

Geographic Influence Upon Noninfectious Diseases Accounting for Fever of Unknown Origin: A Systematic Review and Meta-Analysis

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Background. Diagnostic outcomes for fever of unknown origin (FUO) remain with notable numbers of undiagnosed cases. A recent systemic review and meta-analysis of studies reported geographic variation in FUO-related infectious diseases. Whether geography influences types of FUO noninfectious diagnoses deserves examination.

Methods. We systematically searched Medline (PubMed), Embase, Scopus, and Web of Science databases using medical subject headings published from January 1, 1997 to March 31, 2021. Prospective clinical studies investigating participants meeting adult FUO defining criteria were selected if they assessed final diagnoses. Meta-analyses were based on the random-effects model according to World Health Organization (WHO) geographical regions.

Results. Nineteen studies with significant heterogeneity were analyzed, totaling 2667 participants. Noninfectious inflammatory disorders had a pooled estimate at 20.0% (95% confidence interval [CI], 17.0%–23.0%). Undiagnosed illness had a pooled estimate of 20.0% (95% CI, 14.0%–26.0%). The pooled estimate for cancer was 15.0% (95% CI, 12.0%–18.0%). Miscellaneous conditions had a pooled estimate of 6.0% (95% CI, 4.0%–8.0%). Noninfectious inflammatory disorders and miscellaneous conditions were most prevalent in the Western Pacific region with a 27.0% pooled estimate (95% CI, 20.0%–34.0%) and 9.0% (95% CI, 7.0%–11.0%), respectively. The highest pooled estimated for cancer was in the Eastern Mediterranean region at 25.0% (95% CI, 18.0%–32.0%). Adult-onset Still's disease (114 [58.5%]), systemic lupus (52 [26.7%]), and giant-cell arteritis (40 [68.9%]) predominated among the noninfectious inflammatory group. Lymphoma (164 [70.1%]) was the most common diagnosis in the cancer group.

Conclusions. In this systematic review and meta-analysis, noninfectious disease diagnostic outcomes varied among WHO-defined geographies. Evaluations for FUO should include local variations in disease prevalence.

Keywords. fever; fever of unknown origin; geographic variation; pyrexia; pyrexia of unknown origin.

Over the past 3 decades, fever of unknown origin (FUO) evaluations continues to be associated with high rates of undiagnosed illnesses compared to earlier reports [1–8]. Commonly accepted diagnoses for FUO are organized into 5 sub-categories: infections, cancer or oncology, noninfectious inflammatory disorders (NIIDs), miscellaneous disorders, and undiagnosed febrile illness [1–8]. Numerous factors (eg, environmental, genetic determinants, variations of medical practice, etc)

may influence what diseases underlie FUO outcomes that continue to receive attention. Assisting physicians and patients with geographically relevant disease frequencies in FUO may enhance the evaluation process [3–5]. In a systematic review of literature mainly examining retrospective trial data, Fusco et al [6] reported that the overall incidence of undiagnosed cases ranged from 8.5% to 51.0%, higher than Petersdorf and Beeson [1] found in their classic 1961 series when they reported 7.0% without a diagnosis.

Many clinical variables are commonly cited as predominant factors associated with suboptimal outcomes in FUO studies, such as year of evaluation, physician experience, quality of referral center, and whether fever patterns are continuous, recurrent, or periodic [3–6]. Although regional socioeconomic factors, such as healthcare access and variations in practice patterns, also likely influence diagnostic outcomes, geographical factors may also play a significant role [3–6, 8–12]. For example, within FUO series, infectious diseases prevalence varies depending on the region [3–6, 8–12]; for instance, tuberculosis rates reported in India accounted for 51.1% of FUO diagnoses [10] compared to 6.9% among cohorts from the Netherlands [3–5].

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In a more recent systematic review of the literature with a meta-analysis examining rigorous prospective studies, we reported geographic variation among infectious FOU diagnoses [13]. The 10 most frequent diagnoses were tuberculosis, brucellosis, endocarditis, abscesses, viral infections, pneumonia, urinary tract infections, enteric fever, human immunodeficiency virus (HIV), and malaria. We also reported that 21.9% of cases were undiagnosed. However, the effect of geographical factors influencing noninfectious FOU-associated diseases from prospective trial data has not, to our knowledge, been investigated using a meta-analytic approach.

