

UK CFS/ME Research Collaborative conference report

13-14 October 2015

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Introduction

“I have a much better understanding of the wider research going on, and I feel motivated by meeting patients.”

“It has supported me with new, scientific data which I can call upon to spread awareness of the disease.”

That’s just some of the feedback from researchers who attended the second annual UK CFS/ME Collaborative conference.

With more than 90 research delegates from Norway, Belgium, Australia, New Zealand, the US and the UK, plus an additional 50 patients, carers and advocates, the two-day programme of presentations, discussions and workshops fizzed with enthusiasm and potential.

The CMRC Executive Board extends huge thanks to the Wellcome Trust and Arthritis Research UK, who each made a £10,000 contribution to fund the event and support the ongoing work of the CMRC. This builds on ongoing support from the Medical Research Council which has, over the past two years, provided critical funding for us.

Arthritis Research UK also co-facilitated a workshop, exploring what we can learn from research in the fields of arthritis and CFS/ME and the potential for future collaboration.

I would like to thank the following contributors to this report:

- Simon McGrath (@smjnotes on Twitter)
- Karen Hainsworth
- Russell Fleming
- Dr Charles Shepherd, Honorary Medical Adviser, ME Association
- Dr Neil Abbot, ME Research UK
- Sonya Chowdhury, Chief Executive, Action for M.E.
- Clare Ogden, Head of Communications and Policy, Action for M.E.
- Emily Beardall, Volunteer Pharmacist, Action for M.E.
- Joe Martin, Online Communities Officer, Action for M.E., who filmed the conference presentations for livestream: you can view these online at www.tinyurl.com/actionformeyoutube

Finally, I must extend my gratitude to everyone who supports the work of the CMRC: your contribution, and your commitment to working together, means that we can drive forward much-needed progress in the field of CFS/ME research.

Stephen Holgate
CMRC Chair

The 2016 CMRC conference is provisionally scheduled to take place on Wednesday 12 and Thursday 13 October. To find out more about the CMRC, including how to become an Associate, Student or Professional Member, please visit www.actionforme.org.uk/research/uk-cfsme-collaborative

CONTENTS

- 5 Welcome
Prof Stephen Holgate, UK CFS/ME Research Collaborative Chair

Plenary Session 1: Neuropathology

- 8 Keynote Presentation: Stanford ME/CFS Collaboration: Collaboration, Innovation & Discovery
Prof José Montoya, Stanford University
- 10 Neural correlates of fatigue: a voxel-based morphometric MRI study of CFS/ME
Whitney General, Bristol University
- 11 Brain white matter hyperintensities are not a common finding in CFS
Andreas Finkelmeyer, Newcastle University

Workshops

- 12 Patient reported outcome measures
Dr Kirstie Haywood, Warwick University
- 13 Fatigue matters
Prof Julia Newton, Newcastle University and Prof Chris Macdonald, Arthritis UK
- 13 Autonomic Nervous System
Dr James Frith, Newcastle University
- 14 Neuropathology
Prof Richard Reynolds, Southampton University
- 14 Clinical Trials
Dr Esther Crawley, Bristol University

Plenary Session 2: Widening the Net

- 15 Health & Social Policy Research and M.E.
Prof Liz Perkins, Liverpool University
- 16 Imaging the Neural Correlates of Post-Exertional Malaise in CFS/ME
Dr Mark Edwards, St George's University of London
- 18 The epidemiology of CFS/ME in adolescence
Dr Esther Crawley, Bristol University
- 19 Identifying the biological fingerprints of fatigue
Prof Fai Ng, Newcastle University
- 20 Persistent fatigue induced by Interferon-alpha: a new immunological model for CFS
Alice Russell for Prof Carmine Pariante, King's College London

- 21 Understanding the pathogenesis of autonomic dysfunction in CFS and its relationship with cognitive impairment
Prof Julia Newton, Newcastle University

Plenary Session 3: Autonomic System

- 22 Autonomic Nervous System in CFS/ME
Prof Jo Nijs, Vrije Universiteit Brussel
- 23 Cardiac iodine-123-meta-iodo-benzylguanidine uptake in CFS associates with autonomic function and fatigue severity
Prof Julia Newton on behalf of George Petriades, Newcastle University
- 24 Reduced cardiac volumes in CFS associated with plasma volume but not length of disease
Prof Julia Newton, Newcastle University

Plenary Session 4: Clinical Trials

- 25 Rituximab Trial
Dr Øystein Fluge, University of Bergen
- 26 Post viral CFS/ME patients have normal levels of B cell populations
Dr Caroline Strachan, Leeds Partnerships NHS Foundation Trust
- 27 Cohort Profile: The Collaborative on Fatigue Following Infection (COFFI)
Dr Simon Collin, Bristol University

Plenary Session 5: Sleep

- 28 Sleep and CFS/ME
Prof Jim Horne, Loughborough University
- 29 Assignable causes for fatigue in Primary Sjögren's syndrome: data from the UK primary Sjögren's syndrome registry
Rebecca Lambson, Newcastle University
- 30 From healthy to being ill with post-infectious fatigue syndrome: a qualitative content analysis of illness trajectory
Eva Stormorken, Oslo University

Anne Faulkner Memorial Lecture

- 31 The bigger picture: big data, genomics, epigenetics and metabolomics
Prof George Davey Smith, Bristol University
- 37 Closing Remarks, Reflections & Where Next for the CMRC
Prof Stephen Holgate, UK CFS/ME Research Collaborative Chair
- 38 **Poster presentations**
- 39 **Conference feedback**

Welcome

Prof Stephen Holgate, UK CFS/ME Research Collaborative (CMRC) Chair

Prof Holgate opened the conference, drawing on the [recent landmark report](#) by the Institute of Medicine (IOM).

“We’re dealing with a serious, debilitating condition,” he said. “But what makes it different from many other chronic conditions is that the resulting disability and impairment is substantial.”

Unfortunately, answers remain elusive. “Despite all the efforts we all try to make, we don’t have an effective, mechanistic cause; nor do we have a clearly defined way of diagnosing with some simple test procedures.”

The resulting confusion, along with the historical view that CFS/ME is made up in the minds of patients, has caused a terrible impasse between patients and healthcare professions.

“This is a serious, serious issue,” said Prof Holgate. “Patients often experience hostility from healthcare professionals in terms of diagnosis and management.”

But things are changing. The IOM report crystallises the fact that CFS/ME is a recognisable medical condition, albeit one that encompasses different illnesses within it.

“I think all of us realise we are not dealing with a single disease entity. We are dealing with a complex mix of diseases that are expressing themselves through different causes and mechanisms,” he said.

And even if the IOM report’s suggested name change (systemic exertion intolerance disease) is debatable, the IOM definition is important because it is inclusive: it catches the whole population. Rather than preconceived (and potentially inaccurate) descriptors and subdivisions being imposed up on this illness, this opened the way for stratification using cutting-edge science.

The vision

With research gaining momentum, Prof Holgate presented a new vision for testing for and treating CFS/ME. His involvement with the Medical Research Council (MRC) and the Horizon 2020 programme in Europe on stratified or personal medicine, gives him keen insight into this. And having co-authored a report for the European Union on this topic, Prof Holgate sees a revolution occurring.

“For the very first time, medically and scientifically as well as politically, we’re putting patients at the centre of all this.”

New technology and personalised medicine is the way forward and particularly crucial in a group of diseases that manifests in so many complex and different ways.

Agreeing with the Chair of the National Institutes of Health’s Pathways to Prevention (P2P) programme report, he said, “Innovative biomedical research is urgently needed to identify risk and therapeutic targets. We need to have a greater

understanding of the impact of this condition across the life course. We have to address knowledge gaps.”

Prof Holgate stressed the importance of collecting biological samples from clinically and physiologically phenotyped patients, what the P2P report refers to as the Biomarker Discovery Programme. Any research must include the full range of CFS/ME patients in terms of age, ethnicity and severity.

New researchers are key. “When the MRC initially put some money into this field two or three years ago, it was to bring new voices in,” said Prof Holgate. “We need to bring scientists who are experts in their own field, to come in and help us unpick the complexity of this group of conditions. The methodology and the technology that we need to do this is going to be quite different from what we are used to using in the past.”

The Grand Challenge

Prof Holgate set the CMRC’s Grand Challenge, saying that we must “agree a practical case definition [and then] deliver a pan-UK, joined up approach to phenotyping this group of patients using modern statistical approaches, applied to clinical and physiological routine pathological data.”

Thirdly, he said, we need to collect biological samples, and look at not only disease process but also environmental factors such as diet and chemical exposure. Answers would surface when biological information was integrated with the different phenotypes. Pathway analysis would be used to unpick the causal mechanisms and identify novel therapeutic interventions.

“It sounds all very simple and straightforward but of course it’s not: it’s very complicated and very challenging,” he conceded. “But it is being done in other disease areas and I think this gives us the confidence that we can do it.”

Cancer and diabetes, for example, and Prof Holgate’s own field of asthma are already sub-phenotyping using new methods. “We all thought [asthma] was a homogeneous condition,” he recalled. “We have treatments that are targeted on the basis that it is a homogeneous condition but it turns out that that is not the case.

“New technology and advanced statistical methods have shown that there are six different types of asthma which are very different from each other. Each one of those has a different causative molecular and cellular pathways associated with it.” This explains why current treatments don’t work for all patients.

