

Determinants of the prevalence of gout in the general population: a systematic review and meta-regression

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Determinants of the prevalence of gout in the general population: a systematic review and meta-regression

José M. A. Wijnands · Wolfgang Viechtbauer · Kristof Thevissen ·
Ilja C. W. Arts · Pieter C. Dagnelie · Coen D. A. Stehouwer · Sjef van der Linden ·
Annelies Boonen

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Abstract Studies on the occurrence of gout show a large range in estimates. However, a clear insight into the factors responsible for this variation in estimates is lacking. Therefore, our aim was to review the literature on the prevalence and incidence of gout systematically and to obtain insight into the degree of and factors contributing to the heterogeneity. We searched MEDLINE, EMBASE, and Web of Science (January 1962 to July 2012) to identify primary studies on the prevalence and incidence of gout in the general population. Data were extracted by two persons on sources of clinical heterogeneity, methodological heterogeneity, and variation in outcome reporting. Meta-analysis and meta-regression analysis were performed for the prevalence of gout. Of 1,466 articles screened, 77 articles were included, of which 71 reported the prevalence and 12 the incidence of gout. The pooled prevalence (67 studies; $N = 12,226,425$) based on a random effects model was 0.6 % (95 % CI 0.4; 0.7), however there was a high level

of heterogeneity ($I^2 = 99.9$ %). Results from a mixed-effects meta-regression model indicated that age ($p = 0.019$), sex ($p < 0.001$), continent ($p < 0.001$), response rate ($p = 0.016$), consistency in data collection ($p = 0.002$), and case definition ($p < 0.001$) were significantly associated with gout prevalence and jointly accounted for 88.7 % of the heterogeneity. The incidence in the total population ranged from 0.06 to 2.68 per 1,000 person-years. In conclusion, gout is a common disease and the large variation in the prevalence data on gout is explained by sex, continent on which the study was performed, and the case definition of gout.

Keywords Gout · Prevalence · Incidence · Systematic review · Meta-regression

Introduction

Gout is an inflammatory arthritis which has been associated with the metabolic syndrome, hypertension, kidney

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J. M. A. Wijnands (✉) · K. Thevissen · S. van der Linden ·
A. Boonen
Division of Rheumatology, Department of Internal Medicine,
Maastricht University Medical Center, P.O. Box 5800,
6202 AZ Maastricht, The Netherlands
e-mail: j.wijnands@maastrichtuniversity.nl

J. M. A. Wijnands · I. C. W. Arts · P. C. Dagnelie ·
S. van der Linden · A. Boonen
School for Public Health and Primary Care (CAPHRI),
Maastricht University, Maastricht, The Netherlands

W. Viechtbauer
Department of Psychiatry and Psychology, Maastricht
University, Maastricht, The Netherlands

I. C. W. Arts · P. C. Dagnelie · C. D. A. Stehouwer
CARIM School for Cardiovascular Diseases, Maastricht
University, Maastricht, The Netherlands

I. C. W. Arts · P. C. Dagnelie
Department of Epidemiology, Maastricht University, Maastricht,
The Netherlands

C. D. A. Stehouwer
Department of Internal Medicine, Maastricht University Medical
Center, Maastricht, The Netherlands

disease, and cardiovascular disease [1]. Partially due to the associated co-morbidity, gout has a substantial impact on a patient's health-related quality of life [2] and may be a major health issue in affluent countries [3]. Studies on the prevalence and incidence of gout in the general population show a large range in estimates and an increase in these estimates has often been suggested [4]. However, a clear insight into the factors contributing to this variation in estimates is lacking. Meta-analysis and meta-regression are helpful techniques that may shed light on the reasons for the heterogeneity in the findings.

In systematic reviews, two major types of heterogeneity can be distinguished, i.e. clinical and methodological heterogeneity. *Clinical heterogeneity* refers to differences in patient characteristics or treatment regimen, while *methodological heterogeneity* refers to variation in study design, outcome measures, and the duration of follow up. Several sources of heterogeneity emerged from previous studies on the prevalence and incidence of gout, such as age, sex, geographic region (representing ethnic background and susceptibility to gout) [5], and case definition [6–9]. In contrast to these studies, meta-regression can assess and quantify the effect of these factors on the occurrence of gout simultaneously.

The aim of the present study was to review literature on the prevalence and incidence of gout systematically and to perform a meta-analysis including meta-regression analysis to obtain insight into the degree of and factors contributing to the heterogeneity.

Materials and methods

Data sources and searches

MEDLINE, EMBASE, and Web of Science were searched for primary studies on the prevalence and/or incidence of gout using the free text- and MeSH-search term “gout” with subheading “epidemiology”, and the search term “gout” in combination with “epidemiology”, “prevalence”, and “incidence”. Replacing the search term “gout” by the keywords “crystal arthritis” or “crystal arthropathy” did not lead to additional titles.

The search was limited to articles published in English, German, French, Spanish, or Dutch. Letters, comments, and editorial citations were excluded by adding the search term: NOT “letter” [Publication Type] NOT “comment” [Publication Type] NOT “editorial” [Publication Type]. The search was executed on 22 February 2010 and was last updated on 1 July 2012. References were imported in Endnote and duplicates were removed. Finally, hand search of bibliographies of relevant articles was performed.

Study selection

Two reviewers (JW, SvL) independently screened titles and (if available) the corresponding abstracts. Studies were included if; (1) the aim of the study was to estimate the prevalence and/or incidence of gout; (2) primary data, derived from a new or original research study, were reported; (3) the general population was the target. Any disagreement was resolved after consensus between the two reviewers (JW, SvL). Full-text articles of the selected titles were accessed via PUBMED or were requested from the corresponding authors, after which a full-text review was performed by the first reviewer (JW).

