Hereditary Hemochromatosis:
Are We Ready for Population Screening?

Epidemiology

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Hereditary Hemochromatosis

textbook onset age 40 to 60 in men, less common and later onsets in women

widespread iron deposition

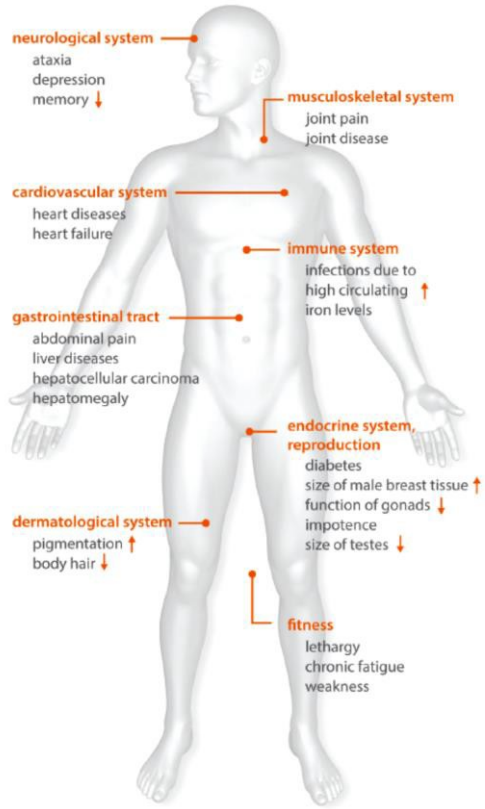
Fatigue, weakness, joint pain, abdominal pain

- Liver – cirrhosis and hepatocellular cancer
- Arthritis / arthropathy
- Diabetes

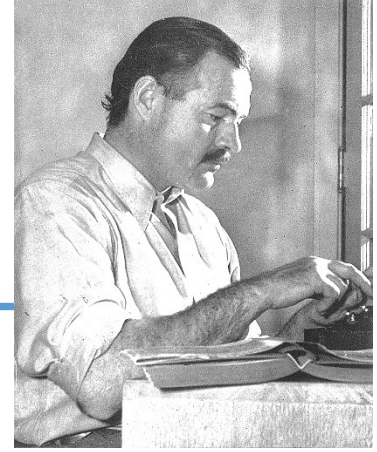
Less common

Susceptibility to infection, cardiomyopathy, arrhythmias, endocrine glands, erectile dysfunction, menstrual problems, *Bronze skin*

(e.g. Powell L et al, The Lancet 2016, Hollerer et al Haematologica 2017)



From: Hollerer et al Haematologica 2017



Ernest Hemingway working on "For Whom the Bell Tolls" 1939

Genetic variants

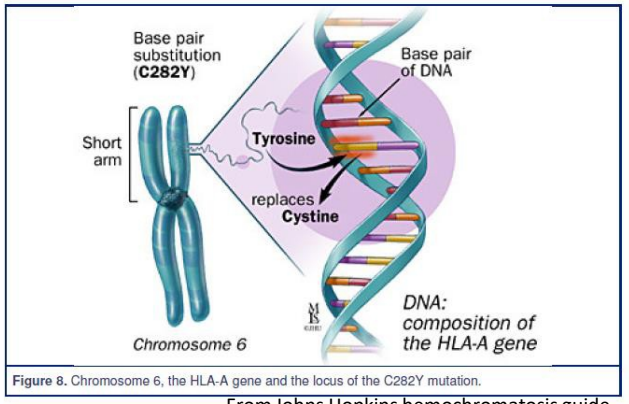


Figure 8. Chromosome 6, the HLA-A gene and the locus of the C282Y mutation.

From Johns Hopkins hemochromatosis guide

Hereditary Haemochromatosis (HH - Type 1) predominantly occurs with European ancestries

