Are *HFE* genotypes robust risk markers?

UK Biobank community cohort:

Baseline (2006-2010):

- n~500,000 community volunteers England, Wales and Scotland
- 40 - 70 years old, some healthy volunteer bias
- C282Y+/+: 1,298 males, 1,604 females
  - p.C282Y/p.H63D 4,959 males and 5,760 females
  - questionnaires, Genetics

Follow-up:

data to mean 13.3 years incident events, routine care

- Hospital inpatient / discharge records
- National cancer registry
- Death certificates
- (limited primary care records - ~half of cohort to 2017)

Group papers on *HFE* outcomes:
(PI Melzer, D)

Baseline/early incident outcomes
Pilling L et al, BMJ 2019

Liver cancer outcomes
Atkins J et al, JAMA 2020

Dementia
Atkins J et al, J Alzheimers Dis. 2021

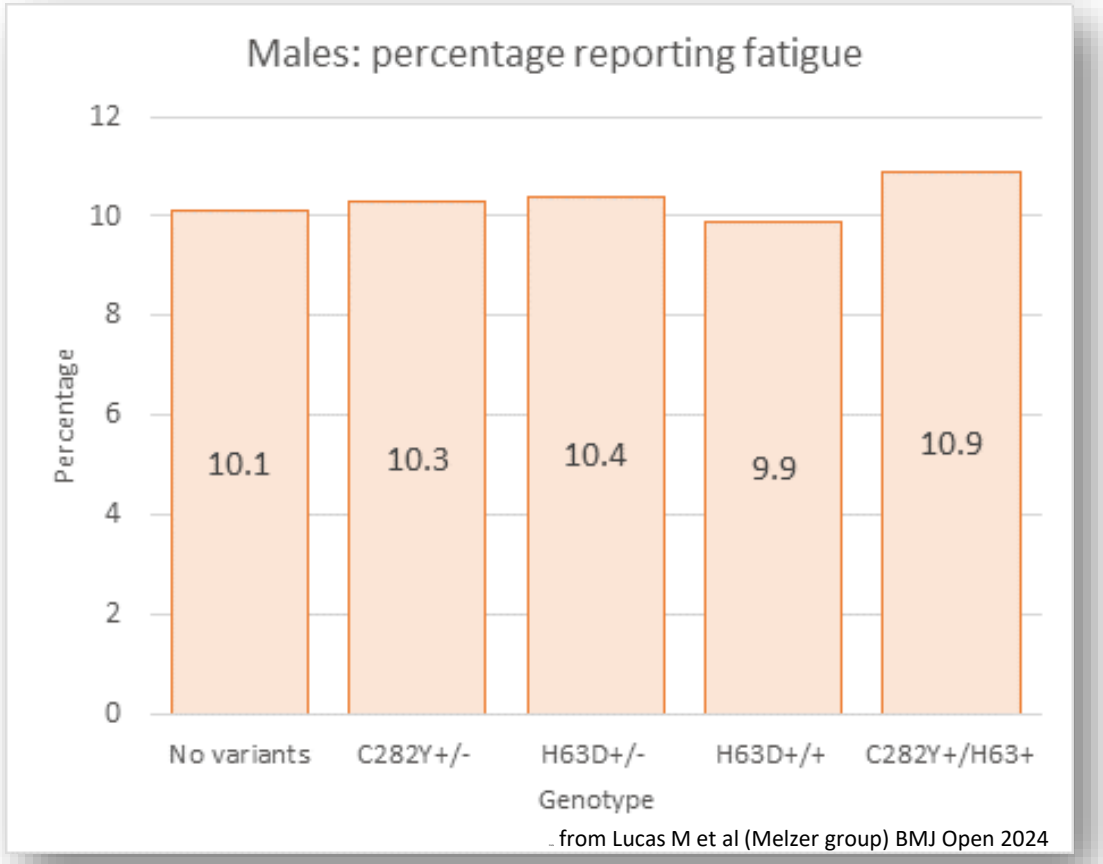
Musculoskeletal outcomes
Banfield L et al, JBMR Plus. 2023

Outcomes ages 40 to 80
Lucas M et al, BMJ Open (in press)

etc

Less severe *HFE* variants

no statistically significant associations: baseline and 13 year follow-up



from Lucas M et al (Melzer group) BMJ Open 2024

"Over the past two weeks, how often have you felt tired or had little energy?":
fatigue = "more than half the days" & "nearly every day".

