Supplemental Material
Data S1.

**Supplemental Methods**

**Description of the model**

We decomposed the variation in attained low-density lipoprotein cholesterol (LDL-C) level by means of a mixed-effect model including one fixed and two random intercepts (inter-family and inter-individual), and one fixed and two random slopes (inter-family and inter-individual), yielding a total of five variance components. Let \( i = 1, 2, \ldots, n \) indicate the family, \( j = 1, 2 \) the individual within the family and \( k = 1, 2 \) the observation within each individual, then the model can be expressed with the equation:

\[
y_{ijk} = \frac{x_{ij}^T \beta + u_i^0 + v_j^0}{\text{intercept}} + \left(\frac{x_{ij}^T y + u_i^1 + v_j^1}{\text{slope}}\right) \times \text{time} + \varepsilon_{ijk}
\]

where

- \( y_{ijk} \) is the logarithm of the LDL-C level for the observation \( k \) (pre-statin LDL-C if \( k = 1 \), on-statin LDL-C if \( k = 2 \)), of the individual \( j \), of the family \( i \);
- the variable \( \text{time} \) assumes the value 0 when \( k = 1 \), i.e. we are considering a pre-statin LDL-C level, and 1 when \( k = 2 \), i.e. we are considering an on-statin LDL-C level;
- \( x_{ij}^T \beta \) and \( x_{ij}^T y \times \text{time} \) represent the adjusting terms for the intercept and the slope respectively;
- \( u_i^0 \) is a random effect normally distributed according to \( \mathcal{N}(0, \sigma_{0,fam}^2) \), and \( \sigma_{0,fam}^2 \) represents the inter-family variance in pre-statin LDL-C level;
- \( u_i^1 \) is a random effect normally distributed according to \( \mathcal{N}(0, \sigma_{1,fam}^2) \), and \( \sigma_{1,fam}^2 \) represents the inter-individual variance in statin response;
- \( v_j^0 \) is a random effect normally distributed according to \( \mathcal{N}(0, \sigma_{0,id}^2) \), and \( \sigma_{0,id}^2 \) represents the inter-individual variance in pre-statin LDL-C level;
- \( v_j^1 \) is a random effect normally distributed according to \( \mathcal{N}(0, \sigma_{1,id}^2) \), and \( \sigma_{1,id}^2 \) represents the inter-individual variance in statin response;
- \( \varepsilon_{ijk} \) represents the residuals, which are normally distributed according to \( \mathcal{N}(0, \sigma_{res}^2) \). \( \sigma_{res}^2 \) is the intra-individual (or residual) variance.

**Data structure and SAS code**

This section presents the data structure and SAS code used in the article to estimate the variance components. For simplicity, we have included only age and sex as adjustment variables in the following description.
The following table includes example data for four individuals grouped in two families.

| FamId | PersonId | PreLDL | OnLDL | Time | Y   | Treatment  | AdjAge | AdjSex |
|-------|----------|--------|-------|------|-----|------------|--------|--------|
| 1     | 1        | 4.0    | 2.5   | 0    | 1.39| No_statin  | 56-57  | M      |
| 1     | 1        | 4.0    | 2.5   | 1    | 0.92| Simva40    | 56-57  | M      |
| 1     | 2        | 3.7    | 2.6   | 0    | 1.31| No_statin  | 62-63  | M      |
| 1     | 2        | 3.7    | 2.6   | 1    | 0.96| Atorva20   | 62-63  | M      |
| 2     | 1        | 2.8    | 2.0   | 0    | 1.03| No_statin  | 58-59  | F      |
| 2     | 1        | 2.8    | 2.0   | 1    | 0.69| Simva20    | 58-59  | F      |
| 2     | 2        | 3.2    | 1.8   | 0    | 1.16| No_statin  | 72-73  | M      |
| 2     | 2        | 3.2    | 1.8   | 1    | 0.59| Atorva40   | 72-73  | M      |