HFE mutations

95% of HH is linked to p.C282Y homozygosity

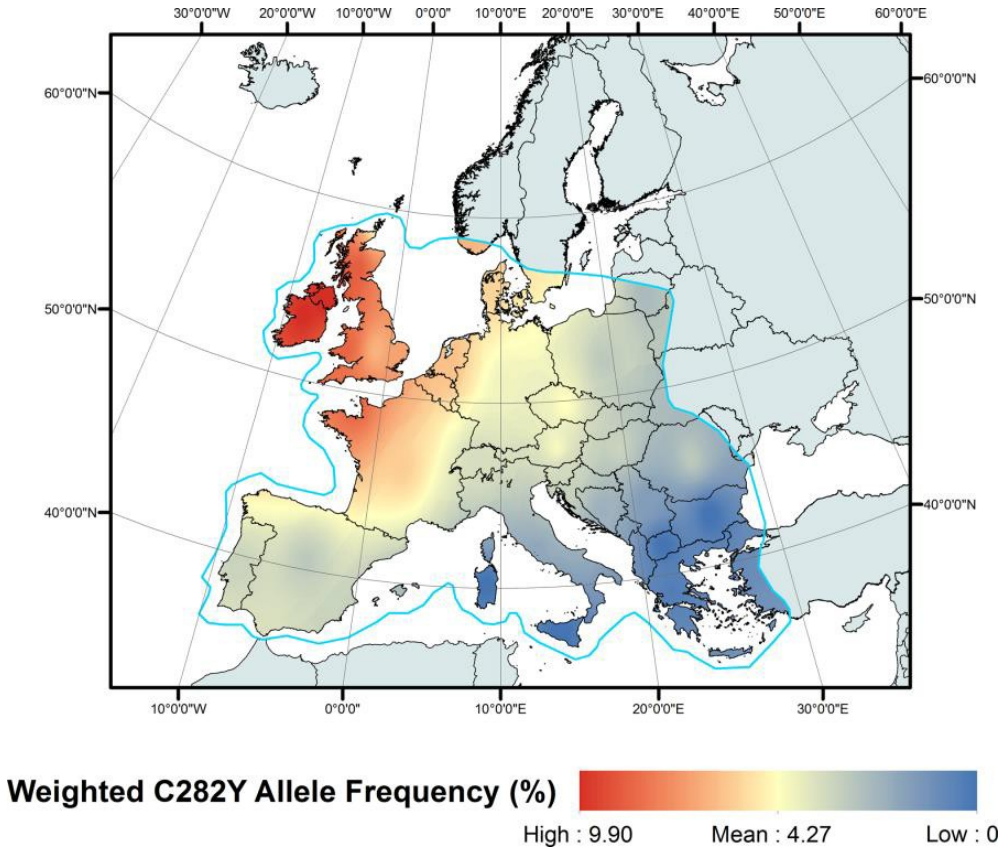
5% p.C282Y/p.H63D

Plus some rare variants

Higher prevalence in northern Europe

– especially Ireland and the UK

But present across European ancestries



Heath et al: American Journal of Physical Anthropology, 2016

Prevalence in North America

HFE p.C282Y homozygosity ('HMZ')

HEIRS study: 99,711 participants across 5 North American Medical Centers

(Adams et al, NEJM, 2005)

White Americans – 1 in 227 people are C282Y homozygote p.(C282Y/C282Y)

Group	Prevalence (%)	95% CI
White	0.44	0.42 to 0.47
Native American	0.11	0.06 to 0.20
Hispanic	0.027	0.022 to 0.032
Black	0.014	0.012 to 0.017
Pacific Islander	0.012	0.0043 to 0.032
Asian	0.000039	0.00015 to 0.00010

Biochemical 'penetrance': e.g. ferritin levels

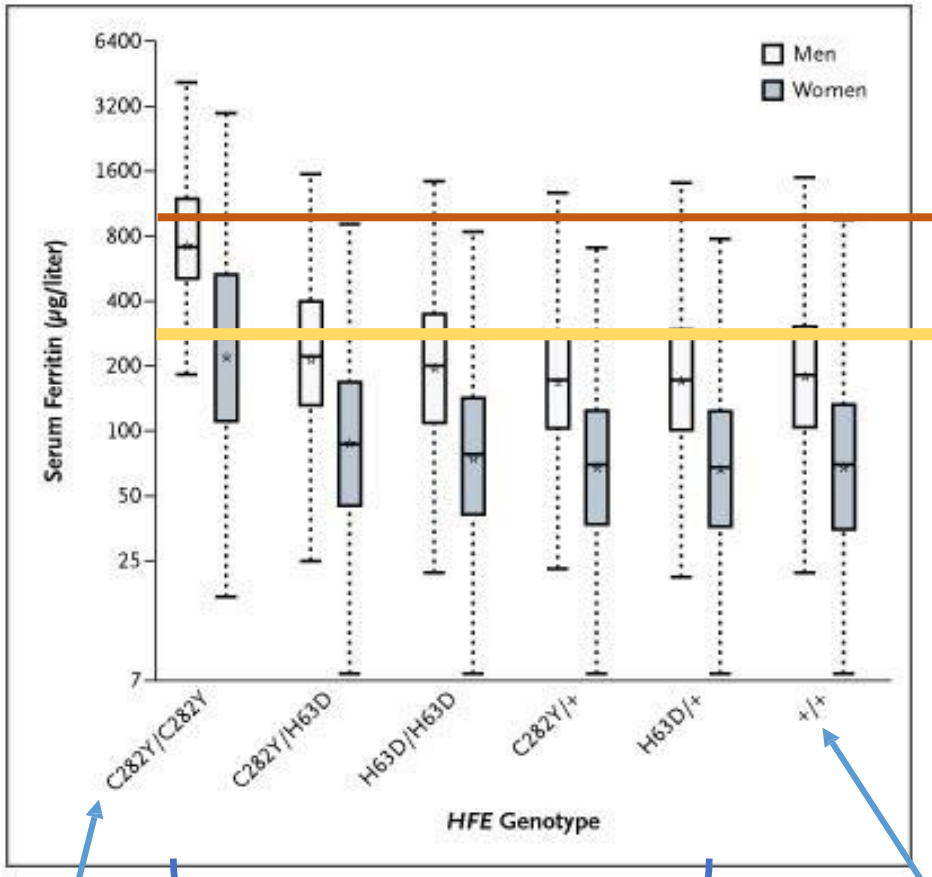
C282Y partially inactivates control of iron absorption from the gut

Stages (of clinical progression):
1. Genetic risk only
2. Iron overload
3. Iron overload & early symptoms
4. Iron overload & organ damage

High risk for later stages in those with ferritin >1000µg/L

Ferritin and transferrin saturation at any one time - only moderately predictive

From Adams et al HEIRS study: N Engl J Med 2005



1000µg/L

abnormal >300µg/L in Men

Homozygotes "HMZ"

Non-HMZ *HFE* mutations

Wild Type (no *HFE* mutations)

