research

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ORIGINAL RESEARCH Prospective cohort study

Mortality and risk of diabetes, liver disease, and heart disease in individuals with haemochromatosis *HFE* C282Y homozygosity and normal concentrations of iron, transferrin saturation, or ferritin

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Study question Is the risk of diabetes, liver disease, and heart disease increased in people with haemochromatosis *HFE* (homoeostatic iron regulator) C282Y homozygosity even when they have normal plasma iron, transferrin saturation, or ferritin, and do individuals homozygous for C282Y with diabetes, liver disease, or heart disease have higher mortality than non-carriers with these diseases?

Methods This prospective cohort study included 132 542 individuals from three Danish cohort studies: Copenhagen City Heart Study (9174 individuals examined 1991-94), Copenhagen General Population Study (103 276 examined 2003-14), and Danish General Suburban Population Study (20 092 examined 2010-13) who had been genotyped for the *HFE* C282Y and H63D variants, 422 of whom were homozygous for C282Y. Age at study enrolment was 20-100 years. Study procedures were similar for the three cohort studies. No individuals overlapped between the three cohort studies, and no individuals were lost to follow-up. Using national registries covering all hospitals and deaths in Denmark, individuals were followed up for 27 years after study enrolment for hospital contacts and deaths. Information on inpatient hospital admissions from 1 January 1977 until 31 December 2018 and emergency department and outpatient visits from 1 January 1994 until 31 December 2018 were obtained from the Danish National Patient Register. Diagnoses were classified according to ICD-8 (international classification of diseases, eighth revision) until 31 December 1993, when it was superseded by ICD-10.

Study answer and limitations When studied according to levels of iron, transferrin saturation, and ferritin in a single blood sample obtained at study enrolment,

risk of diabetes was increased in individuals homozygous for C282Y with normal transferrin saturation (hazard ratio 2.00, 95% confidence interval 1.04 to 3.84) or ferritin (3.76, 1.41 to 10.05) and with normal levels of both ferritin and transferrin saturation (6.49, 2.09 to 20.18). Individuals with C282Y homozygosity and diabetes had a higher risk of death from any cause than did non-carriers with diabetes (1.94, 1.19 to 3.18), but mortality was not increased in individuals with C282Y homozygosity without diabetes. As measurements of iron, transferrin saturation, and ferritin were from a single blood sample at study enrolment, iron overload occurring between study enrolment and onset of diabetes cannot be excluded.

What this study adds Risk of diabetes was increased in individuals homozygous for C282Y with normal levels of transferrin saturation, ferritin, or both, who are not currently recommended for haemochromatosis genotyping. All cause mortality was higher in individuals with diabetes and homozygous for C282Y compared with non-carriers with diabetes, and 27.3% of all deaths among those homozygous for C282Y were potentially attributable to diabetes, indicating that prioritising detection and treatment of diabetes for such people in clinical guidelines on haemochromatosis may be relevant.

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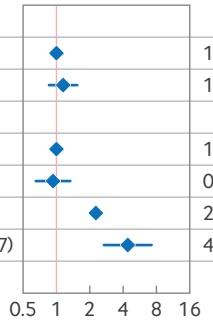
Supported by the Capital Region of Denmark and the Independent Research Fund Denmark. See full article on bmj.com for competing interests. To comply with data privacy regulations, access to original data is possible only in case of collaborative agreement.

Absolute five year risk (%) of diabetes, liver disease, and heart disease diagnosed after study enrolment

Diagnosis by age group (years)	Women		Men	
	Non-carrier	C282Y/C282Y	Non-carrier	C282Y/C282Y
Diabetes				
20-39	0.37	0.54	0.60	0.86
40-49	0.58	0.84	0.94	1.4
50-59	1.4	2.1	2.3	3.3
60-69	2.0	2.9	3.2	4.6
70-79	2.7	3.9	4.3	6.2
≥80	3.0	4.3	4.8	6.8
Liver disease				
20-39	0.28	0.77	0.32	0.87
40-49	0.36	0.98	0.40	1.1
50-59	0.65	1.8	0.73	2.0
60-69	0.80	2.2	0.91	2.5
70-79	0.81	2.2	0.92	2.5
≥80	0.83	2.3	0.94	2.6
Heart disease				
20-39	0.61	0.54	0.98	0.88
40-49	1.4	1.2	2.2	2.0
50-59	3.4	3.1	5.6	5.0
60-69	6.0	5.4	9.6	8.6
70-79	11	10	18	16
≥80	19	18	30	27

Absolute five year risk estimates in percentages are shown for individuals homozygous for C282Y (C282Y/C282Y) and non-carriers for both C282Y and H63D (non-carrier) and stratified according to sex and age categories. Analysis on risk of diabetes included 85 304 non-carriers and 406 individuals homozygous for C282Y as individuals with diagnosis of diabetes before study enrolment were excluded. Analysis on risk of liver disease included 86 561 non-carriers and 418 individuals homozygous for C282Y as individuals with diagnosis of liver disease before study enrolment were excluded. Analysis on risk of heart disease included 82 010 non-carriers and 401 individuals homozygous for C282Y as individuals with diagnosis of heart disease before study enrolment were excluded.

