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

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Guidelines for health policy makers on prevention losses due to ME/CFS in health and economy aspects

CONTENTS

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Abstract

The topic addressed by this report is the extent to which there may be scope for preventive programmes for ME/CFS, and, if so, what economic benefits may accrue from the implementation of such programmes. We address the questions as to whether there is scope for preventive programmes for ME/CFS, and, if so, whether there are health and economic benefits to be derived from the implementation of such programmes. Given that ME/CFS is attributable to a combination of host and environmental risk factors, and that host factors appear to be most prominent, we consider the economic case for prevention programmes, and whether modifiable risk factors for ME/CFS have been identified which could be addressed by such programmes. We note, however, that there is little consensus about the nature and impact of risk factors for ME/CFS, and, as regards those risk factors about which there is general agreement, few are modifiable, and therefore there is little scope for programmes of primary prevention. The possible exception to this is in the use of agrichemicals, where a precautionary principle suggests that Europe-wide programmes of health education to encourage safe use could be beneficial. There is a need for more research on risk factors for ME/CFS, in order to establish a basis for the development of primary prevention programmes. In particular, there is need for more occupation linked ME/CFS research, as occupational risk factors are better defined and also more persistent in time. There is also a need, and the opportunity, for secondary prevention, in order to minimise the diagnostic delays which appear to be associated with both prolonged illness and increased severity, and hence with increased costs. Such a programme of secondary prevention, in more than one country, should address the unwillingness or inability of primary care physicians either to recognise ME/CFS as a genuine clinical entity, or to diagnose it.

1 Introduction

1.1 ME/CFS

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a poorly understood, serious, complex, multi-system disorder, characterized by symptoms lasting at least six months, with severe incapacitating fatigue not alleviated by rest, and other symptoms, many autonomic or cognitive in nature, including profound fatigue, cognitive dysfunction, sleep disturbances, muscle pain, post-exertional malaise, which lead to substantial reductions in functional activity and quality of life [1,2,3]. Symptomatology, severity and disease progression are extremely variable. It most commonly occurs between the ages of 20 to 50, but affects all age groups. Some three quarters of patients are female [4,5,6]. There is no Europe-wide prevalence data,

but if the commonly held belief that there are some 250,000 sufferers in the UK is correct, then there may be some two million patients in Europe as a whole.

1.2 EUROMENE

The EUROMENE network was established to enable a collaborative, Europe-wide approach to address serious gaps in knowledge of ME/CFS. Its working groups focus on epidemiology, biomarkers and diagnostic criteria, clinical research, and socio-economics, the latter being the remit of Working Group 3. The network now has representation from twenty-two countries, and all the working groups have active involvement of researchers from across Europe.

1.3 Working Group 3 (socio-economics)

The objective of Working Group 3 (socio-economics) is to coordinate efforts to determine the social impact of ME/CFS and to appraise the economic damage from the disease, and to do so by enabling the estimation of the burden of ME/CFS to society and the provision of long-term trend estimates for societal impact. The specific tasks for which the working group has responsibility are:

1. To survey European countries existing data on economic loss due to ME/CFS;
2. To develop approaches to calculate direct economic loss due to ME/CFS;
3. To develop approaches to calculate indirect economic burden due to ME/CFS;
4. To provide integrated outcome assessment framework.

1.4 From extrapolation from UK experience, the total cost of ME/CFS in Europe, including direct and indirect healthcare and other costs and productivity losses, may be in the region of €40 billion *per annum* [7], so even a 1% reduction achieved through programmes of prevention would be a substantial sum which should outweigh the costs of such programmes.. The topic addressed by this report is the extent to which there may be scope for preventive programmes for ME/CFS, and, if so, what economic benefits may accrue from the implementation of such programmes. Subsequent sections of this report consider the economic case for prevention programmes, and whether modifiable risk factors for ME/CFS have been identified which could be addressed by such programmes. Finally, proposals are made to carry forward this agenda.

2 The economic case for prevention

2.1 There is evidence shows that many preventive programmes represent value for money, and that therefore there is a strong economic case for implementing them. Such programmes include, for example, targeted supervised tooth brushing, or tobacco control [8]. Such investments in prevention produce value in health care spending, increased productivity and improved quality of life, particularly when directed at the chronic diseases which are the major drivers of health care costs [9]. There are benefits, in terms of both health and the economic consequences of illness, from programmes that are effective, either in preventing illness or in treating it at an early stage, and there is some empirical evidence to support this belief for certain conditions such as colorectal cancer.

2.2 Thus, in many cases there is every reason to invest in a well-defined package of preventive services that are recognized as effective in preventing disease and offer good economic value, as demonstrated by cost-effectiveness studies, and the demonstration of net savings in comparison with the costs of treatment. However, this is not true of all preventive programmes [10]. This is true not only of countries with advanced health care systems, but also of countries like, for example, India [11]. One estimate is that 40% of health care costs in England could be avoidable if action were taken to address the causes of ill health [12].

2.3 There is evidence indicating that health promotion and primary prevention programmes are cost-effective [13], especially when the role of the recipients is passive, as in immunisation programmes, or when the programme is designed to deliver a public good to a whole community, such as fluoridation [14]. A study of the impact on health care utilisation and expenditure trends of a programme of prevention through behaviour modification found that a primary care model based on the doctor-patient relationship can have q positive impact, both in improving health, reducing the prevalence of chronic disease and disability, and reducing expenditure [15]. This is confirmed by a Report of the Surgeon General, which concluded that a water fluoridation coupled with other dental initiatives would improve dental health and cur costs [16]. Another review concluded that there was indeed potential for preventive services to delay or avoid distressing medical conditions that are expensive to treat [17]. Preventive care, particularly for chronic diseases, can help patients, and reduce costs and impacts on economic activity [18].

3 Impediments to Prevention

3.1 A major challenge to successful implementation of programmes of prevention and demonstration of its economic value lies in the innate conservatism of people, and their

unwillingness to change behaviour, as well as reticence when it comes to paying for such programmes [10], particularly as they require both a long-term view and intersectoral cooperation, and it can take many years for benefits of prevention to emerge [12]. There is a significant gap in the availability of full economic evaluation studies focused on primary prevention of mental health problems among the elderly, and some patients do not appreciate the benefits of preventive programmes [13]. The evidence base regarding prevention programmes is very limited [14]. In addition, the empirical evidence on individual prevention activities is rarely precise or definitive, and there is a lack of good studies. The economic benefits diffuse and appear abstract, and it is not always clear which individuals benefit [19]. In some cases, prevention (e.g. fitness, organic food and clothing) can create a prohibitive burden on individual and family budgets. This can lead to serious budgetary constraints and consequent problems of optimisation of benefits.

4 The Content of Prevention

4.1 Prevention may be primary, secondary or tertiary. Primary prevention is designed to stop the onset of disease, often through behaviour modification, while secondary prevention consists of early detection when the disease is asymptomatic, in order to nip it in the bud. Tertiary prevention is designed to mitigate the consequences of disease through disability limitation and rehabilitation. All three have the potential to reduce the costs of disease [9,10]. Prevention should address the causes of illness, be they social, economic or environmental, including housing, education and employment [12]. A focus on health behaviour and environmental and occupational risks is directed towards the main causes of preventable ill health [19]. Important factors to consider in developing prevention programmes include lifestyle, social and community influences, living and working conditions, as well as socioeconomic, cultural and environmental circumstances [20].

5 Evaluation of prevention

5.1 The studies required to support evidence-based decisions on funding preventive programmes include effectiveness studies, simulation modelling, and economic evaluations [9]. In evaluating prevention programmes, aspects to consider include long-term impacts ,non-health and non-monetary impacts, and different impacts across social groups [12]. The focus of investigation should be to determine whether the benefits accruing for the minority who benefit from a preventive intervention offset the costs to the population as a whole. It should be asked

in respect of any intervention whether it is effective in improving health outcomes, and whether or not it is evidence-based [13]. Economic efficiency does not imply that cost should be minimized, or benefit maximized, but rather that cost be compared with benefit, and that net benefit (the excess of total benefits over cost) be maximized [21]. Good quality economic evaluations are needed to support decision making in the allocation of health care resources [13]. Empirical evidence suggests that the most cost-beneficial prevention programmes are primary measures delivered to individuals, and environmental health measures [19]. In considering approaches to evaluation, it is necessary to consider the extent to which modelling methods could be use to project the clinical and spending impact of prevention programmes, and whether wider impacts on employment should be taken into account. There is a need also to determine appropriate time horizons for evaluations, to consider how health benefits, including health-related quality of life should be measured, and the extent to which it is possible to evaluate prevention programmes using traditional academic models [17].

5.2 Return on investment is an important consideration in evaluating the appropriateness of a proposed prevention programme, including questions of effectiveness and its time period, as well as of cost and perspective (i.e. which costs and benefits are included in the analysis) [8]. Systematic and evidence-based approaches to evaluating prevention programmes, and determining whether they constitute value for money, include effectiveness studies, simulation modelling, and economic evaluations. Such programmes, for example, of early detection through screening, should be held to the same cost-effectiveness standard as treatment services [8]. The proper question for prevention is whether it offers good value, in terms return on investment, bearing in mind that addressing a single risk factor can impact on a broad range of conditions, and that the long time horizon creates an opportunity for the compounding of health benefits [10].