This systematic review aimed to evaluate relevant prospective FOU clinical trials [13], summarize their noninfectious diseases findings, and assess the certainty of their evidence to provide a comprehensive understanding of the associations between geographical location and diagnostic yield. The primary objective of this second study companion to our recent report [13] was to establish a global benchmark description of regional noninfectious disease diagnoses that may further assist all physicians in their FOU approach and serve as a comparison basis for future studies.

METHODS

The protocol for this study was registered at the International Prospective Register of Systematic Reviews (PROSPERO) [13]. The study followed the guidelines of preferred reporting items for systematic reviews and meta-analyses (Supplementary Table 1. PRISMA Checklist) [14].

Eligibility Criteria

Prospective clinical trials of FOU that investigated adults were included in English and non-English languages. Relevant non-English trials were translated with online document translation systems (translate.google.com). Studies were eligible if

they (1) assessed patients meeting any adult FOU definition [1–4] and (2) provided reports for diagnoses of the overall categories and etiologic subgroups separately to minimize the chance of unintended selection bias. Studies were excluded if patients did not fit any accepted adult FOU definition [1–4] or were not prospective, or if the risk of bias was judged as unknown. For this research, the risk of bias was judged to be unknown if authors of published studies did not (1) specify the study type (eg, prospective or retrospective), (2) provide the FOU criteria used (eg, consistent with Petersdorf and Beeson [1] or Durack and Street [2] definitions), (3) provide enrollment criteria, or (4) specify outcomes and/or had substantial amounts of missing data.

Search Strategy

A systematic literature search of studies published from January 1, 1997 to March 31, 2021 was conducted across Medline (PubMed), Embase, Scopus, and Web of Science [13]. These databases were searched for terms constructed by a university librarian that included the query strings of (FOU), (fever of unknown origin [Mesh]), (PUO), (pyrexia of unknown origin [Mesh]), (clinical trial), (clinical trial [Publication Type]), and (Prospective Studies [Mesh]) [13]. The starting period was chosen based on the suggested significant modification to the adult FOU criteria by de Kleijn et al [3, 4] in 1997.

Study Selection and Assessment

After titles and abstracts were screened for initial eligibility by W.F.W., and full texts of potentially eligible articles for inclusion and exclusion criteria were independently reviewed by W.F.W. and P.G.A. Data extraction and quality assessment were performed separately. Any discrepancies were resolved through discussion.

Data Extraction

Bibliographic information was extracted for the title, author name, year of publication, journal name, FOU inclusion criteria, primary diagnostic endpoint by FOU category (eg, infectious diseases, NIIDs, oncology, miscellaneous, and undiagnosed), secondary endpoints, setting, and geographical location based upon the 6 World Health Organization (WHO) regions [15]. Background information was extracted for the numbers of patients, age, gender, temperature threshold and method of measurement, duration of fever and hospitalization before final diagnosis, and contribution of potential diagnostic clues (PDCs), biochemical, microbial, and immunological serology, cultures, histology, and imaging studies used in the trials.

Patient Consent Statement

This study was exempted from obtaining formal institutional review board approval and the requirement to obtain informed

Table 1. Demographic Characteristics and Baseline Variables and Final Diagnosis for 2667 Patients With Fever of Unknown Origin

Characteristic	Value (N = 2667)
Age range, years ^a	10–94
Sex, No. (%)	
Male	1431 (53.6)
Female	1236 (46.3)
No diagnosis, no. (%) ^b	449 (21.9)
Final Diagnosis, No. (%)	
Infectious diseases	1049 (39.3)
Noninfectious inflammatory diseases	568 (21.3)
Cancer	404 (15.1)
Miscellaneous ^b	172 (6.9)

^aSeveral reports, including de Kleijn et al [3, 4], enrolled patients less than 18 years of age [10, 11, 19, 20, 22, 24, 26] as long as patients met the adult fever of unknown origin criteria.

^bUndiagnosed cases (449) were reported in all but 2 studies: Wu et al [26] (n = 431) and Xu et al [27] (n = 185). Miscellaneous cases (172) were reported in all but 1 study by Xu et al [27] (n = 185).

patient consent because it was secondary research of publicly available data.

Statistical Analysis

Data were analyzed using the `metaprop` command in Stata version 16 (StataCorp 2019, Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX). Meta-analysis of the proportion of diseases contributing to FOU was performed using study-specific 95% confidence intervals (CIs) calculated using the exact method [16]. The pooled proportions across all studies were estimated using the DerSimonian and Laird random-effect model. Freeman-Tukey double arcsine transformation was used to compute the pooled estimate and perform back-transformation on the pooled estimate. Study heterogeneity was low if I^2 was less than 25.0%, moderate if it was between 25.0% and 50.0%, and high if it was more than 50.0%. This model was also used for subgroup analysis by region. Statistical significance was set at 0.05.

