Response to the Editor and the Reviewers

Dear Editor,

We appreciate your comments and encouragement to reply to the questions raised by the reviewers’ comments, which have contributed to improving the clarity of our message and presentation of our findings.

During this revision process we have detected an error in the calculus of the confidence intervals for the incidence estimations and hazard ratios, which has been corrected in the current version. This correction has no relevant implications.

We have prepared a point-by-point response:

Second reviewer:

The manuscript is interesting, timely and relevant in that it provides real world information in a large population of phenotypic FH patients. The main point of the study is that patients who have phenotypic FH are at increased risk of CV events. Those at the highest risk were younger patients who likely have true monogenic FH and not a polygenic cause for their high LDL cholesterol and those FH patients with additional CV risk factors.

The authors appreciate this assessment of our work. The comments of the reviewer have substantially improved the quality of our work.

However one main issue with the manuscript is that it does not provide information on statin use and CV outcomes. In the methods section the patients’ use of statins and ezetimibe along with adherence were recorded. However none of this information is presented in the results section. The authors need to present this information. They then need to discuss how statin use has impacted CV outcomes, both in the FH cohort and in the control group. For example 13% of patients with phenotypic FH and without ASCVD were not on a statin. Was there a difference in CV outcomes among those FH patients who are on a statin vs. those on no statin therapy? The authors should also provide information on statin intensity and adherence and how that relates to outcomes.
We thank the reviewer for this comment, this is a very relevant question. We agree with this suggestion and thus have added the description of the lipid lowering therapy potency and patient treatment adherence to Table 1. We have also classified the patients’ exposure to statins or ezetimibe considering the cholesterol reduction capacity of the drug, as follows: low, <30%; moderate, 30-50%; high, 50-60%; and very high, >60% [14].

We have further carried out the analyses suggested by the reviewer examining the effect of FH-P on the incidence of ASCVD by statin use. The results of such analysis show that the presence of FH-P associates with a remarkable excess of risk in patients without treatment but only with a slight risk increase in patients with statin treatment (Figure 2). The models of the group receiving lipid-lowering medications were adjusted for cardiovascular risk factors, and by statin potency and adherence. This excess of risk also attenuates with age in both groups (treated and non-treated). As in the general analysis, the effect in secondary prevention was less marked.

Figure 2. Hazard ratios of the presence of Familial Hypercholesterolemia phenotype on atherosclerotic cardiovascular disease by statin use, in primary and secondary prevention.

These results agree with previous reports on the association of prolonged lipid-lowering treatment with a huge reduction in ASCVD in patients with FH (1). Note that most treated patients in our cohort had been at least 3 years on statins, but probably most of them had been on statins for a very long time (because we do not have information about treatment before 2006).
We have included this analysis in the manuscript, with the corresponding explanations in the text.

**Methods:**

“We classified patients’ exposure to statins or ezetimibe according to the cholesterol reduction capacity of the drug, as follows: low, <30%; moderate, 30-50%; high, 50-60%; and very high, >60% [14]”

And

“We also performed the main analysis stratified by statin use.”

**Results:**

“The effect of FH-P upon the ASCVD incidence by LLT use showed a marked excess of risk in patients without treatment but only a slight increase in patients with statin treatment (Figure 2). The excess of risk also attenuated with age in both groups. As in the general analysis, the effect on secondary prevention was less marked. The models of the group receiving LLT were adjusted by cardiovascular risk factors, and additionally by statin potency and adherence to treatment.”

**Discussion:**

“The results from the stratified analysis by LLT use are of particular interest. These results agree with previous reports that observed association of prolonged lipid-lowering treatment with a huge reduction in ASCVD in patients with FH [24]. In patients who were not receiving LLT, the excess of risk was critical, particularly in primary prevention. Of note, most treated patients in our cohort had been at least 3 years on statins, but the majority of them had probably been on statins for a very long time (because we do not have information about treatment before 2006). These results support the idea of early and sustained treatment with LLT as the key point in the management of FH-P.”


Another limitation to the study is that the control group was not age matched. It is somewhat surprising that the IR of ASCVD in the control group without ASCVD was as high as 7.1 per 1000 person years and that the IR risk of ASCVD in the FH cohort was only 2 fold higher. I would think that given the older age of the FH cohort along with their other CV risk factors (which were much more prevalent compared to the control group) that for primary prevention the risk would have been higher.
Many thanks for this comment. The reviewer is right, the control group was not age matched and the incidences were crude, but the hazard ratios were age adjusted. In response to the reviewer’s concern, we have included the information of the adjusting variables in the table’s footnotes.

This comment is very interesting. Previous studies included genetic identification and referrals from specialized clinical settings, primary care, and evaluation of their FH-affected relatives. This probably explains the differences between the characteristics of our study population and other reports: the mean age of FH-P individuals in our study was 60.5 in the group without previous ASCVD, and 67.7 in group with previous ASCVD, while in most of the previous studies the mean age was below 50 years. In our study, the global incidence of ASCVD in FH-P individuals was only slightly higher than in the control group, mainly because of the effect in older patients. Our results show that the excess of risk in young individuals, is marked [e.g., HR (95%CI) in <35 years: 7.13 (2.85-17.84) in 35-45 years 3.78 (2.42-5.91)]. A similar interaction the hazard ratios of FH with age has been observed previously (17).

We have included this comment in the Discussion section:

“The global older mean age of the population in our study could explain the lower effect of FH-P on ASCVD compared to previous reports in genetically identified individuals who were younger than those included in our analysis; whereas the effect in the younger subgroup was similar.”

A second reason would relate with the previous reviewer’s comment. Long term LLT, which is present in most patients with FH-P, may have reduced the lipid burden, which in turn, likely reduced the incidence of ASCVD in this group. In this regard, we have added a comment in the text, as stated in the previous response.


Minor points:

1. In figure 1 in the top box it should be subjects ≥ 18 years old not 8.

We appreciate this remark. Please note that we included persons <8 years old at the beginning of the population selection, and excluded those <18 years on a posterior step (see criteria of excluded patients in the flowchart).