Report of the third UK CFS/ME Research Collaborative conference
Newcastle
28-29 September 2016

Introduction

More than 90 scientists and people affected by CFS/ME came together at the third annual UK CFS/ME Research Collaborative (CMRC) conference in October.

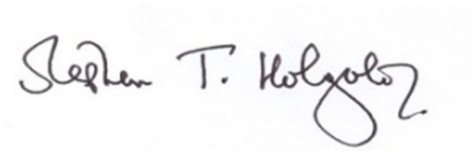
Travelling from countries including Canada, Australia and North America, delegates heard about the exciting launch of the new ME/CFS Epidemiology and Genomics Alliance project (MEGA) and watched presentations exploring a range of topics including big data, biomarkers, pain and autonomic dysfunction.

It was immensely encouraging to see new faces, and to hear the enthusiasm and commitment from not just those with experience in the field of CFS/ME but also those brining in expertise from other disciplines. On behalf of the Executive Board of the CMRC Executive Board I extend a sincere thank you to all those whose energy and enthusiasm made the event possible.

I would also like to thank the following specifically:

- Karen Hainsworth, for contributing to this report
- Katrina Pears, Volunteer, Action for M.E., for contributing to this report
- Emily Beardall, Volunteer Pharmacist, Action for M.E., for contributing to this report
- Sonya Chowdhury, Chief Executive, Action for M.E.
- Clare Ogden, Head of Communications and Policy, Action for M.E.
- Joe Martin, Communications Officer, Action for M.E., who filmed the conference presentations for livestream: you can view these online at www.tinyurl.com/actionformeyoutube

As we move forward with MEGA – you can read more about this throughout the report – I hope that you share my excitement and optimism about changing the field of CFS/ME research. Thank you to all those who continue to support the work of the CMRC, and who push for the collaborations needed to effect real progress.



Stephen Holgate
CMRC Chair

All in at the Solve ME/CFS Initiative
Dr Zaher Nahle, Solve ME/CFS Initiative

Key point summary

- The Solve ME/CFS Initiative has two functions: facilitating and supporting the research of others, and generating research in-house.
- The Institute of Medicine report had a "domino effect" in terms of increasing interest in CFS/ME research.
- Misperceptions about the illness are common, despite robust evidence. Patients must be empowered to have control over their own data.
- Targeted research is essential to move the field forward, working in collaboration with others.

Dr Nahle said he would offer two presentations in one, speaking about the work of his organisation and its perspective on the CFS/ME research landscape. "I have a section called the No Spin zone, covering misconceptions and misperceptions about the illness, that I would like to share with you," he said.

The Solve ME/CFS Initiative (SMCI) has two functions. One is facilitating and supporting the research of others, through a variety of mechanisms including its grant making programme (the Ramsay Awards), biobank and patient registry services, and medical webinars for influencers and thought leaders.

This year it is also embarking on a research-generating effort, taking on in-house projects in collaboration with others. Dr Nahle explained he would talk specifically about three initiatives, focusing on pathways and biomarker discovery, and also SMCI's work with Memorial Sloan Kettering Cancer Center on potential drug screening.

"I want to give as much information as I can, seeking partnerships, synergies and potential collaborations," he said.

SMCI is non-profit organisation dedicated solely to the cause of CFS/ME, and has been in business since 1987. It engages in all aspects from advocacy to research – but research continues to the core of its work. All its directors have experience of the illness and its scientific board counts among them world leaders in CFS/ME, medicine and technology. Its President Carol Head, said Dr Nahle, is very committed to the cause.

Giving an overview of key events in the history of CFS/ME, he highlighted that this is not a new disease: "Darwin himself could have been diagnosed, according to the Fukuda criteria." Outbreaks have been reported in the UK, dating back to the 1930s, with confusion over the cause. In the US, attention started to be paid when outbreaks occurred in upstate New York and Nevada. The enters for Disease Control and Prevention (CDC) commissioned a working group to study this, resulting in the Fukuda criteria, published in 1994, which was never meant to be a clinical criteria.

A variety of other criteria have been put together by similar assemblies, such as the Canadian Consensus Criteria (2003), and the Institute of Medicine's report (2015). The latter

was significant, says Dr Nahle, because “it was the first time the medical establishment had decried the lack of investment in CFS/ME.”

Dr Nahle described how he made a graph by plotting the number of publications on certain illnesses as a function of time. It shows that publications about CFS/ME were on the rise in the 1980s, consistent with the attention paid to the outbreaks.

However, when the graph is adjusted to add other illnesses, the considerable knowledge gap on CFS/ME is revealed – see Figure 1. Furthermore, when you look at funding per patient for CFS/ME in the US, the figure amounts to less than $2 a year.

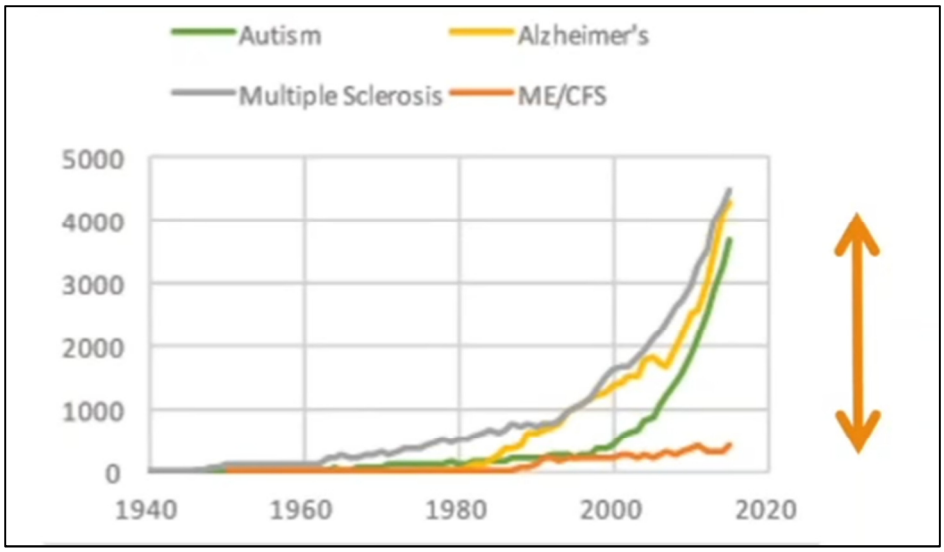


Figure 1: Number of peer-reviewed research publications by disease, 1940 to present

Dr Nahle was moved to thank all the scientists, institutions and collaborations, including the CMRC, who move CFS/ME research forward despite the lack of funding. “Things are beginning to change now,” he said, partly thanks to the Institute of Medicine report, commissioned by a number of federal agencies. “What we are seeing now is a domino effect in response to the report.”

