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SUPPLEMENTARY METHODS

Data acquisition and download

The 2021 GBD study provides a comprehensive examination of the health consequences associated with 371 diseases, injuries, and impairments, along with 88 risk factors across 204 nations and territories (1). And it offers detailed insights into the data, methodologies, and statistical modelling employed in previous reports (2). This investigation draws its determinations and 95% uncertainty interval (UI) for prevalence, incidence, and YLDs relating to AA from the GBD 2021 data.

Burden description

Prior to and throughout the course of the global pandemic caused by the COVID-19, we conducted a series of comprehensive assessments with the objective of quantifying the global, national, regional burden of AA, including its prevalence, morbidity, mortality, and YLDs. The investigation examined the demographic variables that influence the impact of AA, analyzing the distribution of the disease's burden across different sex groups.

Joinpoint regression analysis

In the present study, the Joinpoint regression analysis model was employed, which is a common statistical methodology utilized in epidemiological research to assess temporal trends in disease prevalence or mortality (3). This model demonstrates a high degree of efficacy in the identification and quantitative characterization of significant change points within time-series data pertaining to the incidence, prevalence, and YLDs of AA across the global scope. Moreover, to gain an understanding of the trends in the data set as a whole, the average annual percent change (AAPC) was calculated. This encapsulates the aggregated trend data spanning the entire period from 1990 to 2021, allowing for a more comprehensive assessment. From the standpoint of statistical analysis, an APC or AAPC estimate, accompanied by a 95% CI lower bound that exceeds zero, indicates an upward trajectory within the specified time interval. Conversely, an APC or AAPC estimate accompanied by a 95% CI upper bound that is below zero indicates a downward trend. When the 95% CI for the APC or AAPC encompasses zero, it can be inferred that the trend has remained stable. The specific details of the equations and model formulation utilized in the Joinpoint regression analysis can be found in the **JOINPOINT REGRESSION ANALYSIS**.

SDI, World Bank income group, and decomposition methodology

The study utilized the sociodemographic index (SDI), an indicator that quantifies a region's sociodemographic advancement on the basis of income, education, and fertility circumstances (4). The data from a total of 204 countries and territories were classified into five regions in accordance with the SDI, which encompasses the following five categories: low, low-middle, middle, high-middle, and high. Moreover, the categorization of income adopted by the World Bank was employed for the purposes of income grouping (5). In the present study, we employed decomposition analysis to disaggregate the incidence, prevalence, and YLDs of AA by population age structure, population growth, and epidemiologic changes (6,7).

Cross-country inequality analysis

In order to ascertain the degree of SDI-related inequality of AA Burden across countries, the slope index of inequality and concentration index were employed (8). Slope index of inequality was determined by means of regression analysis, whereby country-level incidence, prevalence and YLDs associated with AA in all age groups were regressed on a socio-demographic development-related relative position scale, defined by the midpoint of the cumulative class range of the population ranked by SDI. The concentration index for health inequality was calculated by fitting a Lorenz concentration curve to the observed cumulative relative distribution of the populations ranked by SDI and the incidence, prevalence, and YLDs of disease. Furthermore, the area under the curve was numerically integrated (9).

Associated diseases with AA

Autoimmune diseases such as atopic dermatitis, rheumatoid arthritis have been linked to AA. The presence of AA has been demonstrated to cause morphological disfigurement, which has a significant negative effect on patients' quality of life (10). We selected major comorbidities associated with AA that were analyzed in the meta-analysis reported by previous studies (11–13) and provided in GBD 2021 study, including autoimmune, other skin diseases, and neurological disorders. The number of comorbidities that met eligibility was twenty-one. We investigated the correlation of age-standardized incidences between AA and associated diseases in different sex and age to explore consistency and comorbid pattern across diverse subgroups.

Projection analysis

Bayesian age-period-cohort (BAPC) model was used to predict the incidence, prevalence, and YLDs number and rate of IBD from 2022 to 2050. In essence, the age-period-cohort model, which is a logarithmic linear Poisson model, postulates that the multiplicative impact of age,

period, and cohort is reflected in a Poisson distribution, and that a link function specific to the model is utilised (14). In order to estimate the predicted results, we utilized the GBD 2021 database. The number and age-standardized rate of AA incidence, prevalence, and YLDs in 2021 were taken as the benchmark, with an annual increase of 1% serving as a negative reference point and an annual decrease of 1% as an optimistic reference point. A BAPC model was implemented using R package BAPC.

Statistical analysis

The variables were expressed in number, percentage, and ratio. The Joinpoint regression model was employed for the purpose of analyzing the APC in the number of cases, the rate of incidence, prevalence, and YLDs, in addition to observing the temporal trends in AA. Pearson's correlation analysis was conducted to ascertain the relationship between AA burden and its associated diseases, stratified by sex, among individuals aged pre- and post-14 years. All analyses and visualization were executed using R (version 4.3.3). $P < 0.05$ was considered statistically significant.

JOINPOINT REGRESSION ANALYSIS

Time trend analysis is an important component of epidemiological research. Traditional regression models primarily fit and evaluate the overall trend of disease distribution within the study period from a global perspective, failing to capture local variation characteristics. In 1998, Kim et al. first proposed the Joinpoint regression model. The core idea of this model is to establish segmented regression based on the temporal characteristics of disease distribution. By dividing the study time into different intervals through several Joinpoints, the trend in each interval is fitted and optimized, allowing for a more detailed assessment of the specific disease change characteristics within different intervals of the overall time range (3). The Joinpoint regression model, developed by the Division of Cancer Control and Population Sciences at the National Cancer Institute of the United States, has been widely applied in the field of trend studies on disease incidence and mortality rates.

