Author's response to reviews

Title: "The association between stressful life events and depressive symptoms among Cypriot university students: a cross-sectional descriptive correlational study"

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Author's response to reviews: see over
Dr Annemieke van Straten  
(c/o Rita Aguirre)  
Journal Editorial Support  
BioMed Central  

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BMC Public health journal  
Re: Revised  MS: 8678551299718690  “The investigation of stressful life events as significant predictors of depressive symptoms among Cypriot University students: a cross-sectional descriptive correlational study”  

Dear Dr. Annemieke van Straten  

We would like to thank the three reviewers and yourself for taking the time to evaluate the above manuscript. We are very grateful for the constructive comments and suggestions, which helped further clarify some important issues and improve the paper.  

The association between stressful life events and depression is well established in the literature. Nevertheless, with regards to university student populations, the vast majority of previous studies mainly examined the relationship between certain stressful life events and the prevalence of depressive symptoms. Rather than individual events, in this study we used a scale to investigate the association between the number and severity among 36 life events experiences in the past 12 months and students’ depressive symptoms. We were happy to see that the reviewer recognized the additional contribution of this study to the stress and depression literature and the important implications for prevention among university populations.  

Indeed, the cross-sectional nature of the study does not permit any inference with regards to the direction of association between stressful life events and depression. At least with regards to some life events, reverse causality may be at play. For instance, job loss, or failing a course may be the result rather than the cause of depression.
true that depression research has given increasing consideration to the possibility of complex and reciprocal relations between stress and depression. Not only does stress increase risk for depression (i.e., a stress exposure model of depression), but depression, or depressogenic vulnerabilities, in turn, also increases susceptibility to stressful events that are at least in part influenced by the individual (i.e., stress generation; Hammen, 1991). Unfortunately, the cross-sectional nature of our study does not permit any inference with regards to the direction of the observed association between life events and depressive symptoms.

As a result, we have made some changes to address this comment:

(1) We have changed the title of the manuscript to “Stressful life events and depressive symptoms among Cypriot university students: a cross-sectional descriptive correlational study”

(2) We have removed or rephrased any sentences that may have implied a causal relationship.

(3) We expanded on this matter in the Limitations, and

(4) as also requested by the reviewers, we have now included a paragraph on stress generation in our discussion.

Additionally, we have now read through the manuscript and all the necessary revisions concerning both the structure and quality of written English have been made.

Finally, we have now addressed all the comments and suggestions made by the reviewers. Below, please find our point-by-point responses as well as relevant action. Corresponding changes are also highlighted in the manuscript. As a result of the reviewers’ suggestions, we should note that the reference list/numbering has changed. Also, during revising the manuscript for grammar and syntax, we have made some other generally minor changes to the text as a result.

Thank you again for considering our manuscript for publication in the BMC Public Health.

Yours sincerely,

Sokratis Sokratous
Response to the reviewers’ comments:

Reviewer (1): Dr Mae Lynn Reyes-Rodriguez

General comments:
We thank the reviewer for her constructive comments. We have revised the manuscript for grammatical and other errors (e.g. references/citations). Responses to the specific recommendations raised by the reviewer appear below. Changes in the manuscript as a response to the comments of the reviewer appear highlighted in yellow in the revised manuscript.

Abstract:
*In the sentence of the aim of the study in abstract, there is a number (36) that I’m assuming is from a reference that should be deleted. The same issue is presented in the main document.*

**Response:** The number 36 was referring to the total number of items included in the scale LESS. Indeed, this was confusing, as also noted by Miguel Roca, and has now been removed.

The spell out of CES-D is not complete- should be “Center for Epidemiologic Studies Depression Scale”

**Response:** This has now been corrected both in the Abstract as well as on page 3 in the Methods section.

*Background_The reference # 25 doesn’t match with the topic that authors are referring in the sentence.*

**Response:** We thank the reviewer for spotting this. The reference has been replaced with the correct one (# 25).
At the end of the second paragraph, authors mentioned about differences of stressful experience for those in college versus those who are not in college. Please elaborate in this point and provide examples about differences between both groups

Response: Indeed, this was confusing, as also noted by Daniel Johnson, and the sentence has been rephrased in order to focus on the specific stresses faced by University students. (see page 4, last paragraph).

