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LETTER TO THE EDITOR

Problems with latent class analysis to detect data-driven subtypes of depression

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Depressed patients differ considerably with respect to symptom profiles, course of illness and treatment response. These differences likely contribute to the on average low efficacy of treatment, and drive the search for more homogenous subtypes of depression in order to facilitate treatment decisions in clinical practice.[1] Latent class analysis (LCA) presents a common statistical method in current depression research that aims to identify depressed patients with similar symptom profiles.[2–4] LCA recovers hidden groups in multivariate data of heterogenous populations such that subjects within classes are similar to each other but different form subjects in other classes. It does so by dividing subjects into groups for which the observed variables are unrelated within each class, so-called 'conditional independence'.[5] Given the heterogeneity and multifactorial nature of depression,[6] LCA and other multivariate subtyping strategies may yield subtypes with a more homogenous etiology, course of illness or treatment response, than subtyping depressed patients purely on one characteristic, such as with or without anxiety or psychotic features.

In a recent report in *Molecular Psychiatry*, Milaneschi *et al*.[7] used LCA and identified three classes described as 'severe typical' (*T*), 'severe atypical' (*A*) and 'moderate'. The two depressed classes *T* and *A* differed predominantly with regard to appetite and weight symptoms: most *T* subjects reported appetite and weight decrease, but almost none reported appetite or weight gain; for *A* subjects, it was the other way around. Importantly, *T* and *A* subtypes did not differ substantially with respect to other depressive symptoms, illustrated by the fact that increased appetite/weight perfectly predicted membership in *A* (area under the receiver operating characteristic curve (area under curve) = 0.99, sensitivity 98.4%, specificity 99.5%), and decreased appetite/weight predicted membership in *T* very well (area under curve = 0.81, sensitivity 87.8%, specificity 72.8%). Both *T* and *A* classes are consistent with results from prior LCA-based depression studies. [2,3,8]

We commend the authors for their insightful study with important findings concerning the genetic background of depression, in particular that severe depression—especially when it involves appetite and weight loss (*T* class)—shares genetic risk factors with schizophrenia. Milaneschi *et al.* also demonstrated that results from multivariate classification procedures such as LCA can be used to derive more parsimonious subtypes that could serve as an alternative in case complete symptom data are unavailable (for example, in case of missing data in combined genome-wide association study data sets), which would complicate the application of classical LCA,[9] as well as other multivariate subtyping techniques that we advocate below. However, we see several difficulties with the LCA-results and their interpretation that are common in the literature and not limited to the report by Milaneschi *et al.*[7]

First, the symptom profiles of *T* and *A* were remarkably similar and mainly differed regarding appetite/weight loss or gain. This implies that substantive variability is likely to remain among patients *within* these two classes with regard to other symptoms, etiology, course and prognosis, raising concerns about the value of the identified classes as means to effectively decrease the heterogeneity of depression. Validation studies are needed to test whether the *T* and *A* subtypes, despite their relatively similar symptom profiles, are differentially associated with clinically relevant external variables such as course of illness, family history or treatment outcome.

The second point pertains to the validity of these classes. Like prior reports,[2,3,8] LCA classes were primarily based on weight/appetite differences that possibly reflect methodological artifacts based on violations of conditional independence. In LCA, associations between symptoms are assumed to be explained exclusively by their relation with the underlying depression subtype: symptoms within classes are statistically independent, conditional on class membership.[10–12] However, appetite/weight gain excludes appetite/weight loss in most patients (and vice versa), making these symptom-variants inherently dependent. High levels of dependence might exist as well for other opposite depressive symptoms, such as insomnia versus hypersomnia and psychomotor agitation versus psychomotor retardation. In such cases, local independence can always be achieved by increasing the number of LCA classes to account for this dependence, for instance with appetite/weight gainers allocated to a different class than appetite/weight losers.[10] The strong dependence between weight and appetite symptoms can therefore dominate the model and lead to biased parameters and posterior classifications as well as artificial classes.

Several solutions exist to account for this problem of local dependence, such as local dependence models or using Bayesian priors in so-called 'flexible LCA'.[12,13] A recent study applied both LCA and flexible LCA to depression data; regular LCA identified weight/appetite-based classes, whereas these classes disappeared in flexible LCA, which found classes differing primarily on anxiety.[4] The results emphasize the possible methodological artificiality of appetite/weight based LCA classes. Controlling for violations of conditional independence and analyzing common symptoms beyond the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for depression (like anxiety) may provide important venues for future research.

Third, the authors labeled the class with increased appetite/weight as 'atypical', which is custom in studies with similar results.[2,8] However, the symptom profile of this LCA-class differs considerably from the atypical specifier in the DSM, which includes additional criteria such as hypersomnia, mood reactivity, leaden paralysis and interpersonal rejection sensitivity. Using the term 'atypical' for a class mainly characterized by increased appetite and weight might lead to further confusion in the already conflicting and contentious literature on subtypes of major depression, in which labels such as 'atypical' are used in different contexts for different combinations of criteria.[1] To prevent confusion, we suggest to use different labels for latent classes if there is no substantial overlap with specifiers used in the DSM.

Lastly, LCA assumes that classes differ only qualitatively, contrasting evidence that depression may be dimensional for some people. [11] Hybrid factor mixture models combine aspects of both LCA and factor models, allowing for the identification of classes that differ both in terms of qualitative and quantitative aspects.[14] Since the classical LCA studies, like the study by Milaneschi *et al.*,[7] already showed promising results, addressing the abovementioned challenges will further benefit the search for empirically based depression subtypes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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HM van Loo[1,2], RBK Wanders[1], KJ Wardenaar[1] and EI Fried[3]
[1]*University of Groningen, University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion regulation, Groningen, The Netherlands;*
[2]*Department of Psychiatry, Virginia Commonwealth University, Virginia Institute for Psychiatric and Behavioral Genetics, Richmond, VA, USA and*
[3]*University of Leuven, Faculty of Psychology and Educational Sciences, Research Group of Quantitative Psychology and Individual Differences, Leuven, Belgium*
E-mail: h.van.loo@umcg.nl

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