Author’s response to reviews

Title: Life situation of women impaired by Thalidomide embryopathy in North Rhine Westphalia - a comparative analysis of a recent cross-sectional study with earlier data

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Author’s response to reviews:

to the Editor: we have done all the required changes. Please let us know if we have missed anything.

In addition every author signed the ICMJE conflict of interest form.

Gunilla Sydsjö, PhD (Reviewer 1): Thank you for the opportunity to read this paper.

I think some of the results are very interesting and worth discussing.

Thank you for reading of this article, your comments have well-improved the manuscript.

My main topics about the paper:
The rational for doing this?

There has been until now no longitudinal study on the effects of thalidomide impairment in any larger sample-size, neither both sexes nor one.

Is this of interest for readers and researcher worldwide or are the results mainly of interest for the German society?

My suggestion is to public in a more suitable paper for the German public.

Since individuals have been impaired by thalidomide worldwide we feel that the results found are worth spreading to a large community. The complete study of Peters et al (2015) has been published in German. An interest in such studies exist, since the other large survey done by Kruse et al (2012) on individuals impaired by thalidomide and also focusing on Germany has been translated for the Thalidomide Trust and is offered for download on several websites (e.g. http://www.fiftyyearfight.org/images/Heidelberg_study_ENGLISH.pdf).

Therefore we believe the findings should be published internationally.

The introduction is much to long and focus on the situation when the Thalidomide was introduces and withdrawn from the German market.

I do believe that this done in many countries after the alarms about the impact on the children.

We have internationalized and shortened the introduction, thank you for this comment.

Way not included the affected men also?

Because the study of Nippert et al (2002) focused only women and we wanted to get an idea of longitudinal effects on hopefully some of the same sample, since this has not been done before.
There is a problem not knowing if the women are investigating twice or have only answered the questioners once.

This is a problem that we are aware of. The study of Nippert et al (2002) was only a mail survey where the questionnaires were returned anonymized. Since no longitudinal study has been attempted as of yet, as above we went for all that we could get while being aware of potential methodological shortcomings.

The number of participates.

The number of participants is about a quarter of all the women impaired by thalidomide living in North Rhine-Westphalia. While it keeps the number of participants down we can at least hope for some overlap of the two samples due to the restricted area of residence.

The financial compensation for the women -have they received that from the state? Is that a factor not working and maybe work part time.

Thank you for this question we have included this information in the manuscript. The issue of raised compensation and therefore early onset of retirement is also picked up in the discussion section.

I think there need to be control group of a twice as many women from the ordinary population that also needs to be age matched.

Our main goal was to compare the two samples over time to get an idea of the long-term effects. However we have included into the results-section that both studies found that the impaired have poorer health than the general population.

Also there needs to be a discussion in health care and assistance - the possibility to get assistances. Is it a problem in Germany and might it be a financial question?
Thank you for this question, we have tried to strengthen the part about the connections between the raise of the compensation, the onset of early retirement and the problems of finding qualified help in the discussion-section.

The strength in this study is that the investigation has been thorough and performed by professionals. And also it is a well written paper.

We are fully aware of all the weaknesses and methodological shortcomings of this comparison but since as of yet there is no longitudinal study about the long term effects of the impairment of thalidomide we went for the best we could to at least get an idea of what is going on in the long term. Also we tried to be very open about the methodological imperfections of this comparison and list all the limitations.

Anne Kjersti Daltveit (Reviewer 2): Review "Life situation of women affected by Thalidomide embryopathy in North Rhine-Westphalia - a comparative analysis of a recent cross-sectional study with earlier data"

Thank you for your thorough reading of this article, this has strongly improved the manuscript.

In this paper data from two studies are compared - one study published in 2002 with 104 women (N2002) and one study published in 2015 with 115 women (P2015). For both studies data are collected in North Rhine-Westphalia. The aim of this paper is "to compare the previously collected data of N2002 with the recently collected data of P2015 and therefore close this gap of knowledge as to current health problems and anticipated health problems, medical care and assistance."