Next steps

Prof Holgate has a plan to get things moving. “The patient charities will be needed to help us recruit patients across the whole country,” he said. “We need the health professions, scientists, statisticians and clinicians to come together to agree a national protocol and to start looking into the multi-omics technology platforms.”

Meanwhile, he intends to run a two-day workshop for key stakeholders in non-CFS/ME research fields, who are already using this technology for analytical work. The hope is their knowledge and insight will take CFS/ME research to a new level.

Such big plans are inspiring but they also come with a warning. “This is going to mean putting aside personal ambition and looking at the whole effort as a national effort: everybody is going to gain if we do it properly,” said Prof Holgate. “It’s about joining forces and translating the theoretical way of moving this forward into a reality.”

And though the complexity of CFS/ME will present its own challenges, Prof Holgate is sure of one thing: “We can deliver on this if we put our minds to it.”

Plenary Session 1: Neuropathology

Keynote Presentation: Stanford ME/CFS Collaboration: Collaboration, Innovation and Discovery

Prof Jose Montoya, Stanford University

Prof Jose Montoya leads the multidisciplinary [ME/CFS Initiative](#) at Stanford University, a research group that explores the role of infection in the condition. He opened the first plenary session by inviting delegates to join him in a minute's silence in tribute to his close colleague Dr A Martin Lerner, who had recently died. Dr Lerner had worked with Prof Montoya on a number of research studies, including the use of antiviral treatment.

Like Prof Holgate, Prof Montoya referred to the impact of the Institute of Medicine (IOM) report and is a supporter of the new IOM diagnostic definition for CFS/ME. He believes that clinicians need a simple and accurate way of making a diagnosis, one better than currently available options. Work from Prof Montoya's Stanford group indicates that there is a strong (90%) concordance between Canadian, Fukuda and IOM definitions.

He highlighted that people with CFS/ME had been ignored and humiliated by the very people who were supposed to be helping them – the medical profession. "I have a wish and a dream that medical and scientific research societies in the US will apologise to their CFS/ME patients," he said.

Turning to treatment, Prof Montoya described how the publication of a flawed clinical trial involving acyclovir had led to the view that CFS/ME was not caused by Epstein–Barr virus (EBV) infection and that antiviral drugs do not have any role in the treatment of CFS/ME.

Despite this, he has been involved in a number of the clinical trials that have assessed the efficacy and safety of the antiviral drug, valganciclovir. This is a treatment option involving a lower dose than is normally used in other situations, over a prolonged period of time (at least six months and possibly much longer), that he now uses for some CFS/ME patients with considerable success.

In addition to antiviral activity and reduction of latent HHV-6 replication, Prof Montoya believes that this drug may have immunomodulatory effects in CFS/ME as well (it can decrease the level of white blood cells called monocytes and reduce microglia activation in mice).

Prof Montoya then described some of the other research that his multidisciplinary group at Stanford are carrying out on a large group of CFS/ME patients, along with healthy controls, with the help of a \$5 million anonymous donation.

Immune function studies

These look at the response to infection with various organisms and the role of immune system chemicals called cytokines, and how the cytokine pattern changes over time (less or more than three years – the [Hornig/Lipkin study](#)), as well as daily fluctuations in cytokines relating to activity levels.

To do so they can measure more than 50 individual cytokines and have access to a cohort of around 200 CFS/ME patients and 400 controls. The team at Stanford intend to examine the function and role of natural killer (NK) cells. A proposed research study will also involve a detailed study of the role of NK cell status and function in CFS/ME.

Virology studies

These examine the role of latent herpes viruses including EBV and HHV-6 and how low NK function may be maintaining HHV-6 activation in CFS/ME. Prof Montoya also referred to research involving Torque viruses. Torque teno virus is considered to be a relatively new global marker of immune function and the more immunosuppression occurs, the higher the level of torque viruses.

Prof Montoya pointed out that torque viruses have been found to be lower in CFS/ME – adding further support to the role of immune system activation.

Neuroimaging studies

These look at both grey and white matter in the brain. One study has used diffusion tensor imaging, an MRI based technique that can visualize location, orientation and anisotropy of white matter tracts in the brain. This study has recently been published and reported a very significant structural abnormality involving the right arcuate fasciculus.

This structure contains fibres, which connect different areas of the brain. The fibres are thicker in the right arcuate fasciculus of CFS/ME patients than in healthy controls and the inference that nerve fibre transmission is therefore affected could turn out to be a diagnostic marker for CFS/ME.

Genetic studies

These examine human leukocyte antigen characteristics and a genetic predisposition to CFS/ME.

You can read more about the [Stanford ME/CFS Initiative team](#) on its website.

Neural correlates of fatigue: a voxel-based morphometric MRI study of CFS/ME Whitney General, University of Bristol

The University of Bristol's Whitney General outlined the history of brain grey matter investigations in ME/CFS, and described the voxel-based morphometric experiments she and her colleagues have undertaken to explore changes in grey matter volume in the brain, relating these to fatigue and cognitive performance.

The study includes 22 patients with CFS/ME (19 females) who have a mean age of 36.4 and had been ill for, on average, 21 months; plus 22 sex- and age-matched healthy controls.

All participants had a high-resolution structural brain scan in 3Tesla MRI scanner at Clinical Research and Imaging Centre in Bristol, and then completed the Chalder fatigue questionnaire within the next three months.

The results show that, compared to healthy controls, CFS/ME patients have increased grey matter density in sensory brain regions and the frontal lobe; these are largely involved with executive function and attention.

Results also show decreased brain grey matter density in the posterior medial parahippocampal gyrus; this part of the brain is involved with memory.

Ms General put forward the tentative hypothesis that prolonged hyperactivity might be responsible for later atrophy, as reported by reduced grey matter in the occipital and frontal lobes of CFS/ME patients (Puri et al, 2012).

She suggested we need much larger sample sizes, longitudinal studies, and the use of structural MRI studies alongside functional ones, to see if increased grey matter is associated with early stages of CFS/ME, and decreased grey matter is associated with symptom severity and length of illness.

Brain white matter hyperintensities are not a common finding in ME/CFS
Dr Andreas Finkelmeyer, Newcastle University

Dr Finkelmeyer discussed the history of brain white matter hyperintensities, ie. areas that show abnormally high signal intensities in certain types of MRI scans.

He described his recent study using fluid-attenuated inversion recovery (FLAIR) imaging, with careful exclusion of patients with co-morbid depression, and subjects matched with controls for age, sex and physical activity levels. Each underwent several FLAIR scans, and white matter hyperintensities from the scans were extracted using a semi-automated method based on intensity and location with subsequent consensus review.

Dr Finkelmeyer found no evidence for increased white matter hyperintensities burden in his sample of 41 CFS/ME patients, with few, weak correlations with objective measures of cognition; and no correlation with self-reported cognitive difficulties.

Workshops

Conference delegates were able to attend one of five workshops. The first two were open to all, while the others were for Professional and Student Members of the CMRC.

Patient-reported outcome measures

Dr Kirstie Haywood, Royal College of Nursing Research Institute (RCRNI), University of Warwick and PhD student Roxanne Parsons, University of Bristol

Dr Kirstie Haywood leads the Patient Reported Outcomes research theme at the Warwick Medical School and Roxanne Parsons is a PhD student, supervised by Dr Haywood, and Drs Esther Crawley and Ali Heawood. Roxanne is developing a patient-reported outcome measure (PROM) for children with CFS/ME.

The workshop, developed in collaboration with a sub-group of members of Action for M.E.'s Patient and Carer Reference Group, sought to discuss, explore and identify aspects of health and well-being that should be included in a patient-completed questionnaire or PROM, developed to capture how patients feel, what they can and cannot do and their ability to live normal, productive lives.

The workshop began with a definition of PROMs are and how they are developed, with specific reference to Roxanne's current programme of work, and their potential contribution to healthcare.

This was followed by lively and engaged discussions with participants discussing how CFS/ME interferes with people's lives and what should be included in a new PROM specific to the lived-experience of CFS/ME. The 14 participants included people with long-standing CFS/ME (currently mild/moderate impact), carers of an individual with severe, long-standing CFS/ME, a representative from a patient organisation, and researchers with a specific interest in CFS/ME.

The importance of a PROM that captures what really matters to people with CFS/ME was discussed at length. Two over-riding categories emerged from the discussion:

- the importance of symptoms associated with CFS/ME – including pain, increased sensitivities, sleep disruption, poor memory or concentration
- the consequence and impact of these symptoms on an individual's ability to live a 'normal', productive life.

The importance of recognising the individual nature of CFS/ME and how 'treatment success' might be differently defined was discussed. For example, for some, success may be reflected in a relatively minor change in an important outcome. For many, managing well and being able to do what you want to do were viewed as important outcomes. However, the importance of payback and the frustration associated with CFS/ME was discussed by all participants. One commented: "It's not 'Can you do it?' it's what happens after!"

There was clear consensus from the group of the importance of developing a patient-derived PROM that captured the issues that really matter to patients. Such a measure does not currently exist. The results from the workshop will be synthesised and used to inform the development of future grant application.