He spoke about actions taken by the US National Institutes of Health (NIH) in this respect, along with initiatives at the Centers for Disease Control and Prevention. This includes CFS/ME being included in a recent Grand Round (the mechanism by which its highlights focus on key issues and challenges related to a specific health topic) and the establishment of a Technical Development Work Group, to which Dr Nahle belongs, to consider recommendations made by the Institute of Medicine report.

Furthermore, the US Agency for Healthcare Research and Quality has issued an unprecedented addendum to its 2014 evidence review on the suitability and efficacy of CBT and GET for CFS/ME.

Combined with the potential of the work being done in the –omics field, there are reasons to be hopeful.

No Spin zone

Patients are frequently being told they look normal, said Dr Nahle. But as the study results in Figure 2 show, CFS/ME patients are more disabled than people with cancer, diabetes, stroke and many other serious diseases.

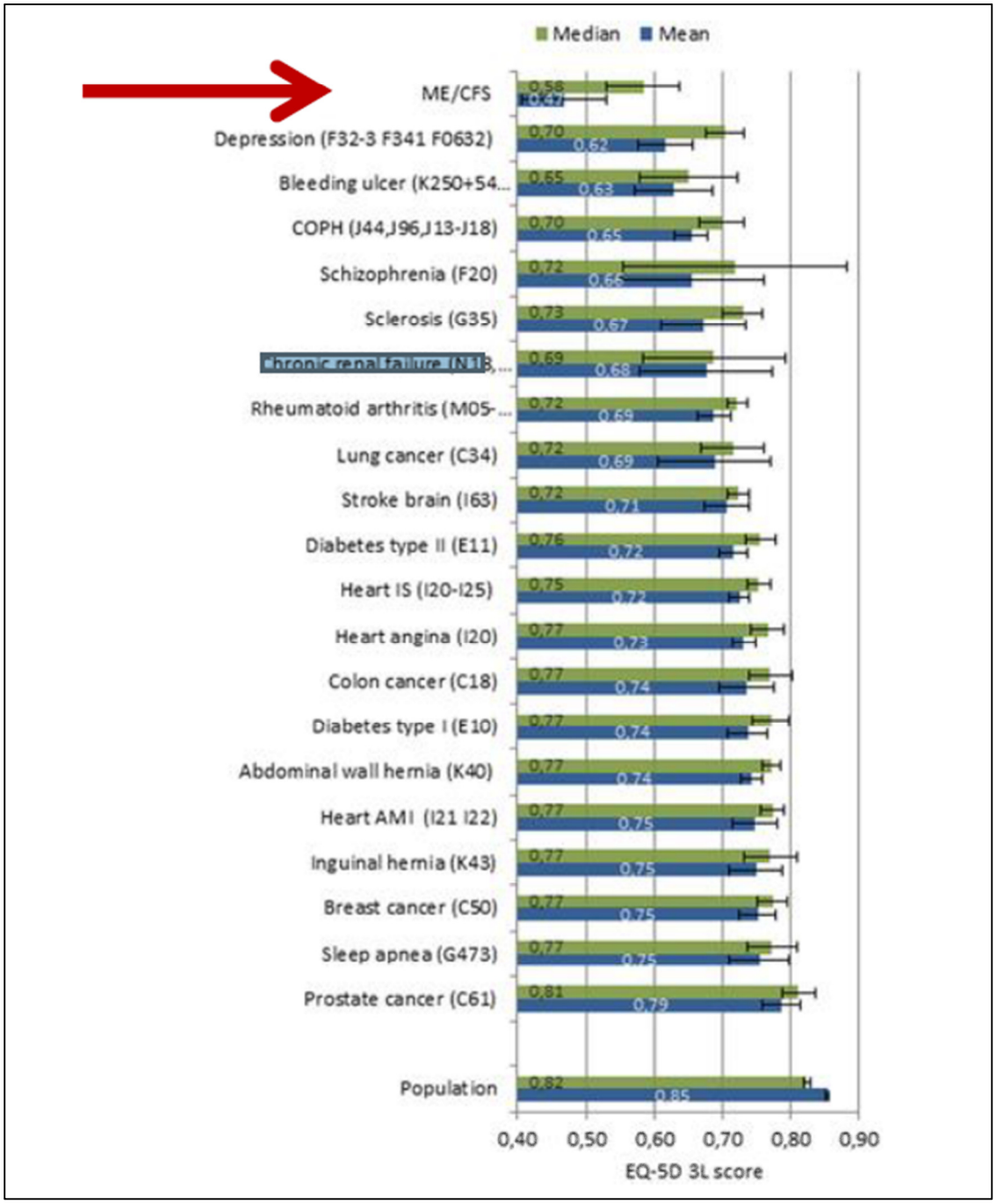


Figure 2: Quality of life for patients with CFS/ME ranks the lowest when compared to other devastating diseases. Source: Hvidberg at al (2015) The Health-Related Quality of Life for Patients with CFS/ME. PLoSONE 10(7): e0132421. doi:10.1371/journal.pone.0132421

The second part of Dr Nahle's No Spin zone is that CFS/ME is caused by depression or anxiety, said Dr Nahle. But actually the opposite is true; depression and/or anxiety are the

most common emotional responses to medical illnesses so it's not surprising that many patients experience these. This is not a causality issue – quite the opposite (see Figure 3).

