Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: results from the EPOCA study

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Summary

Background. The characteristics and burden of childhood arthritis have never been studied on a worldwide basis. We aimed to investigate the prevalence of disease categories, treatment modalities and disease status across different geographic areas.

Methods. International paediatric rheumatologists were asked to enrol a consecutive sample of children with juvenile idiopathic arthritis. Each patient underwent retrospective and cross-sectional assessments. Parent-reported outcomes were collected through a multidimensional questionnaire, translated in the language of all participating countries. Level of disease activity and damage were correlated with wealth of the country, expressed as gross domestic product per capita.

Findings. Between 2011 and 2016, 9,137 patients were enrolled at 130 centres in 49 countries, grouped in 8 geographic areas. A wide variability in the prevalence of disease categories across areas was seen, which included the rate of uveitis. Median age at disease onset was lower in Mediterranean Europe (3.5 years) and Scandinavia (4.7 years) than in other settings (6-7.4 years). Biologic disease-modifying anti-rheumatic drugs (DMARDs) were prescribed most frequently in Northern Europe (46%) and North America (38.6%) and less frequently in Eastern Europe (25.1%), Africa & Middle East (24.4%) and Southeast Asia (21.1%). Patients living in lower-resource countries had greater disease activity and damage than patients cared for in wealthier countries. Damage was associated with length of disease between onset and referral.

Interpretation. Our study documents a variability in the prevalence of disease phenotypes and disparities in therapeutic choices and outcomes across geographic areas. The disease burden was greater in lower-resource countries, possibly in relation to inequalities in the access to biologic

DMARDs, and was related to the delay in referral to specialist paediatric rheumatology care. These findings necessitate public health efforts aimed to improve equity in access to effective treatments and the structure and process of care.

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Introduction

The term juvenile idiopathic arthritis (JIA) embraces a heterogeneous group of disorders, all manifesting joint inflammation, but with different clinical phenotype, disease course, and outcomes as well as with distinct genetic background and pathophysiology[1]. It is the most common chronic rheumatologic condition in children and a leading cause of short- and long-term disability. The current International League of Associations for Rheumatology (ILAR) classification recognizes 7 disease categories, defined on the basis of clinical and laboratory features present in the first 6 months of illness[2].

A number of epidemiologic studies have shown a marked disparity in the prevalence of JIA subsets among different geographic areas or racial/ethnic groups[3]. This variability may reflect diversity in genetic determinants and, perhaps, environmental triggers or etiopathologic pathways. However, subtype frequency has been so far investigated only in single countries or particular regional settings (e.g. Scandinavia) and has never been looked for through systematic analyses on a worldwide basis.

In the past two decades, the management of JIA has been revolutionised by the earlier introduction of methotrexate (MTX), the more widespread use of intra-articular corticosteroids and, most importantly, the introduction of biologic disease-modifying anti-rheumatic drugs (DMARDs)[4,5]. This progress has increased markedly the potential to achieve disease remission or, at least, minimal levels of disease activity. However, in spite of the availability of several randomized controlled trial data[6] and the publication of consensus-based therapeutic recommendations and treatment plans[7-9], there are no standardized and universally agreed therapeutic protocols. Treatment approaches are, thus, likely variable across paediatric rheumatologists practicing in different countries. Obtaining

information on medication choices made by practitioners involved in the care of children with JIA may help to harmonize the therapeutic strategies internationally.

A number of studies have evaluated the outcomes for children with JIA. Altogether, the analyses published in the last 10 years have documented a marked decrease in the proportion of patients who experience serious long-term functional impairment as compared with the older surveys, whereas the percentage of patients who enter adulthood with persistently active disease may not be diminished[10,11]. However, some of the reported studies have included patients who received their follow-up assessment over a wide time frame, and therefore may not entirely reflect the progresses achieved with contemporary therapies. In addition, data have been mostly derived from Western European and North American nations, which implies that their results may not be generalizable. To obtain reliable insights on how children followed in international paediatric rheumatology centres are currently doing there is the need to evaluate their disease status through large-scale multinational studies.

Recently, concern has been raised that the demanding objectives mandated by the recent therapeutic progress may not be achievable for children living in low-income countries, where costly biologic DMARDs may not be available or affordable[12]. For some of these children, particularly those with the more severe systemic or polyarticular forms, the administration of prolonged doses of glucocorticoids may be the sole therapeutic option to control disease activity symptoms. However, long-term administration of these medications exposes them to their serious side effects. As a result, children living in developing countries are at greater risk of accumulating disease-related or treatment-related damage than children followed in Western paediatric rheumatology centres.

Addressing this important issue requires the investigation of whether different accessibility to certain medications leads to inequalities in disease outcomes across countries or regions.

Against this background, the primary objective of the present multinational study, named "EPidemiology, treatment and Outcome of Childhood Arthritis throughout the world" (EPOCA study), was three-fold: 1) to investigate the prevalence of JIA categories in different geographic areas; 2) to gain information on the medications administered by international paediatric rheumatologists; 3) to evaluate the disease and health status of children with JIA living in diverse parts of the world.

Methods

Study design and patient selection. To obtain figures generalizable on a worldwide basis, the involvement of a large number of countries in different continents was sought for. To reach this goal, participation in the study was first proposed to all national coordinating centres (n = 65) that are part of the Paediatric Rheumatology International Trials Organization (PRINTO) and to one leading paediatric rheumatology centre in the US and Canada. Each centre that agreed to participate was, then, asked to invite all qualified and potentially interested paediatric rheumatology centres in its country to join the study.

To avoid a bias in the selection of patients, each participating centre was asked to enrol in the study a total of 100 patients meeting the ILAR criteria for JIA[2] seen consecutively over a 6-month time frame or, if the centre did not expect to see at least 100 patients within 6 months, to enrol all patients meeting the same criteria seen consecutively within the first 6 months after the study start.

The study was carried out in compliance with the Helsinki Declaration. All participating centres obtained the approval of the study protocol by their local Ethics Committee, according to national

laws. The parents or guardians of all patients and healthy children provided written informed consent to participation in the study.

Study assessments. All patients were assessed according to a standard protocol. Each patient underwent a retrospective evaluation, based on the review of the clinical chart, and a cross-sectional assessment, made by the attending physician.