The data were analyzed in SAS using the procedure PROC MIXED as described below.

```sas
data VarCompAnalysis;
input FamId PersonId PreLDL OnLDL Time Y Treatment $10. AdjAge $6. AdjSex $1.;
datalines;
  1 1 4.0 2.5 0 1.39 No_statin 56-57 M
  1 1 4.0 2.5 1 0.92 Simva40 56-57 M
  1 2 3.7 2.6 0 1.31 No_statin 62-63 M
  1 2 3.7 2.6 1 0.96 Atorva20 62-63 M
  2 1 2.8 2.0 0 1.03 No_statin 58-59 F
  2 1 2.8 2.0 1 0.69 Simva20 58-59 F
  2 2 3.2 1.8 0 1.16 No_statin 72-73 M
  2 2 3.2 1.8 1 0.59 Atorva40 72-73 M
...;
run;

proc mixed data= VarCompAnalysis noclprint cl covtest method=ml asycov;
class FamId PersonId Treatment AdjAge AdjSex;
model Y = Treatment AdjAge AdjSex AdjAge*Time AdjSex*Time / solution;
  random Intercept time / sub=FamiId type=vc;
  random Intercept time / sub=PersonId(FamId) type=vc;
run;
```

Evaluation of model assumptions

As described in the previous section the model assumes normality and homoscedasticity of the random effects. To evaluate how this assumption, or the lack of it, influenced our results, we performed a visual check of the normality and homoscedasticity of the residuals using a conditional standardized residuals vs. fitted values plot and a quantile-quantile plot (QQ-plot) for the conditional standardized residuals (figure S1 and S2). These plots revealed that the assumptions of normality and homoscedasticity of the residuals are generally true, except for few observations. In addition, we performed a bootstrap analysis resampling the families with replacement. We sampled 2541 families of first-degree relatives and 1599 spousal pairs one
hundred times and estimated variance components, and percentages of variance explained as done in the main models. Thereafter, we calculated the summary estimates and confidence intervals by means of medians and 2.5- and 97.5-percentiles. The results of this analysis are included in table S1 and show very similar results to the main analysis.
Evaluation of the robustness of the variance components estimates

To test the robustness of the model chosen for the main analysis in estimating inter-family variance components, we performed several sensitivity analyses using alternative models. The following sections describes these models in more detail.

Covariance between the inter-family random effects

The main model is based on the assumption of random effects being independent of each other. The data available allow us to identify one covariance, in particular the covariance between the inter-family random intercept and the inter-family random statin response. We, therefore, repeated the main analysis adding this covariance term to the model.

Modelling only statin response

In this alternative model, we used the difference between the logarithm of the pre-statin and the on-statin LDL-C levels as outcome. Consequently, each individual contributed with one observation to the model and therefore it was only possible to distinguish between two variance components: the inter-family variance in statin response and the intra-individual (residual) variance that, here, includes the inter-individual variance in statin response and two times the residual variance from the main model. Adjustment was made in the same way as in the main model in the intercept part.

Modelling only the untreated LDL-C level

The main model is based on the specific population of statin initiators having two registered LDL-C measurements, one before and one after statin initiation. To have an alternative and potentially more accurate estimate of the inter-family variance in untreated LDL-C level, we extended our population by not requiring statin treatment and an on-statin LDL-C measurement. In particular, we identified all adults (≥18 years old) resident in Denmark (known address) with a registered untreated LDL-C measurement, i.e. the individual had to be naive to all lipid-lowering drugs at the time of the laboratory test (n=1,682,420). If more measurements were available for one person, then one was chosen randomly. In this cohort, we identified families of first-degree relatives and spousal pairs as described in the methods section for the main analyses (940,959 first-degree relatives and 440,634 spouses). The model included the logarithm of the untreated LDL-C level as outcome and one fixed and one random intercept, allowing the identification of the inter-family variance in untreated LDL-C level and the intra-individual (residual) variance. The model was adjusted for age, sex, period, region of residence, education and disposable household income. Due to computational issues, we randomly sampled one tenth of the families/pairs available (the analysis included 94,193 first-degree relatives and 44,064 spouses).

Results

Results are presented in table S11. In the first two alternative models, where the population included was the same as in the main model, we observed results very similar to the main model. In the third alternative model, where we extended the study population, we found an inter-family variance component of untreated LDL-C level twice that from the main analysis for first-degree relatives, while the estimate was similar for spouses. The main analysis is based on individuals that initiate statin, while this is not the case for all individuals used in the alternative model. Thus, the finding may indicate that statin initiation also is related to factors shared by first-degree relatives, i.e. genetics or shared behaviors not shared to the same
degree by spouses. Moreover, the difference observed in the third model underlines the need for caution in generalizing the results from this study to populations other than statin initiators.