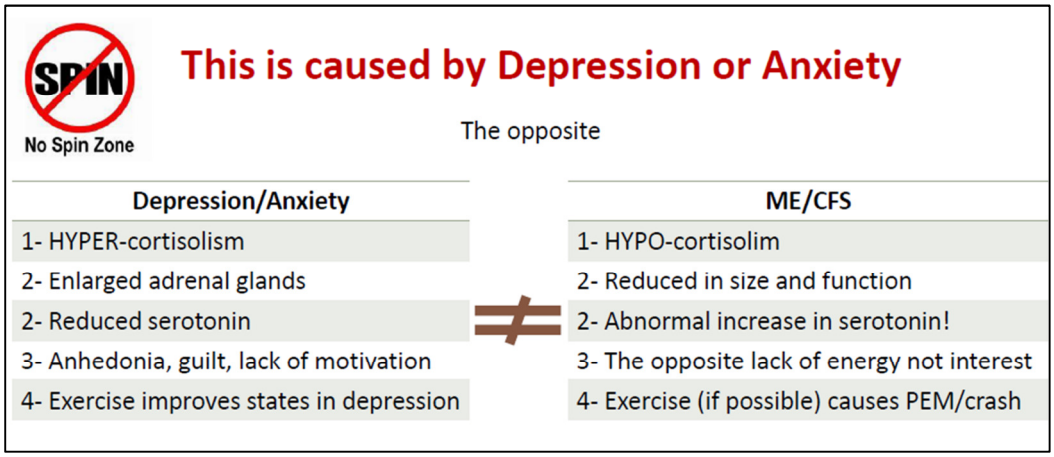


Figure 3: Depression and/or anxiety are the most common emotional responses to medical illnesses

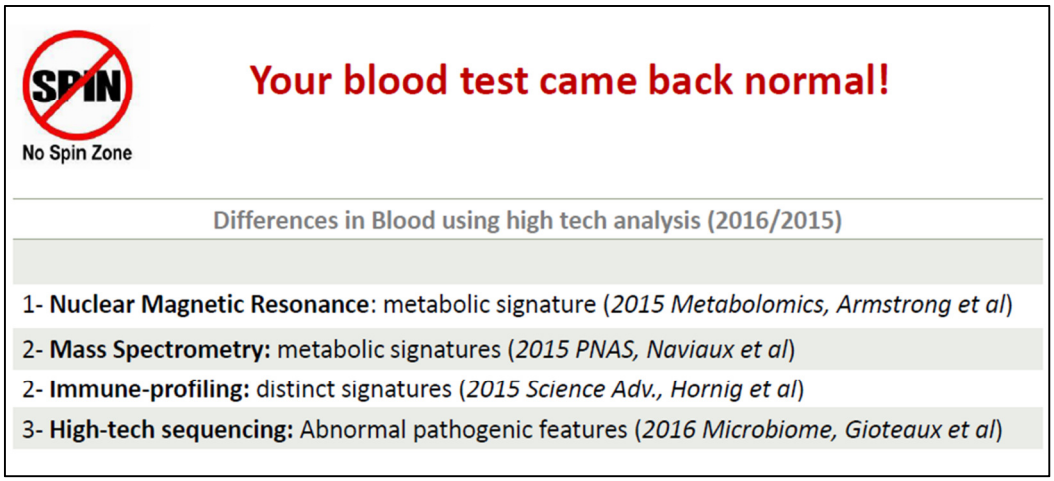


Figure 4: Differences in Blood using high tech analysis (2016/2015)

Thirdly, Dr Nahle highlighted how patients are frequently told that their blood test has come back normal. But his response is: what YOU measured in my blood came back normal. With more detailed analysis, there is much to discover, as illustrated in Figure 4. For example, Armstrong's 2015 study identified a clear metabolic signature in CFS/ME patients.

Objectives and priority areas

Moving on to the work of the SMCI, Dr Nahle highlighted its objectives and priority areas, noting their similarities to those of the CMRC. These are:

- increase understanding of the molecular basis of CFS/ME
- identify a reliable biomarker and credible testing for CFS/ME
- develop effective treatment(s) for CFS/ME patients.

Within those objectives, it has established three key areas of focus: bioenergetics, immunity and inflammation, and neuroendocrine biology. “We know that, in science, the answers never come from where you expect,” said Dr Nahle. “So we are keeping an open mind about other areas as well. All are part of a continuum and very much interconnected.”

Looking at the philosophy of science, three research domains must come together if we are to fix complex problems. These are illustrated in Figure 5.

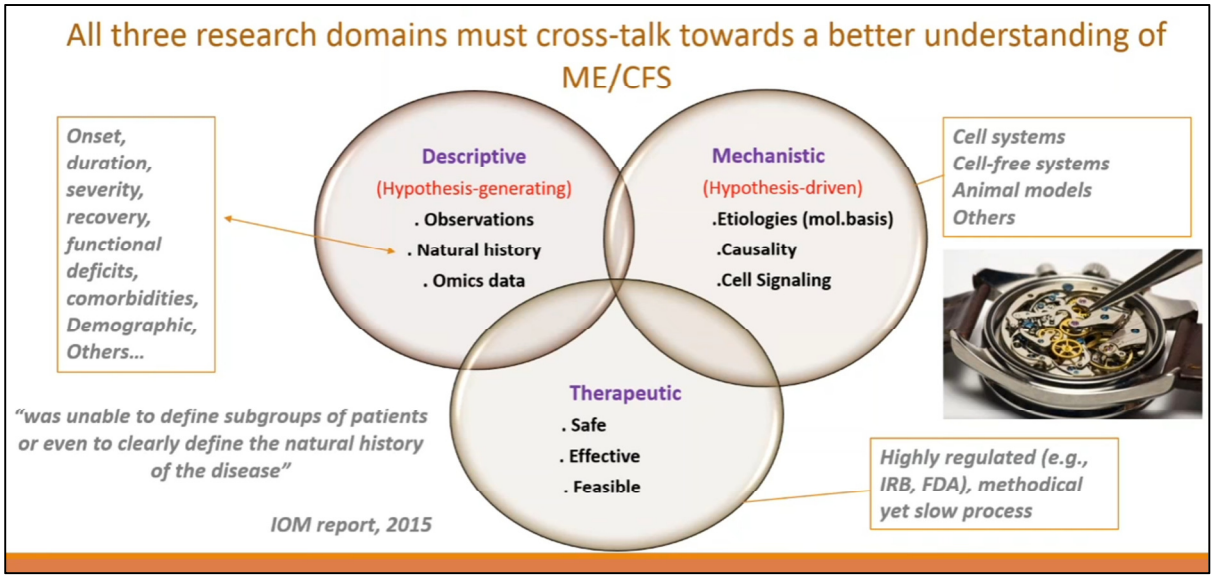


Figure 5: SMCI research philosophy

The first is descriptive research – surveys, -omics data – that helps you to prioritise and develop hypotheses; the natural history of the disease is a very important factor in this, an area of knowledge severely lacking in CFS/ME. The second area is mechanistic understanding, delving in to deep mechanisms about causality, aetiology and underlying signalling pathways. Both of these are very important in developing safe and effective therapies, the third area, through rational drug design

Ramsay Award programme

SMCI’s grant-making programme, the Ramsay Award, has already gone through two cycles in 2008 and 2012. The awards range in size from $35-55,000 with the possibility of renewal based on results.

The programme received international submissions for this year’s cycle, with only 40% coming from the US: the rest were split between the UK, Australia and Germany. A high number of applications came from female scientists, and 40% of were from early-stage career researchers. “We have seen a diversity in topics and background that reflects the pleiotropic complex nature of CFS/ME,” said Dr Nahle. *[Addendum: SMCI announced the latest recipients of its Ramsay Award programme on its website in December 2016.]*

Related to this, the organisation launched the meetME Travel Award programme, aimed at facilitating participation of underrepresented groups in meetings and conferences focused on CFS/ME. The first was awarded to a student in the UK.

Moving on to the SMCI biobank, Dr Nahle explained that they aimed to reduce the barriers faced by scientists when it comes to acquiring samples for study. The capacity of the biobank is being increased by the addition of further data, and the only criteria for those who apply to use the biobank is that they use rigorous science. Examples of work being undertaken at the moment include Dr Jay Chung at the National Institute of Health, looking at biomarkers; and an auto-immunity study at the University of Vermont.

Dr Nahle announced the imminent launch of a 21st century patient registry. This is separate from the biobank, and offers great value, because it tells us about the natural history of the disease: diagnostic data, prognosis, quality of life, disparity data, drug interactions. This can help refine sub-groups in study design, and is key in supporting essential longitudinal studies to determine patterns and progression of disease.

To launch a patient registry effectively, you need the right platforms and the right number of patients to generate reliable data. Submitting applications to the Robert Wood Johnson Foundation and the Genetic Alliance, the SMCI received initial seed funding to set up the platforms it needed.

Every year for the past 12 years, the US government's Health and Human Services committee on CFS/ME (the CFS Advisory Committee or CFSAC) has made a recommendation that a resource must be set up in order to better understand the natural history of the disease. The IOM report was unable to define sub-groups of patients, and this is a major barrier to progress. For these reasons, the SMCI set up its patient registry, and is seeking collaboration with others to support this work on an ongoing basis.

The platform itself is in process of being set up, and will be a simple interface where patients and professionals can submit information. There will be a premium on privacy. "You must empower patients to have control over their own data," said Dr Nahle. Figure 6 shows the results of a survey of thousands of patients in the US, which looked at data sharing and informed consent. Most patients fall in the yellow sphere, where they want each study using their data to contact them in advance to get their specific consent. Fewer than 16.5% did not want their data used at all.

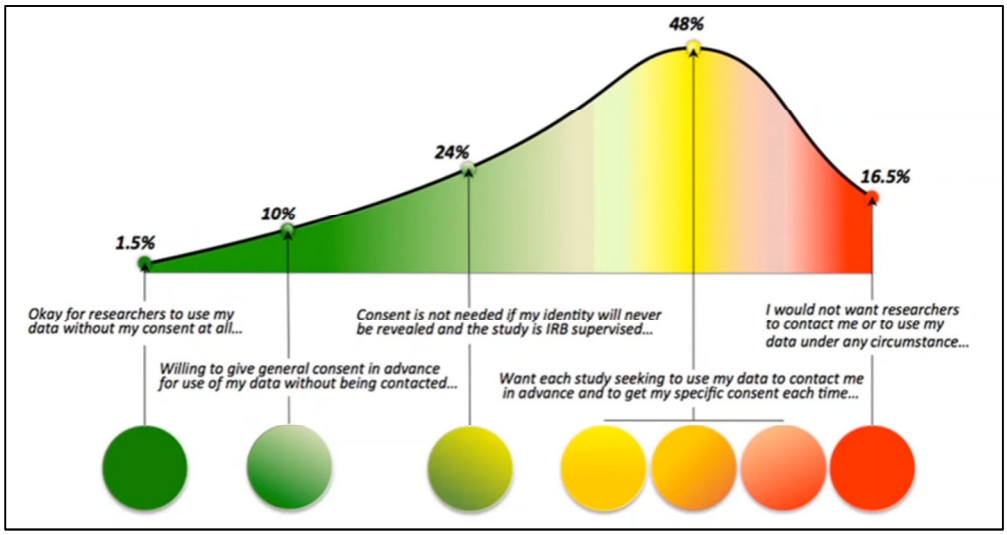


Figure 5: Results of patient survey on how data is used

Using this scale, patients contributing to the register are asked to indicate how they would like their data to be used. Other features of the registry include links to large health record systems, and compatibility with the Precision Medicine million-person study currently ongoing in the US.

Medical education and other projects

Another key segment of the SMCI's work is medical education. The organisation invites public officials, for example from the CDC or NIH, to give updates; recordings are then shared publically on YouTube.

Dr Nahle then moved onto talk about his organisation's Targeted Initiative research programme, to "change the status quo and invest in areas that we think can change the field a little bit."

Focusing on three initiatives, the first is pathway and biomarker discovery, a collaboration with Dr Sue Levine and Prof Maureen Hanson.

Working in partnership with Metabolon, a metabolomics company, the team is studying the same patients involved in Prof Hanson's gut microbiome project (*Genome Medicine*, 2015), which means they are well characterised. "It's hypothesis driven but also a hypothesis-generating combination," he said.

The second project focuses on senescence, the phenomenon by which cells lose their capacity to function. This is a collaboration between SMCI and Dr Sheila Stewart, Washington University and Dr Masashi Narita, University of Cambridge, both experts in this area. Senescence is the phenomenon by which cells lose their capacity to function. It is controlled also by DNA damage response and other factors, such as telomere dysfunction and oxidative stress, and it's known that many of these happen in CFS/ME. In fact, an analysis of reduced telomere length in CFS/ME has been published by the CDC's Dr Beth Unger (*Faseb Journal*, 2016) and the SMCI is collaborating with the CDC on this project.

