CHAPTER 6

Non-response to statin therapy: The importance of distinguishing non-responders from non-adherers in pharmacogenetic studies.

Stella Trompet, Iris Postmus, P Eline Slagboom, Bastiaan T Heijmans, Andrea B Maier, Brendan M Buckley, Naveed Sattar, David J Stott, Ian Ford, Rudi GJ Westendorp, Anton JM de Craen, J Wouter Jukema

Abstract

In pharmacogenetic research, genetic variation in non-responders and high-responders are compared with the aim to identify the genetic loci responsible for this variation in response. However an important question is whether the non-responders are true non-responders or whether they actually are non-adherent? Therefore, we describe, within the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) the characteristics of both non-responders and high-responders of statin treatment in order to possibly discriminate non-responders from the non-adherers. Here, we demonstrate that subjects that do not respond to statin therapy are younger ($p=0.001$), more often smoke ($p<0.001$), have a higher alcohol consumption ($p<0.001$), have lower total cholesterol levels ($p<0.001$), have a lower prevalence of hypertension ($p<0.001$), and have lower cognitive function ($p=0.035$) compared to subjects who highly respond to pravastatin treatment. Moreover, we showed that excluding non-responders and/or non-adherers in pharmacogenetic studies provides more robust results, since standard errors are lower. Our results suggest that non-responders to statin therapy are more likely to be non-adherers, since they have more characteristics that we assume to be indicators of high self-perceived health and low disease awareness, making the subjects less adherent to study medication. We suggest that in pharmacogenetic research, extreme non-responders are excluded to overcome the problem that non-adherence is investigated instead of non-responsiveness.

Introduction

Hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the most commonly prescribed drugs for the prevention of cardiovascular disease worldwide. Statins lower plasma cholesterol levels with 30-50% and are associated with a reduction of cardiovascular events of 20-40% [1]. Statins are generally well tolerated and are believed to have relatively few side effects [2]. However, clinical response is highly variable and not all subjects appear to benefit from statin therapy, only about a third of treated patients achieve the international guideline specified lipid lowering goals [1].

Pharmacogenetic studies aim to find genetic variation that is responsible for the variable response to drug treatment. For that purpose genome-wide genetic variation in high responders and non-responders is usually compared with the aim to identify genetic loci associated with the variation in response [3;4]. Especially in whole genome sequencing studies, only the two extreme phenotypes e.g. the extremely good responders and the non-responders are chosen to reduce costs and enhance efficiency [5]. However, for correct interpretation of this comparison it is essential to be sure that non-responders have actually taken the drug and are not non-responders due to non-adherence.

Pharmacogenetic research is usually best executed in randomized controlled trials, since adherence to medication is closely monitored, by for example, questionnaires, pill count and nowadays electronic medication monitoring devices [6]. However, this monitoring system does not provide certainty that subjects are actually adherent to their medication. Non-adherers can relatively easily work around the control mechanisms, e.g. by discarding drugs before the pill count. Moreover, assessing plasma levels of drugs does not guarantee adherence, apart from the last days before the study blood drawn. In other words, are we capable in discriminating non-responders from non-adherers in pharmacogenetic research? And how should we optimally deal with this problem in pharmacogenetic analyses?

Using data of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) [7;8], we here describe baseline characteristics of differential responder groups to statin treatment in order to find discriminatory factors between likely non-responders and likely non-adherers. Furthermore, we propose how to deal with the misclassification of false non-responders in pharmacogenetic analyses.

Methods

We used data from the PROSPER study [7;8]. In short, the PROSPER study is a prospective multicenter randomized placebo-controlled trial to assess whether treatment with 40 mg daily pravastatin diminishes the risk of major vascular events in elderly. Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5,804 subjects were randomly assigned to pravastatin (n=2,891) or placebo treatment (n=2,913). At baseline, a brief medical history was taken, vital signs were recorded, and a fasting venous blood sample was collected for biochemical and hematological checks and for lipoprotein quantification. In addition, a Mini-Mental State Examination was conducted to test for cognitive function. Adherence was measured by pill count every three months.