Retrospective assessment included demographic data, ILAR category; history of uveitis; results of antinuclear antibody (ANA), rheumatoid factor (RF), and HLA-B27 determination; and medications received from disease onset to cross-sectional assessment.

Cross-sectional assessment included standardized joint examination; physician's global rating of overall disease activity on a 21-numbered circle visual analogue scale (0 = no activity; 10 = maximum activity); and measurement of cumulative (ie articular and extra-articular) damage through the Juvenile Arthritis Damage Index (JADI) (0 = no damage; 89: maximum damage) [13]. Laboratory tests included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

The level of disease activity was measured using both the Juvenile Arthritis Disease Activity Score 10 (JADAS10) (0 = no activity; 40 = maximum activity) [14] and its clinical (3-item) version, cJADAS10 (0 = no activity; 30 = maximum activity)[15,16]. Inactive disease was defined according to Wallace[17] and JADAS10 and cJADAS10[16,18] criteria. PRINTO centres underwent regular remote training on how to collect data or perform patient assessments; however, the study was intended to reflect routine clinical practice.

Prior to the study visit, a parent of the child completed the national-language translation of the parent proxy-report and child self-report version, respectively, of a 4-page multidimensional

questionnaire. The questionnaire includes the assessment of child's physical function, overall well-being, intensity of pain, health-related quality of life (HRQL), and morning stiffness. For the purpose of the present study, the questionnaire was translated and cross-culturally validated into 54 languages of 52 countries, as described elsewhere[19]. To obtain reference data, the questionnaire was also completed by the parents of 4822 age-matched healthy children in all geographic areas.
Data were collected on an SQL database (Microsoft SQL Server) placed on an dedicated secure web server powered by PRINTO. Participating investigators entered their patient data through their personal member area of the PRINTO study website.

Assessment of gross domestic product (GDP). The GDP of each country in 2012 was obtained from a database of the World Bank Group (www.worldbank.org) and was expressed as US$1000 per capita. Countries were divided into those with "higher GDP" or "lower GDP" based on whether their GDP was greater or lower, respectively, than the median GDPs of all participating countries (15,500 US$).

Statistics. Descriptive statistics were reported as medians and interquartile ranges for continuous variables and as absolute frequencies and percentages for categorical variables. Comparison of quantitative and categorical variables was made by means of the nonparametric analysis of variance (Kruskal-Wallis test) and the chi-square test, respectively. Due to the large number of comparisons and because the differences could be easily visually captured, the figures for the prevalence of ILAR categories among and between geographic areas were interpreted only qualitatively. To explore the relationship between cJADAS10 and GDP, linear models were fitted on the mean cJADAS10 per country and the GDP, weighed on the number of observations per country. We examined the effect of

predictors of disease damage in a multiple logistic regression analysis, in which the JADI score was the dependent outcome. We used R statistics version 3.5.0 for all statistical analyses.

Role of the funding source. The study was funded by the IRCCS Istituto Giannina Gaslini, Genoa, Italy which provided financial support, using funds of PRINTO, to the participating centres for translation of the multidimensional questionnaire and data collection. AR had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 2011 and November 2016, 9,137 children with JIA were enrolled at 130 centres in 49 countries. For the purpose of the analysis, the countries involved in the study were grouped in 8 geographic areas: Scandinavia (n = 845), Central Europe (n = 832), Mediterranean Europe (n = 2400), Eastern Europe (n = 2044), North America (n = 523), Latin America (n = 849), Africa & Middle East (n = 1209) and Southeast Asia (n = 379). The list of countries and their grouping modality are provided in the supplementary Table S1.

The frequency of ILAR categories in geographic areas is presented in Figure 1. Systemic arthritis was distinctively more common in Southeast Asia (33%) and, to a lesser extent, Latin America (17·6%) and Africa & Middle East (16·9%) than in the other areas (4·2-8·5%). The frequency of oligoarthritis was highest in Mediterranean Europe (56·7%), and its frequency was comparable across the other areas (30·7-41·5%), except for Southeast Asia, where it was distinctly less common (10·8%). RF-negative polyarthritis was most prevalent in North America (31·5%) and less common in Southeast Asia (12·7%), whereas RF-positive polyarthritis was more frequent in Latin America (11·2%) and

Southeast Asia (7·9%). Psoriatic arthritis was uncommon in all settings (1·3-7·1%). There was a disproportion of the enthesitis-related arthritis (ERA) category in Southeast Asia (29·8%), whereas its prevalence was similar in the other areas (9·2-15%), except for a lower prevalence in Mediterranean Europe (5·4%).

Table 1 shows the main demographic features and the frequency of uveitis in geographic areas. There was a greater prevalence of females in all groups, except for Southeast Asia, in which there was an overrepresentation of males, perhaps due to the relatively greater prevalence in this area of the ERA category of JIA, which is characterized by male predilection[1]. The median age at disease onset was lower in Mediterranean Europe (3.5 years) and Scandinavia (4.7 years) than in the other geographic areas (6-7.4 years). This difference was not only accounted for by the greater prevalence of oligoarthritis (which is generally characterized by early onset) in these two geographic areas, but was also observed when the analysis was restricted to the sole category of RF-negative polyarthritis (results not shown). The prevalence of uveitis was highest in Northern Europe and Mediterranean Europe (19·2% and 19%, respectively) and lowest in Latin America (6·5%), Africa & Middle East (6·1%) and Southeast Asia (5·1%). These differences were not related to a disparity in the prevalence of oligoarthritis, which is considered the disease subtype most closely associated with uveitis[20]. However, among patients with the categories of RF-negative polyarthritis, psoriatic arthritis and undifferentiated arthritis the prevalence of uveitis was comparable to that seen in oligoarthritis in Northern Europe and Mediterranean Europe, whereas in the other geographic areas the prevalence of uveitis was much lower in these categories than in oligoarthritis.

