Author’s response to reviews

Title: Patterns of Complementary and Alternative Medicine Use among Individuals with Reported Positive Exceptional Experiences in Relation to Cancer

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Author’s response to reviews: see over
Dear editor,

Please find attached a revised version of the article (Ref no. 2097198161181934) now entitled “Patterns of Complementary and Alternative Medicine Use among Individuals with Reported Positive Exceptional Experiences in Relation to Cancer” for consideration for publication in BMC Complementary and Alternative Medicine.

We would like to thank all three reviewers for their insightful criticism and positive feedback. We have been inspired to make a number of changes we feel have improved the manuscript considerably. In summary, we have revised the title and the abstract of the paper to reflect more precisely the goal and results of our analysis. We have also simplified the graphic representations of the data, and have revised the discussion of the results as clarified in detail below. We have noted each reviewer’s comment, followed by an explanation of the revision.

Our statistician, Dr Alex Ploner, has also prepared a brief, technical description of the statistics used in this article. This might be of interest to publish as an appendix. We attach it here for your perusal.

We hope you will now find this manuscript acceptable for publication in its present form and look forward to hearing from you in the near future.

Sincerely,

Johanna Hök, corresponding author
Reviewer 1

The metric used, the number of specific CAM therapies used within each category, needs to be better justified. It is not clear what this purports to measure. Rather than indicating a dedication to CAM, it could indicate that patients are looking for something, but not finding it. In my view, a patient who tries 8 different therapies one time each seems much less dedicated than a patient who uses the same therapy 8 times. The measure used indicates a very different interpretation of the same observation.

We argue, based on a number of criteria and previous definitions in the literature (e.g. Balneaves et al, 2006) that our entire sample represents users with an unusual degree of commitment, regardless of the number of therapies used by each individual. We suggest that there may be different types of commitment, and argue, in agreement with this reviewer (page 17-18) that the number of CAM therapies is an inadequate single indicator of committed CAM use. We have now also complemented our discussion on page 17-18 in accordance with this reviewer’s comments:

As for the choice of metric for the data, we present PCA results for the correlation matrix of counts in each category although we have evaluated other options. We have for example investigated the use of covariances instead of correlations (i.e. weighting categories according to frequency) and binary category indicators instead of counts (i.e. completely removing category frequency from the analysis). The results, while not shown, were similar enough to merit retaining the approach presented here.

Description of the analysis as principal components analysis is not exactly correct. Biplots are closely related to PCA, but are not the same as standard PCA. Since the loadings are not presented, it is difficult evaluate some of the statements made. Specifically, unless the loadings in the first PC are all of similar magnitude, the statement that PC1 reflects the number of therapies reported across all CAM categories is a bit misleading.

We apologize for the omission of the table listing the loadings for the two first two principal components, with their bootstrap confidence intervals which should have been part of the original manuscript. This necessary data is now presented in Table 4.

Biplots as a versatile procedure for displaying multivariate data graphically are indeed not automatically equivalent to principal component analysis. However, by arranging the singular values between row and column space as we have done, we can make them equivalent, which was the case in Figure 1 of the original manuscript. We have now tried to make this data more readily accessible for the reader, and have presented the data graphically in three figures (Figures 2, 3 and 4). We hope this new presentation addresses the reviewers’ concerns.

The category ‘treatment centers’ has been described as ‘integrative medicine’ and there is substantial literature about this. However, this describes the setting and the inclusion of BHC, but does not describe the specific types of CAM therapies employed. I’m not sure this represents a valid category in the taxonomy presented.

On page 12 in the results section we have clarified the content of this category as well as the motivation for it as a separate category. As noted, usage in this category was based on the study participants references to the environment itself and interaction with staff as therapeutic, rather than reference to specific therapies themselves.
The discussion should address the limitations of the sample studied. The results of quantitative analysis have limited generalizability due to the way in which the sample was selected. Further, the contention that this sample is comprised of ‘committed’ CAM users has not really been validated. Even if they are committed users, they are probably not representative of the population of committed users.

We completely agree with the reviewer that our sample consists of self-selected volunteers, and that it would be hard, if not impossible, to characterize the underlying population with any kind of precision. While we have made this point repeatedly in the original manuscript’s abstract, methods description and discussion section, we also agree that it needs to be made more forcefully. Consequently, we have emphasized that this sample is self-selected in the introduction on page 6. We have also have made the language in the abstract and discussion section (page 15) more explicit regarding this.

As for the degree of commitment among study participants, our use of the term is in based on Balneaves et al’s use of the term, as noted in the introduction (see page 6). We feel that the strength with which participants attributed their survival and well being to the use of various CAM modalities, as well as the fact of them actively volunteering for an extensive interview, argues a more than casual use of CAM. We have clarified our motivation for this in the discussion on page 17-18.

