Global incidence and prevalence of autoimmune hepatitis, 1970–2022: a systematic review and meta-analysis

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Summary

Background Autoimmune hepatitis (AIH) varies significantly in incidence and prevalence across countries and regions. We aimed to examine global, regional, and national trends in incidence and prevalence of AIH from 1970 to 2022.

Methods We conducted a thorough search of the PubMed/MEDLINE, Embase, CINAHL, Google Scholar, and Cochrane databases from database inception to August 9, 2023, using the search term "autoimmune hepatitis" in combination with "incidence," "prevalence," or "trend." Only general population-based observational studies with larger samples sizes were considered for inclusion. Studies that recruited convenience samples, and those with fewer than 50 participants were excluded. Summary data were extracted from published reports. A random effects model was used and pooled estimates with 95% CI were used to calculate the incidence and prevalence of AIH. Heterogeneity was evaluated using the I^2 statistic. The study protocol was registered with PROSPERO, CRD42023430138.

Findings A total of 37 eligible studies, encompassing more than 239 million participants and 55,839 patients with AIH from 18 countries across five continents, were included in the analysis. Global pooled incidence and prevalence of AIH were found to be 1.28 cases per 100,000 inhabitant-years (95% CI, 1.01–1.63, I^2 = 99·51%; number of studies, 33; sample population, 220,673,674) and 15.65 cases per 100,000 inhabitants (95% CI, 13.42–18.24, I^2 = 99·75%; number of studies, 26; sample population, 217,178,684), respectively. The incidence of AIH was greater in countries with high Human Development Index (>0.92), in North America and Oceania (compared with Asia), among females, adults (compared with children), and high latitude (>45°). Similar patterns in AIH prevalence were observed. Pooled AIH prevalence increased gradually from 1970 to 2019 (1970–1999; 9.95 [4.77–15.13], I^2 = 95·58% versus

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2015–2022; 27.91 [24.86–30.96], I^2 = 99·32%; cases per 100,000 inhabitants). The overall incidence and prevalence of AIH, as well as some subgroup analyses of the studies, displayed asymmetry in the funnel plots, suggesting potential evidence of publication bias.

Interpretation AIH incidence and prevalence have increased significantly and exhibit substantial variation across regions worldwide. Further research is required to assess the incidence and prevalence of AIH, specifically in South America and Africa.

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Keywords: Autoimmune hepatitis; Incidence; Prevalence; Global trend; Systematic review and meta-analysis

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Research in context

Evidence before this study

A thorough search of PubMed/MEDLINE, Embase, CINAHL, Google Scholar, and Cochrane databases, from inception to August 9, 2023, was performed to gather information on AIH incidence and prevalence without language restrictions. The primary search terms were "autoimmune hepatitis" combined with "incidence," "prevalence," or "trend" using the "AND" operator. We found several studies on AIH incidence and prevalence published since the previous meta-analysis. Although there was a meta-analysis study conducted in the year 2019, it is important to note that certain large-scale studies were excluded from this review, and it did not provide detailed information on income, age, data sources, or specific subtypes of AIH. Furthermore, no global or temporal trend of AIH was included in the analysis.

Added value of this study

This systematic review and meta-analysis examined the incidence and prevalence of AIH from 1970 to 2022, incorporating data from 34 studies with a total of 239,345,726 participants and 55,839 patients with AIH across 18 countries on five continents. Global pooled incidence and prevalence of AIH were found to be 1.28 cases per 100,000 inhabitant-years (95% CI, 1.01–1.63) and 15.65 cases per 100,000 inhabitants (95% CI, 13.42–18.24), respectively. The incidence of AIH was greater in countries with high HDI (>0.92), in North America and Oceania (compared with Asia), among females, adults (compared with children), and high latitude (>45°). Pooled AIH incidence increased gradually from 1970 to 2022. Similar patterns in the prevalence of AIH were observed.

Implications of all the available evidence

Our study provides insights into the incidence and prevalence of AIH across various factors such as income, sex, age, geographical region, geographic latitude, diagnostic criteria, data source, and disease type. These findings highlight the consistent increase in the incidence and prevalence of AIH, suggesting that it may become a significant global health concern. Further studies focusing on South America and Africa are required to better understand the incidence and prevalence of the disease in these regions.

Introduction

Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disease, characterized by circulating autoantibodies, elevated serum IgG levels, and histologic interface hepatitis.[1] The disease is believed to lead to a loss of immunologic tolerance, triggered by environmental factors in genetically predisposed individuals.[2] While AIH predominantly occurs in women, it is seen in individuals of all races and age groups worldwide.[3] Clinically, the disease exhibits phenotypes varying from asymptomatic to severe liver failure.[4] Diagnosis is typically based on clinical, biochemical, serologic, and histological findings, using the diagnostic scoring system provided by the International Autoimmune Hepatitis Group (IAIHG).[5–7]

A recent systematic review reported higher incidence and prevalence of AIH in women than in men and higher prevalence in European and American populations than in Asian populations.[8] However, this study included only 22 studies on AIH and did not investigate factors including income, age, or data source or comprehensively analyse global trends in AIH.

In light of the increasing number of AIH cases[9,10] contributing to a growing disease burden, a systematic review and meta-analysis offering precise estimations of the incidence and prevalence of AIH is urgently needed. Therefore, our study aimed to comprehensively analyse global, regional, and national trends in the incidence and prevalence of AIH from 1970 to 2022. We examined incidence and prevalence of AIH in the general population, and conducted subgroup analyses based on income, sex, age, geographical area, geographic latitude, diagnostic criteria, data source, and disease type.

Methods

Search strategy and selection criteria

This systematic literature review and meta-analysis was conducted to evaluate global trends in the incidence and prevalence of AIH. This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[11] and the protocol was registered with PROSPERO (registration no. CRD42023430138).

PubMed/MEDLINE, Embase, CINAHL, Google Scholar, and Cochrane databases were searched from their inception dates to August 9, 2023, to find studies reporting the incidence or prevalence of AIH (according to appropriate diagnostic guidelines) in any age group. Studies including participants from the general population or community-based datasets were considered eligible.

Several exclusion criteria were applied to ensure validity of the results. First, studies that did not accurately calculate prevalence or incidence were excluded. Second, studies that recruited convenience samples, such as individuals attending health checkups at screening clinics, employees at institutions, or university students were excluded. Third, studies with <50 participants were excluded. As no interventional studies were available, we included general population-based observational studies with larger sample sizes, published in English. In addition, studies published in a language apart from English with abstracts written in English were included.

The search strategy involved conducting a database search using the terms "AIH" or "autoimmune hepatitis," combined with the free text terms "incidence," "prevalence," or "trend," using the "AND" set operator. Initially, 7326 studies were screened; subsequently, titles and abstracts of all selected studies were rescreened to identify potential suitability. After the initial screening, non-eligiable studies were excluded (Table E1 and Fig. 1). A recursive search was conducted using the bibliographies of all eligible papers. Two investigators (JWH and DKY) independently evaluated eligibility, and discrepancies were resolved through discussion with a third investigator (JSK).

