Visit-to-visit lipid variability: clinical significance, effects of lipid-lowering treatment, and (pharmaco)genetics

Running title: Literary review of visit-to-visit lipid variation

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Highlights

- Visit-to-visit lipid variability is increasingly being linked to adverse outcomes.
- Levels may depend on dosage and dosing schedule of lipid-lowering agents.
- Genome-wide testing provides no evidence for effects of common variants.
- Study heterogeneity and likely publication bias impede literary interpretation.
- There exists ample room for phenotype harmonisation amongst studies.

Abstract

In recent years, visit-to-visit variability of serum lipids has been linked to both clinical outcomes and surrogate markers for vascular disease. In this article, we present an overview of the current evidence connecting this intra-individual variability to these outcome measures, discuss its interplay with lipid-lowering treatment, and describe the literature regarding genetic factors of possible interest. In addition, we undertook an explorative genome-wide association analysis on visit-to-visit variability of LDL-C and HDL-C, examining additive effects in 2,530 participants from the placebo-arm of the PROSPER trial. While we identified suggestive associations ($p<1x10^{-6}$) at 3 different loci (KIAA0391, ACCN1, DKK3), previously published data from the GWAS literature did not suggest plausible mechanistic pathways. Given the large degree of both clinical and methodological heterogeneity in the literature, additional research is needed to harmonize visit-to-visit variability parameters across studies and to definitively assess the possible role of (pharmaco)genetic factors.

Keywords: visit-to-visit variability, lipoprotein, gwas, pharmacogenetics, risk factor, vascular disease

Introduction

There is a growing body of evidence showing that, in addition to average levels, fluctuations in various traditional risk factors may be of importance to cardiovascular risk assessment. For example, it is now well-established that higher intra-individual variability of blood pressure (BP)[1-3] and lower variability in heart rate[4, 5] associate with various adverse outcomes. However, lipid concentrations are also known to fluctuate substantially, even on a day-to-day basis.[6, 7]

Modulated by a myriad of factors including biological, sampling, analytical, and clinical conditions,[8] this measurement 'noise' may lead to uncertainty in clinical practice, making repeated lipid measurements necessary before determining that a patient is above a disease or risk threshold, or when evaluating the efficacy of lipid-level altering treatments.

Recent evidence suggests that visit-to-visit variability of lipids may independently associate with adverse outcomes. Here, we present an overview of the current literature linking this intra-individual variability of lipids to clinical outcomes, describe its relation to lipid-lowering treatment, and briefly summarize which genetic variants have previously been found to contribute to increased lipid variability. In addition, we present data from the first genome-wide association study (GWAS) on visit-to-visit variability of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels, using data from the PROspective Study of Pravastatin in the Elderly at Risk for vascular disease (PROSPER).

Clinical significance

In 1960 an interesting collection of observations was published by Groover et al., who examined 177 military personnel over 5 years. Comparing cholesterol fluctuations over this period, it appeared that the group of individuals who had developed clinical manifestations of coronary artery disease had greater fluctuations in the preceding years (though no formal statistical testing was performed).[9] It wasn't until 34 years later that researchers from the Framingham study reported that greater long-term intra-individual variability in total cholesterol (TC) associates with all-cause mortality over a 24-year period in men, and with cardiovascular and coronary disease incidence and mortality in both sexes.[10]

Only recently has an interest in the clinical impact of visit-to-visit variability of lipids re-emerged, with a number of studies showing that various metrics of higher variability also associate with clinical outcomes over shorter periods of follow-up (**Table 1**). Of these, five studies have reported that higher intra-individual lipid variability is predictive of higher occurrence of adverse cardiovascular events. First, researchers from the Treating to New Targets (TNT) study found that variability of LDL-C is a predictor of cardiovascular events and mortality, independent of statin treatment, average LDL-C levels, and medication adherence as determined through pill count in individuals with stable coronary artery disease.[11] These findings were recently replicated for measures of variability in HDL-C and triglycerides in the same population, additionally showing evidence that both LDL-C and triglyceride variability associate with incident diabetes.[12] Similar findings between LDL-C variability and vascular events and all-cause mortality were shown in post-hoc analyses of the Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL) trial of 8,658 patients with previous MI.[13] In addition, Boey et al. observed that variability of LDL-C and HDL-C levels associated with 5-year occurrence of major adverse cardiac events after surviving ST-segment elevation myocardial infarction.[14] Lastly, a recent large-scale investigation of over 3.5 million individuals from the Korean National Health Insurance System (NHIS)

cohort without a history of MI and stroke showed that higher TC variability linearly associated with greater incidence of MI, stroke and all-cause mortality.[15]

Visit-to-visit variability of lipids has also been demonstrated to associate with other outcomes. Chang et al. found that fluctuations of HDL-C, but not LDL-C, associate with a higher risk of diabetic nephropathy progression in type 2 diabetes patients.[16] Both LDL-C and HDL-C variability have additionally been shown to associate with decline in glomerular filtration rate, but not with incidence of albuminuria.[17] Findings from the Korean NIHS also suggest that lipid variability is related to change in kidney function, as analyses in almost 8.5 million individuals showed that increasing TC variability associated with progression to end-stage renal disease.[18] Furthermore, higher variability of LDL-C was shown to cross-sectionally associate with lower cognitive test performance in four cognitive domains, lower cerebral blood flow, and greater white matter hyperintensity volume, in older individuals at high risk for vascular disease, independent of average LDL-C levels and statin treatment.[19] In addition, relatively smaller studies have shown cross-sectional associations between higher LDL-C variability and obstructive sleep apnea[20] and maximum carotid intima-media thickness.[21]

Several hypotheses have been put forward to explain these observational findings. On the one hand, lipid variability might simply be a risk marker for distinct pathological processes leading to adverse outcomes. These include (sub)clinical disease (e.g. inflammation, cancer, kidney or liver disease), but also use of, or non-adherence to, various types of medication.[22] If so, interventions specifically aimed at reducing variability are not likely to be effective. On the other hand, lipid variability might represent a novel modifiable risk factor. In the past, intermittent high-fat diets have been used to induce atherosclerotic lesions in animals.[23, 24] Moreover, it has recently been shown that lipid lowering treatment in both animal models and humans may lead to changes of the cholesterol content of plaques,[25, 26] which may have consequences for plaque stability.[27, 28] These studies provide circumstantial evidence that fluctuations in lipid levels could also causally lead to a higher occurrence of adverse events.

