European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (*EUROMENE*)

COST action CA15111

Deliverable 2

Survey on ME/ CFS including epidemiology, diagnosis and health/social care in Europe from participating countries and from ECDC datasets

The main task of **WG1 on Epidemiology of ME/CFS** during this first period was to retrieve and summarize the available data on ME/CFS across Europe including prevalence, clinical case definition and health-care from EUROMENE participating member countries and from ECDC datasets.

No epidemiological data analysis has previously been conducted across EUROMENE - member countries according to the current and former clinical case definitions for ME/CFS. The aim of this study was to collect the current available data (abstracts/full texts retrieved from Pubmed) for case ascertainment and outcome measures on estimated prevalence rate of ME/CFS from EUROMENE countries.
This is the first study focused on exploring sociodemographic and illness characteristics of ME/CFS cohorts across E.U. countries using a web-survey (EpiME study) (as shown in Table 1). It is vital for identifying potential risk factors and predictors associated with ME/CFS epidemiology and for guiding decisions regarding health-care provision, diagnosis, and management of ME/CFS across Europe. Taking all this into account, a final peer-review manuscript based on a systematic review from all data collected will be prepared and submitted to the Eur J Epidemiol by Dr Fernando Estevez (University of Granada, Spain) and Dr Jesus Castro shortly.

Table 1: Metadata summary on ME/CFS epidemiology from EUROMENE-member countries using a web-based survey (***EpiME study***)

OUTCOMES	GERMANY	NORWAY	SPAIN	SWEDEN	UK	IRELAND	THE NETHERLANDS	ITALY
Paper found (refs. attached)	1 paper (Abst)	5 papers P1: (full text) P2: (Abst) P3: (full text) P4: (full text) P5: (full text)	1 paper (Abst)	2 papers P1: (Abst) P2: (full text)	7 papers P1: (Abst) P2: (full text) P3: (full text) P4: (full text) P5: (full text) P6: (full text) P7: (full text)	1 paper (full text)	2 papers P1: (Abst) P2: (Abst)	4 papers P1: (Abst) P2: (full text) P3: (full text) P4: (full text)
Case definition	CF was assessed as a broader criteria. No case definition for CFS or ME was used.	P1, P2, P3 and P5: 1991 Oxford Criteria, including PVFS subtype. P4:1994 CDC/Fukuda definition	P1: 1994 CDC/Fukuda definition & 2003 CCC	P1 & P2: 1994 CDC/Fukuda definition	**ADULTS** P1: 1986 Ramsay definition P2: 1994 CDC/Fukuda definition, 1991 Oxford criteria & 2002 Australian criteria P3: 1994 CDC/Fukuda definition P4: 1991 Oxford criteria & read codes P6: 1994 CDC/Fukuda definition, 2003 CCC and ECD **CHILDREN & ADOLESCENTS** P5: Non-clinical, trained interviewers according to ICD-10 P7: 2007 NICE clinical guidelines	Face-to-face case-GPs interview	P1 & P2: 1988 CDC/Holmes definition	P1: 1988 CDC/Holmes definition P2: 1998 CDC/Holmes & 1994 CDC/Fukuda definitions P3 & P4: 1994 CDC/Fukuda definition

OUTCOMES	GERMANY	NORWAY	SPAIN	SWEDEN	UK	IRELAND	THE NETHERLANDS	ITALY
Study design	Cross-sectional cohort study, based on a random German general population survey	P1: Cross-sectional study (data from NPR) P2: Longitudinal population-based study (data from various National Registries) P3: Norwegian population-based registry (2008-2012) P4: Clinical cross-sectional study P5: Case-control study	Nationwide representative, retrospective, cross-sectional cohort study	P1: Population-based Swedish Twin Registry (2009-2012) P2: Prospective nested case-control study in a population-based sample	**ADULTS** P1: Community-based postal survey P2: Prospective primary care-based study P3: Baseline data analysis from a trial of complex interventions for fatigue P4: Population-based cohort study according to GPRD P6: Cross-sectional prevalence-based cohort study **CHILDREN & ADOLESCENTS** P5: Random general prospective community-based study P7: ALSPAC birth cohort	Prospective survey from Irish GPs Purpose-designed questionnaires tested by pilot study and sent to 200 random selected GPs	P1: 4 family practices in Leiden P2: Cross-sectional study	P1: General recruited population P2: Questionnaires for general population with persistent fatigue P3: Cross-sectional cohort study as part of The Blood Biobank (Immunogenetics Lab, University of Pavia) P4: Descriptive population-based AMCFS registry