However, the results from the first two alternative models demonstrate the stability of the chosen model when analyzing the variability in LDL-C level among statin initiators, reinforcing our conclusion of no major influence of genetic constitution on statin response.
Table S1. Variance components for LDL-C levels and statin response in cohorts of first-degree relatives and spousal pairs (results from bootstrap analysis*).

|                          | First-degree relatives |                       | Spousal pairs |                       |
|--------------------------|------------------------|-----------------------|---------------|-----------------------|
|                          | Variance component†   | Percentage of the     | Variance      | Percentage of the     |
|                          | (95% CI)               | total variance (95% CI)| component†   | total variance (95% CI)|
| Variance in pre-statins LDL-C level |                       |                       |               |                       |
| Inter-family variance     | 0.010(0.007,0.012)     | 7.4%(5.6%,9.3%)       | 0.003(0.001,0.006) | 2.6%(0.4%,4.8%)     |
| Inter-individual† variance | 0.039(0.035,0.043)     | 30.0%(27.8%,32.1%)    | 0.041(0.036,0.048) | 31.7%(28.1%,36.3%)  |
| Variance in statin response |                       |                       |               |                       |
| Inter-family variance     | 0.005(0.001,0.009)     | 3.8%(0.8%,6.4%)       | 0.008(0.003,0.012) | 5.9%(2.6%,9.3%)     |
| Inter-individual† variance | 0.059(0.051,0.067)     | 45.0%(40.7%,49.1%)    | 0.063(0.045,0.077) | 48.6%(35.1%,56.5%)  |
| Residual variance         | 0.018(0.015,0.021)     | 13.6%(10.6%,16.8%)    | 0.015(0.009,0.025) | 11.7%(7.0%,19.6%)   |

CI Confidence Interval
† The bootstrap analysis was performed resampling the families with replacement. We sampled 2541 families of first-degree relatives and 1599 spousal pairs one hundred times and estimated variance components and percentages of variance explained as done in the main models. Thereafter we calculated the summary estimates and confidence intervals by means of medians and 2.5- and 97.5-percentiles.

* The model was adjusted for age, sex, period, region of residence, indication for statin treatment, education, disposable household income, type and dose of the initial statin prescription.

‡ Inter-individual (but within-family) variance.
Table S2. Codes used in the definition of indication for treatment.
The hierarchical algorithm was previously introduced by Kildemoes et al. 16 and is presented here in a revised form. Individuals were classified in one of the three exclusive indication groups according to the diagnosis-, surgery- and drug codes in the table below. If individuals fulfilled the criteria for more than one category, they were classified according to the highest one.

| Indication                              | Diagnosis codes (ICD8 and ICD10) | Surgery codes (NOMESCO Classification of Surgical Procedures) | Drug codes (ATC codes) |
|----------------------------------------|----------------------------------|---------------------------------------------------------------|-----------------------|
| **Individuals with established CVD**   |                                  |                                                               |                       |
| Myocardial infarction                   | 410.00-410.99 i21-i23, i24.1, i25.2 |                                                              |                       |
| Ischemic Heart Disease                  | 411.00-414.99 i20, i24-i25 (ex. i24.1, i25.2) | KFNA-KFNG                                                   | ≥2 C01D, C01d+B01A   |
|                                        |                                  |                                                              | (within 6 months)    |
| Stroke                                 | 432-437 i63-i66, i69.3-i694 G45-G46 |                                                              |                       |
| Peripheral arterial disease            | 440-441, 444.00-444.49 i70-171, i73.9-174.9, K55.0 | KPE, KPF (only KPxE, KPxF, KPxH, KPxP, KPxQ) |                       |
| Potential atherosclerotic conditions    | 400-404 (ex. 401.99), 427, 424, i11-i15, i34-37, i44-i50 | KPCG10, KPDG10, KPDG21-24 KPA, KPB, KPC, KPD (only KPxE, KPxF, KPxH, KPxP, KPxQ) | C01A, C01B, C03C, B01AC(-04, -06, -07, -30) |
|                                        |                                  |                                                              | (≥ 2 filled prescriptions in 6 months) |
| **Individuals without established CVD, but with other cardiovascular risk factors** | |                                                               |                       |
| Diabetes                               | 249.00-250.99 E10-E11          |                                                               | A10 (≥ 2 filled prescriptions in 6 months) |
| Chronic renal insufficiency            | 403.99, 404.99, 581-584, 590.09 E10.2, E11.2, E13.2, E14.2, I12-I13, N03-N04, N07-N08, N11, N18, Z940, Z99.2 (874.40, 943.00, 943.40, 949.1, 949.2 at least 12 times and for at least 90 days) | S74.8-S74.9 KKAS0-KKAS2 BJFD2 or BJFD at least 12 times and for at least 90 days |
| Primary hypertension                   | 401.99 i10                      |                                                               | C02, C07, C08, C09, C03B, C03A (≥ 2 filled prescriptions in 6 months) |
| Familial hypercholesterolemia          | 272.00 E78.08                  |                                                               |                       |