Current knowledge on lipid variability has important limitations. As recently argued for research on visit-to-visit variability of BP,[29] standardized definitions should be developed to facilitate comparisons across studies and assess whether reduction of variability will improve outcomes. Much of the evidence in favour of clinical significance of lipid variability stems from post-hoc analysis of trials, or from research with participants at high risk for vascular disease. However, the recent studies performed within the nationwide Korean NIHS suggest that these relationships might also hold for the general population, and may even be more pronounced within low-risk groups (e.g. younger age, or in absence of comorbidities such as obesity and diabetes).[15, 18] To date, all studies have solely examined mid- to long-term lipid variability (i.e. months to years). While these studies have consistently shown that higher lipid variability associates with worse clinical outcomes, these investigations are largely incomparable due to the heterogeneity in chosen outcomes of interest and metrics of variability. More specifically, five different metrics have been used, though all are known to be susceptible to either trend effects or mean levels in a repeated measurements setting (**Supplemental Table 1**). Moreover, there exist large differences in source population and study design, fasting status, number and regularity of lipid measurements, and selection of covariates. In addition, we should acknowledge the likely presence of submission and publication bias, as evidenced by the substantial publication time gaps between the Air Force and Framingham articles and the more recent publications. It therefore remains to be seen whether lipid variability truly reflects a reproducible phenomenon, and whether more short-term (e.g. daily or weekly) fluctuations also hold promise for clinical risk assessment.

Nonetheless, if it can be shown that appraisal of lipid variability could benefit risk assessment, this might influence ordering patterns of lipid levels in clinical practise. Researchers working with large-scale data from the Korean NHIS have recently shown that incorporating variability of different cardiovascular disease risk factors (including intra-individual variability of total cholesterol) substantially improved cardiovascular risk predictability compared with single measurement values or taking the average of repeated measurements[30], though this was not examined separately for lipid variability. These findings are

in line with a previous simulation study showing that blood pressure and cholesterol variability may lead to substantial misclassification when cardiovascular risk assessment is based on single measurements[31], and with increasing evidence that incorporating repeated measurements can improve cardiovascular risk prediction.[32] Based on the current literature it is however not yet possible to make recommendations on the necessity of repeated lipid measurements in clinical practise either before or after starting lipid lowering treatment, beyond which is already viewed as necessary to overcome short-term fluctuations in lipid levels.

Interplay with lipid-lowering treatment

To date, few studies have systematically examined the effects of lipid-lowering treatment on intra-individual variability of lipids. Commencement of statin treatment has been shown to lead to a minor decline in absolute values of visit-to-visit lipid variability in clinical trials,[19] as measured by the intra-individual standard deviation, with more intensive statin treatment leading to even more stable LDL-C levels.[11, 13] While these dose-dependent results are not always seen in observational studies, this may be due to different prescription patterns.[14] It is currently unknown whether drug-class effects exist, which have been described in research on visit-to-visit BP variability,[33, 34] though a cross-over study in 26 individuals with type 2 diabetes suggests that these might depend on the methods of measuring and calculating lipid profiles.[35, 36]

Despite this absolute decrease, results (**Table 2**) from our PROSPER study suggest that statin therapy may also lead to a relative increase in lipid variability. This likely occurs because declines in average levels of lipids will generally be larger than declines in variability, which will influence relative metrics such as the coefficient of variation. However, it is expected that absolute declines will be of greater importance in clinical settings, offsetting any relative increase.

Another treatment-related factor contributing to intra-individual variability of lipids is non-adherence,[37] as has similarly been shown for antihypertensive medication and visit-to-visit variability of BP.[38] While combined pharmacological treatment modalities may reduce adherence-associated variability,[39] adjusting for non-adherence is often difficult due to the absence of reliable assessment methods,[40, 41] which may limit which studies are best suited to investigate effects of visit-to-visit variability in absence of non-adherence. However, studies which have performed analyses stratified by use of lipid-lowering agents have shown either highly comparable[19] or more pronounced[15, 18] associations between variability and clinical outcomes in individuals not using lipid-lowering medication. It is therefore unlikely that, at least in those studies, the findings can be explained solely by non-adherence. Dosing schedules can also influence variability. While high-dose monthly dosing of PCSK9-inhibitors are known to produce substantial fluctuations of LDL levels in between injections,[42, 43] there exists tentative trial evidence that adverse neurocognitive events may be more prevalent, independent of on-treatment lipid levels.[44] It will therefore be of interest for PCSK9-trials to examine the possible influence of lipid variability on cognitive test performance in greater detail.

Genetic basis of visit-to-visit variability of lipids

While over 157 loci associated with blood lipid levels have been identified and annotated through large-scale efforts,[45] little is known about the genetic predisposition for intra-individual variability of lipids. The same applies to variability of other physiological measures. For example, to date just one GWAS has been published on visit-to-visit variability of BP,[46] which many consider the poster child of intra-individual variability.

Previously, Pereira et al. assessed the association between 11 genetic polymorphisms involved in lipid metabolism and intra-individual variability of total cholesterol and HDL-C in up to 458 men and women

from 27 feeding or supplement trials designed to change serum cholesterol.[47] The authors found evidence that two polymorphisms may increase the variability of total cholesterol (ApoA4 -347 (0.015 mmol/l higher geometric mean of the intra-individual standard deviations for genotype 12/22 versus genotype 11, p=0.02); MTP -493 (0.017 mmol/l higher for genotype 11 versus genotype 12/22, p=0.004)). In a study of 117 men with peripheral arterial disease, it was reported that those heterozygous for the ApoB EcoRI polymorphism had higher within-individual variation of total serum cholesterol concentration over a period of 5-10 years using annual lipid measurements.[48] Furthermore, Porkka et al. examined the influence of selected genetic markers on long-term variability of serum lipids in up to 320 subjects aged 3-18 years at baseline over 3-year intervals during a 6-year follow-up period.[49] They found that ApoB Xbal genotypes significantly influenced variability of TC and LDL-C levels in both sexes, and variability of triglycerides in males only. Moreover, ApoAI/CIII genotype influenced variability of TC and LDL-C levels but again, only in males. Finally, by comparing within-pair differences in monozygotic twins, possible 'variability gene effects' on lipid levels of genes in the Kidd blood group locus and of the TaqIB polymorphism in the CETP gene have been demonstrated by Berg and colleagues.[50, 51]

As no other studies have examined whether commonly occurring genetic variants are of importance to visit-to-visit variability of lipids, we undertook an explorative genome-wide association study on intra-individual variability of LDL-C and HDL-C, as fluctuations in specifically these two lipid traits have recently been shown to associate with clinical outcomes.

GWAS

We included 2,530 individuals from the placebo-arm of the PHArmacogenetic study of Statin in the Elderly at risk (PHASE).[52,53] Genotyping was conducted using Illumina 660-Quad beadchips and

imputation with MACH imputation software based on the Hapmap built II release 23. We excluded variants with a minor allele frequency below 1%, and those with an imputation quality below 0.3.

Lipid levels were assessed after an overnight fast. LDL-C was directly measured, and visit-to-visit variability of both LDL-C and HDL-C was defined as the intra-individual standard deviation over each individual's lipid measurements at 3, 6, 12, 24, and 36 months after randomisation.

The association analyses were conducted using PROBABEL software (http://www.genabel.org/). For both LDL-C and HDL-C variability, an additive linear regression model was used. Given the negligible difference in absolute values of visit-to-visit variability between the two trial arms, we did not undertake genome-wide association analyses on the interaction terms with statin treatment. However, as non-adherence to pravastatin might influence the degree of visit-to-visit lipid variability, the analyses presented here were conducted solely in the placebo group. All analyses were adjusted for age, gender, principal components of ancestry (n=4), and mean intra-individual lipid level during follow-up. The p-value threshold for genome-wide significance was set at $5x10^{-8}$.

Known host genes for variants of note found in the GWAS were located via the SCAN database (http://www.scandb.org/).[54] Furthermore, we searched Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk),[55] a curated database holding publicly available results from large-scale GWAS, for evidence of plausible mechanistic pathways for these three variants. In addition, we examined our GWAS results for the lead SNPs for loci previously found to associate with either LDL-C or HDL-C levels at a genome-wide significant level in the largest lipid GWAS to date.[45] As some lead SNPs were associated with both traits this list comprised 124 different lead SNPs. To account for multiple testing, the p-value threshold for statistical significance was set at 0.0002 (i.e. 0.05/248 tests).

Results

We did not observe any genome-wide significant associations for additive effects on lipid variability (**Figure 1**). However, we did detect two suggestive ($p<1x10^{-6}$) signals for LDL-C variability (KIAA0391 and Amiloride-sensitive cation channel 1 neuronal (ACCN1)) and one for HDL-C variability (Dickkopf WNT Signaling Pathway Inhibitor 3 (DKK3)), as shown in **Table 3**. Q-Q plots did not reveal evidence of systematic bias (**Supplementary Figure**).

In order to examine possible mechanistic pathways leading to lipid variability, we queried the three suggestive lead SNPs shown in **Table 3** in the Phenoscanner database. However, with the exception of nominal associations with body-mass index and height (p-values between 0.05 and 0.001), no traits were shared by multiple variants (data not shown).

Finally, as shown in **Supplemental Table 2** and **3**, no previously reported lead SNPs for loci associated with either LDL-C or HDL-C levels attained statistical significance after correction for multiple testing.

Discussion

In this narrative review we have presented the literature on visit-to-visit lipid variability to date. While the exact role of lipid lowering treatment remains to be elucidated, it is evident that the substantial clinical and methodological heterogeneity among studies impedes drawing strong conclusions regarding possible clinical significance. Furthermore, our current genome-wide association results suggest that most genetic variants, including those that influence mean LDL-C or HDL-C levels, are not associated with intra-individual variability of lipids, or that their effects are too small to detect with our current sample size. Replication studies will therefore be necessary to determine whether these explorative findings reflect true associations or merely statistical noise. Given the negligible difference in absolute values of lipid variability between the two PROSPER trial arms, it appears unlikely or at least doubtful that clinically relevant pharmacogenetic-guided interventions will be based on common genetic variants.

The major limitations of our association analysis were the relatively small sample size, though not dissimilar to the sole GWAS study on visit-to-visit variability of BP, and the inclusion of exclusively European-descent participants. Future studies on (pharmaco)genetic effects on intra-individual lipid variability should carefully consider issues of non-adherence. In addition, the influence of number of visits, the effect of duration of time between measurements, and the proximity of lipid measurements to drug administration may be important to consider.[47, 56, 57]

It should further be noted that intra-individual lipid variability will presumably vary within and among populations due to varying genetic and environmental factors, which could limit the generalizability of any given study.[47] For example, it is likely that genetic factors of importance will differ between younger and older populations, as age- or clinical disease-related disturbances to homeostatic mechanisms will be of little significance to younger populations. This is supported by research on the heritability of intra-individual BP variability, as researchers from the Twins UK cohort found that environmental factors were responsible for over 80% of the variance in variability in older age groups, versus over 50% for twin pairs younger than 51 years.[58] However, given that age-related loss of physiological homeostasis would presumably lead to greater overall intrinsic variability,[59] there might exist genetic variants of importance to visit-to-visit variability of multiple physiological measures in older populations.

Future studies could focus on overall genetic predisposition to lipid levels in greater detail, by examining loci previously found to associate with lipid metabolism,[45] as those individuals genetically predisposed to certain lipid levels might be less likely to vary from visit-to-visit. In addition, factoring in lipid-lowering treatment may enhance power for the detection of genes of importance to intra-individual variability of lipids, especially if genetic loci have a differential effect conditional on the treatment. Gene-environment-wide interaction studies (GEWIS) using a joint meta-analysis (JMA) approach may therefore provide further insight into the (pharmaco)genetic background of visit-to-visit variability of lipids.[60] While these methods are promising, there remains ample room for the development of methodology and statistical

software packages to detect genetic loci affecting visit-to-visit variability, which account for phenotypic variability across individuals.[61]

In summary, while visit-to-visit variability could be a novel prognostic marker for clinical practice, additional efforts are needed to harmonise phenotype definitions across different studies, and replication studies are required to definitively assess the possible importance of (pharmaco)genetic factors.

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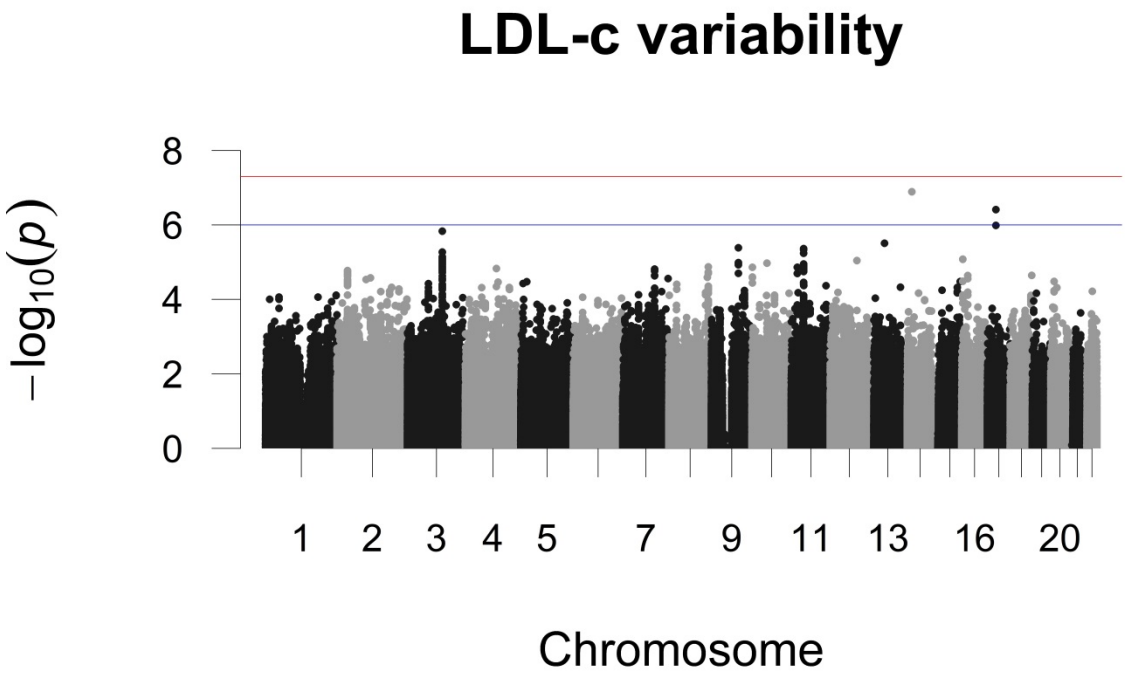
Figure legend

Figure 1. Genome-wide Manhattan plots for visit-to-visit variability of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), as measured by the intra-individual standard deviation, in the placebo group (n=2,530) of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Individual $-\log_{10}$ p-values are plotted against their genomic position. Adjusted for age, gender, mean intra-individual lipid level during follow-up, and principal components of ancestry (n=4).


LDL-c variability
$-\log_{10}(p)$
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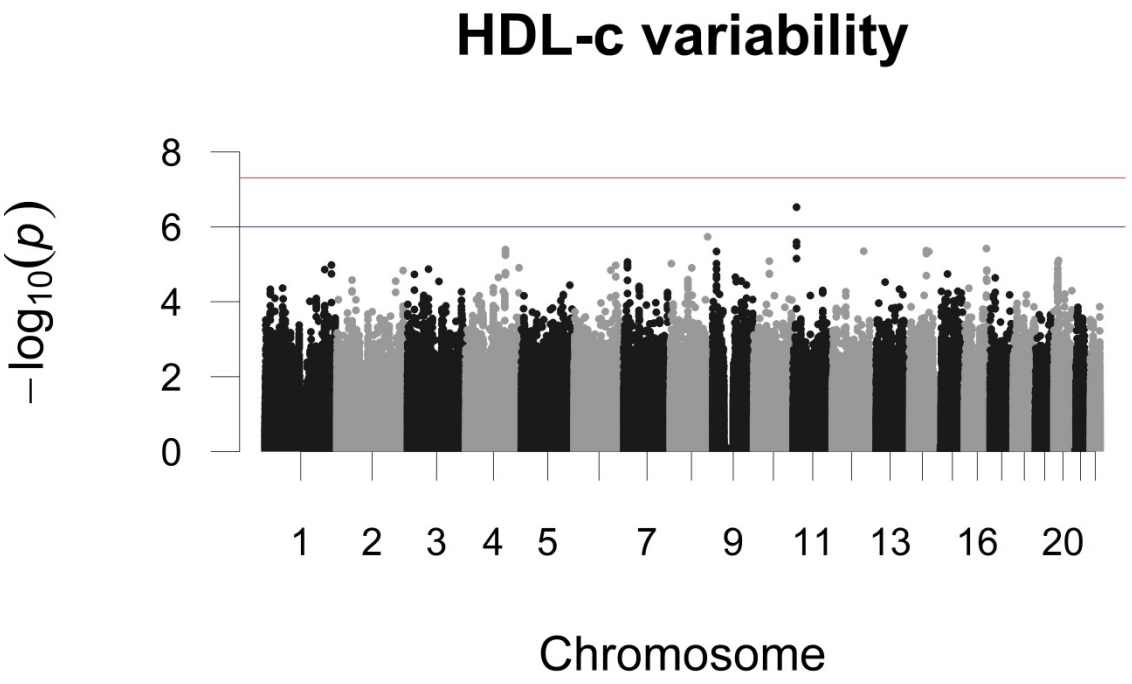
Chromosome


