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Association between faecal occult bleeding and medicines prescribed for chronic disease: a data linkage study.

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Abbreviations: CI: confidence intervals, CRC: colorectal cancer, FIT: faecal immunochemical test for haemoglobin, f-Hb: faecal haemoglobin concentration, gFOBT: guaiac faecal occult blood test, GP: general practitioner, OR: odds ratio, UK: United Kingdom, USA: United States of America.

ABSTRACT

Aims

The presence of detectable faecal haemoglobin (f-Hb) has been shown to be associated with all-cause mortality and with death from a number of chronic diseases not known to cause gastrointestinal blood loss. This effect is independent of taking medicines that increase the risk of bleeding. To further investigate the association of f-Hb with chronic disease, the relationship between f-Hb and prescription of medicines for a variety of conditions was studied.

Design

All subjects (134 192) who participated in guaiac faecal occult blood test (gFOBT) screening in Tayside, Scotland, between March 2000 and March 2016, were studied in a cross-sectional manner by linking their gFOBT result (abnormal or normal) with prescribing data at the time of the test.

Results

The screening participants with an abnormal gFOBT result were more likely to have been being prescribed medicines for heart disease, hypertension, diabetes, and depression than those with a normal test result. This association persisted after adjustment for sex, age, and deprivation (OR 1.35 (95%CI: 1.23 – 1.48), 1.39 (1.27 –

1.52), 1.35 (1.15 – 1.58), 1.36 (1.16 – 1.59), all $P < 0.0001$, for the four medicine categories, respectively).

Conclusions

The results of this study confer further substantial weight to the concept that detectable f-Hb is associated with a range of common chronic conditions which have a systemic inflammatory component; we speculate that f-Hb might have potential in identifying individuals who are high risk of developing chronic conditions or are at an early stage of disease.

INTRODUCTION

In a previous publication, we described an association between faecal haemoglobin detected using a guaiac faecal occult blood test (gFOBT) and increased risk of death from a variety of chronic disease processes, including circulatory disease.¹ As part of this work, the association between the presence of faecal haemoglobin (f-Hb) was corrected for encashed, prescribed, medicines that could cause bleeding (classified as aspirin, or all medicines that could cause bleeding) since this was a potential confounding factor. It was found that aspirin and all medicines that could cause bleeding were both associated with an increased risk of an abnormal gFOBT result but correcting for use of these medicines had little effect on the association between f-Hb and any of the causes of mortality studied, including circulatory disease.

One interpretation of this observation is that these medications have minimal effect on gastrointestinal blood loss, but are independent markers of chronic disease, and therefore associate with gFOBT abnormality, which we believe is also a marker of chronic disease. For this reason, we investigated the association between gFOBT result abnormality and a range of prescribed medicines for other chronic conditions, including heart disease, hypertension, diabetes and depression.

To achieve this, we used the Scottish Bowel Cancer Screening Programme database as described in our previous publication.¹ In Scotland, gFOBT screening started on 20th March 2000 with a Demonstration Pilot in three of the 14 regional NHS Boards which are responsible for the protection and the improvement of their population's health (Grampian, Tayside and Fife)² and was subsequently rolled out

as a Screening Programme to the rest of Scotland, starting in July 2007. By linking the Pilot screening data and subsequent Programme data with a comprehensive medicine prescribing database, it was possible to study the association between gFOBT result abnormality and prescribed medicines.

METHODS

Study population

The study population included all males and females living in NHS Tayside who returned testable gFOBT kits in the Scottish arm of the UK Colorectal Cancer Screening Demonstration Pilot (March 2000 to June 2007) or the subsequent rolled-out Scottish Bowel Screening Programme (from July 2007 to March 2016).

Untestable gFOBT kits included those with insufficient or excess faeces and those with delayed return to the laboratory for analysis.^{2,3} The age range for invitation to participate in the Pilot was 50–69 years and this was increased to 50–74 years for the Programme. NHS Tayside was selected since the full history of community medicine prescribing for all residents registered with a general practitioner (GP) is available. The first gFOBT result available for each participant in the study population was used to classify subjects as test result abnormal or normal. It is possible that some individuals with normal test results may have received a subsequent abnormal test result, but the conclusions would not be invalidated since this would decrease rather than amplify any differences between the test result abnormal and normal groups. The test results, classified as abnormal or normal, were accessed from the Bowel Screening Scotland (BoSS) database.