The frequency of use of anti-arthritic medications is presented in Table 2. Systemic corticosteroids were used less frequently in North America (17%) and Central Europe (23·4%) and

most commonly in Southeast Asia (77%) and Africa & Middle East (65·9%). Intra-articular corticosteroids were administered more commonly in Northern Europe (73·5%) and Mediterranean Europe (52·6%) and less frequently in North America (12·2%). Usage of oral MTX was most popular in Northern Europe (67·1%) and less preferred in North America (33·5%), whereas this medication was given parenterally most frequently in Mediterranean Europe (48·2%) and less frequently in Eastern Europe (18·6%). Biologic DMARDs were prescribed most commonly in Northern Europe (46%) and North America (38·6%) and less frequently in Eastern Europe (25·1%), Africa & Middle East (24·4%) and Southeast Asia (21·1%).

Table 3 reports the proportion of patients with abnormal values of physician-centred and parent-reported outcome measures, composite scores and acute phase reactants and with inactive disease at cross-sectional visit. Overall, physician-centred measures of disease activity were more frequently abnormal in patients from Eastern Europe and North Africa & Middle East and less frequently impaired in patients from Western Europe and North America. Eastern Europe and North Africa & Middle East cohorts, together with those from Latin America and Southeast Asia, had a greater frequency of damage (31.9-36.2%) than the cohorts from Western Europe and North America (14.8-19.5%). The differences across geographic cohorts were less pronounced for parent-reported outcomes, although patients from Mediterranean Europe had a lower frequency of pain and morning stiffness and of impairment of physical function and HRQL than the other patient groups. The frequency of inactive disease was greater in children living in Mediterranean Europe and lower in those cared for in Scandinavia, Eastern Europe, North Africa & Middle East and Southeast Asia.

The correlation between the mean cJADAS10 value and the GDP of the country of residence of the patients is depicted in Figure 2. There was an inverse correlation between the GDP and the

cJADAS10, which means that children living in lower-resource countries had, on average, a higher level of disease activity than children living in wealthier countries. Similar findings were observed for the frequency of disease damage in at least one site, measured in patients with at least 2 years of disease duration, which was greater in countries with lower GDP than in countries with higher GDP (Figure 3).

To gain further insights into the determinants of disease damage, we examined the effect of four main potential predictors (gender, age at disease onset, disease duration at first visit at referral centre, and country GDP) in a multivariable analysis, in which the total JADI score was the dependent outcome. For sake of simplicity, we grouped patients in four "functional phenotypes": oligoarthritis, polyarthritis, ERA and systemic arthritis. Gender was not associated with damage in any functional phenotype, whereas damage was independently associated with younger age at disease onset in oligoarthritis and systemic arthritis, with country GDP in oligoarthritis, polyarthritis and ERA, and with longer disease duration at first visit in all functional phenotypes (supplementary Table S2).

Discussion

The EPOCA study provides a thorough overview of the prevalence of ILAR categories, the therapeutic choices made by the caring physician and the disease and health status in a very large cohort of children with JIA currently followed in international paediatric rheumatology centres. Because patients in 49 countries in 5 continents were enrolled in the study, our results are likely generalizable to JIA patients seen worldwide. A careful method of sampling was applied to minimize a bias in patient selection and to ensure the representativeness of the series included at each

participating centre. The reliability of the results was also guaranteed by the use of a standardized and uniform protocol of clinical assessment and data collection.

Our results confirm the wide variability in the prevalence of JIA subtypes across geographic areas observed in previous smaller studies[21-26]. The most relevant findings regard the greater prevalence of systemic arthritis and enthesitis related arthritis in Southeast Asia and of oligoarthritis in Mediterranean Europe. Conversely, systemic arthritis was less common in Northern Europe and North America and oligoarthritis and RF-negative polyarthritis were rarely observed in Southeast Asia. RF-positive polyarthritis and psoriatic arthritis were the least common categories in all geographic settings.

In addition to these diversities, patients seen in Mediterranean Europe had a markedly younger age at disease onset than those living in other geographic settings. This observation may be partly explained by the greater prevalence of oligoarthritis, which typically occurs at an early age, particularly when accompanied by the presence of circulating ANA[1]. However, a similar disparity in onset age was seen when the comparison was restricted to the RF-negative polyarthritis subset. This finding supports the emerging concept that most patients included in the ILAR category of RF-negative polyarthritis have the same clinical features as those with oligoarthritis, irrespective of the different number of affected joints[27]. A recent proposal for the revision of JIA classification has outlined early-onset ANA-positive JIA as a separate disease category[28].

A remarkable diversity was also seen in the prevalence of uveitis, which is the most frequent extra-articular complication of non-systemic JIA [1] and is most closely associated with early onset of disease and ANA positivity[20]. Ocular involvement was recorded most commonly in Northern and Mediterranean Europe and less frequently in Latin America, Africa & Middle East and Southeast Asia.

Uveitis was overall most prevalent in the oligoarthritis category in all geographic areas. However, in the four European settings and in North America it was also detected, although with some variability, in a sizeable proportion of children with RF-negative polyarthritis, psoriatic arthritis and undifferentiated arthritis. Conversely, in Latin America, Africa & Middle East and Southeast Asia uveitis was rarely seen in RF-negative polyarthritis and never identified in psoriatic arthritis and undifferentiated arthritis.

The observed phenotypic variability underscores the existence of true diversities in disease characteristics across races or ethnic groups, which may be related to different genetic determinants and, perhaps, environmental triggers. These phenotypic differences between genetically heterogeneous populations should be taken into account in future genetic analyses, etiopathogenetic investigations and classification essays.

The analysis of the use of anti-arthritic medications revealed a large variability in the frequency of choices across paediatric rheumatologists practicing in different parts of the world. Systemic corticosteroids were prescribed more commonly in Southeast Asia and Africa & Middle East than in the other geographic areas, particularly North America and Central Europe. Intra-articular corticosteroids were more popular in Northern and Mediterranean Europe than in North America. Oral administration of MTX was selected most frequently in Northern Europe and less commonly in North America, whereas the parenteral route was preferred in Mediterranean Europe, but was less favoured in Eastern Europe. The frequency of use of biologic DMARDs was highest in Northern Europe and North America and lowest in Eastern Europe, Africa & Middle East and Southeast Asia.

The inconsistencies in medication use highlights the need of large-scale consensus initiatives aimed to harmonize the therapeutic approaches across international paediatric rheumatology

practitioners. It is, however, a matter of concern that the frequency of use of the costly biologic DMARDs was lower in geographic areas that mostly include developing countries. The lesser use of these medications in lower-income settings may be at least in part related to limitations in accessibility or affordability and implies that many children with chronic arthritis in the world may not benefit from the recent advances in disease management.