Authors presented many information about prevalence of depression and stressful events in many countries but is not clear about other studies conducted in Cypriot. What is the prevalence of depression in the general population in Cypriot? How that prevalence compare with the prevalence in college population? More background information is needed related with depression in this specific culture.

Response: As far as we are aware, this is the first study that has investigated the prevalence of depressive symptoms among Cypriot University students. We have now discussed this issue at the first paragraph on page 13 in the Discussion section of the manuscript. With regards to the prevalence of depressive symptoms among the general population in Cyprus, there is only limited data. In a national survey conducted by Kiliari et al. [24], with four hundred and sixty-five Cypriot adults of an average age of 53 years, this was found to be around 3.2%-5.1%. We have now included this information (and reference) in the Discussion section.
Methods:

**Instruments**

It is not clear in which language the instruments were administered, and if the questionnaires were translated and/or adapted for this population in the current study or previous studies. Please provide more information about the questionnaires.

**Response:** A Greek version of the instruments (CES-D and LESS) was administered. We have now specified this in the Methods section and provided more information about the translation and cultural adaptation of the questionnaires in the Methods, Instruments section (page 7, first paragraph). Concerning the LESS scale, this is in fact the first time that it has been used in the Greek language. In contrast, the CES-D scale has been used in the Greek language previously (in populations in Greece) but it has never been used in a sample of Greek-Cypriot students before. Although there is evidence for the generality of CES-D in Greece, some expressions in the items of the scale may be understood differently by different populations (depending on cultural background).

Reference is needed for the three-week test-re-test reliability coefficient for the CES-D. There is information about the psychometric properties of instruments and no reference is provided. Please revise this section carefully and be sure that appropriate citation is provided.

**Response:** The proper citation has been provided with regards to the psychometric properties of CES-D [see page 8, The depression inventory of the Center for Epidemiology Studies (CES-D)].
The Life Events Scale for Students. In the second sentence of the second paragraph, the reference of Linden is not provided.

**Response:** The reference of Linden has been added [see page 8, The Life Events Scale for Students (LESS)].

More information is needed about the small sub-study (n=100). It is not clear if this sub-study was conducted before or after the big study and how the sample was recruited, how comparable are the samples. If this sub-study will be included in the manuscript, it is important to provide more information about the methods.

**Response:** The sub-study using a sample of 100 postgraduate students was performed before the main study in order (a) to assess the readability level and general comprehension of the final Greek version of instruments (LESS and CES-D) as well as (b) to obtain culturally-specific weights of items in LESS. These students were not included in the main research. More information about the sub-study has been provided (see page 9, third paragraph).

**Sample**

*Would be good to have more information about the university background, what kind of students tend to enroll in this university, etc.*

**Response:** We agree with the reviewer that not providing a basic description of the University is an important omission. Information has been added on page 6 in section Study population and design. Specifically, CUT is one of only two public Universities in the Republic of Cyprus. Unlike private universities, there are no fees and access to a place is via the national examinations. With a total of two thousand forty hundred fifty two (N=2,452) active students is the second largest University on the island after the University of Cyprus. It consists of 10 Departments in 5 schools, mainly in fields of a technological nature.
It is not clear if some participants were excluded due to missing data.

**Response**: Eligible participants were 1783 while the final sample consisted of 1500. Amongst the 283 non-participants, there were 240 students who were absent on the survey day, and hence did not participate in the survey while a further 20 students were present but refused to participate. Only 23 participants were excluded from the analysis due to missing data. This has now been clarified on page 6, 1st paragraph in the Methods, Study population and design section of the manuscript.

**Data Analysis**

The first sentence mentioned that demographic variables were described by calculating frequencies and relative frequencies, what that means?