From the pravastatin users (n=2,891), we excluded all subjects who were withdrawn from the PROSPER study in follow-up because they refused study medication or did not attend the follow-up visits (n=346). From the remaining subjects (n= 2,545) the percentage achieved LDL lowering after statin treatment was calculated by taking the mean LDL level for all post statin treatment measurements at month 3, 6, 12, 24 and 36, minus the baseline LDL level, divided by the baseline LDL level and multiplied by 100. If data of one of the measurements for one individual was missing, we took the mean of only the available measurements of that individual as post statin treatment measurement. These data were available for 2,519 subjects.

We then created five groups of achieved LDL lowering (=<10%; 10-20%; 20-30%; 30-40%; >40% LDL lowering) and compared baseline characteristics between these groups. Based on clinical experience, non-responders were defined as =<10% decrease in LDL cholesterol levels and high-responders were defined as >40% decrease in LDL cholesterol levels.

First, we assessed whether there were differences in baseline characteristics between the five groups of achieved LDL lowering using ANOVA. Baseline characteristics included sex, age, education, smoking, alcohol use, BMI, blood pressure, cholesterol level, history of hypertension, diabetes, and vascular disease, and cognitive function. We also assessed differences in baseline characteristics between the non- and high-responders with a student's t-test for continuous variables or the Pearson Chi-square test for categorical variables.

Second, we used binary logistic regression to assess the relative risk of being a non-responder based on the clinical characteristics that were significantly different

between the high and low groups in the first analysis. Continuous measurements were dichotomized based on sex-specific medians. All analyses were adjusted for age and country of origin, and where necessary additionally adjusted for sex. Third, we calculated the number of risk factors per subject and assessed the association between the number of risk factors and non-responder status with binary logistic regression analysis adjusted for age, sex, and country of origin. The sum of the risk scores was not available in seven subjects of the high-responders and in one subject of the non-responders because of missing data of one of the clinical characteristics.

Fourth, we compared the non-adherers based on the pill count with the non-responders based on LDL lowering for baseline characteristics with a student's t-test for continuous variables or the Pearson Chi-square test for categorical variables. Subjects were defined as a non-adherer if they returned more than 18 (20%) pills in the preceding 90 days before their study visit (mean pill count over maximum number of study visits per individual) [9]. Non-responders were those with LDL lowering <10%. There were 24 subjects in both groups, who were excluded from this analysis to facilitate statistical comparison.

Finally, we performed a Genome-Wide Association Study (GWAS) to analyze the genetic variation associated with variation in LDL lowering in all subjects (n=2272) and repeated this analysis with the exclusion of the subjects classified as non-responders (leaving n=2167), with the exclusion of the non-adherers (leaving n=2160) and with the exclusion of both non-responders and non-adherers (leaving n=2078). The total number of subjects is lower in this analysis since the GWAS has not been executed in all PROSPER subjects, since genotyping failed or they were excluded based on the GWAS quality control criteria [10]. No subjects were excluded based on phenotypic outliers. For this analysis, we used 2.5 million imputed SNPs within the PHASE study (the PHArmacogenetic study of Statins in the Elderly) [10]. The analysis was performed with ProbABEL software (http://www.genabel.org/), adjusted for age, sex, and country [11].

Results

Table 1 shows the baseline characteristics of the five groups of percentage LDL lowering after pravastatin treatment. There were significant differences between the groups for sex, current smoker, history of hypertension, age, education, cognitive function, alcohol use, and level of total cholesterol. Moreover, when we compared the baseline characteristics of the 114 non-responders with the characteristics of the 734 high-responders to pravastatin therapy, we found that subjects who did not

respond to pravastatin therapy were by average 1 year younger (p=0.001), more often smoked and drank more alcohol (both p<0.001), had lower total cholesterol levels (p<0.001), had lower prevalence of hypertension (p<0.001), and had lower cognitive function (p=0.035) compared to subjects who highly responded to pravastatin therapy.

Table 1. Association between groups of % LDL lowering to statin treatment and clinical variables