Along the same line, we found that the outcomes for children living in lower-resource countries were not as good as those for children cared for in high-income geographic settings, as shown by the inverse correlation between the GDP of the country and both the level of disease activity and amount of damage, and the greater frequency of disease damage in countries with lower GDP.

Another key factor consistently associated with the presence of disease damage in all disease phenotypes was the length of disease between onset and first observation at referral centre. A number of studies have documented a delay in access to specialist paediatric rheumatology care of many children with new-onset JIA and emphasized its adverse impact on long-term disease outcomes[29,30].

Several limitations are seen in our study. It has been argued that the differences observed between geographic areas may reflect underrepresentation of milder forms of JIA, particularly oligoarthritis, because of referral bias, which could be attributed to restrictions in access to healthcare facilities. However, addressing this issue would have required a population-based analysis, which was not feasible. It is possible that only JIA patients with poor clinical status visit clinics in countries with lower GDP, and patients with better status in rich countries seek medical care. While this possibility cannot be excluded, the study was designed to incorporate a consecutive cross section of patients seen in various countries. Cross-sectional EPOCA data cannot address definitely whether the biology

of JIA is more severe in less wealthy versus wealthy countries. There was a disproportion in the number of patients included in the various geographic areas and some highly populated countries, such as China, Japan and others, could not be involved. This limitation may affect the generalizability of our findings.

In summary, our multinational survey of childhood arthritis confirms the wide variability in the prevalence of disease phenotypes, which includes the frequency of uveitis and the age at disease onset, and documents marked disparities in treatment choices by caring physicians and in disease outcomes in term of disease activity and damage. The disease burden at cross-sectional visit was greater in children living in lower GDP countries than in those cared for in higher GDP countries, which could be partially related to inequitable access to the costly biologic DMARDs. The delay in referral to specialist paediatric rheumatology care was found to be a major determinant of disease damage. Recognition of disparities in disease and health status between countries calls for public health efforts aimed to improve the structure and process of care, with the ultimate goal of improving the outcomes for children with JIA in all countries.

Panel: **Research in context**

Evidence before this study

We did a systematic search in PubMed for articles published in English between Jan 1, 1980 and June 15, 2018. Our search terms included “juvenile idiopathic arthritis”, “juvenile rheumatoid arthritis”, “juvenile chronic arthritis”, “epidemiology”, “prevalence”, “management”, “treatment”, “therapy”, “outcome”, “disease activity”, and “damage”. We searched for articles by title and abstract to identify relevant studies. Studies were also sought within reference lists of eligible studies. Our search results

showed several studies assessing the prevalence of disease phenotypes, frequency of therapeutic interventions and disease outcomes for childhood arthritis within single countries or particular regional settings. However, we didn't find any studies that assessed these issues systematically on a worldwide basis.

Added value of this study

By studying 9 137 patients with juvenile idiopathic arthritis enrolled in 49 countries in 5 continents, we found a wide variability in the prevalence of disease categories, frequency of uveitis and age at disease onset across geographic areas. There was a disparity in the therapeutic choices among international paediatric rheumatologists, which included an inequality in the prescription of the costly biologic disease-modifying anti-rheumatic drugs. Disease activity and damage were greater in patients living in lower-resource countries than in patients cared for in wealthier countries. Cumulative damage was associated with delay in referral to specialist paediatric rheumatology care.

Implication of all the available evidence

The data of our study, indicating disparities between geographic areas, present an important challenge to official bodies, regulatory agencies, scientific societies and parent and patient organizations. Lessening these inequalities requires public health efforts, which may be potentially as important as the introduction of new therapies.

Contributors

The study was designed jointly by authors AC, NR, AM and AR. Data were collected by authors GG, AAl, AAg, JDI, ED, BF, DF, SMG, CL, DJL, CM, PM, DM, SN, IO, IR-R, CSM, NS, GS, MT, NW and by collaborators. The statistical analyses were done by authors AP, FB, EHPvD and AC. The first and

subsequent versions of the report were written by authors AR and AC, edited by authors NR and AM, and revised critically by all authors and collaborators. All authors and collaborators participated in data collection, data analysis, and data interpretation, and have approved the final study report.

Declaration of interests

AR has received grant support and/or speaking or consultant fees from AbbVie, Bristol-Myers Squibb, Novartis, Pfizer, Roche, and Johnson & Johnson outside the submitted work. AC reports personal fees from Abbvie and non-financial support from Pfizer outside the submitted work. NR reports personal fees from AbbVie, Amgen, Biogenidec, Alter, AstraZeneca, Baxalta Biosimilars, Biogenidec, Boehringer, Bristol-Myers Squibb, Celgene, CrescendoBio, EMD Serono, Hoffman-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Servier, Takeda, and UCB Biosciences and other financial relationships from Bristol-Myers Squibb, GlaxoSmithKline, Hoffman-La Roche, Novartis, Pfizer, Sanofi-Aventis, Schwarz Biosciences, Abbott, Francesco Angelini SPA, Sobi, and Merck Serono outside the submitted work. AM reports personal fees from Abbvie, Boehringer, Celgene, CrescendoBio, Janssen, Meddimune, Novartis, NovoNordisk, Pfizer, Sanofi Aventis, Vertex, and Servier and other financial relationships from BMS, GlaxoSmithKline (GSK), Hoffman-La Roche, Novartis, Pfizer, Sanofi Aventis, Schwarz Biosciences, Abbott, Francesco Angelini S.P.A., Sobi, and Merck Serono outside the submitted work. GG, AA, EHPvD, CM and AP do not report competing interests.

