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**TITLE:** Incidence, prevalence, and mortality of autoimmune hepatitis in England 1997-2015. A population-based cohort study.

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## **ABBREVIATIONS**

Autoimmune Hepatitis (AIH); United Kingdom (UK); Clinical Practice Research Datalink (CPRD); Hospital Episode Statistics (HES); International Classification of Diseases 10<sup>th</sup> edition (ICD-10); Office of Population Censuses and Surveys (OPCS); Index of Multiple Deprivation (IMD); Office of National Statistics' (ONS); Hepatitis B Virus (HBV); Hepatitis C Virus (HCV); Primary Sclerosing Cholangitis (PSC); Primary Biliary Cholangitis (PBC); Hepatocellular Carcinoma (HCC);

Confidence Interval (CI); Non-alcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH).

## **CONFLICTS OF INTEREST**

The authors who have taken part in this study declare that they have no conflict of interest with respect to this manuscript.

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## **ABSTRACT**

**Background & Aims:** There are few population-based studies of the incidence and mortality of autoimmune hepatitis. The burden of the disease and how it has changed over time have not been fully explored. We conducted a population-based cohort study on the incidence and mortality of autoimmune hepatitis in England, 1997–2015.

**Methods:** From the Clinical Practice Research Datalink we included 882 patients diagnosed with autoimmune hepatitis in England, 1997-2015. The patients were followed through 2015, and we calculated the sex- and age- standardised incidence and prevalence of autoimmune hepatitis. We examined variation in incidence by sex, age, calendar year, geographical region, and socioeconomic status, and incidence rate ratios were calculated with Poisson regression. We calculated all-cause and cause-specific mortality.

**Results:** The overall standardised incidence rate of autoimmune hepatitis was 2.08 (95% confidence interval 1.94-2.22) per 100,000 population per year, higher in women, higher in older age, and independent of region and socioeconomic status. From 1997 to 2015 the incidence doubled from 1.27 (95% confidence interval 0.51-2.02) to 2.56 (95% confidence interval 1.79-3.33) per 100,000 population per year. The 10-year cumulative all-cause mortality was 31.9% (95% confidence interval 27.6-36.5), and the 10-year cumulative liver-related mortality, including hepatocellular carcinoma was ~ 10.5%.

**Conclusions:** This population-based study showed that the incidence of autoimmune hepatitis doubled over an eighteen-year period. The incidence was particularly high in older women and was similar across all regions of England and independent of socioeconomic status. Patients with autoimmune hepatitis had a high mortality.

**KEYWORDS:** epidemiology; registry; cohort study; hepatitis, autoimmune; incidence; prevalence; prognosis.

**Lay summary**

Autoimmune hepatitis is a chronic inflammatory liver disease. We studied the English population and found that the incidence of autoimmune hepatitis doubled from 1997 to 2015. The resulting prevalence was 19 per 100,000 population, i.e. more than 10,000 English people live with AIH in 2015. The patients with autoimmune hepatitis had a high mortality with a 10-year mortality of 32%.

## **INTRODUCTION**

Autoimmune hepatitis (AIH) is a female-predominated chronic inflammatory liver disease. The aetiology is complex and likely involves interactions between genetic and environmental factors.<sup>1,2</sup> The incidence rate of AIH from various regions of the world ranges from 0.4 to 3.0 per 100,000 population per year.<sup>3-7</sup> Some authors have reported a stable incidence over time,<sup>5,8-10</sup> others an increasing incidence.<sup>3,6,7,11-14</sup> Apart from sex, age, and calendar time, socioeconomic status and region of residence may affect the likelihood of being diagnosed with AIH.<sup>15,16</sup> Evaluation of the variation in AIH incidence over time and place may provide novel insight into the risk factors for AIH. For this purpose, population-based studies over long periods are crucial.

AIH is regarded a treatable disease with effective immunosuppressive medical therapy.<sup>17</sup> Even so, the reported 10-year cumulative mortality for patients with AIH ranges widely from 4% to 74%. Some previous studies concluded that patients with AIH have a higher mortality than the general population,<sup>5,7,14,18-23</sup> others that patients with AIH have a similar mortality to that of the general population.<sup>24-29</sup>

We conducted a population-based study of AIH over nearly two decades and across all regions of England. We aimed to report the incidence and prevalence of AIH and to determine trends and variation in incidence and prevalence by sex, age, calendar year, socioeconomic status, and geographical region. We also aimed to report data on mortality, causes of death, and liver transplantation for patients with AIH.

