Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Letter to the editor regarding: "A haemochromatosis-causing HFE mutation is associated with SARS-CoV-2 susceptibility in the Czech population" clinica chimica acta 538 (2023) 211–215

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Dear Editor,

We read with great interest the article "A haemochromatosis-causing HFE mutation is associated with SARS-CoV-2 susceptibility in the Czech population" by Hubacek and colleagues [1]. We would like to thank the authors for this interesting article exploring the association between haemochromatosis-causing *HFE* mutations (p.C282Y and p.H63D) and the risk of COVID-19. In this article, the authors found that the rs1800562 (p.C282Y) minor allele, the main mutation causing the iron overload disorder hereditary haemochromatosis, was associated with an increased risk of COVID-19 infection but not severity. However, the authors found no association with rs1799945 (p.H63D).

Possible links between iron and COVID-19 have previously been suggested [2], with one study, including data on more than 30 countries, showing that *HFE* p.C282Y mutations were significantly associated with COVID-19 prevalence and mortality in univariate analyses, but not in multivariate models [3]. However, the COVID-19 Host Genetics Initiative has previously shown no association of COVID-19 with either the p.C282Y or p.H63D variants in a genome-wide association study meta-analysis [4]. Similarly, we found no significant association in 451,270 UK Biobank participants of European descent of either the p.C282Y or p.H63D mutations with the risk of COVID-19.The UK Biobank is a large volunteer cohort of participants aged 40 to 70 years at baseline (2006–2010), followed up via electronic hospital records, death records and COVID-19 testing data to October 2021 (demographic characteristics of the cohort have been described elsewhere [5]). Our previous research has shown that female p.C282Y homozygotes are somewhat protected from iron overload due to menstrual periods and therefore males are at an increased risk of adverse outcomes such as liver disease and liver cancer [6], but also infections such as pneumonia [5]. We therefore stratified results by sex.

In the original study, Hubacek et al show an increased COVID-19 risk in those with at least one *HFE*-associated p.C282Y allele (p.C282Y homozygotes and heterozygotes combined; unadjusted OR:1.69, 95 % CI: 1.21–2.35) compared to those with no mutations. Hubacek et al found that the frequency of the p.C282Y allele was almost identical across asymptomatic, symptomatic, and hospitalised COVID-19 survivors. In the UK Biobank, participants with at least one *HFE*-associated p.C282Y allele were not at an increased risk of being a COVID-19 hospital inpatient compared to those with no mutations, in either men (OR: 1.07, 95% CI: 0.96–1.19) or women (OR: 0.99, 95% CI: 0.87–1.14), adjusting for age, assessment centre and ten genetic principal components which accounted for population genetics sub-structure [5]. When separating the estimates for p.C282Y homozygotes and heterozygotes (since hereditary haemochromatosis is a recessive disorder), there were still no significant associations. The risk of being a COVID-19 hospital inpatient was not significantly increased in male (OR: 1.53, 95% CI 0.98–2.39) or female (OR: 0.78, 95% CI: 0.39–1.58) p.C282Y homozygotes compared to those with no p.C282Y or p.H63D mutations. Likewise, the risk of any COVID-19 positive test or COVID-19 mortality in male or female p.C282Y homozygotes was not significantly increased (see Table 1). There were also no increases in risk of COVID-19 in other p.C282Y/p.H63D genotype groups compared to those with no mutations.

The differences in these results could be explained by the greater numbers included in the UK Biobank study. The UK Biobank is the largest community cohort of p.C282Y homozygotes to date (n = 2,902/451,270). We examined 27,194 COVID-19 cases (including 3,557 COVID-19 hospital inpatients and 988 COVID-19 deaths) and 424,076 non-COVID-19 participants (compared to 617 COVID-19 cases and 2,559 controls in the original study). Differences in results could also possibly be explained by the adjustment for confounders which were not included in the original study. The time period of the original study was March to September 2020, and our analyses in UK Biobank included data from March 2020 to October 2021 which could reflect different strains of COVID-19 being included. Also, different approaches to controlling the pandemic in the UK compared to the Czech Republic may partially explain differences in the results seen.

In conclusion, the risk of COVID-19 (any positive test, being a hospitalised inpatient or death due to COVID-19) was not significantly increased in males or females with hereditary haemochromatosis genotypes (p.C282Y or p.H63D) compared to those with no mutations in UK Biobank participants of European descent. However, it is important to note that the estimates in UK Biobank do not exclude a modest effect and more work may be needed to confirm findings in other cohorts.

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Table 1
Odds of COVID-19 in p.C282Y homozygotes compared to those with no p.C282Y/p.H63D mutations in UK Biobank*.

	COVID-19 Positive	COVID-19 Hospitalisation	COVID-19 Death
		Odds Ratio (95% CI)	
Male p.C282Y homozygotes	0.83 (0.65–1.06)	1.53 (0.98–2.39)	1.70 (0.80–3.61)
Female p.C282Y homozygotes	0.90 (0.72–1.12)	0.78 (0.39–1.58)	1.71 (0.63–4.62)

*Adjusted for age, assessment centre and ten genetic principal components.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data are available on application to the UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/register).

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