Gilbert’s syndrome in the primary care setting: a cohort study

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Abstract (word count = 247)

Background & aims: Interest in Gilbert’s syndrome has increased recently following genetic studies showing lower rates of heart disease but higher rates of adverse reactions to certain drugs. We examined trends in Gilbert’s syndrome recognition and the association with gallstones and death using The Health Improvement Network primary care database.

Methods: Patients with a diagnosis of Gilbert’s syndrome and a bilirubin level >17µmol/L (n=4,266) were compared to patients with similar sociodemographic characteristics but with a bilirubin level below 17µmol/L (n=21,968). Adjusted incidence rate ratios (IRRs) rates for gallstones and death were estimated.

Results: The incidence of recorded Gilbert’s syndrome for the whole database was 1.3/10,000 patient years (PYs) and varied according to age, gender and social deprivation. Over 25,000 PYs of follow-up there were 668 new cases of gallstones and 1174 deaths. The incidence of gallstones was 40/10,000 PYs in the Gilbert’s cohort compared with 25/10,000 PYs in the comparison cohort. Mortality rates were 24/10,000 PYs in the Gilbert’s cohort versus 50/10,000 PYs in the comparison cohort. Men with Gilbert’s were more likely to have gallstones than women with the condition (adjusted IRR: 2.2 in men [95%CI; 1.7-2.8] and 1.4 in women [95%CI; 1.0-1.8]). Mortality rates were around half in patients with Gilbert’s syndrome (adjusted IRR: 0.5 [95%CI; 0.4-0.7]).

Conclusions: Recognition of Gilbert’s syndrome is associated with factors other than autosomal genetic variation. Abdominal pain may be a symptom of Gilbert’s syndrome due to gallstones and antioxidant properties of moderately high bilirubin may explain lower death rates.
Introduction

Gilbert’s syndrome (MIM#143500) is a common form of unconjugated hyperbilirubinaemia caused by an inherited deficiency in the bilirubin-conjugating enzyme UDP-glucuronosyltransferase 1-1 (UGT1A1) [1]. The condition is highly prevalent ranging from 3-12% of the population depending on the mode of diagnosis [1-3]. Intermittent jaundice is the only clinically recognised symptom, which can be triggered by infections, certain drugs and situations associated with low caloric intake such as gastrointestinal illness, surgery and fasting [4-7]. Some studies and patient information websites report that gastrointestinal symptoms and chronic fatigue are also symptoms [4, 8, 9] though this has not always been confirmed [10].

Gilbert’s syndrome is historically regarded as a benign trait and clinical recognition is often incidental to routine laboratory investigations [11-13]. However, there has been renewed interest in the condition following the results from more recent genetic association studies. For instance, homozygosity for the gene promoter variant termed UGT1A1*28, which underlies the condition in Europeans [1], has been associated with an increased risk of developing gallstones [14-16] and also a predisposition to certain adverse reactions to drugs requiring UGT1A1-mediated glucuronidation for elimination [17]. Greatly reduced rates of cardiovascular disease (CVD) have also been reported for people homozygous for UGT1A1*28 [18], which may reflect the potent antioxidant/anti-inflammatory properties of bilirubin [18, 19]. Thus recognition of Gilbert’s syndrome may be useful, not only for excluding more serious hepatobiliary disease, but also for estimating disease risk, informing the
need for secondary care referrals in patients presenting with hyperbilirubinaemia and monitoring response to drugs requiring UGT1A-mediated glucuronidation.

There have been no large population-based studies on Gilbert’s syndrome in the general population. The aim of this study was to use The Health Improvement Network (THIN), a United Kingdom (UK) primary care database to: 1) examine the recording of Gilbert’s syndrome in primary care and 2) obtain estimates of the risk of gallstones and death relative to patients without evidence of Gilbert’s syndrome.