Treatment

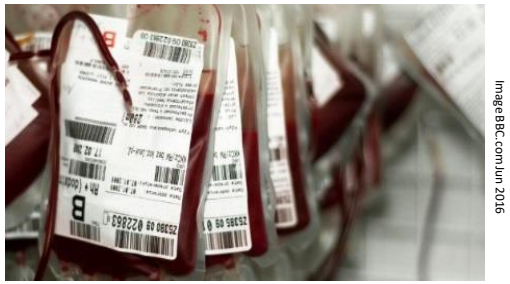


Image BBC.com Jun 2016

Phlebotomy effective at correcting iron overload

- Intensive initially
- Maintenance – 4 or 5 times per year
- *(maintenance blood can be used for transfusion for others)*

Good response

- fatigue, weakness, abdominal pain
- Liver fibrosis

Limited response

- cirrhosis
- arthritis
- diabetes

so need to treat before this damage established

Eg: Powell L et al, Lancet 2016; Kealey P, Journal R-Coll Physicians Edinburgh, 2018)

Reduction in liver fibrosis after phlebotomy in group identified in family screening

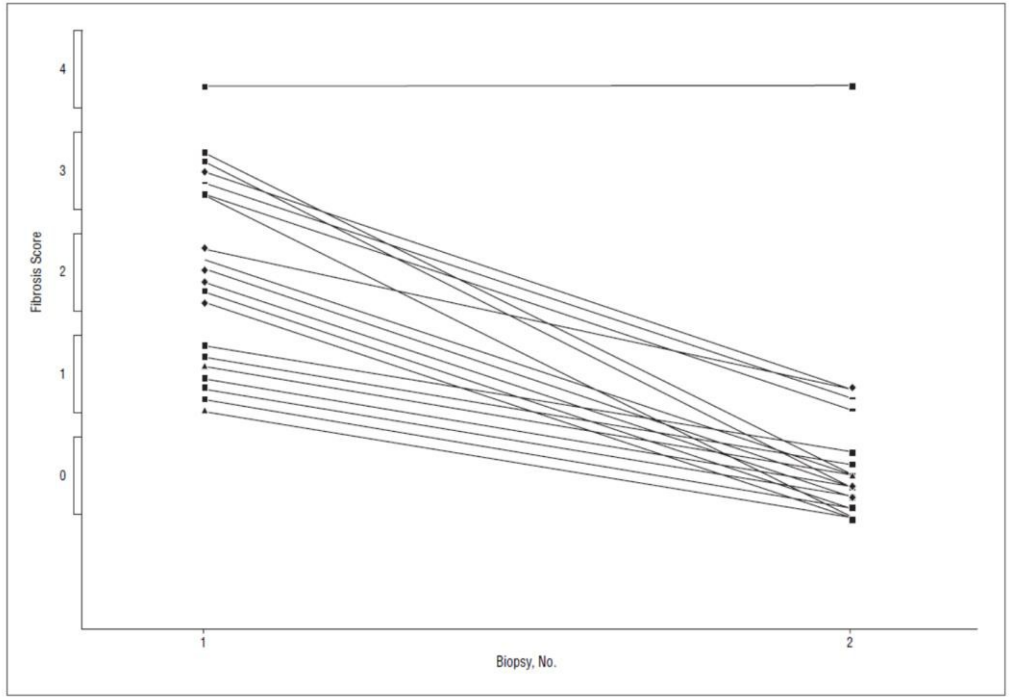


Figure 4. Reduction in fibrosis following phlebotomy therapy. Twenty-five subjects underwent a second liver biopsy after phlebotomy. Five subjects were excluded from analysis owing to significant alcohol intake (>60 g/d). In the remaining 20 subjects, the fibrosis score improved significantly following removal of iron by phlebotomy except where cirrhosis was present.

7.5 fold reduction in fibrosis scores except in cirrhosis

(Powell L et al, Arch Internal Medicine, 2006)

US Preventive Services Task Force - HH report

Whitlock EP et al, Annals of Internal Medicine, 2006

HH Screening for primary care clinicians: ***Review to February 2005***

Key questions:

1: What is **the risk** for developing clinical hemochromatosis in p.C282Y homozygotes?

2: Does **early treatment** reduce morbidity and mortality?

3: Can groups at risk be **readily identified before** genetic screening?

Noted insufficient data on precise penetrance and no RCTs of treatment

On 'very small numbers': 38% to 50% of C282Y HMZ develop iron overload

cirrhosis (6.3%), diabetes (3.6%),

limited data on male and females separately, limited follow-up time

So: supported family screening & testing of high risk symptomatic groups

Penetrance to clinical diagnosis

HFE p.C282Y homozygous mutation

Wide range of estimates from clinical and smaller studies: 1% to 50%

Larger 'community' studies with genotyping:

low rates of associated disease, except in p.C282Y homozygote males with very high ferritin levels

Beutler et al Lancet 2002: Kaiser Permanente health appraisal clinics, sample n=41,038, n=152 HMZ

"less than 1% of homozygotes develop frank clinical haemochromatosis"

i.e. full syndrome, after excluding prevalent cases

Liver problem or hepatitis: p.C282Y HMZ 8.1 % vs 4.1% wild type OR 2.1 95% CI 1.1 to 4.0

HEIRS study: 5 North American centers, primary care patient sample n=99,711, n=299 HMZ

more liver disease in male p.C282Y homozygotes (Adams et al NEJM 2005)

higher prevalence chronic fatigue & metacarpophalangeal joint swelling with higher serum ferritin levels

Healthiron study (Allen et al, NEJM, 2008): population sample n=31,000 (203 HMZ) in Melbourne, Australia

Male p.C282Y homozygotes with serum ferritin level ≥1000 µg/L were more likely to report fatigue, use of arthritis medicine, and a history of liver disease

etc

UK Biobank

500,000 volunteers

aged 40 to 70: baseline interview – 2006 to 2010

Assays: including liver enzymes, *but no blood iron studies (so far)*

Follow-up…..