Fatigue matters

***Prof Julia Newton, Newcastle University and
Prof Chris Macdonald, Arthritis Research UK***

The aim of this workshop was to explore similarities and differences between the fatigue experienced by people with arthritis, and people with CFS/ME. Prof Macdonald highlighted that:

- there are biologics (genetically-engineered proteins derived from human genes) for rheumatoid arthritis (RA)
- RA patients try to use pacing but report that it doesn't help them
- physical exercise only moderately affects fatigue in RA patients
- cognitive behavioural therapy has been found to be helpful for things such as realistic expectations (eg. I must do the housework or I'm a bad mother) leading to pushing too hard.

He also proposed a model for RA involving psychological factors, inflammation, pain, anxiety, deconditioning and behaviours such as pushing too hard.

Based on her work with the Clinics for Research and Service in Themed Assessments (CRESTA) in Newcastle, Prof Newton pointed out that:

- fatigue in CFS/ME means forced resting rather than elective resting
- disease severity apparently doesn't relate to fatigue severity
- CRESTA is a general fatigue clinic, not specifically for CFS/ME
- concept mapping has been used to identify common needs needing to be met for all fatigue patients (Hackett et al, 2011).

Discussions led to suggestions for areas to investigate and take forward, including:

- teenage pre-illness physical symptoms eg. growing pains, as possible predictors for adult rheumatology conditions
- earlier diagnosis
- earlier advice on managing fatigue
- disease-modifying treatments similar to those for RA being made available to CFS/ME
- follow-up treatment beyond the short management courses (eg. pain classes, Expert Patient Programme) and the predefined block of clinic sessions at CFS/ME clinics.

Autonomic Nervous System

Dr James Frith, Newcastle University

Dr Frith is a Clinical Senior Lecturer, working in the Institute for Ageing and Institute of Cellular Medicine, Newcastle University. He is also a practising clinician, working as a Consultant Geriatrician in the Newcastle Hospitals NHS Foundation Trust.

Dr Frith's research interest is falls and syncope (blackouts, fainting and unexplained falls) with a particular interest in the condition orthostatic hypotension (a drop in blood pressure on standing upright which can cause dizziness, fatigue, falls and syncope).

Participants in this workshop considered the following questions:

- Are treatments used in other autonomic disorders (such as orthostatic hypotension) translatable to CFS/ME or POTs?
- Are non-drug therapies such as bolus water drinking, compression hosiery and physical counter-maneuvres acceptable/achievable/deliverable to the most severe cases?
- Are medications such as midodrine effective?
- How can we improve the evidence-base for treatments for CFS/ME associated autonomic disorders?
- Is it possible to stratify people with CFS/ME according to their autonomic responses and would this help direct treatment?

Neuropathology

Prof Richard Reynolds, University of Southampton

As Prof Hugh Perry, originally scheduled to lead this workshop, was unable to attend the conference, Prof Richard Reynolds stepped in. Topics discussed included:

- linking neuropathology to symptoms
- the findings of dorsal root ganglionitis that have been reported from the UK post-mortem research group
- brain banking
- lumbar punctures
- are abnormalities in the brain focal or general?
- where do we go next in relation to investigating the neuropathology of ME/CFS with neuroimaging?

Those who participated, which included keynote speaker Prof Jose Montoya, also briefly discussed the role of cytokine-mediated neuroinflammation and a [new clinical trial](#) (Roerink et al, 2015) involving a drug called anakinra that inhibits the pro-inflammatory cytokine IL-1. A member of the clinical trials group from the Netherlands was present at this workshop.

Clinical Trials

Dr Esther Crawley, University of Bristol

Topics discussed included:

- current trials and plans for future trials
- issues specific to conducting trials in CFS/ME (patient heterogeneity, differences in severity)
- the need for improved patient reported outcome measures
- whether we could tackle particular features of CFS/ME (eg. pain or sleep)
- how to measure sleep in paediatric CFS/ME and whether this would be a good mediator or outcome to study
- participants suggestions for future trials

Plenary Session 2: Widening the Net

In search of a diagnosis – what the literature tells us about the patient experience

Prof Liz Perkins, University of Liverpool

Prof Perkins holds the William Rathbone VI Chair of Community Nursing at University of Liverpool, and her presentation reviewed literature on medically unexplained symptoms, and the experiences of those affected by CFS/ME, before looking at strategies for living with the condition.

Prof Perkins explained that a diagnosis is a necessity in modern developed societies, but that the inability to identify the causes of illness presents particular problems.

She made particular reference to Action for M.E.'s 2014 *ME Time to Deliver* survey. This found that it can take up to two years for patients to receive a diagnosis, during which a “diagnostic limbo-land” ensues.

There is a vast literature on ‘medically unexplained symptoms’ but most of it is concerned with the healthcare-provider experience; very little information exists on how patients defined their own experience of illness – the patient perspective is largely missing.

Referring to Lisa Whitehead’s work on the illness trajectory in ME patients, Prof Perkins reviewed the hopes of recovery in the early stages of illness, the experiences with GPs, the quest for treatments, and the individual’s development of strategies for coping with illness, including rest, pacing, pain medication and coping strategies.

Imaging the Neural Correlates of Post-Exertional Malaise in CFS/ME **Dr Mark Edwards, St George's University of London**

Dr Edwards is a neurologist specialising in the field of movement disorders. He became interested in chronic fatigue and CFS after encountering patients with neurological symptoms that did not readily fit into any diagnoses.

He presented details of a new project, funded by the Medical Research Council (MRC), which seeks to understand the mechanism of a key symptom in CFS/ME: post-exertional malaise, commenting that “If we understand more about mechanism, we’d be able to understand a little bit more about treatment.”

This collaborative project also involves: Dr Neil Harrison, Reader in Neuropsychiatry, University of Sussex; Dr James Kilner, Senior Lecturer in Motor Control, University College London; The Department of Sports and Exercise Science, University of Brighton; and the Sussex ME Association, who “have been particularly helpful talking about this project and helping to get it off the ground.”

Dr Edwards went on to say that post-exertional malaise “comes with a range of different phenomena – physical phenomena – relating to pain, weakness, fatigue and cognitive phenomena such as cognitive slowing, fogginess etc.

“And there is this interesting phenomenon that at least for some people it has this slightly delayed onset; so somebody might have a period of exertion one day and then the next day all of this hits in a very big way.”

The range of post-exertional malaise symptoms experienced are very similar to the “sickness response”, a range of physical and cognitive symptoms that occur across species in response to acute infection/inflammation.

There is clear evidence for a network of structures in the brain that are involved in generating such symptoms – Dr Edwards cited work done by Dr Neil Harrison, which involved giving typhoid vaccinations to health people, and then scanning their patterns of brain activation.

“What you routinely see, across different scans using different techniques, is activation of a particular brain structure, the insula. This seems to be related to how strongly people perceive these symptoms that are happening.

You can do further work in actually tracking a network of structures which seem to be involved in taking information from the body and sending it to the brain. The insula is of particular important in processing this information: it is generating the symptoms that people experience.

“And this is something called the *interoceptive* network – the network of brain structures which lets us take information from the body and lets us interpret it.”

Dr Edwards posited two questions:

- What happens to these networks when people with CFS/ME are experiencing post-exertional malaise?

- How are changes in these networks in people with CFS/ME similar or different changes that happen in people experiencing acute infection and inflammation?

He then went on to outline his new study, which will recruit 20 people with CFS/ME, and 20 healthy age and sex matched participants. It will also utilise previous data from healthy people experiencing acute inflammation/infection for comparison.

Subjects will undergo a baseline scan, allowing Dr Edwards and his team to map their interoceptive network. Blood samples will also be taken to look at immune activation. They will then undergo a specialised exercise protocol, defined on the basis of their individual heart rate and exercise capability. This will be repeated 24 hours later.

“This is going to allow us to look at what the neural correlates are – what the patterns of brain activation are – particularly in these structures when people are experiencing post-exertional malaise,” concluded Dr Edwards.

CMRC Chair Prof Holgate highlighted that the competition to get such a study funded by the MRC (specifically by the Neurosciences Board) would have been “incredibly high” and commended Dr Edwards and his team.

The epidemiology of CFS/ME in adolescence

Dr Esther Crawley, University of Bristol

Dr Esther Crawley presented some early results from the Avon Longitudinal Study of Parents and Children (ALSPAC) within which identification is being made of cases of CFS/ME.

She began by highlighting how CFS/ME is frequently very disabling and prolonged in children and young people, yet we are prevented from setting up adequate services or conducting research because we don't know basic data such as how common it is, what causes it – essential for future prevention and development of new treatments – its natural history or the patterns of the condition.

Dr Crawley is now investigating:

- prevalence and persistence of CFS/ME in young people aged 13-17 years
- heterogeneity of the illness
- risk factors for CFS/ME at 13, 16 and 17 years old.

The study is ongoing and work so far has concentrated on data for 16 and 17 year olds. Indications are that the prevalence of CFS/ME at 16 years old is 1.86% overall (2.46% for girls and 1.28% for boys). At age 18, this increases to 2.99% overall, though these figures are based on complete case analysis, unlike the data for 16 year olds.

Looking at gender differences, the prevalence of CFS/ME is higher in females during adolescence, but persistent CFS/ME appears to be greater in males.

The study will also look at factors associated with long term fatigue, the relationship between those with fatigue and those with pain, and risk factors for developing CFS/ME.

Identifying the biological fingerprints of fatigue

Prof Wan-Fai Ng, Newcastle University

There are common biological pathways underpinning fatigue, and unique patterns of biological changes (“fingerprints”) exist in the body’s peripheral blood (with an emphasis on the immunological pathways).