Data analysis

Data extraction was conducted independently by two investigators (JWH and DKY) using Microsoft Excel version 2013 (Redmond, WA, USA). The following data were collected for each study: first author, publication year, country, patient identification, diagnostic criteria for AIH, study design (retrospective or prospective), study duration, patient age, total number of samples providing data, and number of patients with AIH. All studies were assessed for risk of bias (RoB) using the criteria developed by Hoy et al.[12] Based on an evaluation of nine items, a study was deemed to have low RoB if three or fewer items were relevant, and high RoB if seven or more were applicable.

A comprehensive subgroup analysis was conducted based on several variables including income, sex, age, geographical area, diagnostic scoring system, data source, and disease type. The countries in the study were categorized based on Human Development Index (HDI).[13] Countries with an HDI >0.92, including Canada, Denmark, Finland, Germany, Iceland, Japan, New Zealand, Norway, Singapore, South Korea, Sweden,
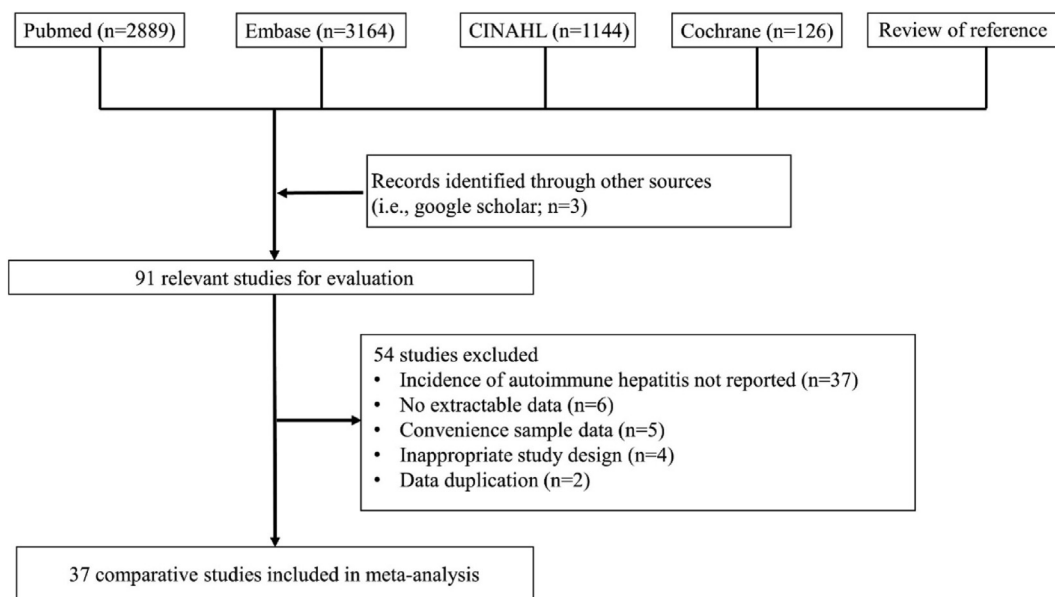

Fig. 1: Flow diagram of study design.

Taiwan, the Netherlands, the United Kingdom, and the United States, were classified in one group. Countries with an HDI <0.92, such as Argentina, Brunei, Israel, and Spain, were classified into another group. In this study, countries were categorized into two groups based on latitude: countries with a latitude of 45° or higher, and countries with a latitude of less than 45°. Countries with a latitude of 45° or higher included Canada, Denmark, Finland, Germany, Iceland, Japan, Norway, Sweden, Netherlands, United Kingdom, and the United States. Countries with a latitude of less than 45° included Argentina, Brazil, Israel, New Zealand, Singapore, South Korea, Spain, and Taiwan.

Diagnostic scoring systems for AIH were introduced by the IAIHG in 1993,[7] 1999,[6] and 2008.[5] The 1993 scoring system included multiple parameters such as liver histology, serum biochemistry, serum immuno-globulins, serum autoantibodies, viral markers, other etiological factors, and response to therapy.[7] Compara-tively, the 1999 scoring system had several modifica-tions, including changes to the alkaline phosphatase (ALP):aspartate aminotransferase (AST) (or alanine transaminase [ALT]) ratio, drug history, liver histology, response to therapy, and exclusion of markers of infection with hepatotropic viruses other than hepatitis A, B, and C.[6] The 2008 scoring system was modified to be a practical tool for routine clinical practice, based on four parameters: liver histology, autoantibody titers, gamma-globulin levels, and absence of viral hepatitis.[5] Overlap syndrome (overlap of AIH with primary biliary cirrhosis [PBC] or primary sclerosing cholangitis [PSC]) was diagnosed based on the IAIHG study.[14]

Subgroup analysis was conducted on studies without researcher validation or explicit diagnostic criteria for AIH, such as code-based studies (k = 10), as well as on strict studies with researcher validation or explicit diagnostic scoring systems for AIH (k = 21).

A random-effects model was used to merge the proportions of patients with AIH from each included study to determine the global incidence and prevalence of AIH. Subgroup differences in incidence and preva-lence were analyzed using mean differences with 95% CIs. Heterogeneity was evaluated using the I^2 statistic,[15] which measures heterogeneity among studies, with higher values indicating greater heterogeneity. Pooled estimates with 95% CIs were used to compare the global incidence and prevalence of AIH. The meta-analysis is based on a log transformed scale to address the sparse data issue. Egger's test and funnel plots were used to identify publication bias. Bayesian statistics were used to generate a 95% prediction interval (PI) and assess robustness and uncertainty of the main findings.[16] Additionally, for analyses where publication bias was detected, sensitivity analyses using the trim-and-fill method were conducted to assess the robustness of the results. Pooling analysis by the Mantel-Haenszel method was used to calculate the pooled odds ratios

for sex and age, with 95% CIs. Pearson correlation analysis was performed to examine the relationships between country-specific HDI values and the incidence and prevalence of AIH, as well as between country-specific latitude and AIH incidence and prevalence. P value for trends was calculated using proportion trend test to investigate time trends. The main results were calculated using Microsoft Excel and R software (version 3.1.1; R Foundation, Vienna, Austria), and all tables were generated using these tools. Statistical significance was set at a two-sided P value <0.05.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors (JSK and DKY) has full access to all the data in the study and has final responsibility for the decision of submission to the journal for publication.

