PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cumulative inflammatory burden and obesity as determinants of insulin resistance in patients with established rheumatoid arthritis: cross-sectional study
AUTHORS	Manrique-Arija, Sara; Mena-Vazquez, Natalia; Ureña, Inmaculada; Rioja, José; Valdivielso, Pedro; Ginel-Mendoza, Leovigildo; Abad-Sánchez, Salomé; Jiménez-Núñez, Francisco G.; Oliver-Martos, Begoña; Fernandez-Nebro, Antonio

VERSION 1 – REVIEW

REVIEWER	Raili Müller Tartu University Hospital, Estonia
REVIEW RETURNED	06-Oct-2020

GENERAL COMMENTS	Overall it was an interesting and up- to date work to read on an important topic. The RA group was well- described, followed- up and treated according to current recommendations. The control group was matched to RA patients taking into account not only age and gender but also BMI. There are some minor details that could be improved: 1. Can you please describe the matching process in detail- how were the controls found? What was the process of "randomly selecting healthy volunteers". Were the controls exact matches or what was the allowed range of deviation in BMI? 2. It was stated that a validated questionnaire was used to assess adherence to mediterranean diet. I couldn't find the data describing the potential association between diet and IR in your results or tables (the same goes for physical activity except for sedentary lifestyle in table 4) 3. Can you please describe how was sedentary lifestyle determined? 4. It is well known that glucocorticoid usage is an important determinant of reduced insulin sensitivity, altered BC and obesity in RA. How many of the patients in your RA group had used/ were using glucocorticosteroids? Was glucocorticoid usage associated with IR? 5. Is the VAS reported in table 1 patient or physician global? 6. It is difficult to understand what was the proportion of patients using specific DMARDs. You describe that of biologics most of the patients received antiTNFs or tocilizumab. What was the proportion of cDMARD and bDMARD agents used? Was there a difference between biologic/conventional treated patients in the presence of IR? 7. On lines 8-28 under strengths and limitations you have actually described you results and conclusions. 8. In table 4 some of the abbreviations are unclear (IMC, PCR)

REVIEWER	Piero Ruscitti University of L'Aquila, Italy
REVIEW RETURNED	21-Oct-2020

GENERAL COMMENTS	In this work, the authors assessed the prevalence of insulin resistance and its predictive factors. Of interest, the concentration of IL-1beta was associated with IR, suggesting furtherly the pathogenic role of this cytokine in this context. Some revisions are needed. The data concerning the results of the COMORA study and relative sub-analyses should be discussed in ordert o better understand the rationale behind the study [Dougados M, et al. Ann Rheum Dis. 2014;73:62-8, Radner H, et al. J Rheumatol. 2015;42:1099-104]. The hypothesis of a close association between uncontrolled disease activity and metabolic comorbidities has been also proposed [Ruscitti P, et al. PLoS One. 2017 Jul 12;12:e0181203; Crepaldi G, et al. PLoS One. 2016 Jan 12;11(1):e0146991]. These features should be better detailed. The inflammatory mechanisms of T2D, which could be exaggerated by RA, should be better discussed [Donath MY, et al. Nat Rev Immunol 2011;11:98-107; Giacomelli R, et al. Expert Rev Clin Immunol 2016;12:849-855; Ruscitti P, et al. Clin Exp Immunol 2015;182:35-44]. Furthermore, in this context, a specifically designed clinical trial has been recently published, investigating IL-1 inhibition as a "bidirectional" therapy in patients with RA and T2D [Ruscitti P, et al. PLoS Med. 2019 Sep 12;16(9):e1002901]. A discussion of that would be of interest. IL-6 is also overexpressed in insulin resistance and impairs insulin action in liver and adipose tissue. The involvement of IL-6 in regulation of hepatic insulin sensitivity has been highlighted by neutralizing IL-6, which showed the subsequent enhancement of hepatic insulin sensitivity [Fève B, et al. Nat Rev Endocrinol 2009;5:305-311]. A better discussion of these features could help in better contextualise the results of the present evaluation. The limitations of this work should be furtherly discussed in order to better understand the design of the study.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:
Reviewer: 1
Overall it was an interesting and up- to date work to read on an important topic. The RA group was well- described, followed- up and treated according to current recommendations. The control group was matched to RA patients taking into account not only age and gender but also BMI.
There are some minor details that could be improved:
1.Can you please describe the matching process in detail- how were the controls found? What was the process of "randomly selecting healthy volunteers"?
Reply: Malaga is a province of Andalusia (Southern Spain). There are two Rheumatology Services in the province. The Rheumatology Services of the "Hospital Regional Universitario de Málaga" (HRUM)

serve a population area of 591,285 people. In our Rheumatology service, patients from the rheumatoid arthritis onset cohort were consecutively selected. On the other hand, there are 14 health centres in our population area. The control group was made up of healthy controls selected from among those who attended a health centre in the same geographic area, met the inclusion criteria and none of the exclusion criteria. The controls were matched with the cases for age, sex, race, and BMI (according to WHO classification: normal range [19–24·9 kg/m2], overweight [25–29·9 kg/m2] and obesity [≥ 30 kg/m2]).

This has been better explained in the text according to the reviewer's comments:

Pag. 9, last paragraph: "The control group was made up of healthy controls selected from among those who attended a health center in the same geographic area. All controls fulfilled all of the inclusion criteria and none of the exclusion criteria. The controls were matched with the cases for age, sex, race, and BMI. According to BMI, each control was taken from the same group of the WHO classification for each RA patient (normal range:19–24.9 kg/m2; overweight :25–29.9 kg/m2 and obesity: ≥ 30 kg/m2)".

2.Were the controls exact matches or what was the allowed range of deviation in BMI?

Reply: Controls were matched with cases for age, sex, race, and body mass index (BMI). Regarding the BMI, the type of matching was according to the WHO classification. The patients were classified into 3 groups according to the BMI ranges of the WHO classification. The ranges of the WHO classification were: normal range (19-24.9 kg / m2), overweight (25-29.9 kg / m2) and obesity (≥ 30 kg / m2).

VERSION 2 – REVIEW

REVIEWER	Raili Müller Tartu University, Estonia
REVIEW RETURNED	13-Nov-2020

GENERAL COMMENTS	The paper has improved and can be considered appropriate for publication.