## **MATERIALS AND METHODS**

This is a population-based cohort study of English patients registered with a diagnosis of AIH in primary or secondary care between 1997 and 2015. The study is population-based using routine healthcare records, and no patient enrolment was involved. The study was approved by the

Independent Scientific Advisory Committee for MHRA Database Research, United Kingdom (UK) (protocol 17\_110RA).

## **Data sources**

We extracted data from the Clinical Practice Research Datalink (CPRD) that contains records collected from general practice in the UK since 1987.<sup>30</sup> These records include sex, dates of birth and death, dates of diagnoses defined by Read codes, biochemical tests, and medical prescriptions. Read codes are recorded in primary care on the basis of clinical consultations and other resources such as hospital discharge notes and discharge diagnoses codes. General practices usually upload data to the CPRD on a monthly basis, and a dataset available for research use is concurrently generated on that basis. Data quality is assessed by the CPRD against criteria defining patient-level ‘acceptability’ and practice-level ‘up-to-standard’ time quality. The CPRD is representative of the overall UK population in terms of age, sex, and ethnicity.<sup>30</sup> 57% of the CPRD practices have consented to linkage to other data sources. Since 1997, individual-level data has been linked with data from the Hospital Episode Statistics (HES) database. This database includes dates of admission and discharge, discharge diagnoses coded according to the International Classification of Diseases 10th edition (ICD-10), and procedure codes according to the Office of Population Censuses and Surveys (OPCS) classification. The CPRD is also linked to deprivation data defined by quintiles of Index of Multiple Deprivation (IMD) at a general practice-level and at a patient-level.<sup>31</sup> For the current study we used practice-level data because the denominator is the whole of the CPRD population, and access to deprivation data for each individual was not permitted. A patient is assigned an IMD score based on the average socioeconomic status in the area (each containing around 150 dwellings), in which the general practice is situated. Deprivation data in such an area have been found to be a reasonable proxy for the level of deprivation of the entire general practice population.<sup>32</sup> Since 1998, linkage to the Office of National Statistics’ (ONS) death registry has been available. The registry includes information on causes of death based on information from death certificates. The causes of death are

classified according to the ICD-10, and for each patient one *underlying* cause of death is defined by World Health Organisation standardised criteria.<sup>33</sup>

### **Study population**

We included all permanently registered patients in the CPRD, who were acceptable for research and eligible for linkage between 1 April 1997 and 31 December 2015. Cases of AIH were defined by CPRD registration of a Read code compatible with AIH or by HES registration of an ICD-10 diagnosis of AIH between 1 April 1997 and 31 December 2015 (Read codes: J63B.00 autoimmune hepatitis, J614000 chronic persistent hepatitis, J614111 autoimmune chronic active hepatitis, or J614100 chronic active hepatitis; ICD-10 codes: K73.2 chronic active hepatitis or K75.4 autoimmune hepatitis). We excluded patients who at any time during follow-up were registered with a Read code or an ICD-10 code compatible with alcoholic fibrosis or cirrhosis; viral hepatitis, i.e. hepatitis B virus (HBV) or hepatitis C virus (HCV), a positive test result for HBV or HCV, or an antiviral treatment for HBV or HCV; or another autoimmune liver disease, i.e. primary sclerosing cholangitis (PSC) or primary biliary cholangitis (PBC) (Supplementary Table 1 shows codes for exclusion).

A patient was identified as incident, if 1) the first Read code or ICD code for AIH occurred between 1 April 1997 and 31 December 2015; 2) the patient had been registered at the same general practice for at least 12 months before the diagnosis; and 3) data from that general practice were up-to-standard. The 12-month time gap after registration ensured that prevalent AIH patients were not misclassified as incident ones.<sup>34</sup> Patients with an AIH diagnosis date concurrent with a date of death were excluded. All other patients with a code for AIH occurring between 1 April 1997 and 31 December 2015 were considered prevalent AIH cases. Incident AIH patients were classified as having or not having cirrhosis at the time of AIH diagnosis. Cirrhosis was defined by registration of



a code compatible with cirrhosis or a cirrhosis complication before or within the 6-month period after the time of AIH diagnosis (Supplementary Table 2 shows codes defining cirrhosis).