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Table 1. Demographic features and frequency of uveitis

	Scandinavia (n = 845)	Central Europe (n = 832)	Mediterranean Europe (n = 2400)	Eastern Europe (n = 2044)	North America (n = 523)	Latin America (n = 849)	Africa & Middle East (n = 1209)	Southeast Asia (n = 379)
Girls	593 (70·2%)	538 (64·7%)	1763 (73·5%)	1303 (63·7%)	374 (71·5%)	550 (64·8%)	745 (61·7%)	164 (43·3%)
Boys	252 (29·8%)	294 (35·3%)	637 (26·5%)	741 (36·3%)	149 (28·5%)	299 (35·2%)	463 (38·3%)	215 (56·7%)
Age at onset (years)	4·7 [2·2; 9·4]	6·4 [2·7; 10·4]	3·5 [1·9; 7·3]	6·7 [3; 10·7]	7·4 [3·1; 10·9]	6·8 [3·6; 10·5]	6 [2·9; 9·8]	7 [3·9; 10·7]
Interval onset-referral (years)	0·3 [0·1; 0·8]	0·4 [0·2; 1]	0·3 [0·1; 0·9]	0·3 [0·1; 1]	0·3 [0·1; 0·8]	0·4 [0·2; 1]	0·4 [0·2; 1·5]	0·6 [0·2; 2]
Disease duration (years)	5 [2·5; 8·4]	3·8 [1·8; 6·7]	4·4 [1·9; 7·7]	3·4 [1·6; 6·2]	4·4 [1·9; 8]	4·6 [2·1; 7·3]	2·8 [1·2; 5·4]	3·9 [1·9; 6·7]
Uveitis	161 (19·2%)	94 (11·5%)	450 (19%)	183 (9·1%)	59 (11·5%)	54 (6·5%)	71 (6·1%)	19 (5·1%)

Data are median (1^{st}-3^{rd} quartile) unless otherwise indicated. $P < 0{\cdot}001$ for all comparisons

Table 2. Medications administered before the cross-sectional visit

	Scandinavia (n = 845)	Central Europe (n = 832)	Mediterranean Europe (n = 2400)	Eastern Europe (n = 2044)	North America (n = 523)	Latin America (n = 849)	Africa & Middle East (n = 1209)	Southeast Asia (n = 379)
Systemic glucocorticoids	327 (38·7)	161 (19·4)	972 (40·5)	851 (41·6)	88 (16·8)	419 (49·4)	721 (59·6)	248 (65·4)
Intra-articular glucocorticoids	621 (73·5)	168 (20·2)	1262 (52·6)	603 (29·5)	64 (12·2)	189 (22·3)	255 (21·1)	97 (25·6)
Methotrexate	635 (75·1)	483 (58·1)	1698 (70·8)	1320 (64·6)	311 (59·5)	681 (80·2)	859 (71·1)	298 (78·6)
Oral	567 (67·1)	380 (45·7)	1029 (42·9)	1078 (52·7)	175 (33·5)	480 (56·5)	505 (41·8)	170 (44·9)
Parenteral	306 (36·2)	195 (23·4)	1119 (46·6)	377 (18·4)	171 (32·7)	304 (35·8)	452 (37·4)	209 (55·1)
Leflunomide	32 (3·8)	16 (1·9)	29 (1·2)	14 (0·7)	22 (4·2)	24 (2·8)	15 (1·2)	29 (7·7)
Sulphasalazine	49 (5·8)	48 (5·8)	60 (2·5)	327 (16)	40 (7·6)	58 (6·8)	110 (9·1)	119 (31·4)
Cyclosporine	9 (1·1)	12 (1·4)	85 (3·5)	29 (1·4)	2 (0·4)	27 (3·2)	25 (2·1)	8 (2·1)
Biologic medications	389 (46)	254 (30·5)	815 (34)	514 (25·1)	202 (38·6)	275 (32·4)	295 (24·4)	80 (21·1)
Etanercept	295 (34·9)	138 (16·6)	571 (23·8)	384 (18·8)	134 (25·6)	152 (17·9)	199 (16·5)	35 (9·2)
Infliximab	105 (12·4)	26 (3·1)	61 (2·5)	19 (0·9)	22 (4·2)	40 (4·7)	17 (1·4)	12 (3·2)
Adalimumab	140 (16·6)	98 (11·8)	225 (9·4)	97 (4·7)	56 (10·7)	63 (7·4)	81 (6·7)	0 (0)

Abatacept	23 (2·7)	16 (1·9)	24 (1)	10 (0·5)	15 (2·9)	19 (2·2)	8 (0·7)	0 (0)
Anakinra	19 (2·2)	25 (3)	79 (3·3)	2 (0·1)	7 (1·3)	3 (0·4)	36 (3)	0 (0)
Canakinumab	0 (0)	12 (1·4)	25 (1)	6 (0·3)	1 (0·2)	5 (0·6)	3 (0·2)	0 (0)
Tocilizumab	17 (2)	29 (3·5)	54 (2·2)	65 (3·2)	9 (1·7)	58 (6·8)	36 (3)	40 (10·6)

Data are number (percentage). $P < 0{\cdot}001$ for all comparisons

Table 3. Frequency of abnormal values of physician-centred and parent-reported outcome measures, composite scores and acute phase reactants and of disease activity states at cross-sectional visit

	Scandinavia (n = 845)	Central Europe (n = 832)	Mediterranean Europe (n = 2400)	Eastern Europe (n = 2044)	North America (n = 523)	Latin America (n = 849)	Africa & Middle East (n = 1209)	Southeast Asia (n = 379)
Physician-centred outcomes								
Physician's global assessment > 0[a]	515 (61·0)	461 (55·4)	1097 (45·7)	1586 (77·6)	283 (54·1)	473 (55·7)	883 (73·0)	220 (58·0)
Active joint count > 0	278 (32·9)	308 (37·0)	819 (34·1)	1147 (56·1)	174 (33·3)	399 (47·0)	620 (51·3)	132 (34·8)
JADI-Articular > 0	121 (14·3)	81 (9·7)	252 (11·0)	534 (26·1)	77 (14·7)	273 (32·2)	298 (24·7)	95 (25·1)
JADI-Extra-articular > 0	71 (8·4)	62 (7·5)	218 (9·5)	326 (15·9)	29 (5·5)	120 (14·1)	238 (19·7)	69 (18·2)
JADI total score > 0	165 (19·5)	123 (14·8)	411 (17·9)	666 (32·6)	96 (18·4)	307 (36·2)	400 (33·1)	121 (31·9)
Parent-reported outcomes								
Parent's global assessment > 0[a]	612 (72·6)	548 (67·1)	1214 (51·0)	1394 (68·7)	294 (57·1)	445 (52·4)	815 (68·5)	220 (58·0)
Parent's pain assessment > 0[a]	603 (71·5)	533 (64·4)	1102 (46·2)	1387 (68·4)	328 (63·7)	441 (51·9)	733 (61·2)	193 (50·9)

