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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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SCHOLARONE™
Manuscripts

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3 **The prevalence and incidence of myalgic encephalomyelitis/chronic fatigue**
4 **syndrome in Europe: the EURO-epiME study from the European network**
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6 **EUROMENE. A protocol for a systematic review.**
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13 **Running head:** Protocol of the EURO-epiMe study
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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

1
2
3 new H2020 and further Framework programme collaborative research projects. Further
4 information about the EUROMENE network is available at:
5 http://www.cost.eu/COST_Actions/ca/CA15111 and <http://www.euromene.eu/>.
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9 EUROMENE consists of six coordinated working groups. Working group 1
10 focuses on the epidemiology of ME/CFS and leads the EUROpean Epidemiological
11 Study for ME/CFS (EURO-EpiME study). One specific aim of this study is to estimate
12 the prevalence and incidence of ME/CFS in Europe. As a first step, we will
13 systematically review the available literature from European countries in order to
14 provide a robust summary and identify new challenges on the field. It seems likely that
15 more data on the prevalence and incidence of ME/CFS will be needed, both for Europe
16 as a whole and within the European countries. Previously, systematic reviews have been
17 conducted including studies from many parts of the world [17–19]. However, these
18 previous reviews: (i) were conducted more than 5 years ago [20], (ii) did not report the
19 incidence of ME/CFS, and (iii) did not include children or adolescents.
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32 **Objective**

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

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

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3 by contacting – via email - all the members of EUROMENE to provide, if available,
4 prevalence rates, incidence rates or both of ME/CFS in their countries according to
5 national registers, publications in their own languages, or any other accessible source.
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8 9 **Selection of studies for inclusion to the review**

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

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24 The methodological quality of the eligible studies will be evaluated with the Joanna
25 Briggs Institute-Checklist for Prevalence Studies [21]. Before applying it, six members
26 of the research team (i.e., F.E.-L., L.N., J.A., S.S., E.L., and M.M.) will develop an
27 agreed appraisal of the tool. This appraisal will be published with the review as
28 supplementary information. The reporting quality of the eligible studies will be
29 evaluated using the observational studies in epidemiology (STROBE) checklist [22].
30
31 Two independent researchers (i.e., A.I. and X.W.) will evaluate the methodological and
32 reporting quality of the included works. When controversies emerge, studies will be
33 discussed with two other members of the team in order to reach a consensus (i.e., E.B.S.
34 and D.P. for methodological and reporting quality, respectively). The quality
35 assessment will be considered when discussing the findings.
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48 **Data extraction and management**

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

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17 We anticipate that studies on the prevalence and incidence of ME/CFS in Europe will
18 prove to be scarce and heterogeneous. The preliminary findings of the review will be
19 presented in a EUROMENE meeting (i.e., February 8, 2018, in Sofia, Bulgaria) where
20 we will discuss the appropriateness of performing meta-analyses.
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26 A narrative (descriptive) synthesis is planned if meta-analyses are not feasible.

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28 We will pay special attention to possible factors related to heterogeneity of the findings
29 (e.g., diagnostic criteria, quality of the study) in order to find patterns that should be
30 considered in future research. Attention will be also paid to the characteristics of the
31 studied populations (e.g., age group, gender).
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37 We will undertake meta-analyses only where pooling of quantitative data is possible.
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39 The meta regression analysis will be performed to investigate the sources of
40 heterogeneity of any ME/CFS pooled prevalence estimate.
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44 **Presentation and reporting of results**

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46 We will report the findings of the present literature review in accordance with the
47 preferred reporting items for systematic reviews and meta-analyses (i.e., the PRISMA
48 statement [23]). A flow diagram (Figure 1) will illustrate the process of study selection
49 from retrieved records to included studies. For transparency purposes, supplementary
50 files will show which studies were excluded at every stage of the review.
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3 In accordance with the data extraction, a table will show the main characteristics of the
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5 studies included. Information on the quality of the methodology and reporting of the
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7 studies will also be available.
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10 If meta-analyses are performed, we plan using comprehensive meta-analysis
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12 (CMS) to combine data of prevalence or incidence from different studies to estimate the
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14 mean effect. We will select an appropriate model in terms of studies that we include and
15
16 calculate pooled ME/CFS prevalence and incidence. We will compare the results of
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18 random-effects and fixed-effect meta-analyses in sensitivity analyses.
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20 **Ethics and dissemination**