HDL-c variability
$-\log_{10}(p)$
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Chromosome

Table 1. Chronologically listed studies which have reported on associations between visit-to-visit lipid variability and (sub)clinical outcomes

Clinically overt cardiovascular disease						
First author (year)	Study population/design	Lipid traits	Variability metric(s)	Number of, and time between, measurements	Model covariates	Main results
Groover[9] (1960)	177 men aged 40 to 60 years, comparison between individuals who did (n=16) and did not develop CAD, cross-sectional analysis	TC (non-fasted)	% difference between highest and average of measurement(s)	≥6 yearly measurements for 5 consecutive years, time intervals unspecified	None (no formal statistical testing)	Greater deviations from 5-year average within CAD group
Kreger[10] (1994)	1,505 women and 1,407 men aged 30 to 62 years, population-based cohort, follow-up of 24 years	TC (non-fasted)	RMSE	6 biennial measurements	Age, average slope of TC, mean TC	Higher variability associated with all-cause mortality and cardiovascular and coronary incidence and mortality in both sexes
Bangalore[11] (2015)#	9,572 patients aged 35 to 75 years with known CAD, post-hoc analysis from RCT comparing atorvastatin 80 versus 10 mg/day, median follow-up of 4.9 years	LDL-C (fasted)	s.d., ASV, CV, cVIM	At week 12, at 12 months, thereafter annual, minimum of 2 post-baseline measurements	Age, adherence (pill count), mean LDL-C, treatment arm	Higher variability associated with higher incidence of any coronary or cardiovascular event, all-cause mortality, MI, and stroke
Boey[14] (2016)	130 patients aged 54.1 ± 9.3 years with ST-segment elevation myocardial infarction and surviving to discharge, mean follow-up of 62.4 ± 30.5 months	LDL-C, HDL-C (non-fasted)	s.d., CV, cVIM	9.1 ± 4.5 LDL-C measurements, 9.3 ± 4.5 HDL-C measurements, minimum of 3 from two months after discharge, with variable measurement schedules	Mean lipid levels, diabetes mellitus	Higher variability in both LDL-C and HDL-C associated with higher risk of major adverse cardiac event (death, MI, stroke, unplanned revascularization, heart failure admission)
Bangalore[13] (2017)	8,658 patients aged 62 ± 9.5 years with previous MI, post-hoc analysis from RCT comparing atorvastatin 80 mg/day versus simvastatin 20 mg/day, median follow-up 4.8 years	LDL-C (fasted)	s.d., ASV, CV, cVIM	At week 12, 24, year 1, thereafter yearly	Demographics, treatment arm, cardiovascular comorbidities, mean LDL-C	Higher variability associated with risk of any coronary or cardiovascular event, all-cause mortality, and MI
Kim[15] (2017)*	3,656,648 individuals aged 44.9 ±12.6 years without history of MI and stroke, population-based cohort, median follow-up of 8.3 years	TC (fasted)	s.d., CV, VIM	3-6 measurements during 6 years (4.2±1.2), time intervals unspecified	Demographics, cardiovascular comorbidities, baseline and/or mean TC, lipid-lowering treatment	Higher variability linearly associated with incidence of MI, stroke and all-cause mortality
Waters[12] (2017)#	9,572 patients aged 35 to 75 years with known CAD, post-hoc analysis from RCT comparing atorvastatin 80 versus 10 mg/day, median follow-up of 4.9 years	LDL-C, HDL-C, TG (fasted)	s.d., ASV, CV, cVIM	At week 12, at 12 months, thereafter annual, minimum of 2 post-baseline measurements	Demographics, cardiovascular comorbidities, mean lipid levels, treatment arm, change in lipid levels	Higher variability in each lipid trait associated with incidence of coronary and cardiovascular events. In addition, LDL-C and TG variability associated with incident diabetes.

Table 1 continued.