The third big data project is a functional genomics study to uncover potential drugs screening in CFS/ME, a project in collaboration with Memorial Sloan Kettering Cancer Center and Dr Scott Lowe, Chair, Cancer Biology and Genetics Program. This uses using platforms and technologies that will allow the team to look at phenotypes and certain changes in the potential of cells from patients, such as the increase of the cytotoxicity potential in blood cells.

This type of analysis requires collaboration and considerable groundwork in the laboratory, in a long and time consuming process. "But I'm very excited about this kind of screening, particularly because they already have the compounds on the market that correspond to these druggable targets," says Dr Nahle. "So if we find something we can rapidly accelerate it."

Dr Nahle closed his presentation by thanking all scientists working on CFS/ME and the patient community, "supporting us with money but also literally with blood."

States, traits and diagnosed conditions: implications for the design of population-based studies of human health and disease

Prof George Davey Smith, MRC Integrative Epidemiology Unit, University of Bristol

Key point summary:

- Virtually all medical conditions are directly part of a spectrum, or reflect a liability which lies along a spectrum.
- Wide inclusion criteria and large sample sizes are needed to remove selection bias from studies and reveal the whole picture.
- Subgroups within broad disease groups may reflect varying combinations of liability and specific exposures.
- Attempts to identify and dissect such subgroups should be carried out at the analysis stage, with replication.

Prof Davey Smith began by explaining that although he is not an expert on CFS/ME, he has experience of working on the design of large-scale biomedical epidemiological studies of other conditions, the principles of which are applicable to the type of CFS/ME study being discussed at the conference.

The normal and the pathological

The debate about whether health and disease are two discrete states goes back hundreds of years, but the view of Claude Bernard, who established the use of the scientific method in medicine in the 1860s, was that: "*Health and disease are not two essentially different modes as the ancient physicians believed and some practitioners still believe. They should not be made into distinct principles, entities which fight over the living organism and make it the theatre of their contest. These are obsolete medical ideas. In reality, between these two modes of being, there are only differences of degree: exaggeration, disproportion, discordance or normal phenomena constitute the diseased state*."

This has become clearer in the studies of disease in the time since. Between the 1950s and 1970s, there was fierce debate central to British medicine, about what constitutes the difference between normal and pathological blood pressure. One view, by Baron Robert Platt was that hypertension is a distinct disease, separate from the rest of the population with normal blood pressure, having a bimodal distribution, shown in figure 1 as two peaks.

Contrary to this, Sir George Pickering proposed that instead, blood pressure is normally distributed, as in the bell curve in figure 1, and that blood pressure being defined as hypertension or not is arbitrary. The association of blood pressure to important cardiovascular events such as stroke or coronary heart disease is linear.

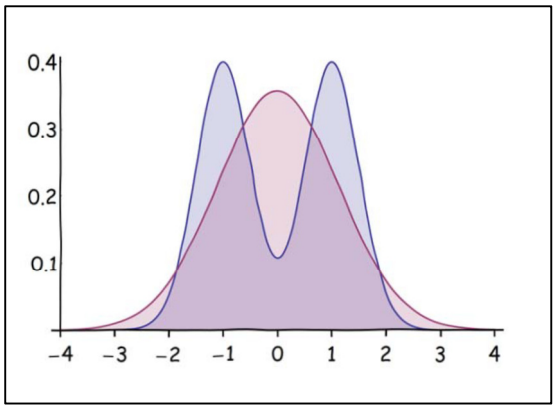


Figure 1: Platt versus Pickering

This debate raged in the pages of medical journals at the time, similar to the way that there are often heated debates now in the field of CFS/ME. The cause of these debates is often that data available at the time is rather limited and does not reveal a clear picture.

As shown in figure 2, it is possible to incorrectly interpret the curves as fitting Platt's hypothesis of having bimodal distribution, when in reality the distribution is normal with a slight tail, and the association with disease risk is continuous.