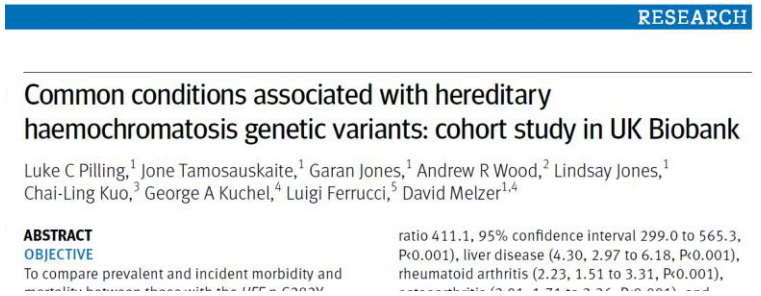
hospital admission records, cancer registry, death certificates

GP records – recently released on ~250,000

MRI in a subset, including iron imaging

Consent – no individual feedback of genotypes: so results are under routine clinical care

HFE p.C282Y prevalence in UKB



RESEARCH

Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank

Luke C Pilling,[1] Jone Tamosauskaite,[1] Garan Jones,[1] Andrew R Wood,[2] Lindsay Jones,[1] Chai-Ling Kuo,[3] George A Kuchel,[4] Luigi Ferrucci,[5] David Melzer[1,4]

ABSTRACT
OBJECTIVE
To compare prevalent and incident morbidity and

ratio 411.1, 95% confidence interval 299.0 to 565.3, P<0.001), liver disease (4.30, 2.97 to 6.18, P<0.001), rheumatoid arthritis (2.23, 1.51 to 3.31, P<0.001),

451,243 European descent (on genetic clustering)
p.C282Y homozygotes ('HMZ'): sample size=2,890
0.64% of population, or 1 in 156
Male HMZ 1294, Female 1596, mean age ~57 years

Follow-up – now max 11 years, mean 8 years

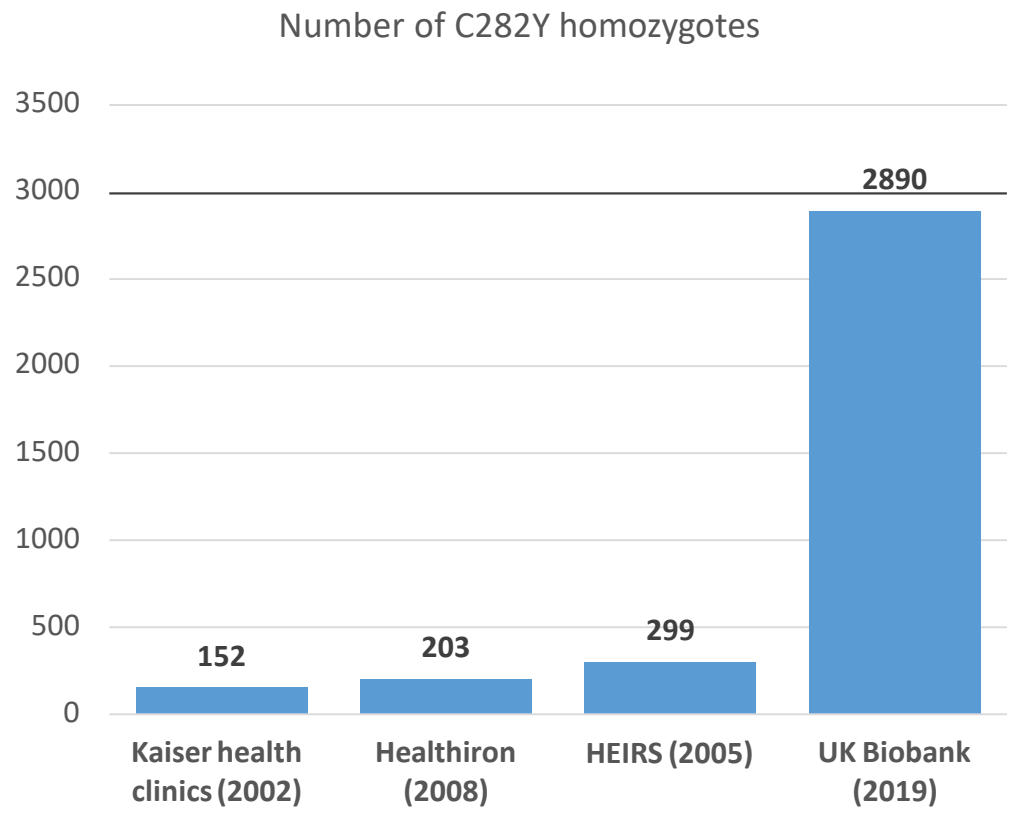
UK Biobank: C282Y allele frequency similar to other UK studies

UKB = 7.3%: Alspac (Bristol UK) 7.9%, TwinsUK 6.9%

0.68% in 10,500 Welsh blood donors (Jackson HA, BJH, 2001: no diagnosed HH)
(0.9 in Generation Scotland cohort, 0.88 in UKB)

approx. 350,000 people in the UK

UKB 14.3% C282Y heterozygous (i.e. one copy of the mutation)
15.1% in Welsh blood donor study