RESULTS

Search Results and Study Characteristics

Of 732 screened articles, 48 publications were included for full-text review (Supplementary Figure 1) [13]. The use of Google's web-based electronic translating tool was successful in the screening and review process of published reports for this study. It did not require human translation services for further evaluation. Nineteen of these English language studies [3–5, 7, 9–12, 17–28] were included in our analyses (Supplementary Table 2), resulting in 2667 participants [13]. Table 1 summarizes the baseline characteristics of participants from the studies included in our quantitative analyses. Infections (39.3%) and NIIDs (21.3%) constituted the most prevalent categories.

Outcome of Meta-Analysis

The random-effects pooled proportions with 95% exact CIs and the overall pooled estimates for each type of noninfectious FOU category (eg, noninfectious inflammatory, oncology, miscellaneous, and undiagnosed conditions) are shown in Table 2. Noninfectious inflammatory disorders had a pooled estimate at 20.0% (95% CI, 17.0%–23.0%). Undiagnosed illness also had a pooled estimate at 20.0% (95% CI, 14.0%–26.0%). The pooled estimate for cancer was 15.0% (95% CI, 12.0%–18.0%). All analyses demonstrated significant across-study heterogeneity.

Subgroup analyses by region indicated significant heterogeneity in the prevalence across WHO regions. Noninfectious inflammatory disorders were most prevalent in the Western Pacific region, with a pooled estimate of 27.0% (95% CI, 20%–34%). The highest pooled estimate for cancer was in the Eastern Mediterranean region with 25.0% (95% CI, 18%–32%).

Outcomes of Diagnostic Categories

The 10 most common diagnoses overall listed by region are in Table 3. Available data on final noninfectious diseases diagnoses and diagnostic categories are listed in Table 4. The diagnoses were subdivided according to the WHO geographic region.

Noninfectious Inflammatory Disorders

Among available data, 195 (34.3%) were collagen-vascular diseases (as categorized in prior studies, including autoimmune conditions), 58 (10.2%) were vasculitis syndromes, and 42 (7.4%) were noninfectious granulomatous conditions. European studies generated more data in this category (204 of 295 [69.2%]) compared to other regions combined (91 of 295 [30.8%]). Participants with collagen-vascular diseases were primarily diagnosed with adult-onset Still's disease (114 [58.5%]),

Table 2. Results of Random-Effects Meta-Analysis Estimating Pooled Proportions of FOU Noninfectious Disease Categories^a

	Pooled Proportion Comparison of Disease Categories (95% CI)			
	Subcategory Characteristics, No. (%)			
	NIID	ONC	MIS	UD
Pooled proportion, (95% CI)	0.20 (0.17–0.23)	0.15 (0.12–0.18)	0.06 (0.04–0.08)	0.20 (0.14–0.26)
Number of studies included	19	19	18	18
I^2 statistic, (95% CI)	74% (60–84)	77% (65–85)	82% (72–88)	92% (89–94)
	Pooled Proportion Comparison Across Regions (95% CI)			
EMR	0.19 (0.13–0.25)	0.25 (0.18–0.32)	0.01 (0.00–0.04)	0.15 (0.10–0.22)
EUR	0.21 (0.17–0.25)	0.13 (0.09–0.18)	0.07 (0.05–0.1)	0.23 (0.14–0.33)
SEAR	0.13 (0.09–0.17)	0.18 (0.14–0.23)	0.02 (0.00–0.06)	0.16 (0.10–0.22)
WPR	0.27 (0.20–0.34)	0.12 (0.08–0.18)	0.09 (0.07–0.11)	0.13 (0.10–0.16)
<i>P</i> value for between groups	.01	.02	<.01	.2

Abbreviations: AFR, African Region; AMR, Region of the Americas; CI, confidence interval; EMR, Eastern Mediterranean Region; EUR, European Region; FOU, fever of unknown origin; MIS, miscellaneous causes; NIID, noninfectious inflammatory conditions; ONC, oncology/neoplastic conditions; SEAR, Southeast Asian Region; UD, undiagnosed; WPR, Western Pacific Region. NOTE: Thresholds for interpretation of I^2 statistic heterogeneity for this study were low if less than 25.0%, moderate if between 25.0% and 50.0%, and high if more than 50.0%. Higgins JPT and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21:1539–1558.