### **Death and transplantation**

Information on date of death and underlying cause of death was obtained from the ONS death registry. Underlying causes of death were categorised as follows: Liver-related (including cirrhosis and cirrhosis complications other than infections and hepatocellular carcinoma [HCC]); HCC; any other cancer; infection; cardiovascular disease (including cerebrovascular disease and excluding infections); respiratory cause (excluding infections); and other causes of death. Information on liver transplantations was obtained from the HES database (Supplementary Table 3 shows codes for causes of death and liver transplantation).

### **Statistical analyses**

#### *Incidence and prevalence*

The person-time at risk for developing AIH for an individual began after 1 January 1997, when the patient had been registered at a general practice for at least 12 months, and after the data were up-to-standard. The person-time at risk ended at the time of AIH diagnosis, cessation of registration at the general practice, the last data collection by the CPRD, death, or end of study on 31 December 2015 (whichever came first). We calculated the overall incidence rate of AIH as the number of incident AIH patients divided by the total person-time at risk. The incidence rates were stratified by sex, age group, calendar year, practice-level IMD, and geographical region. We calculated the point prevalence of AIH on 31 December 2015 as the number of AIH patients diagnosed before and still alive on that date divided by the total number of included CPRD patients who were alive on that date. We used direct standardization to standardise incidence and prevalence rates to the European standard population's sex and age distribution in 2013.<sup>35</sup>

We evaluated the time trend in AIH incidence using calendar year as a continuous variable in a Poisson regression model fitted to estimate incidence rate ratios of AIH, adjusted for sex, age group, IMD, and geographical region. The likelihood ratio test was used to test for interactions between calendar year, sex, and age. A Poisson regression model for each sex was then applied to estimate adjusted incidence rate ratios. We extracted the percentage-wise change in AIH incidence per calendar year.

### *Sensitivity analyses*

We repeated calculations of AIH incidence rates *including* AIH patients with potential overlap diagnoses with PSC or PBC, i.e. patients who at any time during follow-up were registered with a code compatible with PSC or PBC.

### *Mortality and transplantation*

The person-time for risk of death began at the time of AIH diagnosis and ended at death, cessation of registration at the general practice, the last data collection by the CPRD, or end of study on 31 December 2015 (whichever came first). For our cohort of incident AIH patients, we firstly calculated the all-cause mortality rate as the number of deaths divided by the total person-time at risk of death, and we calculated the 5- and 10-year cumulative mortality based on the Kaplan Meier estimator. The rates were stratified by sex, age groups, IMD, and cirrhosis. Secondly, we calculated cause-specific mortality rates as the number of deaths from a specific underlying cause divided by the total person-time at risk of death, and we calculated the 5- and 10-year cumulative mortality from each cause based on the cumulative incidence function allowing for the competing risk from other causes of death.<sup>36</sup> Thirdly, we calculated the 5- and 10-year cumulative incidence of liver transplantation with death as a competing risk, and we calculated the 5- and 10- year cumulative incidence of death without transplantation, with transplantation as the competing risk. We used Stata version 14.2 for all analyses.

## RESULTS

### Incidence and prevalence

We identified 1,008 patients diagnosed with AIH between 1997 and 2015, but 126 were excluded from our primary analysis: 31 with a diagnosis of alcoholic liver disease or with a diagnosis date concurrent with their date of death (<5 of whom on the basis of the latter); 33 with HBC or HCV; and 62 with a diagnosis of PSC or PBC.

Our final cohort included 882 incident patients with AIH from 10 regions of England; 662 (75.1%) were women (median age at diagnosis was 60 years [interquartile range 49-71]). The remaining 220 (24.9%) were men (median age at diagnosis was 54 years [interquartile range 39-68]). There were no missing data on sex, age, geographical region, or IMD. In the 882 patients with AIH, 156 (17.7%) had cirrhosis at the time of diagnosis, and a total of 26.0% had developed cirrhosis at the end of follow-up.

For both men and women, the overall incidence rate peaked around 70 years of age (Figure 1). For the 1997-2015 period, the standardised incidence rate was 2.08 (95% confidence interval [CI] 1.94-2.22) per 100,000 population per year with a doubling in incidence from 1997 to 2015 (Table 1 and Figure 2). The standardised incidence rate was higher in women than in men. The standardised point prevalence on 31 December 2015 was 19.24 (95% CI 18.08-20.41) per 100,000 population.

