treated with phlebotomy. We aimed to test HFE p.C282Y homozygote associations with prevalent and incident morbidity in the large UK Biobank sample of European descent. We also examined how iron supplement use may affect associations between p.C282Y homozygosity and morbidity.

Methods We studied 451,243 participants of European descent (aged 40 to 70 years) from the UK Biobank. Data were available on prevalent and incident adverse health outcomes from baseline questionnaires and from up to 9.4 years hospital inpatient follow-up (mean 7 years). Participants also reported baseline dietary supplement use. We tested associations between p.C282Y homozygosity, prevalent and incident outcomes, and iron supplement use, using logistic regression and Cox proportional hazard regression, adjusted for age, sex, genotyping array type and genetic principal components.

Results 2,890 participants were p.C282Y homozygotes (0.6%, or 1/156), of whom 7.3% (210/2890) had haemochromatosis diagnosed at baseline, increasing to 15.1% (437/2890) by the end of follow-up. p.C282Y homozygotes had substantial excess prevalent and incident morbidity including haemochromatosis, liver disease, arthritis and diabetes compared to those with no mutations (combined measure of excess incident morbidity; men, HR: 3.37, 95% CI: 2.87–3.97; women, HR: 2.99, 95% CI: 2.51–3.55). A sub-analysis of 200,975 older participants (aged 60–70 years) showed that both male and female p.C282Y homozygotes also had an increased likelihood of Fried frailty and chronic pain.

In p.C282Y homozygotes undiagnosed with haemochromatosis, the intake of iron supplements or multivitamins increased the likelihood of frailty (OR: 2.15, 95% CI: 1.22–3.77) and incident osteoarthritis (HR: 1.86, 95% CI: 1.02–3.41).

Conclusion In a large community volunteer sample, HFE p.C282Y homozygosity was associated with substantial excess morbidity, frailty and chronic pain in both men and women. In p.C282Y homozygotes undiagnosed with haemochromatosis, taking iron supplements or multivitamins was an additional risk factor for developing morbidity, including frailty and osteoarthritis. Since the p.C282Y associated iron overload can be prevented and treated, these findings suggest there is a need for expanded case finding and screening for hereditary haemochromatosis. It also suggests that warnings and controls on iron containing supplements may be needed.