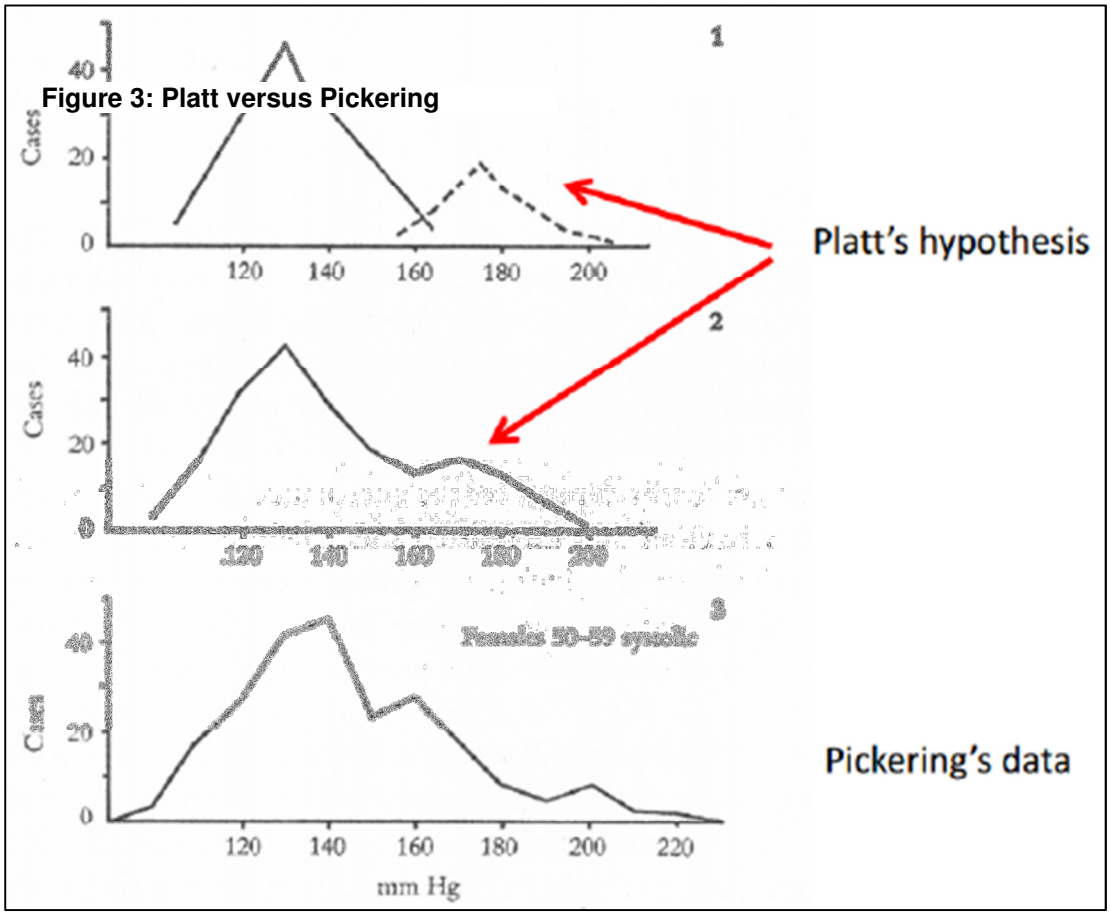


Figure 2: Number of cases against blood pressure (mmHg)

Now it is well established that blood pressure data support a continuity hypothesis. With different aetiologies feeding in to this normal distribution, it does not matter whether a person's blood pressure is raised from living on crisps or because there is a genetic tendency to have high blood pressure; both increase the risk of heart attack or stroke.

In figure 3, the distribution of blood pressure among those who went on to die of heart attack or stroke and the survivors shows considerable overlap, with a shift of the distribution to the right in those who succumbed .

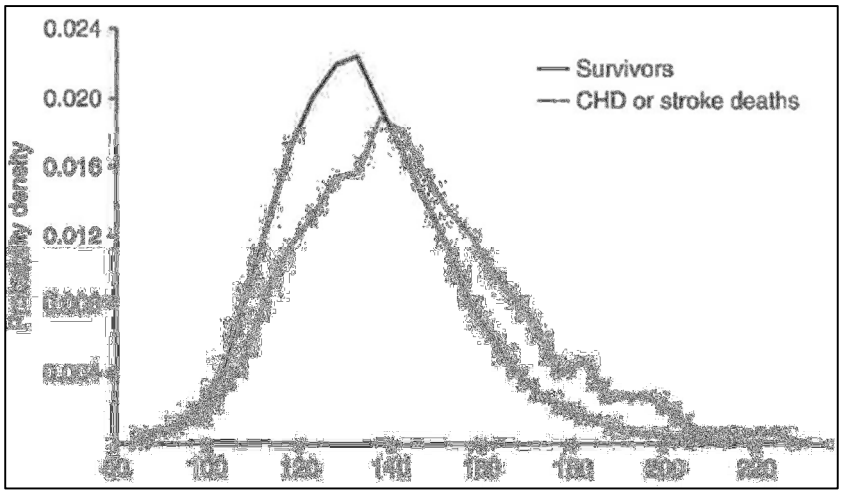


Figure 3: Distribution of systolic blood pressure (mmHg) in men who died from a heart attack or stroke compared with survivors. Rose D. The strategy of Preventive Medicine 1992

There are many other examples of this throughout medicine, such as glycated haemoglobin (HbA1c), which is an indicator of blood glucose levels, and increased risk of mortality (Khaw et al, 2002). Similarly, intraocular pressure and glaucoma (Leske et al, 2002), and bone heel ultrasound and fracture risk (Khaw et al, 2004) show these patterns.

Notion of liability

The notion of liability suggests that conditions have an underlying liability which is continually distributed. These models have been used in genetics since 1901, when Pearson introduced them. Figure 4 depicts liability as a normal distribution with the notion that individuals affected will be at the far right. However, anyone has the potential to develop the disease, but the probability increases as liability increases.

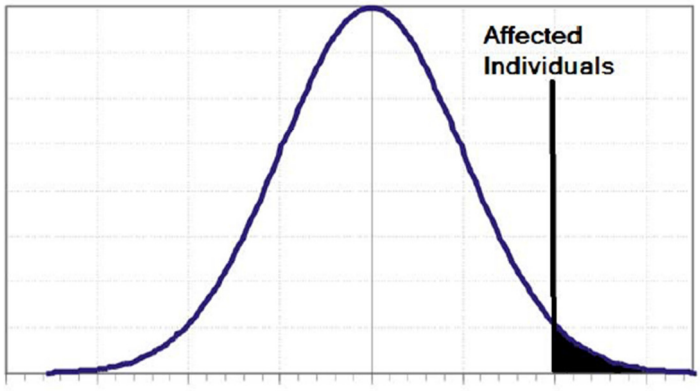


Figure 4: Standard liability model

Implications

Categorical outcomes (eg. heart attack, death, stroke) can have continuously distributed underlying liabilities with increasing probability of transition into disease state with increasing level of liability. Understanding contribution to liability provides inroads into understanding disease causation and potential prevention. Such models apply, to differing degrees, to virtually all medical conditions.

Considering autism where, in extreme forms, there is no doubt about the diagnosis, there is clear polygenicity (the contribution of many genetic variants) to what becomes the same diagnosed condition.

Looking at traits related to autism, such as social, communication and daily living skills, they are continuously distributed in the population. The Simons Simplex study looked at single cases of autism in a family; their siblings who did not have the diagnosis were also recruited as controls.

The siblings share genetics with the cases, and have a higher distribution of the traits when compared to the general population. There is a considerable overlap between cases and control siblings, as shown in figure 5. Although it can seem like a distinct condition in some cases, there is some arbitrariness in saying where the line is drawn between an autism diagnosis and no diagnosis.