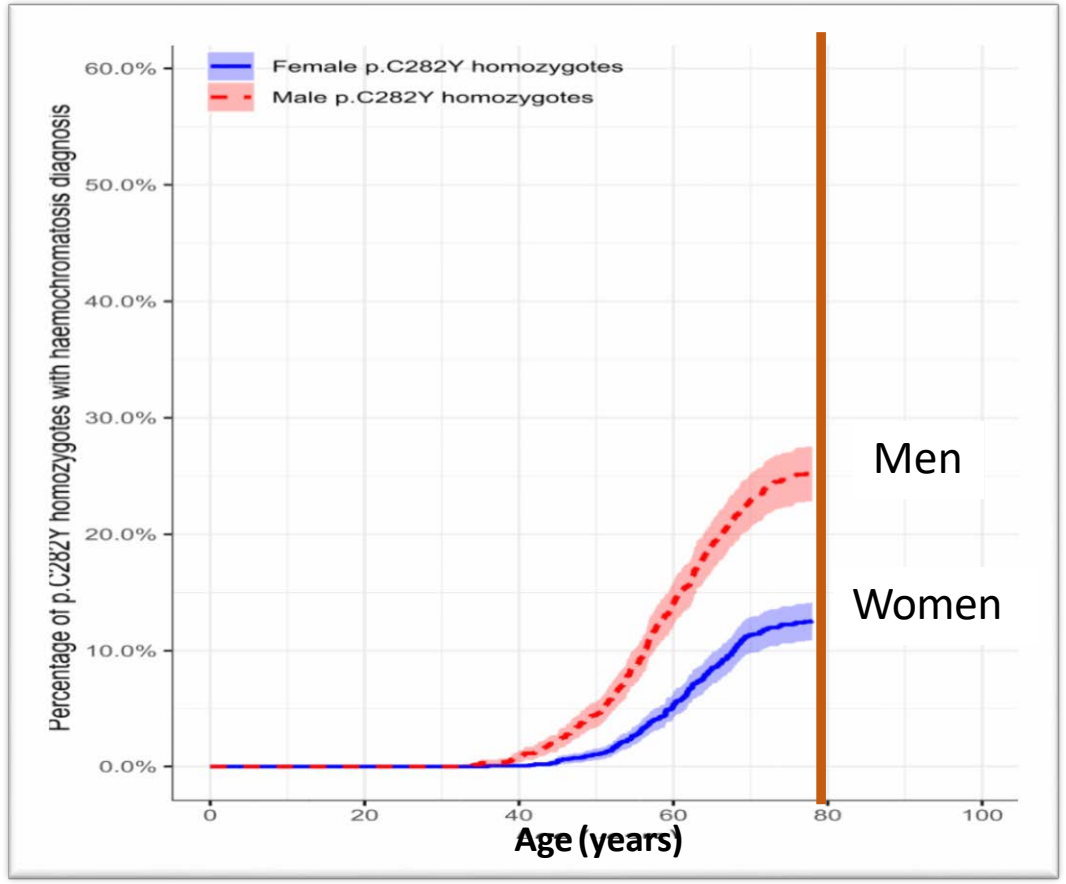


Prevalence data from Pilling L et al, BMJ, 2019

Age at hemochromatosis diagnosis (p.C282Y HMZ)

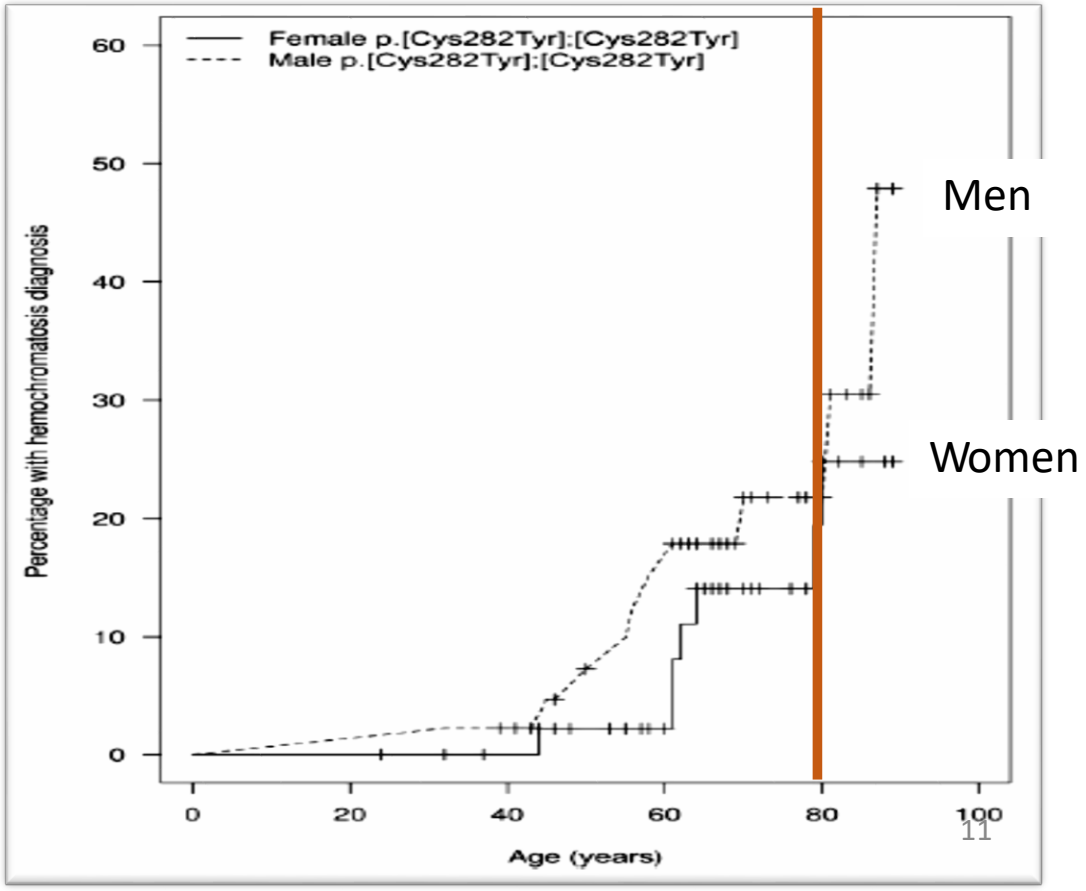
UK Biobank (usual care, n=2890)

