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1 **Worldwide trends in all-cause mortality of auto-immune systemic** 2 **diseases between 2001 and 2014**

3
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33
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36

37 **Abstract**

38

39 ***Aim***

40 To describe changes in the 2001-2014 mortality of 6 autoimmune systemic diseases (AISDs),
41 namely Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc), Idiopathic
42 Inflammatory Myopathies (IIM), Sjögren's Syndrome (SS), Mixed Connective Tissue
43 Disease (MCTD) and ANCA-associated vasculitis (AAV) at the country-, continent-, and
44 world-levels.

45

46 ***Methods***

47 Mortality data were retrieved from the World Health Organization (WHO) mortality database
48 for each disease, based on ICD-10 codes. We computed age-standardized mortality rate
49 (ASMR) as the estimated number of deaths per million inhabitants and its 95% confidence
50 interval (95%CI). The association between gender, geographical areas and disease-specific
51 mortality was analyzed using multivariate Poisson regression. The 2001-2014 temporal trends
52 were analyzed using Jointpoint software.

53

54 ***Results***

55 In 2014, the worldwide ASMR for SLE was 2.68 (95%CI: 2.62 - 2.75) deaths/millions
56 inhabitants, 1.46 (1.42 – 1.51) for SSc, 0.47 (0.44 – 0.49) for IIM, 0.17 (0.15 – 0.18) for SS,
57 0.11 (0.10 – 0.13) for MCTD and 0.53 (0.50 – 0.56) for AAV, with ASMRs generally lower
58 in Europe than in North America, Latin America and Asia. Between 2001 and 2014, the
59 worldwide ASMR decreased significantly for SSc (-0.71%/year), IIM (-1.65%/year) and
60 AAV (-1.01%/year; $p < 0.001$ for all) and increased for SS (+1.53%/year, $p = 0.01$). The
61 worldwide ASMR of SLE decreased significantly between 2001 and 2003 (-6.37%, $p < 0.05$)
62 before increasing slightly between 2004 and 2014 (+0.58%, $p < 0.01$).

63

64 ***Conclusions***

65 We observed a strong heterogeneity of standardized mortality rates across all countries
66 analyzed for 6 autoimmune diseases. Those results further highlight the impact of world-wide
67 inequities and major gaps in access to care and strategies for diagnosis and management of
68 rare diseases, a crucial finding for world-wide physicians, patient associations and policy
69 makers.

70 **Introduction**

71

72 Autoimmune systemic diseases (AISDs) are a heterogeneous group of conditions
73 characterized by an immune dysregulation resulting in inflammation and multi-organ
74 involvements [1]. The prevalence of autoimmune diseases is currently estimated to range
75 from 4-5 % of the general population in developed countries [2,3], and is expected to increase
76 globally [4]. The care of patients with AISDs is often challenging [5], and despite recent
77 advances in immunosuppressive treatments [6–8], the burden of AISDs remains high [9–11].
78 World-wide differences in AISDs mortality are largely multifactorial and involve the role of
79 different genetic backgrounds [12], socio-economic level and access to care [13], the variable
80 efficacy of treatments [14], their side-effects, as well as the burden of comorbidities [15,16].
81 Also, methodological differences in mortality assessment methods may limit inter-country
82 comparability. As of today, AISD mortality has essentially been studied in limited
83 geographical areas such as at a given institution-, region- or more rarely country-level, mostly
84 using registries or cohorts [10,17–19]. While these approaches have provided important data,
85 inter-country comparisons from different sources are limited and a global overview of AISDs
86 mortality is currently lacking. Noteworthy, worldwide data on AISD mortality are of major
87 interest to policymakers as well as to physicians involved in the care of these rare diseases.

88 Here, we used publicly available data from the World Health Organization (WHO), to analyze
89 worldwide temporal trends of mortality data for six AISDs, namely Systemic Lupus
90 Erythematosus (SLE), Systemic Sclerosis (SSc), Sjögren’s Syndrome (SS), Idiopathic
91 Inflammatory Myopathies (IIM), Mixed Connective Tissue Disease (MCTD) and Anti-
92 Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis (AAV).