Dr Wan-Fai Ng described his use of primary Sjögren's syndrome (an autoimmune condition with several clinical features similar to CFS/ME) as a disease model, undertaking a comprehensive analysis of the immune system to identify biological fingerprints and explore whether these biomarkers are present in CFS/ME patients.

Using whole blood genome-wide expression array and serum protein profiling, Prof Ng is aiming to:

- compare blood samples from primary Sjögren's syndrome patients in order to identify a “biological fingerprint” for fatigue
- assess the potential utility of such biological fingerprints in CFS/ME.

Serum profiling has so far revealed that IP-10, IFN-alpha and perhaps other cytokines are important factors in the prediction model of fatigue. This may inform future research into the biological basis of fatigue.

Persistent fatigue induced by interferon-alpha: a new immunological model for CFS/ME

Alice Russell for Prof Carmine Pariante, King's College London

Alice Russell began by describing how there is a large body of research showing dysregulation of the immune system in CFS/ME, including:

- triggering by infective agents
- elevated levels of pro-inflammatory markers
- presence of neuroendocrine abnormalities
- symptoms similar to behavioural disturbances occurring in context of pro-inflammatory conditions.

However, the majority of the evidence so far has been derived from cross-sectional comparisons of CFS/ME patients and controls.

Miss Russell proposed that a solution to this might be a prospective research design which allows for:

- monitoring of biological and behavioural changes from the perspective of infective or immune triggers
- identification of those factors that contribute to the development of the illness
- further exploration of the role of clinical and psychosocial variables, and whether they moderate or mediate the effect of inflammation and fatigue.

Based on these principles, she went on to outline a study which uses the persistent fatigue precipitated by interferon-alpha (IFN- α) as a proxy model to understand how an exogenous inflammatory trigger leads to a pattern of biological and behavioural changes that is associated with persistent fatigue, even when the exogenous inflammatory stimulus is no longer present. The study will also seek to validate the model by comparing the chronic hepatitis C (HCV), patients who experience persistent fatigue, using a sample of CFS/ME patients and healthy controls.

IFN- α is a pro-inflammatory cytokine and the standard treatment for HCV, injected weekly for 24-48 weeks. While it boosts the natural immune response and inhibits replication of the virus, it may also induce a range of debilitating side effects, including neutropenia, anaemia and persistent fatigue.

Preliminary data from the study (which aims to recruit 100 HCV patients undergoing IFN- α treatment, 50 CFS/ME patients, and 50 healthy controls) indicates that:

- a proportion of patients go on to develop persistent fatigue after treatment with IFN- α
- fatigue levels remain high even in the absence of the pro-inflammatory stimulus and a number of these patients continue to experience debilitating fatigue, at higher levels than experienced by the general population
- higher salivary cortisol levels in response to awakening, and lower diurnal cortisol levels in CFS/ME patients versus HCV-fatigued patients.
- but there are no differences between either group and healthy volunteers
- patients treated with IFN- α provide a potential basis on which to model the pathogenesis of CFS/ME.

Understanding the pathogenesis of autonomic dysfunction in CFS/ME and its relationship with cognitive impairment
Prof Julia Newton, Newcastle University

Prof Julia Newton described more of her results from her case-controlled autonomic dysfunction study, funded by the Medical Research Council and designed to address two areas.

The first is the pathogenesis of autonomic dysfunction in CFS/ME, specifically determining whether it is:

- a primary abnormality in brain autonomic centres
- due to abnormalities in the hypothalamic–pituitary–adrenal axis
- a problem of downstream autonomic nervous system control
- secondary to hypovolaemia which has resulted in compensatory autonomic abnormalities.

The second area is the relationship between autonomic dysfunction and cognitive impairment in CFS/ME, specifically to explore:

- whether autonomic dysfunction and cognitive impairment in CFS/ME are caused by similar underlying central processes, causing damage to both autonomic and cognitive brain centres,
- or whether cognitive impairment is secondary to peripheral hypotension arising from autonomic dysfunction and resulting in reduced cerebral perfusion and cerebral damage.

Patients were screened using the SCID-I assessment tool to exclude major depression prior to the main study, and the DePaul Symptom Questionnaire (DSQ) to differentiate between diagnostic criteria. In addition, COMPASS and COGFAIL questionnaires were administered for self-reported autonomic and cognitive features respectively and the Task Force® Monitor was used for autonomic assessment. A number of neuropsychological tests were also administered for objective cognitive assessment.

Prof Newton explained that results show clinically significant differences between DSQ subgroups on activity levels, subjective and objective autonomic and cognitive function. Visuospatial memory, verbal memory and psychomotor speed were also significantly different between DSQ subgroups.

This indicates phenotypic differences between DSQ subsets and suggests that elucidating the symptoms seen in CFS/ME, or its disease spectrum, will support research into its underlying pathophysiology and enable more tailored treatment. It also reinforces the need to better understand the underlying causes of CFS/ME to allow appropriate identification and management.

Plenary Session 3: Autonomic System

Autonomic Nervous System in CFS/ME

Prof Jo Nijs, Vrije Universiteit Brussel

Leading a unique program of research into CFS/ME in Brussels, Prof Jo Nijs' focus was the pathophysiology of post-exertional malaise in CFS/ME and the role of the autonomic nervous system.

He emphasised that CFS/ME is characterised by a dramatic increase in pain and other symptoms after exercise, a phenomenon not seen to the same extent in other illnesses. The main determinants of post-exertional symptoms can involve the immune or autonomic nervous systems and central sensitisation, and he discussed each of these in turn. Exercise has large immune effects in healthy people, but there is evidence that in CFS/ME it can increase complement activation, oxidative stress, or gene expression.

In the past, Prof Nijs has implicated brain-derived neurotrophic factor, also produced by immune cells, in the development of CFS/ME, and this protein may also increase the excitability of the nervous system. Looking at the autonomic nervous system, he suggested that while Prof Julia Newton's work had shown sympathetic impairment in CFS/ME, the role of the parasympathetic system may also be important.

The vagus nerve, for example, contains 70% of the parasympathetic branch of the autonomic nervous system, but it also informs the brain about inflammation, and could be involved in dysfunctional responses to exercise, including in the recovery phases which may lack appropriate parasympathetic activity in CFS/ME, increasing pain.

Prof Nijs also discussed the possibility that CFS/ME patients might have a dysfunction of endogenous analgesia (the body's own way of reducing pain), something not seen in patients with other chronic illnesses such as rheumatoid arthritis. This aspect is allied to the problem of central sensitisation (an abnormal increase in the firing of nerve cells lying deep within the central nervous system) observed in people with CFS/ME and fibromyalgia.

Cardiac iodine-123-meta-iodo-benzylguanidine uptake in CFS/ME associates with autonomic function and fatigue severity

Prof Julia Newton on behalf of George Petriades, Newcastle University

Prof Julia Newton outlined a new cardiac MRI study, designed to confirm previous results using an expanded sample size.

This study looks at heart size in CFS/ME (do people with CFS/ME have smaller volume hearts?) as well as plasma volume and red cell mass, as there is some evidence to indicate that people with CFS/ME have low plasma volumes and that intravenous saline infusions can be of benefit in some cases.

The study also investigates the possible presence of other cardiac abnormalities in CFS/ME, and if any of these abnormalities are caused by deconditioning. Early findings indicate that this is unlikely as there does not appear to be any relationship to length of disease.

Instead, reduced cardiac volume may constitute a (pre-existing) vulnerability for developing CFS/ME, though larger, preferably longitudinal studies would be needed to support this hypothesis.

Importantly, there is also a relationship between plasma volume and the severity of fatigue symptoms experienced by people with CFS/ME, suggesting that this has the potential to be a therapeutic target.

Prof Newton will continue this work by submitting a funding application to the Medical Research Council's Confidence in Concept scheme, aiming to explore whether IV boluses of fluid (volume expansion) impact upon cardiac volumes and symptoms.

Reduced cardiac volumes in CFS/ME associated with plasma volume but not length of disease

Prof Julia Newton, Newcastle University

Prof Newton explained that this small study involves the use of a complex investigative technique called cardiac iodine -123 meta-iodo-benzylguanidine (123-I-MIBG) uptake to investigate the role of the sympathetic nervous system in CFS/ME and whether this is linked to fatigue.

Findings indicate that impaired cardiac 123-I-MIBG uptake is associated with increased fatigue severity in CFS/ME. This suggests that the autonomic dysfunction frequently seen in people with CFS/ME might be related, at least in part, to abnormalities in cardiac sympathetic innervation, having an effect on symptoms.

During the discussion that followed, Prof Newton emphasised the importance of maintaining a good fluid intake, especially in people who have evidence of autonomic dysfunction.

The discussion also covered a controversial approach, which is more popular in the USA, of treating people with saline infusions (to increase plasma volume) and the potential value of using the drug erythropoietin, which increases red cell mass.

Plenary Session 4: Clinical Trials

Rituximab Trial

Dr Øystein Fluge, University of Bergen

Dr Øystein Fluge sketched out the scientific background to the rituximab programme, which started when researchers at Haukeland University Hospital noticed that one patient with CFS/ME experienced “unexpected and marked recovery of CFS/ME symptoms lasting for five months during and after cytotoxic chemotherapy for Hodgkin’s disease.”