Abstract Conclusion: The conclusion should report what is learned from this study. The issue about patient safety was not investigated; it is speculation about a possible implication. This statement does not belong in the conclusion section.

We agree with this criticism and have deleted this sentence from the abstract.

The phrases ‘specific CAM’, ‘different CAM’, ‘three CAM’, ‘seven CAM’ should probably be ‘specific CAM therapy’, ‘different CAM therapies’, ‘three CAM therapies’, ‘seven CAM therapies’

We thank the reviewer for noticing these unfortunate formulations. Revisions have been made accordingly.

First paragraph of findings has 26 of the participants with breast or gynecologic tumors, and Table 2 has 17 + 7 = 24.

We appreciate this observation, that allowed us to correct the mistake. We have now revised these figures according to original data.

Based on the biplot, I would group energy ther, spiritual lit and biobased into one category, manip body and mind body into a second, and treat cent and altmed into a third. In addition, the length of the vectors in the biplot indicate the relative variability of the different categories.

Except for including the BioBased therapies with SpiritualLit and EnergyTher, we have come to the same conclusion (p.12/13 of the original manuscript). However, we feel that while BioBased is indeed most closely correlated with the pair SpiritualLit/EnergyTher, it is correlated with ManipBody/MindBody to an only marginally lesser degree. In the revised manuscript, we clarify these relationships on page 13.
Reviewer 2

Abstract - When I read the abstract background I was expecting some qualitative analysis. I was confused by 'mixed - method approach' and the 'explorative' nature of the interviews. What was the purpose of the unstructured interviews - is this (hopefully rich) data to be analysed in further paper(s). It seems that what we have here is some sort of mapping/patterns of CAM usage. Can this be made more explicit /clarified in this part of the abstract?

We agree with the reviewer that the focus of the study, expressed both in the title and abstract, needed to be clarified. We are grateful for the suggestion to use the term “map”, which we have now included in both the title and the abstract. We have also added a comment in the text that other articles based on this material provide more in-depth explorations of the experiences of the participants.

Background - page number for quotation in text

The cited page number is now included.

Page 9 and 12 - biplot - can the authors add more information for readers.

Prompted by suggestions from two reviewers, we have made efforts to ease reading and understanding of the statistical analyses and findings in the revised manuscript, and have submitted a brief and more detailed technical appendix for possible publication. Furthermore, and maybe even more importantly, we have reduced the exclusive focus on the biplot throughout. We now present separate discussion of usage patterns among CAM modalities and usage patterns among study participants. We have also added an auxiliary cluster analysis of the usage patterns among study participants.

Findings In the Method section (p.7) there was a statement used to describe the approach as allowing insight into people's perspective related to 'extreme' and 'extraordinary' accounts, the title itself includes the phrase '...positive "Exceptional" experiences" but yet the paper seems focused on a mapping exercise of usage. I didn't get an understanding or insights into these perspectives. Are there further papers being prepared on this?

We agree that the study context needed to be clarified, which we have done in the background on page 6.

Patterns of CAM usage (p.12) I did not find the patterns easy to understand. The authors need to make the Figure 1 more accessible to readers. Perhaps some sort of key or shading/blocking to clarify the relationships? Need to define Eigenvalues d= 1 Maybe a statistician can advise

The statistician among the authors (AP) has on balance decided to be flattered by the implied compliment for his avoidance of professional jargon. We agree completely with the reviewer's assessment (shared also to some degree by the other reviewers) that Figure 1 in the original manuscript was too complex to be accessible. In the revised manuscript, we have presented this content in three auxiliary plots (Figures 2-4) as well as a first figure which motivates the analysis. We have also revised the discussion of the results accordingly.
We thank the reviewer for noticing these typing errors that were revised accordingly.

**Conclusions/Recommendations** The discussion and conclusions are appropriate and supported by the analysis of the data. I would like to have known more about the purpose of the 1-3 hour interviews. It seems to me that structured interviews seeking the mapping information maybe have provided the data required for this investigation.

As noted above, we agree that the larger study context and needed to be clarified, which we have done in the background on page 6.

We'd also like to add that we see quantitative and qualitative analysis of the usage data as complementary. One of the results we have further clarified in the manuscript is the clustering of the study participants into different usage groups, as well as the identification of the most typical representatives among members of these groups, allowing a more focused qualitative investigation than otherwise.

*I would recommend Minor essential Revision - suggest revisiting the title of the paper, the background in the Abstract and also the Method section to reflect the mapping/pattern of usage information extrapolated from the data. I would also recommend that Figure 1 be revisited to make it easier to understand in relation to the interpretation in the text.*

We have made all efforts to follow this reviewer’s recommendations, as outlined above.

**Reviewer 3**

This reviewer had no suggestions for changes.