Data extraction

Data were extracted by two independent reviewers (JW, KT). In case of disagreement, a third reviewer (AB) was consulted and consensus reached. In addition to study identification, data extraction comprised sources of *clinical heterogeneity* (mean age of the sample, male/female distribution, country, setting), and sources of *methodological heterogeneity* (year in which data collection began, sampling frame to recruit study population, sampling method, exclusion criteria, response rate, representativeness of study population for the general population, case definition for gout, duration of follow up in case of an incidence study, consistency in case finding and case definition throughout the study). Finally variables related to *outcome reporting* were extracted (figures on prevalence and/or incidence including its numerator and denominator, confidence intervals, measure of prevalence and/or incidence).

Data synthesis and analysis

Variables in meta-regression analyses

With regard to *clinical heterogeneity*, the percentage of males and the mean age of the sample were included in the analyses as continuous variables. Continent of study execution was subdivided into seven categories: Europe, North America, South America, Africa, Asia, Oceania, and “indigenous people” (composed of Maori, Aborigines and Inuit). Indigenous people were analysed as a separate category since these individuals represent a unique population in which high gout prevalences are generally found, partly due to a marked genetic predisposition for hyperuricaemia [6, 10]. The setting was subdivided into urban, rural, or a combination of both.

With respect to *methodological heterogeneity*, year in which data collection began (or publication year if not reported) was handled as a continuous variable. The following four variables were scored dichotomously: response

rate was deemed appropriate if either 75 % or more of the sampled subjects participated, or if participation was <75 % but data analysis included a non-responder analysis showing no difference in participants' characteristics between responders and non-responders; the sampling method was appropriate if a random selection was used; consistency in data collection was appropriate if the approach was similar across all participants; and representativeness of the study population if the methods used to select the study population were deemed appropriate to obtain a studied sample truly representative of the general population. The following two variables were categorized. The sampling frame was categorized into census list, household register, convenience sample, general practitioner database, hospital database, list of specific group of subjects (employees of a company), and geographic sampling. The case definition of gout was categorized into seven categories. The first two categories comprised a self-reported diagnosis of gout or self-reported symptoms suggestive of gout recorded by a questionnaire or an interview. Categories 3 and 4 involved a 2-step case definition in which a self-reported screening question (as in categories 1 and 2) was followed by a confirmation of cases based on additional clinical criteria, physical exam, or ICD codes. In case health professionals examined all participants the case definition was coded with category 5. Finally, ICD codes/free text search in general practitioner medical records or hospital medical records were coded as categories 6 and 7, respectively.

For *outcome reporting*, the measure of prevalence was dichotomized as lifetime or period, and the measure of incidence as proportion or incidence rate.

Prevalence studies

Where possible, data from individual articles were subdivided into independent *samples* to allow for separate results based on sex, ethnic group, setting, or location (e.g. instead of computing a single prevalence rate for an article, prevalence rates for the male and female subsamples were included in the meta-analysis). To avoid statistical dependence in the estimates, if an article reported the prevalence of a specific population over time, only the most recent estimation was used. The prevalence for each sample was calculated using raw data (i.e. number of cases divided by the sample size). In case of a missing numerator, the number of cases was back-calculated from the reported prevalence rate (%) and the sample size.

Prevalence rates were transformed with the logit (log odds) transformation before further analysis [11, 12]. The sampling distribution of a logit transformed rate is better approximated by a normal distribution, especially when the true prevalence rate is close to zero. For samples with zero

cases, we used the standard bias/continuity correction of adding $\frac{1}{2}$ to the number of cases and non-cases before computing the logit transformed rates.

To estimate the pooled prevalence, the transformed prevalence rates were combined in a meta-analysis using a random-effects model. The pooled result and the corresponding confidence interval bounds were then back-transformed to yield an estimate of the average prevalence rate. Based on the results from the random-effects model, a 95 % prediction interval was calculated, which provides an estimate of the range where future prevalences are expected to fall in 95 % of the individual study settings [13]. The amount of heterogeneity between studies was estimated using the empirical Bayes estimator and reported in terms of the I^2 -statistic [14].

A sensitivity analysis, excluding studies with “low study quality”, was not performed because of scientific objections to computing a quality rating score or weighting of quality items [15]. Instead, the contribution of methodological and clinical aspects of diversity (including aspects of quality) to the heterogeneity was explored by performing meta-regression analyses using mixed-effects models [16]. Univariable and multivariable models were fitted, using the empirical Bayes method to estimate the amount of residual heterogeneity [14], and model coefficients were tested using the Knapp and Hartung method [17]. Pairwise comparisons were obtained for categorical variables with p values adjusted by Holm's method [18]. We estimated the amount of heterogeneity accounted for by moderators by computing the proportional reduction in the amount of heterogeneity when the moderators are included in the model [16].

Sensitivity analyses were performed using two alternative modeling approaches for the multivariable meta-regression analysis, i.e. using a mixed-effects logistic regression model with random effects per observed outcome and a beta-binomial model with logit link function. All analyses were performed with R using the packages *metafor* [19], *lme4* [20], and *VGAM* [21].

Incidence studies

Due to the small number of articles on the incidence of gout we chose to describe these studies and to inspect the data carefully rather than conducting meta-regression analyses.

Results

Study selection

The literature search provided a total of 2,126 hits (PubMed: $n = 1,018$, EMBASE: $n = 664$, Web of

Science: $n = 444$). After removing duplicates, 1,466 titles, the majority including abstracts, were screened for eligibility, resulting in 86 candidate titles. For 10 studies no full text could be retrieved despite the use of interlibrary loan services and a search for contact details of first authors.

