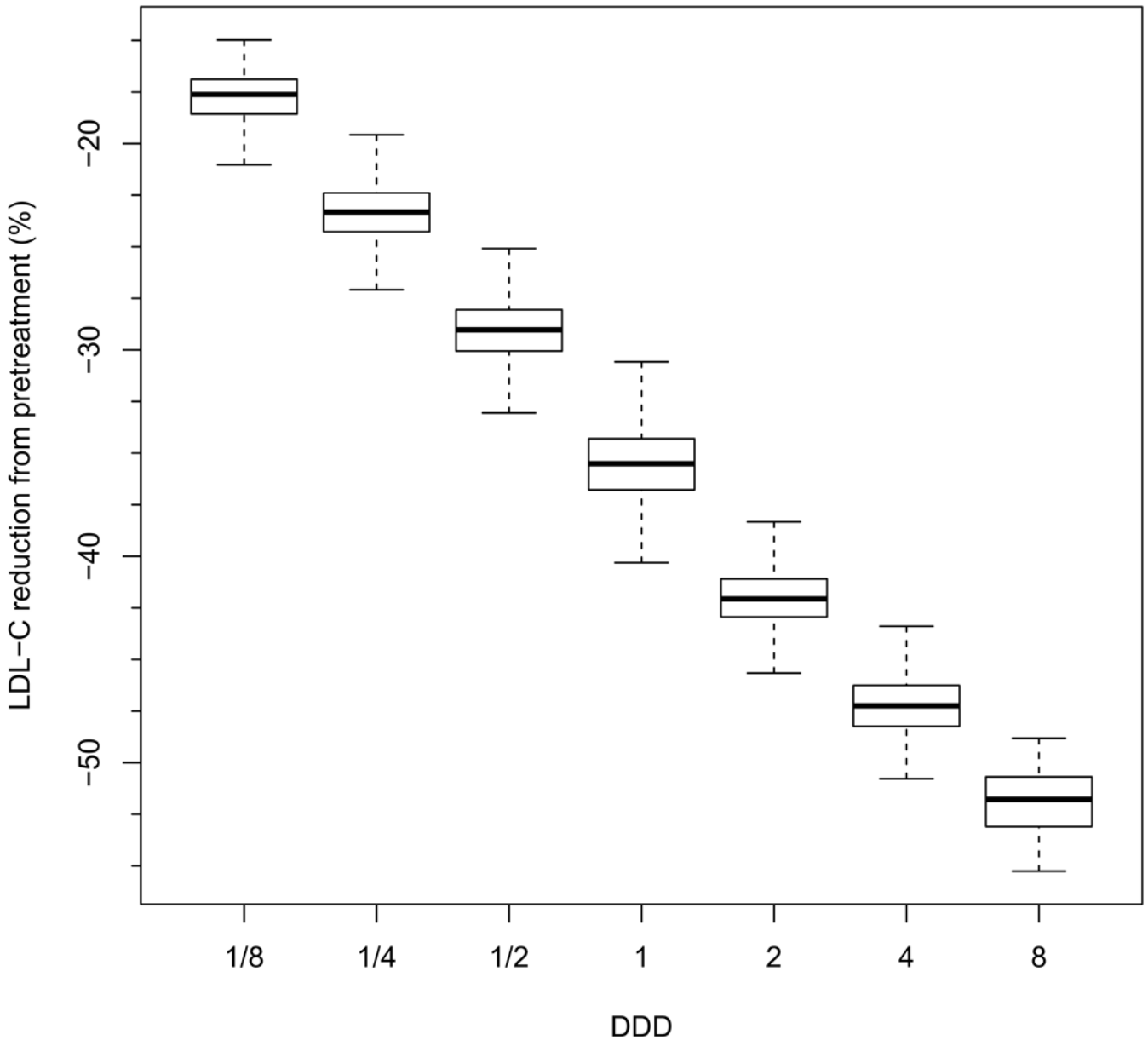

Figure 2:

Statin dose-response. A significant log-linear dose-response was observed in the full cohort after adjusting for pre-specified covariates (adjusted $\beta = -5.59$, SE = 0.11, $P < 10^{-300}$, N = 33,139). Data presented as the median (midline), interquartile range (box), and Tukey whiskers (dotted lines) of fitted values. Outliers are not shown.

