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## Letter to the Editor

# Statistical relationship networks in psychiatric research: The case of delirium in the context of COVID-19<sup>☆</sup>



## Las redes de relación estadística en la investigación psiquiátrica: el caso del delirio en el contexto de COVID-19

Dear Editor,

On 2 December 2020, an article was published in the Journal referring to the lack of evidence on the approach to delirium in the context of COVID-19, for which a consensus was drawn up on its diagnosis and treatment in the context of a pandemic.<sup>1</sup>

Delirium is characterised by an acute change in attention, awareness and cognition. It is a common condition in older adults with physical or mental illness which, in addition to being considered a geriatric emergency, increases morbidity and mortality rates.<sup>2</sup> Aetiologically, the risk factors for delirium can be divided into predisposing factors, which are those that reinforce the initial vulnerability to delirium (e.g., advanced age), and precipitating factors, which are the acute changes that trigger the syndrome (eg COVID-19 infection).<sup>1</sup>

The association between delirium and COVID-19<sup>1</sup> specifically involves multifactorial mechanisms, such as direct neurological invasion, cerebrovascular disease and, more indirectly, hypoxia, fever, dehydration, inflammation (pro-inflammatory cytokine storm), medications and metabolic abnormalities. It is therefore important to understand the dynamic interaction of the mechanisms that reinforce this comorbid relationship, which is of particular relevance at the current time.

The purpose of this letter is to present the network model of statistical relationships (directed or undirected), composed of zero-order correlations or partial correlations<sup>3</sup> that connect the nodes (variables) and structure the dynamic model. This method is inclusive, with various clinical measurements related to psychiatry,<sup>4,5</sup> including: cognitive and neuropsychological<sup>6</sup>; neuroanatomical<sup>7</sup>; biochemical<sup>8,9</sup>; genomic<sup>10,11</sup>; and anthropometric and physiological.<sup>4</sup>

The essential importance of network analysis is that it allows the interaction of the phenotypic structure and the biomarkers of the predisposing delirium risk factors (eg, frailty

syndrome phenotype<sup>12,13</sup> or another more comorbid clinical diagnosis, determination of the polygenic risk<sup>11</sup>), and precipitating factors linked to COVID-19 (e.g., inflammatory biomarkers and cytokines<sup>8</sup>) that affect the central nervous system and cause neuropsychiatric disorders. At the same time, the inclusion in the network system of the self-report instruments Confusion Assessment Method for the Intensive Care Unit and Delirium Diagnostic Tool-Provisional, discussed in the study by Franco et al<sup>1</sup> for the diagnosis of delirium, enable new clinical hypotheses on the factors and modulators with the greatest clinical implications in the dynamics of delirium and COVID-19 to be assessed and explored.

One of the most closely related vulnerability factors in adults with delirium is frailty syndrome, with this being multifactorial in nature and involving components of social, physical and psychological stress.<sup>13</sup> For frailty, the assessment instruments for delirium patients include the frailty index or phenotypic characteristics of this syndrome.<sup>12,13</sup>

The network model is a multivariate analysis composed of multiple regularised non-linear relationships (elimination of more spurious relationships using the LASSO estimator) after multivariate control of the network elements.<sup>3,4</sup> This enables the inclusion of variables of a diverse nature that assess multiple aspects of health and their comorbid condition, as well as the dynamic concurrence between the various aetiological and modulating factors.<sup>3,4</sup> The graphic representation makes it easy to interpret: the thicker the connection between the nodes (variables), the greater the statistical relationship.<sup>3,4</sup>

The estimation of the network's bridge nodes (high centrality indices) indicate a greater clinical implication in the study sample, that is, a greater requirement in the current context to explain the essential pathophysiological links that exacerbate the functioning of various comorbid health conditions related to delirium. These central elements of the network affect the interactions of the concomitant components, that is,

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a greater measure of this bridge node increases the likelihood of strengthening the other relationships, and vice versa; it is possible that its decrease or a smaller measure may reduce the other connections and even generate a collapse in the entire network structure.<sup>3,4</sup> This network approach is therefore essential for the planning and personalised implementation of psychiatric intervention programmes with greater efficacy in light of the impact of COVID-19.

The network method allows comparison of two or more network structures<sup>6,8,10</sup>; for example, according to the clinical condition or the control of the network covariates.<sup>6,8,10</sup> Another utility of the simultaneous estimation of networks is to assess before and after an intervention (pre-post test) to determine the dynamic variation between these networks at two or more different points. This makes it possible to specify the effects of a treatment by reducing the connection of the most central symptoms of the network.<sup>14</sup>

Another recent study assessed two networks of anxiety and depression symptoms in two stages: the beginning of the COVID-19 outbreak and after the peak.<sup>15</sup> Simultaneous network estimation is essential for a better understanding of the interactive concurrence between mechanisms and modulators of various psychiatric conditions by specific groups<sup>3,4</sup> (e.g., according to delirium subtypes). At the same time, it is also possible to estimate network changes over time using directed networks, and this has been used to longitudinally assess the dynamics of moods over the first 20 days of the mandatory quarantine for COVID-19 in Spain.<sup>16</sup>

In conclusion, the network analysis represents a valuable methodological and practical contribution to psychiatric research to provide a better explanation of the dynamic functioning (associative patterns of mutual influence) of the risk factors of various mental health conditions such as delirium (in this syndrome it consolidates new avenues for research into the hypothesis of cerebral insufficiency) and the relationship with the clinical manifestations of COVID-19. These results enable the implementation of better integrated care and the development of specific interventions required for patients with delirium<sup>17</sup> and other psychiatric disorders with complex and multifactorial aetiology, using the approach of dynamic network models systems.<sup>18</sup>

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