After full text review 12 articles did not meet the inclusion criteria (3 titles referred to congress abstracts only, 3 did not provide primary data, and in 6 the target was not the general population). Five further articles were excluded because they reported on the same study population and the paper providing the most complete data on clinical and methodological heterogeneity was considered. The hand search of bibliographies of relevant articles resulted in an additional 7 articles and 11 new articles were included after the last update (1 July 2012). Finally, 77 articles were included, of which 71 reported prevalence and 12 incidence (Fig. 1).

Prevalence

Study characteristics

In the 71 articles [22–92], 172 independent samples were identified (Online Resource 1). Table 1 presents characteristics of these samples. Studies were carried out between 1950 and 2012. The total number of individuals in these 71 articles was unknown as denominators were not reported in all studies. Approximately 50.9 % (range 0–100 %) of the total population was male with an average age of ~ 45 (31–79) years. Studies were mainly conducted in Asia (61 out of 172, 35.5 %) and Europe (48 out of 172, 27.9 %). Fifty-five (38.2 % of 144) studies used a census and 37 (25.7 % of 144) a general practitioner database for sampling individuals. The case definition most frequently used was the 2-step approach where self-reported symptoms was followed by further confirmation (52 out of 172, 30.2 %).

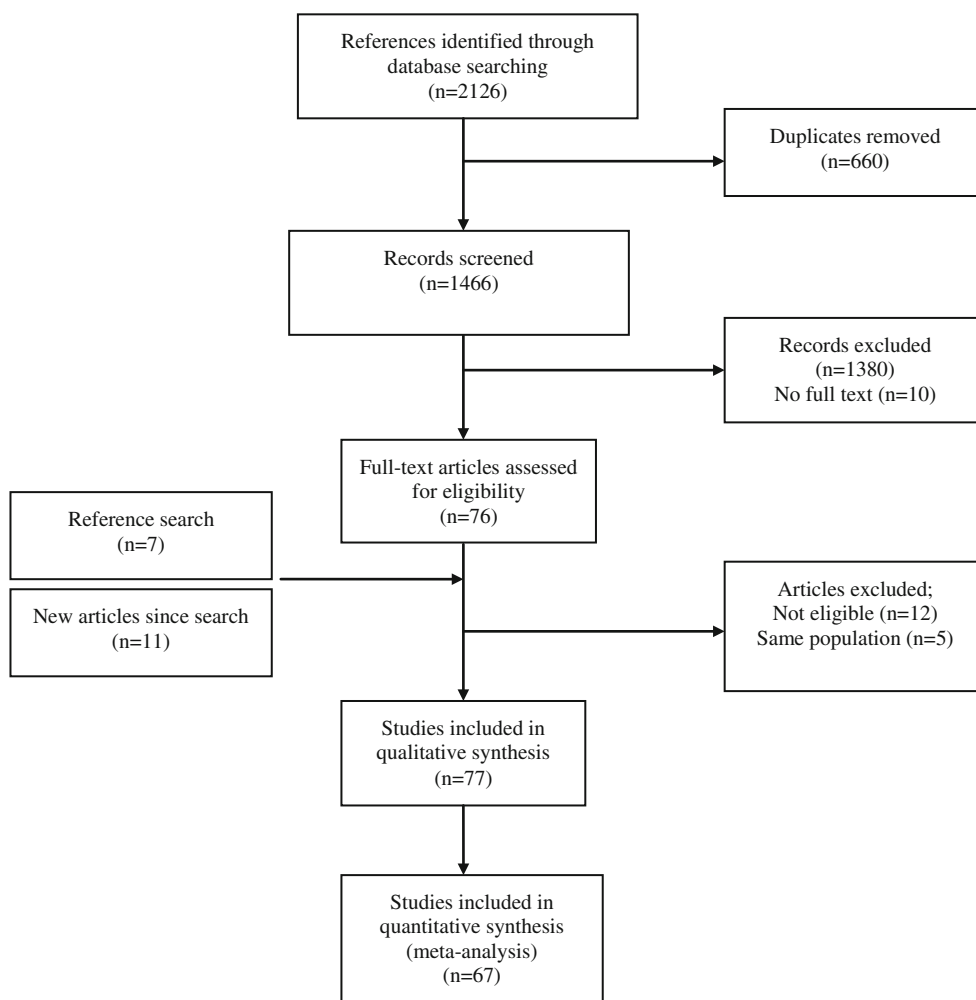


Fig. 1 Selection of studies for the systematic review of the prevalence and incidence of gout

Table 1 Characteristics of 71 studies reporting the prevalence of gout that were considered as sources of heterogeneity

Clinical heterogeneity	Methodological heterogeneity	Outcome reporting
<i>Mean age (n = 129)</i>	<i>Start data collection (n = 172)</i>	<i>Measure of prevalence (n = 166)</i>
Range 31–79	Range 1950–2012	1. Life time prevalence (n = 141)
Median 43.0	Median 1994	2. Period prevalence (n = 25)
Mean 44.4	Mean 1990	
<i>% Males (n = 165)</i>	<i>Response rate (n = 172)</i>	
Range 0–100	1. Adequate: n = 119 ^a	
Median 48.8	2. Non-adequate: n = 53	
Mean 50.9	<i>Sampling method (n = 172)</i>	
<i>Continent (n = 172):</i>	1. Random: n = 128	
1. Europe: n = 48	2. Non-random: n = 44	
2. North America: n = 16	<i>Consistency data collection (n = 172)</i>	
3. South America: n = 9	1. Approach was similar across all participants: n = 157	
4. Africa: n = 6	2. Approach was not similar across all participants: n = 15	
5. Asia: n = 61	<i>Sampling frame (n = 144):</i>	
6. Oceania: n = 22	1. Census: n = 55	
7. Indigenous people: n = 10 (composed of Maori, Aborigines and Eskimos)	2. Household register: n = 27	
<i>Setting (n = 159)</i>	3. Convenience sample: n = 8	
1. Rural: n = 37	4. General practitioner database: n = 37	
2. Urban: n = 54	5. Hospital database: n = 4	
3. Combination urban en rural: n = 68	6. List of specific group of subjects: n = 5 (e.g. employees of a company)	
	7. Geographic sampling: n = 8	
	<i>Representation general population (n = 172)</i>	
	1. Yes: n = 26	
	2. No: n = 146	
	<i>Case definition (n = 172)</i>	
	1. Self-reported diagnosis: n = 18	
	2. Self-reported symptoms: n = 11	
	3. 2-step approach diagnosis: n = 10	
	4. 2-step approach symptoms: n = 52	
	5. Diagnose health professional: n = 46	
	6. Medical record general practitioner: n = 31	
	7. Medical record hospital: n = 4	