Some comments:

Title: I would prefer "Women impaired by Thalidomide embryopathy" before "Women affected by Thalidomide embryopathy", as the term "affected by" could also relate other persons than the impaired person (family etc.).
Abstract:
I am not familiar with use of the term "inferential statistical methods" in such studies.

We have changed this to “inductive”

In the abstract it is stated that “…face a poorer health status than women their age in the general population”. In the Results section of the text no comparison with the general population is made, only comparisons between 2002 and 2015. Comparison with the general population is, however, mentioned in the Discussion. If these comparisons are suggested to represent a main result of this study - as indicated in the abstract, I suggest that they should be included in the Results section. I understand that it will not be possible to perform statistical tests with the general population, but they can still be included as observed data and for example added to the tables.

Thank you for this comment; we have moved the comparisons with the general population to the results section.

Introduction/background:
In the aims you state that you want to "close the gap of knowledge…” Based on a relatively weak study design with crossectional data as compared to a stronger design with longitudinal data, I think it is too ambitious to say "close this gap" here.

We have changed the wording.

Methods:
There is a flowchart for the data collection for the 2015 survey but not for the 2002 survey - why not?
Thank you for this comment, we have added the flowchart

What were the data collection periods for the two surveys? This is to some extent mentioned in the Methods section for the 2015 data, but could be more clearly presented for example in the tables.

We have included this information into the manuscript.

Since the two surveys took part in the same geographical area it is relevant to know if the participants to some extent participated in both surveys. The problem is mentioned under "strengths and limitations", but no estimate is given. Can this be estimated, for example based on an estimate of number of impaired women in the district?

We can only estimate that in Peters et al (2015) about a quarter of the impaired living in North Rhine-Westphalia participated in the study. The study of Nippert et al (2002) was only a mail survey where the questionnaires were returned anonymized. Therefore we feel if we gave an estimator all we would be doing is guessing.

In principle, alternative statistical methods should be used if participants are measured more than once, but the bias due to this most likely minor.

Since we don’t know how many of them have been measured twice we decided to treat them as independent in the statistical analysis while being aware of the potential statistical problems of working this way. Therefore we mentioned it in the limitations. Analyzing the data as paired samples would have been worse in our opinion since than we would have had to find a way to match the samples which would have potentially induced an even larger bias or resulted in a loss of sample-size.
Results:

Table 1: I would like to have range of age in addition to mean. The range of age is for example relevant in order to understand the increased level of education between the two surveys. (Range for the 2015 data are given in the Results).

Thank you for this comment; we have added this to the manuscript.

Table 1: Statistical testing is not performed for all variables; the reason for this is explained in the Methods section but could also be given in a footnote.

Thank you for this comment; we have added this to the manuscript.

What is the meaning of the last sentence in Results: "Additional data that was collected in 2002 was provided by the author"? I suggest that you had access to original data from the 2002 study.

We had access to the original data, but in some cases only in an aggregated form due to data safety regulations. Since there are not so many women impaired by thalidomide in this restricted area of residence in some cases too much information can lead to possible unblinding. To avoid this, for some variables data was only made available in an aggregated manner.

Discussion lines 228+ and 236+. You compare your population with the German female general population. To me this is as interesting as the presented comparison between the two surveys. Have you considered to include some descriptive numbers for the general population in the tables?

Our main goal was to gain insight into the longitudinal data. However we have moved the comparisons with the general population into the results section.

Discussion lines 269+. The large differences found in the educational background is discussed, and a possible selection bias is considered. Because this is a very descriptive study, I would not
put too much focus on the statistical tests in tables 1 & 2 and think that the interpretation of the tables should be based on observed data.

Thank you for this comment. We have tried to strengthen the fact that all tests are of explorative nature only in the methods section.

But since you suggest that much of the difference in education is due to selection, have you considered to perform tests with adjustment for education?

The problem is that –as mentioned above- we have partially only access to aggregated data from 2002 due to data safety regulation. Therefore unfortunately we cannot provide these adjusted tests.