ICD International Classification of Disease; ATC Anatomical Therapeutic Chemical Classification; CVD Cardiovascular disease.
Table S3. Characteristics of the cohorts of siblings and parent-offspring pairs.

| Characteristics at statin initiation | Cohort                  |
|--------------------------------------|-------------------------|
|                                      | Siblings | Parent-offspring pairs |
| Number of individuals                | 2075           | 3116                     |
| Number of families                   | 1026           | 1558                     |
| Age [median(IQR)]                    | 53( 49, 58)    | 58( 48, 72)             |
| Female sex                           | 966( 46.6% )   | 1660( 53.3% )           |
| Period                               |              |                          |
| 2008-2014                            | 694( 33.4% )   | 1239( 39.8% )           |
| 2015-2016                            | 779( 37.5% )   | 1122( 36.0% )           |
| 2017-2018                            | 602( 29.0% )   | 755( 24.2% )            |
| Region of residence                  |              |                          |
| Capital region                       | 1018( 49.1% )  | 1799( 57.7% )           |
| Zealand                              | 287( 13.8% )   | 378( 12.1% )            |
| Southern Denmark                     | 410( 19.8% )   | 465( 14.9% )            |
| Northern Denmark                     | 360( 17.3% )   | 474( 15.2% )            |
| Education (years)*                   |              |                          |
| <10 years                            | 605( 29.2% )   | 1033( 33.2% )           |
| 10-12 years                          | 944( 45.5% )   | 1373( 44.1% )           |
| 13-15 years                          | 374( 18.0% )   | 515( 16.5% )            |
| ≥15 years                            | 115(  5.5% )   | 147(  4.7% )            |
| Disposable household income†         |              |                          |
| 1 quintile                           | 170(  8.2% )   | 415( 13.3% )            |
| 2 quintile                           | 282( 13.6% )   | 697( 22.4% )            |
| 3 quintile                           | 419( 20.2% )   | 603( 19.4% )            |
| 4 quintile                           | 479( 23.1% )   | 604( 19.4% )            |
| 5 quintile                           | 632( 30.5% )   | 658( 21.1% )            |
| Indication for statin treatment      |              |                          |
| Established CVD                      | 686( 33.1% )   | 1265( 40.6% )           |
| Other risk factors for CVD‡          | 593( 28.6% )   | 832( 26.7% )            |
| No registered risk factors for CVD   | 796( 38.4% )   | 1019( 32.7% )           |
| Initial statin type and dose         |              |                          |
| Simvastatin 10 mg                    | 55(  2.7% )    | 92(  3.0% )             |
| Simvastatin 20 mg                    | 303( 14.6% )   | 445( 14.3% )            |
| Simvastatin 40 mg                    | 735( 35.4% )   | 1268( 40.7% )           |
| Atorvastatin 10 mg                   | 110(  5.3% )   | 157(  5.0% )            |
| Atorvastatin 20 mg                   | 253( 12.2% )   | 323( 10.4% )            |
| Atorvastatin 40 mg                   | 348( 16.8% )   | 487( 15.6% )            |
| Atorvastatin 80 mg                   | 271( 13.1% )   | 344( 11.0% )            |

IQR, interquartile range; CVD cardiovascular disease
* 85 individuals with missing information for education were imputed using mode imputation as 10-12 years.
† 232 individuals with missing information for disposable household income were imputed as 10th decile in adjustment, consequently here as 5th quintile (mode imputation).
‡ Other risk factors for CVD includes diabetes, hypertension, chronic kidney disease and familial hypercholesterolemia (cf. table S2 for definitions).
### Table S4. Variance components for LDL-C levels and statin response in the cohorts of siblings and parent-offspring pairs.

