Reviewer's report

Title: Major Depression Epidemiology from a Diathesis-Stress-Threshold Conceptualization

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Reviewer: jean-christophe chием

Reviewer's report:

This manuscript presents an interesting exploratory research on the complex topic of depression evaluation using computer simulation. A diathesis-stress model is conceptualized and analyzed with interesting results and discussion. However, the simulation methodology needs to be strongly revised. The description of the model is really ambiguous and I am not sure I understood the details of the model. In addition, while I understand the case of the simplicity of the model and the exploratory power of simulation tools, some choices and assumptions in the implementation need to be discussed, justified or tested. I am sure that if the revision provides a clear non-ambiguous methodology description and meets the other points mentioned below this manuscript will bring a valuable insight into the field of depression.

Major

1) Introduction

a) p6: “the goal was to determine,...” no exact determinist answer can be found with the simulation you designed; insist here on the exploratory aspect of your methodology. (Edmonds B (2010) Bootstrapping Knowledge About Social Phenomena Using Simulation Models. Journal of Artificial Societies and Social Simulation 13) Hence, the word ‘determine’ is too strong.

2) Methodology description

Model description

a) Code should be provided

b) I had a hard time to understand your model and I think improvement in this section could enhance the quality of your work. The description should provide enough information so as to be replicable by other programmers and in other softwares (see Edmonds and Hales 2003 Replication, Replication and Replication: Some Hard Lessons from Model Alignment Journal of Artificial Societies and Social Simulation vol. 6, no. 4)

c) I am not sure I understand your entire model. The whole description should be reworked. If I understood well, your model is a monte carlo simulation (or microsimulation or even individual-based model) which can be defined by the set of 2 equations:
Dep(t) = diathese(t) * stress(t)

Stress(t+1) = stress(t) * 1/diathese(t)

The initial values (diathesis(0) and stress (0) are generated at random with a lognormal distribution. The diathesis is set permanently for each agent.

Among other ambiguities I actually could not figure what you meant with the following: “The duration of effect of the simulated stressor was also related to the diathesis in the model. During each two weeks interval the stress level was diminished by an amount inversely proportional to the diathesis and the value of this variable was allowed to carry over into the calculation of depressive symptoms in the next interval" This part needs to be rephrased and be more explicit, possibly using equations.

Lognormal distribution of stress and diathesis.

d) The lognormal distribution justifying “to represent stress and diathesis because it does not assume negative values, such that meaningless negative levels of depressive symptoms would not emerge”. While you specify you do not try to mimick measurable biological or social data, the distribution is a strong assumption that require some justifications. (see e-i)

e) The question of the scale. You mention that negative values of depressives symptoms are meaningless , zero being then a minimal bound, but no maximum is mentioned. These are strong assumptions and a word of caution on this type of scale would clarify the meaning of the scale you use. Beside the meaning of the mean and stdv should be explored.

f) If only to keep positive values, other distribution could be used (exponential?, poisson?) possibly with less parameters. You could either further justify the use of the lognormal or use possible other distributions which could be another way to discuss your model. A hint over the meaning of the parameters should be attempted.

g) I suggest introducing the description of the scale and the explanation of the distribution as soon as possible. The part “Depressive symptom levels were conceptualized as the product of stress level and diathesis such that the model produced a new level of depressive symptoms for each entity in every simulated two week interval.” should come earlier in the text.

h) The use of “ *a* probability distribution” is a bit speculative at the beginning of the methodology (p7, line 4 and 6). Otherwise, just specify at random.

i) p7 : “a mean that this software calls” . You justify some part of the algorithm by the Arena-specific terms. Your model should be independent of the language and software used (avoid “a” mean and “a” standard deviation as it is specific to *the* distribution you choose). You can provide arena-specific information, together with the implementation in supplemental information.