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22 As systematic reviews use publicly available data, no formal ethical review and
23
24 approval is needed. The findings of this systematic review will address a specific aim of
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26 the European network EUROMENE (i.e., to summarise the available data of the
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28 prevalence and incidence of ME/CFS in Europe). The findings will be included in
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30 EUROMENE reports and published in a paper in a peer-reviewed journal and presented
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32 at conferences and meetings.
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35 The findings of the present systematic review will be widely communicated to
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37 society using mass media (e.g., interviews on radio, newspaper, television and the
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39 Internet). Since our findings may have an impact on policy and healthcare practice, we
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41 will also present them to policymakers and healthcare providers. We will present our
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43 findings to patients with ME/CFS (e.g., by direct communication with representative
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45 patient organisations, and by giving talks to local associations of people with ME/CFS).
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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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doi:10.1016/j.jcms.2010.11.001

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3 Figure 1. Flow diagram for study selection

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

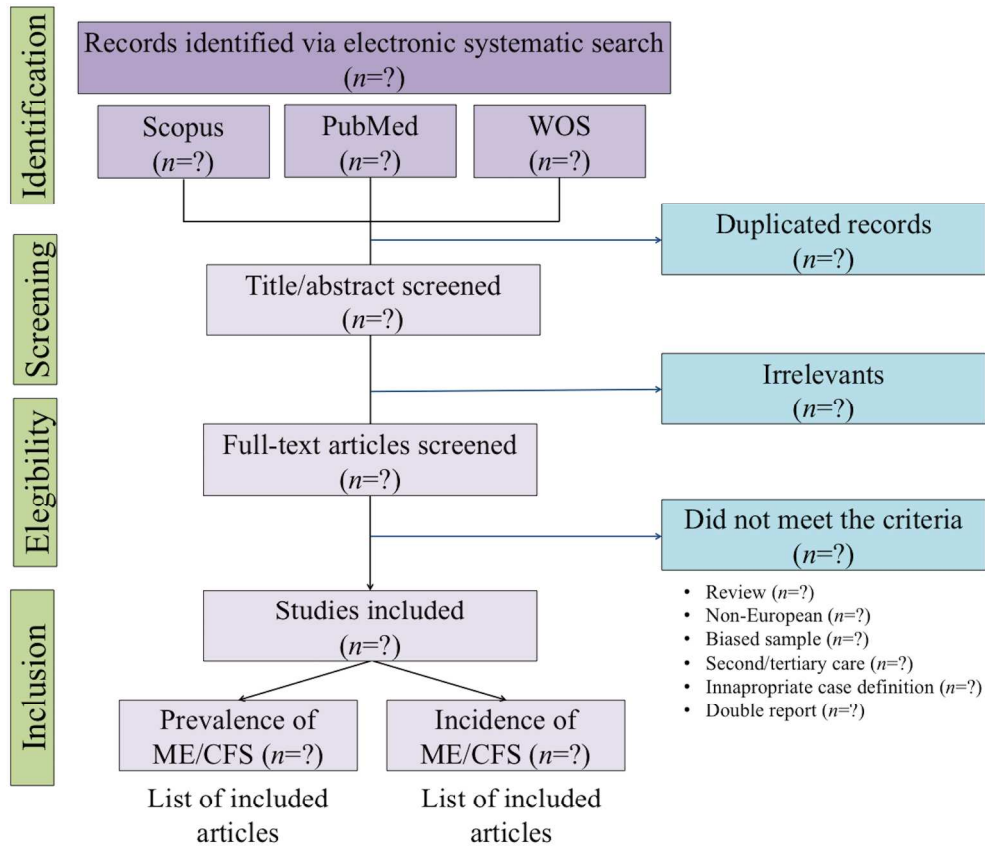


Figure 1. Flow diagram for study selection

423x423mm (300 x 300 DPI)