^aThe pooled portion comparisons are inclusive of FOU infectious diseases association reported in [13]. Pearson's χ^2 test method was used to determine the *P* value between groups.

Table 3. Top 10 FUO Diagnoses Overall and by WHO Region^a

Diagnosis, No. (n = %)	WHO Region ^a			
	EMR (n = 86)	EUR (n = 679)	SEAR (n = 373)	WPR (n = 286)
Overall (n = 1424)				
Tuberculosis (285; 20.0)	Brucellosis (11; 12.8)	Tuberculosis (106; 15.6)	Tuberculosis (120; 32.2)	Tuberculosis (51; 17.8)
Lymphoma (164; 11.5)	Systemic lupus (9; 10.5)	Adult-onset Still's disease (69; 10.2)	Leukemia (34; 9.1)	Brucellosis (38; 13.3)
Adult-onset Still's disease (114; 8.0)	Viral infection (9; 10.5)	Giant-cell arteritis (39; 5.7)	Enteric fever (20; 5.4)	Lymphoma (35; 12.2)
Brucellosis (81; 5.7)	Tuberculosis (8; 9.3)	Endocarditis (34; 5.0)	Non-Hodgkin's Lymphoma (18; 4.8)	Adult-onset Still's disease (29; 10.1)
Endocarditis (62; 4.4)	Endocarditis (8; 9.3)	Urinary tract infection (31; 4.6)	Adult-onset Still's disease (15; 4.0)	Pneumonia (27; 9.4)
Abscess (61; 4.3)	Urinary tract infection (6; 7.0)	Non-Hodgkin's Lymphoma (26; 3.8)	Hodgkin's Lymphoma (12; 3.2)	Viral infection (21; 7.3)
Leukemia (59; 4.1)	Abscess (5; 5.8)	Abscess (25; 3.7)	Endocarditis (12; 3.2)	Systemic lupus (14; 4.9)
Pneumonia (54; 3.8)	Enteric fever (4; 4.7)	Viral infection (25; 3.7)	Human immunodeficiency virus (12; 3.2)	Leukemia (10; 3.5)
Urinary tract infection (54; 3.8)	Non-Hodgkin's Lymphoma (3; 3.5)	Brucellosis (22; 3.2)	Urinary tract infection (11; 2.9)	Abscess (10; 3.5)
Systemic lupus (52; 3.7)	Human immunodeficiency virus (3; 3.5)	Pneumonia (22; 3.2)	Malaria (11; 2.9)	Endocarditis (8; 2.8)

Abbreviations: EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, Southeast Asian Region; WHO, World Health Organization; WPR, Western Pacific Region.

^aRank is based upon the total number of cases overall and within each WHO region. The geographical regions of Africa and the Americas lacked any data for comparison.

systemic lupus (52 [26.7%]), and polymyalgia rheumatica (11 [5.6%]). Eastern Mediterranean cohorts had more systemic lupus cases recorded than other regions. Forty of 58 (68.9%) participants with vasculitis syndrome in this composite were diagnosed with giant-cell arteritis. The studies reviewed did not provide age-related information. For the subset of noninfectious granulomatous diseases, most (26 of 42 [61.9%]) had sarcoidosis [3, 4, 12, 17, 20, 22, 25].

Cancers

Of the 404 patients who had an oncological explanation, 234 (57.9%) had a hematologic malignancy. Rates were higher among studies from Europe (98 [41.9%]) and Southeast Asia (84 [35.9%]). Lymphomas accounted for the largest number in this category (164 [70.1%]), followed by leukemias (59 [25.2%]), multiple myeloma (8 [3.4%]), and myelodysplastic disease (3 [1.3%]). Because of the insufficient number of reports on solid tumors ($n = 27$), we could not conclude outcome differences by disease or region.

Miscellaneous Disorders

One hundred seventy-two participants (6.9%; range, 0.0%–13.1%) were diagnosed with a miscellaneous condition. Among 103 (59.9%) participants reported from European studies, conditions included drug fever (18.4%), thyroid disease (16.5%), habitual hyperthermia (10.7%), gout and pseudogout (4.8%), venous thrombosis events (2.9%), Familial Mediterranean Fever (2.9%), Addison's disease (1.9%), and Dressler's syndrome (1.9%). Thyroid diseases occurred across all regions. Kikuchi's disease presented an increased pattern across

Western Pacific (15 [42.8%]) and Southeast Asian regions (4 [26.7%]).