5.3 Health-related behaviours reflect individual characteristics and environmental influences, so different individuals and groups vary in terms of risk of developing chronic diseases and outcomes.[20]. The authors propose a decision-making framework based on the principles of economic efficiency, which takes account of both health benefit and resource costs, and identifies strategies that maximise societal benefits for defined levels of resource input [21]. The authors ask how modelling techniques can provide more rigorous projections of both the clinical outcomes and the spending impact of prevention programmes [17]. A review of health promotion programmes addressing fall prevention in the elderly found enormous differences

in methods and quality [13]. Offering a wide range of preventive healthcare services should have the effect of reducing healthcare spending [18].

5.4 There is a need to elucidate the nature and extent of the evidence that demonstrates cost-effectiveness of disease and injury prevention programs and clinical prevention services [9]. The cost-effectiveness of prevention as a whole is problematic, because such an evaluation may combine interventions of proven effectiveness with others the effectiveness of which is more dubious [10]. Preventive medicine should aim to reduce emergency department attendances and thereby reduce hospital admissions, by identifying and addressing those factors in the community which predispose to such attendances [18]. A systematic review found such large methodological differences in cost-effectiveness studies of falls prevention programmes that the findings of the different studies were not comparable, and it was impossible to draw any general conclusions [13].

5.5 There is a variety of possible approaches to evaluating the health and economic impacts of preventive programmes. Some are of more use to decision makers than others, particularly where they cover a long timespan [17]. Interventions for the prevention of chronic non-communicable diseases (NCDs), and certain types of injuries [mainly address] programmes designed to modify health-related behaviours and their interaction with environmental influences [20]. Research conducted in the UK since the 1970s stressed the relationship between socioeconomic position and health [22]. The WHO Commission on the Social Determinants of Health worked on the basis of a conceptual framework in which two main groups of determinants were identified, viz. structural (e.g socioeconomic and political contexts, social structures and socioeconomic position); and intermediary factors (e.g. biological, behavioural, health system and psychosocial factors, living and working conditions) [23].

5.6 Taking into account the above considerations, the questions must be addressed, firstly as to whether there is scope for preventive programmes for ME/CFS, and, if so, whether there are health and economic benefits to be derived from the implementation of such programmes. The answer to the first question depends on whether theres are risk factors for ME/CFS which are capable of modification by means of such programmes, and this is considered in the next section of this report.

6 Risk factors for ME/CFS

6.1 Much of the research on risk factors has focused on psychology. Psychological risk factors reported include perfectionism, self-sacrificial tendencies, unhelpful beliefs about emotions, and perceived stress [24], personality disorders and childhood traumatic experiences [25]. Other psychosocial risk factors proposed include functional somatic syndromes [26], cultural factors [27], other conditions labelled as somatisation disorders such as irritable bowel syndrome.[28], socioeconomic deprivation [29], maladaptive personality, and personality disorders [30], premorbid stress [31], premorbid distress and depression [32], maternal overprotection [33] and childhood trauma [34,35]. Membership of minority ethnic groups has been identified as another possible risk factor for ME/CFS. However, this may be associated with higher levels of anxiety, depression, physical inactivity, social strain and lack of social support, rather than being part of an ethnic minority *per se* [36]. Psychiatric disorders, or shared risk factors for psychiatric disorders, are likely to have an aetiological role in some cases of CFS/ME [37].

6.2 Risk factors identified in children and adolescents include family adversity [38], maternal anxiety or depression [39], It is more common in those who are socially deprived [40], and also among adolescents who experience anxiety and decreased physical activity [41]. However, other authors have found no relationship between childhood trauma and ME/CFS [42], and much of the evidence for psychosocial risk factors for ME/CFS is conjectural and unconfirmed. A systematic scoping review failed to reveal definitive evidence of risk factors for ME/CFS [43]. Another study failed to find any association between maternal or child psychological distress, academic ability, parental illness, atopy, or birth order and lifetime risk of CFS/ME, which was increased by sedentary behaviour [44].. Another study found physical factors such as disability and fatigue to be more prominent as risk factors for ME/CFS than psychosocial factors such as stress and coping [45]. The studies listed above for the most part identified associations rather than causal relationships, and Hickie *et al* concluded that psychological disturbance was likely to be a consequence of ME/CFS, rather than a risk factor for it [46].