^a Response rate ≥ 75 or < 75 % but data analysis included a non-responder analysis

Meta-analysis

The meta-analysis was conducted based on 165 (95.9 %) samples extracted from 67 studies where the raw prevalence was available or could be computed. In total, the 165 samples comprised 237,464 cases and a sample size of 12,226,425 individuals. The observed prevalence ranged from 0 to 26.2 % with an unweighted mean of 1.6 %

(SD = 3.3 %; median = 0.3 %). Thirty-two samples (19.4 %) reported a prevalence of 0 %. The pooled (back-transformed) estimated average prevalence based on the meta-analysis was 0.6 % (95 % CI 0.4; 0.7). The 95 % prediction interval was 0.03–11.16 %. Note that 10 samples with sample sizes larger than 100,000 comprised 94.2 % of the total sample size. The I^2 statistic indicated a very high level of heterogeneity (99.9 %).

Table 2 Univariable meta-regression analyses on the prevalence of gout

Moderator	Univariable analyses				
	β	SE	OR (95 %CI)	<i>p</i> value	<i>R</i> ²
<i>Clinical heterogeneity</i>					
Mean age	0.0625	0.0190	1.06 (1.03; 1.11)	0.001	8.8
% male	0.0153	0.0026	1.02 (1.01; 1.02)	<0.001	20.7
Continent				<0.001	31.2
<i>Reference = Europe</i>					
<i>F(df = 6, df = 158) = 10.8</i>					
North America	0.9253	0.3926	2.52 (1.16; 5.48)	0.020	
South America	-0.7192	0.5250	0.49 (0.17; 1.37)	0.173	
Africa	-0.2869	0.7298	0.75 (0.18; 3.17)	0.695	
Asia	-0.9152	0.2895	0.40 (0.23; 0.71)	0.002	
Oceania	1.2495	0.3741	3.49 (1.67; 7.30)	0.001	
Indigenous people	1.8119	0.4881	6.12 (2.33; 16.05)	<0.001	
Setting				0.641	0.0
<i>Reference = Rural</i>					
<i>F(df = 2, df = 149) = 0.4</i>					
Urban	0.1258	0.3874	1.13 (0.53; 2.44)	0.746	
Combination urban and rural	0.3271	0.3666	1.39 (0.67; 2.86)	0.374	
<i>Methodological heterogeneity</i>					
Start data collection	-0.0032	0.0088	1.00 (0.98; 1.01)	0.719	0.0
Response rate	0.1881	0.2903	1.21 (0.68; 2.14)	0.518	0.0
Sampling method	0.0644	0.3062	1.07 (0.58; 1.95)	0.834	0.0
Consistency data collection	-0.5815	0.5175	0.56 (0.20; 1.55)	0.263	0.2
Sampling frame ^a				0.075	4.9
<i>Reference = Census</i>					
<i>F(df = 6, df = 130) = 2.0</i>					
Household register	0.0007	0.4071	1.00 (0.45; 2.24)	0.999	
Convenience sample	1.5200	0.6300	4.57 (1.31; 15.90)	0.017	
General practitioner database	0.2113	0.3602	1.24 (0.61; 2.52)	0.558	
Hospital database	0.7081	0.8446	2.03 (0.38; 10.79)	0.403	
List of specific group of subjects	-0.7264	0.7809	0.48 (0.10; 2.27)	0.354	
Geographic sampling	-1.1355	0.6900	0.32 (0.08; 1.26)	0.102	
Representativeness study population	-0.3873	0.3764	0.68 (0.32; 1.43)	0.305	0.0
Case definition				<0.001	33.6
<i>Reference = Self-reported diagnosis</i>					
<i>F(df = 6, df = 158) = 11.9</i>					
Self-reported symptoms	-0.3202	0.5300	0.73 (0.25; 2.07)	0.547	
2-step approach diagnosis	-0.9793	0.5500	0.38 (0.13; 1.11)	0.077	
2-step approach symptoms	-2.8317	0.3896	0.06 (0.03; 0.13)	<0.001	
Diagnose health professional	-1.7812	0.4016	0.17 (0.08; 0.37)	<0.001	
Medical record general practitioner	-1.8842	0.4091	0.15 (0.07; 0.34)	<0.001	
Medical record hospital	-1.1179	0.7536	0.33 (0.07; 1.45)	0.140	
<i>Outcome reporting</i>					
Measure of prevalence					
<i>Reference = Life-time prevalence</i>					
Period prevalence	0.3056	0.3863	1.36 (0.63; 2.91)	0.430	0.0

SE standard error, *R*² = the amount of heterogeneity accounted for by the predictor in %

Univariable meta-regression analyses

Mean age, sex, continent, and case definition were significantly associated with the prevalence, accounting respectively for 8.8, 20.7, 31.2, and 33.6 % of the heterogeneity (Table 2). Start of data collection was not significantly associated with the prevalence of gout (*p* = 0.719). Pair-wise comparison showed that in indigenous people (Maori,