The incidence increased between 1997 and 2015 with an average increment per calendar year of 3.1% (95% CI 1.5 to 4.8) for women and 2.5% (95% CI 0.0-5.3) for men. In the adjusted model the incidence was similar regardless of IMD and geographical region (Table 2). We found a three-way interaction between sex, age, and calendar year (likelihood ratio test,  $p=0.003$ ), in that the incidence increment over calendar time was mainly apparent in women of older age.

The sensitivity analysis including AIH patients with potential overlap diagnoses with PSC or PBC comprised 944 patients for an overall standardised incidence rate of 2.23 (95% CI 2.09-2.37) per 100,000 population per year. The inclusion of these patients did not change the incidence patterns.

### **Mortality and transplantation**

Of the 882 patients with AIH, 191 (21.7%) died during a total of 4,216 years of follow-up. The mortality rate was particularly high in the first year after AIH diagnosis compared with the rate thereafter: 10.00 (95% CI 8.00-12.50) vs. 3.31 (95% CI 2.75-3.98) per 100 patients per year. The 10-year all-cause cumulative mortality was 31.9% (95% CI 27.6-36.5). The risk of death was higher for those diagnosed with AIH in older age, in the deprived, and in those with cirrhosis (Table 3).

Information on underlying cause of death was missing for less than five persons. Liver-related causes of death and death from cancers other than HCC dominated (Figure 3), and the mortality rates were especially high in the first year after diagnosis (Table 4).

Thirteen patients with AIH, of whom five had cirrhosis at the time of diagnosis, had a liver-transplantation during the follow-up with a 5-year cumulative incidence of transplantation of 1.3% (95% CI 0.7-2.4) and a 10-year cumulative incidence of 2.2% (95% CI 1.1-3.7). The 5- and 10-year cumulative incidence of death without transplantation was 19.3% (95% CI 16.4-22.4) and 31.4% (95% CI 27.0-35.8), respectively.

## **DISCUSSION**

This population-based study from England showed the highest incidence of AIH among women in their seventies. There was no association with region of residence or socioeconomic status. We found that the incidence of AIH doubled from 1997 to 2015, resulting in a prevalence of 19 per 100,000 population. The 10-year all-cause cumulative mortality was 32% with liver-related cause of

death being predominant. The mortality rate was particularly high during the first year after diagnosis.

Our study is one of the largest population-based studies on AIH incidence spanning more than a decade. Including all regions of England, the study cohort is representative of the entire English population.<sup>30</sup> The completeness of the recorded diagnoses may be a concern. With the routine record-based approach we cannot be certain that every patient with AIH was captured. However, we included patients identified in both primary, secondary, and tertiary care. Our incidence and prevalence estimates are in accordance with other studies using registry diagnoses for AIH patient identification<sup>7,14</sup> as well as in accordance with studies using medical notes, biochemistry, and histology for patient identification.<sup>3,5,6,8-13</sup> This indicates that our case ascertainment is likely to be reasonably complete.

The validity of the routine data diagnoses may also be a concern, as although the validity of diagnostic coding in general practice is high,<sup>37,38</sup> we did not have liver biopsy data or the data to calculate an AIH score to validate the AIH diagnoses<sup>39,40</sup>. However, our current study did use all available data within the routine records combining Read codes we previously identified in primary care<sup>41</sup> with case ascertainment from secondary and tertiary care using selected ICD-10 codes. In the previous study<sup>41</sup> the identified Read codes applied to patients discharged with a valid AIH diagnosis from tertiary care, i.e. patients who had probable or definite AIH according to the International Autoimmune Hepatitis Group simplified score<sup>40</sup> or a liver biopsy compatible with AIH, and who had been given an AIH diagnosis by a hepatologist consultant. We excluded possibly misclassified cases of alcoholic and other autoimmune liver diseases. As for PSC, the ICD-10 code may be unspecific, and therefore we might have excluded cholangitis patients with other aetiology than PSC. We will stress that the exclusion was primarily based on Read codes registered in the CPRD data, and those codes were merely supplemented with ICD-10 codes from the HES. Therefore, it is unlikely that we

greatly under-ascertained the prevalence and incidence of AIH. We did not exclude patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Although this might be a limitation, the awareness of NAFLD and NASH and the completeness of registered diagnoses in the CPRD and the HES have probably changed over time. Hence, we were not confident to use diagnoses codes for these conditions as exclusion criteria. Furthermore, for the patients with AIH any such misdiagnosis is likely to be less of a limitation as these conditions would most likely have been ruled out based on presence of the metabolic syndrome, liver histology, and/or autoantibody profile during the diagnostic workup for AIH. Therefore, it is also unlikely that we greatly over-ascertained the prevalence and incidence of AIH. With the exclusion of patients with diagnoses of the other chronic liver diseases that may have higher associated mortality, our mortality estimates are too unlikely to have been overestimated.