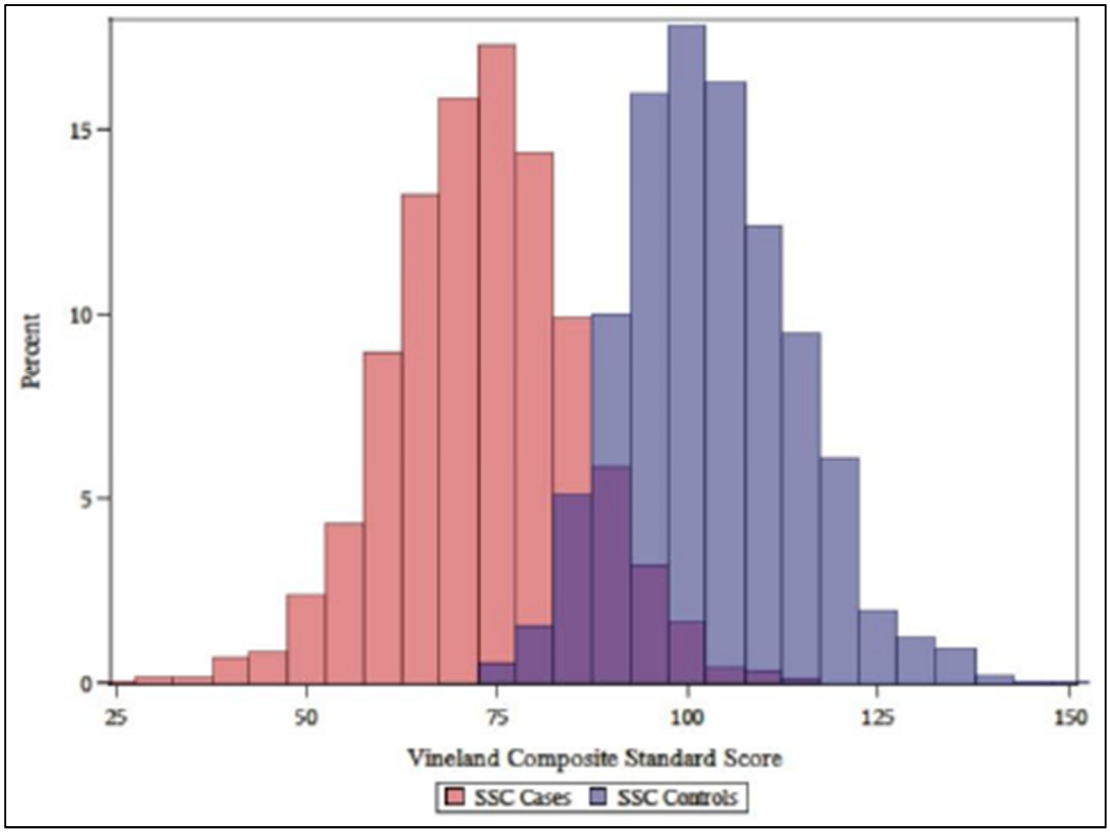


Figure 5: Vineland social, communication and daily living skills in cases and unaffected siblings in the Simons Simplex Collections (SSC). Robinson et al. Genetic risks for autism spectrum disorders and neuropsychiatric variation in the general population. Nature Genetics 2016; 48:552-555

There are not many, but some conditions are exceptions and aren't on a continuum. The disease is either there or not, such as Rabies and Huntington's disease, which are examples of fully penetrant infections on monogenic conditions.

If a condition has many underlying distributed liabilities, then using particular characterisations or categories of characterisations as inclusion criteria for a study, has implications for what the study can show. Mainer ET all's 2016 discussion of diagnoses in overlapping pain conditions shows that by having very proscriptive criteria for inclusion can mean that misleading conclusions are drawn.

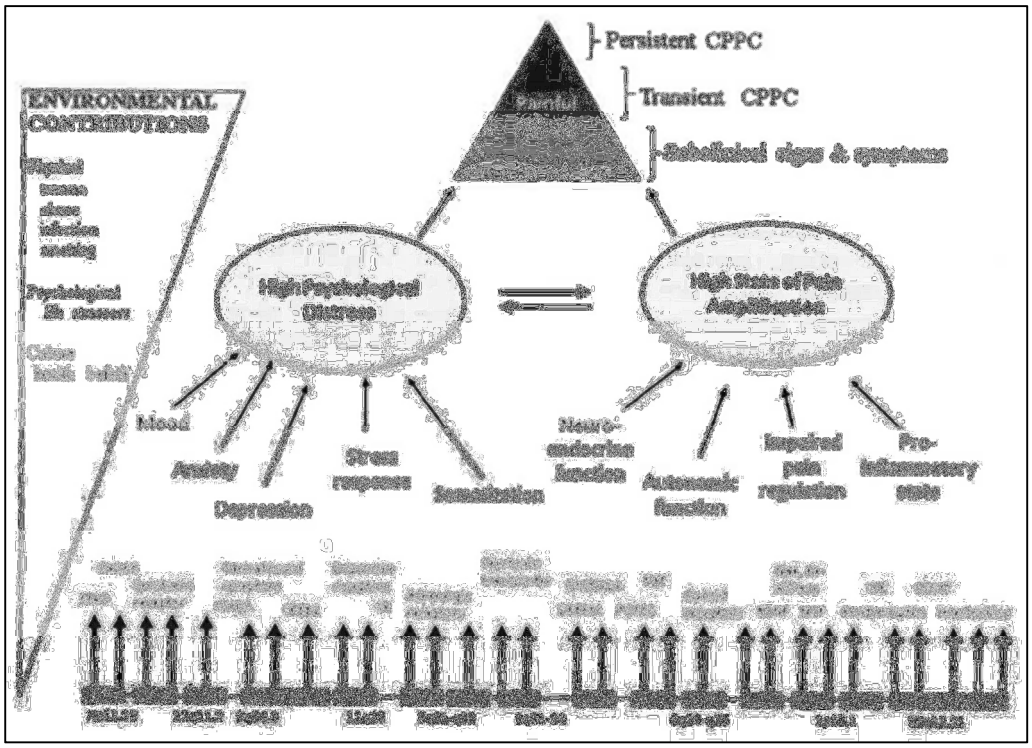


Figure 6: Model depicting determinants that contribute to the risk of onset and maintenance of common chronic overlapping pain conditions. Maixner W et al. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. The Journal of Pain, 17(9) Supp 2 T93-T107

An article by Berk son in 1946 pointed out that sampling in particular ways can give misleading answers. It was thought that gall bladder disease could influence the risk of diabetes. People were having their gall bladder removed as an attempted treatment for diabetes; also, if you had more than one condition you were at increased likelihood of being admitted to hospital.

Berk son pointed out that if a study only includes patients in hospital, there seems to be an association – but a study of the wider population gave no association. This became known as Berk son bias; in causal analysis, it is an example of a collider bias. This is an important consideration in study design, and can be illustrated by using a toy example – see Figure 7.