n=210 at baseline, n=321 incident diagnosed

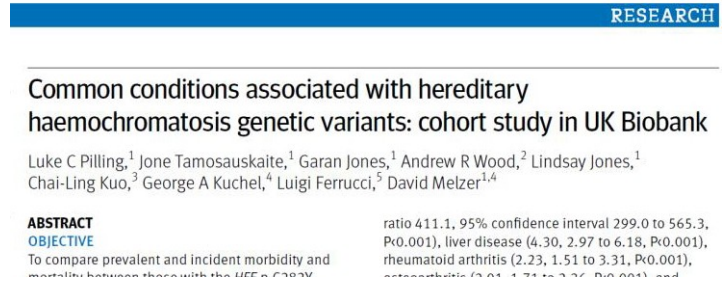


eMERGE 7 US Medical systems biobank (n=98).

Gallego et al, Am J Human Genetics 2015



UKB baseline associations, Men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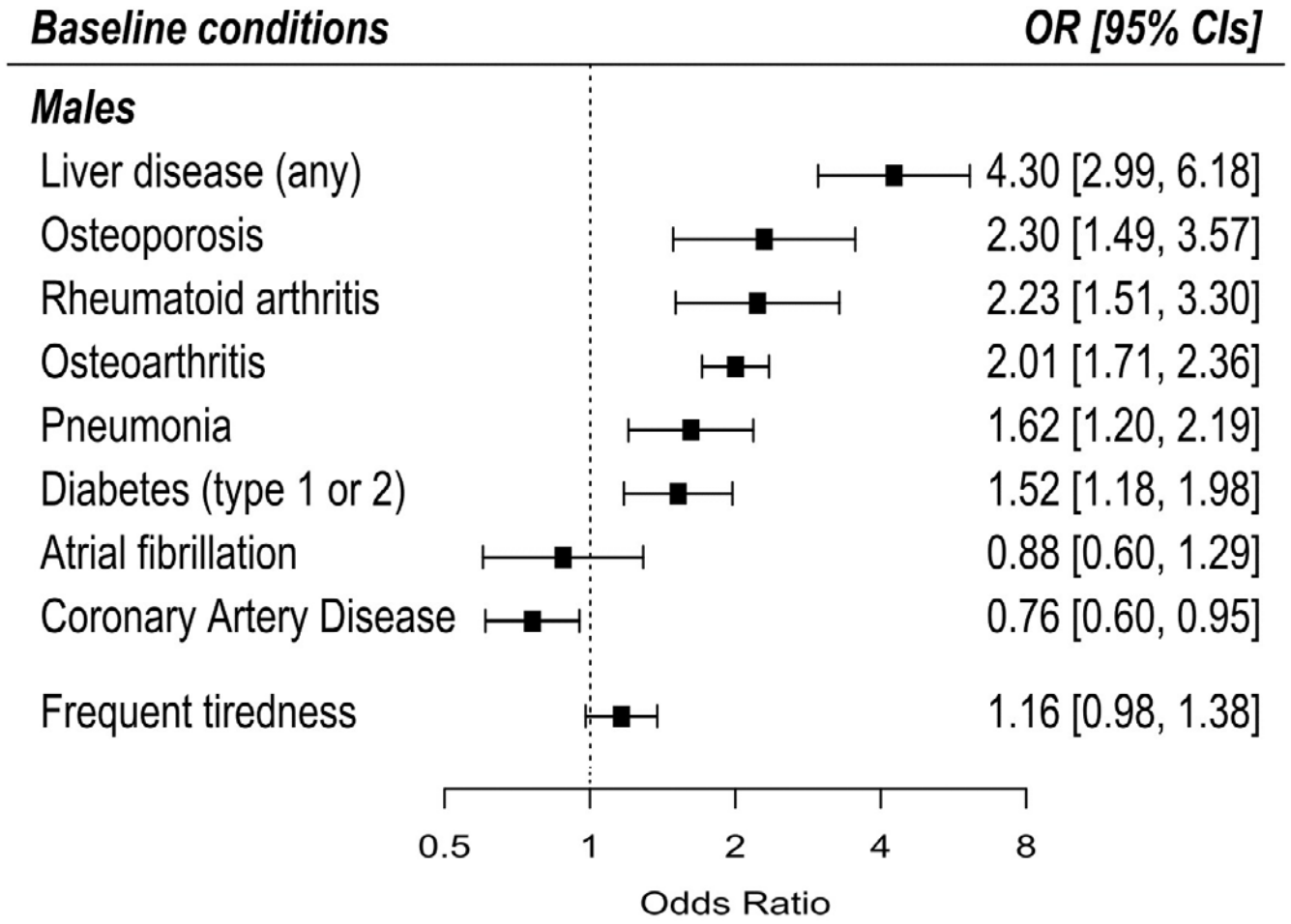
Reported doctor diagnoses to study Nurse, or from inpatient hospital records back to 1997

Women p.C282Y HMZ osteoarthritis only:
OR 1.33 (CI 1.15 to 1.53)