The overall standardised incidence rate of 2.1 per 100,000 population per year in our study is similar to the incidence rates reported in our previous Danish study<sup>14</sup>, a New Zealand study,<sup>8</sup> and a recent Icelandic study,<sup>6</sup> all population-based. We confirmed the well-known female predominance of AIH. In line with previous studies from the UK<sup>9,42-44</sup> and studies from others parts of the world<sup>3,6-8,10,11,13,14,19,45-48</sup> we found an incidence peak in older age. We could not confirm a peak in younger age that was found in some of the studies,<sup>10,14,19,48</sup> and that might relate to risk factor exposures in younger age in some countries. Yet, we cannot rule out that our definition of incident cases may have biased against detecting cases in the younger subset of the CPRD population, who are more mobile and less likely to be permanently registered with the same CPRD general practice.

In the patients with AIH, we found a lower proportion of cirrhosis than in most other studies. However, these studies were from tertiary centres that might have been biased by only including more severe cases of AIH.<sup>10,11,29,47,49</sup> Our study, on the other hand, also includes patients from primary and secondary care and might therefore be able to identify patients diagnosed at an earlier

stage before developing cirrhosis. Two population-based studies found an even lower proportion of cirrhosis at the time of diagnosis than we did,<sup>6,13</sup> and compared with the Danish study, we found a similar final proportion of cirrhosis.<sup>14</sup>

In line with a population-based case-control study,<sup>16</sup> we found no association between socioeconomic status and the incidence of AIH. One review found an association between socioeconomic status (high human development index) on a country level and high AIH incidence,<sup>15</sup> but such a finding does not necessarily reflect an association on an individual level.<sup>50</sup> We did not have access to patient-level socioeconomic status, either, but deprivation data was obtained from smaller areas with presumably smaller variation compared with variation within whole countries.

With a doubling of AIH incidence from 1997 to 2015, we confirmed the findings of our previous Danish study<sup>14</sup> and other population-based studies.<sup>6,7,13</sup> Some authors have reported a stable incidence over time,<sup>5,8-10</sup> yet others an increasing incidence, but arguing that the increase was a result of increased diagnostic activity.<sup>3,11,12</sup> The current study and a previous English study<sup>51</sup> show higher incidence rates than older UK studies from the 1970s and 1990s.<sup>9,44</sup> This may partly be explained by an increased diagnostic ascertainment over time,<sup>3,11,12</sup> but in preliminary data analyses, 2005-2015, there was an overall decline in the testing rates of liver function tests within the whole CPRD dataset (personal communication, Dr Lu Ban). Moreover, if increased diagnostic ascertainment was the only explanation, the incidence would eventually plateau, as the clinical diagnosis rate approached the underlying, true population rate. Similar incidence time trends were reported for many other autoimmune diseases, such as PSC, rheumatoid arthritis, inflammatory bowel disease, and diabetes,<sup>52,53</sup> and therefore there might be an increasing overall awareness of autoimmune diseases. However, in contrast to this, the reported incidence over time of yet other autoimmune diseases such as polymyalgia rheumatica has remained relatively stable over time,<sup>54</sup> for coeliac disease it has increased and then stabilized,<sup>55</sup> and for dermatitis herpetiformis it has declined.<sup>56</sup> We cannot exclude

the possibility that our results partly reflect an increasing incidence of AIH *diagnoses* rather than an increasing incidence of the *disease* AIH, and any such concern would apply to the majority of reported disease incidence estimates. Our study, the Danish,<sup>14</sup> and the Dutch study<sup>13</sup> were large and spanned a long period with sustained incidence increases, and we believe that more people actually developed AIH. Genetic susceptibility to AIH is unlikely to have varied over time to an extent that would have caused a doubling in incidence over 18 years. Therefore, environmental factors may be the more likely explanation, with risk factors either accumulating over time, or protective factors being lost.<sup>57</sup> A recent population-based study, 2006-2015, from Iceland suggested that drug-induced AIH, mainly due to biological drugs, could explain the incidence increase.<sup>6</sup> In the original AIH diagnostic score, revised in 1999,<sup>39</sup> the use of hepatotoxic drugs would count against a diagnosis of AIH, whereas in the simplified AIH score, 2008,<sup>40</sup> that criterion was not included. For our study period, both scoring systems could have been used, and an increasing use of hepatotoxic drugs such as biological drugs may have contributed to our findings.