Predictive Factors of Undiagnosed Diseases

The overall risk of undetermined illness among participants in this study was 21.9% (6.8%–51.0%). Four European studies [3–5, 12, 20] provided data on factors associated with undiagnosed diseases based on referral patterns and whether the fever was classified as continuous, recurrent (defined as 2 episodes of fever followed by intervals of at least 48 hours without fevers), or periodic (defined as 2 episodes of fever followed by intervals of at least 2 weeks without fevers). One study [3] reported a high rate of undiagnosed illness in the recurrent group (56 [50.0%]) compared to the continuous group (111 [20.0%]). Another study [20] reported that 50 of 105 (47.6%) participants with recurrent fever went undiagnosed compared to 48 of 185 (25.9%) with continuous fever. A smaller study [5] reported that 17 of 25 (68.0%) of second opinion referrals (previously evaluated before other study participants) had no diagnosis compared to 20 of 48 (42.0%) who had been referred directly ($P = .05$). The percentage of patients in this study without a final diagnosis did not differ significantly between academic and community hospitals (55% vs 45%).

Clinical Outcomes

Data on clinical outcomes were reported among 13 studies (Table 5) [3–5, 9, 11, 12, 17–20, 23–25, 28]. Among 11 studies [3–5, 9, 11, 12, 17–20, 23–25] reporting mortality data, rates ranged from 1.1% to 23.2% ($n = 141$). Febrile illness-related mortality rates among 6 studies (59 of 74 [79.7%]) were as

Table 4. Noninfectious Diseases Diagnoses by WHO Geographic Region in Patients With Fever of Unknown Origin

Diagnoses	WHO Region ^a , Patients, No. (%)			
	Eastern Mediterranean	Europe	Southeast Asia	Western Pacific
Noninfectious Inflammatory Diseases				
Connective-Tissue Diseases				
Adult-onset Still's disease	1 (5.9)	69 (34.2)	15 (48.4)	29 (67.4)
Behcet's disease	NR	4 (1.9)	NR	NR
Polymyalgia rheumatica	1 (5.9)	10 (4.9)	NR	NR
Polymyositis	NR	2 (1.0)	NR	NR
Rheumatoid arthritis	NR	6 (2.9)	1 (3.2)	NR
Sjogren's syndrome	NR	2 (1.0)	3 (9.7)	NR
Systemic Lupus	9 (52.9)	22 (10.9)	7 (22.6)	14 (32.6)
Vasculitis Syndromes				
Giant cell arteritis	1 (5.9)	39 (19.3)	NR	NR
Henoch-Schoenlein purpura	NR	5 (2.5)	NR	NR
Polyarteritis nodosa	1 (5.9)	6 (2.9)	NR	NR
Wegener's granulomatosis ^b	2 (11.8)	4 (1.9)	NR	NR
Granulomatous Diseases				
Granulomatous hepatitis	NR	3 (1.5)	1 (3.2)	NR
Inflammatory bowel disease ^c	2 (11.8)	9 (4.5)	1 (3.2)	NR
Sarcoidosis	NR	23 (11.4)	3 (9.7)	NR
Total	17	202	31	43
Cancer				
Hematologic				
Hodgkin lymphoma	1 (11.1)	23 (20.4)	12 (13.3)	NR
Leukemia	NR	15 (13.3)	34 (37.7)	10 (20.4)
Lymphoma, unspecified	NR	28 (24.8)	18 (20.0)	35 (71.4)
Non-Hodgkin Lymphoma	3 (33.3)	26 (23.0)	18 (20.0)	NR
Multiple myeloma	1 (11.1)	4 (3.5)	1 (1.1)	2 (4.1)
Myelodysplastic syndrome	NR	2 (1.2)	1 (1.1)	NR
Solid-Organ				
Breast	NR	5 (4.4)	NR	NR
Colon	1 (11.1)	3 (2.7)	2 (2.2)	NR
Gastric	NR	2 (1.8)	NR	NR
Lung	NR	3 (2.7)	2 (2.2)	NR
Prostate	2 (22.2)	NR	1 (1.1)	2 (4.1)
Renal	1 (11.1)	2 (1.8)	1 (1.1)	NR
Total	9	113	90	49
Miscellaneous				
Addison's disease	NR	2 (3.1)	NR	NR
Cirrhosis	2 (50.0)	NR	NR	NR
Dressler's syndrome	NR	2 (3.1)	NR	NR
Drug fever	NR	19 (29.2)	1 (12.5)	NR
Factitious fever	NR	3 (4.6)	NR	NR
Familial Mediterranean fever	1 (25.0)	3 (4.6)	NR	NR
Gout/pseudogout	NR	5 (7.7)	NR	NR
Habitual hyperthermia	NR	11 (16.9)	NR	NR
Hemophagocytic disorder ^d	NR	NR	2 (25.0)	NR
Kikuchi's syndrome	NR	NR	4 (50.0)	15 (62.5)
Venous thrombosis ^e	NR	3 (4.6)	NR	NR
Thyroid disease	1 (25.0)	17 (26.2)	1 (12.5)	9 (37.5)
Total	4	65	8	24

Abbreviations: NR, not reported; WHO, World Health Organization.

^aPercentages are calculated by the subcategory total within WHO columns. The geographical regions of Africa and the Americas lacked any data for comparison.

^bNow referred to as granulomatosis with polyangiitis.

^cIncludes both Crohn's disease and ulcerative colitis.

^dRefers to hemophagocytic lymphohistiocytosis.

^eIncludes both pulmonary embolism and deep vein thrombosis.

Table 5. Studies Reporting Mortality and Spontaneous Fever Resolution Rates

Author, Year	Study Size (n)	Mortality Rate Overall (n, %)	Patients With Undiagnosed Illness (n, %)	Spontaneous Fever Resolution of Undiagnosed Cases (n, %)
Eastern Mediterranean Region				
Adil Khalil et al [23], 2010	55	4, 7.3	11, 20.0	NL
Ali-Eldin et al [24], 2011	93	4, 4.3	12, 12.9	5, 41.7
Total	148			
European Region				
de Kleijn et al [3, 4], 1997	167	20, 12.0	50, 29.9	37, 74.0
Altiparmak et al [17], 2001	50	4, 8.0	4, 8.0	2, 50.0
Vanderschueren et al [20], 2003	290	37, 17.7	98, 33.8	NL
Baicus et al [19], 2003	164	38, 23.2	12, 7.3	9, 75.0
Saltoglu et al [9], 2004	87	11, 12.6	6, 6.8	5, 83.3
Bleeker-Rovers et al [5], 2007	73	5, 6.8	37, 51.0	16, 43.2
Robine et al [25], 2014	103	11, 10.7	52, 50.5	10, 19.2
Cachot et al [12], 2021	87	6, 6.9	26, 29.9	20, 76.9
Total	1021			
South-East Asian Region				
Kejariwal et al [18], 2001	100	NL	14, 14.0	11, 78.6
Mir et al [11], 2014	91	1, 1.1	25, 27.5	24, 96.0
Pannu et al [28], 2021	112	NL	19, 12.5	12, 63.2
Total	303			

Abbreviations: NL, not listed.

follows: 47.5% (n = 28) for oncology; 27.1% (n = 16) for infections; 13.6% (n = 8) for undiagnosed illness (ie, died before a diagnosis could be reached); 6.8% (n = 4) for noninfectious inflammatory conditions; and 5.1% (n = 3) for miscellaneous conditions (eg, pulmonary embolus) [5, 9, 12, 17, 20, 25]. Among 11 studies, rates of spontaneous fever resolution ranged from 19.2% to 96.0% for undiagnosed cases (n = 257) [3–5, 9, 11, 12, 17, 24, 25, 28].

DISCUSSION

Summary of Results

To our knowledge, this study is the first to use a systematic review of prospective FUI trials that included outcomes compared by geographic regions. Overall, we found that NIIDs and miscellaneous conditions were most prevalent in the Western Pacific region. Cancer was described as most prevalent in the Eastern Mediterranean region. Our unique study helps physicians by synthesizing aggregated regional data rather than looking at single and usually local case series. This information may allow FUI patient evaluations to consider more commonplace diagnoses in their area as well as assist in situations in which patients come from different geographies.

Evidence in Context

One earlier systematic review by Fusco et al [6] compared outcomes using a mixture of retrospective and prospective studies retrieved from only 1 database over a shorter 10-year period without standardized geographical targets. In addition, not all

studies included in that review used the standard adult FUI 3-week definition [29]. Moreover, the earlier systematic study may have underestimated the actual rate of conditions and geographic locations by excluding other databases and relevant studies. In contrast, a significant strength of our research is uniformly limiting included studies to prospective cohorts, which is a preferred strategy to strengthen the accuracy of data collection concerning exposures, potential confounders, and endpoints. In addition, estimates derived from our analyses would be considered more robust due to the inclusion of studies using accepted FUI-defining criteria, standardized geographical targets as a comparator, a comprehensive set of databases over a more considerable time period, and a meta-analysis statistical model.