The researchers conducted a pilot case series in 2009, and thereafter a phase II study of 30 CFS/ME patients. As the results were promising, further studies were planned and these are ongoing. They include a randomized, double-blind, placebo-controlled phase III study of 152 patients from five centres in Norway (four in university hospitals), who are being followed up for 24 months.

As previously reported, rituximab appears to be a safe form of treatment in CFS/ME – the side-effects reported so far being upper airways infections, late-onset neutropenia, allergic reactions, and in some cases a worsening of CFS/ME symptoms. Dr Fluge was clear, however, that he does not encourage the use of rituximab for CFS/ME outside of approved clinical trials.

He also gave an overview of a series of smaller studies being conducted by his team, including studies on:

- severe or very severe CFS/ME, using the same rituximab treatment protocol
- endothelial dysfunction in blood vessels (endothelium is part of the blood vessel wall)
- cardiopulmonary exercise testing
- gastrointestinal function.

Post-viral CFS/ME patients have normal levels of B cell populations
Dr Caroline Strachan, Leeds Partnerships NHS Foundation Trust

Dr Strachan described research looking at mechanisms involved in the production of fatigue that is seen in cancer patients during and after treatment with surgery, chemotherapy and radiotherapy.

Cancer fatigue can persist long after treatment is completed and there may be common causative factors, especially involving pro-inflammatory immune system responses to those found in CFS/ME fatigue.

This research includes looking at immune system function, B cell status in particular, in a group of patients with CFS/ME – B cells are a key part of the immune system that are destroyed by the drug Rituximab. To gain a better understanding of how B cells might produce fatigue in CFS/ME, they are currently assessing the production of B cell cytokines following in-vitro stimulation.

Cohort Profile: The Collaborative on Fatigue Following Infection
Dr Simon Collin, University of Bristol

Dr Collin reported on a new epidemiological study – the Collaborative on Fatigue Following Infection (COFFI) – that will investigate fatigue following infectious illnesses, particularly viral infections.

This is a very large collaborative study involving 10 cohorts of patients collected from the USA (including the Katz/Jason study of glandular fever in college students), Australia (the impressive Dubbo and Sydney cohorts from Professors Andrew Lloyd and Ute Vollmer-Conna), New Zealand, the Netherlands and Norway.

The aim is to understand why acute infections can sometimes trigger long-term debilitating symptoms. By bringing together many datasets, statistical power can be increased to investigate causes and risk factors, supported by sharing of biosamples.

The hypotheses being investigated is that post-infection illnesses such as CFS/ME are a consequence of genetic and environment effects, in which susceptible individuals who experience an acute infective illness develop alterations in the neurobehavioural and immunological systems underpinning the acute sickness response, leading to persistent fatigue and other symptoms.

Plenary Session 5: Sleep

Sleep and CFS/ME

Prof Jim Horne, Loughborough University

Prof Horne concentrated on the importance of sleep for the brain and what we know (and don't know) about various components of normal sleep, ways of assessing sleep, eg. Epworth Sleep Score and the Pittsburg Sleep Quality Index, and the management of sleep disturbance.

He considered the various sleep problems that can occur – insomnia, sleep apnoea, hypopnea (shallow breathing and decreased oxygenation of the blood), restless legs syndrome and 'worn out syndrome' – when normal sleep and circadian (body clock) rhythms malfunction.

In purely practical terms, Prof Horne advised that regular short daytime naps can be helpful – but keep them short. Irregular periods of longer daytime napping/sleeping are often unhelpful. Melatonin might be worth trying in some cases but it should be noted that this drug works by synchronising the body clock. It is not a hypnotic drug in the sense that it is sleep-producing.

Professor Horne finished his presentation by looking at some of the research findings relating to sleep disturbance in CFS/ME. Unfortunately, there seems to be no consensus as yet on the science behind this, but problems with initiation of sleep (ie. with dropping off) and reduced slow-wave stage (non-rapid eye movement) sleep have been reported.

Assignable causes for fatigue in Primary Sjögren's syndrome: data from the UK primary Sjögren's syndrome registry
Rebecca Lambson, Newcastle University

Miss Lambson presented some descriptive analyses of the MRC-funded research into the incidence and impact of fatigue in people with Sjögren's Syndrome – an autoimmune condition that can cause debilitating fatigue and which has a number of common features (including the presence of dorsal root ganglionitis) with CFS/ME.

As most primary Sjögren's patients report fatigue as one of their most important problematic symptoms, Miss Lambson stressed the need for screening to ascertain all the other possible causes of fatigue in these patients, such as hypothyroidism, depression, diabetes or anaemia.

Her study found that 55% of people with Sjögren's Syndrome had no assignable cause for fatigue. This subset of patients requires further research into the underpinning biological mechanisms for fatigue.

From healthy to being ill with post-infectious fatigue syndrome: A qualitative content analysis of illness trajectory
Eva Stormorken, University of Oslo

Ms Stormorken described the aftermath of the contamination of public drinking water with in Norway, when more than 2,500 people were infected with the parasite *Giardia lamblia*.

They received antibiotic treatment – some needed two or three courses – and a full recovery was expected. However, a significant percentage developed chronic fatigue and irritable bowel syndrome, whereas a smaller group developed post-infectious fatigue syndrome. The latter group was referred to Prof Harald Nyland, a neurologist specialising in ME.

Ms Stormorken's study described the course of their illness as determined from in-depth interviews. Her central message was that these patients did not receive proper help when required because of lack of knowledge among health professionals, and that an early diagnosis and interdisciplinary intervention could have been beneficial, avoiding the most severe disability and hastening improvement.

The bigger picture: genomics, epigenomics and other omics
Anne Faulkner Memorial Lecture by Prof George Davey Smith, University of Bristol

Prof Davey Smith presented some new and potentially powerful approaches to researching illnesses with unknown causes. The technique uses genetics and genomic data to discover non-genetic, modifiable causes of disease and disease progression.

Genomics looks at common variations in genes, across our whole genome, and attempts to relate these to traits and conditions. These studies have been possible due to the sequencing of the human genome.

Prof Davey Smith began the presentation with some existing examples of CFS/ME genetic studies, to illustrate the need for much larger sample sizes. He picked out several papers at random with small samples (12-76 patients) that were too small and likely to be false positives.

The statistical power of these very small studies is limited because, in order to rule out the possibility of false positives and the results happening by chance, much larger sample sizes are needed.

Genomics

Genomics studies look at common germline genetic associations across the genome, relating them to traits and conditions. This method of research has really expanded in the past few years due to the sequencing of the human genome.

Up until 2005, this field of genetics had similar problems as current CFS/ME research, in that studies with very small sample sizes were carried out, producing false positives and an inability to replicate results. Prof Davey Smith co-authored a paper which suggested that virtually all of the genetic association studies that had been published in journals up until 2002 had resulted in false positives (Colhoun et al, 2003).

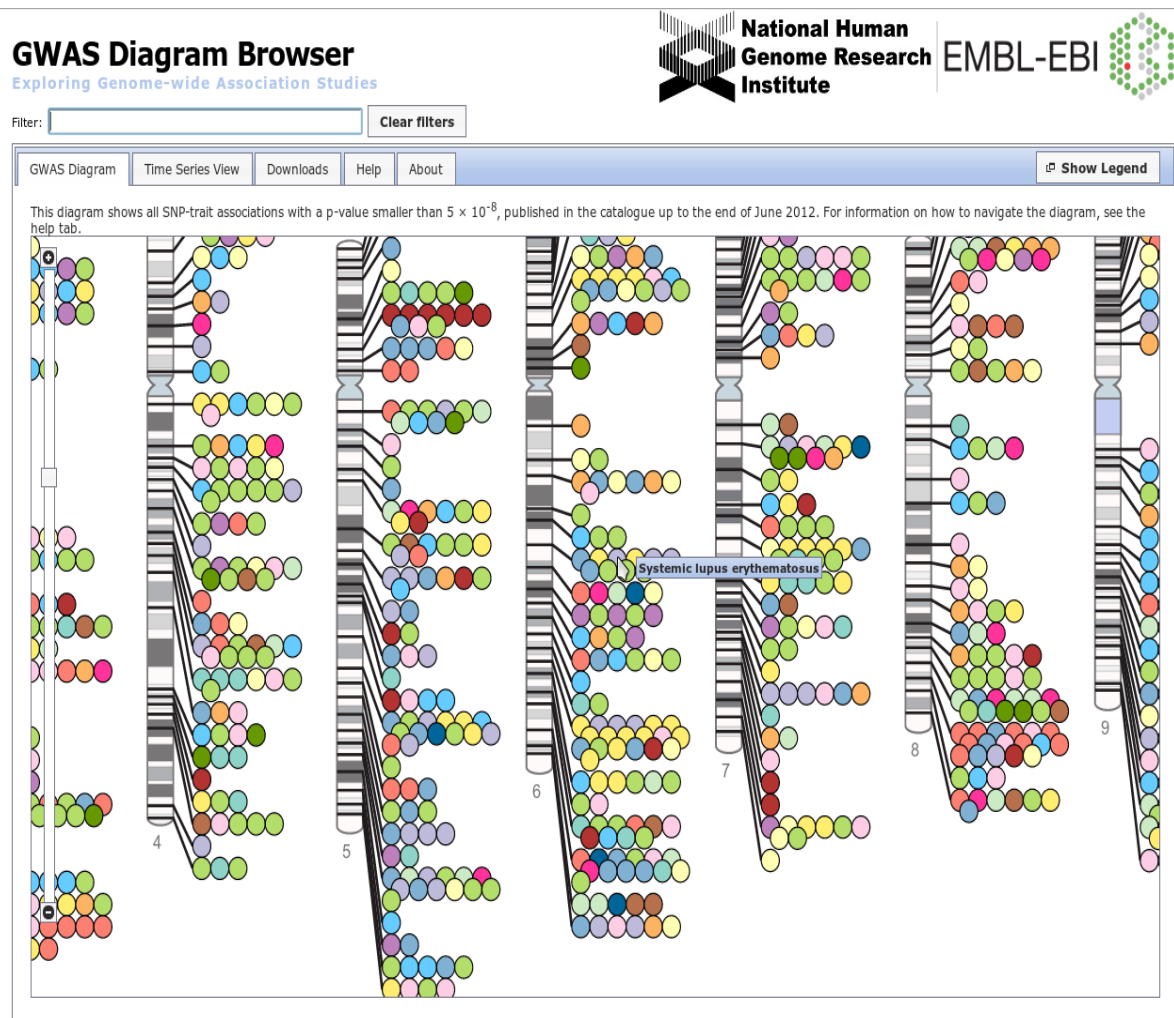
Inadequate sample sizes suggest that the most important factors underlying inability to replicate these associations are publication bias and failure to attribute results to chance.