The screening algorithms used in Pilot and Programme are described in detail elsewhere,^{2,3} but all had a gFOBT kit (*hema-screen*, Immunostics Inc., Ocean, New Jersey, USA, supplied by Alpha Labs Ltd, Eastleigh, Hants, UK) as the initial test, sent in the mail for participants to complete at home and then mail back to the Scottish Bowel Screening Centre Laboratory for analysis.

Prescribing data

The database of community dispensed prescribing was accessed from the Health Informatics Centre (HIC) at the University of Dundee. Four categories of medicines were selected which are used in the treatment of chronic, non-communicable disease, namely, medicines for (1) heart disease (excluding those that can cause bleeding) (2) hypertension, (3) diabetes, and (4) depression. In addition, the category of medicines that can cause bleeding (including aspirin) was studied. The list of medicines included in these categories were derived from the British National Formulary (<http://www.bnf.org>), and the relevant sections of the Formulary are listed in Table 1. Any of these medicines were included in the analysis if there had been an encashed prescription in the 16 weeks up to the date of issue of the screening test result. This period of time was used so that repeat prescriptions for individuals taking medicines long-term, with two-monthly repeats, would be captured. It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

Statistical methods

Chi-squared tests were used to assess demographic differences between those with abnormal and normal test results. The outcomes in terms of medicine prescribing were compared for the groups with abnormal and normal test results using both univariable and multivariable logistic regression. The latter was adjusted for sex, age, and quintile of deprivation as defined by the Scottish Index of Multiple Deprivation,⁴ since all of these have been shown to be associated with gFOBT result abnormality.⁵ All data analyses were carried out using STATA V.14 (Stata, College Station, Texas, USA).

RESULTS

There were 133,921 individuals who had returned testable gFOBT kits during the study period in NHS Tayside; 2714 (2.0%) had an abnormal test result and 131,207 (98.0%) had a normal test result. Table 2 shows that an abnormal test result was more likely in males than in females, and that the abnormality rate increased with both increasing age and increasing deprivation. Prescribing of all the categories of medicines studied was shown to be more likely in those with an abnormal test result.

Univariable logistic regression demonstrated a statistically significant odds ratio, indicating a positive association between an abnormal test result and prescribing of all the categories of medicine studied. Multivariable logistic regression demonstrated that adjusting for sex, age, and deprivation had little effect on these associations,

and, indeed, strengthened the association in the case of medicines for depression (Table 3).

DISCUSSION

The first evidence that f-Hb was associated with disease processes other than colorectal cancer (CRC) or other conditions that potentially cause gastrointestinal bleeding originated in a study from Taiwan. In Taiwan, population screening for CRC employs a quantitative faecal immunochemical test (FIT), which uses antibodies against human globin to estimate f-Hb concentration numerically. An incremental increase in f-Hb was observed to be associated with increasing risk of death from all causes. This effect was still seen after excluding all CRC deaths, indicating that the presence of detectable haemoglobin in faeces predicted life expectancy, independently of its association with CRC.⁶ Recently, this group have also demonstrated a clear association between f-Hb and risk of cardiovascular disease.⁷

One explanation for these findings could be related to medicines taken. Medicines that increase the risk of gastrointestinal bleeding (e.g., aspirin, non-steroidal anti-inflammatory drugs, and warfarin) are more likely to be prescribed in patients with cardiovascular disease, and this might account for the association between f-Hb and cardiovascular disease. However, in our previous study using gFOBT results from the Pilot and Screening Programme in Scotland,¹ we were able to link with prescribing data; although prescribing of aspirin and all drugs that could cause bleeding was associated with an increased likelihood of an abnormal test result,

adjusting for these medications did not substantially alter the association between detectable f-Hb and death from circulatory disease, respiratory disease, digestive diseases (excluding CRC), neuropsychological disease, blood and endocrine disease and non-colorectal cancers.