6.3 <u>Viral aetiology</u>

6.3.1 Viral infections are involved in the aetiology of ME/CFS [47]. Various viral illnesses have been implicated, including for example infectious mononucleosis [48,49,50], and various sites of infection, including gastrointestinal infections [51]. Whether or not a viral infection creates a risk of ME/CFS depends on a number of parameters, including virus burden, strain, patterns of

replication and life cycle [52]. Cases may be epidemic or sporadic, epidemic cases appearing to have a better prognosis [53].

6.4 Agrichemicals and ME/CFS

6.4.1 Fatigue syndromes may be secondary to occupational exposures to organochlorine or organophosphate compounds [54]. One study found that patients with unexplained, persistent fatigue had higher levels of DDE [1,1-dichloro-2,2-bis (p-chlorophenyl) ethane – an organochlorine] compared with controls [55]. It appears that the major hazards of pesticide use are poisoning associated with operator exposure of operators as a result of misuse. UK Press reports assert involvement of organophosphates in the development of ME/CFS, and the risk to highly exposed agricultural workers cannot be disregarded [56]. A study of reports to the Veterinary Medicines Directorate of ill health attributed to pesticide exposure among agricultural workers found that ME'CFS-like symptoms were frequently mentioned, and questionnaire responses indicated an association with organophosphate exposure [57]. Another study found that patients with a fatigue syndrome following organophosphate exposure manifested some differences in symptoms compared with sporadic cases of ME/CFS [58], but both groups conformed to the CDC-94 (Fukuda) case definition [59]. This is confirmed by a study comparing patients with Gulf War syndrome, ME/CFS and the fatigue syndrome associated with organophosphate exposure, which found many similarities between the three conditions, but only patients with ME/CFS manifested peripheral cholinergic abnormalities in vascular endothelium, perhaps indicating a different aetiology [60].. A study of chlorinated hydrocarbon levels in patients with chronic fatigue syndrome concluded that organochlorines may indeed be involved in the aetiology of ME/CFS [61], and it could be that this involvement of such environmental chemicals is in combination with genetic factors [62].

6.4.2 There have been reports of an outbreak of ME/CFS in Nevada at the same time as an increased incidence of non-Hodgkin's lymphoma [63,64]. A causal relationship has been suggested [65], but both conditions may be attributable to exposure to agrichemicals, particularly organochlorines [66]. However, a review of the research literature on the role of chemical exposures in the aetiology of ME/CFS concluded that the evidence of possible associations was inconclusive, and that 'the current level of evidence does not suggest the need for any specific environmental public health action' [67].

6.5 Other risk factors

6.5.1 The risk of ME/CFS is increased if a close family member also has the illness, suggesting a role for genetic factors [68,69]. Other proposed factors include female gender, age, previous exposure to stress or toxins, occupational exposures and infectious diseases [67], poorer health status [70], gynecological conditions and surgery [71], ethnic minority status [72], premorbid unexplained severe fatigue [73,74]. The mechanism through which such risk factors take effect could be oxidative stress [75], while the increased risk of ME/CFS due to profound inactivity, deconditioning or sleep abnormalities may be mediated via neuroendocrine dysregulation [76].

6.5.2 Two reports from the UK ME/CFS Biobank confirmed that little was known about risk factors for ME/CFS [77], and that there was little consistency in published reports [78]. Their studies confirmed the involvement of a variety of infections, including common colds and flu, in the aetiology of ME/CFS [78], while smoking and low income may be risk factors for severe cognitive and sleep problems in ME/CFS [77].

6.6 Perpetuating factors and outcomes

6.6.1 A systematic review asserted that factors associated with worse prognosis included old age, chronic illness, comorbid psychiatric disorders, and, controversially, belief in a physical cause for the illness [79]. Severity of fatigue and psychiatric morbidity at baseline were associated with persistence twelve months later [80]. Among adolescents, risk factors for prolonged illness include older age at the outset, pain, and poor mental health and self-esteem [81]. Cardiovascular morbidity and mortality are increased in ME/CFS. Oxidative damage to DNA is found both in severe depression and ME/CFS, and is also a risk factor for atherosclerosis, hence the increased cardiovascular morbidity in ME/CFS [82]. In addition, reduced coenzyme Q10 may be the cause of chronic heart failure and increased cardiovascular mortality in ME/CFS [83]. In conclusion, it is likely that ME/CFS is attributable to a combination of host and environmental risk factors [84]. In most cases, a number of factors may be involved [85], of which host factors appear to be most prominent [86].