93

94

95 **Methods**

96

97 **Data sources & handling**

98 Data of cause-specific deaths were retrieved from the publicly available WHO mortality
99 database (http://www.who.int/healthinfo/mortality_data/). Retrieved data included the number
100 of cause-specific deaths, age category for each country, year and gender. Population data
101 according to sex and age were retrieved from the United Nations World prospects database
102 (<https://population.un.org/wpp/Download/Standard/Population/>). For geographical analysis,
103 the countries were grouped as follows: Europe, Asia, Oceania, Africa, North America and
104 Latin America.

105

106 **Classification of diseases according to ICD-10 codes**

107 The cause of death was coded based on the International Classification of Disease, tenth
108 revision (ICD-10) available online (<https://www.icd10data.com/ICD10CM/Codes>). We
109 studied deaths caused by systemic lupus erythematosus (ICD-10 codes M32*), Sjögren's
110 syndrome (M350), systemic sclerosis (M34*), idiopathic inflammatory myositis (M33*),
111 mixed connective tissue disorders (M351), and anti-neutrophils cytoplasmic antibodies
112 (ANCA-) associated vasculitis (M301, M313 and M317).

113

114 **Age-standardized mortality rate and temporal trend analysis**

115 We computed age-standardized global and sex-specific mortality rates (ASMR) per million
116 individuals for each country and continent by the mean of direct standardization, using the
117 WHO world reference population as the standard population
118 (<https://seer.cancer.gov/stdpopulations/world.who.html>).

119 For temporal trends, we restricted the analysis to the 2001-2014 period and included only
120 countries with less than 3 years of missing data, without imputation of missing data. We used
121 Joinpoint Regression Program version 4.2.0.2 from the Surveillance Research Program of the
122 US National Cancer Institute (<http://surveillance.cancer.gov/joinpoint>) for temporal trend
123 analysis [20]. This analysis identifies “jointpoints”, i.e. points with a significant change in
124 trend. Linear trends between jointpoints are then computed. An annual percent change (APC)
125 is estimated for each jointpoint by fitting a regression line to the natural logarithm of the
126 ASMRs, using calendar year as a dependent variable.

127

128 **Statistics**

129 The data (ASMR) are expressed as the estimated number of deaths per million inhabitants and
130 its 95% confidence interval (95%CI). The association between country gender and disease-
131 specific mortality and geographical area in 2014 was studied using a Poisson regression
132 analysis. One model was computed for each disease with the continent area as the
133 independent variable. All models were adjusted on age-structure and sex. A p-value < 0.05
134 was considered as statistically significant. Statistical analyses were conducted using SAS
135 version 9.4 (Cary, NC, USA). The figures and correlations were made using GraphPad
136 Prism[®] 7.0 (San Diego, USA).

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143

144 **Results**

145

146 ***Systemic Lupus Erythematosus***

147 For the year 2014, 6418 SLE-related deaths occurred in 84 countries (figure 1A & suppl.
148 table 1), corresponding to 0.021% of all deaths and yielding a global ASMR of 2.68 (95%CI:
149 2.62 - 2.75) per million inhabitants. The ASMR was 4.53 (4.40 - 4.65) for women and 0.79
150 (0.73 - 0.84) for men. The ASMR ranged from 0.11 in Morocco to 27.1 deaths per million in
151 Saint Lucia (figure 2 & supplementary table 1). For the year 2014, the ASMR of SLE in
152 Europe (1.06 [95%CI: 0.98-1.13] deaths/million) was significantly lower than that of Asia
153 (2.16 [2.03-2.29], $p < 0.0001$), Oceania (1.33 [0.97 – 1.70], $p < 0.01$), Latin America (5.53
154 [5.33 – 5.73], $p < 0.0001$) and North America (2.69 [2.53 – 2.84], $p < 0.0001$). The ASMR of
155 Africa (1.27 [1.10 – 1.45]) was similar to that of Europe (figure 2). Based on 64 countries
156 with available data for temporal trend analysis (list available in suppl. table 1), the worldwide
157 ASMR of SLE decreased significantly between 2001 and 2003 (mean APC -6.37%, $p < 0.05$)
158 before increasing slightly between 2004 and 2014 (mean APC +0.58%, $p < 0.01$; table 1).
159 During the same period, the ASMR of SLE decreased significantly (table 1) in Europe ($p <$
160 0.01), North America ($p < 0.0001$) and Oceania ($p < 0.01$), remained stable in Africa ($p =$
161 NS), and increased significantly in Asia ($p < 0.0001$) and Latin America (between 2003-2014,
162 $p < 0.0001$; table 1).