**Patients and methods**

**Data source**

Most general practitioners (GPs) in the UK record patient data electronically and some practices have opted to provide these data for clinical and epidemiological research. THIN primary care database provides anonymized records on over nine million patients registered with over 500 general practices that use the VISION software to record details of consultations (http://csdmruk.cegedim.com/). Information on diagnoses, symptoms, and referrals to secondary care are electronically recorded as Read codes, a hierarchical coding system used in UK primary care [20]. Information on prescriptions and variables such as height, weight, blood pressure, smoking status and laboratory test results are also recorded. The database provides quintiles of the Townsend score measure of social deprivation, which is a composite measure of owner-occupation, overcrowding, car ownership, and unemployment levels derived from UK census data and linked to the patient’s postal code. THIN data is broadly representative of the UK general practice population in terms of demographics and consultation behaviour [21]. Clinical
diagnoses recorded by GPs electronically have recently been shown to be accurate compared with other reliable sources [22].

A cohort design was used to examine trends in recording of new cases of Gilbert’s syndrome between January 1st 2000 and December 31st 2010. A diagnosis of Gilbert’s syndrome was ascertained by the presence of the relevant Read code “C374200”. Incident cases were defined using published methodology [23]. In brief, diagnosis rates in newly registered patients were plotted over 365 days. Initially there is a spike in recording rates of Gilbert’s syndrome just after registration suggesting GPs were entering existing diagnoses in newly registered patients. However, six months after registration the recording rate stabilized and we followed patients up from the latest date of six months after practice registration, the start of the study period (January 1st 2000) or the date when the practice were deemed to record mortality at acceptable rates (AMR date) [24]. Patients exited at the earliest date of Gilbert’s diagnosis, the end of the study period (December 31st 2010), death or transfer to a different practice.

A cohort design was also used to compare rates of symptoms and clinical outcomes in patients with Gilbert’s syndrome to those without evidence of Gilbert’s syndrome. All patients with an abnormal bilirubin level (>17 μmol/L) and a Read code diagnosis of Gilbert’s syndrome were extracted. Within each general practice, a comparison cohort with normal bilirubin levels (≤17 μmol/L) was extracted using stratified sampling to ensure similar characteristics in terms of age, sex and year of bilirubin test. Up to six comparator patients were selected per patient with Gilbert’s syndrome. For each outcome of interest, patients entered the cohort using the same criteria as
above. Patients exited the earliest date of the event of interest, the end of the study period (December 31\textsuperscript{st} 2010), death or transfer to a different practice.

**Outcomes**

The rates of gallstones and all-cause mortality were compared in the two cohorts. A Read code lists for gallstones including cholecystectomy was developed using a previously reported method [25]. Incident events were defined using a method similar to that used for defining new cases of Gilbert’s syndrome described above [23]. Death was ascertained by the presence of a date of death in the patient records.

**Covariates**

General health indicators previously associated with bilirubin levels were selected as covariates as these may influence a diagnosis of Gilbert’s syndrome. These included smoking status, body mass index (BMI), blood pressure, alanine aminotransferase (ALT), alkaline phosphatise (ALP), and the Townsend score of social deprivation. Where multiple values had been recorded, that taken closest to the bilirubin test date was selected. Age, gender and time period were also included to account for any imbalances in the stratified sampling.

**Statistical analyses**

Incidence rates of Gilbert’s syndrome were calculated across age, gender, time period and social deprivation assuming a Poisson distribution, which is appropriate for count data when the event is rare. Multivariable Poisson regression was used to calculate adjusted incidence rate ratios (IRRs) of events in the Gilbert’s syndrome cohort versus the comparison cohort. A complete-case analysis was done with continuous covariates entered into the model. To account for data clustering within
GP practice we used a random effect regression model. Some studies report that the protection against CVD and the risk of gallstones in patients with UGT1A1 deficiency/hyperbilirubinemia may differ across gender [14, 26]. Therefore the likelihood ratio test was used to compare nested models with and without interaction terms between Gilbert's syndrome and gender.

The THIN Scheme was approved by the National Health Service South-East Multi-centre Research Ethics Committee (MREC) and the present study was approved by the Cambridgeshire MREC.