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3 **1 The prevalence and incidence of Myalgic Encephalomyelitis/Chronic Fatigue**
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5 **2 Syndrome in Europe: the Euro-epiME study from the European network**
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7 **3 EUROMENE. A protocol for a systematic review.**
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15 European Network on ME/CFS (EUROMENE)
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31 39 **Running head:** Protocol of the Euro-epiMe study
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3 41 **ABSTRACT**

4 42 **Introduction.** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a
5
6 43 chronic disease involving central nervous system and immune system disorders, as well
7
8 44 as cardiovascular abnormalities. ME/CFS is characterized by severe chronic fatigue
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10 45 lasting for at least 6 months, including such clinical symptoms as tender cervical or
11
12 46 axillary lymph nodes, muscle pain, joint pain without swelling or redness, post-
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14 47 exertional malaise for more than 24 hours, and un-refreshing sleep. Studies on the
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16 48 epidemiology of ME/CFS in Europe only include single countries and, therefore, the
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18 49 prevalence and incidence of ME/CFS in Europe (as a whole) is unknown. One of the
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20 50 purposes of the European Network on ME/CFS (EUROMENE; EU-funded COST
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22 51 Action; Reference number: 15111) is to address this gap in knowledge. We will
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24 52 systematically review the literature reporting figures from European countries to
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26 53 provide a robust summary and identify new challenges.

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29 54 **Methods and analysis.** We will systematically search the literature databases Scopus,
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31 55 PubMed, and Web of Science for studies published in the last 10 years (i.e., after 2007).
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33 56 No language restriction will be applied. Two independent reviewers will search, screen,
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35 57 and select studies as well as extract data about their main characteristics and evaluate
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37 58 their methodological and reporting quality. When disagreements emerge, the reviewers
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39 59 will discuss to reach a consensus. We plan to produce a narrative summary of our
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41 60 findings as we anticipate that studies are scarce and heterogeneous. The possibility of
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43 61 performing meta-analyses will be discussed in a EUROMENE meeting.

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45 62 **Ethics and dissemination.** Ethical approval is not required as only publicly available
46
47 63 data will be included. Findings will be described in EUROMENE reports, published in
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49 64 peer-reviewed journal(s), and presented at conferences. The findings will be also
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65 communicated to policymakers, healthcare providers, people with ME/CFS and other
66 sections of society through regular channels including the mass-media.

67 **PROSPERO registration number:** CRD42017078688.

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72 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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

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88 INTRODUCTION

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

95 For several reasons, ME/CFS is a challenge for scientists. Firstly, to date, the
96 features of ME/CFS have been poorly defined. For instance, an intense physical
97 discomfort (i.e., malaise) along with flares of ME/CFS symptoms (lasting for longer
98 than 24 hours) is observed after minimum physical exertion [6]. However, whether
99 post-exertional malaise is a distinctive feature of ME/CFS is not yet fully agreed [7].
100 Secondly, related to the lack of consensus on its defining features, a large number of
101 disparate criteria for the diagnosis of ME/CFS are currently used worldwide [8]. Indeed,
102 the most common scenario is to diagnose ME/CFS after exclusion of other diseases
103 [4,9–13]. Thirdly, as different diagnostic criteria are used, ME/CFS prevalence and
104 incidence figures are highly variable across studies. For instance, within an Icelandic
105 study [14], the prevalence of ME/CFS ranged from 0 to 5% by means of the Lloyd et al
106 [15] or Holmes et al [16] criteria, respectively.

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

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3 113 new H2020 and further Framework programme collaborative research projects. Further
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5 114 information about the EUROMENE network is available at:
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7 115 http://www.cost.eu/COST_Actions/ca/CA15111 and <http://www.euromene.eu/>.

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9 116 EUROMENE consists of six closely coordinated working groups. Working
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11 117 group 1 focuses on the epidemiology of ME/CFS and leads the European
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13 118 Epidemiological Study for ME/CFS (Euro-EpiME study). One specific aim of this study
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15 119 is to estimate the prevalence and incidence of ME/CFS in Europe. As a first step, we
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17 120 will systematically review the available literature from European countries in order to
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19 121 provide a robust summary and identify new challenges on the field. It seems likely that
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21 122 more data on the prevalence and incidence of ME/CFS will be needed, both for Europe
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23 123 as a whole and within the European countries. Previously, systematic reviews have been
24
25 124 conducted including studies from many parts of the world [17–19]. However, these
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27 125 previous reviews: (i) were conducted more than 5 years ago [20], (ii) did not report the
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29 126 incidence of ME/CFS, and (iii) did not include children or adolescents.

