Acute intermittent porphyria (AIP) has been associated with schizophrenia in some studies, but prior research is limited by the absence of comparison populations. Here, we linked Swedish registers to examine the risk of schizophrenia and bipolar disorder in 717 individuals diagnosed with AIP and their first-degree relatives, compared with matched individuals without AIP and their first-degree relatives. Individuals with AIP had a fourfold increased risk of schizophrenia or bipolar disorder. Similarly, relatives of individuals with AIP had double the risk of schizophrenia or bipolar disorder, suggesting that these associations may be as a result of common genetic influences.

Declaration of interest
None.

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Method
We conducted a cohort study based on Swedish nationwide registers. The Total Population Register contains demographic data on individuals registered as inhabitants since 1968. The Multi-Generation Register includes individuals born in Sweden since 1932 and individuals living in Sweden since 1960. The Swedish Patient Register contains discharge diagnoses for in- and out-patient psychiatric treatment since 1973 and 2001 respectively. The regional ethical review board in Stockholm approved the study.

Individuals with manifest AIP (exposure) and individuals with diagnoses of schizophrenia and bipolar disorder (outcomes) were identified through their first diagnoses of the respective disorder in the Swedish Patient Register. AIP was defined as a phenotypic diagnosis of the disorder according to ICD-9: 277B and ICD-10: E802A.2,5 By this definition, 717 individuals were identified and linked to 2449 of their first-degree relatives. Schizophrenia was defined as at least one in-patient episode of the disorder (ICD-8: 295.0–6, 8–9; ICD-9: 295, A–G, W–X; ICD-10: F20).6–8 We used this definition because in-patient schizophrenia diagnoses have high agreement when compared with research diagnoses.6 Bipolar disorder was defined according to a validated algorithm with 92% agreement when compared with diagnoses based on medical records.10

For each individual with AIP and their first-degree relatives, 100 randomly selected individuals matched on gender and birth year were assigned. These individuals were alive, living in Sweden and without any AIP diagnoses at the time of the first diagnosis of the respective index person with AIP they were matched to. Defined this way, we identified 71698 unexposed individuals and 243965 of their first-degree relatives.

To assess risks of schizophrenia and bipolar disorder in individuals with manifest AIP (and their relatives) compared with individuals without manifest AIP (and their relatives), we estimated risk ratios (RRs) and 95% confidence intervals using conditional logistic regressions. Because shared familial risks, including genetic and environmental factors, are indicated when relatives of individuals with AIP have schizophrenia or bipolar disorder but not manifest AIP,11 we specified the analyses according to these conditions.

Results
Compared with individuals without manifest AIP, individuals with AIP had fourfold increased risks of being diagnosed with schizophrenia (RR = 3.6, 95% CI 2.0–6.4) or bipolar disorder (RR = 3.7, 95% CI 2.1–6.7). First-degree relatives of individuals with AIP had double the risk of schizophrenia (RR = 1.6, 95% CI 1.0–2.7) and bipolar disorder (RR = 1.8, 95% CI 1.0–3.2, online Table D1).

Discussion
We observed that individuals with manifest AIP had a fourfold excess risk of being diagnosed with schizophrenia or bipolar
disorder. Furthermore, first-degree relatives of individuals with AIP had double the risk of both schizophrenia and bipolar disorder. In addition, there seemed to be an overrepresentation of women among those who had both AIP and bipolar disorder, but the small number of observations did not allow formal testing of this potentially important finding. Our findings are consistent with prior reports of an association between AIP and psychotic disorders.12 In the most recent investigation based on Swedish data, 16% of individuals with manifest AIP and 7% of latent AIP mutation carriers had a psychiatric disease.12 Because our study is based on a considerably larger cohort of individuals with AIP as compared with prior studies, and because we were able to assess a matched unexposed cohort, it lends strong support for the idea that AIP is linked to schizophrenia and bipolar disorder.

Latent AIP mutations may be responsible for the finding that first-degree relatives of individuals with AIP, without manifest AIP themselves, also were at increased risk of being diagnosed with schizophrenia or bipolar disorder. This further supports the idea of a shared genetic aetiology. AIP can be seen as a natural model of psychotic and affective illness, as the signs and symptoms in many respects are similar to schizophrenia and bipolar disorder. In AIP, there is a decreased function of tryptophan 2,3-dioxygenase (TDO2) and indoleamine 2,3-dioxygenase (IDO) that forms the first and rate-limiting enzymatic step in kynurenine generation. Intriguingly, the kynurenine pathway has been implicated in both schizophrenia13 and bipolar disorder.14 Altered kynurenine metabolism – although associated with many diseases – could thus be one mechanism behind the observed associations. Another possible underlying mechanism is pleiotropic effects of the PBGD gene.

To our knowledge, this is the first study to explore the association between AIP and bipolar disorder and the largest to date to test the association between AIP and schizophrenia. Also, the matched study design used here rules out possible cohort effects. A few important limitations should, however, be considered: part of the observed associations might be as a result of ascertainment bias if AIP modifies a psychiatric disorder in ways that make patients more likely to receive healthcare (for example by worsening symptoms).1 However, the fact that we found an elevated risk also among relatives of individuals with AIP who themselves did not have a diagnosis of AIP, suggests that this possible concern probably has not severely biased the estimates. Finally, despite our large sample size, the limited precision of the estimates warrants some caution. In sum, we found strong associations between AIP and schizophrenia and bipolar disorder that merit further attention in research and clinical practice.

**Funding**

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Table DS1  Risk of schizophrenia and bipolar disorder in individuals with acute intermittent porphyria (AIP) and their first-degree relatives, compared with individuals without AIP and their first-degree relatives

<table>
<thead>
<tr>
<th>Sample</th>
<th>Total, n</th>
<th>Yes, n (%), female:male</th>
<th>No, n (%)</th>
<th>Risk ratio (95% CI)</th>
<th>Yes, n (%), female:male</th>
<th>No, n (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals with AIP</td>
<td>717</td>
<td>12 (1.7) 7:5</td>
<td>705 (98.3)</td>
<td>3.6 (2.0–6.4)</td>
<td>12 (1.7) 10:2</td>
<td>705 (98.3)</td>
<td>3.7 (2.1–6.7)</td>
</tr>
<tr>
<td>Individuals without AIP</td>
<td>71698</td>
<td>339 (0.5) 190:149</td>
<td>71359 (99.5)</td>
<td>3.24 (2.21–103)</td>
<td>71374 (99.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relatives of individuals with AIP</td>
<td>2449</td>
<td>14 (0.6) 9:5</td>
<td>2435 (99.4)</td>
<td>1.6 (1.0–2.7)</td>
<td>18 (0.7) 11:7</td>
<td>2431 (99.3)</td>
<td>1.8 (1.0–3.2)</td>
</tr>
<tr>
<td>Relatives of individuals without AIP</td>
<td>243965</td>
<td>864 (0.4) 399:465</td>
<td>243101 (99.6)</td>
<td>102 (0.4) 631:396</td>
<td>242938 (99.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acute intermittent porphyria: comorbidity and shared familial risks with schizophrenia and bipolar disorder in Sweden
Martin Cederlöf, Sarah E. Bergen, Henrik Larsson, Mikael Landén and Paul Lichtenstein
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