**Results**

The overall incidence of Gilbert’s syndrome during the study period was 1.3 per 10,000 patient years (95% CI; 1.2-1.3). The prevalence in 2010 (i.e. any patient actively contributing data to THIN in 2010 with a diagnosis in their medical history) was 8.0 per 10,000 persons (95% CI; 7.8-8.2). Since 2000 there has been a general increase in new diagnoses for both men and women with a peak in 2005 and a slight decline in males thereafter (Figure 1). Diagnosis was around two-thirds higher in males than in females and the distribution of age at first recognised diagnosis was quite different across the genders (Figure 1). For males, there was a clear peak in diagnosis at around age 60-70 whereas for women the peak in diagnosis was at age band 30-40. There was a trend for lower diagnosis rates in more deprived postcode areas, which was particularly strong for males with those in the most affluent postcode areas having more than double the incidence rate of Gilbert’s syndrome. This trend remained strong (p<0.001) after accounting for differences in age and time period across social deprivation levels in a multivariable Poisson regression model.
The characteristics of the Gilbert’s cohort (n=4,266) and the comparison cohort (n=21,968) were very similar except for a lower proportion of smokers in the Gilbert’s cohort (Table 1). Over a total of 25,000 PYs of follow-up there were 668 new cases of gallstones and 1174 deaths. The incidence of gallstones was 40/10,000 PYs in the Gilbert’s cohort compared with 25/10,000 PYs in the comparison cohort. There was a significant interaction between Gilbert’s syndrome, gender and the risk of gallstones. A stratified analysis showed that the relative risk of gallstones was over double in men with Gilbert’s syndrome compared to 36% higher in women with Gilbert’s syndrome after adjustment for potential confounders (Table 2). The main reason for the increase in effect size after the addition of potential confounders was the negative confounding effect of BMI. Removing ALT from the regression model, which may be on the causal pathway, did not alter the results. Mortality rates in people with Gilbert’s syndrome were almost half those of the comparison cohort after accounting for potential confounding factors (Table 2). Adjusting for major comorbidity (depression, diabetes, heart disease) did not materially alter the findings.

**Discussion**

This study is the largest population-based analysis of diagnosed Gilbert’s syndrome. We report that diagnosis is more common in men and often first identified later in life. Those with a diagnosis tend to have higher rates of gallstones but a much lower risk of mortality compared to patients without evidence of the condition.

The magnitude of the differences in rates of gallstones in the THIN cohorts is similar to reports for healthy Europeans homozygous for a variant in complete LD with UGT1A1*28 compared to those without the genotype [14]. This European study also reported an interaction with gender where the odds in men homozygous for a variant...
in complete linkage disequilibrium with UGT1A1*28 were 2.3 versus other genotypes whereas the odds for women were only 1.1 and non-significant [14]. Furthermore, this finding was replicated in a sample of South American men and women [14].

Cohort studies in children and adults with inherited haemolytic anaemia, already predisposed to high bilirubin levels due to haemolysis, report similar associations by genotype with those homozygous for UGT1A1*28 having 2-3 times higher rates of gallstones and gallstone surgery [15, 16]. The magnitude of the results from these studies is similar to our own and a higher risk of gallstones could explain why abdominal pain is sometimes cited as a symptom of Gilbert’s syndrome.

Recognition of Gilbert’s syndrome prior to gallstone surgery could be useful to prevent repeat operations in patients with post-surgery jaundice brought on by fasting.

This is the first study to report comparative mortality rates in patients with Gilbert’s syndrome and those without evidence of the condition. The 50% lower mortality rates observed in patients with Gilbert’s syndrome could reflect the systemic antioxidant/anti-inflammatory properties of serum bilirubin [19, 27-31]. The Framingham offspring Cohort study reported that CVD rates were 64% lower in patients homozygous for UGT1A1*28 compared with the other genotypes [18]. While the lower mortality rates in the Gilbert’s cohort may reflect protection against CVD, the major cause of death in the UK, it is possible that protection from other disease related to oxidative stress and inflammation such as diabetes and respiratory disease, also contribute to the relationship.