**Response**: The sentence has been rephrased (see page 9, last paragraph, Data analysis section, first two lines).

**Discussion**:

A reference published in 2000 by Kendler et al., about possible explanation about the stressful events and the number of episodes in the onset of depression should be considered for the discussion section.

**Response**: We thank the reviewer for the suggestion. We have now added this reference to our list and provided a discussion on the “kindling” hypothesis in the Discussion (page 16, last paragraph).
In page 10, in the last paragraph, the authors cited incorrectly the reference that should be Reyes-Rodriguez et al [reference # 23] and also mentioned that the study was conducted in Mexico when the study was conducted in Puerto Rico which is an island at the Caribbean and a territory of U.S.A. In page 11 the same study [23] was cited incorrectly.

**Response**: We thank the reviewer for correcting us on this Reference # 23 has now been corrected (see page 14). As a result, the numbering of the rest of the references has also changed.

**Please discuss if any differences were found by academic year (i.e., freshmen, sophomore, juniors or seniors).**

**Response**: As shown in Table 6 and 7, while higher prevalence of depression was found amongst second-year students compared to freshmen (OR=1.37, p=0.041). However, the association with year of study did not persist after controlling for life events and other socio-demographic variables in multivariable models. The association between depression and life events (both number and severity) was statistically significant irrespective of academic year of study. We have now clarified these issues on page 14, end of first paragraph.

Authors need to discuss in detail clinical implication for prevention and intervention with college population and if there any efforts that have been done in their country and if there any cultural appropriate issue that should be considered.

**Response**: Additional information concerning evidence on clinical implication for prevention has been added at the end of the introduction (page 5 last paragraph) as well as the Conclusion (page 19) section of the manuscript.
References

Many mistakes were found in the references, please double check every reference in order to be sure that you are citing all references correctly. Please correct the reference # 23:

Response: We thank the reviewer for bringing these mistakes to our attention. We have now looked through the references thoroughly, identified and corrected all the mistakes.
Reviewer (2) : Dr Miguel Roca

We thank the reviewer for his constructive comments. Changes in the manuscript as a response to the comments of the reviewer appear highlighted in pink in the revised manuscript.

**Major compulsory revisions**

To study the prevalence of depressive symptoms in a large sample of young population is not an original topic and this is the major problem of the manuscript. The association between depression and stressful life events has been established and the role of stress life events in first onset and recurrences is a controversial perspective of research. In fact, little conceptual attention has been paid to the level of severity of stressful events, the studies typically involving only “major” events as deaths of significant others or serious illness.

**Response:** We thank the reviewer for this very important and helpful comment. Indeed, as the reviewer points out, the majority of previous studies mainly focused on certain stressful life events. Rather than individual events, in this study we used a scale to measure the overall experience in terms of a total of 36 life events (both major and minor) in the past 12 months and showed that there is an association with depressive symptoms with both the number of reported events and, in fact, a stronger association when the severity of these events is considered by calculating a weighted overall score. We enriched the revised manuscript (specifically, the discussion section, pages 13-16) with further discussion on this matter.

The second major concern is the use of the LESS scale and this concern needs to be included at the limitations section: lack of accuracy of the scale and that it doesn’t take into account the individual’s personality, their perception of how difficult the stressor is, nor does it take into account how long the stressor continues for. It is known that the longer a stressor continues, then the more likely it is to cause stress and that the individuals perception of an event is the key to whether they will find a situation stressful or not. For some authors, 12-
months period is a longer period to recall and consider the self-reported severity of stressful life events.

**Response:** We agree with the reviewer that, like other “checklist methods”, LESS has a number of disadvantages. Even though contextual-based interview methods are widely viewed as the gold-standard for documenting stressful life events, they do not easily lend themselves to large-scale studies, such as this one. We have now discussed these issues in detail in the Limitation section of the manuscript (pages 17-18).