Results
Initially, 7326 studies were identified using the search strategy. After evaluating 91 studies, 54 were excluded for reasons such as insufficient data on disease inci-dence, convenience sampling data, inappropriate study design, lack of population-based studies, and data duplication. Eventually, 37 studies (k = 37[9,1017–52]; researcher-validated studies, k = 21[9,21,26–28,30,31,34–38,40–46,48,49]) were deemed eligible, involving 239,345,726 partici-pants (approximately 2.9% of the global population) and 55,839 patients with AIH from 18 different countries (Argentina, Canada, Denmark, Finland, France, Iceland, Israel, Japan, New Zealand, Norway, Singapore, South Korea, Spain, Sweden, Taiwan, the Netherlands, the United Kingdom, and the United States [by country, 10.9% of the global population]) across five continents. Search strategy results are summarized in Fig. 1. All studies were conducted in a single country and included population-based studies on patients with AIH from 1970 to 2022. Twenty studies included both children and adults,[9,10,18–21,23,25,26,30,32,35–38,42,45–47,51] 14 studies included only adults,[17,27,28,31,34,39–41,43,44,48–50] and 4 studies included only children.[24,29,33,52] Table 1 shows detailed character-istics of all the studies that met the inclusion criteria.

In the 33 studies meeting the inclusion criteria, the global pooled incidence of AIH was found to be 1.28 cases per 100,000 inhabitant-years (95% CI, 1.01–1.63; I^2 = 99.51%), with a 95% prediction interval of 0.35–4.70 (Table 2).[9,10,17–19,21,23–29,31–46,48,49,51,52]

Table E6 shows the subgroup differences in in-cidence of AIH in this study. The pooled incidence of AIH was higher in countries with HDI >0.92[9,10,17–21,23,25–28,31,32,35,37–40,42–46,48,49,51,52] compared to coun-tries with HDI <0.92,[24,34,36,41] with 1.63 (95% CI, 1.28–2.07) and 0.73 (95% CI, 0.49–1.08) cases per 100,000 inhabitant-years, respectively. The incidence of AIH in females[9,10,17–19,21,23,25–28,32,34,36,41] was higher than

First author, publication year	Country	Patient identification	Diagnosis criteria	Study design	Period	Age of patients	Total sample	Patients with AIH
Bjarnason et al., 1982	Iceland	Liver biopsy	Clinical, biochemical, and histological features	Retrospective	1970–1979	Adults & Children	225,549	18
Hodges et al., 1982	United Kingdom	Hospital database + liver biopsy	Clinical, biochemical, and histological features	Retrospective	1976–1980	Adults	404,000	14
Ritland et al., 1985	Norway	Hospital database + liver biopsy	Clinical, biochemical, and histological features	Retrospective	1981	Adults	4,117,647[a]	49
Homberg et al., 1987	France	Hospital	Clinical, biochemical, and histological features	Retrospective	1975–1984	Adults & Children	10,761,625	47
Tanner et al., 1989	United Kingdom	Hospital database + liver biopsy	Clinical, biochemical, and histological features	Retrospective	1971–1987	Adults & Children	210,000	15
Byron et al., 1996	Canada	Hospital	Clinical, biochemical, and histological features	Retrospective	1987–1993	Adults & Children	650,000	39
Boberg et al., 1998	Norway	Hospital	Original IAIHG	Prospective, Cohort	1986–1995	Adults	130,000	25
Lee et al., 2001	Singapore	Hospital	Original IAIHG	Retrospective	1990–1996	Adults	567,685	24
Hurlburt et al., 2002	United States	Hospital	Revised IAIHG	Retrospective	1984–2000	Adults & Children	114,219	49
Primo et al., 2004	Spain	Hospital	Revised IAIHG	Prospective, Cross-sectional	1990–2003	Adults	112,003	13
Koay et al., 2006	Taiwan	Hospital	Revised IAIHG	Retrospective, Cohort	2000–2004	Adults	1,846,464	48
Whalley et al., 2007	United Kingdom	Hospital	Code-based definition	Retrospective, Cross-sectional	2003–2004	Adults	200,000	6
Werner et al., 2008	Sweden	Hospital	Revised IAIHG	Retrospective	1990–2003	Adults & Children	715,000	473
Primo et al., 2009	Spain	Hospital	Revised or Simplified IAIHG	Prospective, Cohort	2003	Adults & Children	1,774,736	19
Ngu et al., 2010	New Zealand	Hospital	Revised IAIHG	Retrospective, Prospective	2001–2007	Adults & Children	494,170	121
Delgado et al., 2013	Israel	Hospital	Simplified IAIHG	Retrospective	1995–2010	Adults	995,024[a]	109
Deneau et al., 2013	United States	Hospital	Simplified IAIHG	Retrospective, Cohort	2005–2011	Children	1,466,667[a]	44
Gronbaek et al., 2014	Denmark	Hospital	Code-based definition	Retrospective	1994–2012	Adults & Children	5,648,536[a]	1350
Van Gerven et al., 2014	The Netherlands	Hospital	Revised or Simplified IAIHG	Retrospective	2000–2010	Adults	799,000	146
Chong et al., 2015	Brunei Darussalam	Hospital	Simplified IAIHG	Retrospective	2011	Adults & Children	459,016[a]	28
Jimenez et al., 2015	Canada	Hospital	Revised IAIHG	Retrospective, Cohort	2000–2009	Children (0–18 years)	70,277,839	159
Yoshizawa et al., 2016	Japan	Hospital (Questionnaire)	Revised IAIHG	Retrospective, Prospective	2004–2014	Adults	187,205	48
Danielsson et al., 2017	Sweden	Hospital	Revised IAIHG	Retrospective	1990–2009	Adults & Children	3,664,740[a]	634
Kim et al., 2017	South Korea	National Health Insurance Service database	Code-based definition	Retrospective	2009–2013	Adults & Children	50,008,453	12,447
Sharma et al., 2017	United States	Medical records	Clinical, biochemical, and histological features	Retrospective	1990–2015	Adults	97,222[a]	70
Costaguta et al., 2018	Argentina	Hospital	Simplified IAIHG	Retrospective, Cohort	2003–2013	Children (0–18 years)	10,017,106	56
Puustinen et al., 2019	Finland	Social insurance database	Code-based definition	Retrospective	2008–2015	Adults & Children	6,202,797[a]	887
Valgeirsson et al., 2019	Iceland	Hospital	Simplified IAIHG	Retrospective	2006–2015	Adults & Children	342,007[a]	92
Gronbaek et al., 2020	England	Hospital	Code-based definition	Retrospective, Cohort	1997–2015	Adults & Children	3,591,476[a]	691
Sebode et al., 2020	Germany	Health insurance data	Code-based definition	Retrospective	2011–2014	Adults & Children	8,100,000	1700

First author, publication year	Country	Patient identification	Diagnosis criteria	Study design	Period	Age of patients	Total sample	Patients with AIH
(Continued from previous page)								
Lamba et al., 2021	New Zealand	Hospital	Simplified or Revised IAIHG	Prospective, Cohort	2008–2016	Adults & Children	599,900	165
Tunio et al., 2021	United States	Electronic Health Record data	Code-based definition	Retrospective	2014–2019	Adults & Children	37,161,280	11,600
Webb et al., 2021	United Kingdom	Primary care records	Code-based definition	Retrospective, Cohort	2002–2016	Adults & Children	3,278,496[a]	1116
Bittermann et al., 2022	United States	Administrative claims data	Code-based definition	Retrospective, Cohort	2009–2018	Adults	18,103,568	3386
Sutton et al., 2022	United Kingdom	Hospital	Clinical, biochemical and histological features	Retrospective	2013–2018	Children (0–16 years)	918,000	38
Nielsen et al., 2023	Denmark	Hospital	Simplified IAIHG	Retrospective, Cohort	2004–2021	Adults & Children	48,000	45
Hitawala et al., 2023	United States	Electronic Health Record data	Code-based definition	Retrospective	1999–2022	Adults	70,352,325	20,550

AIH: autoimmune hepatitis; IAIHG: international autoimmune hepatitis group. [a]These results were calculated and estimated using original data.