These are problems that are all rectifiable. If we don't fix them, we risk wasting scientific effort and the rejection of a potentially useful research strategy. Thankfully, the situation has been transformed by groups getting together and carrying out much larger, more useful studies, driven by funders such as the Wellcome Trust.

It had been discovered that particular genetic variants are reliably associated with a large number of traits, including diabetes, obesity and cardiovascular disease. There are now more than 10,000 established, replicable findings.

Studies that examine if common genetic variants are associated with a disease are called Genome-Wide Association Studies (GWAS). The following diagram shows a small section of the chromosome from the GWAS Diagram Browser. The studies can be searched for a specific condition and each dot on the diagram represents a

section associated with traits, with systemic lupus erythematosus highlighted. There are currently no established reliable genetic associations with CFS/ME.



What do robust and reliable genetic associations tell us about the following?

1. Classification of disease

The difficulty with the classification of disease is that diseases often cannot be defined and classified clearly, especially when the aetiology or pathogenesis is unknown. Thus diagnostic terms often only reflect a set of symptoms, as with CFS/ME. Genetic associations can validate an established disease classification and predetermined subcategories of a condition.

2. Causal factors for disease

Germline genetic variation can be used to provide robust evidence of the effects of putative modifiable causal factors for disease without conducting a traditional randomised trial. This approach is known as Mendelian randomisation (MR).

Conventional observational epidemiology studies have provided unreliable evidence regarding causal factors. For example, a study of participants taking a vitamin E supplement suggested vitamin E reduced risk of coronary heart disease by 40% (Rimm et al, 1993). Although studies such as this adjust for confounding risk factors,

such as diet, weight, smoking and alcohol consumption, when later randomised controlled trials were carried out, they found no reduced risk of coronary heart disease from vitamin E compared with placebo.

The reason for this might be that taking vitamin E is strongly associated with other characteristics which influence coronary heart disease risk. This was confirmed by a study (Lawlor et al, 2004) which showed that people taking a vitamin E supplement were less likely to come from a poor background, less likely to smoke and be obese, and more likely to exercise, drink alcohol, and have a low fat diet.

MR can be used to get around confounding factors by using the genetic variation which relates to the factor of interest, in this design the genetic variants maybe referred to as “instrumental variable”. The MR method has been applied in a number of fields, which has both proved and disproved existing theories from observational studies.

To use vitamin D as an example: people naturally have different levels of vitamin D, and some of this variation is down to the versions of genes they have: some have genes that are better at making vitamin D. So you can select people by their vitamin D genes and group these into those predicted to have higher or lower levels of vitamin D (actually testing their vitamin D - related levels shows this technique works very well). The vitamin D genes are randomly spread through the population (this is MR), and not associated with confounding factors such as diet or social class. So this is a better way of testing the true effect of vitamin D.

Genotypes therefore can proxy for some modifiable risk factors, and there should be no confounding of genotype by behavioural, socioeconomic or physiological factors, except those influenced by alleles at closely proximate loci or due to population stratification.

The 10,000 genetic traits in the GWAS catalogue include genetic variants related to health behaviours such as smoking (eg. nicotine receptor variants relate to the degree of which people become addicted to nicotine) and drinking alcohol (eg. some people are naturally intolerant of alcohol), along with genetic variants related to biomarkers.

3. Establishing cause and effect

Bi-directional MR can sort cause from effect. For example, there is an established connection between vitamin D and Body Mass Index (BMI) and so it was thought that vitamin D could lower BMI. MR can be performed bi-directionally, and it has shown that there is no effect of vitamin D on BMI but looking at the reverse, ie. the effect of BMI on vitamin D levels, MR shows that higher BMI leads to lower circulating vitamin D.

The advantage of MR studies are that a huge amount of genome-wide data is already available and can be analysed without performing expensive large RCTs.

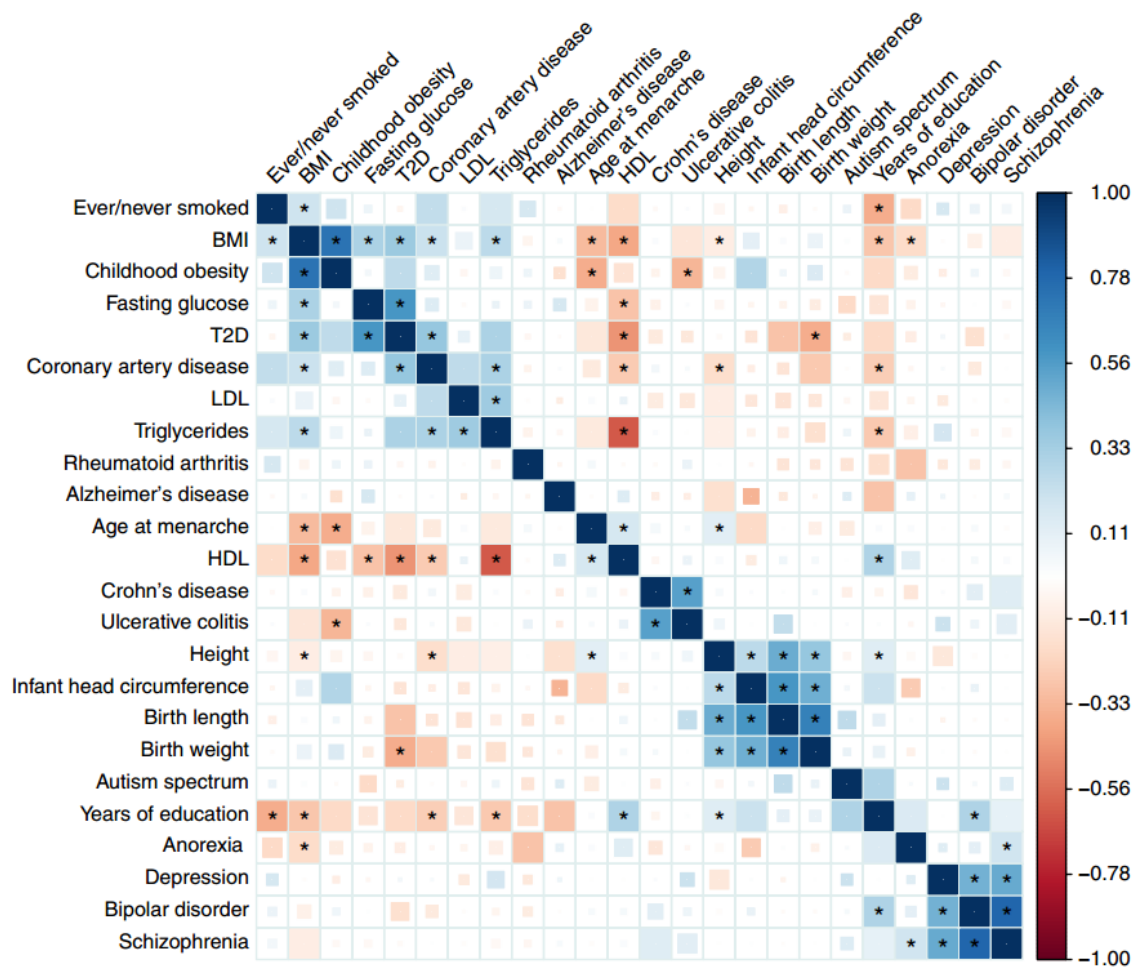
4. Suggesting causes where aetiology is unknown

“Reverse MR” can suggest causes of specific diseases that have not been thought of. For example, large GWAS studies found an association of the genetic variant

related to nicotine addiction with lung cancer. If it hadn't already been known that smoking causes lung cancer, this research would have pointed to smoking being a cause.

5. Genetic overlap of traits

Statistical techniques can show how traits are related, eg. Alzheimer's with low childhood BMI, which may suggest cause in one direction or another. If one trait caused another, a genetic correlation would be seen. Unlike MR this does not give the direction of the causal relationship, however.