	Individuals (No)	Events (No)	PAF for diabetes on death (95% CI)	Hazard ratio (95% CI)
All individuals irrespective of disease				
Non-carrier/non-carrier	87 313	11 737		1.00 (reference)
C282Y/C282Y	422	48		1.16 (0.87 to 1.54)
Diabetes				
Non-carrier/non-carrier without diabetes	82 218	10 094		1.00 (reference)
C282Y/C282Y without diabetes	386	32		0.93 (0.65 to 1.31)
Non-carrier/non-carrier with diabetes	5095	1643	7.8 (7.2 to 8.4)	2.26 (2.15 to 2.38)
C282Y/C282Y with diabetes	36	16	27.3 (12.4 to 39.7)	4.39 (2.69 to 7.18)



Hazard ratio 1.94 (1.19 to 3.18; P=0.008) for death from any cause comparing C282Y/C282Y with diabetes and non-carrier/non-carrier with diabetes

Relative risk of death from any cause in individuals homozygous for C282Y (C282Y/C282Y) and non-carriers for both C282Y and H63D (non-carrier/non-carrier), adjusted for age and sex, including all individuals irrespective of disease with further stratification according to whether or not individuals had diagnosis of diabetes at any time before or after study enrolment. CI=confidence interval; PAF=population attributable fraction

After the detailed description of 311 patients with iron overload by J H Sheldon in 1935,[1] people assumed that iron overload and haemochromatosis were synonymous and that iron overload throughout the body defined and caused the clinical disease. Iron overload was determined by liver biopsy, autopsy, and response to therapeutic phlebotomy. In the 1970s, newer blood tests such as serum ferritin and transferrin saturation became part of the diagnostic testing for iron overload.[2 3] In 2005 data from the Hemochromatosis and Iron Overload Screening (HEIRS) Study introduced genetic testing and showed that approximately 57% of female and 20% of male C282Y homozygous individuals had a normal serum ferritin and/or transferrin saturation without apparent iron overload.[4] Transferrin saturation was found to be highly variable within individuals,[5] and serum ferritin had mostly false positive results in patients without iron overload. Magnetic resonance imaging became a new tool to assess iron overload in the liver and other organs. In light of these developments, research projects unfolded to reconsider population screening of adults at high risk of iron overload by using genetic testing.

Important principles to assess the benefits of screening are a clear understanding of the clinical course in untreated patients and a beneficial effect of treatment in individuals discovered by genetic testing. Previous understanding was that an adult homozygous for C282Y with normal serum ferritin and transferrin saturation will not develop symptoms of haemochromatosis and would not require phlebotomy and frequent follow-up.[6 7] The discovery of these non-expressing individuals can, however, lead to the identification of iron loaded family members (siblings, parents, children).

The study by Mottelson and colleagues sheds new light on the clinical course of individuals who are homozygous for C282Y.[8] Participants from three population based studies in Denmark were pooled and analysed by genetic testing for the C282Y mutation of the *HFE* gene for haemochromatosis. The study design allowed for follow-up of electronic medical and mortality records for up to 27 years after initial testing. The study excluded patients known to have haemochromatosis at study entry, and most patients had a single blood test at baseline that included in many cases serum iron, transferrin saturation, serum ferritin, and genetic testing for haemochromatosis. Participating C282Y homozygous individuals with normal iron test results were followed up for manifestations of haemochromatosis and were found to have a higher risk of diabetes, liver disease, and heart disease than non-carriers.

What the findings mean

Some of these participants developed abnormal iron test results during the follow-up period, although follow-up ferritin testing was not available. The authors suggested that increased follow-up of individuals with non-expressing C282Y should be considered to diagnose diabetes at an earlier age and initiate therapy.