Table 1: Characteristics of previous studies assessing the incidence and/or prevalence of AIH included in our systematic review.

that in males,[9,10,17–19,21,23,25–28,32,34,36,41] with 2.79 (95% CI, 2.14–3.64) and 0.90 (95% CI, 0.65–1.24) cases per 100,000 inhabitant-years, respectively. The odds ratio (OR) for AIH in females compared with males was 3.10 (95% CI, 2.04–4.71). The incidence of AIH was highest in adults aged over 65 years,[10,17–19,25,28,36,41] at 3.59 (95% CI, 2.76–4.68) cases per 100,000 inhabitant-years, followed by adults aged under 65 years[10,17–19,25,27,28,31,34,36,39–41,43,44,48,49] at 1.45 (95% CI, 1.22–1.73) cases per 100,000 inhabitant-years, and lowest in children[10,18,19,24,25,29,33,52] at 0.35 (95% CI, 0.24–0.52) cases per 100,000 inhabitant-years. The OR for AIH in adults aged under 65 years compared with children was 4.14 (95% CI, 2.71–6.33). The incidence of AIH was highest in North America[17,19,27,42,45] at 3.35 (95% CI, 2.71–4.13) cases per 100,000 inhabitant-years, followed by Oceania[9,35] at 1.90 (95% CI, 1.59–2.28) cases per 100,000 inhabitant-years, and lowest in Asia[25,28,34,40,43] at 0.99 (95% CI, 0.60–1.64) cases per 100,000 inhabitant-years. Countries with a geographical latitude above 45°[17–19,21,23,26–28,31,32,37–39,42,44–46,49,51] exhibited an incidence of AIH at 1.83 (95% CI, 1.43–2.35) cases per 100,000 inhabitant-years, while countries with a latitude below 45°[9,24,25,34–36,40,41,43] had an incidence of AIH at 0.93 (95% CI, 0.67–1.31) cases per 100,000 inhabitant-years. Compared with code-based studies,[10,17–19,23,25,32,39] the pooled incidence of AIH was lower in researcher validation case studies,[9,21,26–28,31,34–38,40–46,48,49] at 1.29 (95% CI, 1.02–1.63) versus 2.17 (95% CI, 1.48–3.17) cases per 100,000 inhabitant-years.

Table E2 and Fig. 2(A) show national pooled incidences of AIH in each country. The highest incidence was observed in the United States (2.94 cases per 100,000 inhabitant-years; 95% CI, 1.64–4.23),[17,19,27,33,42] while the lowest incidence was observed in Canada (0.42 cases per 100,000 inhabitant-years; 95% CI, 0.12–1.51).[29,45]

The incidence of AIH over time was reported in 65 subgroup studies divided into 5-year intervals. We found that the incidence of AIH increased over time, with the highest incidence reported from 2015 to 2022. Pooled incidence before 1999 was 1.05 (95% CI, 0.79–1.32) cases per 100,000 inhabitant-years,[10,32,37,41–46,36,48,49] while from 2015 to 2022 it was 3.26 (95% CI, 1.49–5.03) cases per 100,000 inhabitant-years.[9,10,18,19,21] Details of time trends in pooled incidence of AIH are provided in Table E4. Our systematic review showed a significant increase in the incidence of AIH over time ($P_{trend} < 0.001$), as shown in Fig. 3. In addition, temporal trends in the incidence rates of AIH within the longitudinal cohort studies included in our systematic review are presented in Figure E1.

A total of 26 studies were included in our systematic review to estimate the global pooled prevalence of AIH, found to be 15.65 cases per 100,000 inhabitants (95% CI, 13.42–18.24; $I^2 = 99.75\%$) with a 95% prediction interval of 7.00–35.00 (Table 3).[9,10,17–21,23,25,26,28,30–35,37,38,41–44,50–52] Table E7 shows the subgroup differences in prevalence of AIH in this study. The pooled prevalence of AIH was higher in countries with HDI >0.92[9,10,17–21,23,25,26,2831,32,35,37,38,42–44,50,51] compared with countries with HDI <0.92,[30,34,41] with 19.97 (95% CI, 17.00–23.44) versus 9.15 (95% CI, 6.11–13.72) cases per 100,000 inhabitants, respectively. The positive correlation was shown between increasing HDI and the prevalence of AIH (Pearson's R = 0.341, $P < 0.05$) (Figure E2). The pooled prevalence of AIH was higher in females[17–19,23,25,26,28,32,34,35,38,41,50] than in males[17–19,23,25,26,28,32,34,35,38,41,50] (28.04 [95% CI, 21.31–36.89] versus 8.05 [95% CI, 5.87–11.04] cases per 100,000 inhabitants). The OR for AIH in females compared with males was 3.48 (95% CI, 2.29–5.29). The pooled prevalence of AIH was highest in adults aged over 65