	% LDL lowering in response to pravastatin treatment					
	>40% (n=734)	30-40% (n=989)	20-30% (n=502)	10-20% (n=180)	<=10% (n=114)	P ANOVA
Categorical variables (n, %)						
Females	423 (58)	511 (52)	218 (43)	82 (46)	56 (49)	<0.001
Current smokers	126 (17)	244 (25)	151 (30)	65 (36)	54 (47)*	<0.001
History of hypertension	503 (69)	620 (63)	301 (60)	98 (54)	58 (51)*	<0.001
History of diabetes	79 (11)	104 (11)	58 (12)	16 (8)	7 (6)	0.485
History of vascular disease	335 (46)	437 (44)	228 (45)	77 (43)	46 (40)	0.809
Country:						
Scotland	325 (44)	410 (42)	210 (42)	83 (46)	49 (43)	
Ireland	248 (34)	364 (37)	200 (40)	71 (39)	51 (45)	
The Netherlands	161 (22)	215 (22)	92 (18)	26 (14)	14 (12)	0.253
Continuous variables (mean, se)						
Age (years)	75.7 (0.12)	75.3 (0.11)	75.0 (0.15)	75.1 (0.24)	74.6 (0.29)*	0.001
BMI (kg/m^2)	26.9 (0.15)	26.8 (0.13)	26.9 (0.18)	27.1 (0.33)	26.3 (0.42)	0.433
Education (years)	15.2 (0.08)	15.3 (0.07)	15.3 (0.10)	14.5 (0.11)	15.2 (0.19)	<0.001
MMSE (points)	28.1 (0.06)	28.2 (0.05)	28.0 (0.07)	27.8 (0.12)	27.8 (0.14)*	0.010
Alcohol (units/week)	3.5 (0.29)	5.0 (0.27)	7.2 (0.47)	7.2 (0.80)	6.5 (0.90)*	<0.001
Total cholesterol (mmol/L)	5.9 (0.04)	5.7 (0.03)	5.6 (0.04)	5.4 (0.06)	5.3 (0.08)*	<0.001
SBP (mmHg)	156.0 (0.80)	154.0 (0.70)	155.8 (0.99)	153.4 (1.59)	152.8 (2.14)	0.200
DBP (mmHg)	83.8 (0.41)	83.6 (0.36)	83.6 (0.50)	82.7 (0.83)	83.7 (1.04)	0.828

Abbreviations: BMI, Body Mass Index; MMSE, Mini Mental State Examination; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*significant difference between the groups of <=10% and >40% LDL lowering (all p<0.05)

Next, we calculated the relative risk of being a non-responder for the characteristics that significantly differed between high and non-responders with a binary logistic regression model (table 2). The largest relative risk was found for subjects that were current smokers (OR 3.96, 95% CI 2.60-6.03, p=1.4 x 10^{-10}). We also found a higher risk of being a non-responder in subjects without a history of hypertension (OR 2.01, 95%CI 1.32-3.04, p=0.001), with a lower cognitive function (OR 1.46, 95%CI 0.97-2.20, p=0.068), with higher alcohol intake (OR 1.73, 95%CI 1.15-2.59, p=0.008), and with lower total cholesterol levels (OR 3.12, 95%CI 2.02-4.81, p=2.6 x 10^{-7}). The association between number of characteristics in the non-responders compared to

the high responders is also shown in table 2. Compared to subjects with none or 1 risk factor, the relative risk of being a non-responder increased gradually to 14.66 (95%CI 5.51-39.02, $p=7.6 \times 10^{-8}$) for subjects with 5 characteristics. When the summary score was included in the model as a continuous variable, the risk of being a non-responder increased with 1.99 (95%CI 1.65-2.38, $p=1.7 \times 10^{-13}$) per additional characteristic.

Table 2. Association between baseline characteristics and being a non-responder

	High-responders (n=734)	Non-responders (n=114)	OR (95%CI)*	p-value
Baseline characteristics				
Smoking	126 (17)	54 (47)	3.96 (2.60-6.03)	1.43×10^{-10}
No history of hypertension	231 (32)	56 (49)	2.01 (1.32-3.04)	0.001
Low MMSE	379 (52)	68 (60)	1.46 (0.97-2.20)	0.068
High Alcohol	270 (37)	58 (51)	1.73 (1.15-2.59)	0.008
Low TC	318 (43)	81 (71)	3.12 (2.02-4.81)	2.58×10^{-7}
Number of characteristics				
<=1	297 (41)	20 (18)	1.0 (ref)	-
2	256 (35)	26 (23)	1.53 (0.83-2.83)	0.170
3	126 (17)	36 (32)	4.15 (2.28-7.55)	3.22×10^{-6}
4	38 (5)	20 (18)	7.25 (3.53-14.87)	6.54×10^{-8}
5	10 (1)	11 (10)	14.66 (5.51-39.02)	7.57×10^{-8}
Trend			1.99 (1.65-2.38)	1.65×10^{-13}

*The OR represents the risk of being a non-responder when you are in the risk category.