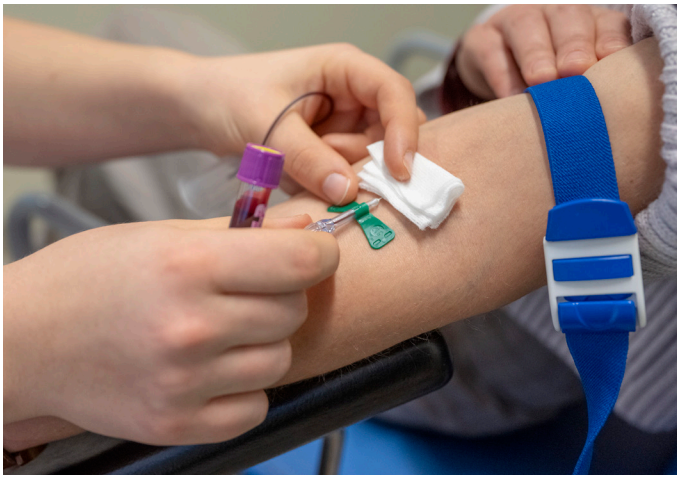
The study's findings related to diabetes challenge evidence from earlier studies. Several large population screening studies of haemochromatosis in the US,[4-10] Canada,[11] and Norway[12] have not found an increase in incidence of diabetes in their overall studies, with liver cirrhosis and hepatocellular carcinoma being the most serious complications. Some of these countries have a much higher prevalence of obesity in the general population than does Denmark, which would increase the prevalence of diabetes in the control population and decrease the relative risk. The pathogenesis of diabetes in haemochromatosis was initially considered to be due to excess iron in the pancreas, but it is more likely to be multifactorial, and many patients with both haemochromatosis and diabetes have insulin resistance often associated with fatty liver and cirrhosis.[13 14] Diabetes does not usually improve with iron depletion by phlebotomy.[15]

One Canadian study followed patients homozygous for C282Y with no haemochromatosis manifestations, who were iron depleted by phlebotomy and followed for up to 17 years. Liver disease, cirrhosis, hepatocellular carcinoma, and joint replacement but not diabetes developed many years after diagnosis and iron depletion therapy.[11]

Clinical implications

This Danish study provides more information on the clinical course of haemochromatosis in untreated C282Y homozygous individuals. A foundation for this study was the Copenhagen Heart Study, which showed that many iron loaded C282Y homozygous individuals did not have progressive iron accumulation and many had a decreasing concentration of serum ferritin over time.[16] These observations and the data analysis in Mottelson and colleagues' paper do not give a strong endorsement to broad population screening for haemochromatosis, as many individuals with the condition do not develop clinical disease and early phlebotomy treatment does not prevent all the manifestations of haemochromatosis. The study is also an excellent example of the research benefits of national public medical data. Population health data provide valuable information to patients and families and guide further health policy.

Early phlebotomy treatment does not prevent all the manifestations of haemochromatosis



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Inequalities in uptake of childhood vaccination in England, 2019-23