Aboriginals, Inuit) and Oceania higher prevalences were found compared to Europe (*p* = 0.004; *p* = 0.013), South America (*p* = 0.002; *p* = 0.009), and Asia (*p* < 0.001; *p* < 0.001) (Fig. 2 and Online Resource 2). Europe and North America reported higher prevalences in comparison to Asia (*p* = 0.022; *p* < 0.001). Within 'case definition', self-reported approaches resulted in higher estimates of prevalences compared with: a 2-step approach using gout

symptoms as a screening question; diagnoses by a health professional; or ICD code/free text in medical records of general practitioners (range p values <0.001–0.029). The 2-step approach based on self-reported diagnosis, diagnosis by a health professional, and ICD code in medical records of general practitioners resulted in a significantly higher prevalence than the 2-step approach based on self-reported symptoms ($p = 0.002$; $p = 0.011$; $p = 0.039$). Finally, within the sampling frame, a convenience sample frame estimates higher prevalence compared with geographic sampling ($p = 0.048$).

Multivariable meta-regression analysis

Table 3 shows the results of the multivariable analysis. Due to collinearity between case definition and sampling frame, the latter was not included in the total model. The multivariable analysis included 109 (63.4 %) samples, comprising a reduced total sample size of 3,813,476 individuals from 47 studies due to missing data on the sources of clinical and methodological heterogeneity. The variables age ($p = 0.019$), sex ($p < 0.001$), continent ($p < 0.001$), case definition ($p < 0.001$), response rate ($p = 0.016$), and consistency in data collection ($p = 0.002$) were significantly associated with gout prevalence (Table 3). Pairwise comparison showed that in indigenous people significantly higher prevalence rates were reported compared to all continents (all $p < 0.01$), except for Africa (supplementary material 2). Note that results on Africa are based on a small number of samples. Studies performed in Oceania and North America estimated significantly higher gout prevalences compared to: Asia ($p < 0.001$; $p < 0.001$); South America ($p = 0.001$; $p = 0.003$); and Europe ($p < 0.001$; $p = 0.002$). Within ‘case definition’, self-reported symptoms and the 2-step approach based on self-reported diagnosis provided significantly higher prevalences in comparison to a 2-step approach based on self-reported symptoms ($p = 0.001$; $p = 0.001$) or a diagnosis by a health professional ($p < 0.001$; $p = 0.002$).

The multivariable model accounted for 88.7 % of the variance. The predicted prevalences based on this model closely corresponded with the observed prevalences in the individuals studies (Fig. 3). Therefore, the prevalence for any given population may be estimated based on the multivariable model as shown in Table 3. For example, a study performed in 2012 in an Asian population (combining both urban and rural area) with a mean age of 44.4 years and 50.9 % males, in which gout is classified using a 2-step approach based on symptoms (representing the population with characteristics that are most frequently reported on), would provide an estimated life time prevalence of 0.03 % (95 %CI 0.01; 0.09). In contrast, a study performed in 2012 in North America with a similar age and

sex distribution, but with a gout diagnosis based on self-reported symptoms, would provide an estimated life time prevalence of 1.37 % (95 %CI 0.43; 4.24). A study with similar characteristics as the latter, but with a 20 years older population (mean age = 64.4 yrs), would result in an estimated prevalence of 2.95 % (95 %CI 0.94; 8.86).

Sensitivity analyses

Sensitivity analyses were performed using two alternative modeling approaches for the multivariable regression analysis: (1) using a mixed-effects logistic regression model with random effects per observed outcome and (2) a beta-binomial model with logit link function. The conclusions with respect to the relevant predictors remained largely unchanged. However, using the first alternative method, the prevalence in Asia was no longer different from the one in Europe, whereas the case definition 2-step approach based on self-reported diagnosis was now significantly different from self-reported diagnosis. Using the beta-binomial model, the case definitions self-reported symptoms and the 2-step approach based on self-reported diagnosis were significantly different from self-reported diagnosis, but the 2-step approach based on self-reported symptoms and a diagnosis by a health professional were no longer different from each other.

Incidence

Study characteristics

Incidence rates were reported in 12 articles [34, 44, 50, 54, 67, 84, 93–98]. Studies were carried out between 1950 and 2012. Due to incomplete method description and missing numerators, denominators, or the number of subjects in the study, the measure of incidence (incidence proportion or incidence rate) was not always clear.

Study results

By scrutinizing extracted data, we observed an influence of duration of follow-up of the cohort on the reported incidence (Table 4). Within the studies with a follow-up ≤ 2 years or in studies reporting annual rates, incidences ranged between 0.06/1,000 and 1.80/1,000, with higher incidences in men (0.12/1,000 to 1.98/1,000) than in women (0.0/1,000 to 0.74/1,000). Within studies with a longer follow-up (>2 years) an incidence of 2.68/1,000 person-years was reported, with incidences varying between 2.8/1,000 to 4.42/1,000 in men and 1.32/1,000 to 1.4/1,000 in women. Follow-up periods ranged from 7 to 52 years. In a study performed in Maori with 11 year follow-up, an incidence of 103/1,000 in men and 43/1,000 in women was reported [34].