Unlike the previous systematic review by Fusco et al [6], in which studies were mainly defined by the Durack and Street [2] criteria, most studies in our review were based upon the Petersdorf and Beeson [1] criteria. The Durack and Street [2] FUI definition proposed 4 subsets: classic Petersdorf and Beeson [1], nosocomial, neutropenic, and HIV-associated. In addition, it replaced Petersdorf and Beeson's [1, 2] last criterion with "uncertain diagnosis after 3 days of hospital stay or more than 2 outpatient visits rather than 1-week of inpatient investigations". Although the review by Fusco et al [6] reported a minor observable association with differences in diagnostic outcomes and defining criteria between studies, we did not observe such a difference in our analysis. An additional factor limiting our capacity to detect an association could be the inclusion of heterogeneous populations with comorbid conditions that differ from that

review. We would venture that it is unlikely that an effect would have been detectable with the inclusion of more studies (10 or more) over a more extended time. In addition, new diagnostic techniques for imaging, immunological, serological, and culture methods may change the time to diagnosis, making arbitrary time-based investigations obsolete. It is important to note that although our evaluation did not observe an increased risk of diagnostic variability based on FOU-defining criteria, it cannot be excluded and should raise caution on a potential type II error for this association.

Among factors predicting cases resulting in undetermined illness, fever pattern differences predominated [3, 5, 12, 20]. Of interest, frequencies of European participants going without a diagnosis in the recurrent or periodic fever groups were higher than if a continuous fever were present (47.6% vs 20.0%–25.9%, respectively) [3, 4, 20]. Insufficient reporting among studies regarding these fever types did not allow for further formal analysis in this study. By comparison, the previous systematic review by Fusco et al [6] also provided no data on the characteristics or outcomes of the patients with these subcategories of fevers. Although the pattern of fever might represent 1 potential risk for undiagnosed illness, we hypothesize that other possible factors likely involve the following: (1) healthcare system-related factors such as atypical manifestations resulting in initial misdiagnoses and prolonged delays between specialist physician referral requests and available appointments; (2) limited resources and few research avenues available to referring physicians; (3) yet to be described diseases; (4) geographic or genetic variations as drivers of malignancy or autoimmune disease as well as the ecology of medical care; and (5) patient-related socioeconomic factors such as limited access to medical care due to unemployment, medical insurance barriers, or significant travel times to an appropriate healthcare site [30–34].

Healthcare Implications

Since 1961, FOU research has been largely performed at single centers, which may obscure significant regional trends and clinical outcomes. For example, the current way of informing physicians about potential FOU causes via repeated individual prospective and retrospective studies or narrative reviews contributes to an incomplete understanding of the diseases associated with this syndrome. In addition, a recent study reported a bias toward physicians overestimating the probability of disease by 2 to 10 times compared to scientific estimates, leading to the overuse of diagnostic procedures with associated patient harms [35]. Without a more comprehensive conceptual differential diagnostic framework, patients and physicians struggle to prioritize FOU evaluation decisions based on patient preferences and clinical judgment. Furthermore, although it remains to be proven, others have noted that physicians using a differential diagnostic checklist had better diagnostic accuracy than controls without [36].

Our aggregated analysis will assist physicians with at least a minimum consideration of the common diagnoses when evaluating a patient, especially if there is only an undifferentiated fever as an objective finding. Tables 2 and 3 are most helpful to a clinician's evaluation, providing a potential menu of common FOU diagnoses that could be further adjudicated based on clinical context. Providing some foundation with a customized geographical estimate of FOU-associated disease prevalence may assist by reducing testing, medical errors, undiagnosed cases, and delay [36]. Furthermore, if this information is reasonably applied to the evaluation of patients with this syndrome, it is unlikely to cause harm, considering it might result in a more accurate and cost-effective evaluation worldwide.