The continuous factors are dichotomized based on sex-specific medians. Adjusted for age and country, the analyses for smoking and hypertension are additionally adjusted for sex.

Abbreviations: OR, Odds Ratio; TC, total cholesterol; SBP, Systolic blood pressure; MMSE, Mini Mental State Examination.

Based on pill count, we defined a non-adherer if they returned more than 18 (20%) pills in the preceding 90 days before their study visit (mean pill count over maximum number of study visits per individual). Within the subjects that highly respond to pravastatin therapy 99.5% were adherent to their study medication based on pill count, whereas in the non-responders group this was reduced to 78.6%. Table 3 shows the comparison between non-adherers of the PROSPER study based on pill count and the non-responders based on LDL lowering. Compared to the non-adherers, non-responders smoked more often (p=0.085) and had higher alcohol intake (p=0.117), lower total cholesterol levels (p=0.020), lower systolic blood pressure (p=0.034), and had less often a history of hypertension (p=0.001) and diabetes (0.273) although not all comparisons were statistically significant different. A major difference between the two groups was the number of subjects with a history of vascular disease. Within the non-adheres, there were no subjects with a

history of vascular disease whereas in the non-responder group, 46 (51%) had a history of vascular disease (p<0.001).

Table 3. Comparison of baseline characteristics between non-adherers and non-responders

	Non-adherers (n=98)	Non-responders (n=90)	p-value
Categorical variables (n, %)			
Females	57 (58)	41 (46)	0.057
Current smokers	34 (35)	41 (46)	0.085
History of hypertension	72 (74)	45 (50)	0.001
History of diabetes	10 (10)	6 (7)	0.273
History of vascular disease	0 (0)	46 (51)	<0.001
Country:			
Scotland	35 (36)	40 (44)	
Ireland	54 (55)	39 (43)	
The Netherlands	9 (9)	11 (12)	0.270
Continuous variables (mean, se)			
Age (years)	75.4 (0.35)	74.5 (0.33)	0.070
BMI (kg/m^2)	26.8 (0.43)	26.0 (0.48)	0.215
Education (years)	15.2 (0.19)	15.0 (0.20)	0.458
MMSE (points)	27.4 (0.17)	27.8 (0.16)	0.074
Alcohol (units/week)	4.9 (0.84)	7.0 (1.07)	0.117
Total cholesterol (mmol/L)	5.68 (0.10)	5.35 (0.10)	0.020
SBP (mmHg)	157.0 (2.01)	150.5 (2.29)	0.034
DBP (mmHg)	84.54 (1.21)	83.08 (1.15)	0.385

Subjects who were both non-responder and non-adherer were removed from the analysis to facilitate statistical comparison.

Finally, we compared the results of the GWA studies on the influence of genetic variation of the LDL lowering response after pravastatin treatment in all subjects (n=2272) and in the sample excluding non-responders (n=2167), in the sample excluding non-adherers (n=2160) and in the sample excluding both non-responders and non-adherers (n=2078). The results of the GWA studies are depicted in figure 1. None of the Manhattan plots show any genome wide significant results (all p>5.0 x 10^{-8}). From 4 SNPs known to be associated with statin response the results for the four different analyses are compared in table 4. The main message of this comparison is that by excluding non-responders or non-adherers, the standard error decreases, indicating that probably noise is removed from the analysis. The beta stays more or less consistent in the analysis in the three restricted study samples, however since the SE decreases, also the p-value decreases.