	Number of studies	Number of participants	Pooled estimates (95% CI)[a]	95% prediction interval	I^2 (%)	P value for I^2	Egger's P value
Overall incidence	33	220,673,674	1.28 (1.01–1.63)	0.35–4.70	99.51	<0.0001	<0.001
Income							
HDI >0.92	26	143,009,677	1.63 (1.28–2.07)	0.51–5.24	99.50	<0.0001	0.0040
HDI <0.92	4	12,898,869	0.73 (0.49–1.08)	0.17–3.12	49.28	0.12	0.59
Sex							
Male	17	61,144,540	0.90 (0.65–1.24)	0.25–3.23	97.73	<0.0001	0.0090
Female	17	66,436,411	2.79 (2.14–3.64)	0.90–8.68	99.27	<0.0001	0.0050
Age group							
Children	8	100,035,200	0.35 (0.24–0.52)	0.09–1.38	90.64	<0.0001	0.77
Adults aged under 65 years	17	87,144,548	1.45 (1.22–1.73)	0.55–3.83	98.51	<0.0001	<0.001
Adults aged over 65 years	8	14,770,970	3.59 (2.76–4.68)	1.04–12.36	97.51	<0.0001	<0.001
Geographical areas							
North America	5	56,129,062	3.35 (2.71–4.13)	1.63–6.89	98.79	<0.0001	0.37
Europe	18	28,118,418	1.38 (1.18–1.61)	0.81–2.34	90.60	<0.0001	0.073
Asia	5	53,604,831	0.99 (0.60–1.64)	0.16–6.01	97.97	<0.0001	0.41
Oceania	3	1,558,288	1.90 (1.59–2.28)	0.58–6.20	0.00	0.70	0.60
Geographic latitude							
Above 45°	21	89,490,232	1.83 (1.43–2.35)	0.60–5.54	99.51	<0.0001	0.013
Below 45°	9	66,874,557	0.93 (0.67–1.31)	0.32–2.71	87.72	<0.0001	0.48
Diagnostic scoring system for AIH[a]							
Before IAIHG	5	5,598,514	1.10 (0.85–1.41)	0.74–1.65	0.00	0.71	0.0070
Original IAIHG	2	697,685	1.03 (0.33–3.19)	NA	49.08	0.16	NA
Revised IAIHG	9	75,340,696	1.04 (0.52–2.09)	0.08–13.23	98.98	<0.0001	0.30
Simplified IAIHG	3	1,385,031	1.83 (0.72–4.69)	NA	81.51	0.0040	0.84
Data source							
Researcher validated	20	15,415,852	1.29 (1.02–1.63)	0.51–3.25	90.41	<0.0001	0.011
Code-based	8	122,530,210	2.17 (1.48–3.17)	0.54–8.71	99.82	<0.0001	0.041
Type							
Type I AIH	8	6,533,380	1.00 (0.55–1.82)	0.13–7.54	91.04	<0.0001	0.027
Type II AIH	8	96,780,945	0.03 (0.02–0.04)	0.02–0.04	0.00	0.70	0.65
Seronegative AIH	3	71,842,811	0.05 (0.00–0.83)	NA	91.21	<0.0001	0.61
Overlap syndrome							
AIH-PBC	5	2,046,594	0.17 (0.09–0.32)	0.06–0.47	0.00	0.59	0.95
AIH-PSC	1	319,403	0.03 (0.00–0.22)	NA	NA	NA	NA
Score							
Definite AIH	6	2,705,442	1.06 (0.49–2.30)	0.08–14.99	91.85	<0.0001	0.64
Probable and definite AIH	6	2,705,442	1.67 (0.95–2.95)	0.22–12.59	95.20	<0.0001	0.95

AIH, autoimmune hepatitis; HDI, human development index; IAIHG, international autoimmune hepatitis group; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; NA, not available.
[a]These results were calculated and estimated using original data.

Table 2: Global pooled incidence of AIH included in our systematic review.

years[17–19,25,50] (44.05 [95% CI, 33.65–57.67]), followed by Adults aged under 65 years[17–19,25,28,30,31,34,43,44,50] (16.05 [95% CI, 13.01–19.80]), and lowest in children[18,19,25,30,33,52] (2.04 [95% CI, 1.01–4.14] per 100,000 inhabitants). The OR for AIH in adults aged under 65 years compared with children was 7.87 (95% CI, 3.77–16.42). The pooled prevalence of AIH was highest in North America (29.57 [95% CI, 27.84–31.40]),[17,19,42,50] followed by Oceania (26.22 [95% CI, 23.32–29.47]),[17,19,42] and lowest in Asia (8.06 [95% CI, 3.39–19.16] per 100,000 inhabitants).[25,28,30,34,43] Countries with a geographical latitude above 45°[17–21,23,26,28,31,32,37,38,42,44,50,51] exhibited a prevalence of AIH at 23.09 (95% CI, 21.33–25.00) cases per 100,000 inhabitants, while countries with a latitude below 45°[9,25,30,34,35,41,43] had a prevalence of AIH at 10.19 (95% CI, 4.99–20.79) cases per 100,000 inhabitants. The positive correlation was shown between increasing latitude and the prevalence of AIH (Pearson's R = 0.447, P < 0.05) (Figure E3)" (Results).

Table E3 and Fig. 2(B) provide information regarding the nationwide pooled prevalence of AIH in individual countries. The highest prevalence was found in the United States (29.55 cases per 100,000 inhabitants; 95% CI, 27.82–31.28),[17,19,33,42,50] while the lowest prevalence
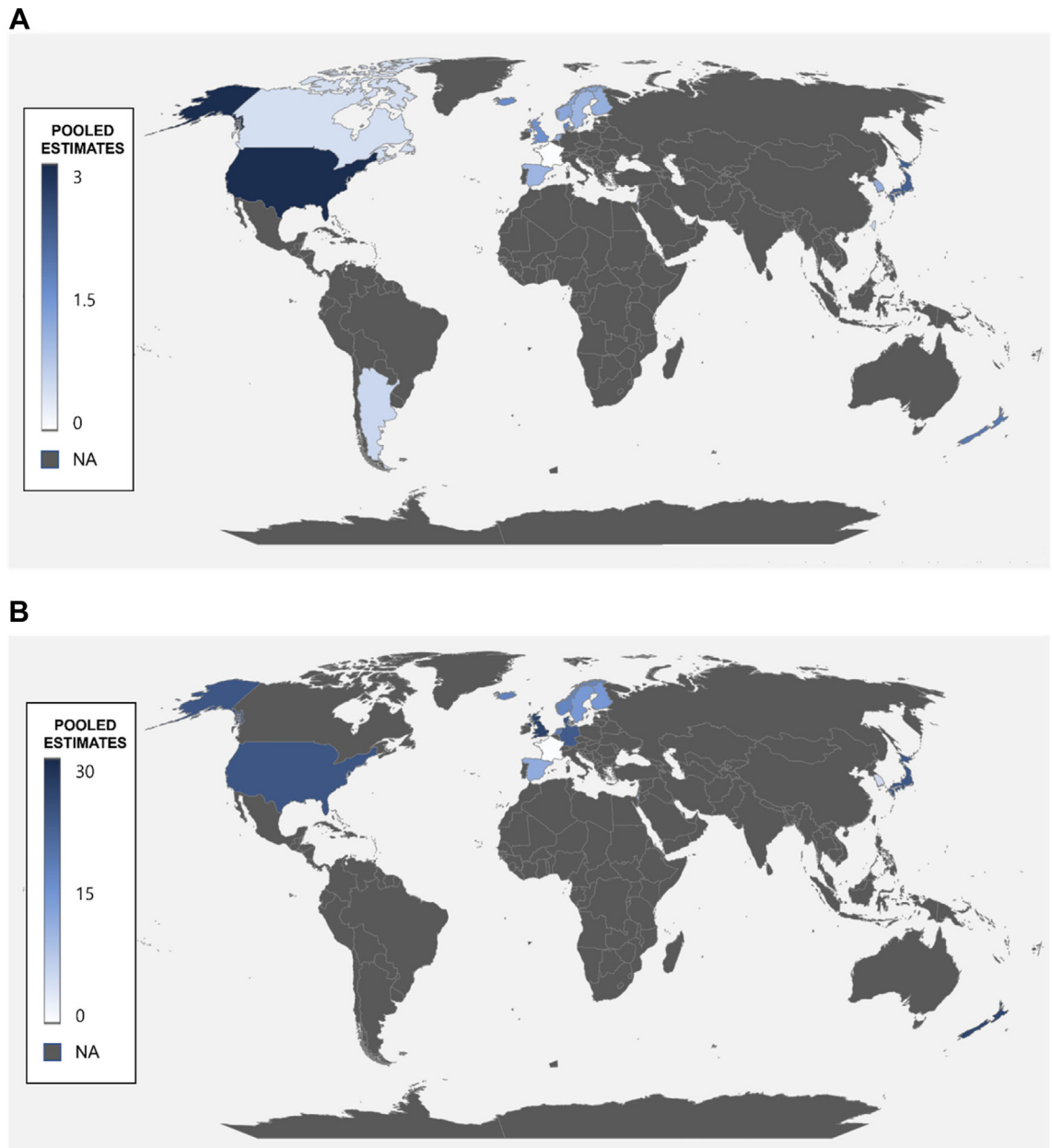
Fig. 2: Global incidence (A) and prevalence (B) of autoimmune hepatitis, 1970–2022. Pooled estimates, cases per 100,000 inhabitant-years for incidence, and cases per 100,000 inhabitants for prevalence.