|                                                   | Siblings         | Parent-offspring pairs |
|---------------------------------------------------|------------------|------------------------|
|                                                   | Variance component* (95% CI) | Percentage of the total variance (95% CI) | Variance component* (95% CI) | Percentage of the total variance (95% CI) |
| **Variance in pre-statin LDL-C level**           |                  |                        |                        |
| Inter-family variance                             | 0.010(0.007,0.015) | 7.6%(4.8%,10.5%)       | 0.010(0.007,0.014)     | 7.6%(5.0%,10.2%)       | 0.99 |
| Inter-individual† variance                        | 0.037(0.033,0.043) | 28.3%(25.0%,31.6%)     | 0.039(0.035,0.044)     | 30.5%(27.4%,33.5%)     | 0.35 |
| **Variance in statin response**                  |                  |                        |                        |
| Inter-family variance                             | 0.007(0.003,0.021) | 5.1%(0.6%,9.6%)        | 0.004(0.001,0.026)     | 2.8%(0.0%,6.5%)        | 0.43 |
| Inter-individual† variance                        | 0.063(0.055,0.074) | 48.4%(42.8%,53.8%)     | 0.056(0.049,0.064)     | 43.2%(38.3%,47.8%)     | 0.16 |
| **Residual variance**                            |                  |                        |                        |
| Intra-individual variance                        | 0.014(0.011,0.018) | 10.6%(7.8%,13.6%)      | 0.021(0.018,0.024)     | 16.0%(13.3%,18.9%)     | 0.009 |
| **Total variance**                               | 0.131            | 100%                   | 0.129                  | 100%                   |

CI Confidence Interval  
* The model was adjusted for age, sex, period, region of residence, indication for statin treatment, education, disposable household income and type and dose of the initial statin prescription.  
† P-value for difference between estimates for siblings and parent-offspring pairs.  
‡ Inter-individual (but within-family) variance.
Table S5. Variance components for LDL-C levels and statin response in cohorts of first-degree relatives and spousal pairs (unadjusted analysis).

|                      | First-degree relatives                      |                      | Spousal pairs                      |                      |                      |                      |
|----------------------|---------------------------------------------|----------------------|------------------------------------|----------------------|----------------------|----------------------|
|                      | Variance component* (95% CI)                | Percentage of the total variance (95% CI) | Variance component* (95% CI) | Percentage of the total variance (95% CI) | p-value*              |
| Variance in pre-statin LDL-C level |                               |                      |                                   |                      |                      |                      |
| Inter-family variance | 0.014(0.011,0.017)                          | 9.5%(7.5%,11.6%)     | 0.006(0.003,0.012)                | 3.8%(1.4%,6.2%)      | 0.0004               |
| Inter-individual† variance | 0.046(0.042,0.050)                          | 32.0%(29.7%,34.2%)   | 0.051(0.046,0.056)                | 35.1%(32.1%,38.0%)   | 0.11                 |
| Variance in statin response |                               |                      |                                   |                      |                      |                      |
| Inter-family variance | 0.004(0.002,0.013)                          | 2.9%(0.3%,5.6%)      | 0.010(0.006,0.018)                | 6.7%(3.3%,10.2%)     | 0.09                 |
| Inter-individual† variance | 0.060(0.054,0.067)                          | 41.9%(38.3%,45.4%)   | 0.061(0.054,0.070)                | 42.3%(37.9%,46.6%)   | 0.88                 |
| Residual variance    |                                             |                      |                                   |                      |                      |                      |
| Intra-individual variance | 0.020(0.017,0.022)                          | 13.7%(11.6%,15.8%)   | 0.017(0.015,0.021)                | 12.1%(9.6%,14.7%)    | 0.34                 |
| Total variance       | 0.143                                       | 100%                 | 0.145                              | 100%                 |                      |

CI Confidence Interval
* The model was adjusted for type and dose of the initial statin prescription.
† P-value for difference between estimates for first-degree relatives and spousal pairs.
‡ Inter-individual (but within-family) variance.
Table S6. Variance components for LDL-C levels and statin response in the cohorts of first-degree relatives and spousal pairs refilling their statin prescription*.

|                          | First-degree relatives | Spousal pairs |
|--------------------------|------------------------|---------------|
|                          | Variance component† (95% CI) | Percentage of the total variance (95% CI) |
| Variance in pre-statin LDL-C level |                        |               |
| Inter-family variance     | 0.009(0.007,0.013) | 8.1%(5.5%,10.6%) | 0.003(0.001,0.015) | 2.3%(0.0%,5.1%) |
| Inter-individual§ variance | 0.038(0.035,0.042) | 34.3%(31.4%,37.2%) | 0.043(0.038,0.048) | 36.4%(32.9%,40.0%) |
| Variance in statin response |                        |               |
| Inter-family variance     | 0.003(0.001,0.015) | 2.9%(0.0%,6.0%) | 0.006(0.003,0.017) | 5.0%(0.9%,9.1%) |
| Inter-individual§ variance | 0.042(0.037,0.049) | 37.9%(33.4%,42.2%) | 0.053(0.046,0.061) | 44.9%(39.6%,50.0%) |
| Residual variance         | 0.019(0.017,0.022) | 16.9%(14.3%,19.6%) | 0.013(0.011,0.017) | 11.3%(8.6%,14.3%) |
| Total variance            | 0.112                  |               | 0.118                  |