163

164 ***Systemic sclerosis***

165 For the year 2014, 4287 SSc-related deaths occurred in 74 countries (figure 1B & suppl. table
166 2), corresponding to 0.014% of all deaths and yielding a global 2014 ASMR for SSc of 1.46
167 (95%CI: 1.42 – 1.51) deaths/million inhabitants. The ASMR was 2.13 (2.06 – 2.21) for
168 women and 0.68 (0.63 – 0.72) for men. The ASMR ranged from 0.025 in Egypt to 16 deaths

169 per million in Brunei (figure 2 & supplementary table 2). For the year 2014, the ASMR of
170 SSc in Europe (1.14 [95CI: 1.07 – 1.20]) was significantly lower than that of Oceania (2.70
171 [2.21 – 3.19], $p < 0.0001$), Latin America (1.36 [1.25 – 1.46], $p < 0.005$) and North America
172 (2.63 [2.49 – 2.77], $p < 0.0001$) (supplementary table 2). The ASMR from available African
173 countries (0.41 [95%CI: 0.30 – 0.51]) were significantly lower compared to Europe ($p <$
174 0.0001). The ASMR of Asia (1.13 [1.04 – 1.21]) was similar to that of Europe. Based on 57
175 countries with available data for temporal trend analysis (list available suppl. table 2), the
176 worldwide ASMR of SSc decreased significantly between 2001 and 2014 (mean APC -
177 0.71%, $p < 0.001$, table 1). During the same period, the ASMR of SSc decreased significantly
178 in North America ($p < 0.0001$), remained stable in Africa, Oceania and Latin America ($p =$
179 NS), and increased significantly in Europe ($p < 0.001$) and Asia ($p < 0.01$; table 1).

180

181 *Idiopathic Inflammatory Myositis*

182 For the year 2014, 1313 IIM-related deaths occurred in 67 countries (figure 1C & suppl. table
183 3), corresponding to 0.004% of all deaths and yielding a global ASMR of 0.47 (95%CI: 0.44
184 – 0.49) deaths per million inhabitants. The ASMR was of 0.54 (0.50 – 0.58) deaths per
185 million for women and 0.39 (0.35 – 0.42) for men. The ASMR ranged from 0.025 in Egypt to
186 11.57 deaths/million in Antigua and Barbuda (figure 2 & suppl table 3). For the year 2014,
187 the ASMR of IIM in Europe (0.26 [0.23 – 0.30]) was significantly lower than that of Asia
188 (0.75 [0.68 – 0.82]), Latin America (0.45 [0.39 – 0.51]) and North America (0.53 [0.47 –
189 0.59], $p < 0.0001$ for all comparisons). The ASMR of Oceania (0.18 [0.06 – 0.30]) and Africa
190 (0.19 [0.11 – 0.26]) were similar than that of Europe ($p =$ NS for both). Based on 43 countries
191 with available data for temporal trend analysis (list available suppl. table 3), the worldwide
192 ASMR of IIM decreased significantly between 2001 and 2014 (mean APC -1.65%, $p <$
193 0.0001 , table 1). During the same period, the ASMR of IIM decreased significantly in North

194 America ($p < 0.0001$), and remained stable in Oceania, Africa, Europe and Asia (between
195 2001 and 2014) (table 1). In Latin America, the ASMR decreased between 2001 and 2004
196 (APC -10.51%, $p < 0.05$), then remained stable until 2014 (APC -0.72%, $p = \text{NS}$; table 1).