Bulik-Sullivan B et al. An atlas of genetic correlations across human diseases and traits. Nature Genetics 2015

What does use of genetic association data not tell us about?

If the sample sizes are inadequate, these studies give unreliable results. This can be worse than having no data at all because such studies can mislead and result in more research being carried out based upon them, wasting research funds. Very large sample sizes, of the order of many thousands, are needed in order to produce reliable evidence.

GWAS do not necessarily tell us about treatment or cures. For example, if MR shows that smoking causes lung cancer, it does not show that stopping smoking treats lung cancer once it has developed. This is the case with many diseases, where once the disease process has been triggered, intervening in what triggered the disease no longer has any effect.

For any condition two studies are needed: a GWAS of having the disease versus not having the disease, to indicate what might cause it. Having a really well-established cohort of people with the disease to look at genetic variants related to disease progression is also required, to reveal information about potential treatments.

Other “omics”

1. Epigenetics

From a blood sample, we can look at epigenetic markers on the germline DNA which are sometimes related to whether that DNA is expressed or not (in over-simplified terms whether the gene is switched on or off). This might tell us how the environment influences or works together with the genome to develop disease or mediate the effect of the disease.

Epigenetic markers aren't protected from change, unlike germline DNA, so they're affected by the same confounding factors that influence exposures in observational studies (like taking vitamins, as discussed above). DNA methylation is the most stable epigenetic measure, and it is the one which has been most studied.

Epigenetics is currently popular in the media, with examples such as epigenetic indicators of sexual orientation, and whether trauma is passed on in the genes of Holocaust survivors, having received considerable recent media attention. Small sample sizes were used in these studies and the findings are often wholly unreliable.

What we can learn from epigenetics is that processes can occur which lead to the same genome being expressed differently. The cells in our body all have the same germline genome. The cells start out the same but then during development they differentiate into different types of cells, such as liver cells and brain cells. Cell division leads to cells becoming specified where liver cells divide they produce more liver cells. Epigenetic processes are therefore key to development. In disease, this means that, as diseased cells divide, the disease is passed on to new cells.

Epigenomics provides ways of studying the mechanisms of gene-environment interaction and provides robust evidence of the experience and timing of some exposures, which could help understand mechanisms of disease. For example, smoking during pregnancy affects foetal DNA which then remains evident until adulthood at least.

2. Other “Omics”

Gene expression is transient and the study of this (transcriptomics) has somewhat been disappointing. It was thought there would lead to reliable predictors of disease progression but so far there are few replicated findings.

Proteomics is the study of a wide range of proteins. This approach has considerable potential, but currently the technology is expensive and difficult to implement in very large-scale studies.

Metabolomics is the study of metabolites, and has considerable potential, as many metabolites (and proteins) are amenable to pharmacotherapeutic manipulation, so can be the target of treatments. Mendelian randomisation can be utilised using genetic variants that are reliably related to proteins and metabolites to investigate how these may be involved in the progression of disease, and therefore are appropriate targets for prevention or treatment. A further technology could be referred to as “immunomics”, the study of a large number of molecules related to immune processes.

Recently platforms that measure large numbers of factors within the immune system are being developed and could be applied to large-scale studies, although currently they are expensive. Microbiomics is the study of the microbiome, as the name implies. This is a highly fashionable area and the headline figure that 9 out of 10 cells in the human body aren't actually human – they are the cells of microbiological organisms that inhabit the human body – is a popular statistic used to suggest that these organisms could have an important influence on human health. Currently there is more hype than solid evidence in this field, but clearly it remains of potentially high importance.

Prof Davey Smith ended his presentation by asking if CFS/ME research should be “business as usual” – i.e. many different groups carrying out under-powered small studies, producing often non-replicable findings - or if there was a better way ahead? He suggested a co-ordinated and collaborative approach and asked conference delegates to work together to find the best way forward for CFS/ME research.

Closing Remarks, Reflections and Where Next for the CMRC ***Prof Stephen Holgate, UK CFS/ME Research Collaborative Chair***

Professor Stephen Holgate closed by commenting on how successful, stimulating and enjoyable the conference had been.

Referring to his plan for the Grand Challenge, and incorporating some of the key points made by Prof Davey Smith about the need to collect “big data” from large cohorts of patients, Prof Holgate stressed the importance of analysing and stratifying information on gene expression, immunology and proteins in CFS/ME into clinical and pathological subgroups.

Designing the specifics of the Grand Challenge, and the grant application needed to fund it, will begin in spring 2016 at a meeting of key CMRC stakeholders, including researchers, funders and charities.

Postscript

Following the conference, the CMRC Board approved the plans for the implementation of the Grand Challenge at its November 2015 meeting.

This national study will collect more than 10,000 samples of data an focus on phenotyping and subtyping data using statistical analysis, bringing in genomics and other areas. Prof George Davey-Smith (see p 31) is very keen to be involved.

Decisions must still be made about:

- whether the Grand Challenge will study adults, or children, or both
- collecting the right type of clinical data
- how to phenotype patients and what objective measurements to use (eg. physiology, known immunology measures, sleep, cognition, psychological, post-exercise fatigue, pain).
- what data is used (new versus previously collected) and how to ensure standard operating procedures.

The level of expertise needed will need to be high and across a range of areas to ensure we collect good clinical phenotypes.

Funding must be secured if the Grand Challenge is to become a reality. The Wellcome Trust has a new collaborative awards scheme, which funds collaborative projects of this nature up to £4m, providing each collaborator plays a proactive part within the project.

A Grand Challenge meeting is being convened in spring 2016 and an outline application could be considered for September. Additional funders could also be considered.

Poster presentations

There was an impressive number of posters this year. A call for abstracts had been launched with a closing date of 31 July 2015, and there were 33 successful submissions which were displayed in the poster room beside the main hall.

Some described in more detail work already given in the shorter presentations, while others brought scientific work to a wider audience. For example, the poster from the UK CFS/ME biobank described progress to date: to July 2015, it had recruited 390 participants (245 CFS/ME cases, 101 healthy controls, and 44 patients with MS) with 22,500 aliquot samples stored.

The CFS/ME Biobank aims to open for the supply of samples to research groups in early 2016. Fees, which are currently being calculated, will be based on cost recovery only. Researchers who wish to register an interest in sample supply should do so by emailing mecfsbiobank@LSHTM.ac.uk

Other posters outlined:

- early work on liver volume and its correlates (Newcastle University)
- muscle and mitochondrial function (University of Liverpool)
- cognitive behavioural therapy specifically for insomnia and sleep disturbances (Newcastle University)
- social care and the challenges faced by CFS/ME patients in accessing it (Action for M.E.)
- rituximab as a treatment in primary biliary cirrhosis (Newcastle University)
- immune responses in CFS/ME (Northumbria University)
- orthostatic abnormalities in a large Dutch CFS/ME cohort (Radboud University Nijmegen)
- salivary cortisol levels in CFS/ME and hepatitis C patients (King's College London)
- functional MRI studies in working memory tasks (University of Bristol)
- multilevel analyses of the prevalence of CFS/ME in the population of Poland (Nicolaus Copernicus University, Bydgoszcz).

Conference feedback

Following the conference, the CMRC contacted all delegates and asked them to complete a feedback survey; it received responses from 35 delegates:

- 46% were a Professional Member of the CMRC
- 30% were an Associate Member of the CMRC
- 18% were an Arthritis Research UK patient group representative
- 6% were a Student Member of the CMRC

Professional and Student Members were asked what value they felt participation in the conference will add or has added for them in their role. They said:

- An up-to-date overview of the various kinds of research that is being conducted in the field, and of early findings and suggested further research and collaborations. It's very exciting to see the scope and quality of current research.
- Helps keep my perspective and understanding wide. With so few specialists in this area, I find I can work in a silo too easily. I need to keep in touch with the breadth of research and management nationally and internationally.
- Generally it was good to hear talks from diverse areas of study. There were also some talks specific to my area of study that were very interesting indeed and provided some aspects to reflect on for future work.
- Some useful research developments.
- Networking.
- It was really useful to get a comprehensive picture of the advances, gaps and challenges in CFS/ME research.
- More knowledge about ongoing studies.
- Much better understanding of the wider research going on. Also motivated by meeting patients.
- It has supported me with new, scientific data which I can call upon to spread awareness of the disease and address further medical community. It also enabled to create a bigger network.
- Meeting and networking with other researchers in the field and experts in other specialities which could benefit my own CFS/ME studies. Forming new research collaborations.
- Increased knowledge of what's going on in the field Potential collaborations
- Excellent networking opportunities.
- The CMRC conference is of immense value for biomedical researchers in the field of CFS/ME. At the moment, each research team is searching for answers under their particular streetlamp. The CMRC conference is the only meeting point (in Europe, possibly globally) at which these teams come together to report their findings, and to generate ideas for future research and collaborations.
- Contact with other researchers – immensely helpful.
- The conference has allowed me to network with various people nationally and overseas. To gain experience in sharing otherwise detailed information in a clear manner to allow everyone to understand the pathology of CFS/ME. I have also gained a broad understanding of CFS/ME from listening to the presentations and viewing the posters.

All delegates were asked how they rated the conference overall.

- 52% said very good
- 35% said quite good
- 13% said average
- 0% said quite poor
- 0% said very poor.