Morning stiffness > 15 min	274 (32·5)	200 (24·3)	292 (12·3)	417 (20·5)	128 (24·9)	157 (18·5)	241 (20·2)	78 (20·6)
Physical function score > 0[b]	491 (58·5)	429 (51·9)	1001 (42·1)	1161 (57·5)	252 (49·2)	457 (54·0)	772 (64·2)	207 (54·8)
HRQL total score >1 SD of HC[c]	341 (41·5)	299 (37·1)	586 (25·5)	779 (39·6)	163 (32·1)	276 (32·9)	465 (39·9)	93 (24·9)
HRQL Physical >1 SD of HC[d,e]	425 (51·0)	355 (43·6)	700 (29·8)	919 (46·0)	187 (36·5)	288 (34·2)	535 (45·3)	132 (35·2)
HRQL Psychosocial >1 SD of HC[d,e]	208 (25·1)	192 (23·8)	428 (18·6)	556 (28·2)	105 (20·6)	223 (26·5)	331 (28·3)	39 (10·3)
Composite disease activity scores								
Median (1st-3rd quartile) JADAS10[f]	3·0 [1; 6·5]	3·0 [1; 6·5]	2·0 [0; 6·0]	5·5 [1·5; 11]	3·0 [0·5; 7]	3·5 [0; 10·7]	5·5 [1; 11·0]	3·3 [0·5; 8·5]
Median (1st-3rd quartile) cJADAS10[g]	3 [0·5; 6·5]	2·5 [0·5; 7]	1·5 [0; 5·5]	5·0 [1; 10·5]	2·0 [0; 6·8]	2·5 [0; 9·5]	5·0 [1; 10]	2·0 [0; 6·0]
Inactive disease								
Wallace criteria	218 (25·8)	269 (32·3)	1084 (45·2)	378 (18·5)	187 (35·8)	294 (34·6)	269 (22·2)	101 (26·6)
JADAS10 criteria	187/636 (29·4)	173/556 (31·1)	854/1893 (45·1)	429/1815 (23·6)	129374 (34·5)	264/721 (36·6)	283/1075 (26·3)	114/348 (32·8)

cJADAS10 criteria	280 (33·1)	297 (35·7)	1161 (48·4)	519 (25·4)	216 (41·3)	354 (41·7)	335 (27·7)	152 (40·1)

Data are number (percentage) unless otherwise indicated; JADI: Juvenile Arthritis Damage Index, HRQL: health related quality of life; JADAS: Juvenile Arthritis Disease Activity Score; cJADAS: clinical (3-item) Juvenile arthritis Disease Activity Score; SD: standard deviation; HC: healthy children. $P < 0{\cdot}001$ for all comparisons

[a]All measured with a visual analogue scale, with range from 0 (best) to 10 (worst)

[b]Score ranges from 0 (no disability) to 45 (maximum disability)

[c]Score ranges from 0 to 30, with higher scores indicating worse HRQL[d]Score ranges from 0 to 15, with higher scores indicating worse HRQL

[e]The SD of HC was calculated for each geographic area on questionnaires completed by the parents of HC

[f]Score ranges from 0 (no activity) to 40 (maximum activity)

[g]Score ranges from 0 (no activity) to 30 (maximum activity)

Legend to figures

Figure 1: Frequency of International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis in the 8 geographic areas. RF: rheumatoid factor

Figure 2: Linear model of the relationship between the mean cJADAS10 per country and the gross domestic product per capita (x 1,000 US$), weighed on the number of observations per country.

Figure 3: Comparison of the frequency of damage, measured in patients with at least 2 years of disease duration and defined as a Juvenile Arthritis Damage Index score > 0, between countries with a gross domestic product (GDP) per capita higher or lower than the median value of all participating countries (15,500 US$). International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis are grouped into “functional categories”: oligoarthritis includes patients with persistent oligoarthritis, psoriatic arthritis and undifferentiated arthritis, and polyarthritis includes rheumatoid factor-positive and rheumatoid factor -negative polyarthritis. $P < 0{\cdot}001$ for all functional categories.