30 31 32 33 127 **Objective**

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35 128 We aim to conduct a systematic review and, if possible, meta-analyses to determine the
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37 129 prevalence and incidence of ME/CFS in Europe.

38 39 130 **Review question**

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41 131 1. What is the prevalence of ME/CFS in Europe?
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43 132 2. What is the incidence of ME/CFS in Europe?
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3 134 **METHODS**

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5 135 **Inclusion criteria**

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7 136 1. Studies reporting either the prevalence or incidence of ME/CFS, including any of
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9 137 the following clinical diagnostic criteria – CDC-1994 [9], Canadian Consensus
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11 138 Criteria [1], London Criteria [21], International Consensus Criteria [10], or Institute
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13 139 of Medicine criteria [22], irrespective of age groups.

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16 140 2. Studies from European countries.

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18 141 3. Studies in community or primary care settings.

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20 142 **Exclusion criteria**

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22 143 1. Studies without primary data (e.g., reviews).

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24 144 2. Studies conducted in biased samples (e.g., vaccines, virus infection, veterans).

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26 145 3. Studies based on self-report of the diagnosis of ME/CFS.

27
28 146 4. Studies with an inappropriate case definition (e.g., CFS-like illness or other clinical
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30 147 criteria, such as the Oxford criteria due to lack of specificity).

31
32 148 5. Duplicate reports. When populations are overlapping, the study with the largest
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34 149 sample size will be included.

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36 150 6. Studies published more than 10 years ago (i.e., before 2008)

37
38 151 No language restriction will be applied.

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41 152 **Search strategy for identifying relevant studies**

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44 153 The search strategy will consist of two stages: a primary systematic literature search on
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46 154 three electronic databases and a complementary search.

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48 155 ***The primary systematic literature search on electronic databases***

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50 156 Two independent reviewers (F.E.-L. and J.C.-M.) will perform a primary electronic
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52 157 search in PubMed, Scopus and Web of Science on January 9, 2018. Table 1 shows the
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54 158 search strategy.

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3 159 ***The complementary search***

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5 160 We will conduct a twofold complementary search as follows: first, we will perform a
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7 161 backward- (by checking reference lists) and forward- (by checking citations) search of
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9 162 the works included in the present review; and second, grey literature will be addressed
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11 163 by contacting – via email - all the members of EUROMENE to provide, if available,
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13 164 prevalence rates, incidence rates or both of ME/CFS in their countries according to
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15 165 national registers, publications in their own languages, or any other publicly accessible
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17 166 source.

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20 167 **Selection of studies for inclusion to the review**

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22 168 Two independent researchers (F.E.-L. and J.C.-M.) will screen records retrieved by the
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24 169 electronic search by titles/abstracts or full text of works for identifying potential studies
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26 170 and their suitability. When disagreements emerge between the two independent
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28 171 researchers, consensus will be obtained through discussion or when required, the
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30 172 opinion of a third researcher (I.J.B.) will be considered.

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33 173 **Assessment of methodological quality and reporting of data**

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35 174 The methodological quality of the eligible studies will be evaluated with the Joanna
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37 175 Briggs Institute-Checklist for Prevalence Studies [23]. Before applying it, six members
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39 176 of the research team (i.e., F.E.-L., L.N., J.A., S.S., E.L., and M.M.) will develop an
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41 177 agreed appraisal of the tool. This appraisal will be published with the review as
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43 178 supplementary information. The reporting quality of the eligible studies will be
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45 179 evaluated using the observational studies in epidemiology (STROBE) checklist [24].
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47 180 Two independent researchers (i.e., A.I. and X.W.) will evaluate the methodological and
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49 181 reporting quality of the included works. When controversies emerge, studies will be
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51 182 discussed with two other members of the team in order to reach a consensus (i.e., E.B.S.
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3 183 and D.P. for methodological and reporting quality, respectively). The quality
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5 184 assessment will be considered when discussing the findings.