197

198 *Sjogren's syndrome*

199 For the year 2014, 438 SS-related deaths occurred in 35 countries (figure 1E & suppl. table
200 4), corresponding to 0.002% of all deaths and yielding a global 2014 ASMR for SS of 0.17
201 (95%CI: 0.15 – 0.18) deaths per million inhabitants. The ASMR was of 0.26 (0.23 – 0.28) for
202 women and 0.05 (0.04 – 0.07) for men. The ASMR of SS ranged from 0.05 in Chile to 1.03
203 deaths per million in Malta (suppl. table 4). For the year 2014, the ASMR of SS was lower in
204 Europe (0.15 [0.13 – 0.18]) compared to North America (0.21 [0.17 – 0.24], $p < 0.005$) and
205 Asia (0.19 [0.15 – 0.23], $p < 0.05$), and was similar to Latin America (0.11 [0.08 – 0.15]) and
206 Oceania (0.11 [0.01 – 0.20]). Based on 24 countries with available data for temporal trend
207 analysis (list available suppl. table 4), the worldwide ASMR of SS increased significantly
208 between 2001 and 2014 (APC +1.53%, $p = 0.01$; table 1). During the same period, the ASMR
209 of SS increased significantly in Latin America ($p < 0.05$) and in Asia ($p < 0.01$), and remained
210 stable in Oceania and North America during the 2001-2014 period. In Europe, the ASMR of
211 SS remained stable between 2001 and 2008, then increased significantly until 2014 ($p < 0.05$;
212 table 1).

213

214 *Mixed Connective Tissue Disease*

215 For the year 2014, 235 MCTD-related deaths occurred in 32 countries (figure 1F & suppl.
216 table 5), corresponding to 0.001% of all deaths and yielding a global 2014 ASMR of 0.11
217 [95%CI: 0.10 – 0.13] deaths per million inhabitants. The ASMR was of 0.17 (0.15 – 0.20) for
218 women and 0.05 (0.03 – 0.06) for men. At the country-level, the ASMR ranged from 0.01 in

219 France to 2.60 deaths/million in the Bahamas (figure 2 & suppl. table 5). For the year 2014,
220 the ASMR for Europe (0.08 [0.06 – 0.10]) was significantly lower than that of Asia (0.19
221 [0.15 – 0.24], $p < 0.0001$) and similar to that of North America (0.12 [0.09 – 0.15]), Latin
222 America (0.08 [0.05 – 0.10]) and Oceania (0.17 [0.00 – 0.50]). Based on 17 countries with
223 available data for temporal trend analysis (list available suppl. table 5), the worldwide ASMR
224 of MCTD remained stable between 2001 and 2014 (mean APC +0.20%, $p = \text{NS}$), but
225 increased significantly in North America ($p < 0.01$), remained stable in Europe and
226 significantly decreased in Asia ($p < 0.01$) and Latin America ($p < 0.0001$; table 1). There were
227 no available data for Africa and Oceania.

228

229 *ANCA-associated vasculitis*

230 For the year 2014, 1350 AAV-related deaths occurred in 51 countries (figure 1D & suppl.
231 table 6), corresponding to 0.005% of all deaths and yielding a global 2014 ASMR for AAV of
232 0.53 (95%CI: 0.50 – 0.56) deaths per million inhabitants. The ASMR was of 0.46 (0.42 –
233 0.49) for women and 0.62 (0.57 – 0.67) for men. The ASMR ranged from 0.07 in Ecuador to
234 1.70 deaths per million in Denmark (figure 2 & supplementary table 6). For the year 2014, the
235 ASMR of AAV in Europe (0.60 [0.55 – 0.65]) was significantly higher than that of Asia (0.33
236 [0.27 – 0.40]) and Latin America (0.32 [0.27 – 0.37], $p < 0.0001$ for both comparisons) while
237 it was similar to that of North America (0.67 [0.60 – 0.74]) and Africa (0.76 [0.00 – 1.83]).
238 The ASMR of Oceania (0.83 [0.56 – 1.09]) was significantly higher than that of Europe ($p <$
239 0.05). Based on 34 countries with available data for temporal trend analysis (list available
240 suppl. table 6), the worldwide ASMR of AAV decreased significantly between 2001 and 2014
241 (mean APC -1.01%, $p < 0.001$; table 1). During the same period, the ASMR of AAV
242 decreased significantly in Europe ($p < 0.01$) and Oceania ($p < 0.05$), and remained stable in
243 Asia during the 2001-2014 period ($p < 0.05$). In North America, the ASMR of AAV remained