4,959 p.C282Y/p.H63D and 4,673 p.H63D+/+ males

5,760 p.C282Y/p.H63D and 5,580 p.H63D+/+ respectively.

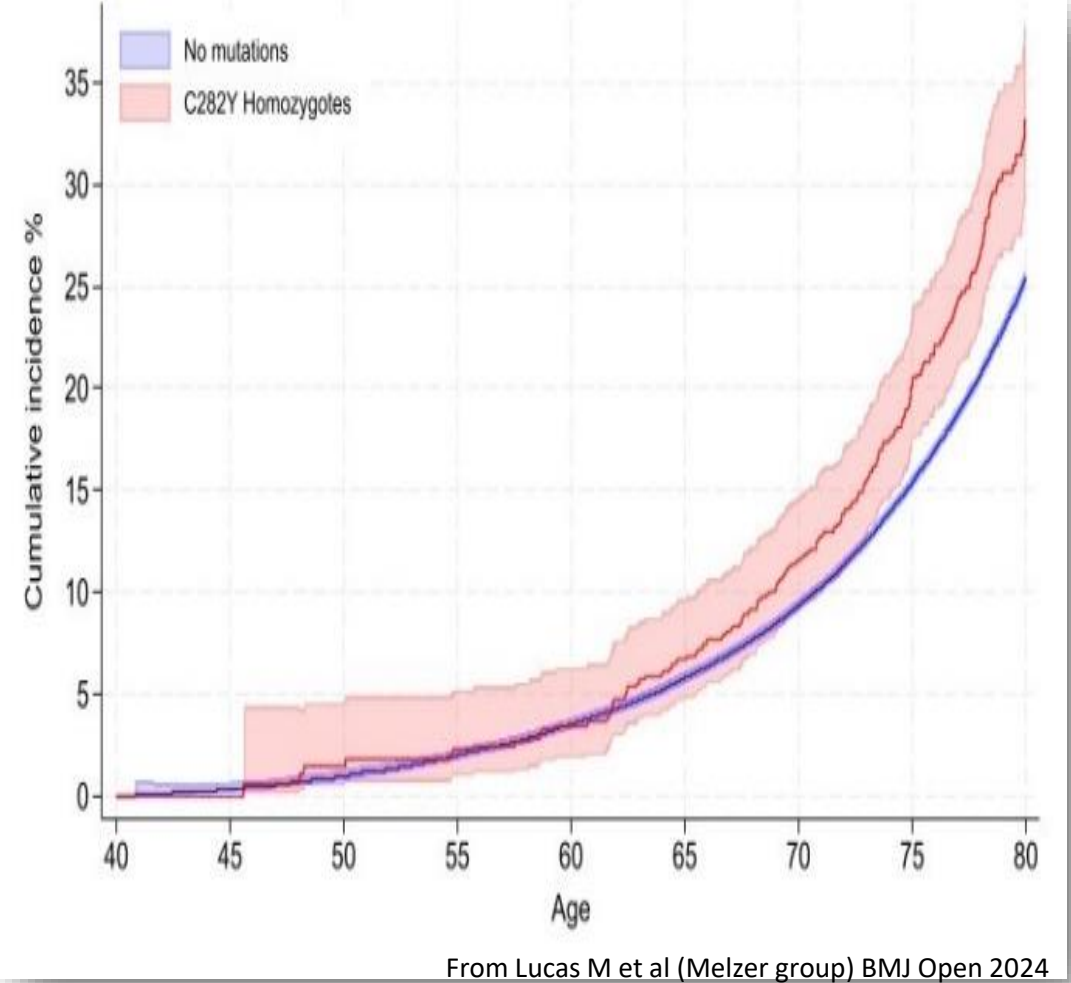
Unfortunately, many develop fatigue, liver disease, arthritis, diabetes, etc

But at approximately the same rate as those without HFE variants

So other causes need to be identified and treated

C282Y+/+ (homozygous)

Excess mortality: n=1,298 males, UK Biobank



From Lucas M et al (Melzer group) BMJ Open 2024

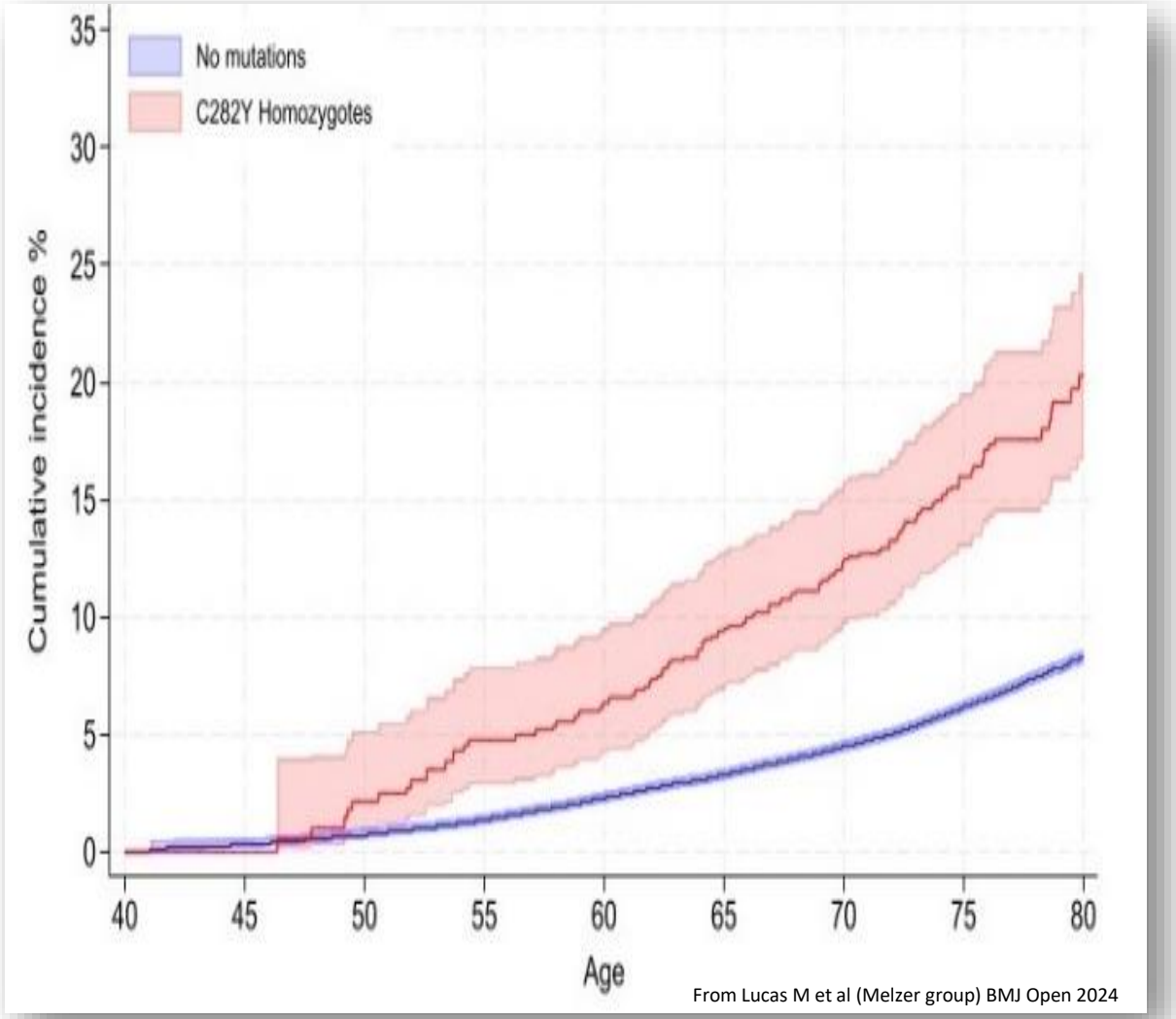
Estimated by age 80:
33.1% of C282Y homozygotes die,
vs 25.4% without *HFE* variants
HR=1.29 (95%CI: 1.12-1.48), $p=4.7*10^{-4}$