Professional and Student Members shared their further comments as follows:

- We need better research presented.
- Very well organised in terms of content and housekeeping. An enthusiastic audience; Prof Stephen Holgate and Prof Jose Montoya must take credit for setting the scene so well.
- It is amazing to think that these meetings are so new.
- Much positivity towards the subject. Less dire visions of the future.
- Very medically focused.

As did Associate Members and an Arthritis Research UK patient group representatives:

- People listened, had information to take forward.
- Very informative and welcoming.
- Strong line-up of speakers, diverse group of attendees, presentations ready to go, easy to find poster space, break-out session useful.
- There wasn't adequate time for collaboration between patients and researchers. Having made the effort to come to Newcastle it would have been great to have been able to attend more of the presentations but I assume there were good reasons: why that was not possible?
- OK the second year was about establishment, but there could have been a bit more discussion around comparative quality, and an overview of current progress towards stratified medicine in the NHS.
- It was a long journey to be only allowed to attend the afternoon workshops and the pre-dinner reception.

All delegates were asked how they rated the venue and facilities:

- 32% said very good
- 49% said quite good
- 19% said average
- 0% said quite poor
- 0% said very poor.

All delegates were asked how relevant the conference was for them and their personal/professional interests:

- 61% said very relevant
- 32% said quite relevant
- 6% said average
- 0% said not very relevant
- 0% said not relevant at all.

Professional and Student Members shared their further comments as follows:

- M.E.-afflicted and a medical advocate for the sufferers, I considered the conference essential in my field.
- Too medical
- Have been able to follow up some contacts from the conference which will hopefully enable me to start some new research. Also, ideas from the conference feeding into more possibilities.

As did Associate Members and an Arthritis Research UK patient group representatives:

- I have fatigue, RSD, hypothyroid and Sjögren's. Info helps me understand myself more
- Interested in fatigue
- Research is vital for me as an M.E. patient.
- While this is a research conference, a little consideration of future strategies for better moving research into practice would have been welcome
- Relevance restricted by the limitations on the parts we were permitted to attend.

All delegates were asked to rate the quality of the presentations:

- 58% said very good
- 36% said quite good
- 6% said average
- 0% said quite poor
- 0% said very poor.

Professional and Student Members shared their further comments as follows:

- Would appreciate some kind of handout/summary of key facts which I could annotate during the lecture. So much really good stuff, but unable to take it all in... help!
- Both oral and poster presentations were all of a very high standard and provided data central to the aims of the conference.
- Some of the talks delivered when members of the patient community might have.
- I would encourage you to invest in some HD equipment to stream future events like that. The quality of YouTube uploads diminishes the flair, since the presentations were superb - from scientific point of view. In order to reach out to more people it would be worth considering, whether future events like that could have more intertwined presentations (promoting and depicting collaboration).

As did Associate Members and an Arthritis Research UK patient group representatives:

- Excellent, great to know how dedicated they are.
- Although some presentations were quite good, some talks had a very low information density. There were a lot of (interesting) plans, but little data/results.
- Liz Perkins presentation was excellent; Mark Edwards very good; Fai Ng good; Julia Newton, Jose Montoya and Stephen Holgate excellent speakers in question time

- The presentations I saw were a bit variable. Some very good, some not so good.
- Varied. I thought a couple of the key presenters were rather lacking in perspective, either for the illness range under consideration (and available treatment parameters), or for the full spectrum of research progress.

Delegates were asked to rate the workshop they attended:

- 37% said very good
- 43% said quite good
- 17% said average
- 3% said quite poor
- 0% said very poor.

Professional and Student Members shared their further comments as follows:

- I'm not sure that it was made clear to the patient participants that the purpose was for them to provide input to researchers for future research design. As often happens, some were very focussed on outlining their own symptoms, history or models explaining their illness and seeking support, which was not the purpose of the discussion. So they felt cut off and that their needs were not met, and people trying to meet the goals of the exercise were frustrated that a lot of time was spent not on task. The process of selecting participants needs to make it clearer what the activity is to be and what the short-term benefits are to be (better research designed by researchers using the input from the workshop) and the long-term benefits (better understanding and treatment of the illness for patients); but not "support group" activities.
- Sharing knowledge amongst fellow professionals working in same field is such a rarity and a real treat.
- A very good idea, but it ran out of steam a bit. A bit more information when we were choosing the workshops would have been useful and would have helped with preparation.
- I have been doing different bedside and technical patient testing of their autonomic systems. It rounded up my knowledge pretty well.
- Very good but started late and insufficient time to feedback

As did Associate Members and an Arthritis Research UK patient group representatives:

- Short discussion. Questions different to email content which I prepared for. People with ME seemed unhappy about doctors not visiting them at home. Learnt people experience fatigue differently: I'm not tired, I'm weak.
- Needed to be longer, very time-limited
- Allotted places on tables mixed people up very well.
- We ran out of time but everyone contributed well.
- If I had known who might be in the workshop sessions I might have prepared differently. My group had only one M.E. patient and one carer. Others were all associated with arthritis: patients/researchers/clinicians with little knowledge of ME so with different assumptions. Good to work with them but didn't realise how much they didn't know.
- This workshop was a bit limited by the scope of the leader's intended work and by her considering information more for informing her research design.

- Very noisy (for my ME) in the main room while discussions were happening but the ability to break out to a quieter area was really good. The workshop itself was very interesting though.

Delegates were asked what plenary sessions, presentations and workshops they would like to see at next year's CMRC conference. Professional and Student Members suggested the following:

- An attempt to synthesise all of the findings about effects/symptoms in each of the body systems (eg. immune, CNS, muscles) to get a whole body/whole illness view, ideally over time. A big ask, I know, but it might contribute further to the goal of collaborative research and understanding to have this 'big picture.' This could either be done as a workshop (whole group or sub-groups, with strong, focussed facilitator(s)), or as a key-note speech.
- Any more insight into immuno-modulatory effect of anti-biotics and therefore their potential role in symptomatic treatment of CFS/ME.
- As an immunologist, maybe a session on the immunology of CFS/ME.
- Maybe something on the challenges of conducting research on the most poorly patients.
- Perhaps some more consideration of the similarity of fatigue in ME and MS.
- More genetics; getting a plan together for a well powered genome-wide association study.
- We definitely need more people stories, actual lives being positively impacted by the recent findings. Scientific facts are crucial, but we're losing quite a lot of impact by focusing just on the data. I enjoyed breaking the beat by social and PR presentations.
- What psychology can offer to improving the lives of people with CFS
- Clinical trials, specifically on methodology
- Patients' point of view. Maybe have a patient give a talk or deliver a workshop if they are well enough. Or do pre-recorded videos of them saying how much they appreciate the amount of research and time that is put into their condition.

Associate Members and an Arthritis Research UK patient group representatives suggested the following:

- Symptoms more important than labels; complimentary treatments; caring for myself during a flare-up.
- Development of fatigue through different illnesses.
- Co-morbidity issues.
- Neuroscience/brain data; I liked the talk about big data. Because attendees are from very different fields, it is important to educate each other on the on the possibilities and limitations of the methods used. A similar educational talk could be done about eg. neuro-imaging, or how to run good clinical trials
- Continued focus on neuropathology and immunology; better clarity by presenters on which case definitions they're using (seemed clear some presenters using quite broad definitions while others using much narrower) and we need to ensure we're talking about the same disease; mix of workshops for clinicians and researchers
- A workshop/presentation on mitochondrial function/ATP; follow up of the Mark Edwards/Neil Harrison study imaging neural correlates of post exertional malaise.

- Sorry to have missed Prof Montoya's keynote speech this time: would it be possible to make available transcripts to Associate Members? Could we cover pain? It's often a major disabling symptom.
- Some concentration on how research can better engage with tackling the persisting major problems of misdiagnosis, delayed diagnosis and limited diagnostic consideration/investigation.
- Potential drug targets? A round-up for collaboration of all ongoing pharmaceutical management/treatment research?

Finally, delegates were asked to share any additional comments or feedback they had about the conference. Professional and Student Members said:

- It was very interesting and encouraging to see all of the good research that is being done, and the links that are being made between people with all sorts of backgrounds and expertise. I think that excellent progress is being made in implementing the goals of the Collaborative.
- Just to say thanks to the organisers. I really enjoyed the conference and it was very relevant to my work
- Very well done, looking forward to next year.
- Keep up the good work. The atmosphere was positive; people were welcoming and communicative.

Associate Members and an Arthritis Research UK patient group representatives said:

- I appreciate the invitation, respect the professionals and stay positive.
- A great opportunity to discuss fatigue problems with various professionals
- Refreshments to supply all attendees. Some of us travelled long distances
- Payment scheme was a bit confusing (what type of delegate one should be, if accommodation was provided on certain dates, etc)
- Thank you for another great conference. So encouraging that collaborations are growing. Feels like ME might be beginning to come in from the cold.
- I have raised potential criticisms, but fully support the initiative and thank those who put in so much effort in leading it
- Please allow Associate Members to participate more fully in next year's conference. At least let us attend the dinner!
- My comments are a bit picky, I know, but thought I'd give feedback for ways of making the conference accessible and inclusive of people with M.E., which are just practicalities really. Really enjoyed the conference though, thanks.

The 2016 CMRC conference is provisionally scheduled to take place on Wednesday 12 and Thursday 13 October. To find out more about the CMRC, including how to become an Associate, Student or Professional Member, please visit www.actionforme.org.uk/research/uk-cfsme-collaborative