We thank reviewer 3 for his kind words. In accordance to comments by the other reviewers, we have attempted to make our analysis more accessible by structuring the graphical presentations and the discussion of our results in more detail. We hope that have preserved the positive qualities of the original manuscript.
A Brief Technical Description of the Method and Findings of the Statistical Analysis

Method

Principal component analysis was used to explore correlations between usage of CAM categories. New variables (principal components, PCs), were introduced to reduce the dimensionality of the usage pattern while retaining as much as possible of the variation in the original data. PCs are computed as weighted sums of the original variables, where the weights of the original variables are referred to as loadings. By definition, the first PC expresses the greatest amount of variation in the data, the second PC the next largest amount etc. By applying the loadings to the values observed for each participant, we also computed the scores along each PC for these participants [Joliffe, Section 1.1 and Property A1].

Calculation of loadings was based on correlations between therapy counts in the seven CAM categories. Using correlations here corresponds to standardising the observed category counts to have mean zero and standard deviation one across all participants. In this manner, all categories have the same weight in calculating the loadings, whereas otherwise, categories would be weighted according to their absolute frequency in the sample. The use of correlations avoids biasing the PC analysis towards categories comprising more treatment modalities at the expense of categories that are more precisely delineated. [Joliffe, p. 22]

Bootstrap confidence intervals were computed for the loadings of the original variables to allow estimation of standard errors and confidence intervals without strong parametric assumptions [Efron & Tibshirani, Example 7.1]. The bootstrapped confidence intervals served as guidelines for the selection of the number of PCs to be retained, and for the interpretation of the loadings. No formal inference to a larger underlying population is intended (and would be difficult, if not impossible, given the self-selected nature of the sample, see also Discussion).

The number of principal components approximating the full data set was chosen based on visual inspection of a plot of variance explained vs. number of PC (scree plot, Joliffe, p. 116) and the pattern of bootstrap confidence intervals for the loadings that did not contain zero.

We chose to represent the usage patterns indicated by the PCs for both treatment categories and study participants both separately and together. The loading plot (Figure 1) shows the original categories in terms of the new PCs, indicating the magnitude and sign of the contribution of each category to the PCs. The plot also represents the approximate correlations between the original categories as expressed by the selected PCs, where a small angle between the vectors representing categories corresponds to strong correlation and an orthogonal angle independence.

We also computed each participant's score on the retained PCs and displayed them in a score plot in order to identify groups of participants with similar usage profiles. In order to aid the visual impression, we also performed a k-means clustering analysis of the scores. The number k of clusters was chosen to maximize a measure of separation between members of different clusters (average silhouette across all subjects, Kaufman & Rousseeuw, Chapter 2).
Findings: Exploratory Statistical Analysis

Patterns of CAM use

Figure 1 shows how much of the variability in the usage data is explained by the successive PCs. We find that PC1 to PC3 account for 42%, 22% and 14%, respectively, of the underlying data, with subsequently smaller contributions from the other PCs. We interpret the curve of percentages as steep between PC1 and PC2, and as flattening out after PC2. This suggests retaining PC1 and PC2 (Joliffe, p.116). We also note that the 95% confidence interval for the percentage of variance explained by PC3 contains 14% (indicated in Figure 1 by the dotted reference line), which is the amount of variance explained by a (hypothetical) variable in the absence of any correlation structure; in other words, the construct PC3 does not explain significantly more variability than a single variable, suggesting it should not be retained (Kaiser's rule, Joliffe, p.114).

We also find only for PC1 and PC2 multiple loadings of the original variables with confidence intervals that do not contain zero, i.e. which are significantly different from zero (Table 4). For PC3, we find only one border-line significant loading, which is likely an artefact caused by sign correction during the bootstrapping process (results not shown).

In summary, we decide to retain the first two PCs, explaining together 63.4% of the variability of the scaled usage counts.

Patterns of treatment categories

All loadings for PC1 are positive. The 95% confidence intervals for five out of seven treatment categories do not contain zero, i.e. these loadings are significantly different from zero. The actual values of the loadings for these categories fall into a fairly narrow band, ranging from 0.38 for Energy therapies to 0.49 for Manipulative & body-based therapies. The two remaining categories, Alternative medical systems and Spiritual/Health literature, have loadings of 0.23 and 0.20, respectively. We interpret this PC as a weighted average of the number of treatments reported within each category, where the significant categories receive approximately the same weight, and the other two categories roughly half the weight.

PC2 has both positive and negative loadings (Table 4), with three categories significantly different from zero: Alternative medical systems and Treatment centres at the one end of the scale with values of -0.64 and -0.44, respectively, and Energy therapies with 0.49 at the other end. The other categories are intermediate, both positive and negative. We interpret this PC as a typical contrast that expresses preference for treatments in categories along the scale indicated by the sign and size of the loadings.