Third, the authors needs to discuss the relation of the results with the models between stressful life events and depression. Could the authors give us some ideas of their results regarding the “kindling” hypothesis (the first episode of a mood disorder is more likely to be preceded by life stress events suggesting a progressive decline as a function of the longitudinal course of illness)?

**Response:** Unfortunately, the cross-sectional nature of this study does not permit any inference with regards to the direction of the observed association between life events and depressive symptoms. Following the reviewer’s suggestion, we have now provided an extensive discussion with regards to this issue in the Discussion section of the manuscript (see page 18).

Finally, what is the impact of the result for prevention strategies to manage life stressful events in young people?

**Response:** As a response to the reviewer comment, we enriched the revised manuscript [in the Introduction, last paragraph, page 5 and in the Conclusion section, page 19] with a further discussion concerning the result for prevention strategies to manage life stressful events in young people.
Minor essential revisions

The academic precedence of the students is not relevant and can help to reduce the size and to improve the quality of the tables.

Response: We appreciate the reviewer’s view. However, we feel that certain background information about the university (i.e. what kind of students tend to enroll in this university, e.t.c) is important, as also the others 2 reviewers (1 and 3) point out. Thus, we prefer to keep this information in the Tables.

The use of the number of self-reported stressful life events (36) at the abstract is confusing, due the reference number of the bibliography.

Response: The number of self-reported stressful life events that appeared in parentheses it the abstract has now been deleted.
Reviewer (3): Daniel Johnson

We were happy to see that the reviewer recognized the contribution this study makes to the literature on stress and depression and we thank him for his constructive comments. Changes in the manuscript as a response to the comments of the reviewer appear highlighted in bright green in the revised manuscript.

1. Major Revisions

1a. From my perspective, the use of the term “depressive symptoms” throughout the report does not capture the construct the authors are examining. As the analyses you report focuses only on participants who scored above the clinical cutoff (>22), why not use “clinically significant symptoms” or even “clinically depressed” or “depression”? True, the CESD cutoff does not constitute a diagnosis of MDD, but the use of “depressive symptoms” in the literature generally refers to the presence of depressive symptoms, which is approximately normally distributed in the population. From a clinical and intervention standpoint, the mere presence of depressive symptoms and having a CESD score >22 are very different things. Furthermore, the link between life stress and depression is likely stronger for those who score above this cutoff on the CESD, compared to those who score in the subclinical range. I believe this needs to be clarified in the report to more clearly present the findings. This would also strengthen the link the authors make to prevention/intervention efforts.

On a related note: why not just use the continuous score from the CESD? Or also include individuals with moderate symptoms (16-22 on the CESD) in the analysis?

Response: Indeed, we thank the reviewer for this important comment. Since, we used the clinical cutoff of 22 in our analysis, the term “depressive symptoms” has now been eliminated from the text and we now use the term “clinically significant depressive symptoms” instead. Furthermore, we have also reported non-parametric correlations between the continuous CES-D scores and the number/score on the LESS (see last paragraph, page 11 in the Results section). Lastly, following the reviewer’s
suggestion, we have repeated the analyses using CES-D≥16 as a cut-off point. Nevertheless, due to the large number of Tables in the manuscript, we decided, instead of adding more detailed results, to simply present the adjusted OR estimates from the multiple logistic regression analysis using the 16 cut-off in the main text of the manuscript (see last paragraph, page 12 in the Results section).

The vast majority of the report discusses the link between stress and depression as unidirectional: greater stress leads to greater depression. Though you have a sentence in the discussion about depression leading to greater stress, I feel that this point needs to be expanded upon. There is a substantial literature supporting “stress generation”, the hypothesis that those who experience depression/depressive symptoms are more likely to be exposed to stressful environmental contexts (see Hammen, 2005 for a review). This link is especially true for clinically depressed individuals, which likely makes up the majority of individuals included in your analysis. Please incorporate the discussion of a bidirectional association between stress and depression in your introduction/discussion.