7 Scope for Prevention in CFS

7.1 What this review has demonstrated is that there is little consensus about the nature and impact of risk factors for ME/CFS, and, as regards those risk factors about which there is general agreement, few are modifiable, and therefore there is little scope for programmes of primary prevention.

7.2 Secondary prevention is a different matter, however. A UK study of risk factors for severe ME/CFS (i.e. being housebound or bedbound) found that early management of the illness appeared to be the most important determinant of severity [87]. This confirmed the findings of an earlier, population-based study, which showed that shorter illness duration was a significant predictor of sustained remission, and thus early detection of CFS is of utmost importance [88], as well as removal of barriers to healthcare utilisation, which are a serious problem [89].

7.3 Previous work undertaken by the Working Group has considered the reasons for delay in diagnosis, which is the principal barrier to healthcare utilisation. We reviewed the literature and conducted a survey among EUROMENE participants [90]. The research literature indicates that a high proportion of primary care physicians are unwilling or unable to diagnose ME/CFS. In Ireland, Fitzgibbon et al in 1997 found that 58% of GPs accepted CFS as a distinct entity [91]. In Belgium, a survey of patients attending a fatigue clinic concluded that only 35% of GPs had experience of CFS, while only 23% had sufficient knowledge to treat the condition [92]. A Norwegian study found that the quality of primary care was rated poor by 60.6% of ME/CFS patients [93]. In a survey of 811 GPs in South-West England, with a response rate of 77%, 48% did not feel confident with making a diagnosis of CFS/ME and 41% did not feel confident in treatment, though 72% of GPs accepted CFS/ME as a recognisable clinical entity [94]. Bayliss et al reiterated that research indicated that many GPs lacked confidence and knowledge in diagnosing and managing people with CFS/ME [95]. A study in South Wales concluded that the level of specialist knowledge of CFS in primary care was low, and only half the GP respondents in their survey believed that the condition actually existed [96].

7.4 A survey of EUROMENE participants suggested that, in some countries, as few as 20% of people with ME/CFS were referred to specialist care, which was in any case very variable in nature. There is official guidance on treatment pathways for ME/CFS only in Spain, Norway, the Netherlands and the UK. In Italy and Latvia, the majority of GPs did not recognize ME/CFS as a genuine entity. This is also true of Spain as a whole, though not of Catalonia. In France, it is generally regarded as psychological in nature. In both the UK and the Netherlands,, it is officially recognised, though many GPs still refuse to accept this. In Catalonia, GPs were said to be confident in diagnosing ME/CFS, but in Latvia, Norway, the Netherlands, France and the UK, there was considerable lack of confidence. The proportion of patients with ME/CFS who consult their GPs and are in fact diagnosed by them was generally said to be low or unknown. In those countries where a proportion was estimated (Spain, France, UK), it was thought to be around 20-50% [7].

7.5 Overall, it is clear that, in Europe, a high proportion of GPs, likely to be at least 50%, do not recognise ME/CFS as a genuine clinical entity and therefore never diagnose it. Among those GPs who do recognise its existence, there is a marked lack of confidence in making the diagnosis and managing the condition. Therefore estimates of the public health burden of the illness, even where these exist, are likely to underestimate substantially its true prevalence [7].

8 Conclusions and Recommendations

8.1 There is little scope for primary prevention programmes for ME/CFS, on either health or economic grounds, since there is little consensus about the modifiable risk factors that could be addressed by such a programme.

8.2 The possible exception to this is in the use of agrichemicals, where a precautionary principle suggests that Europe-wide programmes of health education to encourage safe use could be beneficial.

8.3 In addition, the new European Human Biomonitoring initiative [97] is endeavouring to create a consistent mapping of agri-risks at least for some representative geographical entities. The opportunities arising from this and similar research programmes on biomonitoring and soil would create an opportunity for ecological studies of the geographical distribution of ME/CFS cases, if and when the problem of misdiagnosis is resolved.

8.4 There is a need for more research on risk factors for ME/CFS, including occupational risk factors, in order to establish a basis for the development of primary prevention programmes.

8.5 There is a need, and the opportunity, for secondary prevention, in order to minimise the diagnostic delays which appear to be associated with both prolonged illness and increased severity, and hence with increased costs.

8.6 Such a programme of secondary prevention, in more than one country, should address the unwillingness or inability of primary care physicians either to recognise ME/CFS as a genuine clinical entity, or to diagnose it.

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Appendix – Membership of the Working Group

The following have participated in the activities of Working Group 3:

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Julia Blanco	Fundacio Institut Germans Trias I Pujol, Barcelona, Spain
Elenka Brenna	Universita Cattolica del Sacro Cuore, Milan, Italy
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