OUTCOMES	GERMANY	NORWAY	SPAIN	SWEDEN	UK	IRELAND	THE NETHERLANDS	ITALY
Sample size	147 CF cases and 2265 HCs	P1: 1670 CFS/ME children (born 1992-2012) identified in the NPR. P2: 4822337 (whole population from NPR) & 3737 new CFS/ME cases. P3: 5809 CFS/ME children & adults P4: 873 CFS/ME Patients. P5: 201 CFS/ME cases & 389 HCs.	1757 CFS/ME patients	P1: 31405 individual members on the Swedish Twin Registry. P2: 19192 twins born between Jan. 1935 and Dec. 1958	**ADULTS** P1: Over 1000 CFS/ME patients were registered P2: 2376 CFS/ME subjects (1199 viral onset & 1177 non-viral onset) P3: 141 CFS/ME patients, only 44 cases (31.2%) met 1994 CDC/Fukuda Definition. P4: 22747 CFS/ME patients P6: 143000 CFS/ME cases (3 UK areas) **CHILDREN & ADOLESCENTS** P5: 842 adolescents and their parents. P7: 14541 pregnancies and 13978 children alive at 1 yrs of age.	139 ME/CFS patients	P1: 23000 ME/CFS patients P2: 601 ME/CFS patients & 4027 of the GPs	P1: 205 study participants P2: 127 patients with persistent fatigue by GPs, and only 63 were diagnosed of fatigue by secondary care Internal medicine service (University of Rome) P4: 81 CFS/ME were contacted by telephone P5: 82 CFS cases from AMCFS

OUTCOMES	GERMANY	NORWAY	SPAIN	SWEDEN	UK	IRELAND	THE NETHERLANDS	ITALY
Age range (women: men)	Mean age: 47.9 ± 18.2 yrs. (CF cases: 57.9 ± 17.4 & HCs: 47.3 ± 19.0)	P1: Children and adolescent (mean age: 14.8 ± 2.5 yrs) P2: <30 yrs P3: 1st. age peak: 10-19 yrs & 2nd. age peak: 30-39 yrs (75.4% women) P4: Mean age: 33 ± 12.1 yrs (75.3% women) P5: Birth date range: 1972-1977	P1: 25-40 yrs. (4:1)	P1 & P2: 42-64 yrs.	**ADULTS** P1: N/D P2: 18-45 yrs P3: Mean age: 40.5 ± 10.4 yrs P4: Mean age: 39 ± 13.8 yrs (5:2) P6: 18-64 yrs **CHILDREN & ADOLESCENTS** P5: 11-15 yrs P7: Median age of 16.6 yrs (IQR: 16.5–16.8)	N/D; (66.2% women)	P1: 25-44 yrs (55% women) P2: N/D	P1 & P2: Adult ME/CFS individuals (N/D) P3: Mean age: 44.7 yrs (range: 18-50 yrs) P4: N/D
Health-care setting	Face-to-face contact survey using questionnaires (USUMA Co., Berlín, Germany)	P1: Specialist health care P2: Specialist and primary care P3: Specialist health care service (hospital and outpatient clinics) P4: Patients referred to an outpatient clinic P5: Specialist health care	P1: Tertiary referral clinical center (CFS/ME Unit, Vall d'Hebron University Hospital, Barcelona)	P1: Data collection from the Swedish National Cancer and in-patient hospitalization registries was available P2: General community-based cohort	**ADULTS** P1: Local health centre P2, P3, P4 & P6: Primary care **CHILDREN & ADOLESCENTS** P5: ONS study of children mental health P7: ALSPAC study Website	Primary care	P1: Primary care (family physicians) P2: Primary health care center	P1, P2 & P3: Specialized referral centre for CFS/ME P4: Tertiary referral clinical center (Aviano and Chieti, Pavia)

OUTCOMES	GERMANY	NORWAY	SPAIN	SWEDEN	UK	IRELAND	THE NETHERLANDS	ITALY
Symptoms assessment tools	FQ (German version), EUROHIS-QoL, SOMS-7 and SOM	P1: None (probably various case definitions) P2: None (GPs classification) P3: None (probably various case definitions) P4: Unspecific symptoms questionnaire, FSS P5: None (descriptive-based diagnosis criteria)	P1: Structural Clinical Interview DSM-IV-TR, FIS-40 and SF-36	P1: Phone interview using computer-based data collection system (tools not specified) P2: Data obtained from computer-assisted telephone interview (tools not specified) (1998-2002). Self-reported stress (based on a single question) and personality scales (EPQ) by mailed questionnaire	**ADULTS** P1: Total Fatigue & GHQ P2: 24-item CFS Questionnaire scale, CIS-R, 11-item FQ, 12- items GHQ, MOS-20 & somatic symptom check list P3: 11-item FQ, HADS, WASA & IPQ P4: Diagnostic codes available in read computer system P6: Mailed questionnaires (containing questions related to symptoms, onset, duration, functional assessment & comorbid conditions) **CHILDREN & ADOLESCENTS** P5: A combination of interviews and rating techniques. 12-items GHQ & BPVS-II completed by mother & adolescents, respectively P7: Parental reported data according to questionnaires (for 1-stage process). Child-reported data according to CFQ, SMFQ, SDQ & NPD (for 2-stage process)	The questionnaire comprised a series of open and closed questions	P1: Database analysis P2: N/D	P1, P2 & P3: Questionnaires to obtain information about demographic data and clinical features P4: Questionnaires to obtain information from patients associated to AMCFS

