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The prevalence and incidence of myalgic encephalomyelitis/chronic fatigue syndrome in Europe: the EURO-epiME study from the European network EUROMENE. A protocol for a systematic review.

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Complete List of Authors:	Estévez-López, Fer; University of Granada, Department of Physical Education and Sport, Faculty of Sport Sciences; Utrecht University, Department of Psychology, Faculty of Social and Behavioural Sciences Castro-Marrero, Jesus; Vall d'Hebron University Hospital, CFS/ME Unit, Universitat Autònoma de Barcelona Wang, Xia; University of East Anglia Bakken, Inger Johanne; Norwegian Institute of Public Health Ivanovs, Andrejs; Rigas Stradinas Universitate Nacul, Luis ; London School of Hygiene and Tropical Medicine Sepulveda, Nuno; London School of Hygiene and Tropical Medicine Strand, Elin; Oslo universitetssykehus Ulleval Pheby, Derek; Buckinghamshire New University Alegre, Jose; Vall d'Hebron University Hospital, CFS/ME Unit, Universitat Autònoma de Barcelona Scheibenbogen, Carmen; Charite - Universitatsmedizin Berlin Institut fur Medizin- Pflegepadagogik und Pflegewissenschaft Shikova-Lekova, Evelina; Natsionalen tsentar po zarazni i parazitni bolesti Lorusso, Lorenzo; A.S.S.T. della Franciacorta Capelli, Enrica; Universita degli Studi di Pavia Facolta di Medicina e Chirurgia Slobodan, Sekulic; Univerziteta u Novom Sadu Medicinski Fakultet Lacerda, Eliana; London School of Hygiene & Tropical Medicine Murovska, Modra; Rigas Stradinas Universitate
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The prevalence and incidence of myalgic encephalomyelitis/chronic fatigue syndrome in Europe: the EURO-epiME study from the European network EUROMENE. A protocol for a systematic review.

Fernando Estévez-López[1], Jesús Castro-Marrero[2], Xia Wang[3], Inger J Bakken[4], Andrejs Ivanovs[5], Luis Nacul[6], Nuno Sepulveda[6], Elin B Strand[7], Derek Pheby[8], Jose Alegre[2], Carmen Scheibenbogen[9], Evelina Shikova-Lekova[10], Lorenzo Lorusso[11], Enrica Capelli[12], Sekulic Slobodan[13], Eliana Lacerda[6,*], Modra Murovska[14,*]

[1]Department of Psychology, Faculty of Social and Behavioural Sciences, Utrecht University, Utrecht, The Netherlands; and Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Granada, Spain; [2]Vall d'Hebron University Hospital, CFS/ME Unit, Universitat Autònoma de Barcelona, Barcelona, Spain; [3]Norwich Medical School, University of East Anglia, Norwich, UK; [4]Norwegian Institute of Public Health, Oslo, Norway; [5]Statistics Unit, Riga Stradins University, Latvia; [6] Department of Nutrition and Public Health Interventions Research, London School of Hygiene & Tropical Medicine, London, UK; [7]Oslo University Hospital, Oslo, Norway; [8]Faculty of Health and Society, Buckinghamshire New University, High Wycombe, UK; [9]Institute for Medical Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany; [10]Department of Virology, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria; [11]A.S.S.T. della Franciacorta, Chiari, Italy; [12]Department of Earth and Environmental Sciences, University of Pavia, Pavia, Italy; Medical Faculty Novi Sad, University of Novi Sad, Novi Sad, Serbia; [14]August Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Riga, Latvia.

[*] E Lacerda and M Murovska equally contributed to this work.

Correspondence concerning this article should be addressed to: Fernando Estévez-López, Postdoctoral researcher, Department of Psychology, Faculty of Social and Behavioural Sciences, Utrecht University, Utrecht, The Netherlands. Postal address: Heidelberglaan 1, 3584 CS, Utrecht, The Netherlands. Phone: (+31) 30 253 4700. Email: F.Estevez-Lopez@uu.nl

Running head: Protocol of the EURO-epiMe study

ABSTRACT

Introduction. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is characterized by severe fatigue lasting for at least 6 months. Studies on ME/CFS in Europe only include single countries and, therefore, the prevalence and incidence of ME/CFS in Europe (as a whole) is unknown. One of the purposes of the European Network on ME/CFS (EUROMENE; EU-funded COST Action; Reference number: 15111) is to address this gap in knowledge. We will systematically review the literature reporting figures from European countries to provide a robust summary and identify new challenges.