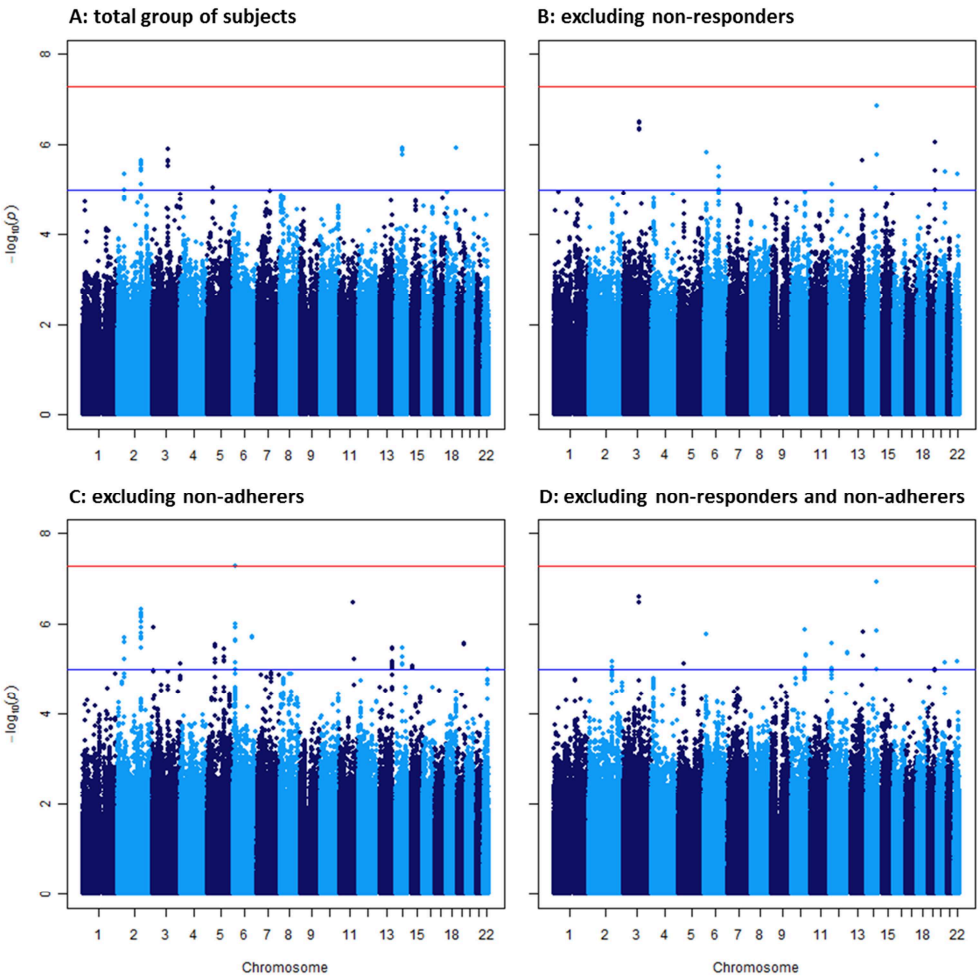

Figure 1. Manhattan plots showing the results of GWA studies on the influence of genetic variation of the LDL lowering response after pravastatin treatment in all subjects (A) and in the sample excluding non-responders (B), in the sample excluding non-adherers (C) and in the sample excluding both non-responders and non-adherers (D).

Discussion

In this study we showed that non-responders to statin treatment differ depending on baseline clinical characteristics from high-responders. Non-responders were more often smokers, drank more alcohol, had a lower cognitive function, were less likely to have hypertension and had lower total cholesterol levels. These characteristics can be considered as indicators of higher self-perceived health and lower disease awareness, indicating that non-responders are less aware of the benefits of using the study medication and are therefore more likely to be non-adherers than non-

responders. Also, compared to the non-adherers based on pill count, non-responders were more likely to be non-adherers since they have more characteristics that correspond with high self-perceived health and low disease awareness. Moreover, we showed that exclusion of the non-responders in the GWAS yielded more robust results, since the standard errors decreased after exclusion. All these results together indicate that pharmacogenetic studies that compare extreme phenotypes might be at least partially biased by the phenomenon of some, perhaps many, non-adherers probably being misclassified as non-responders.

Table 4. Comparison of four SNPs associated with statin response in four different study samples

	N	Beta	SE	p-value
rs10455872 (*LPA*)				
All subjects	2272	-0.0351	0.0123	0.0042
Excl. non-responders	2167	-0.0288	0.0115	0.0122
Excl. non-adherers	2160	-0.0334	0.0124	0.0069
Excl. non-responders + non-adherers	2078	-0.0281	0.0117	0.0162
rs2900478 (*SLCO1B1*)				
All subjects	2272	0.021	0.0065	0.0014
Excl. non-responders	2167	0.020	0.0061	0.0008
Excl. non-adherers	2160	0.022	0.0065	0.0007
Excl. non-responders + non-adherers	2078	0.021	0.0062	0.0006
rs445925 (*APOE*)				
All subjects	2272	0.022	0.0088	0.0121
Excl. non-responders	2167	0.021	0.0082	0.0097
Excl. non-adherers	2160	0.024	0.0090	0.0066
Excl. non-responders + non-adherers	2078	0.024	0.0085	0.0049
rs646776 (*SORT1/CELSR2/PSRC1*)				
All subjects	2272	0.014	0.0058	0.0129
Excl. non-responders	2167	0.016	0.0054	0.0033
Excl. non-adherers	2160	0.018	0.0058	0.0020
Excl. non-responders + non-adherers	2078	0.017	0.0055	0.0020