DDD, defined daily dose; LDL-C, low-density lipoprotein cholesterol.

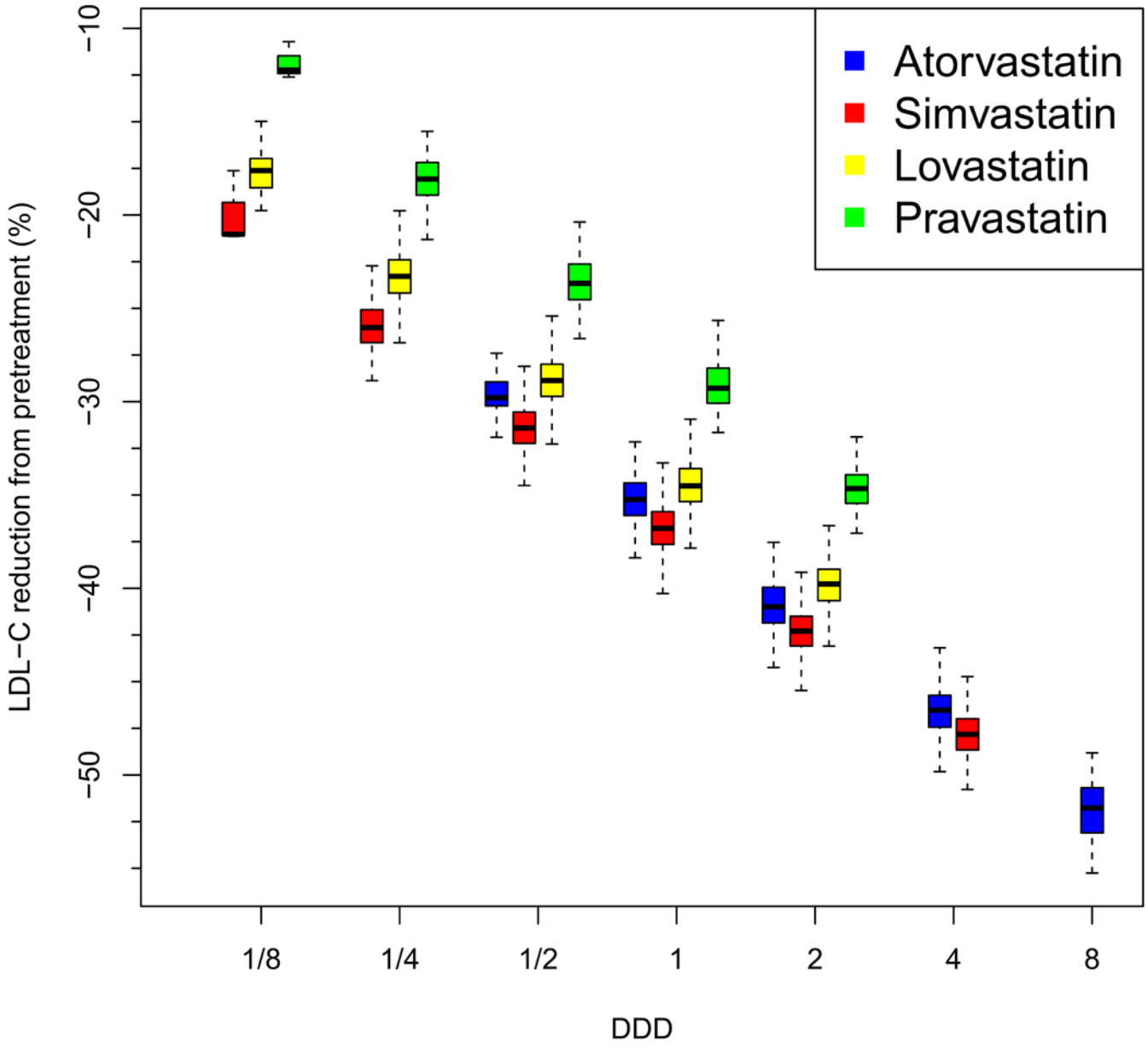

Figure 3:

Statin dose-response by statin type. A significant log-linear dose-response was observed in initiators of lovastatin (β = −5.82, SE = 0.141, $P < 10^{-300}$; N = 20,853), simvastatin (β = −5.47, SE = 0.211, $P = 2.9*10^{-143}$; N=10.452), atorvastatin (β = −4.26, SE = 0.581, $P = 3.9*10^{-13}$; N = 1,266), and pravastatin (β = −4.42, SE = 0.975, $P = 7.2*10^{-6}$; N = 568) after adjusting for pre-specified covariates. Data presented as the median (midline), interquartile range (box), and Tukey whiskers (dotted lines) of fitted values. Outliers are not shown. DDD, defined daily dose; LDL-C, low-density lipoprotein cholesterol.