was observed in Singapore (4.23 cases per 100,000 inhabitants; 95% CI, 2.83–6.31).[43]

The prevalence of AIH over time was reported in 26 subgroup studies, which were divided into 5-year intervals. The prevalence of AIH increased over time. The pooled prevalence was highest in 2015–2022 with 27.91 (95% CI, 24.86–30.96) cases per 100,000 inhabitants,[9,17–19,21,23,50,51] compared with a prevalence of 9.95 (95% CI, 4.77–15.13) cases per 100,000 inhabitants

prior to 1999.[37,42–44,47] Table E5 provides details of time-trend characteristics in the pooled prevalence of AIH. Our systematic review revealed a significant increase in the prevalence of AIH over time ($P_{trend} < 0.001$) (Fig. 3).

Asymmetry of the funnel plots was assessed to determine the risk of publication bias, which was found to be high for both the overall incidence ($P < 0.001$) and prevalence ($P = 0.030$) of AIH based on Egger's test. In addition, some subgroup analyses of the incidence and
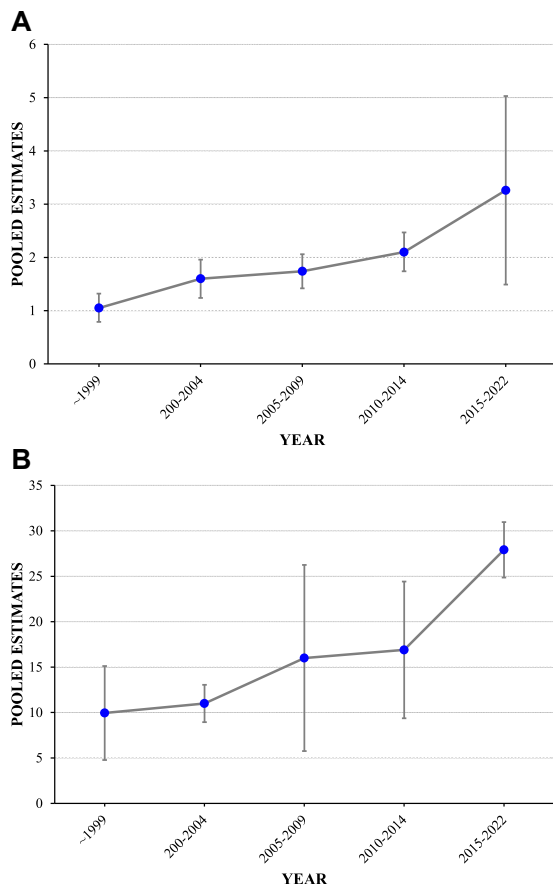
Fig. 3: Time trends of incidence (A) and prevalence (B) of autoimmune hepatitis, 1970–2022. Pooled estimates, cases per 100,000 inhabitant-years for incidence, and cases per 100,000 inhabitants for prevalence.

prevalence studies showed asymmetry in the funnel plots, indicating potential evidence of publication bias. Detailed funnel plots for the incidence and prevalence studies are shown in Figures E4–E55. A sensitivity analysis was conducted using the trim-and-fill method. The results showed that there was no statistically significant difference in the overall incidence of AIH (1.72, 95% CI, 1.38–2.14) and the overall prevalence of AIH (14.31, 95% CI, 12.32–16.63) when compared to the unadjusted analysis results ($P = 0.079$, $P = 0.42$, respectively) (Table E9). In the subgroup analysis of adults aged under 65 years, the adjusted analysis result showed an incidence of 1.99 (95% CI, 1.70–2.34), which was statistically significant when compared to the unadjusted analysis result ($P < 0.05$). However, no statistical significance was observed in other subgroups (Table E9). The adjusted funnel plot using the trim-and-fill method is presented in Figures E56–E67.

A total of 38 studies were assessed to determine RoB, out of which one study was excluded due to a high RoB.[22]

Of the remaining studies, 11 were considered to have a moderate RoB,[18,24,27,28,33,34,37,39,46,48,49] and 26 were evaluated as having a low RoB.[9,10,17,19–21,23,25,26,29–32,35,36,38,40–45,47,50–52] Among the questions used to evaluate the risk in most studies, those that were most frequently evaluated as posing a risk included "Were data collected directly from the patients (as opposed to a proxy)?" (applicable for 24 studies)[10,17–30,32–34,37–39,46,48,49] and "Was some form of random selection used to select the sample or was a census undertaken?" (applicable for 21 studies).[9,24,27,28,30,33–37,39–49] Details of RoB for prevalence studies are provided in Table E8.

Discussion

In this systematic review and meta-analysis, data were collected from 37 studies with a total sample size of 239,345,726 participants and 55,839 patients from 18 countries across five continents. Incidence and prevalence of AIH from 1970 to 2022 were reported. The global pooled incidence of AIH was found to be 1.28 cases per 100,000 inhabitant-years, whereas the global pooled prevalence was 15.65 cases per 100,000 inhabitants. Moreover, the incidence and prevalence of AIH were higher in populations with high HDI (>0.92), females, adults aged over 65 years, North American populations (versus Europe, Asia, and Oceania) and high latitude (>45°). The pooled prevalence of AIH also increased gradually over time, from 9.95 cases per 100,000 inhabitants from 1970 to 1999 to 27.91 cases per 100,000 inhabitants from 2015 to 2022.

Previous studies have examined the incidence and prevalence of AIH in the general population.[8,53] A recent systematic review published in 2019 examined 22 studies on AIH,[8] reporting that its overall incidence was 1.37 cases per 100,000 inhabitant-years, and overall prevalence was 17.44 cases per 100,000 inhabitants. Subgroup analysis showed that European and American populations had a higher prevalence than Asian populations; in addition, a higher prevalence was observed in women and adults aged over 65 years. However, some studies were excluded from the review due to insufficient inclusion of electronic medical databases, resulting in only 22 studies being included. In addition, the review did not provide data on income, age, data source, or specific types of AIH. Furthermore, no global or temporal trend of AIH was included in the analysis. This highlights the importance of conducting research reflecting current trends, as demonstrated in our study.