Figure 2 shows a scatterplot of the loadings in Table 4, with treatment categories shown as vectors. Besides offering a graphical summary of the results outlined above, this is also a graphical approximation of the correlation between treatments counts in the original categories. Consequently, the number of treatments in categories represented by vectors pointing in the same direction have strong positive correlation; in those represented by vectors pointing in opposite directions, strong negative correlations; and finally orthogonal vectors correspond to categories whose treatment counts are mostly uncorrelated.

Consequently, we find that the seven original categories can be grouped into three pairs and one singleton: a) Energy Therapy and Spiritual/Health Literature, b) Manipulative and body-based therapies and Mind-body interventions, and c) Alternative medical systems and Treatment centres. At least for the proportion of original usage data explained by the two PCs retained, the number of treatments between these category pairs is highly correlated. Additionally, Biologically-based therapies are intermediate between a) and b) and about equally (and positively) correlated with each. We also find that the category pairs a) and c) are almost orthogonal, suggesting that the numbers of treatments chosen from them are almost uncorrelated.
**Individual user profiles** The scores of the first two PCs calculated for each user are shown in Figure 3. The origin corresponds to the average user profile, i.e. an average number of treatments per category (first column in Table 5). We interpret the position of a subject in the score plot in accordance with the interpretation of the PCs given above: large positive values for PC1 correspond to a larger number of treatments than a hypothetical average user, weighted across categories as listed in Table 4; large negative values for PC1 correspond to a smaller than average number of treatments, and values close to zero correspond to an average number of treatments (Note that the negative values are introduced by subtracting category mean counts as part of the scaling, prior to the PCA). In Figure 3, these three options are represented by Dinah, Sofia, and Karolina, respectively.

In the same manner, a large positive coordinates for PC2 indicates a stronger than average preference for treatments at the *Energy therapy* and *Spiritual/Health literature* end of the spectrum, whereas a large negative coordinate indicates a stronger than average preference for treatments from the *Alternative medicine* and *Treatment centres* categories, at the expense of the former two categories; a value close to zero indicates no special preference compared to average usage. These three options can also be exemplified by different users, namely Mary, Ellen, and Karolina.

Within the limits of the approximation by only two PCs, similar locations in Figure 3 indicate similar user profiles across categories.

**Grouping user profiles** The user profiles displayed in Figure 3 are not equally distributed, but fall into several groups. However, while some groups are quite clear, like the pair Peter-Victor in the upper right corner, assigning all subjects to a unique cluster involves some degree of subjectivity. We have tried to minimise this degree by a) using an objective algorithm (k-means clustering) to formalise our visual intuition, and b) considering a wide range of possible numbers of clusters for our subjects, from k=2 to k=10, and evaluating the quality of the resulting grouping via the average silhouette width. We found the best solution for k=4 clusters, with silhouette width 0.58, which is displayed in Figure 4, and discussed in detail below. It is however clear that this is only one possible way of clustering the user profiles, the result of an exploratory method (clustering) on top of an exploratory method (PCA), and as such more an attempt at interpretation than a hard result. This is especially true as the solutions for k=3 and k=5 clusters are almost as good in terms of silhouette width (0.54 and 0.55, respectively).

Within these limitations, we find that Cluster A in Figure 4 is the largest, containing 63% of all observations (Table 5); it is characterised by less than average usage of CAM treatments, with a slight bias towards the *Energy therapy* end of the spectrum of categories. This can be seen from the comparing the average treatment count within categories between Cluster A and the whole data set in Table 5: Cluster A has lower counts for all categories, but the average number of treatments within categories *Energy therapy* and *Spiritual/Health literature* is closer to the average count than for categories *Alternative medicine* and *Treatment centres*. Equivalently, we see that the average score for subjects within Cluster A is -1 for PC1 and 0.4 for PC2.

In the same manner, we find that members of Cluster C, the next largest cluster with 18% of the subjects, use on more treatments than the average user (mean PC1=2.3) and have a bias towards categories *Alternative medicine* and *Treatment centres* (mean PC2=-0.7). From Figure 4, we see also that this is the most heterogenous of the four clusters, with considerable variation along both axes. Cluster B, the next largest cluster with 13% of the observations, is somewhat intermediate between A and C, in the sense that it combines overall very average numbers of treatments (mean PC1=0.1) with strong bias towards the categories *Alternative medicine* and *Treatment centres* (mean PC2=-1.9). The smallest cluster D finally, with 5% or measly two subjects, is very distinct and characterised by the use of a large number of treatment modalities across all categories (mean PC1=3.7), but still with a pronounced bias towards the *Energy therapy* and *Spiritual/Health literature* end of the spectrum (mean PC2=3.0), though the latter is likely driven by the extremely high number of *Biologically-based therapies*, which are weighted positively in PC2 (Table 4) for both subjects.