(I) Model Introduction

The Joinpoint regression model includes two types: the linear model ($y = xb$) and the logarithmic linear model ($\ln y = xb$). If the dependent variable follows a normal distribution (or approximately normal distribution) and the sample size is large (usually greater than 100), the linear model is preferred. For example, when the dependent variable is continuous variables like height, weight, etc. If the dependent variable follows an exponential distribution or a Poisson distribution, the logarithmic linear model is more suitable. For instance, when the dependent variable represents epidemiological data based on populations such as incidence rates, number of cases, etc. When analyzing trends in the incidence, prevalence, mortality rates, and DALYs rates of thalassemia based on population data, the logarithmic linear model is generally chosen.

(II) Modeling Method

The grid search method (GSM) is the default modeling approach used by Joinpoint. GSM divides the study data into a grid, with each grid intersection corresponding to a planned scenario.[3] Then, within the specified intervals, it computes performance metrics for the corresponding equations at each point using a fixed step size to determine the optimal function. In essence, the Joinpoint model uses the GSM to establish all possible segment function Joinpoints (i.e., Joinpoints) and calculates the sum of squares errors (SSE) and mean squared errors (MSE) for each possible scenario. It selects the grid point with the smallest MSE as the Joinpoint for the segment function and fits the equation parameters such as β_0, β_1, δ_1, ..., δ_k based on the selected Joinpoints and interval functions (15).

(III) Model Optimization

Monte Carlo permutation test is the default model optimization method in Joinpoint software. Before modeling, it is necessary to set the range of the number of Joinpoints k as $k \in (MIN, MAX)$, where MIN represents the minimum number of Joinpoints, which is usually set to 0; MAX represents the maximum number of Joinpoints. Each permutation test checks the null hypothesis H_0: the number of Joinpoints is $k = k_a$, and the alternative hypothesis H_1: the number of Joinpoints is $k = k_b$. The permutation test starts from k_a=MIN and k_b=MAX. If H_0 is rejected, k is set to $k_a + 1$ for further testing; if H_0 is not rejected, k is set to $k_b - 1$ for another test, until $k_a = k_b$, which means $k = k_a = k_b$ is the preferred number of Joinpoints selected by the permutation test, and the corresponding model is the optimal model (16).

(IV) Index Calculation

Annual percent change (APC) and average annual percent change (AAPC) along with their 95% confidence intervals (CI) are the primary outcome indicators of the Joinpoint model. As the name suggests, APC represents the average annual percentage change of the dependent variable. For example, in a logarithmic linear model $\ln(y) = \beta_0 + \beta_1 x$, where y represents the incidence rate and x represents the year of incidence, the formula for calculating APC in the fitted model can be derived as:

$$APC = \left[\frac{y_{x+1} - y_x}{y_x}\right] \times 100 = (e^{\beta_1} - 1) \times 100$$

The lower and upper limits of the 100(1-α) % confidence interval are respectively:

$$APC_{L(\alpha)} = 100(e^{\beta_1 - s \times t_d^{-1}(1-\alpha/2)} - 1)$$

$$APC_{U(\alpha)} = 100(e^{\beta_1 + s \times t_d^{-1}(1-\alpha/2)} - 1)$$

In the above formula, β_1 represents the regression coefficient, s represents the standard error of β_1, d represents the degrees of freedom, and $t_d(q)$ is the value corresponding to the qth percentile of the t-distribution with d degrees of freedom (such as 95%).

The APC is used to evaluate the internal trend of each independent interval of a segmented function or the overall trend with no connecting points. When it comes to assessing the overall average change trend encompassing multiple intervals, the AAPC is required. The parameter calculation method of AAPC involves weighted calculation of the regression coefficients of each interval based on the width w of the segment intervals. Its

formula is as follows:

$$AAPC = \left(e^{\sum w_i \beta_i / \sum w_i} - 1 \right) \times 100$$

The lower and upper limits of the 100(1-α) % confidence interval are respectively:

$$AAPC_{L(\alpha)} = \left\{ \exp\left[\ln\left((AAPC/100) + 1 \right) - Z_{1-\alpha/2} \sqrt{\sum \tilde{w}_i^2 \tilde{\sigma}_i^2} \right] - 1 \right\}$$

$$AAPC_{U(\alpha)} = \left\{ \exp\left[\ln\left((AAPC/100) + 1 \right) + Z_{1-\alpha/2} \sqrt{\sum \tilde{w}_i^2 \tilde{\sigma}_i^2} \right] - 1 \right\}$$

In the above formula, w_i represents the width of each segment function interval (i.e., the number of years included in the interval), β_i denotes the regression coefficient corresponding to each interval, $\sigma^2 i$ is the variance of β_i, and Z_α represents the corresponding value of the α percentile in the normal distribution.

(V) Software Download

To download Joinpoint software, we visited the website of the National Cancer Institute (https://surveillance.cancer.gov/Joinpoint/download), registered, and submitted our applicatio n information. Software citation: Joinpoint Regression Program, Version 4.9.1.0 - April 2022; Statistical Methodology and Applications Branch, Surveillance Research Program, National C ancer Institute.

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