Response: We agree with the reviewer. We have now expanded upon this issue (as also requested by the second reviewer) in the Discussion (see page 16) as well as in the Limitation section of the manuscript (page 18).

1c. In the Methods section, a rationale (either theoretical or statistical) should be provided for categorizing the Life Events Scale for Students. How is one category different than the other? Why not leave the LESS as continuous for the analysis? Implications of the results may be limited if the categories used are arbitrary. Also, please present the correlations for the continuous LESS scores (number of events and severity) with the continuous depression scores in the paper. This provides an important “baseline” for further analyses.
Response: Following the reviewer’s suggestion, as already mentioned above, we now also present correlations between the continuous CES-D scores and the number/score on the LESS (see last paragraph, page 11 in the Results section). Nevertheless, we chose not to use the LESS score as a continuous variable in the analysis. Not only the distribution of scores was highly skewed but we didn’t feel that log-transforming would add any more meaning to the estimates. Thus, in the absence of theoretical cut-off points of LESS, we formed categories for comparison approximately based on the quartiles of the distribution of scores. Hence, the last category of LESS scores for instance (i.e. 351-1100) comprises of the quartile of participants with the highest scores. The only exception was the first quartile, which was further split into two separate categories (0-49 and 50-150) in order to provide separation between those participants who reported no events (score 0) or single minor events with those reporting major events for example death of parent (score 100), break-up of parents (score 71), major personal injury or illness (score 81) or several more minor events. This is now explained in the last paragraph, page 9 in Methods, Data Analysis.

There is a considerable literature on the limitations of self-report of stressful life events (e.g. Hammen and Shih, 2008). For example, individuals who are depressed may be more likely to recall negative events and more likely to report them as severe, compared to non depressed individuals. Also, in general, people’s report of stressful events over the course of a year is not very reliable. This should be included in the Limitations section.

Response: We have now clarified in the “Methods, Instruments” section of the manuscript that the LESS scale does not describe personal perception, personality traits of feeling about stressful life events. Instead, this scale describes particularly life events and the participant has to check the number of these events that has been occurred in his/her life during the past 12 months but do not rate it themselves. While the use of external weights for the severity of each event may be viewed as an advantage of the tool in this case, we nevertheless agree with the reviewer about the potential differential recall bias. We have acknowledged this as a potential Limitation of the study as well as provided a discussion regarding the use of checklist Vs contextual methods of life event assessment (see last paragraph, Limitations, page 18).
If i am reviewing Table 5 correctly, there were only 13 individuals with more than 16 events in the past year, and of those, only 6 who scored >22 on the CESD. If that is accurate, I think the discussion of the results about this group needs to be attenuated. These findings are for 6 individuals out of a sample of 1,500 and I think that generalizing to larger samples or populations (e.g. depressed individuals, Cypriot students) should be done cautiously, with the recognition of a very small N.

**Response**: We agree with the reviewer that the prevalence estimate based on 13 individuals reporting more than 16 events in the past year is particularly imprecise, as the wide confidence interval would also suggest. We have now merged the last two categories of the number of life events (12-16 and 16-21) and re-run the analyses so that the new estimate is based on a total of 85 students. Nevertheless, it is important to note that we are basing the description of the findings on the stepwise increase observed in the prevalence of depression across categories of increasing number of events, with a gradual increase from 20% among those not reporting any events to double higher among the group of students reporting more than 12 (the last category). In fact, a similar stepwise increase in the prevalence of depression was also observed in the case of LESS scores, in which case, all the categories including the last category of participants are much more sizeable since they are based on the quartile distribution of the scores.

**Minor revisions**

2a. The link between your results and intervention/prevention efforts needs to be expanded upon (Background: final paragraph, and in the abstract). You discuss the importance of screening for depression, but the results are presented such that reducing stress/managing stress may be the more appropriate target for intervention. Your conclusions in the discussion follow more logically from the results you present, but it’s less clear how your paper speaks to increased need for depression screening (rather than, say, stress reduction/intervention or preventative efforts). I would suggest either expanding on this point or removing
it. If you choose to expand on it, this may be a nice place to discuss stress generation.