6 7 185 **Data extraction and management**

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9 186 To manage the retrieved records from the electronic search, we will use the Mendeley
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11 187 Desktop. Two independent researchers (F.E.-L. and A.I.) will extract the following
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13 188 relevant data from the included studies: reference (authors and year of publication),
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15 189 country (city or region when relevant), design (i.e., general population online survey),
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17 190 total sample size (*n* and % of women, *n* and % of migrants), age range, setting (e.g.,
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19 191 primary care), case definition (i.e., diagnosis criteria), dates of data collection, overall
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21 192 prevalence and/or incidence and prevalence and/or incidence by gender and age groups
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23 193 (when available). When discrepancies emerge in the coding between the two
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25 194 researchers' results, these will be discussed with another members of the team (i.e.,
26
27 195 N.S.) to reach a consensus.

28 29 30 31 196 **Data synthesis and analysis**

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33 197 We anticipate that studies on the prevalence and incidence of ME/CFS in Europe will
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35 198 prove to be scarce and heterogeneous. The preliminary findings of the review will be
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37 199 presented in a EUROMENE meeting (i.e., September, 2018, in London, the UK) where
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39 200 we will discuss the appropriateness of performing meta-analyses.

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41 201 A narrative (descriptive) synthesis is planned if meta-analyses are not feasible.
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43 202 We will pay special attention to possible factors related to heterogeneity of the findings
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45 203 in order to find patterns that should be considered in future research. For instance, we
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47 204 will discuss whether the prevalence or incidence of ME/CFS differ according to the case
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49 205 definition used to examine the figures. Attention will be also paid to the characteristics
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51 206 of the studied populations (e.g., age group, gender).

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3 207 We will undertake meta-analyses only where pooling of quantitative data is possible.
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5 208 The meta regression analysis will be performed to investigate the sources of
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7 209 heterogeneity of any ME/CFS pooled prevalence and incidence estimate. The I^2 statistic
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9 210 will be used to investigate the heterogeneity. I^2 of 25%, 50%, and 75% will be appraised
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11 211 as low, moderate, and high, respectively [25].

12 212 **Presentation and reporting of results**

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15 213 We will report the findings of the present literature review in accordance with the
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17 214 preferred reporting items for systematic reviews and meta-analyses (i.e., the PRISMA
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19 215 statement [26]). A flow diagram (Figure 1) will illustrate the process of study selection
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21 216 from retrieved records to included studies. For transparency purposes, supplementary
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23 217 files will show which studies were excluded at every stage of the review. If the present
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25 218 protocol needs amendments, they will be publicly available along with their rationale in
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27 219 the EUROMENE website: <http://www.euromene.eu/>

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30 220 In accordance with the data extraction, a table will show the main characteristics of the
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32 221 studies included. Information on the quality of the methodology and reporting of the
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34 222 studies will also be available.

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37 223 If meta-analyses are performed, we plan using comprehensive meta-analysis
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39 224 (CMS) to combine data of prevalence or incidence from different studies to estimate the
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41 225 mean effect. We will select an appropriate model in terms of studies that we include and
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43 226 calculate pooled ME/CFS prevalence and incidence. We will compare the results of
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45 227 random-effects and fixed-effect meta-analyses in sensitivity analyses.

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3 232 **Ethics and dissemination**

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5 233 As systematic reviews use publicly available data, no formal ethical review and
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7 234 approval is needed. The findings of this systematic review will address a specific aim of
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9 235 the European network EUROMENE (i.e., to summarise the available data of the
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11 236 prevalence and incidence of ME/CFS in Europe). The findings will be included in
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13 237 EUROMENE reports published in paper(s) in peer-reviewed journal(s) and presented at
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15 238 conferences and meetings.

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18 239 The findings of the present systematic review will be widely communicated to
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20 240 society using mass media (e.g., interviews on radio, newspaper, television and the
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22 241 Internet). Since our findings may have an impact on policy and healthcare practice, we
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24 242 will also present them to policymakers and healthcare providers.