Although recognition has generally increased over time, the recording of Gilbert’s syndrome by GPs is markedly lower than the prevalence of the UGT1A1 genotype,
which is present in around 10% in European populations [18]. The under-diagnosis most probably represents the lack of presentation with specific symptoms, the difficulty establishing a definitive diagnosis without genetic testing and the low clinical utility of diagnosing a condition that is perceived to be relatively benign.

Most studies also report that Gilbert’s syndrome is 50-75% more prevalent in men [2, 32]. This could be explained by the higher average levels of bilirubin in men compared with women and also the more dramatic response to environmental factors such as fasting. For example, the increase in unconjugated bilirubin levels following a 400-calorie restricted diet over 24 hours was 27.4μmol/L in men with Gilbert’s syndrome versus 10.8μmol/l in women [13]. Similarly, diagnosis rates are probably higher in non-smokers and in areas of lower social deprivation (where smoking is less common) because bilirubin levels are more likely to exceed the diagnostic thresholds [33]. Rates may also be higher in less socially deprived areas because patients have lower rates of co-morbidity that might otherwise mask more benign traits like Gilbert’s syndrome or patients are better informed and more likely to pursue a diagnosis. The finding that diagnosed cases tend to be healthier in terms of lower BMI, non-smoking status and lower social deprivation is important when considering earlier studies comparing clinical characteristics in patients with Gilbert’s syndrome diagnosed by exclusion criteria alone to control groups that were either unmatched or matched only on age and sex.

The average age of diagnosis in studies from over 20 years ago is generally reported as the mid-thirties [12, 13, 34]. The relatively late age of diagnosis in this study suggests Gilbert’s syndrome is largely an incidental finding during routine lab tests in the modern clinical setting. The high diagnosis rate in women between ages 20-40
could represent routine testing and increased consultation during pregnancy. The high rate around the age of 60 in both men and women may represent incidental diagnoses during routine health checks and liver function testing for drug monitoring such as prior to statin prescription.

The major strength of this study is the sample size. The data are broadly representative of the UK and the prevalence and incidence of recognised Gilbert’s syndrome is probably a fairly accurate reflection of national rates. However, GPs record data for the purpose of patient management and some variables useful for researchers but not directly relevant for patient care, have high levels of missing data. Ethnicity may have also influenced diagnosis of Gilbert’s syndrome and be unbalanced in the two cohorts but is not well recorded in primary care. However, the UK is over 92% white European and this is unlikely to be a strong source of confounding. There are also limitations on the generalisability of the findings. For instance, the results cannot be generalised to all patients with Gilbert’s syndrome because most are undiagnosed and the group we have examined may be a more severe subset with additional genetic variation of UGT1A1 or other enzymes associated with bilirubin elimination. The cohorts were restricted to patients with bilirubin tests in their medical history and although bilirubin testing is now fairly routine in the UK, they may still represent a less healthy sub-population.

Due to the phenomenon of linkage disequilibrium, most UGT1A1*28 homozygotes also have deficiencies in other UGT1A isoforms encoded just downstream of UGT1A1 [35]. All UGT1A isoforms are drug metabolising enzymes and a number of pharmacogenetic studies and investigations in patients with Gilbert’s syndrome suggest altered glucuronidation capacity toward a range of common agents including
aspirin, paracetamol and statins [35-37]. Given the high prevalence of the genetic variation underlying Gilbert’s syndrome and the high burden of adverse reactions to these agents, further research into drug response is warranted. For instance, the Food and Drug Administration recommends UGT1A1*28 testing to identify patients at high risk of life-threatening toxicity to the chemotherapy agent irinotecan [38].

In summary, recognised Gilbert’s syndrome in the primary care setting has generally increased over time and is higher in men and people living in less socially deprived areas. Patients with a record of Gilbert’s syndrome have higher rates of gallstones but lower mortality from any cause. In addition, pharmacogenetic studies on the response to commonly prescribed drugs requiring glucuronidation by UGT1A enzymes is warranted to understand the risk of drug toxicity and whether wider recognition of the condition would be beneficial to patients and GPs.

**Acknowledgements**

None
References


[34] Foulik WT, Butt HR, Owen CA, Jr., Whitcomb FF, Jr., Mason HL. Constitutional hepatic dysfunction (Gilbert's disease): its natural history and related syndromes. Medicine (Baltimore) 1959;38:25-46.


Table 1: Baseline characteristics of a cohort with recognised Gilbert’s syndrome and a comparison cohort selected to have similar age and gender distribution but bilirubin levels ≤17 µmol/L.

<table>
<thead>
<tr>
<th></th>
<th>Gilbert’s cohort (n=4,266)</th>
<th>Comparison cohort (n=21,968)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>2,871 (67)</td>
<td>14,711 (67)</td>
</tr>
<tr>
<td>Serum total bilirubin µmol/L</td>
<td>29 (24-37)</td>
<td>10 (7-12)</td>
</tr>
<tr>
<td>Follow-up in years</td>
<td>9 (5-12)</td>
<td>9 (5-12)</td>
</tr>
<tr>
<td>Age at bilirubin test</td>
<td>48 (35-61)</td>
<td>49 (36-61)</td>
</tr>
<tr>
<td>Consultation rate *</td>
<td>18 (10-28)</td>
<td>17 (9-29)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.9 (22.3-27.8)</td>
<td>26.0 (23.2-29.5)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>80 (70-86)</td>
<td>80 (71-88)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>130 (120-143)</td>
<td>130 (120-145)</td>
</tr>
<tr>
<td>ALP, IU/L</td>
<td>71 (57-91)</td>
<td>76 (61-99)</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>24 (17-33)</td>
<td>25 (18-36)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>427 (10)</td>
<td>6,250 (28)</td>
</tr>
<tr>
<td>Ex</td>
<td>800 (19)</td>
<td>4,252 (19)</td>
</tr>
<tr>
<td>Never</td>
<td>3,039 (71)</td>
<td>11,466 (52)</td>
</tr>
<tr>
<td>Social deprivation score (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (least deprived)</td>
<td>1,402 (33)</td>
<td>6,192 (28)</td>
</tr>
<tr>
<td>2</td>
<td>1,104 (26)</td>
<td>5,132 (23)</td>
</tr>
<tr>
<td>3</td>
<td>856 (20)</td>
<td>4,671 (21)</td>
</tr>
<tr>
<td>4</td>
<td>622 (15)</td>
<td>3,795 (17)</td>
</tr>
<tr>
<td>5 (most deprived)</td>
<td>282 (7)</td>
<td>2,178 (10)</td>
</tr>
</tbody>
</table>

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

* Median consultations in the two years prior to the bilirubin test
Table 2: Incidence of gallstones and death in a cohort of patients with Gilbert’s syndrome and a comparison cohort without evidence of the condition. The results of the multivariable Poisson regression are shown stratified on gender for gallstones due to the presence of effect modification.

<table>
<thead>
<tr>
<th></th>
<th>Gallstones</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Gilbert’s cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events/PYs (per 10,000)</td>
<td>93/2.6</td>
<td>59/1.2</td>
</tr>
<tr>
<td>Incidence rate (95%CI)</td>
<td>(29.1–43.6)</td>
<td>(37.7–62.9)</td>
</tr>
<tr>
<td>Comparison cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events/PYs (per 10,000)</td>
<td>244/14.1</td>
<td>272/6.7</td>
</tr>
<tr>
<td>Incidence rate (95%CI)</td>
<td>(15.3–19.6)</td>
<td>(36.0–45.7)</td>
</tr>
<tr>
<td>Model 1 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRR (95%CI)</td>
<td>1.96</td>
<td>1.13</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>0.39</td>
</tr>
<tr>
<td>Model 2 **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRR (95%CI)</td>
<td>2.17</td>
<td>1.36</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; PYs, person years

* Model 1 = age, gender, time period

** Model 2 = multivariable analysis adjusting for age, gender, time period, blood pressure, body mass index, alanine aminotransferase, alkaline phosphatase, and social deprivation index.
Fig. 1. The incidence of recognised Gilbert’s syndrome in the UK primary care setting across sociodemographic variables.

Time period (A), age band (B) and social deprivation score (C). Error bars represent 95% confidence intervals.