Author's response to reviews

Title: Impact of HFE genetic testing on clinical presentation of hereditary hemochromatosis: new epidemiological data

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Author's response to reviews: see over
We made all the changes required by the Editor to the format of our paper.

**Reviewer 1:** Diane C Tucker

**Major compulsory revisions:** none.

**Minor essential revisions:** none.

**Discretionary revisions:**

We agree with the comment that it could seem counterintuitive that today the age of diagnosis of HH would be higher than it was before the discovery of the HFE gene. What we observed now is that diagnosis of HH is more frequently evoked by physicians or gastroenterologists with respect to mild symptoms observed in patients, and the consequence of this is that the diagnosis of HH is more frequently done today in older men that it was previously. We can now observe a diagnosis of HH done in men older than 65 presenting with fatigue, arthralgia (as illustrated on figure 2A) and with a discrete ferritin elevation. Those C282Y homozygous patients would probably never have been diagnosed ten years ago. So the inclusion of these old diagnosed C282Y homozygous men in our cohort significantly increases the age of diagnosis of HH during the ten last years period. We added this explanation in the “Discussion” section (page 12).

Page 6: we have deleted the “...” at the end of the first paragraph entitled “Determination of biochemical parameter levels and of HFE genotype” in the Method section.

The reviewer has mentioned that the manuscript needs some language corrections. The second reviewer proposed many language corrections throughout the manuscript that we applied.

**Reviewer 2:** Robert Britton

**Major compulsory revisions:**

As our data do not support the conclusion that the availability of HFE genotyping resulted in earlier diagnosis, we made the changes proposed by the reviewer in the text. We deleted the following sentence of the discussion section (page 11): “HH can now be unambiguously diagnosed earlier than it could be before the test was available and this greatly modifies the epidemiology of this disease”.

We switched the headings “yes” and “no” in Table 1.
Minor essential revisions:

We performed all the minor essential revisions proposed by the reviewer and thank him again for the language corrections he made. All the changes we made are marked in red characters in the text. As suggested, we added the reference of Njajou OT et al. (reference no. 46) in the paragraph dealing with the penetrance of the disease in the “Discussion” section (page 11).

Reviewer 3: Claus Hellerbrand

Major compulsory revisions:

We answered to all the questions of the reviewer dealing with alcohol consumption in the first version of the revised manuscript and explained it in the first letter of response to the reviewers (see responses below). However, as mentioned by the reviewer, the changes made in the manuscript were difficult to follow because they were not marked in colour in the revised text. Moreover, the explanations were provided in the “Statistical analysis” section. In order to be more explicit, we removed this explanation from this section and put it at the end of the “Clinical questionnaire” section.

The three questions of the reviewer regarding alcohol consumption were the following ones:

1.- How data concerning alcohol consumption were collected?

In the first revised version of the manuscript, we mentioned in the “Methods” section how data concerning alcohol consumption were collected (Statistical analysis). “The consumption of alcohol was assessed by a detailed item included in the questionnaire, which measured the number of glasses of alcohol drunk each day (including glasses of wine, bier and liquors). These data enabled the quantity of ethanol (in grams) consumed each day, by each patient of the cohort, to be determined.” We removed this explanation from the “Statistical analysis” section and put it at the end of the “Clinical questionnaire” section (page 5).

2.- What was the definition of “excessive alcohol consumption”? 

The definition of excessive alcohol consumption was already presented (Statistical analysis). We mentioned that excessive alcohol consumption was “defined as a daily consumption greater than or equal to 60 grams of ethanol.” We also removed this explanation from the “Statistical analysis” section and put it at the end of the “Clinical questionnaire” section (page 5).

3.- How many patients consumed “excessive amounts of alcohol”? These numbers have to be given for all patients before and after 1996.

In the first revised version of the manuscript, we reported in the “Results” section that in this cohort, 8.0% of the patients declared having excessive alcohol consumption (≥ 60 g/day – n=33) (page 9). We also mentioned that this concerned 9.9% of the patients diagnosed before 1996 (n=9) and 7.4% of those diagnosed after 1996 (n=24).