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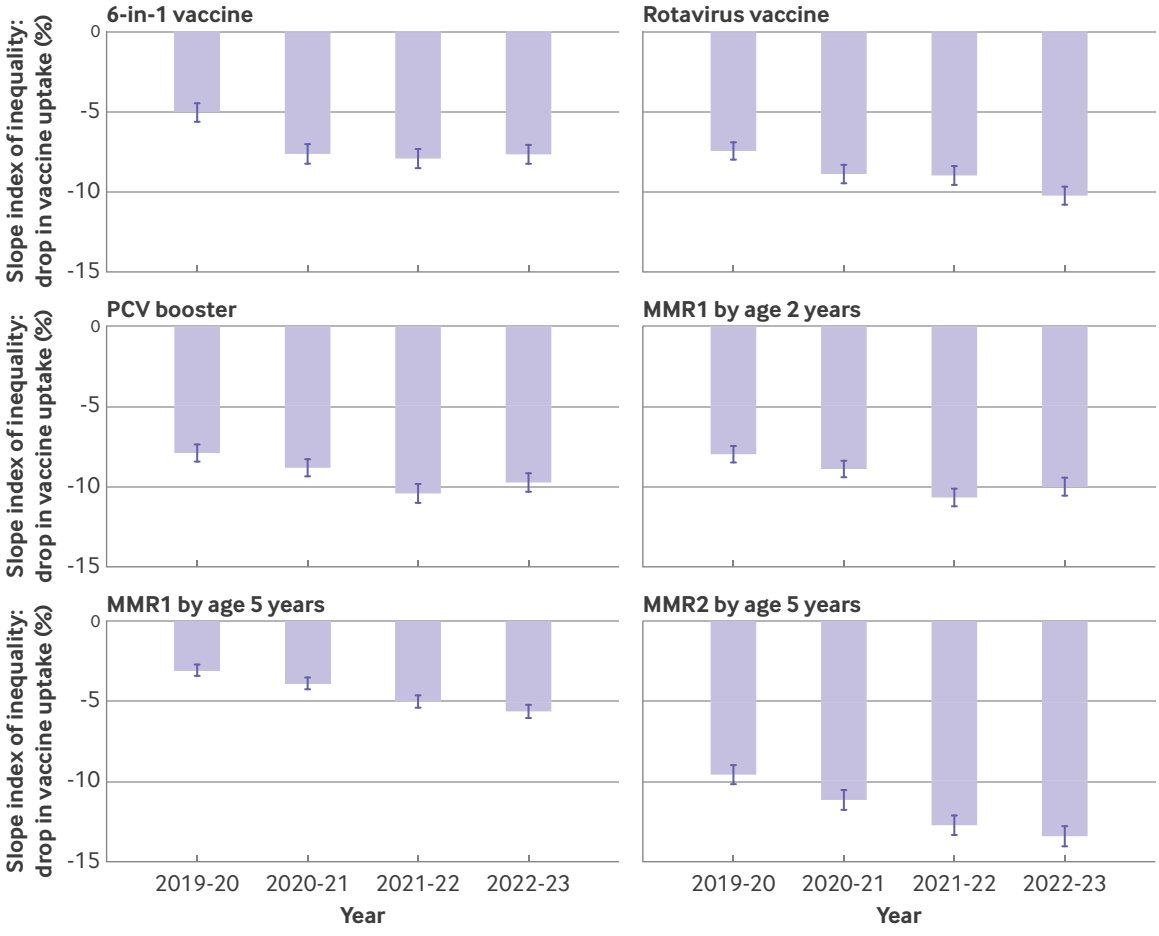
Study question How have inequalities in uptake of childhood vaccines changed in the context of declining childhood vaccination rates in England?

Methods This longitudinal study analysed general practice data for five childhood vaccinations (first and second doses of the measles, mumps, and rubella vaccine (MMR1 and MMR2, respectively), rotavirus vaccine, pneumococcal conjugate vaccine (PCV) booster, and the six-in-one (DTaP/IPV/Hib/HepB) vaccine covering diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b, and hepatitis B) in England. Participants were children younger than 5 years who were eligible for paediatric immunisations between April 2019 and March 2023. Changes in quarterly vaccine uptake over time were compared by deprivation level and region. Regression analyses were used to quantify the change in inequalities in vaccine uptake over time, expressed as changes in the slope index of inequality. This index measures the percentage difference in uptake across the socioeconomic scale, measured based on small area deprivation of general practice population. Susceptibility to measles and rotavirus disease at age 5 years was also estimated.

Study answer and limitations 2 386 317 (2 309 674 for rotavirus vaccine) children included in the study were eligible at age 1 year, 2 456 020 at age 2 years, and 2 689 304 at age 5 years. The absolute inequality in vaccine uptake at baseline (2019-20) was largest for MMR2 in children at age 5 years (slope index of inequality −9.6%, 95% confidence interval (CI) −10.2% to −9.0%). For all vaccinations studied, the slope index of inequality for uptake increased over the study period: from −5.1% to −7.7% for the six-in-one vaccine, −7.4% to −10.2% for the rotavirus vaccine, −7.9% to −9.7% for the PCV booster, −8.0% to −10.0% for MMR1 at age 2 years, −3.1% to −5.6% for MMR1 at age 5 years, and −9.6% to −13.4% for MMR2 at age 5 years. The number of children susceptible to measles by the end of the study period increased 15-fold in the least deprived group (from 1364 to 20 958) and 20-fold in the most deprived group (from 1296 to 25 345). For rotavirus, a 14-fold increase was observed in the least deprived group (from 2292 to 32 981) and a 16-fold increase in the most deprived group (from 2815 to 45 201). Regional analysis showed greatest inequalities in uptake in London and the northern regions. This study relied on aggregated routine health data and therefore could not account for all potential confounders or other explanatory factors.

What this study adds Inequalities in uptake of childhood vaccinations are increasing in England, with noticeable regional differences. Policy and practice should respond quickly by strengthening systems and tackling the drivers of low vaccine uptake for disadvantaged children.

Funding, competing interests, and data sharing
See full paper on bmj.com for details of funding and competing interests. All data are open access and available through original sources.



Bar charts for each of five vaccinations analysed, showing drop in vaccine uptake percentage from least to most deprived deprivation groups as represented by the slope index of inequality. PCV=pneumococcal conjugate vaccine