Author's response to reviews

Title: Use of psychotropics, opioids, anticholinergics and antiepileptics and cognitive decline in the aged: a longitudinal population-based study

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Author's response to reviews: see over
Dear Associate Editor Dr David Vance

We thank you for your editorial comments and the referee feedback. Our study group has revised the manuscript according to these valuable comments. All changes are shown in the manuscript so that they can be easily tracked and evaluated using word processor MS Word.

The answers to the questions and comments are given below point-by-point in the order of your e-mail sent on August 23, 2011.

Referee 2:

1. We think that we have not described our method to collect data about the use of medications in a way which is easy to understand, and the referee has misunderstood the method. We clarify here the method and the reason for using the period of one week prior to the interview to describe the current medication use at baseline and follow-up.

The use of medications was recorded in two data collection phases (baseline and follow-up) by asking about the use of medications during the previous week. Instead of recording the medications used for instance one day prior to the interview or during the day of the interview, we tried to enhance the sensitivity and specificity of medication history so that the medications in long-term use, even those used less frequently than daily or used only as needed, would be included as current medications.

There are long-term medications that are only taken once a week (for example metothrexate for rheumatic arthritis). Hypnotics and sedatives (benzodiazepines or benzodiazepine related drugs, sedative antihistamines and antipsychotics used as hypnotics) are usually prescribed to be taken “when needed”. These examples show that recording the current medication use by the use “one week prior to the examination” gives more reliable data than recording the use based on the use in one day.

The uses of medications were included in the interviews and verified by checking the prescriptions forms and medications (pill boxes) in order to get as reliable data as possible. If the participant was unable to provide the information, it was verified by a close relative or caregiver.

We consider the data about the current use of medications at baseline and at follow-up to be reliable.

We have made some changes to the Methods section in order to clarify the text.
2. We agree that small sample sizes are problematic in terms of statistics and generalization. Previously, we discussed this issue in the Discussion section. Now we added more text about these problems. We do not draw any generalized conclusions between opioid (Op) or anticholinergic (ACh) use and cognitive decline due to the observational, longitudinal study design and small sample sizes.

The cognitive effects of acute or short-term Op administration are well known clinically and experimental studies prove these harmful effects. There are, however, no published epidemiologic data on associations between long-term Op use (alone or concomitantly with other medications) and the risk of cognitive decline in the aged. Our finding about the association between AChs and the risk of cognitive decline has a larger sample size (N=29) than that concerning Ops. This finding is concordant with previous, mainly methodologically poorer, cross-sectional studies. As we found this association in our longitudinal study, the evidence on the association between the use of AChs and the risk of cognitive decline is further strengthened.

In general, epidemiologic study methods can never prove direct causalities but they can show associations. We consider that our finding about the longitudinal association between the Op and ACh use and the risk of cognitive decline is interesting and valuable to be reported for creating new hypotheses and planning future studies with larger sample sizes and longitudinal design.

3. We have defined normal cognitive abilities in this older age group according to previous population based studies that have shown normal variation for cognitive abilities to vary from 24 to 30 MMSE sum points in older populations. Only participants with normal cognitive abilities (MMSE sum points 24 to 30) at baseline were included in our study. Due to this inclusion criterion there was no great variation in cognitive abilities between the participants at baseline.

Request for statistical review

One of the authors (Mr Tero Vahlberg, MSc) is a professional biostatistician. He belongs to our study group and has participated in planning the methods of the study, in statistical analyses and in drafting and revising the manuscript. Thus, we think that our statistical analyses are performed adequately.

Referee1:

Requests for Discretionary Revisions

1. Abstract is revised as proposed. Implications and interpretations are added. Language is made more everyday.

2. Changed.

3. Changed.

4. Changed.

5. Changed.
Requests for Minor Essential Revisions

1. Changed.

2. Changed.

3. Changed.

4. Changed. Professional English copyediting is now checked by an academic English translator Liisa Punkka MA.

5. Changed.

General Comment

Opioids were most strongly associated with cognitive decline during the follow-up. However, due to the small sample size we think that these results cannot be generalized and more studies are needed (please see answer to question 2 of referee 2 above).

We agree that our manuscript contains many tables with a great amount of data. We re-evaluated the need of the tables critically and decided not to delete any of them. We think that the tables help readers to read and interpret our study.

Answers to Associate Editor

The manuscript is now revised. We have tried to rewrite it in a way which is easy to understand.

The indications for the medications have been recorded as diagnoses of diseases (ICD codes). We did not previously add these to the manuscript because this would greatly extend the length of the manuscript and require even more tables to be shown. The indications are not added in the revised manuscript, either. Primary health care resources are similar in all regions in Finland. Guidelines to primary care physicians have been published from the 1980s onwards. Thus, we think that the indications of medications in our sample are based on standard guidelines and medical practice quite similar to the practice in other regions of the country.

The durations of the use of medications have not been collected and recorded in the data of the first round and in the data of the second round. Medications possibly started and stopped between the first and second round have not been recorded. Thus, we cannot use these variables in the analyses. We agree that these kinds of data would give more depth to our analyses. We have now added two new references (Linjakumpu et al.) about the long-term use of medications as shown by the analyses of the Lieto study in order to show the long-term use of many medications analysed in our study.

We resubmit our revised manuscript, which is correctly formatted according to your instructions.

On behalf of the study group

Sincerely Yours

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