Figure 1

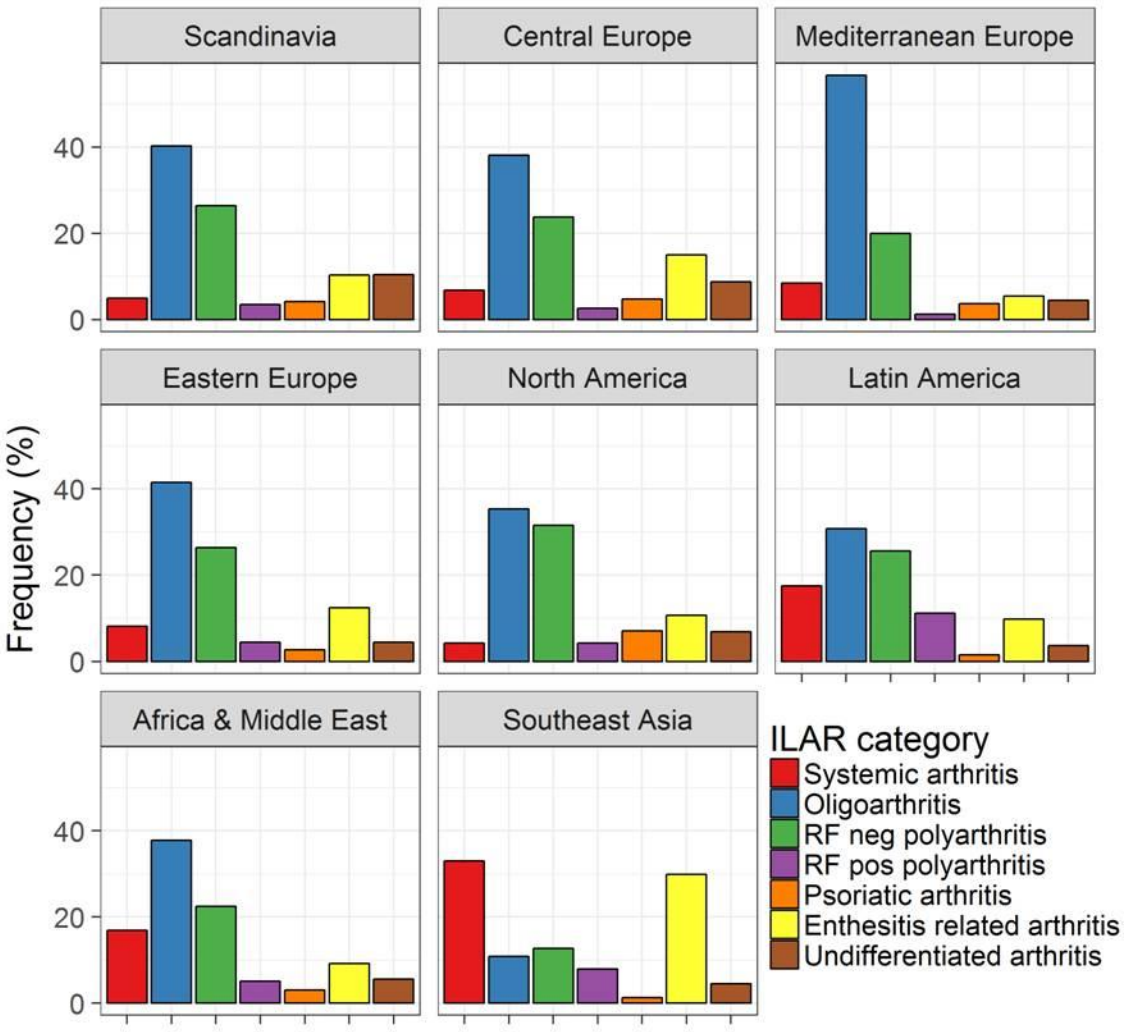

Scandinavia
Central Europe
Mediterranean Europe
Eastern Europe
North America
Latin America
Africa & Middle East
Southeast Asia
Frequency (%)
0
20
40
ILAR category
Systemic arthritis
Oligoarthritis
RF neg polyarthritis
RF pos polyarthritis
Psoriatic arthritis
Enthesitis related arthritis
Undifferentiated arthritis

Figure 2

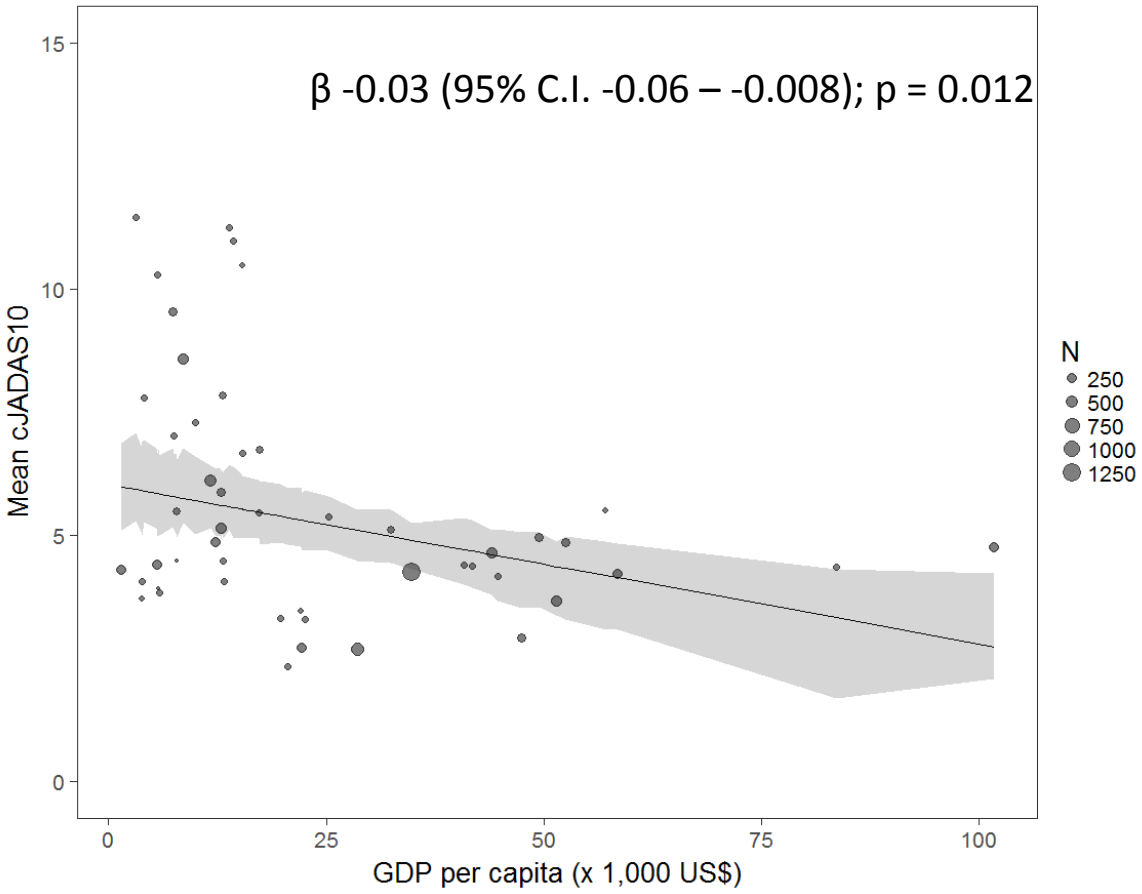
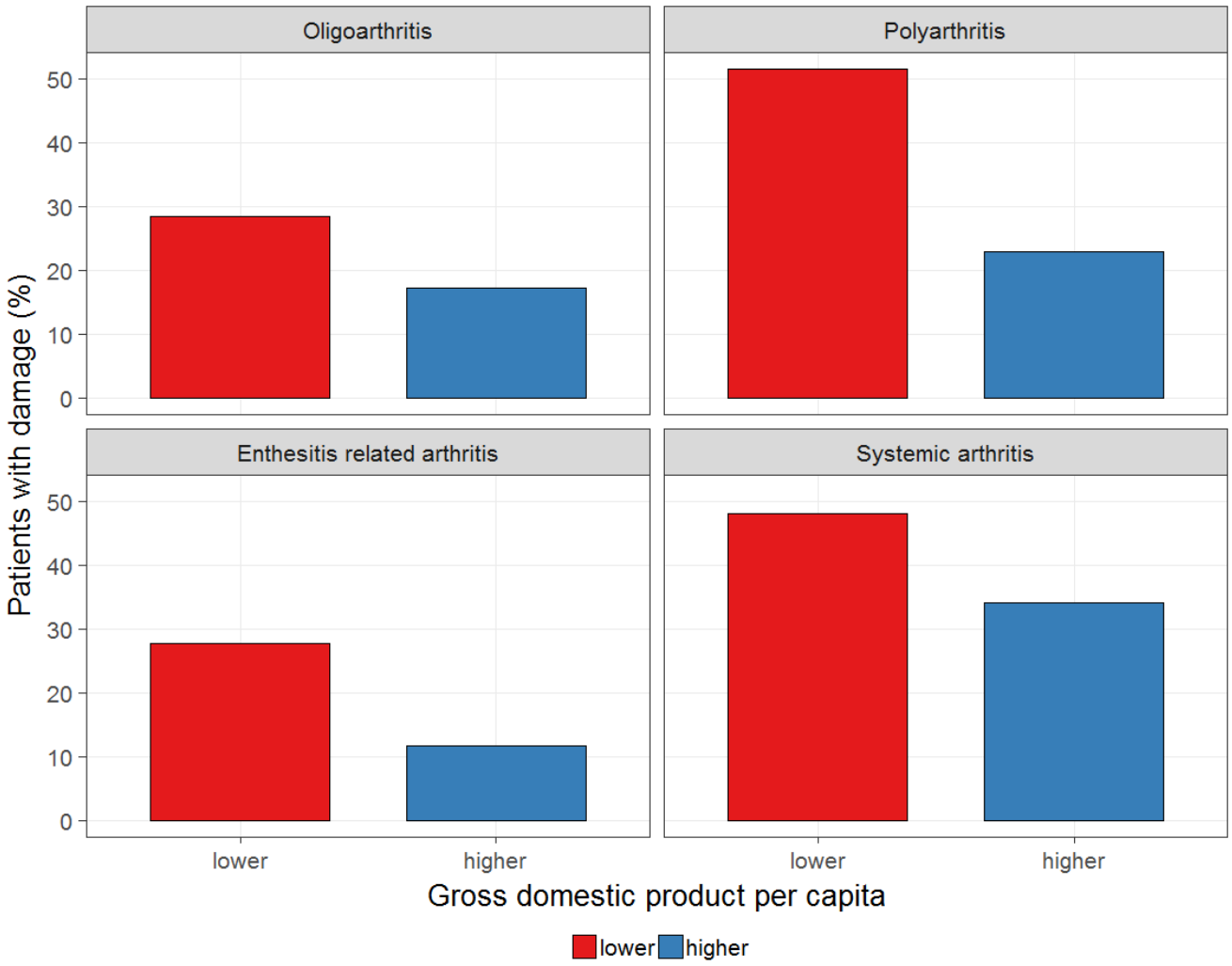