We have suggested that detectable f-Hb could reflect the presence of subclinical colonic inflammation which, in turn, would be a surrogate marker of systemic inflammation and thus of disease processes that have an inflammatory component in their aetiology.¹ Interestingly, further work from Taiwan has demonstrated an association between high f-Hb and components of the metabolic syndrome, including waist circumference, and fasting blood glucose, low high-density lipoprotein and high total cholesterol concentrations.⁸ Given that inflammation is widely accepted to be a driver for the metabolic syndrome,⁹ this is consistent with our hypothesis.

Whatever the underlying reason for the association between f-Hb and death from chronic disease, there was still no evidence of an association between f-Hb and the diseases themselves. Therefore, using medicine prescribing as a surrogate for diagnosis, we investigated prescribing of medicines for heart disease, hypertension, diabetes, and depression, none of which are known to increase the risk of bleeding. We found that prescribing of all of these categories of medicines was significantly more common with participants who had received an abnormal test result.

It is known that male sex, increasing age, and increasing socio-economic deprivation are all associated with higher f-Hb,¹⁰ and this was confirmed in the present study (Table 2). There are similar associations with heart disease,¹¹ hypertension¹² and

type 2 diabetes, ^{13,14} and depression is more common in areas of socioeconomic deprivation¹⁵ although GP consultations for depression are less common in males than females and peak in middle age.¹⁶ Unsurprisingly, therefore, adjusting for sex, age, and deprivation slightly decreased the effect of medicines for heart disease, antihypertensives, and diabetic medication, but strengthened the association with antidepressants. However, in all cases f-Hb was independently associated with prescribing medicines.

This study lends further weight to the concept that the presence of f-Hb can identify individuals suffering from common chronic conditions. Quantitative FIT have many advantages over traditional gFOBT, including that only a single sample of faeces, collected using a user-friendly hygienic device, is required rather than two samples from three bowel motions and, being based upon the interaction of antibodies directed to epitopes on human haemoglobin, no dietary interferences from animal moieties are possible. However, the main advantage is that numerical estimates of f-Hb concentration are generated. We speculate that such quantitative estimates of f-Hb concentrations measured by a faecal immunochemical test (FIT), might be a potential powerful means of identifying individuals who are high risk of developing these conditions or are at an early stage of disease, with the higher the f-Hb, the higher the risk. This would have significant benefits both to the individual and the health care system but will require further investigation by means of following up of cohorts of individuals with previously recorded f-Hb concentrations, or through prospective studies.

Early detection of chronic disease to assess early signs of, for example, stroke, kidney disease, heart disease, type 2 diabetes or dementia is of significant interest. For example, in England, the NHS Health Check is a health assessment for adults aged 40 to 74 years, designed for those who do not have pre-existing conditions.¹⁷ Since screening for bowel cancer is now based throughout the United Kingdom on quantitative FIT, and the uptake of screening has risen markedly as compared to that when gFOBT was used^{18,19} and the age range is being expanded in England, Wales and Northern Ireland to match the 50 to 74 years used in Scotland, many individuals will have a quantitative f-Hb estimate, which could be used to communicate risk of future chronic conditions and their minimisation. Moreover, it is estimated that about 10% of all consultations in primary care are for lower gastrointestinal symptoms: FIT are becoming very widely used in the triage of such patients²⁰ and, thus, a quantitative estimate of f-Hb is also available for a further large number of individuals, with whom discussion could be valuable. Such interventions might be particularly directed to (1) those who participate in screening and have a detectable f-Hb but below the threshold used for referral for bowel visualisation and (2) those patients who present with symptoms, have a detectable f-Hb and undergo further investigation, but have no significant bowel disease detected.

Take home messages

- Participants in screening with an abnormal gFOBT result are more likely to have been being prescribed medicines for heart disease, hypertension, diabetes and depression than those with a normal test result.
- Detectable faecal haemoglobin is associated with a range of common chronic conditions, possibly due to inflammation in the colorectum, a surrogate marker of systemic inflammation.
- It is speculated that faecal haemoglobin might have potential in identifying individuals who are high risk of developing chronic conditions or are an early stage of disease.