**Response:** We agree with the reviewer about the importance of stress reduction preventative efforts or interventions. Addition information has been added in the abstract (page 2), in the Background (final paragraph, page 5) and in the Conclusion sections of the manuscript (page 19).

2b. It seems to me that there are considerable discrepancies between the Cypriot student ratings of severity of life events, as compared to the original sample for the LESS (Table 1). For example, there are differences of 15-20+ points for eight of the LESS items. I may have missed it, but do you discuss why these ratings are discrepant in the different samples? Could this influence your results?

**Response:** Indeed, there are differences in the magnitude of 15-20 points in 8 out of the 36 LESS items (for which only one moved downwards – jail term). However, for 28 (78%) of the items, the change was only in the range of 0-15 points. As a result of these differences, there are some differences in the ranking. Generally, it appears that Cypriot students rate financial, job or studies-related problems, even of a minor nature, as more stressful compared to the original Canadian sample. It is not clear whether this reflects a true cultural difference and/or perhaps a period effect (since the original study was performed some decades ago Vs Cyprus in the pre-financial crisis period). It is also likely to reflect different financial circumstances between the two samples. For instance, one out of three students in this sample report having a day job. These issues have now been discussed further in the “Differences in the ranking and weights of the LCU for the stressful life events on the LESS scale between the original study and the Cypriot sample of students” on page 10-1. In any case though, the observed differences should not be cause for concern. In fact, it is exactly because cultural and/or period effects might affect the generalisability of the weights of the original study, that we felt it was more appropriate to use locally-calibrated weights.
2c. There are several spelling mistakes and awkwardly worded sentences in the manuscript, particularly in the discussion. For example, the reference to Kendler’s paper is a bit unclear (discussion: 3rd paragraph) and the first few sentences of the paragraph starting with “Finally,” (discussion: 4th paragraph) could use some revision.

**Response:** The recommended revisions have been made.

2d. Please include more discussion of the null findings for number of life events. This is of particular interest, given the comparison to relatively robust findings for the severity score on the LESS. Why might there be such disparities between the number of events and the severity ratings?

**Response:** While we found an association between depressive symptoms and both severity as well as number of events, the results appear more robust when using the severity score. We found a 3-fold increase in the odds of reporting clinically significant depressive symptoms among the quartile of participants with the highest scores. In contrast, while we also observed a positive association between depressive symptoms and increasing number of events, this was weaker and the OR estimate became marginally statistically significant only among the 5% of participants reporting more than 12 events. This is more likely to be due to better exposure classification with the use of the score (rather than the number of events) since it is a function of both the number of events and severity of each event and, as a result it may differentiate better between participants who might report a similar number of events albeit of a different severity rating. We comment on this issue in the Discussion (page 15, 2nd paragraph)
3. Discretionary revisions

3a. In the Background (2nd paragraph) you discuss that college students experience “unique” stressors, but then list stressors that are universal to individuals in this age group, regardless of education (e.g., transition to adulthood, adaptation, individuation). It makes most sense to remove these that are not unique to college students, or to rearrange the paragraph.

**Response:** The paragraph has been rearranged (page 4, last paragraph).

3b. In the discussion (4th paragraph), you describe results from other studies looking at specific types of events. Because you do not address the impact of specific event categories in your analysis, I would suggest removing these sentences.

**Response:** The paragraph has been rearranged to give a clear picture concerning the impact of the minor life events (specific event categories) on the clinically significant depressive symptoms (page 14 first paragraph).

3c. You reference a “small but growing literature” examining depression and life events (Discussion: final paragraph), but there is a large literature examining these constructs. There are several nice reviews that you could cite to acknowledge the work that has been done in these fields (e.g. Kessler, 1997; Hammen, 2005).

**Response:** A paragraph including these studies has been added in the manuscript and the sentence “small but growing literature” has been deleted.