CI Confidence Interval
* Only families where all members refilled their statin prescription within 24 weeks after the first prescription were included in the analysis (3743 first-degree relatives and 2352 spouses)
† The model was adjusted for age, sex, period, region of residence, indication for statin treatment, education, disposable household income and type and dose of the initial statin prescription.
‡ P-value for difference between estimates for first-degree relatives and spousal pairs.
§ Inter-individual (but within-family) variance.
Table S7. Variance components for LDL-C levels and statin response in the cohorts of first-degree relatives and spousal pairs with a refilling pattern consistent with the use of one pill per day*.

|                      | First-degree relatives |                  | Spousal pairs |                  | p-value‡  |
|----------------------|------------------------|------------------|---------------|------------------|-----------|
|                      | Variance component†   | Percentage of the total variance | Variance component†   | Percentage of the total variance |          |
|                      | (95% CI)               | (95% CI)         | (95% CI)      | (95% CI)         |           |
| **Variance in pre-statin LDL-C level** |                        |                  |               |                  |           |
| Inter-family variance | 0.007(0.005,0.013)     | 7.5%(4.0%,11.0%) | 0.003(0.001,0.018) | 3.4%(0.0%,7.3%) | 0.12      |
| Inter-individual§ variance | 0.038(0.034,0.043)   | 38.7%(34.7%,42.6%) | 0.038(0.032,0.044) | 36.8%(32.0%,41.7%) | 0.56      |
| **Variance in statin response** |                        |                  |               |                  |           |
| Inter-family variance | 0.002(0.000,0.011)     | 1.7%(0.0%,5.6%)  | 0.006(0.003,0.021) | 5.6%(0.2%,11.0%) | 0.25      |
| Inter-individual§ variance | 0.034(0.028,0.042)   | 33.9%(28.0%,39.4%) | 0.038(0.031,0.048) | 37.3%(30.0%,44.3%) | 0.45      |
| **Residual variance** |                        |                  |               |                  |           |
| Intra-individual variance | 0.018(0.016,0.021)   | 18.3%(14.9%,21.9%) | 0.017(0.014,0.021) | 16.8%(12.8%,21.3%) | 0.61      |
| **Total variance**    | 0.100                  | 100%             | 0.102         | 100%             |           |

CI Confidence Interval

* Only families where all members refilled their statin prescription within 24 weeks after the first prescription and where the number of pills of the first statin prescription covered between 75% and 150% of the days to refill, indicating the use of one pill per day, were included in the analysis (2338 first-degree relatives and 1484 spouses).

† The model was adjusted for age, sex, period, region of residence, indication for statin treatment, education, disposable household income and type and dose of the initial statin prescription.

‡ P-value for difference between estimates for first-degree relatives and spousal pairs.

§ Inter-individual (but within-family) variance.
Table S8. Variance components for LDL-C levels and statin response in cohorts of first-degree relatives and spousal pairs (extra adjustment).

|                      | First-degree relatives | Spousal pairs | p-value* |
|----------------------|------------------------|---------------|----------|
|                      | Variance component*    | Percentage of the total variance | Variance component* | Percentage of the total variance | p-value* |
|                      | (95% CI)               | (95% CI)      | (95% CI) | (95% CI)      |         |
| Variance in pre-statin LDL-C level |  |  |  |  |  |
| Inter-family variance | 0.009(0.007,0.012)     | 7.2%(5.3%,9.1%) | 0.003(0.002,0.010) | 2.6%(0.4%,4.8%) | 0.002 |
| Inter-individual\‡ variance | 0.039(0.036,0.042)     | 29.7%(27.4%,31.9%) | 0.041(0.037,0.045) | 31.2%(28.3%,34.0%) | 0.41 |
| Variance in statin response |  |  |  |  |  |
| Inter-family variance | 0.004(0.002,0.013)     | 3.4%(0.5%,6.2%) | 0.008(0.005,0.017) | 6.0%(2.2%,9.7%) | 0.27 |
| Inter-individual\‡ variance | 0.060(0.054,0.066)     | 45.7%(42.1%,49.3%) | 0.063(0.056,0.071) | 48.3%(43.8%,52.7%) | 0.38 |
| Residual variance     | 0.018(0.016,0.021)     | 14.0%(12.0%,16.1%) | 0.016(0.013,0.019) | 11.9%(9.6%,14.5%) | 0.20 |
| **Total variance**    | 0.131               | 100%            | 0.131               | 100%            |         |

CI Confidence Interval

* The model was adjusted for age, sex, period, region of residence, indication for statin treatment, education, disposable household income, type and dose of the initial statin prescription and whether the pre-statin LDL-C level was measured during an acute inpatient contact.

‡ P-value for difference between estimates for first-degree relatives and spousal pairs.

\‡ Inter-individual (but within-family) variance.
Table S9. Variance components for LDL-C levels and statin response in the cohorts of first-degree relatives and spousal pairs excluding on-statin LDL-C measurements <6 weeks from statin initiation*.  

|                      | First-degree relatives | Spousal pairs | p-value‡ |
|----------------------|------------------------|---------------|----------|
|                      | Variance component†    | Percentage of the total variance (95% CI) | Variance component† | Percentage of the total variance (95% CI) |
| **Variance in pre-statin LDL-C level** |                        |               |          |
| Inter-family variance | 0.007(0.005,0.012)      | 5.4%(2.8%,7.9%) | 0.003(0.001,0.015) | 2.7%(0.0%,5.6%) | 0.18 |
| Inter-individual§ variance | 0.038(0.034,0.043)      | 29.0%(25.9%,32.2%) | 0.035(0.031,0.041) | 28.1%(24.3%,31.9%) | 0.70 |
| **Variance in statin response** |                        |               |          |
| Inter-family variance | 0.007(0.004,0.019)      | 5.4%(1.2%,9.7%) | 0.010(0.006,0.023) | 8.2%(2.7%,13.6%) | 0.44 |
| Inter-individual§ variance | 0.061(0.053,0.071)      | 46.9%(41.7%,52.0%) | 0.061(0.052,0.072) | 48.5%(42.1%,54.6%) | 0.71 |
| **Residual variance** |                        |               |          |
| Intra-individual variance | 0.017(0.015,0.021)     | 13.2%(10.5%,16.2%) | 0.016(0.013,0.020) | 12.6%(9.3%,16.2%) | 0.77 |
| **Total variance** | 0.130                  | 100%          | 0.126    | 100% |

CI Confidence Interval
* Only families where all members had their on-statin LDL-C measured 6 weeks or more after statin initiation were included in the analysis (2534 first-degree relatives and 1666 spouses).
† The model was adjusted for age, sex, period, region of residence, indication for statin treatment, education, disposable household income and type and dose of the initial statin prescription.
‡ P-value for difference between estimates for first-degree relatives and spousal pairs.
§ Inter-individual (but within-family) variance.
Table S10- Variance components for LDL-C levels and statin response in the cohorts of first-degree relatives and spousal pairs after exclusion of individuals with very low or very high levels of pre-statin LDL-C or on-statin LDL-C.*†.

|                          | First-degree relatives |               | Spousal pairs |               |           |               |           |           |           |
|--------------------------|------------------------|---------------|---------------|---------------|-----------|---------------|-----------|-----------|-----------|
|                          | Variance component‡ (95% CI) | Percentage of the total variance (95% CI) | Variance component‡ (95% CI) | Percentage of the total variance (95% CI) | p-value§ |
| Variance in pre-statin LDL-C level |                       |               |               |               |           |               |           |           |           |
| Inter-family variance    | 0.009(0.007,0.012)     | 6.6%(4.7%,8.4%) | 0.004(0.002,0.009) | 2.8%(0.8%,4.8%) | 0.007    |
| Inter-individual‖ variance | 0.039(0.036,0.042)     | 29.9%(27.6%,32.1%) | 0.039(0.035,0.043) | 29.8%(27.1%,32.4%) | 0.95     |
| Variance in statin response |                       |               |               |               |           |               |           |           |           |
| Inter-family variance    | 0.004(0.002,0.013)     | 3.3%(0.5%,6.2%) | 0.007(0.004,0.016) | 5.6%(1.9%,9.3%) | 0.34     |
| Inter-individual‖ variance | 0.060(0.055,0.067)     | 46.6%(42.9%,50.1%) | 0.068(0.062,0.076) | 52.6%(48.2%,56.9%) | 0.04     |
| Residual variance        | 0.018(0.016,0.020)     | 13.6%(11.7%,15.7%) | 0.012(0.010,0.015) | 9.2%(7.0%,11.5%) | 0.004    |
| Total variance           | 0.130                   | 100%            | 0.130           | 100%          |           |

CI Confidence Interval

* In this analysis, individuals with very low or very high values for pre-statin LDL-C or on-statin LDL-C were excluded together with their families (11 first-degree relatives [0.41%] and 8 spouses [0.25%] were excluded in total). Extreme values were defined as values below the 0.05% quantile or above the 99.5% quantile of the distribution of pre-statin LDL (on-statin LDL-C respectively) in the total population of statin initiators having both LDL-C measurements.

† Overall, we observed minimal differences in the inter-family variance components compared with the result of the main analysis (Table 2). More specifically, among first-degree relatives, the decomposition of the variance in attained LDL-C was virtually unaltered, while, among spouses, the inter-individual variance in statin response accounted for a bigger share compared to the main analysis (Table 2), at the expense of the inter-individual variability in pre-statin LDL-C and the residual variance.

‡ The model was adjusted for age, sex, period, region of residence, indication for statin treatment, education, disposable household income and type and dose of the initial statin prescription.

§ P-value for difference between estimates for first-degree relatives and spousal pairs.

‖ Inter-individual (but within-family) variance.
Table S11. Comparison of inter-family variance components estimated in the main model and in alternative models.

For further description of the alternative models, see Data S1.

|                | Main model (see Table 2)          | Alternative model          |
|----------------|----------------------------------|----------------------------|
| **Alternative model: model with covariance between the inter-family random intercept and the inter-family random statin response** |                        |                            |
| **First-degree relatives** |                                    |                            |
| Inter-family variance in statin response | 0.004 (0.002, 0.013) | 0.003 (0.001, 0.020) |
| % of total variance | 3.3% (0.5%, 6.2%) | 2.4% (0.0%, 5.4%) |
| Inter-family variance in pre-statin LDL-C level | 0.010 (0.008, 0.013) | 0.009 (0.007, 0.012) |
| % of total variance | 7.4% (5.5%, 9.3%) | 6.9% (4.9%, 8.9%) |
| **Spousal pairs** |                                    |                            |
| Inter-family variance in statin response | 0.008 (0.005, 0.017) | 0.008 (0.005, 0.017) |
| % of total variance | 6.0% (2.2%, 9.7%) | 6.1% (2.3%, 9.9%) |
| Inter-family variance in pre-statin LDL-C level | 0.003 (0.002, 0.010) | 0.004 (0.002, 0.010) |
| % of total variance | 2.7% (0.5%, 4.9%) | 2.8% (0.5%, 5.0%) |

**Alternative model: model including only statin response**

|                | Main model (see Table 2)          | Alternative model          |
|----------------|----------------------------------|----------------------------|
| **First-degree relatives** |                                    |                            |
| Inter-family variance in statin response | 0.004 (0.002, 0.013) | 0.003 (0.001, 0.020) |
| % of total variance | 3.3% (0.5%, 6.2%) | -                           |
| **Spousal pairs** |                                    |                            |
| Inter-family variance in statin response | 0.008 (0.005, 0.017) | 0.008 (0.005, 0.017) |
| % of total variance | 6.0% (2.2%, 9.7%) | -                           |

**Alternative model: model including only the untreated LDL-C level**

|                | Main model (see Table 2)          | Alternative model          |
|----------------|----------------------------------|----------------------------|
| **First-degree relatives** |                                    |                            |
| Inter-family variance in untreated LDL-C level | 0.010 (0.008, 0.013) | 0.020 (0.019, 0.021) |
| % of total variance | 7.4% (5.5%, 9.3%) | -                           |
| **Spousal pairs** |                                    |                            |
| Inter-family variance in untreated LDL-C level | 0.003 (0.002, 0.010) | 0.002 (0.001, 0.005) |
| % of total variance | 2.7% (0.5%, 4.9%) | -                           |

*†‡§‖ Since the alternative model does not contain all the variance components included in the main model, it is meaningless to compare the percentages from the two models because of the different denominator. We, instead, calculated an approximate percentage of the total variance by substituting in the main model the estimate of the inter-family variance with the corresponding estimate obtained from the alternative model. By use of this approach, we obtained: 2.3% (*), 6.2% (†), 14.2% (‡) and 1.8% (‖).

* † ‡ § ‖ This analysis included 94,193 first-degree relatives and 44,064 spouses
The figure shows the conditional standardized residuals plotted against the fitted values from the model. Nine observations are not included in this graph because of conditional standardized residuals < -5.
The figure shows the quantiles of conditional standardized residuals plotted against the quantiles of the normal distribution. Nine observations are not included in this graph because of conditional standardized residuals < -5.