HFE p.C282Y HMZ versus wild type



Chronic pain & frailty

Older group (60 to 70 years) in UK Biobank, baseline

Journals of Gerontology: Medical Sciences
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doi:10.1093/gerona/glv270
Advance Access publication January 16, 2019

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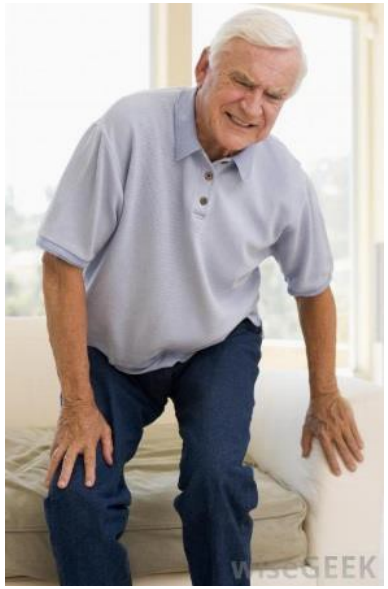
OXFORD

Research Article

Hereditary Hemochromatosis Associations with Frailty, Sarcopenia and Chronic Pain: Evidence from 200,975 Older UK Biobank Participants

Jone Tamosauskaite,[1] Janice L. Atkins, PhD,[1,a] Luke C. Pilling, PhD,[1,a] Chia-Ling Kuo, PhD,[2,3] George A. Kuchel, MD,[2] Luigi Ferrucci, MD, PhD,[4] and David Melzer MBBCh, PhD[1,2,*]



Chronic pain (3+ months)

Male p.C282Y HMZ: associations with hip, back, shoulder/neck

Sarcopenia (muscle weakness): OR=2.38: 1.80–3.13, $p = 9.70 \times 10^{-10}$

Frailty: OR=2.01: 1.45–2.80, $p = 3.41 \times 10^{-05}$

– based on weakness, fatigue and weight loss

p.C282Y HMZ women: Excess pain at ages 65 to 70:
chronic knee, hip and back pain.

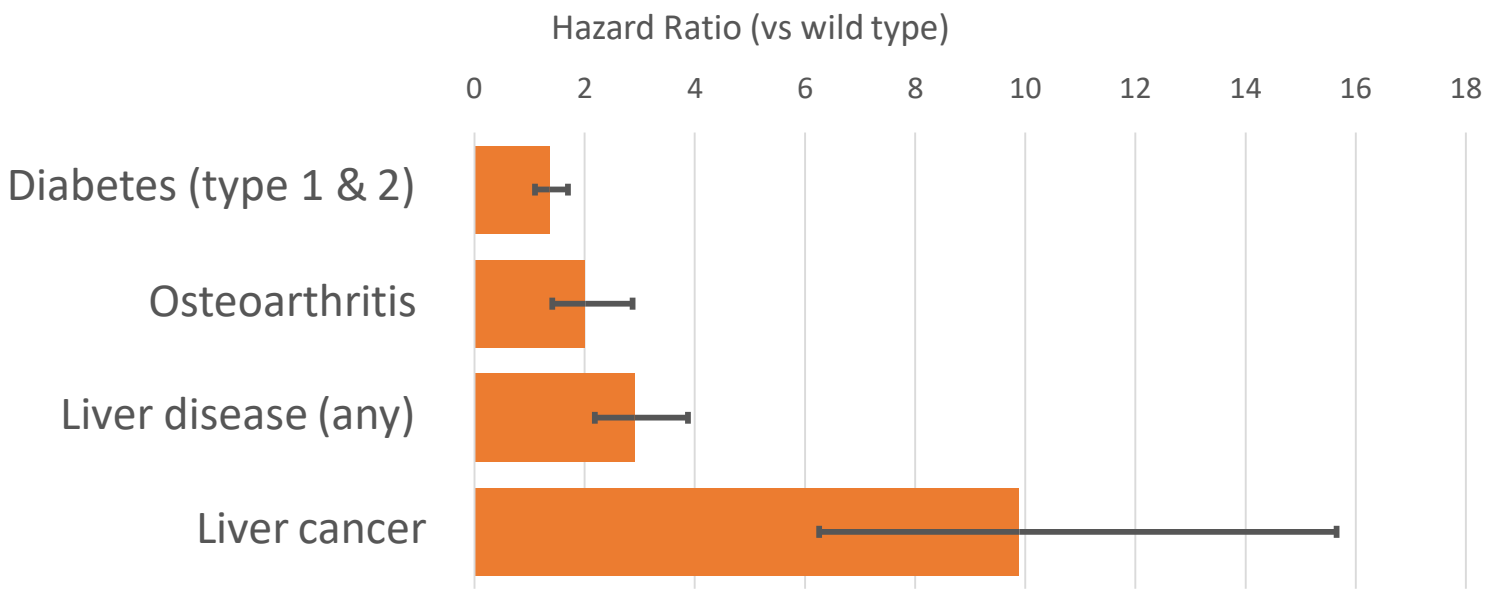
From Tamosauskaite J et al, J Gerontology Medical Sciences 2019

incident diagnoses only: men

i.e.: minimising possible biased response to UKB

– hospital inpatient records to 2017

Males: HMZ versus wild type



Females –
Osteoarthritis HR=1.54 (1.11 to 2.15)

Adjusted for age, sex, 10 genetic principal components, assessment centre and chip. Removing related participants – little changed

robust to excluding HH diagnoses at baseline
- also osteoarthritis and diabetes excluding liver disease (reducing hospital admission biases)

Mortality by *HFE* p.C282Y in UKB

Heterozygotes HR = 0.99 (0.96 to 1.03)

consistent with previous heterozygote evidence – no excess mortality.