244 stable between 2001 and 2010, then decreased significantly until 2014 ($p < 0.05$). In Latin
245 America, after an initial stability between 2001 and 2005 ($p = 0.06$), the ASMR of AAV
246 significantly increased until 2014 ($p < 0.01$; table 1).

247

248 **Discussion**

249

250 In this study, we used world-wide data from the World Health Organization to analyze
251 worldwide mortality data of 6 auto-immune and systemic conditions, namely SLE, SSc, SS,
252 IIM, MCTD and AAV. One main strength of the study is the use of standardized mortality
253 rates as a way to account for differences in the heterogenous age structure of the populations
254 studied. Further, we were able to analyze temporal changes in all-cause disease-specific
255 mortality data over a span of 14 years.

256

257 While not totally unexpected, the main finding of the study is the strong heterogeneity of
258 standardized mortality rates across all countries analyzed. For SLE, mortality ranged from
259 0.11 to 27.1 deaths per million inhabitants, a significant ≈ 250 -fold variation in ASMRs.
260 While those differences may arise from a broad variety of causes, including differences in
261 disease severity, access to care and diagnosis delays, drug availability and treatment
262 strategies, as well as several reporting biases (*see limitations*), our results underline the strong
263 world-wide inequities to which are confronted patients with auto-immune systemic diseases.
264 Also, our study further confirmed that global mortality rates of AISDs were significantly
265 higher for women, for SLE, SSc, IIM, SS and MCTD.

266

267 Further analysis at the continent level (considering North-America and Latin America
268 separately, due to their important geopolitical and economical differences) revealed that in

269 many cases disease-specific mortality rates were lower in Europe compared to the other
270 continents, except for AAV. Strikingly, Latin America had a > 5 fold higher ASMR compared
271 to Europe for SLE, a difference which was not observed for the 5 other AISDs. This suggests
272 that disease-specific factors, such as the role of the complex genetic background [12] or the
273 environment [21,22], might be at play.

274

275 *Limitations:* As reported in the methods, we chose to exclude countries with more than 3
276 missing data over the considered time-span to increase the robustness of temporal trend
277 analysis. Nevertheless, we were able to analyze detailed mortality data for a large sample of
278 countries, which represents the largest scale analysis for auto-immune diseases to date.
279 Temporal trend analysis revealed that between 2001 and 2014, the worldwide all-cause
280 mortality significantly decreased for SSc, IIM, AAV, remained stable for MCTD, and
281 increased significantly for SS and SLE (during the 2003-2014 period for the latter, see table
282 1). The efficiency of data collection and mortality attribution to a specific cause may vary
283 from one country to another, as may vary the age structure of the considered populations. To
284 minimize this effect, we used standardized mortality rates according to the WHO reference
285 population, hence increasing data comparability between the various regions studied. Changes
286 in the mortality reporting system (*e.g.* ICD version) might also explain some brutal changes
287 such as the dramatic increase in MCTD-related ASMR between 2008 and 2009 in North
288 America. Finally, only all-cause disease-specific mortality data are available in the WHO
289 database. Therefore, we were not able to analyze separately the role of disease activity, end-
290 stage organ damage [16], cardiovascular complications [23], or other causes of death which
291 are all important mortality factors in patients with AISDs [24].

