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The way forward: A case for longitudinal population-based studies in the field of functional somatic syndromes

This special issue is focused on functional somatic syndromes or disorders (FSDs): syndromes that do not have a known underlying pathophysiology. Among the most important examples are irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), and fibromyalgia (FM). Although there is an ongoing debate between the lumpers (who argue that all FSDs are in fact manifestations of one single disorder) and splitters (who argue that despite communalities, the differences should not be ignored) [1], most researchers currently agree that FSDs share at least a common core. It is increasingly recognized that FSDs are not discrete diseases but heterogeneous clusters of fluctuating common functional symptoms with no clear boundaries between healthy and disordered. Remarkably, we have not yet translated this increasing knowledge into our research designs. Despite the fact that we do not know how many symptoms a person needs of which types for how long to become a case of what exactly, the field of FSDs is filled with cross-sectional case-control studies. In this editorial, I will identify some of the problems associated with the current approach, after which I will make a case for longitudinal population-based studies as the way forward to further increase our knowledge on the etiology of FSDs.

Generally speaking, well-performed case-control studies may be as informative and valid as cohort studies [2]. However, when case-control designs are used to study the etiology of FSDs, specific problems arise.

First, it is unclear whether the current diagnostic criteria that are based on the presence of specific symptoms are valid. This is illustrated by the two more or less competing approaches in the literature. One set of studies is investigating symptom patterns across FSDs [3], suggesting that symptoms are largely shared between FSDs. At the same time, a second set of studies is investigating symptom patterns within specific FSDs. These studies increasingly recognize symptomatic subgroups within specific syndromes. For example, IBS is often split into constipation and diarrhea predominant [4], whereas factor analyses have defined subtypes of FM [5] and CFS [6]. Thus, on the one hand, several FSDs are regarded as manifestations of a single underlying disorder, whereas on the other hand, specific FSDs are split in subsyndromes. Both approaches question the validity of the current diagnostic boundaries.

Second, case-control studies typically compare patients with a diagnostic label for their symptoms with patients without these symptoms for the presence of presumed risk factors. In case of FSDs, both the presumed risk factors and the prognosis might be influenced by the presence of a diagnostic label. In order to understand this, it is important to realize that the core symptoms of FSDs are very common in the general population. For example, many people in the general population fulfill the criteria for CFS, although only a minority of them receives a formal diagnosis. There are no objective parameters that are able to distinguish states of FSDs and health; instead, the diagnoses are purely based on the reported symptoms and the exclusion of other explanations for them. It is conceivable that receiving a syndrome label is not only related to symptom severity but also to personal characteristics including help-seeking behavior, beliefs and expectations [7]. This implies that personality characteristics that are different between FSDs cases and controls might be more related to the labeling of functional symptoms than to the development of them. This problem is further amplified by the potential of an FSDs label to worsen prognosis [8].

Third, the diagnostic criteria of different FSDs include different temporal criteria. According to the internationally accepted criteria, a CFS diagnosis requires persistent or relapsing fatigue of six or more consecutive months, a diagnosis of FM widespread pain for at least three months, and a diagnosis of IBS recurrent abdominal pain or discomfort at least three days per month during the previous three months. This implies that differences between risk factors for FSDs that are found in case-control studies might be related to the chronicity of symptoms rather than to their type. It is important to note that case-control studies in the FSDs field are typically based on prevalent and not incident cases.

Fourth, case-control studies have to define a threshold for caseness, and this also has consequences for the control group. Typically, the international criteria are used, and controls are not allowed to have any symptoms. For example, the case definition for IBS requires having symptoms at least three days per month during the previous three months. This means that people having symptoms for one or two days per month, or only during the previous two

months, do not add to the literature. Given the fact that the symptoms that characterize IBS are common, these groups of people with subthreshold symptoms might be quite substantial. On the other hand, as controls, people without any IBS-related symptoms are often included, and this is also a highly specific group. The severity threshold leads to a loss of information, while in fact this threshold is debatable.

Fifth, different FSDs have different research traditions. If risk factors are differentially associated with FSDs, it is sometimes not obvious whether these are real differences or whether they are due to methodological differences in the research field of FSDs. For example, studies toward stress-axis responses in IBS often use colorectal distension as a stressor, in contrast to studies in other syndromes that more often use pharmacological or psychological challenges.

In summary, case-control studies are complicated in the study of the etiology of functional syndromes. Since we assume that FSDs are not discrete diseases, we need to translate this view on FSDs into our research designs.