Excluding diagnosed hemochromatosis at baseline
HR=1.22 (CI 1.05 to 1.43), p=0.01

Not statistically significant in female C282Y+/+

liver disease: cumulative incidence clinically diagnosed

in 1,298 C282Y homozygous males, UK Biobank

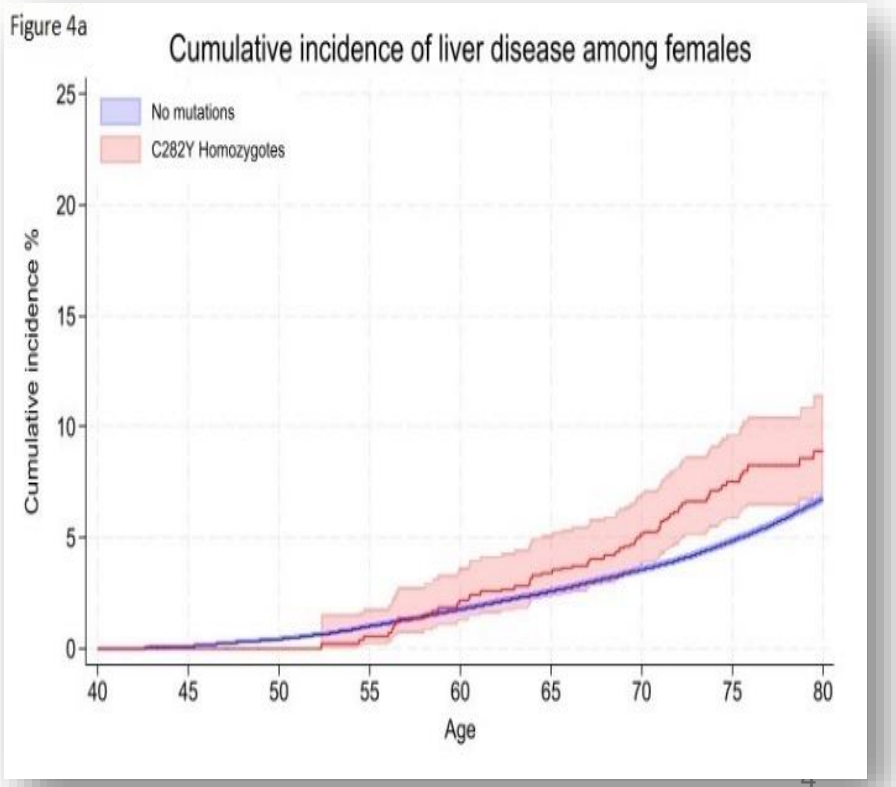


From Lucas M et al (Melzer group) BMJ Open 2024

Males -cumulative incidence liver cancer by age 80:

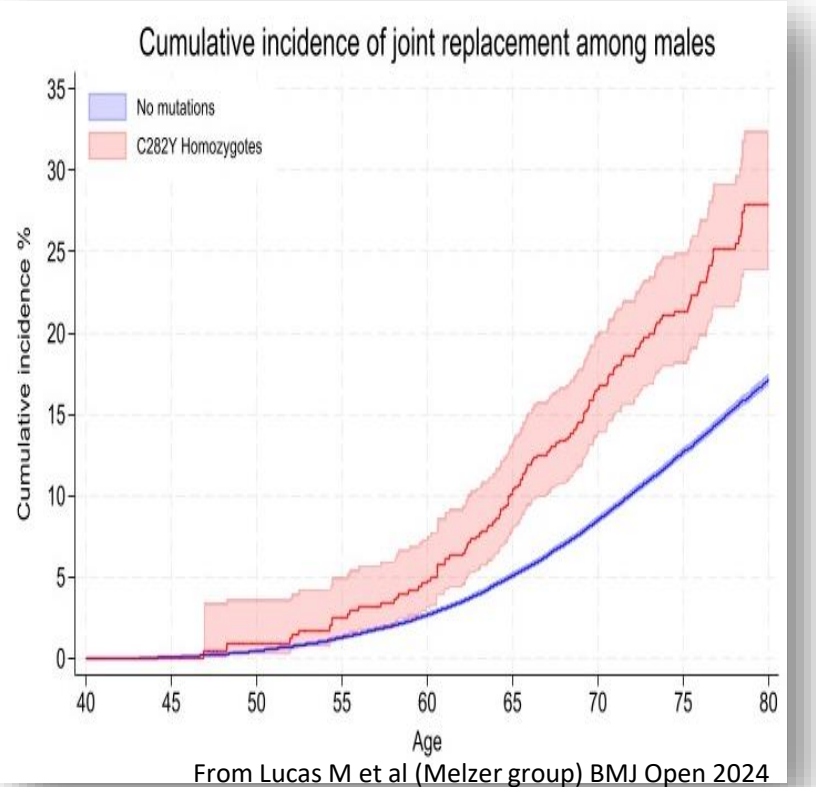
5.5% (95% CI: 3.8% to 8.0%)

0.8% without *HFE* variants

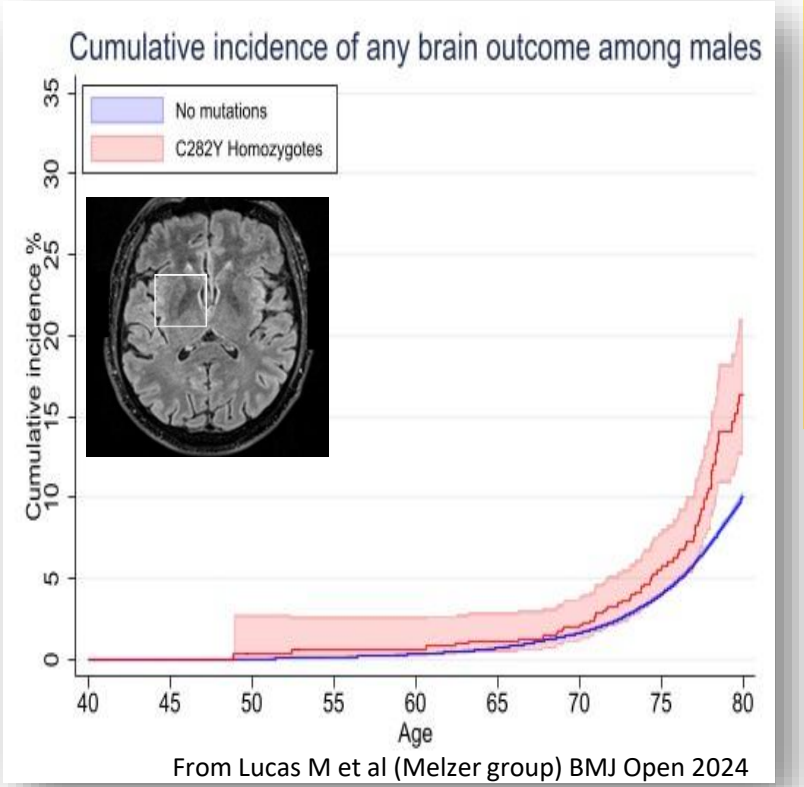


other outcomes

in 1,298 C282Y homozygous males, UK Biobank



From Lucas M et al (Melzer group) BMJ Open 2024



From Lucas M et al (Melzer group) BMJ Open 2024

p.C282Y+/+ males
Modest increase in diabetes
No increase in e.g. heart outcomes

female C282Y+/+
significant increases in musculoskeletal and brain outcomes

See also: Atkins JL, Alzheimers Dis. 2021,

Casanova F, et al Med Genet. 2024

hemochromatosis diagnosis in routine care

in C282Y homozygous groups

UK Biobank

Estimated diagnosed age 80:

Males: 56% (95%CI 51.4% to 61.6%)

Females: 40% (95% CI 36.7% to 44.5%)