OUTCOMES	GERMANY	NORWAY	SPAIN	SWEDEN	UK	IRELAND	THE NETHERLANDS	ITALY
Comorbid conditions	N/D	P1: Neurasthenia (9.3%), anxiety/depression (13.8%), sleep disturbance and muscle pain (9.5%), and asthma (17.5%) Remaining papers: N/D	FMS, MPS, degenerative or mechanical spinal disease, sicca syndrome, shoulder tendinopathy, epicondylitis, CTS, PF, hypovitaminosis D, HCL, MCS, dysthymia, PAD, PD, LHL, endometriosis, and thyroiditis	P1: N/D P2: Stress and PD	**ADULTS** P1: N/D P2: Psychological disorders and functional impairment P3: Depression (mean score: 9.8 ± 3.8), anxiety (mean score: 11.6 ± 4.9) P4: FMS P6: Anxiety (70.9%) and depression (55.8%) **CHILDREN & ADOLESCENTS** P5: Anxiety, depression, conduct disorders and maternal distress P7: Psychological problems, life difficulties and school attendance	N/D	P1: N/D P2: Depression & FMS	P4: 5% for autoinmune disorders Remaining papers: N/D

FOOTNOTES

- The (English) key-words combination was:

[('epidemiology' OR 'prevalence' OR 'incidence) AND ('chronic fatigue syndrome' OR 'myalgic encephalomyelitis' OR 'CFS/ME' OR 'ME/CFS') AND ('COUNTRY')]

- No epidemiological data were available for the remaining EUROMENE participating member countries
- All (English) abstracts/full texts and databases were retrieved from Pubmed (except Norway, also searched from OvidSP)

ABBREVIATIONS

• ALSPAC: Avon Longitudinal Study of Parents and Children

• AMCFS: Associazione Malati di CFS

• BPVS-II: British Picture Vocabulary Scale-11

• CCC: Canadian Consensus Criteria

• CF: Chronic Fatigue defined by German study

• CFQ: Chalder Fatigue Questionnaire

• CIS-R: Revised Clinical Interview Schedule

• CTS: Carpal Tunnel Syndrome

• DMS: Diagnostic and Statistical Manual of Mental Disorders

• ECD: Epidemiological Case Definition developed by two of the authors to validate epidemiological research studies

• EPQ: Eysenck Personality Questionnaire

• EUROHIS-QoL: 8-item measure for QoL, derived from the WHOQoL-100 and the WHOQoL-BREF

• FIS: Fatigue Impact Scale

• FMS: Fibromyalgia

• FQ: 11-item self-report Fatigue Questionnaire

• FSS: Fatigue Severity Scale

• GHQ: General Health Questionnaire

• GPs: General Practitioners

• GPRD: General Practice Research Database

• HADS: Hospitalary Anxiety and Depression Rating Scale

• HCL: Hypercholesterolemia

• HCs: Health Controls

• ICD-10: International Classification of Disease, 10th Revision, Classification of Mental and Behavioral Disorders

• IPQ: Illness Perceptions Questionnaire

• IQ: Intellectual Coefficient

• LHL: Ligamentous Hyperlaxity

• MCS: Multiple Chemical Sensitivity

• MOS-20: 20-item Medical Outcome Study-Health Survey Short Form

• MPS: Myofascial Pain Syndrome

• N/D: No data

• NPD: National Pupil-level longitudinal Database

• NICE: National Institute for Health and Care Excellence

• NPR: Norwegian Patient Registry

• ONS: Office for National Statistics

• PAD: Panic-Anxiety Disorder

• PD: Personality disorder

• PF: Plantar Fasciitis

• PVFS: Post-Viral Fatigue Syndrome (ICD-10 G93.3)

• SDQ: Strengths and Difficulties Questionnaire

• SF-36: 36 items Short-Form Health Survey

• SMFQ: Short Moods and Feelings Questionnaire

• WASA: Work and Social Adjustment Questionnaire

The overall task for the first period of **the Working Group 4 on Clinical research/diagnostic criteria** was to survey clinical criterions used in EU countries to set-up diagnosis of ME/CFS and to analyse existing clinical criterions guidelines in order to find-out optimal criteria set. A survey was conducted among the fifteen participating EUROMENE countries and a questionnaire was developed and sent to the respective country members.