HMZ: n=148 deaths

HR= 1.22 (95%CI 1.03 to 1.43) p=0.02 versus wild type

Lifetable ages 40 to 75:

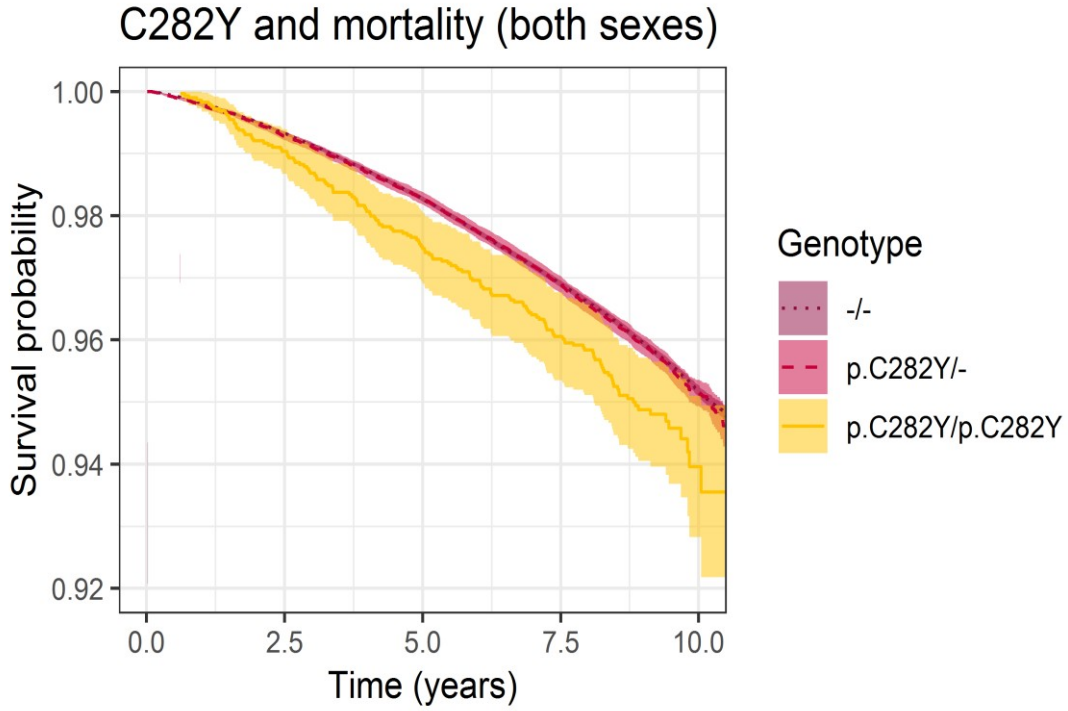
Men: 1 in 23 additional HMZ men die by age 75

difference 4.4% i.e. HMZ=19.5% 95%CI 15.8 to 24

versus no HFE mutations =15.1% CI 14.7 to 15.5

Women: currently 1 in 38 additional deaths in HMZ

– not (yet) statistically significant



Adapted from Pilling L et al, BMJ, 2019 with longer follow-up:
original finding n=107 deaths in homozygotes,
published HR =1.23 (CI 1.01 to 1.48, p=0.04)

Epidemiology conclusions

1: **risk** for developing clinical hemochromatosis in p.C282Y homozygotes?

p.C282Y homozygotes do get substantial excess morbidity, some excess mortality (especially males)

Onsets at older ages common

Substantial pain and arthritis, in addition to liver disease

3: **readily identifiable before** genetic screening?

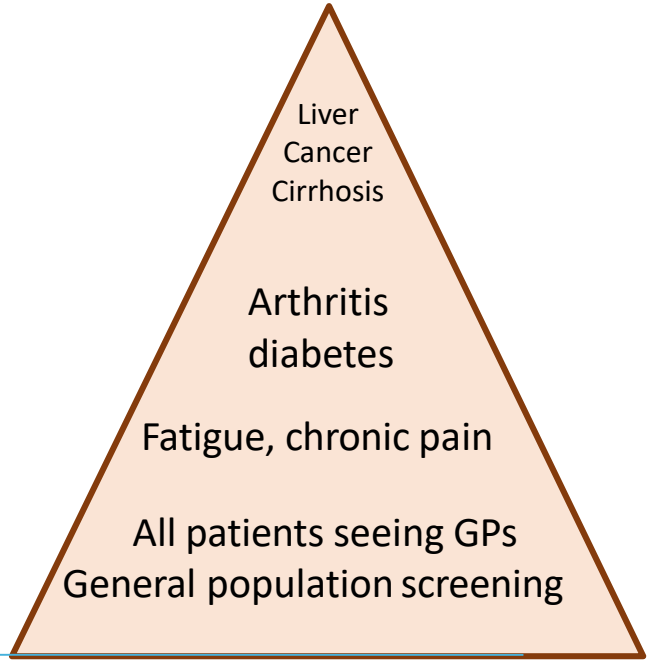
Many are not being diagnosed early under routine care (UKB, eMERGE)

Difficult to diagnose without routine testing

– e.g. fatigue & arthritis common anyway

Primary prevention – population screening

Secondary prevention – clinical screening



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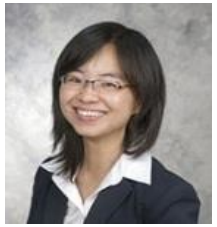
George A Kuchel – UCHC Center on Aging



Luigi Ferrucci M.D., US National Institute on Aging, NIH

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