The incidence and prevalence of AIH in our study showed 3.1-fold and 2.8-fold increases, respectively, compared with rates prior to the 2000s. There are several potential reasons for this increase. First, it may be associated with a higher incidence of other autoimmune diseases; age- and sex-standardized incidence rates of various autoimmune diseases have shown an increase in recent years.[54] A significant percentage of

	Number of studies	Number of participants	Pooled estimates (95% CI)[a]	95% prediction interval	I^2 (%)	P value for I^2	Egger's P value
Overall prevalence	26	217,178,684	15.65 (13.42–18.24)	7.00–35.00	99.75	<0.0001	0.030
Income							
HDI >0.92	21	213,227,973	19.97 (17.00–23.44)	9.19–43.42	99.77	<0.0001	0.12
HDI <0.92	3	1,566,043	9.15 (6.11–13.72)	NA	75.00	0.018	0.72
Sex							
Male	13	93,583,856	8.05 (5.87–11.04)	2.31–28.07	99.40	<0.0001	0.17
Female	13	106,521,438	28.04 (21.31–36.89)	9.04–86.99	99.81	<0.0001	0.22
Age group							
Children	6	19,443,377	2.04 (1.01–4.14)	0.15–26.92	97.33	<0.0001	0.96
Adults aged under 65 years	12	126,351,940	16.05 (13.01–19.80)	6.50–39.62	99.75	<0.0001	0.11
Adults aged over 65 years	5	35,575,631	44.05 (33.65–57.67)	12.59–154.13	99.48	<0.0001	0.72
Geographical areas							
North America	4	125,734,165	29.57 (27.84–31.40)	22.57–38.74	97.91	<0.0001	0.36
Europe	14	36,666,398	16.56 (13.31–20.61)	6.72–40.82	98.90	<0.0001	0.25
Asia	5	52,217,383	8.06 (3.39–19.16)	NA	99.66	<0.0001	0.58
Oceania	2	1,094,070	26.22 (23.32–29.47)	NA	0.00	0.34	NA
Geographic latitude							
Above 45°	17	161,554,992	23.09 (21.33–25.00)	16.64–32.05	98.86	<0.0001	0.053
Below 45°	7	53,236,251	10.19 (4.99–20.79)	0.75–139.18	99.20	<0.0001	0.15
Diagnostic scoring system for AIH[a]							
Before IAIHG	1	212,500	8.00 (4.97–12.87)	NA	NA	NA	NA
Original IAIHG	2	697,685	8.45 (2.17–32.87)	NA	95.46	0.0010	NA
Revised IAIHG	7	9,361,665	16.57 (12.63–21.75)	6.46–42.50	95.00	<0.0001	0.48
Simplified IAIHG	3	1,385,031	27.43 (10.46–71.92)	NA	98.08	<0.0001	0.33
Data source							
Researcher validated	14	6,774,799	15.53 (12.94–18.64)	7.55–31.96	94.90	<0.0001	0.24
Code-based	9	201,738,235	20.55 (16.21–26.06)	8.33–50.67	99.90	<0.0001	0.21
Type							
Type I AIH	7	6,346,713	11.00 (6.74–17.95)	1.89–64.13	98.00	<0.0001	0.40
Type II AIH	3	12,791,557	0.43 (0.33–0.56)	0.08–2.38	0.00	0.61	0.74
Seronegative AIH	2	1,130,950	1.44 (0.11–19.25)	NA	92.49	<0.0001	NA
Overlap syndrome							
AIH-PBC	4	8,669,763	1.22 (1.01–1.48)	0.80–1.86	0.00	0.66	0.87
AIH-PSC	3	8,555,544	0.46 (0.23–0.91)	NA	71.35	0.03	0.92
Score							
Definite AIH	6	10,704,115	8.30 (4.87–14.13)	1.19–58.04	98.04	<0.0001	0.90
Probable and definite AIH	6	10,704,115	11.64 (7.28–18.62)	2.07–65.39	98.28	<0.0001	0.70

AIH, autoimmune hepatitis; HDI, human development index; IAIHG, international autoimmune hepatitis group; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; NA, not available.
[a]These results were calculated and estimated using original data.

Table 3: Global pooled prevalence of AIH included in our systematic review.

patients with AIH also exhibit concomitant extrahepatic autoimmune disorders, particularly Hashimoto's thyroiditis, type I diabetes mellitus, and inflammatory bowel disease (IBD).[55] In addition, the prevalence of obesity, a risk factor for autoimmune diseases, has also increased significantly.[56,57] Hence, the observed global rise in the incidence of autoimmune diseases might be interconnected. Secondly, there may be an influence of changing environmental exposures. Pathogenesis of AIH is believed to occur when genetically predisposed individuals are exposed to environmental triggers.[58] Antibiotics are considered an independent risk factor

for the development of AIH,[59] and nitrofurantoin and minocycline have historically been associated with drug-induced AIH.[60] Recently, biologic agents such as infliximab, adalimumab, and natalizumab have also been reported to cause drug-induced AIH.[61] Considering the continued increase in IBD prevalence,[62] the increasing prevalence of AIH may be caused by these factors. Thirdly, changes in diagnostic criteria for AIH may also be a contributing factor. The IAIHG scoring system for AIH has undergone several modifications over time. While the 1993, 1999 system included multiple parameters,[6,7] the 2008 system was based on four parameters

and designed for routine clinical practice[5]; Due to their convenience of use in clinical practice, the simplified criteria have gained popularity as a primary diagnostic tool in AIH. The advancement of diagnostic tools leading to an increase in disease incidence is supported by examples such as the introduction of pancreatic enzyme testing, which resulted in a more than 60% increase in acute pancreatitis cases.[63] In this study, the incidence of AIH using the revised IAIHG criteria was 1.04 (95% CI, 0.52–2.09), while using the simplified IAIHG criteria, the incidence was 1.83 (95% CI, 0.72–4.69). Therefore, the adoption of simplified criteria is associated with improved disease awareness, enhanced diagnosis, and a notable increase in AIH diagnoses.

