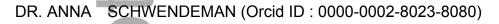


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To the Editor:

We thank Dr. Vuilleumier for his interest in our review paper on high-density lipoproteins (HDLs) in systemic lupus erythematosus (SLE)[1] and his comments on anti-apolipoprotein A-1 (apoA-1) autoantibodies. Dr. Vuilleumier raises an important point that the prevalence of high anti-apoA-1 IgG levels is not specific to SLE, which we fully agree with. The prevalence of anti-apoA-1 autoantibodies in

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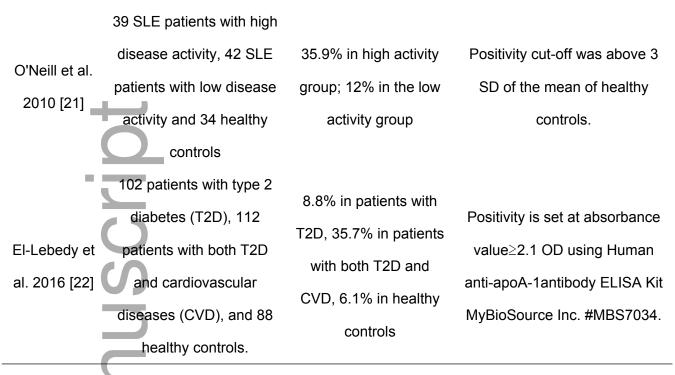
different disease settings has been summarized in Table 1. Inconsistent results could be attributed to the assay-to-assay differences introduced by different enzyme-linked immunosorbent assay (ELISA) assays and different positivity cut-off values used [2].

Questions were also raised concerning whether anti-apoA-1 IgG is an independent predictor of cardiovascular (CV) events in SLE patients. Indeed, anti-apoA-1 IgG has not been found to be independently associated with CV events in SLE [3, 4]. As pointed out by Dr. Vuilleumier, anti-apoA-1 IgG has been found to be associated with CV events in a broad array of clinical settings [5]. Such inconsistency certainly deserves further investigation.

Dr. Vuilleumier also raised questions about our hypothesis that oxidized apoA-1 may play a role in inducing anti-apoA-1 autoantibodies. We acknowledge that the formation of anti-apoA-1 autoantibodies could be attributed to various genetic and environmental factors, as argued by Dr. Vuilleumier. At the same time, our hypothesis is based on our experience in the biopharmaceutics field, where oxidation and misfolding are recognized immunogenic factors for therapeutic proteins and peptides [6, 7]. In the case of apoA-1, oxidation at Met-112 and Met-148 has been suggested to cause conformational change of apoA-1 by disrupting the α -helix structure [8, 9]. Methionine oxidation on apoA-1 has also been shown to induce the formation of amyloid fibril, which could be immunogenic [10]. Studies by Vinditto et al. showed that apoA-1 peptide with oxidized Met-148 could bind with goat polyclonal antibodies against human apoA-1 [11], and oxidized apoA-1 appeared to be more immunogenic in mouse models [12]. In addition to methionine oxidation, apoA-1 could undergo other oxidative modifications such as 3-chlorotyrosine and 3-nitrotyrosine in autoimmune settings [13, 14]. Particularly, 3-nitrotyrosine modification has been proven to be immunogenic for other proteins and was suggested to be responsible for impaired immunological tolerance [15]. Thus, further studies on 3-chlorotyrosine and 3-nitrotyrosine modified apoA-1 species would be helpful to investigate the underlying mechanisms of anti-apoA-1 autoantibodies in autoimmune settings.

Reference	Population	Prevalence	Note
-		19.9%	Positivity cut-off corresponds to
Antiochos et			97.5% of the reference
al. 2017 [16]			distribution from 140 healthy
Satta et al. 2018 [17]	237 HIV positive patients		blood donors.
		58%	Positivity cut-off corresponds to
			97.5% of the reference
	with no current		distribution from 140 healthy
	lipid-lowering therapy		blood donors.
Pruijm et al. 2012 [18]		71 patients on maintenance 20% hemodialysis	Positivity cut-off corresponds to
			97.5% of the reference
			distribution from healthy blood
	nemodialysis		donors.
	CO shows at a id outbritis		Positivity cut-off corresponds to
Vuilleumier et	69 rheumatoid arthritis	17% in RA patients and	97.5% of the reference
al. 2010 [19]	(RA) patients and 46 matched controls	2% in healthy control	distribution from healthy blood
			donors.
Nigolian et al. 2019 [4]	76 individuals satisfying	43%	Positivity cut-off corresponds to
	76 individuals satisfying		97.5% of the reference
	at least four ACR SLE		distribution from 48 healthy
	criteria		donors.
Dutues et al	55 SLE patients and 150	260/ in CLE actions	Positivity cut-off was above 5
Butuca et al. 2007 [20]	age- and sex-matched	36% in SLE patients 0.7% in healthy control	SD of the mean of healthy
	healthy subjects		controls.

Table 1. Prevalence of anti-apoA-1 autoantibodies in different populations.



SD: standard deviation, OD: optical density.

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