Methods and analysis. We will systematically search the literature databases Scopus, PubMed, and Web of Science. No language or year of publication restriction will be applied. Two independent reviewers will search, screen, and select studies as well as extract data about their main characteristics and evaluate their methodological and reporting quality. When disagreements emerge, the reviewers will discuss to reach a consensus. We plan to produce a narrative summary of our findings as we anticipate that studies are scarce and heterogeneous. The possibility of performing meta-analyses will be discussed in a EUROMENE meeting (i.e., February 8, 2018, in Sofia, Bulgaria).

Ethics and dissemination. Ethical approval is not required as only publicly available data will be included. Findings will be described in EUROMENE reports, published in peer-reviewed journal(s), and presented at conferences. The findings will be also communicated to policymakers, healthcare providers, people with ME/CFS and other sections of society through regular channels including the mass-media.

PROSPERO registration number: CRD42017078688.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first review on the prevalence and incidence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in Europe.
- We will include validated ME/CFS case definitions and the whole lifespan. Studies based on self-report will be excluded.
- A potential limitation of this review is the possible small number of studies available and their high heterogeneity.
- This review will identify new challenges in the field, and will indicate whether more data on the prevalence and incidence of ME/CFS in Europe as a whole or in single countries are required.

INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has heterogeneous clinical features and is characterized by severe fatigue lasting for at least 6 months, that is medically unexplained and not relieved by resting [1]. Consequently, ME/CFS often imposes a huge burden on daily life with negative impacts on health-related quality of life, labour status, and social and familial relationships [2–4]. Societal disbeliefs may add to the burden for people with ME/CFS [3,5].

For several reasons, ME/CFS is a challenge for scientists. Firstly, to date, the features of ME/CFS are poorly defined. For instance, an intense physical discomfort (i.e., malaise) along with flares of ME/CFS symptoms (lasting for longer than 24 hours) is observed after physical exertion [6]. However, whether post-exertional malaise is a distinctive feature of ME/CFS is not yet fully agreed [7]. Secondly, related to the lack of consensus on its defining features, a large number of disparate criteria for the diagnosis of ME/CFS are currently used worldwide [8]. Indeed, the most common scenario is to diagnose ME/CFS after exclusion of other diseases [9–11,4,12,13]. Thirdly, as different diagnostic criteria are used, ME/CFS prevalence and incidence figures are highly variable across studies. For instance, within an Icelandic study [14], the prevalence of ME/CFS ranged from 0 to 5% by means of the Lloyd et al [15] or Holmes et al [16] criteria.

To address the above-mentioned caveats and others it is imperative to understand comprehensively ME/CFS. With this purpose, the European Network on ME/CFS (EUROMENE) was established. This (EU-funded COST Action; Reference number: 15111) multidisciplinary network involves patients, stakeholders, researchers, clinicians, and industry. We intend to align ME/CFS research within the established landscape of European biomedical research by developing additional proposals to the

new H2020 and further Framework programme collaborative research projects. Further information about the EUROMENE network is available at: http://www.cost.eu/COST_Actions/ca/CA15111 and http://www.euromene.eu/).

EUROMENE consists of six coordinated working groups. Working group 1 focuses on the epidemiology of ME/CFS and leads the EUROpean Epidemiological Study for ME/CFS (EURO-EpiME study). One specific aim of this study is to estimate the prevalence and incidence of ME/CFS in Europe. As a first step, we will systematically review the available literature from European countries in order to provide a robust summary and identify new challenges on the field. It seems likely that more data on the prevalence and incidence of ME/CFS will be needed, both for Europe as a whole and within the European countries. Previously, systematic reviews have been conducted including studies from many parts of the world [17–19]. However, these previous reviews: (i) were conducted more than 5 years ago [20], (ii) did not report the incidence of ME/CFS, and (iii) did not include children or adolescents.

Objective

We aim to conduct a systematic review and, if possible, meta-analyses to determine the prevalence and incidence of ME/CFS in Europe.

Review question

1. What is the prevalence of ME/CFS in Europe?
2. What is the incidence of ME/CFS in Europe?

METHODS

Inclusion criteria

1. Studies reporting the prevalence of ME/CFS irrespective of age groups.
2. Studies from European countries.
3. Studies in community or primary care settings.