Several potential factors contribute to the regional and national variations found in the incidence and prevalence of AIH. First, the distribution of predisposing human leukocyte antigen (HLA) genes varies by ethnicity and geographical region. Genetic factors are believed to have a significant impact on development of AIH. Specifically, certain HLA genes, such as DR3 and DR4, are more prevalent in European and North American populations.[2,64] These genetic variations contribute to the observed regional and national differences in the incidence and prevalence of AIH. However, unlike North America, where the majority of studies were conducted after 2017,[17,19,27,42,45,50] Europe has consistently reported studies on the incidence and prevalence of AIH since 1982. Considering the gradual increase in the incidence and prevalence of the disease, the lower incidence and prevalence in Europe compared to North America could be attributed to the inclusion of earlier studies. Second, the impact of environmental factors differs across regions. Several studies have reported microbiome alterations in patients with AIH[2] as well as an association between the enrichment of *Veillonella dispar* and disease severity.[65] Factors such as living conditions, lifestyle habits, and diet may influence the intestinal microbiome and contribute to the development of AIH.[66] In addition, a recent study in Iceland revealed an association between the use of biologics and increased incidence of AIH.[21] These differences in environmental factors may have contributed to regional variations in the incidence and prevalence of AIH. Thirdly, this could also be explained by the hygiene hypothesis. Epidemiological studies have reported a decrease in the incidence of infectious diseases and an increase in allergic/autoimmune diseases in developed countries.[67,68] In this study, a higher incidence of AIH in countries with higher HDI was observed compared to countries with lower HDI. HDI represents the average of health, knowledge, and standard of living in a country, indicating its level of development. This aligns with the hygiene hypothesis. Fourthly, this could be due to differences in the availability of advanced healthcare services. For AIH, diagnostic procedures such as liver biopsy and autoimmune serological testing are essential. But in regions with underdeveloped healthcare services, these tests may not be conducted, leading to an underreporting of the true incidence or prevalence of AIH. This could potentially exaggerate the disparity in disease rates between countries with high and low HDI. Studies on the Healthcare Access and Quality (HAQ) index have also reported differences in HAQ index scores, particularly between low and high sociodemographic index groups.[69]

Our study shows a gradual increase in the incidence and prevalence of AIH, with the highest rates observed in adults aged over 65 years. Approximately 25% of patients with AIH are asymptomatic,[56,57] however, the disease progresses in a similar manner regardless of symptoms.[4] Moreover, AIH is associated with a two-fold increased risk of death[70] and can contribute to acute-on-chronic liver failure,[71] indicating a significant health burden. Consequently, early detection and treatment of asymptomatic patients is crucial. Additionally, adults aged over 65 years tend to have a milder disease course and better treatment response, leading to overall improved prognosis.[72] Therefore, conducting diagnostic testing and providing active treatment for AIH in adults aged over 65 years is extremely important.

This study has several limitations. First, the available data on the incidence and prevalence of AIH lacks sufficient representation of South American and African patients. We investigated the incidence and prevalence of AIH in the general population, focusing primarily on North America, Europe, Asia, and Oceania. There is insufficient relevant literature available for South America and Africa (except for Argentina), making it challenging to establish a comprehensive understanding of regional differences in the incidence or prevalence of AIH. To address this limitation, we aimed to present an additional analysis by country to express regional differences. Second, the studies included in our analysis exhibited significant heterogeneity, warranting a cautious interpretation of the results. Several factors contributed to this heterogeneity, including differences in genetic predisposition, environmental factors, characteristics of prevalence studies, changes in diagnostic criteria for AIH, and demographic or cultural variations among study populations. To address this, we conducted subgroup analyses to elucidate the sources of heterogeneity. Despite the observed heterogeneity, our summary data provide valuable insights into the global perspective of the incidence and prevalence of AIH. Third, nonvalidated code-based studies were included in the data analysis. Considering the importance of study validation for data analysis, we conducted case validation assessments for all included studies; ten code-based studies lacked validation. In addition, Bittermann et al. reported that relying solely on ICD codes may not allow for reliable identification of true AIH cases using administrative data.[73] However, excluding code-based studies made it challenging to capture recent trends of

incidence and prevalence of AIH, as seven out of the eleven studies published after 2019 were code-based.[10,17–20,23,50–52] Additionally, other systematic reviews and meta-analyses on gastrointestinal diseases have used ICD-10 codes to diagnose the disease.[63] When conducting subgroup analysis using researcher-validated cases, a lower incidence of AIH was observed compared with code-based studies (1.29 [95% CI, 1.02–1.63] versus 2.17 [95% CI, 1.48–3.17] per 100,000 inhabitant-years). This suggests that a code-based approach may lead to overestimation of the incidence of AIH, emphasizing the need for cautious interpretation. Fourth, the temporal trend analysis presented in this study should be interpreted with caution. For instance, prior to 2008, there was no specific ICD code for AIH, and the transition from ICD-9 to ICD-10, advancements in diagnostic techniques, and improved access to high-quality healthcare services could have impacted the results. To address this issue, we conducted analyses stratified by code-based and researcher-validated study designs. However, the potential for milder cases to be more accurately diagnosed due to advancements in diagnostic technology and improved access to high-quality healthcare services still remains, warranting caution in the interpretation of the results. Fifth, the range of HDI values covered in this study was relatively narrow. Subgroup analysis of AIH incidence and prevalence was conducted based on HDI categories. The HDI classification designates 0.8 and above as "very high," and all 18 countries included in this study had HDI values of 0.8 or higher. This aspect should be interpreted with caution. Sixth, the interpretation of the association between geographic latitude and the incidence and prevalence of AIH. While the study revealed that countries with a geographic latitude above 45° exhibited significantly higher incidence and prevalence of AIH compared to countries below 45°. Notably, countries such as Iceland, Sweden, Finland, Norway, and Canada, with latitudes above 66°, did not show correspondingly high incidence and prevalence rates. This suggests that the interpretation of a linear relationship between latitude increase and AIH incidence and prevalence should be approached with caution. Due to the diagnostic complexity of AIH, in regions with limited healthcare access, there may be underreporting of the actual incidence or prevalence of AIH. Moreover, in areas with a high prevalence of viral and toxic liver diseases, or among elderly men, AIH is frequently not included in the initial diagnostic considerations. Consequently, the possibility of an unknown rate of undiagnosed cases in the incidence and prevalence of AIH exists.

Despite these limitations, this study had several strengths. A comprehensive search of multiple databases was conducted to identify relevant studies on AIH. Furthermore, the study presented a temporal trend in AIH incidence and prevalence, visually illustrating its increasing global burden. Compared with a previous study conducted in 2019,[8] this analysis provided a more in-depth examination of AIH by considering factors such as income, age, data source, and specific AIH types. This study also introduces global maps depicting the incidence and prevalence of AIH. In addition, by providing prediction intervals, advanced statistical techniques can be used to further investigate the incidence and prevalence of AIH. Finally, the analysis focused exclusively on studies involving the general population with AIH, ensuring a comprehensive representation of the disease.

In conclusion, our study provides insights into the incidence and prevalence of AIH across various factors such as income, sex, age, geographical region, diagnostic criteria, data source, and disease type. These findings highlight the consistent increase in the incidence and prevalence of AIH, suggesting that it may become a significant global health concern. Further studies focusing on South America and Africa are required to better understand the incidence and prevalence of the disease in these regions. Moreover, the substantial variation observed in the incidence and prevalence of AIH worldwide emphasizes the potential influence of genetic and environmental factors on this disease. Continued efforts to explore these factors are essential to develop a comprehensive understanding of AIH as well as targeted interventions for this disease.

Data sharing statement
All data relevant to the study are included in the article or uploaded as online supplemental information. The full search strategy and key results used to generate data that inform the conclusions of this systematic review can be found in online supplemental material.

Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102280.

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