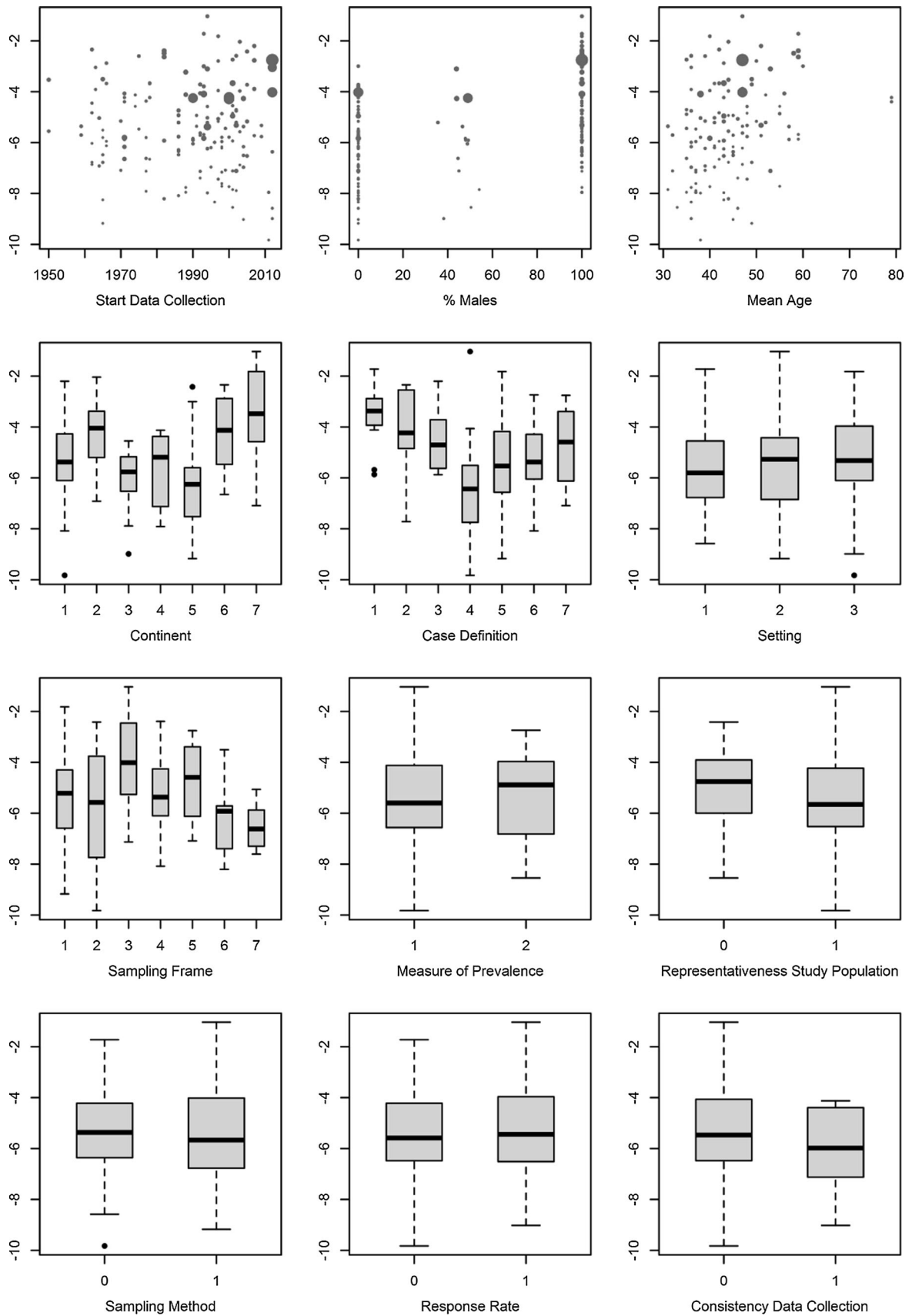


Fig. 2 Scatterplots for the continuous predictors and *boxplots* for the categorical predictors with the y-axis corresponding to the logit transformed prevalence rates plotted proportional to the sample sizes. *Continent* (1 Europe, 2 North America, 3 South America, 4 Africa, 5 Asia, 6 Oceania, 7 Indigenous people). *Case definition* (1 Self-reported diagnosis, 2 Self-reported symptoms, 3 2-step approach diagnosis, 4 2-step approach symptoms, 5 Diagnose health professional, 6 Medical record GP, 7 Medical record hospital). *Setting* (1 rural, 2 urban, 3 combination). *Sampling frame* (1 Census, 2 Household register, 3 Convenience sample, 4 General practitioner database, 5 Hospital database, 6 List of specific group of subjects, 7 Geographic sampling). *Measure of prevalence* (1 lifetime prevalence, 2 period prevalence)

Note that some studies calculated incidence rates or proportions using an unconventional method, that is, by dividing new cases by the number of individuals re-examined after 11 years [34]; by using a denominator based on only the re-examined individuals with hyperuricemia [97]; or by dividing new cases (2002–2003) by census data of 2001, not excluding prevalent cases [54].

Six articles studied the incidence of gout over time. Four did not find evidence for an increasing or decreasing trend in incidence [50, 67, 84, 98]. However, Currie et al. [44] noted a significant difference between the incidence in