Patients with FOU continue to pose a difficult diagnostic challenge. Development of general algorithms encompassing the full range of etiologies to assist physicians is also tricky because there are so many variances in the incidence of underlying illnesses among patient cohorts. Our findings identify some variations among clinical outcomes and geographic parameters that could be used as predictive indicators to increase the diagnostic yield. Although proportions varied across WHO regions in our study (Table 2), this information is not substantially different to justify the idea that patients should undergo completely distinct clinical evaluations based on their location. Understanding local disease prevalences along with the history-taking and physical examination process to find any relevant PDC still serves as the foundation for evaluating an immunocompetent patient with FOU. We believe using our study's results will serve as an aid in evaluating these patients.

Limitations

This study has limitations. First, we did not have access to individual-level data from studies as published data, because all differed in reported information. An analysis of age and gender differences in the noninfectious inflammatory disease and oncology categories would have been helpful but could not be performed due to a lack of reported data. In addition, some geographical regions, such as Africa and the Americas, lacked any recent data for comparison.

Classification of diseases within FOU categories also has limitations. For example, Kikuchi-Fujimoto disease, an inflammatory condition, differed between noninfectious inflammatory disorders in some reports [10, 28] and miscellaneous conditions in other reports [11, 25, 26]. Familial Mediterranean Fever, an autoinflammatory disorder, also differed in classification as a noninfectious inflammatory disorder and miscellaneous condition among reports [23, 25]. Although the impact of these reporting differences is expected to be low for these uncommon conditions, the outcomes in future studies should have these diseases codified within a standard category to avoid over- and underestimation of disease prevalences within FOU categories [37, 38].

We could not perform a complete analysis with between-study variations and geographical representation because of incomplete data reporting. For example, disease prevalences in Africa and the integration of migrants into the local healthcare systems of Europe may change results over time [39, 40]. In addition, the WHO geographic classification system has limitations. For example, disease prevalences in Turkey differ from Northern European locations but are included in a single WHO region. Turkish FUO diagnoses appear more reflective of Asian and Eastern Mediterranean disease rates. Therefore, to prevent the effects of Turkey's higher infection rates, European outcomes may need to be separated [13].

More studies within smaller geographic regions would be preferred to understand more regional disease rates. The relatively small number of included studies and high heterogeneity must be considered when interpreting results from this study. The high heterogeneity may have been caused by (1) different clinical assessment methods (ie, the studies used different criterion checklists and did not assess the attributability of clinical findings in a standardized way), (2) different types of diagnostic testing methods (cultures, serology, imaging, and molecular tests), (3) different probabilities of disease prevalence in the different studies, or (4) variations associated with how the individual patient or demographic groups seek care within a particular geographic location and society in the use of healthcare resources (ie, ecology of medical care) [30].

Standardizing clinical assessment could alleviate the first of these potential causes. More extensive meta-analyses should investigate the role of disease prevalences, methods of evaluating clinical diagnostic clues, and diagnostic testing protocols using meta-regression. However, because our analyses included prospective clinical studies of different socioeconomic conditions, healthcare practice patterns, and geographical locations, we believe the findings of these diagnoses are relevant for FUO evaluations in routine healthcare. In addition, it will serve as a basis for understanding future research efforts and disease trends.

More extensive, structured studies would further benefit the diagnosis and management of FUO. Without adding studies in all WHO regions, findings will be skewed to Europe, because this is where most studies were performed. It is notable that in Africa and the Americas, no prospective studies have been performed since 1992 [41]. Looking at an earlier era, among 3 North American community hospitals from 1984 to 1990, Kazanjian [41] reported that 86 of 6250 (1.4%) infectious diseases consults met the classic criteria for FUO. We surmise FUO accounts for fewer hospital consults in the United States than in earlier eras due to the ongoing shift to safe outpatient evaluations, although firm data are lacking.

Because of medical advances since that report and the decades-long lack of North American study in the field, there is a need to prioritize funding to support high-quality research that promotes global FUO science and focus upon

improving evaluation efficiency and outcomes for patients. Comprehensive regional prospective studies would further assist physicians in anticipating commonly encountered diagnoses that need to be performed, particularly in the Americas and Africa. The absence of studies may be based on a lack of funding as a research priority. Alternatively, a global patient registry from defined medical centers may help inform long-term trends.

CONCLUSIONS

This systematic review and meta-analysis compared FUO non-infectious diseases outcomes with a standard geographic classification system. Prevalence of these FUO diagnostic categories differs among regions as do the frequency of specific diagnoses. The certainty of this evidence is limited due to the risk of bias in included studies, observed statistical heterogeneity, and the lack of prospective studies of recent vintage done in either North America or Africa. Nonetheless, clinical evaluation for patients with prolonged unexplained fevers should consider geographical variations in disease prevalence.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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