In order to choose the most informative research design to study the etiology of FSDs, it is important to first take a closer look at the etiology of FSDs. The fact that FSDs appear to be composed of symptomatic subgroups implies that different etiological trajectories might result in a specific FSD. At the same time, it is evident that many risk factors are shared between FSDs, suggesting that largely comparable etiological trajectories might result in different FSDs. This apparent paradox is elucidated by Rothman's [2] model of causation. In this model, a disease is the end result of an etiological trajectory that is composed of component causes, which are the conditions and events contributing to the etiology of a disease. An example of a candidate component cause for FSDs is *Campylobacter* gastroenteritis, which is prospectively linked to an increased risk of the development of IBS [9,10]. However, the vast majority of patients with this infection never develops IBS, indicating that this infection is not a sufficient cause. In Rothman's model, the onset of a disease is equivalent to the completion of a sufficient cause. A sufficient cause is a set of component causes that inevitably produce disease and can be interpreted as an etiological trajectory to disease. Interestingly, different sufficient causes could be the start of the same disease (etiological heterogeneity within disorders). In biology, this is known as the concept of equifinality: the same end state may be achieved via many different trajectories. If a component cause is absent in a given person, and the person still gets the disease, it means that the component cause is not a necessary cause and this person has developed the disease via an alternative sufficient cause. For example, the majority of IBS patients probably never had *Campylobacter* gastroenteritis. In addition, sufficient causes leading to different FSDs might have highly overlapping component causes (etiological homogeneity among disorders). For example, *Campylobacter* gastroenteritis is also prospectively linked to an increased risk of the development of CFS, although to a lesser degree compared to IBS [10].

Thus, there are several etiological trajectories to disease in FSDs. Some of these trajectories might be largely shared between FSDs, other trajectories might be specific for FSD subtypes, and largely different trajectories might result in the same FSD. One important consequence of the heterogeneity in etiological trajectories is that, by treating FSDs as homogeneous entities, the expected effect sizes of risk factors are low and the power of studies consequently limited. This is due to the fact that risk factors that are only involved in a subsample of etiological trajectories are diluted by the etiological trajectories (sufficient causes) that do not contain that specific risk factor (component cause). It is evident that large samples are needed to study etiological heterogeneity.

In my opinion, the complex etiology of FSDs can only be further elucidated by studies meeting the following characteristics.

First, studies need to be longitudinal, for several reasons. Longitudinal research is the only way to characterize the etiological trajectories that are relevant among and across disorders and thus the only research design that fully acknowledges the complex etiology that is conceptually recognized. Longitudinal studies will also identify which correlates of FSDs are mere consequences or epiphenomena of the FSD instead of contributing to the etiology. As an example, a high incidence of specific viral antibodies in CFS patients could indicate a role of these viruses in the etiology or could reflect an altered immune function that may be cause or consequence of the disease [11]. It is important to realize that consequences of outcomes are likely more highly correlated with the outcomes than are risk factors [12]. In addition, longitudinal studies have the potential to improve diagnostic criteria. Longitudinal studies toward symptom patterns over time could contribute to an empirically based typology of different FSDs and thus provide an alternative perspective to that offered by the current diagnostic criteria. A similar approach has already been useful in the study of depression and anxiety [13]. Such study toward symptom trajectories over time could approach the question whether FSDs are characterized by FSD-specific symptom clusters or whether they only differ in their current concerns or in the relative severity of symptoms.

Second, we need population-based studies instead of studies comparing clinical samples with healthy controls. This will avoid the problem of studying labeling instead of existence of symptoms, while at the same time guaranteeing that all participants in the whole range of health to disease add to the results. In addition, population-based studies enable us to investigate several different FSD end points without much additional work. As such, a population-based cohort can give an integrated estimate of the FSD-related health effects of a given component cause. The main drawback of a large population cohort is the costs associated with repeated measurements of several component causes and clinical end points. One solution for this problem is to identify ongoing cohort studies that already include relevant

biopsychosocial risk factors and add clinical end points that are relevant for the study of the etiology of FSDs. An additional advantage is that these cohorts are usually focused around the objective detection of medically explained diseases and therefore enable to exclude objectively determined pathologies.

Third, as clinical end points, we should study diversity, severity and chronicity of functional symptoms in addition to the existence of a specific FSD. Thus, we will avoid the problems in case definition (questionable validity of diagnostic boundaries, the arbitrariness of the threshold for caseness and the different temporal criteria) while still being able to translate new to existing literature. In addition, this will enable to integrate findings in different syndromes. It would be a major step forward if we identified a gold standard for the measurement of functional symptoms. Although using a specified instrument may not be possible in all studies, it will be possible to validate existing instruments against this gold standard.

It is time that specialists from different fields unite their forces in order to come to a shared approach. This will finally make clear if FSDs are separate entities in real life or just in the minds of the observers.

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