Exclusion criteria

1. Studies without primary data (e.g., reviews).
2. Studies conducted in biased samples (e.g., vaccines, virus infection, veterans).
3. Studies based on self-report of the diagnosis of ME/CFS.
4. Studies with an inappropriate case definition (i.e., either CFS-like illness or the Oxford criteria).
5. Duplicate reports. When populations are overlapping, the study with the largest sample size will be included.

No language or year of publication restriction will be applied.

Search strategy for identifying relevant studies

The search strategy will consist of two stages: a primary systematic literature search on three electronic databases and a complementary search.

The primary systematic literature search on electronic databases

Two independent reviewers (F.E.-L. and J.C.-M.) will perform a primary electronic search in PubMed, Scopus and Web of Science on January 9, 2018. Table 1 shows the search strategy.

The complementary search

We will conduct a twofold complementary search as follows: first, we will perform a backward- (by checking reference lists) and forward- (by checking citations) search of the works included in the present review; and second, grey literature will be addressed

by contacting – via email - all the members of EUROMENE to provide, if available, prevalence rates, incidence rates or both of ME/CFS in their countries according to national registers, publications in their own languages, or any other accessible source.

Selection of studies for inclusion to the review

Two independent researchers (F.E.-L. and J.C.-M.) will screen records retrieved by the electronic search by titles/abstracts or full text of works for identifying potential studies and their suitability. When disagreements emerge between the two independent researchers, consensus will be obtained through discussion or when required, the opinion of a third researcher (I.J.B.) will be considered.

Assessment of methodological quality and reporting of data

The methodological quality of the eligible studies will be evaluated with the Joanna Briggs Institute-Checklist for Prevalence Studies [21]. Before applying it, six members of the research team (i.e., F.E.-L., L.N., J.A., S.S., E.L., and M.M.) will develop an agreed appraisal of the tool. This appraisal will be published with the review as supplementary information. The reporting quality of the eligible studies will be evaluated uisng the observational studies in epidemiology (STROBE) checklist [22]. Two independent researchers (i.e., A.I. and X.W.) will evaluate the methodological and reporting quality of the included works. When controversies emerge, studies will be discussed with two other members of the team in order to reach a consensus (i.e., E.B.S. and D.P. for methodological and reporting quality, respectively). The quality assessment will be considered when discussing the findings.

Data extraction and management

To manage the retrieved records from the electronic search, we will use the Mendeley Desktop. Two independent researchers (F.E.-L. and A.I.) will extract the following relevant data from the included studies: reference (authors and year of publication),

country (city or region when relevant), design (i.e., general population online survey), total sample size (*n* and % of women), age range, setting (e.g., primary care), case definition (i.e., diagnosis criteria), dates of data collection, overall prevalence or incidence and prevalence or incidence by gender and age groups (when available). When discrepancies emerge in the coding between the two researchers results will be discussed with two other members of the team (i.e., N.S.) to reach a consensus.

Data synthesis and analysis

We anticipate that studies on the prevalence and incidence of ME/CFS in Europe will prove to be scarce and heterogeneous. The preliminary findings of the review will be presented in a EUROMENE meeting (i.e., February 8, 2018, in Sofia, Bulgaria) where we will discuss the appropriateness of performing meta-analyses.

A narrative (descriptive) synthesis is planned if meta-analyses are not feasible. We will pay special attention to possible factors related to heterogeneity of the findings (e.g., diagnostic criteria, quality of the study) in order to find patterns that should be considered in future research. Attention will be also paid to the characteristics of the studied populations (e.g., age group, gender).

We will undertake meta-analyses only where pooling of quantitative data is possible. The meta regression analysis will be performed to investigate the sources of heterogeneity of any ME/CFS pooled prevalence estimate.

Presentation and reporting of results

We will report the findings of the present literature review in accordance with the preferred reporting items for systematic reviews and meta-analyses (i.e., the PRISMA statement [23]). A flow diagram (Figure 1) will illustrate the process of study selection from retrieved records to included studies. For transparency purposes, supplementary files will show which studies were excluded at every stage of the review.

In accordance with the data extraction, a table will show the main characteristics of the studies included. Information on the quality of the methodology and reporting of the studies will also be available.

If meta-analyses are performed, we plan using comprehensive meta-analysis (CMS) to combine data of prevalence or incidence from different studies to estimate the mean effect. We will select an appropriate model in terms of studies that we include and calculate pooled ME/CFS prevalence and incidence. We will compare the results of random-effects and fixed-effect meta-analyses in sensitivity analyses.