Other outcomes						
First author (year)	Study population/design	Lipid traits	Variability metric(s)	Number of, and time between, measurements	Model covariates	Main results
Chang[16] (2013)	864 type 2 diabetic patients aged 62.7 ± 11.8 years, mean follow-up of 3.8 years	TC, LDL-C, HDL-C, TG (fasted)	s.d.	8.5 ± 1.5 measurements, measured either quarterly or every 6 months	Demographics, smoking, disease duration, kidney function, ACEI/ARB, lipid-lowering treatment	Higher HDL-C variability associated with higher risk of diabetic nephropathy progression
Smit[19] (2016)	4,428 patients aged 70 to 82 years at high risk of vascular disease, post-hoc analysis from placebo-controlled RCT of pravastatin 40 mg/day, with MRI substudy of 535 participants, cross-sectional analyses stratified by treatment arm	LDL-C (fasted)	s.d.	4 post-baseline measurements at months 3, 6, 12, 24 (92% with all 4)	Demographics, cardiovascular comorbidities, mean LDL-C	Higher variability associated with worse cognitive performance at month 30 for selective attention, processing speed, immediate and delayed recall, and with lower cerebral blood flow and greater white matter hyperintensity load at end of study, in both treatment arms
Ng[20] (2017)	190 patients aged 54.0 ± 8.8 years with known CAD, cohort followed up after overnight sleep study, cross-sectional analyses	LDL-C (fasted)	cVIM	8.1 ± 4.2 (minimum of 3) measurements during 53.2 ± 25.3 months, time intervals unspecified	Diabetes mellitus, hyperlipidemia	Higher scores on apnea-hypopnea index associated with greater visit-to-visit variability
Takenouchi[21] (2017)	162 type 2 diabetic patients aged 62 ± 10 years, cross-sectional analyses	LDL-C (fasted)	s.d.	94% had 6 measurements measured during 12 month period, time intervals unspecified	Age, sex	Higher variability associated with maximum carotid intima-media thickness
Ceriello[17] (2017)	Type 2 diabetes patients, 2 cohorts: 4,231 with median age of 67.4 (IQR: 60.3-73.4) and normoalbuminuria, 7,560 aged 65.0 (58.5-71.3) with eGFR $\geqslant$ 60 mL/min/1.73 m^2, median follow-up 3.4 years (range 1.7-4.2)	TC, LDL-C, HDL-C, TG (fasting status unspecified)	s.d.	≥5 measurements over 3 years, time intervals unspecified	Demographics, baseline lipid levels/blood pressure/kidney function, glucose- and lipid-lowering treatment, ACEI/ARB, duration of diabetes	No associations with incident albuminuria. However, higher variability in LDL-C and HDL-C associated with increased risk for decline in eGFR below 60 mL/min/1.73 m^2
Kim[18] (2017)*	8,493,277 individuals aged 48.5 ± 13.8 years and free from ESRD, population-based cohort, median follow-up 6.1 years	TC (fasted)	s.d., CV, VIM	3-5 measurements over 6 years (3.5 ± 0.8), time intervals unspecified	Demographics, cardiovascular comorbidities, baseline and/or mean TC, lipid-lowering treatment, baseline kidney function	Graded association between higher variability with incident ESRD

#/*: complete/partial overlap in study populations. RCT denotes randomized clinical trial; CAD, coronary artery disease; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; RSME, square root of mean squared error ; s.d., standard deviation; ASV, average successive variability; CV, coefficient of variation; (c)VIM, (corrected) variation independent of mean; ACEI/ARB, angiotensin converting enzyme inhibitor or angiotensin receptor blocker.

Table 2. Demographic characteristics and lipid parameters for the PROSPER study

	Placebo (n=2,530)	Pravastatin (n=2,504)	p-value
Age at randomisation	75.31 ± 3.35	75.33 ± 3.35	-
Females (%)	1309 (51.7)	1300 (51.9)	-
Lipid parameters at baseline (mmol/L)			
LDL-C	3.79 ± 0.78	3.80 ± 0.81	-
HDL-C	1.28 ± 0.34	1.29 ± 0.36	-
Lipid parameters during follow-up (mmol/L)*			
No. of measurements	4.39 ± 0.82	4.39 ± 0.81	0.98
Average LDL-C	3.70 ± 0.76	2.56 ± 0.65	<0.001
LDL-C variability (standard deviation)	0.33 ± 0.21	0.32 ± 0.24	0.02
LDL-C variability (coefficient of variation)	0.09 ± 0.06	0.13 ± 0.13	<0.001
Average HDL-C	1.33 ± 0.36	1.40 ± 0.38	<0.001
HDL-C variability (standard deviation)	0.12 ± 0.08	0.13 ± 0.08	0.001
HDL-C variability (coefficient of variation)	0.09 ± 0.05	0.09 ± 0.05	0.53

Unless otherwise specified, data are presented as mean ± standard deviation. P-values calculated using Student t-test and Pearson's chi-square test when appropriate.

LDL-C denotes low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

* calculated per-individual, over months 3 to 36

Table 3. Genetic variants independently associated with lipid variability at $p < 1x10^{-6}$ (n=2,530)

Trait	Lead SNP	Chr.	Position	Gene*	Coding allele (CA)	Noncoding allele	Freq. CA	Beta †	s.e.	p-value
LDL-C variability	rs2295463	14	34806024	KIAA0391	C	T	0.98	-0.115	0.022	1.3×10^{-7}
	rs11867369	17	29243349	ACCN1	C	T	0.09	0.050	0.010	3.9×10^{-7}
HDL-C variability	rs4757730	11	11971832	DKK3	G	T	0.90	0.016	0.003	3.0×10^{-7}