Table 3 Multivariable meta-regression analysis on the prevalence of gout

Moderator	Multivariable analysis ^a			
	β	SE	OR (95 %CI)	p value
<i>Clinical heterogeneity</i>				
Mean age	0.0393	0.0164	1.04 (1.01; 1.07)	0.019
% male	0.0168	0.0016	1.02 (1.01; 1.02)	<0.001
Continent				<0.001
<i>Reference = Europe</i>				
North America	1.3281	0.3544	1.87 (1.87; 7.63)	<0.001
South America	-0.3626	0.4541	0.70 (0.28; 1.72)	0.427
Africa	2.726	1.1326	15.27 (1.61; 145.05) ^c	0.018
Asia	-0.7383	0.3306	0.48 (0.24; 0.92)	0.029
Oceania	1.5363	0.3636	4.65 (2.26; 9.58)	<0.001
Indigenous people	2.8163	0.4083	16.7 (7.42; 37.63)	<0.001
Setting				0.250
<i>Reference = rural</i>				
Urban	0.3840	0.2460	1.47 (0.90; 2.39)	0.122
Combination urban and rural	0.1722	0.3148	1.19 (0.64; 2.22)	0.586
<i>Methodological heterogeneity</i>				
Start data collection	-0.0007	0.0082	1.00 (0.98; 1.02)	0.937
Response rate	0.6193	0.2523	1.86 (1.13; 3.07)	0.016
Sampling method	-0.2410	0.2310	0.79 (0.50; 1.24)	0.300
Consistency data collection	-1.5058	0.4742	0.22 (0.09; 0.57)	0.002
Representativeness study population	-0.1987	0.3257	0.82 (0.43; 1.57)	0.543
Case definition				<0.001
<i>Reference = self-reported diagnosis</i>				
Self-reported symptoms	0.7527	0.4396	2.12 (0.89; 5.09)	0.090
2-step approach diagnosis	0.8079	0.4985	2.24 (0.83; 6.04)	0.109
2-step approach symptoms	-0.8786	0.3987	0.42 (0.19; 0.92)	0.030
Diagnose health professional	-0.8818	0.3979	0.41 (0.19; 0.91)	0.029
Medical record general practitioner	-0.3065	0.4548	0.74 (0.30; 1.82)	0.502
Medical record hospital	-0.1233	0.7535	0.88 (0.20; 3.95)	0.870
<i>Outcome reporting</i>				
Measure of prevalence				
<i>Reference = life-time prevalence</i>				
Period prevalence	0.1449	0.2964	1.16 (0.64; 2.08)	0.626

^a Due to collinearity between case definition and sampling frame, the latter was excluded from multivariable analysis

^b Intercept of multivariable model: $\beta = -6.4984$; SE = 16.2324

^c The small number of samples within the level “Africa” resulted in the large 95 %CI

SE standard error

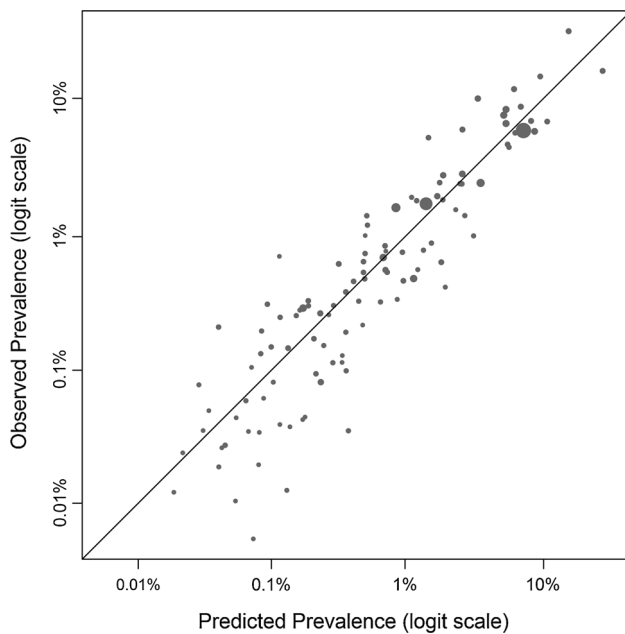


Fig. 3 Scatterplot for the predicted prevalence based on the multi-variable model and the observed prevalence, both on the logit scale

1971–1972 (0.29/1,000) and 1974–1975 (0.35/1,000) in England, but not in Scotland, Wales, and Great Britain as a whole. Arromdee et al. [93] reported that the age and sex adjusted incidence for all gout did not significantly increase ($p = 0.10$) during a 20-year interval, but found a twofold increase in incidence of primary gout only (subjects not on thiazide or diuretics).

Discussion

This study was the first to assess the determinants of the worldwide prevalence of gout in the general population in a systematic manner. Our results showed a pooled prevalence of 0.6 % (95 % CI 0.4; 0.7) across 67 articles. However, the prevalence estimates were extremely heterogeneous. Therefore, the pooled prevalence should be interpreted with caution. Our multivariable model explained 88.7 % of the heterogeneity and showed an independent influence of age, sex, continent of study execution, consistency in data collection, response rate, but also case definition. In addition, we found that crude incidence rates of gout varied between 0.06/1,000 and 2.68/1,000 across 12 articles.

The previously reported lower prevalence of gout in females and higher prevalence in Oceania [87, 99], North America [5], and among indigenous people (Maori, Aborigines and Inuit) [68, 87] was confirmed in the present study. A higher prevalence in North America has been attributed to the presence of varying ethnic groups on this

continent, including Filipinos and African Americans with high gout prevalences ascribed to the shift from a low-purine diet to a high-purine Western diet in case of immigrants [100] and higher rates of hypertension [101].

Case definition accounted, in the univariable analysis, for 33.6 % of the heterogeneity. A 2-step approach based on diagnosis and self-reported approaches to define gout resulted in the highest estimates of the prevalence of gout. While a previous study suggested that self-report of *physician-diagnosed* gout is an adequate proxy of the actual prevalence [102], we were not able to distinguish this specific self-reported diagnosis from a simple self-reported diagnosis method due to small subsamples. Note that the 2-step approaches were most often used and therefore could have influenced the pooled prevalence.

Because of the limited number of incidence studies a meta-analysis was not possible. Surprisingly, statistical approaches to calculate incidence rates were imprecise and often the exact numerator and denominator were not reported. When incidence rates are assessed over a long time frame, it is assumed that the incidence remains constant during the period of study. However, when assessing a closed cohort, gout incidence will increase with increasing age. This is probably why we found that studies with a long follow-up reported higher incidence rates in comparison to studies reporting an annual incidence.

Among the incidence studies six articles reported incidences across time, of which only two found an increase. Also, our meta-regression analysis of the prevalence rate did not show a significant influence of year of study execution. However, in case a study reported prevalences over time, only the most recent estimation was considered. Nevertheless, only two of the four studies that compared annual prevalence rates for different time points directly [43, 50, 84, 90] reported the increase to be significant [43, 90]. Based on our results, we suggest that there is insufficient evidence for a time trend in the worldwide prevalence and incidence of gout. However, we acknowledge that our finding may represent the absence of evidence, rather than evidence of absence.