Ethics and dissemination

As systematic reviews use publicly available data, no formal ethical review and approval is needed. The findings of this systematic review will address a specific aim of the European network EUROMENE (i.e., to summarise the available data of the prevalence and incidence of ME/CFS in Europe). The findings will be included in EUROMENE reports and published in a paper in a peer-reviewed journal and presented at conferences and meetings.

The findings of the present systematic review will be widely communicated to society using mass media (e.g., interviews on radio, newspaper, television and the Internet). Since our findings may have an impact on policy and healthcare practice, we will also present them to policymakers and healthcare providers. We will present our findings to patients with ME/CFS (e.g., by direct communication with representative patient organisations, and by giving talks to local associations of people with ME/CFS).

AUTHORS' CONTRIBUTIONS

FE-L, JC-M, XW, EL, and MM designed the protocol. FE-L drafted the manuscript. FE-L, JC-M, XW, IJB, AI, LN, NS, EBS, DP, JA, CS, ES-L, LL, EC, SS, EL, MM revised and approved the final version of the manuscript. MM and EL are the chair and vice chair of the EUROMENE action, respectively.

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Competing interests: None declared.

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Figure 1. Flow diagram for study selection

WOS, web of science; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome.

Table 1. The primary systematic literature search strategy on the electronic databases

Database	Search terms combination
Scopus	({epidemiology} OR {prevalence} OR {incidence}) AND ({chronic fatigue syndrome} OR {myalgic encephalomyelitis} OR (4) OR (5))
PubMed	("Fatigue Syndrome, Chronic"[Mesh] AND (("Incidence"[Mesh] OR "Epidemiology"[Mesh] OR "epidemiology" [Subheading]) OR "Prevalence"[Mesh] OR "Cross-Sectional Studies"[Mesh]))
Web of science	(“epidemiology” OR “prevalence” OR “incidence”) AND (“chronic fatigue syndrome” OR “myalgic encephalomyelitis” OR “CFS/ME” OR “ME/CFS”)

Mesh, medical subject headings

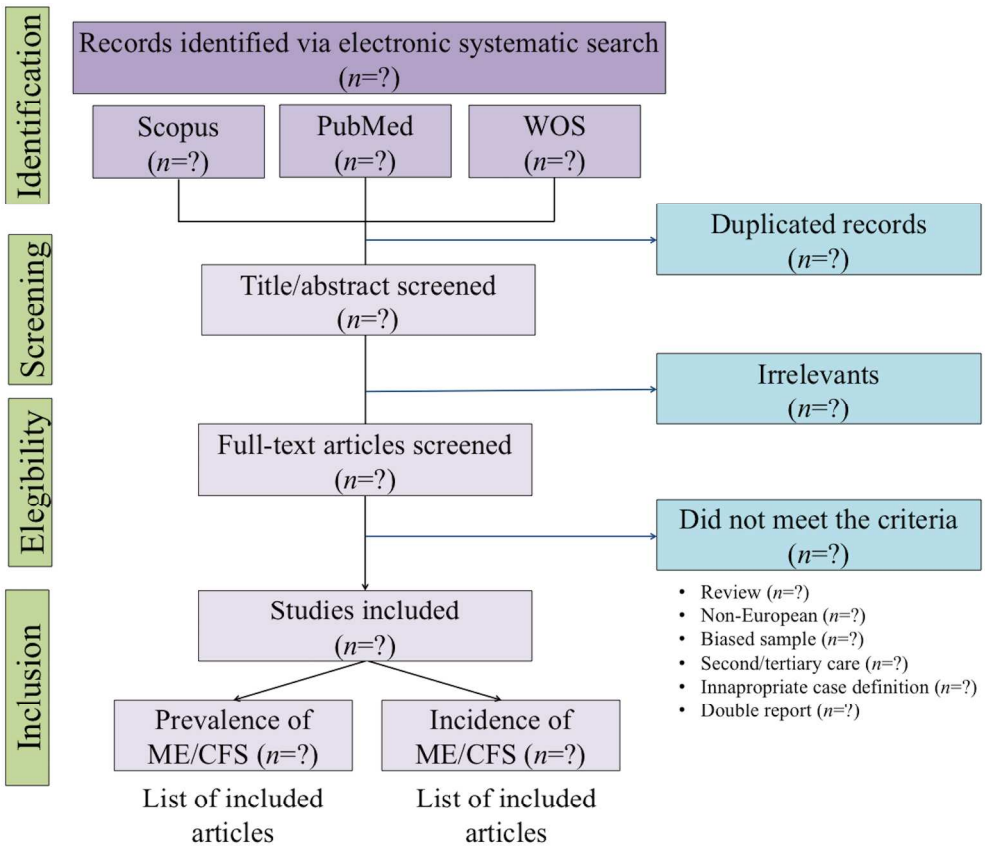

Figure 1. Flow diagram for study selection

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
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[1]Department of Psychology, Faculty of Social and Behavioural Sciences, Utrecht University, Utrecht, The Netherlands; Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Granada, Spain; and School of Health Sciences, Ulster University, Northern Ireland, UK; [2]Vall d'Hebron University Hospital, CFS/ME Unit, Universitat Autònoma de Barcelona, Barcelona, Spain; and Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY, USA; [3]Norwich Medical School, University of East Anglia, Norwich, UK; [4]Norwegian Institute of Public Health, Oslo, Norway; [5]Statistics Unit, Riga Stradins University, Latvia; [6] Department of Nutrition and Public Health Interventions Research, London School of Hygiene & Tropical Medicine, London, UK; [7]National Advisory Unit on CFS/ME, Oslo University Hospital, Oslo, Norway; [8]Faculty of Health and Society, Buckinghamshire New University, High Wycombe, UK; [9]Vall d'Hebron University Hospital, CFS/ME Unit, Universitat Autònoma de Barcelona, Barcelona, Spain; [10]Institute for Medical Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany; [11]Department of Virology, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria;

[12]A.S.S.T. della Franciacorta, Chiari, Italy; [13]Department of Earth and Environmental Sciences, University of Pavia, Pavia, Italy; [14]Department of Neurology, Medical Faculty Novi Sad, University of Novi Sad, Serbia; [15]August Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Riga, Latvia.

[*] E Lacerda and M Murovska equally contributed to this work.

Correspondence concerning this article should be addressed to: Fernando Estévez-López, Postdoctoral researcher, Department of Psychology, Faculty of Social and Behavioural Sciences, Utrecht University, Utrecht, The Netherlands. Postal address: Heidelberglaan 1, 3584 CS, Utrecht, The Netherlands. Phone: (+31) 30 253 4700. Email: F.Estevez-Lopez@uu.nl

Running head: Protocol of the Euro-epiMe study

ABSTRACT

Introduction. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic disease involving central nervous system and immune system disorders, as well as cardiovascular abnormalities. ME/CFS is characterized by severe chronic fatigue lasting for at least 6 months, including such clinical symptoms as tender cervical or axillary lymph nodes, muscle pain, joint pain without swelling or redness, post-exertional malaise for more than 24 hours, and un-refreshing sleep. Studies on the epidemiology of ME/CFS in Europe only include single countries and, therefore, the prevalence and incidence of ME/CFS in Europe (as a whole) is unknown. One of the purposes of the European Network on ME/CFS (EUROMENE; EU-funded COST Action; Reference number: 15111) is to address this gap in knowledge. We will systematically review the literature reporting figures from European countries to provide a robust summary and identify new challenges.

Methods and analysis. We will systematically search the literature databases Scopus, PubMed, and Web of Science for studies published in the last 10 years (i.e., after 2007). No language restriction will be applied. Two independent reviewers will search, screen, and select studies as well as extract data about their main characteristics and evaluate their methodological and reporting quality. When disagreements emerge, the reviewers will discuss to reach a consensus. We plan to produce a narrative summary of our findings as we anticipate that studies are scarce and heterogeneous. The possibility of performing meta-analyses will be discussed in a EUROMENE meeting.

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communicated to policymakers, healthcare providers, people with ME/CFS and other sections of society through regular channels including the mass-media.

PROSPERO registration number: CRD42017078688.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The main strengths of this protocol rely on its carefully designed search strategy, inclusion and exclusion criteria, and time span coverage.
- The search strategy will address the potential EU studies published in non-English national languages, and we will include currently accepted ME/CFS case definitions, to minimise selection bias.
- Studies based on self-report will be excluded, and the search time of 10 years will enable us to picture the ME/CFS occurrence in Europe.
- The European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE), a network of established researchers on ME/CFS, will conduct the proposed systematic review, which can increase credibility and reliability of the findings.
- A potential limitation of this review may be a small number of studies available and their potential high heterogeneity.

INTRODUCTION

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) has heterogeneous clinical features and is characterized by severe fatigue lasting for at least 6 months, that is medically unexplained and not relieved by resting [1]. Consequently, ME/CFS often imposes a huge burden on daily life with negative impacts on health-related quality of life, labour status, and social and familial relationships [2–4]. Societal disbeliefs may add to the burden for people with ME/CFS [3,5].

For several reasons, ME/CFS is a challenge for scientists. Firstly, to date, the features of ME/CFS have been poorly defined. For instance, an intense physical discomfort (i.e., malaise) along with flares of ME/CFS symptoms (lasting for longer than 24 hours) is observed after minimum physical exertion [6]. However, whether post-exertional malaise is a distinctive feature of ME/CFS is not yet fully agreed [7]. Secondly, related to the lack of consensus on its defining features, a large number of disparate criteria for the diagnosis of ME/CFS are currently used worldwide [8]. Indeed, the most common scenario is to diagnose ME/CFS after exclusion of other diseases [4,9–13]. Thirdly, as different diagnostic criteria are used, ME/CFS prevalence and incidence figures are highly variable across studies. For instance, within an Icelandic study [14], the prevalence of ME/CFS ranged from 0 to 5% by means of the Lloyd et al [15] or Holmes et al [16] criteria, respectively.

To address the above-mentioned caveats and others it is imperative to understand comprehensively ME/CFS. With this purpose, the European Network on ME/CFS (EUROMENE) was established. This (EU-funded COST Action; Reference number: 15111) multidisciplinary network involves patients, stakeholders, researchers, clinicians, and industry. We intend to align ME/CFS research within the established landscape of European biomedical research by developing additional proposals to the

new H2020 and further Framework programme collaborative research projects. Further information about the EUROMENE network is available at: http://www.cost.eu/COST_Actions/ca/CA15111 and http://www.euromene.eu/).

EUROMENE consists of six closely coordinated working groups. Working group 1 focuses on the epidemiology of ME/CFS and leads the European Epidemiological Study for ME/CFS (Euro-EpiME study). One specific aim of this study is to estimate the prevalence and incidence of ME/CFS in Europe. As a first step, we will systematically review the available literature from European countries in order to provide a robust summary and identify new challenges on the field. It seems likely that more data on the prevalence and incidence of ME/CFS will be needed, both for Europe as a whole and within the European countries. Previously, systematic reviews have been conducted including studies from many parts of the world [17–19]. However, these previous reviews: (i) were conducted more than 5 years ago [20], (ii) did not report the incidence of ME/CFS, and (iii) did not include children or adolescents.

Objective

We aim to conduct a systematic review and, if possible, meta-analyses to determine the prevalence and incidence of ME/CFS in Europe.

Review question

1. What is the prevalence of ME/CFS in Europe?
2. What is the incidence of ME/CFS in Europe?

METHODS

Inclusion criteria

1. Studies reporting either the prevalence or incidence of ME/CFS, including any of the following clinical diagnostic criteria – CDC-1994 [9], Canadian Consensus Criteria [1], London Criteria [21], International Consensus Criteria [10], or Institute of Medicine criteria [22], irrespective of age groups.
2. Studies from European countries.
3. Studies in community or primary care settings.

Exclusion criteria

1. Studies without primary data (e.g., reviews).
2. Studies conducted in biased samples (e.g., vaccines, virus infection, veterans).
3. Studies based on self-report of the diagnosis of ME/CFS.
4. Studies with an inappropriate case definition (e.g., CFS-like illness or other clinical criteria, such as the Oxford criteria due to lack of specificity).
5. Duplicate reports. When populations are overlapping, the study with the largest sample size will be included.
6. Studies published more than 10 years ago (i.e., before 2008)

No language restriction will be applied.

Search strategy for identifying relevant studies

The search strategy will consist of two stages: a primary systematic literature search on three electronic databases and a complementary search.

The primary systematic literature search on electronic databases

Two independent reviewers (F.E.-L. and J.C.-M.) will perform a primary electronic search in PubMed, Scopus and Web of Science on January 9, 2018. Table 1 shows the search strategy.

The complementary search

We will conduct a twofold complementary search as follows: first, we will perform a backward- (by checking reference lists) and forward- (by checking citations) search of the works included in the present review; and second, grey literature will be addressed by contacting – via email - all the members of EUROMENE to provide, if available, prevalence rates, incidence rates or both of ME/CFS in their countries according to national registers, publications in their own languages, or any other publicly accessible source.

Selection of studies for inclusion to the review

Two independent researchers (F.E.-L. and J.C.-M.) will screen records retrieved by the electronic search by titles/abstracts or full text of works for identifying potential studies and their suitability. When disagreements emerge between the two independent researchers, consensus will be obtained through discussion or when required, the opinion of a third researcher (I.J.B.) will be considered.

Assessment of methodological quality and reporting of data

The methodological quality of the eligible studies will be evaluated with the Joanna Briggs Institute-Checklist for Prevalence Studies [23]. Before applying it, six members of the research team (i.e., F.E.-L., L.N., J.A., S.S., E.L., and M.M.) will develop an agreed appraisal of the tool. This appraisal will be published with the review as supplementary information. The reporting quality of the eligible studies will be evaluated using the observational studies in epidemiology (STROBE) checklist [24]. Two independent researchers (i.e., A.I. and X.W.) will evaluate the methodological and reporting quality of the included works. When controversies emerge, studies will be discussed with two other members of the team in order to reach a consensus (i.e., E.B.S.

and D.P. for methodological and reporting quality, respectively). The quality assessment will be considered when discussing the findings.

Data extraction and management

To manage the retrieved records from the electronic search, we will use the Mendeley Desktop. Two independent researchers (F.E.-L. and A.I.) will extract the following relevant data from the included studies: reference (authors and year of publication), country (city or region when relevant), design (i.e., general population online survey), total sample size (*n* and % of women, n and % of migrants), age range, setting (e.g., primary care), case definition (i.e., diagnosis criteria), dates of data collection, overall prevalence and/or incidence and prevalence and/or incidence by gender and age groups (when available). When discrepancies emerge in the coding between the two researchers' results, these will be discussed with another members of the team (i.e., N.S.) to reach a consensus.

Data synthesis and analysis

We anticipate that studies on the prevalence and incidence of ME/CFS in Europe will prove to be scarce and heterogeneous. The preliminary findings of the review will be presented in a EUROMENE meeting (i.e., September, 2018, in London, the UK) where we will discuss the appropriateness of performing meta-analyses.

A narrative (descriptive) synthesis is planned if meta-analyses are not feasible. We will pay special attention to possible factors related to heterogeneity of the findings in order to find patterns that should be considered in future research. For instance, we will discuss whether the prevalence or incidence of ME/CFS differ according to the case definition used to examine the figures. Attention will be also paid to the characteristics of the studied populations (e.g., age group, gender).

We will undertake meta-analyses only where pooling of quantitative data is possible. The meta regression analysis will be performed to investigate the sources of heterogeneity of any ME/CFS pooled prevalence and incidence estimate. The I^2 statistic will be used to investigate the heterogeneity. I^2 of 25%, 50%, and 75% will be appraised as low, moderate, and high, respectively [25].

Presentation and reporting of results

We will report the findings of the present literature review in accordance with the preferred reporting items for systematic reviews and meta-analyses (i.e., the PRISMA statement [26]). A flow diagram (Figure 1) will illustrate the process of study selection from retrieved records to included studies. For transparency purposes, supplementary files will show which studies were excluded at every stage of the review. If the present protocol needs amendments, they will be publicly available along with their rationale in the EUROMENE website: http://www.euromene.eu/

In accordance with the data extraction, a table will show the main characteristics of the studies included. Information on the quality of the methodology and reporting of the studies will also be available.

If meta-analyses are performed, we plan using comprehensive meta-analysis (CMS) to combine data of prevalence or incidence from different studies to estimate the mean effect. We will select an appropriate model in terms of studies that we include and calculate pooled ME/CFS prevalence and incidence. We will compare the results of random-effects and fixed-effect meta-analyses in sensitivity analyses.

Ethics and dissemination

As systematic reviews use publicly available data, no formal ethical review and approval is needed. The findings of this systematic review will address a specific aim of the European network EUROMENE (i.e., to summarise the available data of the prevalence and incidence of ME/CFS in Europe). The findings will be included in EUROMENE reports published in paper(s) in peer-reviewed journal(s) and presented at conferences and meetings.

The findings of the present systematic review will be widely communicated to society using mass media (e.g., interviews on radio, newspaper, television and the Internet). Since our findings may have an impact on policy and healthcare practice, we will also present them to policymakers and healthcare providers.

