We thank both reviewers for their well-considered and reasonable critiques to our work. We have revised the manuscript accordingly and detail these changes here as well. Our point-by-point responses are included below in **bold**, and verbatim text added to the manuscript is noted in **red bold** font. We have also included line numbers for the changes for your convenience.

The manuscript applies AI to investigate which are the factors that are independently associated with plasma cholesterol levels in the diversity outbread mice dataset.  
As expected, gender and diet are the major factors correlating with changes in cholesterol levels. Intriguingly calcium levels appear to the third.  
The manuscript will benefit from the following analysis if feasible:  
-Correlation of plasma cholesterol levels with the extension of the atherosclerotic plaque

**We agree that this is an important pathophysiology that was not measured in this study, so we are unable to perform this analysis. We do look forward to using these data in future studies using mouse models with atherogenic susceptibility, such as *Apoe* or *Ldlr* knockout mice. This is now noted in the limitations section on lines 226-228.**

**Finally, as cardiovascular disease is extremely rare in mice of this age we did not assess cardiovascular disease, or atherogenic lesions as an endpoint in this study.**

-Correlation of cholesterol content in lipoprotein subsets with calcium levels.

**We have done this analysis for HDL-C which was directly measured and non-HDL-C which was calculated based on the total cholesterol and HDL-C. We are unable to detect other apolipoproteins such as VLDL or chylomicrons or separate those from non-HDL-C, nor are we able to evaluate correlations with subpopulations of lipoprotein particles. The correlations between serum calcium and these values are now presented in Supplementary Figures 2D-C and below. Due to the absence of CETP, most cholesterol in mouse blood is in the HDL fraction, as opposed to most humans where LDL is enriched, in part by CETP-mediated LDL->HDL transfer.**

-Correlation of cholesterol with the other parameters when a cholesterol rich diet is used.  
-Evaluation of the translational relevance of the findings by for instance investigating the correlation between plasma chol levels, atherosclerosis and calcium in human datasets.  
  
  
Additional analysis.  
-How do the authors explain the weaker association between plasma chol and plasma TG in figure 2, panel A, male mice on HFHS diet compared to normal diet?  
  
  
Reviewer: 2  
  
Comments to the Author  
Comment:  
The authors analyzed in two distinct mouse datasets, Diversity Outbred and BXD, using a machine learning approach. This is an attractive study; however, some concerns are needed to address.  
  
Major concerns:  
1.      How long was the HSFS diet fed to the mice?  
2.      Are all of these mouse datasets from healthy mice fed NCD or HFHS? Are these phenotypes, including the relationship between cholesterol and calcium, for healthy cases and are different in disease conditions?  
3.      Aging is also thought to be an important factor in elevated calcium and/or cholesterol levels. Do the authors’ findings apply to both young and old?  
4.      Authors described that these data reflect associations between calcium and the HDL pool because of the absence of CETP in mice. Is there possibility that calcium levels affect LDL-C or both?  
5.      Are patients with hypercalcemia more likely to have dyslipidemia or vice versa? Any reports?  
  
Minor points:  
1.      There is no citation in texts and figure legend in Figure 1C. Please add.  
2.      The lines of HFHS group in Figures 1 and 2 are hard to see due to the light color. Please change it.