Comment: Humoral responses against HDL are linked to lipoprotein traits, atherosclerosis, and pathogenic pathways during early arthritis stages: Reply

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Dear Editor,

We would like to thank our colleagues Drs Pagano and Vuilleumier for their insightful commentary [1] on our article [2]. In this reply, we address the points raised by the authors in order to promote and expand scientific discussion, and guide the readers on these topics.

Pagano and Vuilleumier made a point on the need of including standard echogenicity characteristics of atherosclerosis plaques in the light of their associations with vulnerability and cardiovascular hazards. We absolutely agree with the authors, and we would like to note that our study included a plaque characterization (referred to as 'plaque risk') based on echogenic properties (plaque border, echo-density, calcification status and plaque burden) according to previous literature [3]. In fact, we have observed a positive association with other biomarkers [4]. However, anti-HDL/ApoA1 responses (both IgG/M) failed to show any association with plaque characteristics, opposed to plaque occurrence and extent.

With regards to the lack of associations with the cIMT, we would like to note that our cohort exhibited an overall low cIMT mean value, as previously reported for early arthritis populations [5,6], despite their high cardiovascular risk. In fact, only 8 (9.75%) patients exhibited a cIMT>0.90 mm (all of them presenting with atherosclerosis plaques), despite the significant plaque burden (46(59.7%)) observed in our group. It must be noted that cIMT and plaque occurrence are not equivalent, either in terms of their biological substrate as well as in their risk prediction capabilities. This is especially in rheumatic conditions, where divergent trajectories have been observed [7]. In fact, previous studies have also found low cIMT values and low cIMT progression despite a significant burden of traditional cardiovascular risk factors in RA. It must be noted that IMT may be confounded by other processes (such as smooth muscle hypertrophy/hyperplasia), associations with IMT may not be linear (and sex-dependent), and standardization is challenging. Actually, many studies point to a greater value of plaque occurrence rather than cIMT, and the recent consensus by the European Society of Cardiology recommends against its systematic use, while recognizing the value of plaque assessment [8].

These points were connected in the letter to the lack of associations between atherosclerosis and most traditional cardiovascular risk factors. We do agree this result may be benefited by a deeper discussion. It is well supported that traditional risk factors can explain a limited portion of the total cardiovascular risk in RA [9]. A recent study put this fact into figures, revealing that traditional risk factors only account for 49% of the total risk [10]. Indeed, it has been speculated that traditional and non-traditional risk factors may 'compete' with each other for their contribution to total cardiovascular risk burden [9]. Therefore, it is to be expected that traditional

risk factors fail to predict cardiovascular outcomes (or show a poor performance to do so) in RA populations. We have observed similar results in previous studies [11,12], with traditional risk factors poorly predicting cardiovascular outcomes. This may be especially relevant in early populations, as these patients present with lower prevalence of traditional risk factors but with higher levels of inflammation, as reported in our study. Taken together, we consider that this observation is supported by the current literature in this field.

Finally, our colleagues pointed to a potential incomplete literature coverage and existing literature interpretation regarding anti-ApoA1 literature. Although we may understand the point made, we respectfully disagree on these terms, and we would like to clarify our point. We commented on the "lack of associations between anti-ApoA1 responses and cardiovascular outcomes in a number of conditions" as a potential explanation to enlighten the differences in significance between anti-HDL and anti-ApoA1/PON1 responses in our results as well as in the literature, mostly in inflammatory conditions. We are aware of the massive amount of literature supporting a role for anti-ApoA1 antibodies, but we consider that discrepancies (and negative results), even if rare, may be informative as well and help us to clarify underlying causes of the findings discussed. Then, our claim was meant at accounting for the differences between anti-HDL and anti-ApoA1 responses in the specific setting therein collated and should not be taken as an absolute judgement for or against anti-ApoA1 overall. This being said, we are aware of the enormous relevance of the anti-ApoA1 responses, hence their inclusion in our research aims at the same level than the anti-HDL approach. Therefore, our study by no means negates nor neglects the relevance of anti-ApoA1, rather it can certainly be seen as a step forward demonstrating its independent association with cardiovascular outcomes in early RA, its incremental added value, and its early elevation in the arthralgia stage, among other findings.

We sincerely share the enthusiasm of our colleagues for the anti-HDL/ApoA1 responses and their promising present and future, and we sincerely hope we can contribute together to unravelling of these biological signatures in human health and disease.

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DISCLOSURE STATEMENT

The authors have declared no conflicts of interest.

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