Calibration of the parameters and Goodness of fit.
j) You first describe the data for the comparison as “‘an’ epidemiologic data source” (p8). This epidemiologic data source should be mentioned, its source and its nature. At this point in the text, it is not clear if it is the CCHS or the data liberation initiative (?). I recommend describing your data first in the methodology.

k) While I understand the explorative aspect of the study, the calibration procedure require larger comments and details. You somehow use a trial-error optimization process that, at first sight, does not provide a unique set of optimal parameters. I suggest providing a clear experimental plan with different values for each parameters and give a hint to the reader how you converge to the values you indicate in table 1 and 2. For example, this could be done by combining your tables 1 and 2 with several of your experiences and highlighting your choice. A graphical representation (radar chart?) could be even better. This will also clarify your explanation of your results (P8: In general,…)

NB: this could be easier also if you give an interpretation to the parameters of the distribution (or with less parameters, with other distribution as mentioned earlier)

3) Results

a) It’s not clear to me what your point-prevalence refers to as your population gathered different ages? What reference point in time do you use? What population is considered?

b) (1st question) Figure 3 does not correspond to the text in the result (p11-12): “Figure 3 shows a Kaplan-Meier curve for MD incidence. The steep slope in the younger age range followed by a flattening over subsequent years confirms declining incidence with age.” and I then expect a graph age vs incidence. I find instead a graph weeks since onset vs percentage recovered?

=> I think this figure is not provided with K-M curve is not provided?

c) 3rd question. As mentioned, your Cox model is done on a large sample and the signification of your test is then boosted. Hence I would recommend to be more careful about the “prediction concept” (p12): a pattern of elevated symptoms and sub-threshold episodes could explain subsequent incidence in the stress-diathesis-threshold conceptualization

d) 4th question (p12-13): I am not convinced by the use of the ‘10 first years’ necessary to define the ‘past episodes’. This period identifies roughly the adolescence. I suggest rephrasing your question: “the frequency MD episodes in adolescence would affect the risk of future ones”.

e) What is the population considered to compute results in Table 3? The asterisk in Table 3 is ambiguous: Are removed entities considered?

Minor

1) Introduction

a) Associate MD to major depression, once in the beginning of the text. Mental
disease or mood disorder also correspond to this abbreviation.

b) p4: “it is widely acknowledged ,...” would require a reference

c) p5: While the evaluation of depression is a complex matter; underestimation, as well as over-estimation of depression are both debated and argued. A word over this overestimation would emphasize even more the complexity of depression.


2) Methodology
a) Figure 1. I don’t think the symbolic picture as entity is needed and even confuses about the fact that you are representing a population.

b) Shouldn’t the number of entities be considered as a parameter? Is there a reason why you use 100000 entities?

3) Results
a) The first sentence in the results could be part of the methodology. Likewise, age of ‘birth’ and ‘death’, number of entities, could be part of the methodology.

b) Figure 2 (p11): “…presents a histogram of simulated age at onset of MD”. => I understand “presents a histogram of simulated age at onset of *first episode of * MD”.

c) Figure 3: I advice to set your origin of the axis at (0,0)

e) Figure 2 and 3: I suggest providing an empirical curve for comparison of both figures.

f) Table 2: Proportion of 2 week*s* episodes

g) 4rth question (p12-13): I think the use of only 10 years (15-25) somehow modulate your concept of diathesis. Do you want to focus on the genetic factors? Because focusing on this period of 10 years, possible acquired (non- genetic) factors of diathesis might be missed (work -, family- related burden).

4) Discussion
a) I don’t understand : “MD has generally been defined as an episodic condition, but may also be viewed as *an* application of a threshold to an inherently dimensional underlying processes.” What do you mean with “inherently dimensional underlying processes”.

b) I don’t understand : “but the simulations presented here suggest that this need(*is*?) not necessarily fundamental to the behavior of the condition.”
result are you referring to?

Discretionary

1) I do not have access to the software Arena and i am not aware of its capabilities. However, i find from the description of this software that it's mainly dedicated to 'business' applications. If ever you have a specific reason for the choice of this software, it would be useful to mention it. Otherwise, from what i understand of your description, your model could be easily implemented on free software like R, Netlogo,… For example, it would be a possible way to replicate/verify your model, with one of these softwares.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests