Title: Utilization of complementary and alternative medicine (CAM) among children from a German birth cohort (GINIplus): patterns, costs, and trends of use

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Author's response to reviews: see over
Utilization of complementary and alternative medicine (CAM) among children from a German birth cohort (GINIplus): patterns, costs, and trends of use

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Dear Editor,

We thank both reviewers for their useful suggestions. We tried to consider and implement their recommendations as detailed below. We pasted the reviewers’ original queries/comments into the response letter to the reviewers (written in bold letters) and added our response below the reviewers’ comments. Our suggested modifications are highlighted in grey.

Additionally, we made two further minor corrections:

In the section with the authors’ contribution (page 20 line 3), we changed the initials for Silke Britta Wolfenstetter to SW, since it was wrongly reported with SB in the old manuscript. In Table 2, we replaced the term “Myrtol standardized” by “Myrtol® standardized”.

Furthermore, we added the information that informed consent was also given by the participating adolescents (page 9 line 10/11).

We would be pleased if you consider our revised manuscript suitable for publication.

Yours sincerely

Salvatore Italia, Helmut Brand, Joachim Heinrich, Dietrich Berdel, Andrea von Berg, Silke B. Wolfenstetter
Response to Reviewer #1 (Alfred Laengler):

1. The authors should give some information about the validation process of the questionnaire used

Thank you for this hint. We have added the following information with the respective reference [12] (page 5 line 24-26):

The design of the questionnaire on drug utilization corresponds to the validated questionnaire from the German KiGGS-Study that was conducted with 17641 children [12].


2. The authors categorize in 6 categories they define by their own. The data would be comparable with the international literature if the authors would categorize their data according to the NCCAM-categories.

To our knowledge, there is no universally valid definition of CAM, and we agree that such a uniform definition would be desirable. The NCCAM definition might be one approach to achieve this goal. For the analysis of the data from the 10-year follow-up, we decided to use the BfArM categories for particular therapeutic systems (phytotherapy, homeopathy, anthroposophic medicine), since our data are based on a German study population. For practical reasons, we grouped homeopathy and anthroposophic medicine into one category (see also our response to your following query). For consistency, we used the same methodology and categorization for the 15-year follow-up as well.

However, we only defined drugs as CAM that were defined as CAM by NCCAM as well. In contrast to our definitions, NCCAM grouped herbs, vitamins, minerals, and probiotics into their category “Natural products”. Based on this definition, we performed a sensitivity analysis and grouped our categories 3-5 (Herbal drugs, nutritional elements, minerals and trace elements, microorganisms) into the category
“Natural products”. As displayed in the table below, study area and income still have no significant impact, but the ORs for maternal education are lower and no longer significant. This may be due to the fact, that now also users of the categories 4-5 were included. Analysed separately, the use of the categories 4-5 (vitamins, nutritionals, minerals and trace elements, microorganisms) were not predicted by maternal education. Hence, these categories seem to “distort” the results when grouped with herbal drugs.

<table>
<thead>
<tr>
<th>Table 1. Sensitivity analysis</th>
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<td><strong>Gender</strong></td>
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<td><strong>Study area</strong></td>
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<td>Munich</td>
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<td><strong>Maternal education</strong></td>
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<td>Secondary school</td>
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<tr>
<td>≤60% of MEI</td>
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Bold numbers = significant at p<0.05  *p<0.01  **p<0.0001
MEI = median equivalence income

We have added the following comment to the limitations (page 18 line 9-12):

Due to potentially different definitions of CAM, the comparability of our results with other internationals findings may be limited with regard to the predictors and the prevalence of overall CAM use.

2. The authors state, that the categorie "Homeopathy" contains anthroposophic medicine as well. But Homeopathy and anthroposophic emdicine are not the same Kind of CAM. Even at the BfArM there are two different commissions für homeopathy and anthroposophic medicine (and one for phytotherapy as well. So the authors should Name this category "homeopathy/anthroposophic medicine“ ore make two different categories.

We agree that anthroposophic drugs are not the same kind of medicine as homeopathic drugs, and it was not our intention to equate both therapy approaches. To our knowledge, only four pharmaceutical companies in Germany produce anthroposophic medicinal products (Weleda, Wala, Helixor, Abnoba). An allocation to a new modality “Anthroposophic drugs” would
only be possible, if we exactly knew the manufacturer of the reported drug. Many drugs were reported without providing the pharmaceutical identification number PZN (we mentioned on page 13 line 1 that the PZNs were available for 300 CAM). Only 12 drugs were clearly identified as anthroposophic drugs. There were too few drugs to group them into an extra modality and analyse the respective predictors of use. Hence, we regarded it as reasonable to allocate anthroposophic drugs to the modality “Homeopathy”, since many anthroposophic drugs are prepared according to the production specification described in the Homeopathic Pharmacopoeia HAB.

To avoid misunderstanding, we have renamed the category in the methods section as proposed by the reviewer (page 6 line 18-21):

(1) Homeopathic/anthroposophic drugs (afterwards referred to as ‘Homeopathy’): Drugs that have been prepared according to the production specification of the Homeopathic Pharmacopoeia HAB [13], including anthroposophic remedies and biochemic remedies (Schuessler salts).

For stylistic reasons (width of the columns, etc.), we would suggest to keep the term “Homeopathy” in the tables and figures.

Additionally, we have added the following sentence on page 11 line 5:

Twelve drugs were clearly identified as anthroposophic remedies.

3. It is unclear why herbal drugs which are available by prescription only were excluded from Analysis (page 6 line 19ff)

Drugs with potent alkaloids (e.g., opium alkaloids such as noscapine, codeine, or morphine) or cardiac glycosides (e.g., digitoxin) contain active pharmaceutical ingredients that are no synthetically manufactured chemical substances but are extracted from plants. Following the definition for herbal drugs as defined in our methods section, drugs with e.g., morphine or codeine would belong to the CAM modality “2” (herbal drugs). Additionally, we excluded those drugs with allergen extracts from pollen used for desensitization.

In sum, only 10 drugs from the 2489 reported drugs were affected by our exclusion criterion (exclusively drugs containing noscapine, morphine, or allergen extracts), and were allocated to the modality “conventional” drugs. We already used the same methodology for a study published in 2012 (Reference [3] in our manuscript.

We have added a short comment in the results (page 9 line 25/26 and page 10 line 1):

As defined in the methods section, 10 prescription drugs containing opium alkaloids (noscapine, morphine) or allergens extracted from pollen were excluded from the CAM modality ‘herbal drugs’.

4. "homeopath" are categorised as CAM Providers; this suggests that they are consulted as complement or alternative to a conventional physician. But in Germany much conventional physicians are eligible for using the appendix "homeopath" together with e.g. "pediatrician". (page 7 line 6)

Thank you for your helpful comment.

With regard to your comment, we performed a sensitivity analysis. A new “Provider User” variable was defined where homeopaths were excluded from the definition as a CAM
provider (assuming that all homeopaths were also conventional physicians with a respective appendix). According to the new definition, there would have been 254 “Provider Users” (instead of 324 “CAM provider users” as defined in the manuscript). The results are given in the table below. For comparison, we also displayed the ORs as reported in Table 3 of the manuscript. The sensitivity analysis yielded only one slight difference (highlighted in green), as this OR was somewhat lower and this result was no longer significant (p=0.0532). However, if those twelve children who consulted a homeopath in the past 12 months and at the same time reported no consultation with a physician during the last year would also have been included in the sensitivity analysis, this OR would again be significant (p=0.0488). Nevertheless, we have added a respective comment in the limitations as follows (page 17 line 21-25):

With regard to children who consulted a CAM provider, it must be considered that a homeopath may be a conventional physician who uses the term “homeopath” as an additional title. However, a sensitivity analysis that excluded a “homeopath” from the definition as a ‘CAM provider’ yielded no substantial differences with regard to the predictors of consultation with ‘non-conventional’ health providers.

<table>
<thead>
<tr>
<th></th>
<th>CAM providers (n=324)</th>
<th>Providers, homeopaths excluded (n=254)</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Female</td>
<td>1.19 (0.94–1.50)</td>
<td>1.18 (0.91–1.53)</td>
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<tr>
<td><strong>Study area</strong></td>
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<tr>
<td>Munich</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Wesel</td>
<td><strong>0.57</strong> (0.44–0.74)</td>
<td><strong>0.58</strong> (0.44–0.78)</td>
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<tr>
<td><strong>Maternal education</strong></td>
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<tr>
<td>Junior high school</td>
<td><strong>2.57</strong> (1.50–4.39)</td>
<td><strong>2.40</strong> (1.35–4.26)</td>
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<tr>
<td>Baccalaureate</td>
<td><strong>2.80</strong> (1.59–4.92)</td>
<td><strong>2.52</strong> (1.38–4.62)</td>
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<tr>
<td>University degree</td>
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<td><strong>1.82</strong> (0.99–3.35)</td>
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<td><strong>Household income</strong></td>
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<td>≤60% of MEI</td>
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<td>1.45 (0.96–2.20)</td>
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</tr>
</tbody>
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Bold numbers = significant at p<0.05  *p<0.01  **p<0.0001  
MEI = median equivalence income

5. page 11 line 15-17 can be destroied without loss of Information because this Information is given in the methods section already

We agree that the definition is already given in the methods section. For transparency reasons, we wanted to add just one sentence in the results section (page 6 line 22-26) simply to quantify the number of trace elements/vitamins (which is not given the methods section) that were excluded from the CAM modalities “4” (minerals and trace elements) and “3” (nutritionals). If you consider this information not adequate, we can remove the lines 15-17, otherwise we would suggest to keep this information in the manuscript.
6. page 12 line 8-11 gives Information which can be deleted without loss of substantial Information.

The authors agree that the information on the ORs is given in Table 3 as well. However, in line 8-11 we shortly summarized the results with concern to the predicting effect of maternal education on medicinal CAM use and stated in words that our results showed an impact of maternal education on the use of herbal drugs only (and CAM use in general), but not on homeopathy use. This was also important to show other researchers that the single CAM modalities may be analysed separately and not as whole, since many authors have examined CAM use in general only. Moreover, some readers may prefer to look at tables only, whereas other readers may expect a short summary of the essential results in the text. We think that the lines 8-11 improve the fluency of the text and would suggest to keep the lines 8-11.

7. page 16 line 5 ff is very speculativ und not covered by the results of this study. The idea, that health-insurance coverage of CAM-remedies may be the reason for the decline in CAM-use from the 10-years to the 15-years cohort is in contrast to the theory presented on page 17 line 11-14.

The authors totally agree that precise data whether the drugs were prescribed by a physician would have been very useful for this study question. When the questionnaire for the 15-year follow-up was designed, the results concerning the strong decline of CAM use were not foreseeable. The data of the 15-year follow-up showed a substantial decrease of CAM use, and we should try to explain this drop instead of leaving it uncommented. The decrease may have other reasons we do not know such as a lower acceptance of CAM among 15-year-old adolescence compared with 10-year-old children. 15-year-old children could also have used fewer drugs in general, but this seems not to be the case since overall drug consumption was almost stable (41.0% vs 43.5%) and conventional drug use even increased (34.1% vs 30.6%) in the 15-year-old.

We have added the following sentence and the reference [26] (page 18 line 6-9):

Nevertheless, the proportion of over-the-counter drugs (such as medicinal CAM) among all prescribed drugs is estimated to be 17% [26]. The aforementioned figure may be somewhat lower in the present cohort, since the figure refers to the whole German population including children younger than 12 years.

Bundesverband der Arzneimittel-Hersteller e.V. Der Arzneimittelmarkt in Deutschland in Zahlen (2013) [https://www.bah-bonn.de/index.php?eID=dumpFile&t=f&f=4089&token=3ec3eb2533e1c4c5ab6a42e783f0651d200c7e08]

We further suggest to slightly modify the sentence on page 17 line 15-18:

Additionally, it must be considered that 15-year-old children may begin to make own decisions concerning their (self-) medication and CAM use may also have been influenced by the children’s educational level, which was not assessed by this study.
8. The conclusions are not covered by the results and should be totally renewed

According to your proposal, we modified the paragraph as follows (page line 4-16):

This may have contributed to the decrease in medicinal CAM use in children from the GINI-15 cohort compared with those from GINI-10, but other reasons such as a possibly lower acceptance of CAM among adolescents (compared with younger children) may have contributed to the drop in CAM use as well. Since 2012 [24], German statutory health insurance companies have again had the possibility to reimburse the costs of over-the-counter drugs (including medicinal CAM such as homeopathy, herbal drugs, etc.). Nevertheless, still many health insurance companies do not cover expenditures on CAM or limit the coverage of CAM to a fixed yearly amount [25]. For health insurers, it might be valuable information if reimbursement of CAM influences the decision of insured persons to choose a specific health insurance company.

Future studies assessing exactly how many medicinal CAM are prescribed by physicians may support policy makers and health care managers in their further decision-making process concerning the inclusion of CAM in the list of reimbursable therapy approaches.

Response to Reviewer #2 (Dominik Schöndorf):

The conclusion “The present results may support policy makers and health care managers in their further decision making-process concerning the inclusion of CAM in the list of reimbursable therapy approaches” appears to be incongruous since prescription rate or percentage of privately insured participants are unknown as the authors themselves state. Or were parents and children asked whether they would choose a health assurance with a greater financial support of CAM if possible?

Thank you for your comment. We modified the conclusions and integrated your thoughts as follows (see also response to reviewer #1 query 8):

For health insurers it might be valuable information if reimbursement of CAM influences the decision of insured persons to choose a specific health insurance company.

Reference number 12 seems to be redundant

This reference was added to provide further information on the study population. We agree that it is not essential and will therefore remove the reference number 12 from the manuscript.

The questionnaires (main und self-administered) should be added to appendix

After consultation with the institute management, we are sorry to inform you that it is not possible to add the questionnaires as supplementary material to publications. Nevertheless, we may answer specific queries referring to the questionnaire. Additionally, we may also supply a copy of the questionnaire on personal request. Please note that the questionnaire is in German.
**Further comments/corrections**

Additionally, we made two further minor corrections.

In the section with the authors contribution (page 19 line 7), we changed the initials for Silke Britta Wolfenstetter to SW, since it was wrongly reported with SB in the old manuscript. In Table 2, we replaced the term “Myrtol standardized” by “Myrtol® standardized”.

Furthermore, we added the information that informed consent was also given by the participating adolescents (page 9 line 10/11).

Thank you very much again to both reviewers for their helpful suggestions and we would be pleased if you consider our revised manuscript suitable for publication.

Yours sincerely

*Salvatore Italia, Helmut Brand, Joachim Heinrich, Dietrich Berdel, Andrea von Berg, Silke B. Wolfenstetter*