Only a few studies have investigated differences between non-responders and high-responders of statin therapy [12-15]. Each study showed that characteristics that are indicators of better self-perceived health like age, the number of comorbidities and diet habits are different between non- and high-responders and are therefore more indicators of non-adherence [16;17]. However, we cannot rule out the possibility that these characteristics are actually real factors that determine whether a subject responds biologically different to statin therapy. For example, high-responders of statin therapy have higher baseline cholesterol levels, probably since subjects with higher baseline cholesterol levels could also decrease more in cholesterol level (simply because a greater absolute but also relative change is achievable) after statin therapy compared to subjects with low baseline cholesterol. In this case it is still not

certain if this variable can help us to discriminate between non-responders and non-adherers. However, in various subgroup analyses within the PROSPER study we found no evidence that there is an interaction between any of the clinical characteristics and statin response [8].

The comparison with the actual non-adherers of the PROSPER study based on pill count at each study visit also does not give a conclusive answer. Adherence to study medication in randomized controlled trials like the PROSPER study, is closely monitored by for example questionnaires and by pill count [6]. However, this monitoring system does not provide certainty that subjects are actually adherent to their study medication. Non-adherers can relatively easily work around the control mechanisms, e.g. by discarding a reasonable number of pills before the study visit. Since we showed that the non-responders of pravastatin therapy based on the clinical outcome LDL lowering had more characteristics that we think coincide with high self-perceived health and low disease awareness, we think we have missed non-adherers by using the pill count monitoring system. On the contrary, none of the non-adherers had a history of vascular disease compared to 51% of the non-responders, which indicates that in the non-responder group subjects are included, s.a. those with a history of vascular disease, that likely are adherent and therefore biologically non-responders to the drug.

In many pharmacogenetic studies, non-responders are compared to high-responders to investigate which genetic variation is responsible for this difference in response [5]. However we believe that by using this comparison the best power and most efficiency is reached, there is the possibility that actually the non-adherent phenotype is investigated. Hence, instead of finding genetic variation responsible for the variation in response to therapy, genetic variation for adherence is assessed. Therefore we assessed the difference in analyses when we perform pharmacogenetic research in all subjects compared to pharmacogenetic research excluding the non-responders and/or non-adherers. Our results suggest that in all analyses excluding non-responders and/or non-adherers the noise of the possible non-adherence is reduced since the standard errors were decreased, which cannot be the result of a larger sample size.

Our suggestion is that in pharmacogenetic research, another strategy should be followed to find the genetic variation responsible for the difference in response to (statin) therapy instead of comparing the extreme phenotypes (high- vs. non-responders). We propose three different strategies that may be followed to exclude the problem of investigating non-adherence instead of non-responsiveness. First, all

subjects should be investigated with a total range of responsiveness as a continuous phenotype. In this way the extreme non-responsive cases which are possible non-adherers will not have large weight in the analyses compared to an analysis where non-responders and high-responders are compared. The second proposed strategy is to exclude subjects with non-responsiveness and/or non-adherence and investigate the moderate-responders to the high-responders to be sure that the non-adherence phenotype is excluded from the analysis. And the third, most sophisticated, strategy is to use a propensity score based on various clinical characteristics associated with non-adherence to match high-responders to non-responders. This analysis will exclude any possible confounding from non-adherence from the study. Unfortunately, we could not perform such analysis due to low statistical power.

In conclusion, pharmacogenetic studies that are investigating the difference between non- and high-responders were almost certainly in part investigating the non-compliant phenotype, since non-responders have clinical characteristics that coincide with high self-perceived health and low-disease awareness and that are also very common in non-adherers. Other strategies, as proposed herein, should be used to investigate the relation between genetic variation and responsiveness to (statin) treatment.

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