



## Commentary

## Is there such a thing as a symptom cluster: The paradigm shift in symptom science requires a philosophical reflection



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I read with great interest the article written by Zhu et al. who urged a paradigm shift in current symptom research from system clusters to system networks and described the untapped potential of network analysis in identifying core symptoms, clustering symptoms, symptom network density, and microlevel interactions among symptoms.<sup>1</sup> I highly commend the advocacy to shift the symptom science focus from ‘clusters’, which tend to hold a static closed-system view about symptoms, to ‘networks’, which highlight the dynamic interaction among symptoms from an open-system perspective. Nevertheless, I argue that if we want a shift in how symptom research is conducted, we cannot remain our arguments at the methodological level and leave the philosophical foundation on which they are based untouched. A paradigm shift must start with the questioning of its philosophical underpinnings.

In this commentary, I start with a critique of the positivist view that symptom cluster researchers tend to hold. Drawing on the complexity science, I then illustrate the strengths and limitations of the symptom network research method described by Zhu et al. Lastly, I call for a complementary small data paradigm in symptom network research to inform personalized symptom care.

A symptom cluster is defined as the stable concurrence of two or more symptoms that may or may not share the same etiology.<sup>2,3</sup> The basic presumption underlying current symptom cluster research is a positivist worldview: a realist ontology that there is an external reality about symptom clusters—an ultimate truth on what they are and how they work, and an objective epistemology—researchers’ jobs are to measure clusters using well-established tools; uncover the working mechanisms, and promote the generalizability of clusters to other chronic conditions.<sup>3</sup> Human symptoms, under this worldview, tend to be considered as a closed system, which is made up of a bunch of single symptoms with limited internal and external interactions, such that we can divide them into distinct and stable segments and explain the high-level symptom clusters by reducing them into low-level phenotypic and molecular mechanisms. I challenge this presumption by arguing that symptom cluster is more of a human-constructed concept underpinned by a relativist ontology and a subjective epistemology. Ontologically, there is no such biological phenomenon as a symptom cluster; symptom clusters do not exist ‘out there’ waiting to be discovered; it is the researchers who create and rationalize clusters (ie, perceptual criteria for reality). More

importantly, there is no compelling evidence of the distinct clustering effect that is different from the effects of the co-existence of symptoms. To put it in another way, no emergent properties are proved to be caused by the clustering effect (ie, causal criteria for reality). In addition, the concept of symptom cluster lacks strong theoretical underpinnings<sup>3,4</sup> that can explain its general working mechanisms, including the process of how symptoms cluster together and the impacts caused by clustering. Epistemologically, the categorization of symptoms is full of researchers’ interpretations influenced by their backgrounds, interests, and preconceptions, and varies when introducing new symptom variables or using different analytic methods. Therefore, I hold that there is no such a single reality on symptom clusters and their working mechanisms. Rather than being considered as real entities, symptom clusters may be more appropriate to be regarded as a concept and situated within a constructivist paradigm, which appreciates multiple interpretations of symptom clusters, multiple truths about their working mechanisms, and the heterogeneity of individual symptoms. Limitations exist in current symptom cluster research, which can hardly be resolved at the empirical level. A critical paradigmatic reflection, especially at the ontological level, is fundamental to moving the field forward.

Next, drawing on the philosophy of complexity science, I contend that human bodies<sup>5,6</sup> and diseases, like cancer,<sup>7</sup> are inherently complex adaptive systems with the features of openness, evolutionary processes, emergent properties, etc. Symptoms are not only the results of evolving diseases but also the manifestations of complex and dynamic interactions among internal and external environments. That is to say, the mechanisms which trigger the manifestation of symptoms are always idiosyncratic. Symptoms are often interconnected holistically as an expression of the state of individual health. The symptom network approach proposed by Zhu et al. remedies some of the limitations of symptom cluster research in that: (1) symptom networks are real both perceptually and causally with strong theoretical support from complexity science, which makes it possible to uncover the overall patterning of symptoms, or in general, the truths about symptoms; (2) symptom networks embrace the complexity of real-world human symptoms, rather than reducing them into segments; (3) symptom networks can capture the dynamic interactions among symptoms over time and support the development of population-level symptom care interventions. However, Zhu et al.

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situated the symptom network approach in the big data context (described as ‘symptomics’ in their text) and implied that population-level symptom networks can guide individualized patient care. I argue that the big data approach, akin to evidence-based medicine, can inform the development of interventions at the population level to get an average effect on symptom outcomes. However, since it neglects the specificity of individual symptoms, the interventions when used in individual cases will have varied likelihoods of success, thus insufficient to achieve the full personalized care promise.

Following the argument above, I propose a complementary small data paradigm in symptom network research to inform personalized care.<sup>8,9</sup> Small data refers to ‘the rigorous use of data by and for a specific N-of-1 unit’.<sup>8</sup> It allows for in-depth explorations of complex and idiosyncratic symptoms and the surrounding bio-psycho-social context of an individual. While the big data approach uses population-level symptom data to generate interventions to inform individual symptom care (ie, from general to particular), the small data approach develops personalized interventions through a thorough investigation of the causal mechanisms of individual-level symptom networks, which is likely to inform the generation of population-level interventions by clustering individuals with similar causal mechanisms (ie, from particular to general).<sup>8</sup> Here I refer to the complexity-informed fundamental care approach described by Conroy et al.<sup>10</sup> and propose a seven-step small data symptom network paradigm for patient care: (1) engage with the individual patient to gain rich patient narratives on symptoms and their potential relationships; (2) create a personalized symptom network and uncover its potential causal mechanisms by analyzing the narratives and other sources of information, such as the medical records and lab tests; (3) co-develop a personalized symptom care plan with the patient based on the identified causal mechanisms and implement the care plan; (4) measure the effects and explain them through a process evaluation of the care plan, the quality of implementation and measurements, and the underlying mechanisms; (5) refine the causal mechanisms and care plan based on the evaluation to achieve satisfying symptom outcomes for this patient; (6) develop context-sensitive causal explanations for symptom networks by repeating the above five steps in patients with distinct symptom-relevant characteristics. The step is to build a theoretical understanding of what type of patients with what kind of symptom network patterns are likely to be caused by what (and therefore can be treated with a particular symptom care plan); (7) develop a population-level symptom care protocol and provide symptom care by clustering patients with similar context-sensitive causal explanations. This seven-step small data

approach aligns well with the narrative medicine and patient-centered care tenets which offer enormous opportunities for its implementation. However, the small data approach poses challenges for research. For example, the massive, messy, and often longitudinal data will make the analytic process challenging. It is not a linear process to identify the causal mechanisms, but requires iterative refinement and sometimes interdisciplinary efforts. Therefore, a more practical and maybe optimal approach is the complementary use of big and small data symptom network paradigm to guide personalized symptom care, eg: the big data approach offers insights on the general organizing patterns of symptoms; the small data approach further develops and refines the patterns in an individual through analyzing patient narratives and medical records. This approach can facilitate the close collaboration between researchers (the big data approach) and healthcare professionals (the small data approach) and is likely to translate research evidence into practice timely. Research is necessary to further explore how these two approaches can work together to inform personalized symptom care.

### Declaration of competing interest

None declared.

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