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26 243 **Patient and public involvement**

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28 244 EUROMENE is multidisciplinary network cooperating with patient organizations via
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30 245 Web platform. Patient organisations are benefiting from dedicated events, dedicated
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32 246 printed media and interaction through social media. We will present our findings to
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34 247 patients with ME/CFS (e.g., by direct communication with representative patient
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36 248 organisations, and by giving talks to local associations of people with ME/CFS).
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38 249 General public will be reached through the Action website, oral presentations and
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40 250 interviews.

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3 256 **AUTHORS' CONTRIBUTIONS**

4 257 FE-L, JC-M, XW, EL, and MM designed the protocol. FE-L drafted the manuscript.

5 258 FE-L, JC-M, XW, IJB, AI, LN, NS, EBS, DP, JA, CS, ES-L, LL, EC, SS, EL, MM

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9 259 revised and approved the final version of the manuscript. MM and EL are the chair and

10
11 260 vice chair of the EUROMENE action, respectively. FE-L will be the guarantor of the

12
13 261 review

14
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16
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22
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28
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30
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32
33 271 study did not have any role in the design, decision to publish, or preparation of the

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35 272 protocol.

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41 274 **Competing interests:** None declared.

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361 Figure 1. Flow diagram for study selection

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

364

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365 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")

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367 Mesh, medical subject headings

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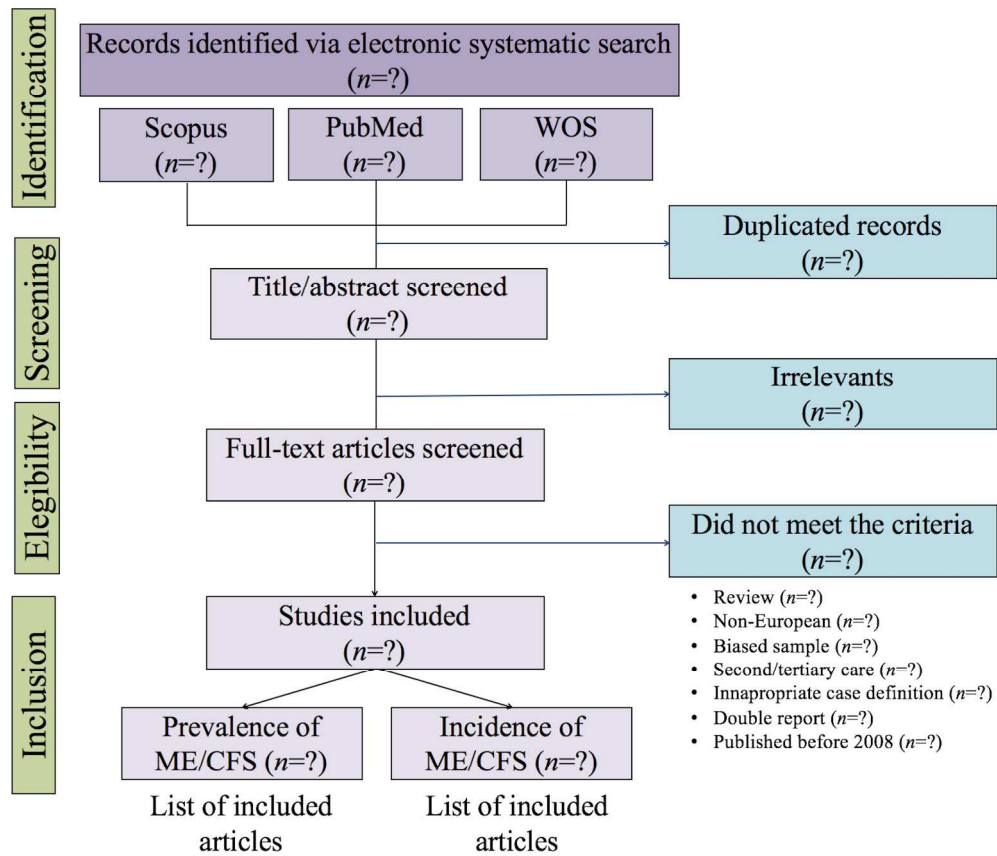


Figure 1. Flow diagram for study selection

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