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Contributors: GL performed the statistical analyses and contributed to the writing of the manuscript. KNB contributed to the data analysis and the writing of the manuscript. CGF directed the gFOBT analyses from 2000 until 2010, participated in analysis of results, and contributed significantly to the writing of the manuscript. RJCS conceived the study, prepared the first and final drafts of the manuscript, and is the guarantor for the study.

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Table 1. Medicine categories examined

British National Formulary category (http://www.bnf.org)	Medicine category
2.8, 2.9, 6.3, 10.1.1	Medicines that increase the risk of bleeding (Includes: non-steroidal anti-inflammatory drugs including aspirin, anticoagulants, antiplatelet medicines, and corticosteroids).
2.1, 2.2, 2.3, 2.4, 2.6, 2.7, 2.12	Medicines for heart disease (excluding categories that can cause bleeding and antihypertensives i.e., positive inotropic drugs, diuretics, anti-arrhythmic drugs, beta-blockers, anti-anginal drugs, sympathomimetics, lipid-regulating drugs).
2.5	All anti-hypertensive medicines.
6.1	All medicines for diabetes.
4.3	All medicines for depression.

Table 2. Demographic characteristics of abnormal and normal faecal occult blood test (gFOBT) result groups, and comparison between the groups.

	Abnormal gFOBT result (n = 2714) n (%)	Normal gFOBT result (n = 131 207) n (%)	Comparison of abnormal and normal gFOBT result groups P- value*
Males	1 658 (2.6)	61 220 (97.4)	<0.001
Females	1 056 (1.5)	69 987 (98.5)	
Age at screening (years: median, IQR)	58 (52-65)	54 (50-62)	<0.0001
Age group at screening (years)			<0.0001
50-54	992 (1.5)	66 778 (98.5)	
55-59	520 (2.2)	23 242 (97.8)	
60-64	511 (2.5)	19 948 (97.5)	
65-69	526 (3.0)	17 190 (97.0)	
70 +	165 (3.9)	4 049 (96.1)	
SIMD 1 (most deprived)	514 (3.2)	15 505 (96.8)	<0.0001
	440 (2.5)	17 169 (97.5)	
SIMD 2	481 (2.0)	23 169 (97.8)	
SIMD 3	819 (1.8)	45 704 (98.2)	
SIMD 4	444 (1.5)	28 790 (98.5)	<0.0001

SIMD 5 (least deprived)			
Medicines that can cause bleeding	796 (29.3)	24 163 (18.4)	<0.0001
Medicines for heart disease	710 (26.2)	22 060 (16.8)	<0.0001
Medicines for hypertension	857 (31.6)	28 632 (21.8)	<0.0001
Medicines for diabetes	168 (6.2)	4 870 (3.7)	<0.0001
Medicines for depression	171 (6.3)	7 040 (5.4)	0.03

*Chi-squared test

Table 3. Association between guaiac faecal occult blood test (gFOBT) abnormality and medicine prescribing, unadjusted and adjusted for age, gender and deprivation. Univariable logistic regression: Outcome is abnormal gFOBT result.

	Univariable logistic regression. Odds ratio (95% CI) P-value	Multivariable logistic regression. Adjusted for sex, age, and deprivation. Odds ratio (95% CI) P-value
Medicines that can cause bleeding	1.84 (1.69 – 1.99) <0.0001	1.52 (1.39 – 1.66) <0.0001
Medicines for heart disease	1.75 (1.61 – 1.91) <0.0001	1.35 (1.23 – 1.48) <0.0001
Medicines for hypertension	1.65 (1.52 – 1.79) <0.0001	1.39 (1.27 – 1.52) <0.0001
Medicines for diabetes	1.71 (1.46 – 2.01) <0.0001	1.35 (1.15 – 1.58) <0.0001
Medicines for depression	1.19 (1.01 – 1.39) 0.03	1.36 (1.16 – 1.59) <0.0001