Some limitations to this study need to be considered. First, we cannot exclude possible language bias and availability bias in study inclusion as we limited our search to five languages and published articles. Second, due to unavailability of some data from the primary papers, we had to exclude four articles from the meta-analyses. Third, coding the different aspects of clinical and methodological heterogeneity entails some subjectivity, however, coding was independently performed by two reviewers and disagreement resolved by consensus. Fourth, we used mixed-effects logistic regression model for the meta-regression analysis which may have influenced our results. However, sensitivity analyses showed that the impact of the used

Table 4 Characteristics and results of studies reporting incidence rates of gout

Reference	Data collection	Geographic location and setting	Sampling frame 1. Case definition 2. Case definition	Study characteristics ^a	Baseline age yrs: total (men, women) Gender: % men	Follow-up (yrs)	Sample size; 1. N 2. Person-years	Unadjusted incidence per 1,000 persons-years (*) or persons at risk	
								Total	Male/female
Arromdee [93]	1977–1978 and 1995–1996	America Urban	1. Hospital database 2. Screening text using ACR	1. No 2. Yes 3. Yes 4. Yes		2		1978: 0.35	
								1996: 0.56	
Bhole [94]	1950–2000	America Urban + rural	1. Census 2. Clinical exam	1. No 2. Yes 3. Yes 4. Yes	Age: (46; 47) Gender: 44 %	52	1.	M: 4.0*	
							M: 1,951 F: 2,476	F: 1.4*	
Brauer [34]	1963–1974	NZ Maori Rural	1. Unknown 2. Self-reported symptoms	1. No 2. No 3. Yes 4. Yes	Age: ~ 42 Gender: 47 %	11	M: 49,571 F: 73,164	M: 103 F: 43	
							1.		
Campion [95]	1963–1978	America Urban + rural	1. Convenience sample 2. Clinical exam	1. No 2. No 3. No 4. Yes	Age: 42 Gender: 100 %	14.9	1.	M: 2.8*	
							M: 2,046		
Currie [44]	1971–1975	UK Urban + rural	1. GP database 2. ICD	1. Yes 2. Yes 3. Yes 4. Yes		5	M: 30,147	1971: 0.26	
							1.	1975: 0.30	
Elliot [50]	1994–2007	UK Urban + rural	1. GP database 2. ICD	1. Yes 2. Yes 3. Yes 4. Yes		13	Total: 374,832	Range: 0.25–0.35	
							1.	1994: 132	
							Total: ~ 920,000	2007: 1.23	
								Range: 1.12–1.35	
								2007: M: 1.83 F: 0.64	

Table 4 continued

Reference	Data collection	Geographic location and setting	Sampling frame 1. Sampling frame 2. Case definition	Study characteristics ^a	Baseline age yrs: total (men, women) Gender: % men	Follow-up (yrs)	Sample size; 1. N 2. Person-years	Unadjusted incidence per 1,000 person-years (#) or persons at risk	
								Total	Male/female
Hannova [54]	2002–2003	Czech Republic Urban + rural	1. GP and specialist referral to cooperating rheumatologist 2. Wallace criteria	1. No 2. Yes 3. Yes 4. Yes	Age: ~ 52 (53, 51) Gender: 48 %	1	1. M: 73,906 F: 79,938	0.41	M: 0.69 F: 0.16
Isomaki [96]	1974	Finland Urban + rural	1. Referral to Rheumatism foundation hospital 2. Clinical exam AND GP and hospital lists; free text search	1. Yes 2. No 3. No 4. No		1	1. Total: 275,600	0.06	M: 0.12 F: 0.0
Mikulis [67]	1991–1999	UK Urban + rural	1. GP database 2. Oxmis coding system	1. Yes 2. Yes 3. Yes 4. Yes	Gender: 49 %	10	2. Total in 1999: 1,716,276	Range: 1.19–1.80 1999: 1.31*	
O'Sullivan [97]	1964	America Urban	1. Census 2. Clinical exam	1. No 2. Yes 3. Yes 4. Yes	Gender: 48 %	1	1. Total: 4,612	1.0	
Soriano [98]	2000–2007	UK Urban + rural	1. GP database 2. ICD	1. Yes 2. Yes 3. Yes 4. Yes		7	1. Total: 1,775,505	2.68 2001: 2.67 2007: 2.52	M: 4.42 F: 1.32 2001: M: 4.48 F: 1.28 2007: M: 4.01 F: 1.25 2005: M: 1.56 2009: F: 0.38 Range: 2009 M: 1.50 F: 0.52
Trifiro [84]	2005–2009	Italy Urban + rural	1. GP database 2. ICD and free text search	1. Yes 2. Yes 3. Yes 4. Yes		5	2005: 0.93 2009: 0.95 Range: 0.96–1.04		

^a 1. Representativeness study population; 2. Sampling method; 3. Response-rate; 4. Consistency data collection Studies are not clear on the method used to calculate the incidence rate (1,000 person-years vs. persons at risk)

method was rather small. Finally, associations of the gout prevalence with population averages, such as age and sex, across studies may not reflect findings within studies.

In conclusion, the results of this systematic review show that gout is a common disease. A large part of the heterogeneity between studies on the prevalence of gout can be explained by sources of clinical heterogeneity, such as the world region in which the study was performed, and the percentage of males in the study population, but also by the case definition of gout. Researchers should carefully formulate their case definition to facilitate comparison between studies. In addition, more research is needed to support the possible time trend towards increasing prevalence or incidence of gout in the general population.

Conflict of interest The authors have no conflict of interest associated with the work reported in this paper.

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