292

293

294

295 **Conclusions**

296 Altogether, we used world-wide data from the World Health Organization to analyze detailed
297 temporal trends of standardized all-cause disease-specific mortality rates for 6 major systemic
298 auto-immune conditions. Our results reveal major differences in mortality between those 6
299 AISDs, and the generally better prognosis in Europe versus other geographical regions,
300 including North America. Those results further highlight the impact of world-wide inequities
301 and major gaps in access to care and strategies for diagnosis and management of rare diseases,
302 a crucial finding for world-wide physicians, patient associations and policy makers.

303

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308

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311

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- 396
397

398 **Figure legend**

399

400 **Figure 1. Temporal trends in ASMR for 6 auto-immune diseases for the 2001-2014**
401 **period**

402 ASMR estimates are shown with their 95% confidence interval (95%CI). The brutal change
403 found in the 2015 Oceania ASMR is due to missing data from Australia this same year.

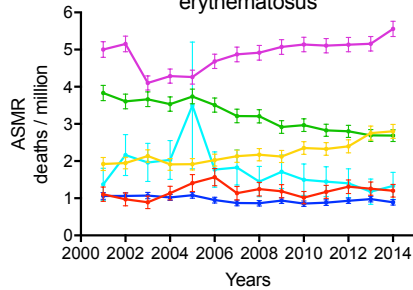
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405 **Figure 2. Age-standardized mortality rate for the year 2014**

406 Mortality rates in number per million, color-coded by quartiles for (A) Systemic lupus, (B)
407 Systemic sclerosis, (C) Idiopathic inflammatory myopathies, (D) Sjögren's syndrome, (E)
408 Mixed connective tissue disease and (F) ANCA-associated vasculitis. Countries in white are
409 those without available data.

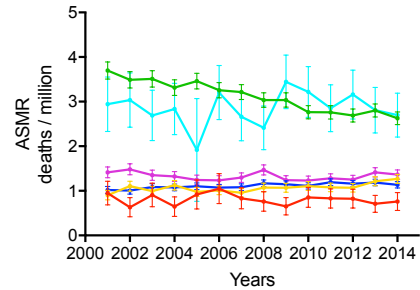
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Systemic lupus erythematosus



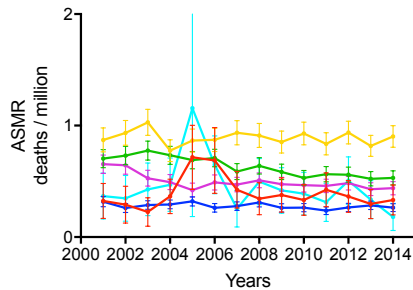
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Systemic sclerosis



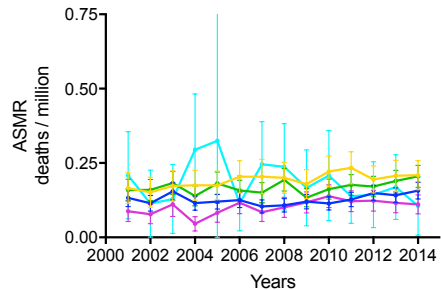
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Inflammatory myositis



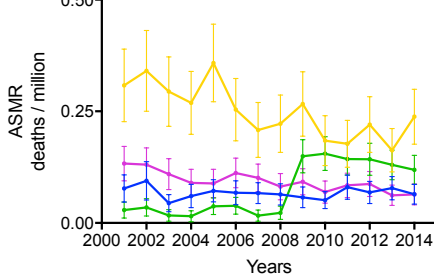
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Sjögren's syndrome



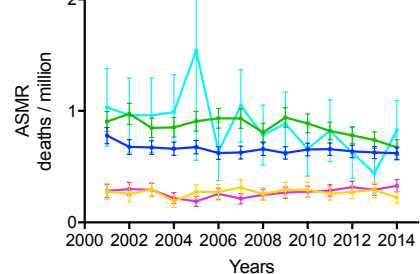
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Mixed connective tissue disorder