Chr., chromosome; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

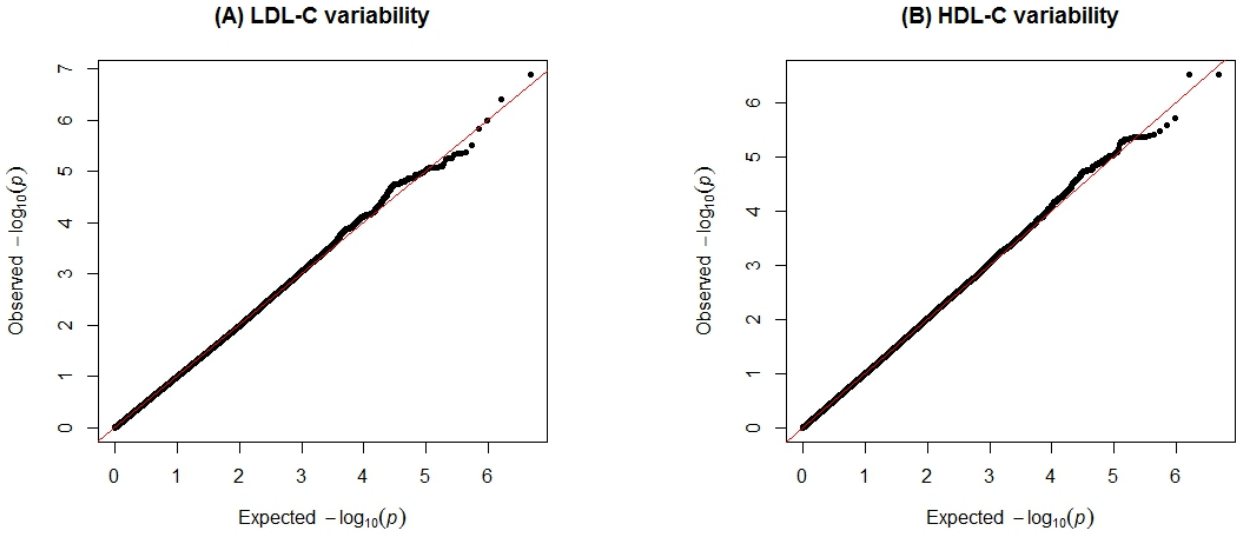
* As reported by the SCAN database (available at http://www.scandb.org).

† Beta for per-allele additive effect on lipid variability (intra-individual standard deviation, mmol/L), adjusted for age, sex, mean intra-individual lipid level, and principal components of ancestry (n=4).

Supplemental Table 1. Metrics of lipid visit-to-visit variability used in the literature

Measure	Formula	Properties
Square root of mean squared error (RSME)	$\sqrt{\frac{\sum_{i=1}^{n}(x_i - \hat{x}_i)^2}{n-2}}$ With $\hat{x}_i$ obtained from fitting *x* against time	Takes (assumed to be linear) trend of repeated measurements into account, but is susceptible to differences in mean follow-up levels
Standard deviation (s.d)	$\sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{(n-1)}}$	Dependent on mean follow-up levels, and susceptible to trend across measurements
Coefficient of variation (CV)	$\frac{s.d.}{\bar{x}}$	Largely independent of mean follow-up levels, but susceptible to trend effects
Average successive variability (ASV)	$\frac{\sum_{i=1}^{n-1}\lvert x_{i+1} - x_i\rvert}{n-1}$	Largely independent of trend effects, but susceptible to differences in mean follow-up levels
Corrected variation independent of mean (cVIM)	$VIM = \frac{s.d.}{\bar{x}^{beta}}$ With *beta* obtained from fitting s.d. on $\bar{x}$, after natural log-transformation. $cVIM = \frac{(VIM \times \overline{CV})}{VIM}$	Independent of mean follow-up levels, but susceptible to trend effects

x_i denotes the *i*-th measurement of a set of *n*-measurements



No g λ's: (A) 0.995; (B) 1.002

Supplemental Table 2. Lead SNPs for previously reported loci for LDL-C levels.

SNP	Chr.	Locus	LDL-C var.	HDL-C var.
rs10102164	8	SOX17	0.03	0.66
rs10128711	11	SPTY2D1	0.56	0.56
rs10401969	19	CILP2	0.35	0.24
rs10490626	2	INSIG2	0.66	0.29
rs11065987	12	BRAP	0.51	0.89
rs11136341	8	PLEC1	0.92	0.55
rs11220462	11	ST3GAL4	0.9	0.21
rs11563251	2	UGT1A1	0.11	0.47
rs1169288	12	HNF1A	0.07	0.85
rs12027135	1	LDLRAP1	0.61	0.56
rs1250229	2	FN1	0.11	0.5
rs12670798	7	DNAH11	0.62	0.73
rs12748152	1	PIGV-NR0B2	0.12	0.44
rs12916	5	HMGCR	0.75	0.26
rs1367117	2	APOB	0.89	0.54
rs1564348	6	LPA	0.43	0.19
rs17404153	3	ACAD11	0.54	0.27
rs174546	11	FADS1-2-3	0.25	0.55
rs1800562	6	HFE	0.55	0.49
rs1800961	20	HNF4A	0.03	0.57
rs1883025	9	ABCA1	0.39	0.78
rs2000999	16	HPR	0.76	0.31

rs2030746	2	LOC84931	0.85	0.26
rs2072183	7	NPC1L1	0.68	0.77
rs2131925	1	ANGPTL3	0.13	0.57
rs2255141	10	GPAM	0.42	0.38
rs2328223	20	SNX5	0.69	0.74
rs2479409	1	PCSK9	0.21	0.34
rs2642442	1	MOSC1	0.5	0.17
rs267733	1	ANXA9-CERS2	0.51	0.62
rs2710642	2	EHBP1	0.85	0.46
rs2902940	20	MAFB	0.28	0.3
rs2954029	8	TRIB1	0.05	0.72
rs314253	17	DLG4	0.94	0.43
rs3177928	6	HLA	0.05	0.63
rs364585	20	SPTLC3	0.16	0.72
rs3757354	6	MYLIP	0.42	0.93
rs3764261	16	CETP	0.05	0.48
rs3780181	9	VLDLR	0.65	0.06
rs4253776	22	PPARA	0.7	0.48
rs4299376	2	ABCG5/8	0.18	0.02
rs4420638	19	APOE	0.79	0.97
rs4530754	5	CSNK1G3	0.5	0.92
rs4722551	7	MIR148A	0.83	0.72
rs492602	19	FLJ36070	0.68	0.28
rs4942486	13	BRCA2	0.85	0.17
rs514230	1	IRF2BP2	0.16	0.1
rs5763662	22	MTMR3	0.41	0.92
rs6029526	20	TOP1	0.93	0.92
rs629301	1	SORT1	0.26	0.78
rs6511720	19	LDLR	0.38	0.61
rs6818397	4	LRPAP1	0.2	0.87
rs6882076	5	TIMD4	0.19	0.55
rs7570971	2	RAB3GAP1	0.34	0.65
rs7640978	3	CMTM6	0.42	0.57
rs8017377	14	NYNRIN	0.39	0.43
rs964184	11	APOA1	0.003	0.37
rs9987289	8	PPP1R3B	0.06	0.47