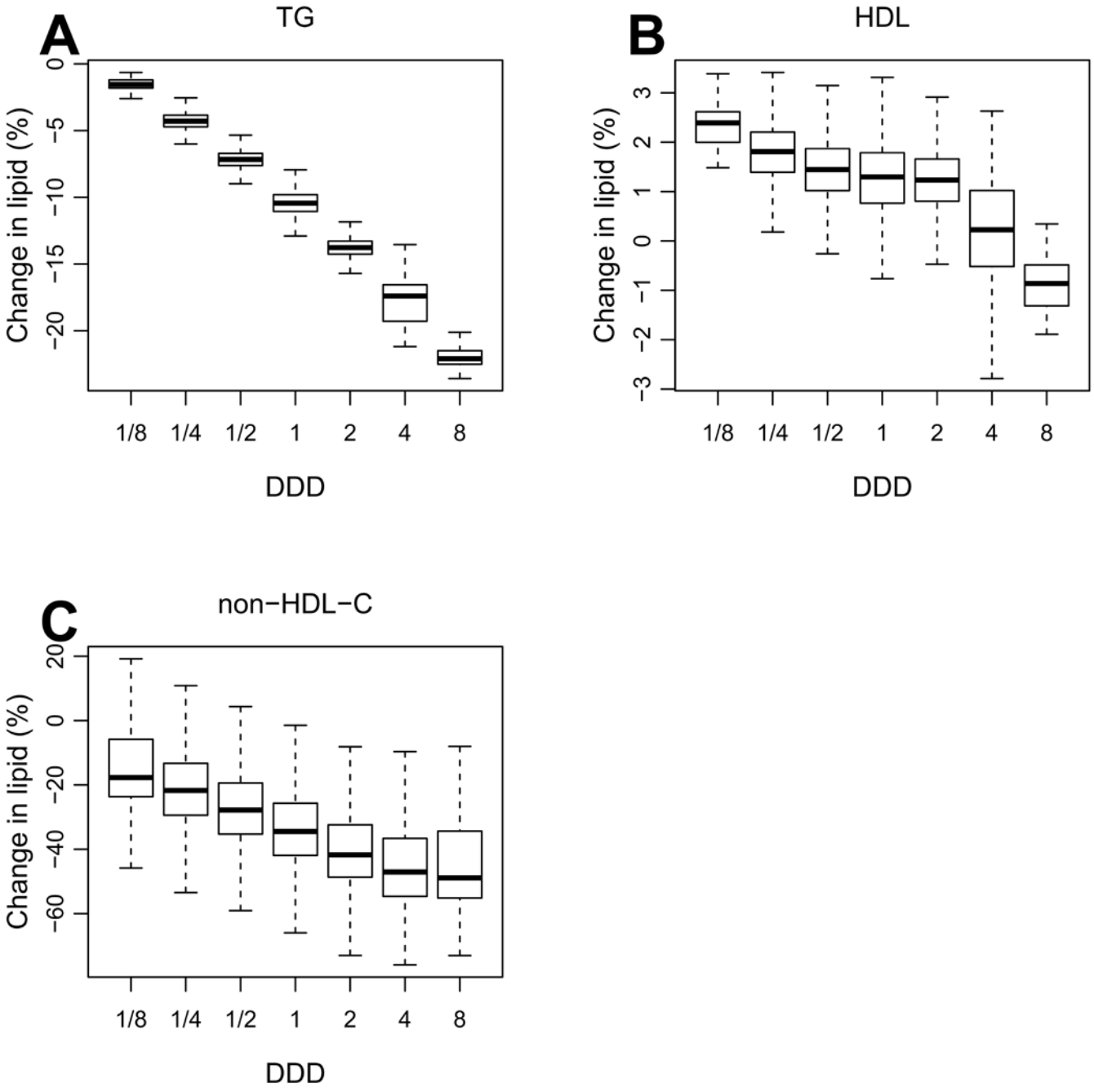

Figure 4:

Statin-induced triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C) changes across defined daily dose (DDD). A significant log-linear dose-response was observed for TG ($\beta = -2.90$, SE = 0.24, $P = 2.0*10^{-33}$), HDL-C ($\beta = -0.41$, SE = 0.10, $P = 2.4*10^{-5}$), and non-HDL-C ($\beta = -5.27$, SE = 0.10, $P < 1.0*10^{-300}$) lowering after adjusting for pre-specified covariates. Data presented as the median (midline), interquartile range (box), and Tukey whiskers (dotted lines) of fitted values. Outliers are not shown. Y-axis scales vary across panels.

Table 1.

Demographics of study population

Characteristics	Total (N = 33,139)
Age (at statin initiation)	64.2 (57.3–71.1)
Females	17,500 (52.8%)
Race/ethnicity (self-reported)	
White/European	27,185 (82.0%)
Black/African	1,155 (3.5%)
Hispanic/Latino	2,553 (7.7%)
East Asian	2,246 (6.8%)

Data presented as median (interquartile range), or count (%).

Table 2.

Clinical characteristics of study population

Characteristics	Total (N = 33,139)
BMI (kg/m^2) at statin initiation	27.9 (25.5–31.5)
Diabetes mellitus	6,385 (19.2%)
Hypertension	19,375 (58.5%)
Cigarette use (current or former)	16,254 (49.0%)
Pretreatment lipid panel (mg/dL)	
TC	240 (212–266)
LDL-C	154 (130–176)
TG	144 (103–202)
HDL-C	51 (42–61)
Non-HDL-C	186 (160–211)
Initial statin dispensed	
DDD mean (SE)	0.90 (0.004)
Lovastatin	20,853 (62.9%)
Simvastatin	10,452 (31.5%)
Atorvastatin	1,266 (3.8%)
Pravastatin	568 (1.7%)

Data presented as median (interquartile range) or count (%) unless indicated otherwise.

BMI, body mass index; DDD, defined daily dose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; SE, standard error, TC, total cholesterol; TG, triglycerides.

Table 3.

Predictors of low-density lipoprotein cholesterol (LDL-C) response to statin therapy (percent reduction)

Covariate	Univariate		Multivariate	
	Beta (SE)	P-value	Beta (SE)	P-value
Log_2(DDD)	−6.17 (0.090)	$<10^{-300}$	−5.59 (0.115)	$<10^{-300}$
Simvastatin*	−8.61 (0.205)	$<10^{-300}$	−2.14 (0.244)	$1.8*10^{-18}$
Atorvastatin*	−8.71 (0.509)	$2.0*10^{-65}$	−0.66 (0.529)	0.210
Age†	−0.10 (0.010)	$4.9*10^{-24}$	−0.09 (0.010)	$5.8*10^{-21}$
Pravastatin*	7.32 (0.753)	$2.7*10^{-22}$	5.47 (0.707)	$9.9*10^{-15}$
Diabetes	2.28 (0.248)	$3.4*10^{-20}$	0.96 (0.244)	$8.3*10^{-5}$
Female	−1.23 (0.196)	$3.6*10^{-10}$	−0.89 (0.185)	$1.3*10^{-6}$
Smoking	0.96 (0.196)	$8.8*10^{-7}$	0.96 (0.185)	$2.5*10^{-7}$
BMI	0.07 (0.019)	$1.4*10^{-4}$	0.01 (0.019)	0.444
Black/African‡	1.12 (0.534)	0.036	0.34 (0.503)	0.502
East Asian‡	−0.40 (0.390)	0.303	−0.82 (0.373)	0.027
Hispanic/Latino‡	0.41 (0.367)	0.259	0.41 (0.347)	0.236
Hypertension	−0.17 (0.199)	0.404	−0.01 (0.197)	0.954

*Lovastatin was set as the reference group

†Age at statin initiation

‡White/European was set as the reference group

BMI, body mass index; DDD, defined daily dose; SE, standard error.

Full multivariate model adjusted R^2 = 0.134 (0.007 when DDD and statin type are removed)