In line with the Danish study<sup>14</sup> and a recent study from Finland<sup>7</sup> the incidence increase was more distinct in women than in men, particularly in older women. These findings might be attributable to a lower threshold for autoimmune trigger mechanisms in women due to female hormones, whereas the interpretation of the interaction with older age remains unclear. Future studies of risk factors for AIH will need to make separate analyses for men and women and for the young and the old.

In line with most previous studies,<sup>5,7,14,18-23</sup> our findings support the notion that patients with AIH have a high mortality. We were unable to include details on hospital care or medical management of the patients, as CPRD data, even with linkage with HES, cannot reliably determine such details. We found a 10-year mortality risk of 32% that was higher than in the other studies, and this is likely to be partially explained by a higher median age of our study cohort. Lower age undoubtedly also contributed to the findings of mortality risks as low as 4% from other studies, but the selection of



patients with AIH in those studies could also be of significance: one study solely included patients with type 1 AIH;<sup>26</sup> other studies were single-centre studies and may consequently have included a selected group of patients with a favourable prognosis;<sup>24,25,29</sup> and two studies included Japanese patients, who often present with less severe disease.<sup>27,28</sup> Furthermore, one of the Japanese studies<sup>28</sup> evaluated survival only in patients who were followed more than 12 months after AIH diagnosis. These patients would have had to survive 12 months after diagnosis to be included in the analysis, and this would have biased the survival curve upwardly.<sup>58</sup> Likewise, one English study<sup>29</sup> only included patients who had a diagnostic liver biopsy *and* a further biopsy while on medical treatment for AIH, and this could also have biased the survival curve.<sup>58</sup> Another English study included 245 patients who fulfilled the diagnostic criteria for AIH and found a higher mortality than in the general population.<sup>23</sup> The results from our current larger population-based study suggest that AIH in England is still a dangerous disease, and in line with other studies,<sup>5,14,18,19,21,22,29</sup> the mortality was higher in those diagnosed in older age and in those with cirrhosis. The excess mortality rate in those with a lower affluence corresponds to the findings from a study on deprivation and associated mortality in England and Wales.<sup>59</sup>

One single centre study on mortality in patients with AIH<sup>26,27</sup> found that liver-related death accounted for as little as 0%,<sup>60</sup> others found it to account for as much as 50%,<sup>26,27</sup> but these studies were small. Larger population-based studies with long-term follow-up<sup>5,7,14,21,22</sup> found a frequency of liver-related death, including HCC, of 32-49% and death from other cancers of 15-25%; and our findings are comparable to theirs. Extending the results from the other studies, we quantified the cause-specific cumulative risks of death in the patients with AIH, and we found a high long-term mortality risk that was mainly liver- and cancer-related. The all-cause mortality rate and the rate from liver-related causes and other cancers were particularly high in the first year following AIH diagnosis. The current results substantiate the finding of a pronounced excess mortality in the first year after diagnosis from our previous Danish study.<sup>14</sup> In line with some,<sup>7,14,20,21</sup> but not all,<sup>5,22</sup>

population-based studies, only 1.5% of our English study cohort had a liver transplantation. This proportion is slightly higher than expected, based on the 2017/2018 National Health Service annual report on liver transplantations in the UK,<sup>61</sup> and even more patients with AIH might benefit from transplantation.

In conclusion, we found a high incidence of AIH in England, particularly in women in their seventies. The incidence of AIH in England is increasing, and studies to identify risk factors are increasingly important. We found a high mortality in English patients with AIH, and the mortality rate from liver- and cancer-related causes were especially high in the first year after AIH diagnosis.

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## **FIGURE LEGENDS**

**Figure 1. Sex- and age-specific incidence rates of autoimmune hepatitis in England, 1997-2015.**

**Figure 2. Sex and age- standardised incidence rates (SIR) of autoimmune hepatitis in England for each calendar year 1997-2015.** Incidence rates were standardised with the direct method to the European standard population's sex and age distribution 2013.

**Figure 3. Stacked curve of cause-specific cumulative incidence of death following autoimmune hepatitis diagnosis.** Estimates were based on the competing risk estimator of cumulative incidence of death with other causes of death as competing risks.