β -0.03 (95% C.I. -0.06 – -0.008); p = 0.012
Mean cJADAS10
15
10
5
0
0
25
50
75
100
GDP per capita (x 1,000 US$)
N
250
500
750
1000
1250

Figure 3


Oligoarthritis
Polyarthritis
Enthesitis related arthritis
Systemic arthritis
Patients with damage (%)
0
10
20
30
40
50
lower
higher
Gross domestic product per capita
lower
higher

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Supplementary Table 1. Geographic areas, participating countries and centres and number of patients enrolled.

Geographic area	Country	Number of centres	Number of patients
Africa & Middle East	Algeria	1	70
	Egypt	1	100
	Georgia	1	100
	Islamic Republic of Iran	2	122
	Libya	1	100
	Oman	2	58
	Saudi Arabia	1	100
	South Africa	1	91
	Turkey	5	468
Central Europe	Belgium	2	100
	Germany	6	322
	Netherlands	2	210
	Switzerland	1	100
	United Kingdom	1	100
Eastern Europe	Bulgaria	2	200
	Croatia	1	100
	Czech Republic	1	103
	Estonia	1	110
	Hungary	2	206
	Latvia	1	100
	Lithuania	1	101

	Poland	2	156
	Romania	6	311
	Russian Federation	1	100
	Serbia	3	249
	Slovakia	2	108
	Slovenia	1	100
	Ukraine	1	100
Latin America	Argentina	5	373
	Brazil	3	231
	Chile	1	49
	Colombia	1	22
	Ecuador	1	23
	Mexico	1	100
	Paraguay	1	51
Mediterranean Europe	France	1	100
	Greece	3	275
	Israel	2	118
	Italy	18	1300
	Portugal	1	80
	Spain	6	527
North America	Canada	2	208
	United States	3	315
Scandinavia	Denmark	3	303
	Finland	5	173

	Norway	3	301
	Sweden	2	68
Southeast Asia	India	3	275
	Thailand	1	104

Supplementary Table 2. Multiple regression analysis of predictors of damage, measured in patients with at least 2 years of disease duration and defined as a Juvenile Arthritis Damage Index score > 0.

	Estimate	Standard error	*P*
Oligoarthritis			
Country GDP per capita (x 1000 US$)	-0·009	0·002	<0·001
Age at onset (years)	0·035	0·012	0·004
Interval onset-referral (years)	0·089	0·022	<0·001
Sex	0·093	0·103	0·364
Polyarthritis			
Country GDP per capita (x 1000 US$)	-0·043	0·004	<0·001
Age at onset (years)	0·046	0·025	0·068
Interval onset-referral (years)	0·297	0·042	<0·001
Sex	0·081	0·232	0·726
Enthesitis related arthritis			
Country GDP per capita (x 1000 US$)	-0·017	0·004	<0·001
Age at onset (years)	0·056	0·031	0·069
Interval onset-referral (years)	0·097	0·047	0·040
Sex	0·212	0·221	0·338
Systemic arthritis			
Country GDP per capita (x 1000 US$)	-0·010	0·015	0·494
Age at onset (years)	-0·189	0·072	0·009
Interval onset-referral (years)	0·690	0·109	<0·001
Sex	-0·032	0·507	0·950

GDP: gross domestic product