Many diagnoses later in life

in both UK and US eMERGE medical centers

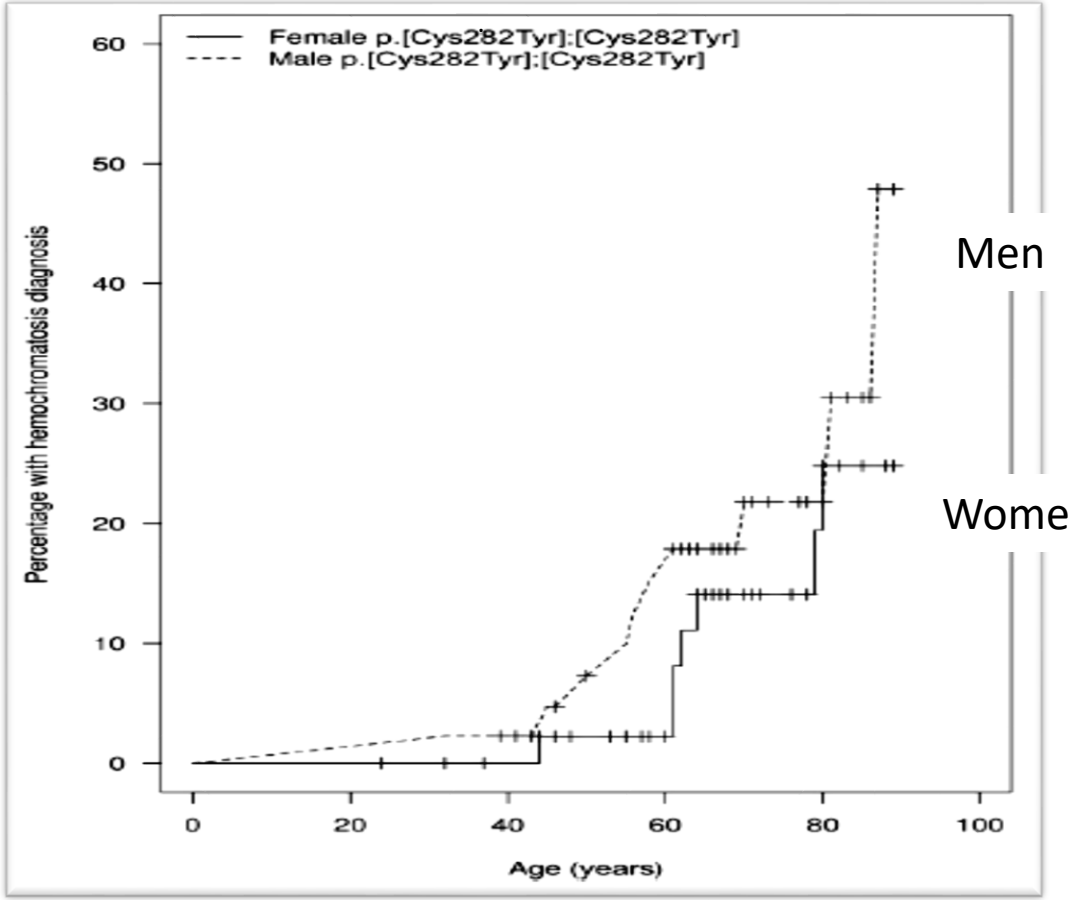
So:

Identifying C282Y+/+ risk early

- many would be diagnosed eventually, but too late?

eMERGE 7 US Medical systems biobank (n=98).

Gallego et al, Am J Human Genetics 2015



Acknowledgements

University of Exeter Medical School

Janice Atkins

Luke Pilling

Mitch Lucas
Lucy Banfield
Karen Knapp
Francesco Casanova
Jane Masoli
Christine Heales

biobank uk

Funders

NIHR | National Institute for Health and Care Research

MRC Medical Research Council

US **National Institute on Aging**
(iron and dementia)

Collaborators include:
Paul Adams, Western University, Canada
Luigi Ferrucci, (US) National Institute on Aging/NIH
Jeremy Shearman, South Warwickshire NHS

Chia-Ling Kuo, George Kuchel
David Steffens, Suzy Torti
Frank Torti: University of Connecticut

Et. al.