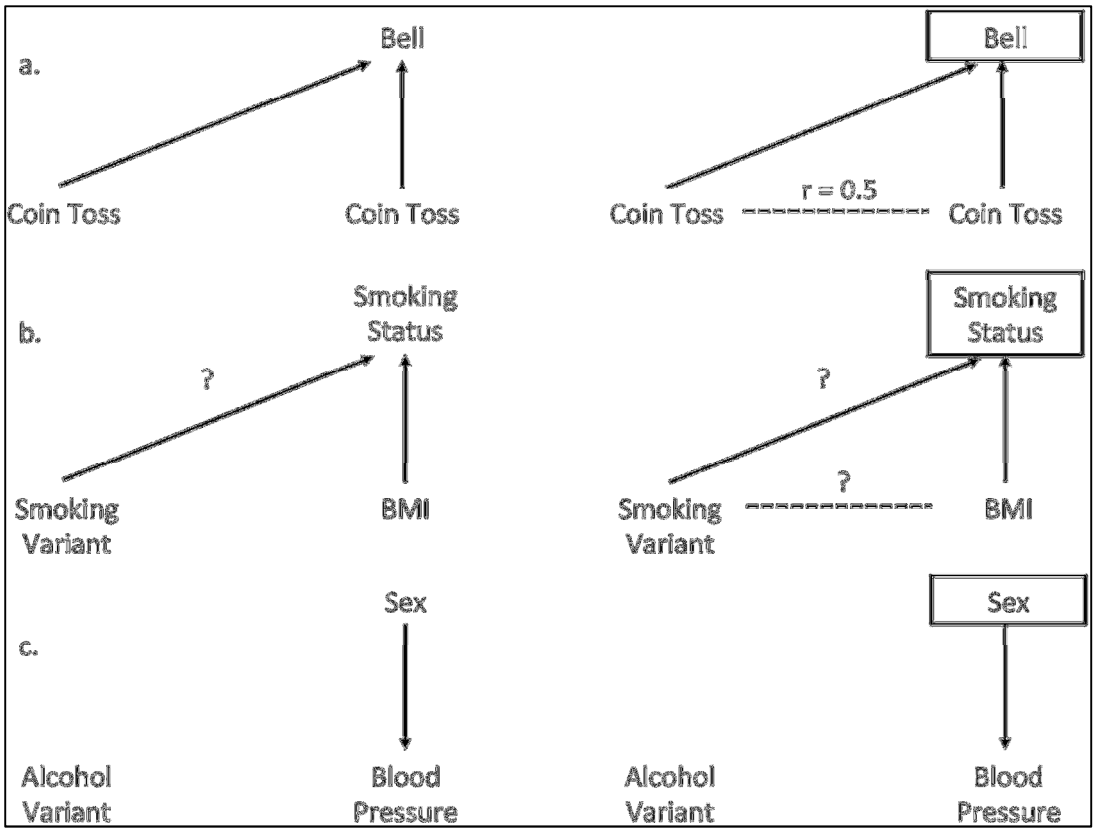


Figure 7: Illustration of collider bias. Panel A shows the basic premise of collider bias. In this example, a bell is sounded wherever either coin come up "heads." The result of one coin toss is independent of the other. However, if we stratify on the bell ringing, seeing "heads" on both coins is not independent and a spurious correlation is induced. Panel B shows this with the example of stratifying on smoking status. If the variant used as an instrument for heaviness of smoking is also associated with smoking status (ie. ever-smoker versus never-smoker), and if BMI also influences smoking status, then there is a risk of collider bias if we stratify on smoking status. Panel C shows an example where stratification will not introduce collider bias, as sex is not an effect of either possession of a genetic variant that predicts alcohol consumption or of blood pressure. Source: Gage SH, Davey Smith G, Ware JJ, Flint J, Munafò MR (2016) G = E: What GWAS Can Tell Us about the environment. PLoS Genet 12(2): e1005765. doi:10.1371/journal.pgen.1005765

If sampling is related to highly proscriptive definitions, this can lead to automatic associations of factors amongst study participants that do not reflect what exists in the underlying population – or reflect meaningful or potentially causal associations, eg. gall bladder disease appearing to cause diabetes when it does not.

If representative samples with available data are recruited, the "proscriptively defined group" can still be investigated and if biases cause the associations this can be revealed. Even if proscriptive definitions are not biasing findings, they do not help – and indeed generally weaken – efforts to identify meaningful associations.

Prof Davey Smith concluded that using strict inclusion criteria is a lose-lose situation. An example highlighting this is a genome-wide association study into migraine (Atilla et al, 2013). As with CFS/ME, there were debates about what is or is not a migraine, whether tension headaches are a type of migraine, and whether the study should have been restricted to participants that have migraine with aura. If that restriction had been followed, very few findings would have emerged.

Having very broad categories for inclusion means more is revealed about the underlying liability, such as a shared biological basis between migraine without aura and coronary artery disease but a negative correlation genetically (Winsvold et al, 2015), and a positive genetic correlation between migraine without aura and ischaemic stroke (Malik et al, 2015). These correlations would not have been found if only migraine with aura had been studied.

Another example is the Avon Longitudinal Study of Parents and Children, involving a cohort of children with samples taken from cord blood when they were born, and followed up for 25 years. This was a very representative sample at initiation and the study examined whether these children continued to participate in the study.

It is now known that there are 108 genetic variants associated with schizophrenia risk, which are also present in the general population. A score can be calculated for how many variants an individual has. Very few people have zero and very few have 108, giving a score with a normal distribution. Looking at study participation as the child grows older revealed that those continuing to participate had lower scores for schizophrenia variants, whereas non-responders had higher scores.

The non-participation was not because they have developed schizophrenia (they were too young to do so) but it reflects underlying liabilities, like willingness to take part in studies. That can lead to serious biases in studies and associations seen in participants that are different to those in the general population.

Conclusions

Virtually all medical conditions are either directly part of a spectrum (like hypertension) or reflect a liability which lies along a spectrum. Subgroups within broad disease groups may reflect varying combinations of liability (“diathesis”) and specific exposures (“stress”).

Both are important. Selection of apparently highly specific case groups, even when intended to clarify the situation, can create biases. Attempts to identify and dissect such subgroups should be carried out at the analysis stage (with replication). Broad, representative criteria and recruitment strategies should be used for informative population-based studies.