Patient and public involvement

EUROMENE is multidisciplinary network cooperating with patient organizations via Web platform. Patient organisations are benefiting from dedicated events, dedicated printed media and interaction through social media. We will present our findings to patients with ME/CFS (e.g., by direct communication with representative patient organisations, and by giving talks to local associations of people with ME/CFS). General public will be reached through the Action website, oral presentations and interviews.

AUTHORS' CONTRIBUTIONS

FE-L, JC-M, XW, EL, and MM designed the protocol. FE-L drafted the manuscript. FE-L, JC-M, XW, IJB, AI, LN, NS, EBS, DP, JA, CS, ES-L, LL, EC, SS, EL, MM revised and approved the final version of the manuscript. MM and EL are the chair and vice chair of the EUROMENE action, respectively. FE-L will be the guarantor of the review

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Figure 1. Flow diagram for study selection

WOS, web of science; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome.

Table 1. The primary systematic literature search strategy on the electronic databases

Database	Search terms combination
Scopus	({epidemiology} OR {prevalence} OR {incidence}) AND ({chronic fatigue syndrome} OR {myalgic encephalomyelitis} OR {myalgic encephalomyelitis} OR {CFS/ME})
PubMed	("Fatigue Syndrome, Chronic"[Mesh] AND (("Incidence"[Mesh] OR "Epidemiology"[Mesh] OR "epidemiology" [Subheading]) OR "Prevalence"[Mesh] OR "Cross-Sectional Studies"[Mesh]))
Web of science	(“epidemiology” OR “prevalence” OR “incidence”) AND (“chronic fatigue syndrome” OR “myalgic encephalomyelitis” OR “CFS/ME” OR “ME/CFS”)

Mesh, medical subject headings

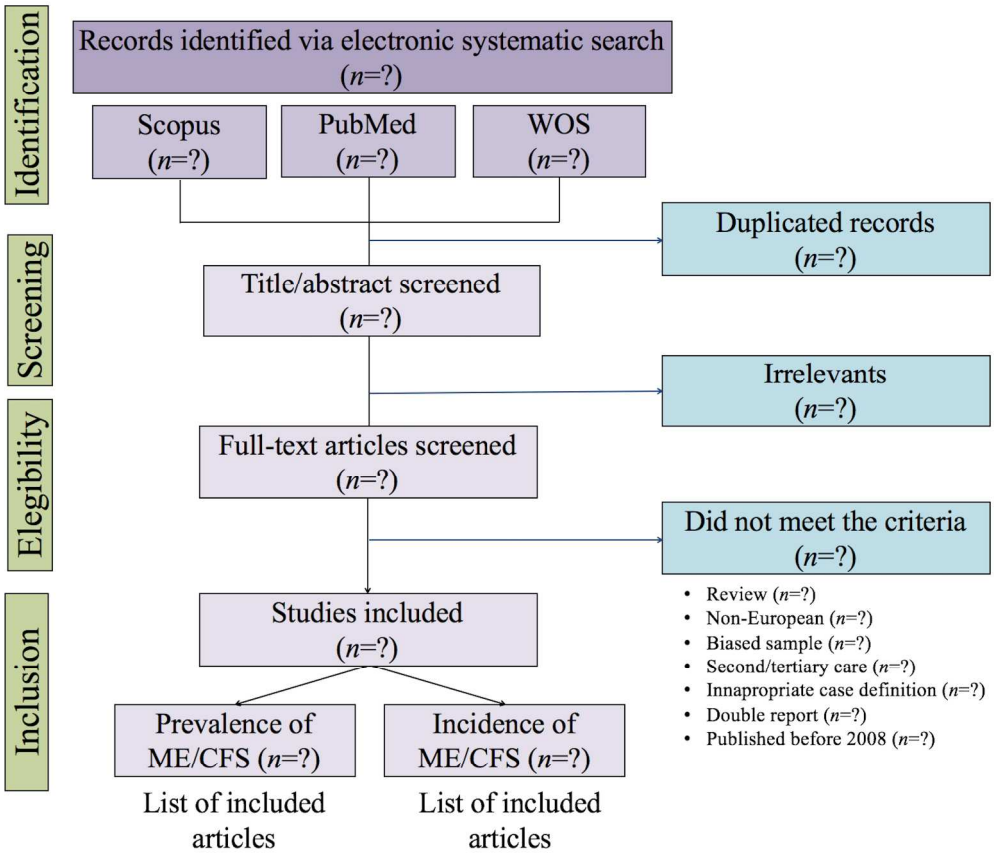

Figure 1. Flow diagram for study selection

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