The following four countries reported to have national guidelines for diagnosis and diagnostic criteria on ME/CFS: Spain, Italy, UK, and Norway. The Canadian Consensus Criteria from 2003 (CCC) and the Fukuda criteria from 1994 were recommended in three of the guidelines, and the Oxford criteria was suggested in the third one. All the guidelines recommended and in three of the other countries a psychosocial investigation was conducted as part of the diagnosis. The blood tests suggested varied between the countries and various methods and tools for mapping symptoms were used in the different countries. Some countries used separate criteria for children while others did not.

The following four countries reported to have national guidelines for clinical approaches in ME/CFS: Spain, UK, Norway, and Belgium. Procedure for symptom and illness management as well as for Rehabilitative strategies proposed are most often Graded Exercise Therapy, Cognitive Behavioural Therapy and pacing/activity regulation/mind-body strategies.

Five of the countries reported having either a local, regional or a national register for ME/CFS; Latvia, Norway, Spain, Germany and Finland. A total of seven countries reported having a structured biobank; Latvia, Norway, Spain, Germany, UK, Italy and France. Four countries had specific governmental research projects dedicated to ME/CFS; Latvia, Norway, Spain and UK.

The Canadian Consensus Criteria was suggested as standard case definition for research in the EUROMENE countries. The Fukuda criteria may be applied for those already using it and do not want to change to CCC. It was suggested to use a standardized and validated symptom registration tool able to classify within different case definitions and more specific DePaul Symptom Questionnaire and SF-36 were recommended. Methods for assessment of other health information will be further discussed in the working group.

The Working Group 3 on Socio-economics surveyed the available data on the economic implications of ME/CFS. No data was found among existing European health-related databases, and more recently it was confirmed this by searching ECDC databases and the national databases linked to it. No data were found in any of these databases relating to ME/CFS or any of its synonyms (myalgic encephalomyelitis, chronic fatigue syndrome, CFS/ME, or ME and CFS separately).
In the light of this, a review of published literature was carried out. Initial searches were conducted by Derek Pheby and Xia Wang, and a paper has been submitted for publication by Elenka Brenna and Lara Gitto.

Problems of interpretation of published material:

1) Lack of comprehensive case ascertainment: The willingness of doctors to diagnose ME/CFS varies from country to country, but everywhere falls well

short of 100% of cases. This renders any comparative assessment of economic implications very problematic.

2) Lack of consistency of case definitions: Those few cost-of-illness studies that have been published have used a variety of case definitions, which vary markedly in terms of inclusiveness. Consequently, a wide range of estimated costs has emerged, as the table below indicates:

TABLE 2: Cost-of-illness studies of ME/CFS

Report	Country	No. Cases	Source	Case Definition Used	Est. Cost/case
Collin et al, 2011	UK	2170	Secondary care	National Outcomes Database (London definition)	£7558
Sabes-Figuera et al, 2010	UK	222	Primary care	i. Fatigue > 3 months ii. >4 on Chalder Fatigue Scale iii. Age 16-75 iv. No recent change in medication v. Normal FBC, ESR, thyroid function	£7756
Jason et al, 2008	USA	21	Community-based prevalence study	CDC-1994 (Fukuda)	US$8675
Reynolds et al, 2004	USA	235	Wichita study	CDC-1994 (Fukuda)	US$20000
Bibby and Kershaw (Sheffield Hallam report), 2007	UK	2971	Self-selected	Medically diagnosed cases	£16128
Lloyd & Pender, 1992	Australia	42	Population-based prevalence study	Holmes definition	Aus$9514

3) Impact of Case Definitions: Jason (2017) has estimated the impact of differences in case definition on prevalence, and reported that there was a tenfold difference in prevalence between inclusive and exclusive case definitions. This is consistent with a UK study indicating that the Canadian definition identified approximately 50% of those cases identified by the CDC-1994 (Fukuda) definition.

In order to enable the subsequent milestones and deliverables for WG3 to be completed, there is a need for a pan-European agreement on a case definition for ME/CFS to be reached. At the same time, there is a need for a consistent methodology to be developed to enable comparable data to be colected in all participating countries. Consequently, we are watching carefully the work of the working groups the responsibilities of which include epidemiology and case definitions.