Data are presented as p-values for additive effects on visit-to-visit lipid variability as measured by the intra-individual standard deviation. Lead SNPs as reported by Willer CJ, Schmidt EM, Sengupta S, et al. Discovery and refinement of loci associated with lipid levels. *Nat Genet.* 2013;45:1274-1283.

Supplemental Table 3. Lead SNPs for previously reported loci for HDL-C levels.

SNP	Chr.	Locus	LDL-C var.	HDL-C var.
rs10019888	4	C4orf52	0.19	0.2
rs11065987	12	BRAP	0.51	0.89

rs1121980	16	FTO	0.29	0.51
rs11246602	11	OR4C46	0.69	0.53
rs11613352	12	LRP1	0.48	0.43
rs11869286	17	STARD3	0.56	0.77
rs12145743	1	HDGF-PMVK	0.99	0.97
rs12328675	2	COBLL1	0.13	0.76
rs12678919	8	LPL	0.31	0.17
rs12748152	1	PIGV-NR0B2	0.12	0.44
rs12801636	11	KAT5	0.07	0.19
rs12967135	18	MC4R	0.41	0.27
rs13076253	3	ACAD11	0.98	0.23
rs13107325	4	SLC39A8	0.54	0.01
rs13326165	3	STAB1	0.84	0.25
rs1367117	2	APOB	0.89	0.54
rs1532085	15	LIPC	0.14	0.78
rs1689800	1	ZNF648	0.04	0.84
rs16942887	16	LCAT	0.15	0.56
rs17145738	7	MLXIPL	0.65	0.78
rs17173637	7	TMEM176A	0.1	0.34
rs174546	11	FADS1-2-3	0.25	0.55
rs17695224	19	HAS1	0.55	0.9
rs1800961	20	HNF4A	0.03	0.57
rs181362	22	UBE2L3	0.33	0.63
rs1883025	9	ABCA1	0.39	0.78
rs1936800	6	RSPO3	0.42	0.86
rs2013208	3	RBM5	0.06	0.52
rs2255141	10	GPAM	0.42	0.38
rs2290547	3	SETD2	0.18	0.45
rs2293889	8	TRPS1	0.62	0.61
rs2412710	15	CAPN3	0.78	0.31
rs2602836	4	ADH5	0.04	0.91
rs2606736	3	ATG7	0.4	0.27
rs2652834	15	LACTB	0.62	0.69
rs2814982	6	C6orf106	0.89	0.22
rs2923084	11	AMPD3	0.09	0.88
rs2925979	16	CMIP	0.38	0.79
rs2954029	8	TRIB1	0.05	0.72
rs2972146	2	IRS1	0.59	0.05
rs3136441	11	LRP4	0.24	0.22
rs3764261	16	CETP	0.05	0.48
rs3822072	4	FAM13A	0.46	0.58
rs386000	19	LILRA3	0.72	0.12
rs4129767	17	PGS1	0.52	0.35
rs4142995	7	SNX13	0.25	0.87
rs4148008	17	ABCA8	0.31	0.92
rs4420638	19	APOE	0.79	0.97

rs442177	4	KLHL8	0.8	0.25
rs4650994	1	ANGPTL1	0.69	0.27
rs4660293	1	PABPC4	0.49	0.06
rs4731702	7	KLF14	0.64	0.81
rs4759375	12	SBNO1	0.02	0.61
rs4765127	12	ZNF664	0.83	0.31
rs4846914	1	GALNT2	0.13	0.003
rs4917014	7	IKZF1	0.92	0.81
rs4983559	14	ZBTB42-AKT1	0.63	0.41
rs499974	11	MOGAT2-DGAT2	0.46	0.78
rs581080	9	TTC39B	0.94	0.88
rs605066	6	CITED2	0.45	0.27
rs6065906	20	PLTP	0.73	0.57
rs629301	1	SORT1	0.26	0.78
rs6450176	5	ARL15	0.55	0.8
rs645040	3	MSL2L1	0.65	0.95
rs6805251	3	GSK3B	0.97	0.39
rs702485	7	DAGLB	0.95	0.38
rs7134375	12	PDE3A	0.6	0.59
rs7134594	12	MVK	0.05	0.34
rs7241918	18	LIPG	0.52	0.96
rs7255436	19	ANGPTL4	0.83	0.55
rs731839	19	PEPD	0.54	0.46
rs737337	19	ANGPTL8	0.16	0.81
rs7941030	11	UBASH3B	0.84	0.48
rs838880	12	SCARB1	0.27	0.95
rs964184	11	APOA1	0.003	0.37
rs9686661	5	MAP3K1	0.37	0.78
rs970548	10	MARCH8-ALOX5	0.54	0.49
rs998584	6	VEGFA	0.42	0.52
rs9987289	8	PPP1R3B	0.06	0.47

Data are presented as p-values for additive effects on visit-to-visit lipid variability as measured by the intra-individual standard deviation. Lead SNPs as reported by Willer CJ, Schmidt EM, Sengupta S, et al. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. 2013;45:1274-1283.