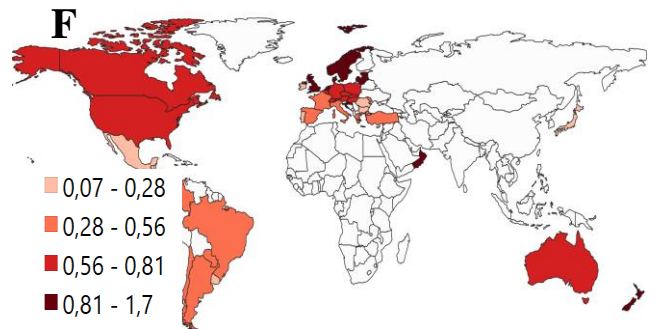
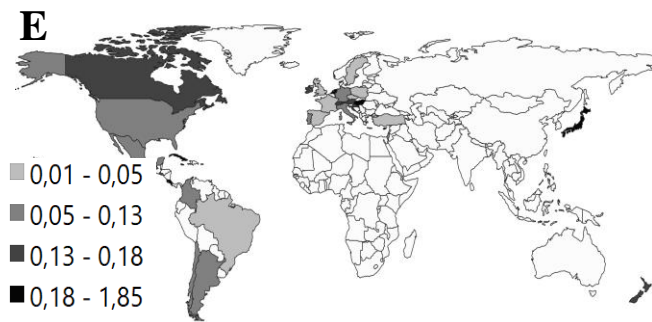
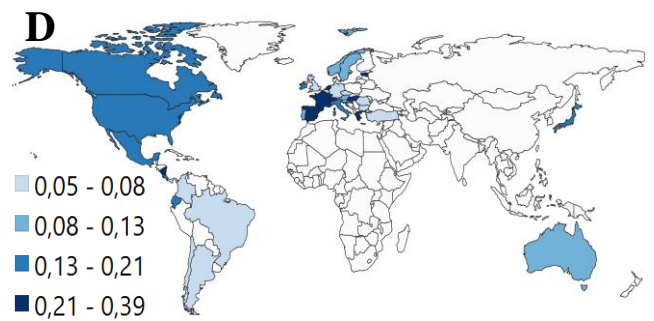
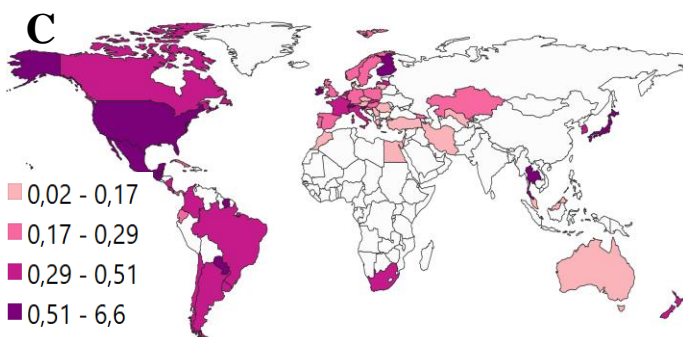
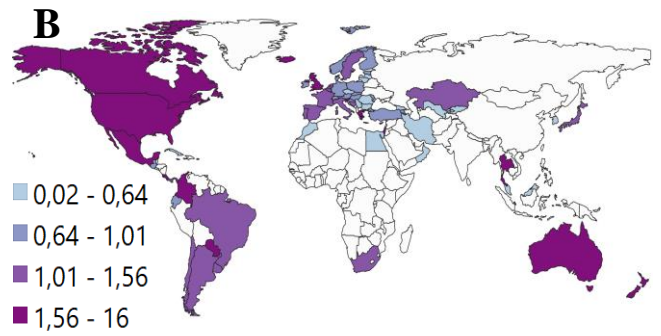


- Asia
- Europe
- North America
- Latin America

ANCA-associated vasculitis



- Asia
- Europe
- North America
- Latin America
- Oceania



Age-standardized mortality rate (by quartiles) for the year 2014: (A) Systemic lupus, (B) Systemic sclerosis, (C) Idiopathic inflammatory myopathies, (D) Sjögren's syndrome, (E) Mixed connective tissue disease and (F) ANCA-associated vasculitis.