Author’s response to reviews

Title: Treated incidence and Baseline Characteristics of Substance induced psychosis in a Norwegian catchment area.

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

We thank the editor for giving us the opportunity to respond to reviewers’ comments. We have addressed these to the best of our abilities and revised the manuscript accordingly.

Revisions made are presented in detail below.

**Editor’s request**
A Competing Interest section has been added to the revised manuscript as requested (page 15).

**Feedback from reviewer #1**

1.1. For instance, the authors mention that many individuals initially diagnosed with SIP will eventually be diagnosed with a primary psychotic disorder and that this might be due to diagnostic problems or to the evolution of the illness – then why is it important to distinguish the two groups, especially using the diagnostic system that is criticized? Furthermore, The SCID is not very good at distinguishing someone who abuses a drug that increases the likelihood of developing schizophrenia (and is hospitalized for psychosis) from a brief psychotic episode in someone who abuses cannabis or methamphetamines. The article should be more critical of all these problems and offer a better justification for their study.»

Reply: Although we are aware of DSM-IV limitations as outlined in the manuscript it remains the most widely used diagnostic system in psychiatric research. Furthermore, SCID is well established and takes into account many forms of patient information and it is the authors’ opinion that diagnoses presented in the manuscript are set based on all available information and has achieved good inter-rater reliability several times.

Other more specialized instruments, such as PRISM had not been validated in Norwegian at the time of SCID and therefore not available to our study at time of inclusion.

In order to make this clearer we have made the following changes:

The following has been added (page 7, lines 6-7)
“SCID diagnoses were made on the basis of patients’ own account, co-lateral information and information from patients’ files. Strict DSM-IV criteria were applied for diagnoses.”
Clinical judgement according to DSM-IV criteria for psychotic disorders may be challenging when psychosis co-occurs with substance misuse or there is an inadequate substance-free period. In such cases, the default DSM-IV diagnosis would be SIP or psychosis NOS, due to the lack of fulfillment of criteria for serious mental illness [42].

Diagnosing psychotic disorders using DSM-IV criteria may be challenging in a clinical setting when psychosis co-occurs with substance misuse or with an inadequate substance-free period. In such cases, the default DSM-IV diagnosis would be psychosis NOS, due to the lack of fulfillment of criteria for serious mental illness [1].

In our opinion, the distinction between SIP and primary psychosis is important because - the treatment for SIP is abstinence from substance and differs from treatment of primary psychoses.

…but distinguishing and studying groups is important as they demand different treatment approaches and are often excluded from studies.

Scrupinizing possible initial SIP diagnoses closely by sound diagnostic practice would help shed light on the trajectory from substance abuse to primary psychosis.

Future research should focus on a common methodology to determine incidence rates and characteristics of SIP patients necessary to inform best delivery of care but also to shed light on the trajectory from substance abuse to primary psychosis.

1.2. - In the paper, after the description of the SCID as the diagnostic measure, it is mentioned that in the case of ‘refusers’ – does that refer to people refusing to do the SCID or to people refusing to stop using drugs for 4 weeks? This needs to be clarified.

Reply: We believe that this may be a misunderstanding based on an unclear formulation.

In the original manuscript we described this in the following manner:
“...but distinguishing and studying groups is important as they demand different treatment approaches and are often excluded from studies.“

In order to clarify we have changed “refusers” to non-consenters in the manuscript. Non-consenters refer to patients refusing to sign informed consent with regards to study participation.

Diagnoses for non-consenters, that is, patients who did not sign informed consent, were either made through SCID or clinical diagnoses from patients’ files.”

1.3. Were all the participants hospitalized and street-drug free for at least a month?
Reply: We thank the reviewer for this comment and added the following sentence to make it clearer (page 13, lines 7-8)
“In our sample, around half of SIP patients (53.5%) were hospitalized at time of inclusion, thus making it easier for the research team to observe patients substance-free.

1.4. When were participants assessed (in acute phase or after stabilization)?

Reply: For clarification, we have added the following:
(page 7, line 8)
“Patients were assessed by a member of the detection team within one week.”

And (page 7, lines 8-10)
“If patients scored positive for abuse of drugs at intake, a longer period (> 4 weeks) of drug-free observation would be initiated before a diagnostic conclusion was made, where possible”

1.5. Who conducted the assessments?

Reply: We have made the following changes:

Original text:
“The Structured Clinical Interview for the DSM-IV (SCID) was used for diagnostic purposes [40].“

Changed text (page 7, lines 4-6)
“The Structured Clinical Interview for the DSM-IV (SCID) was used for diagnostic purposes in all included patients (41) and performed by a member of the research team. The team consisted of clinically experienced and trained research personnel who performed all evaluations (42)”

1.6. Was there any form inter-rater reliability checks?

Reply: We have added the following for clarification (page 8, lines 4-7)
“Good inter-rater reliability was achieved on major parameters in the research group previously [2], and recently; in 2012 a new score were obtained for central measures from 9 randomly selected clinical vignettes from the baseline data. Reliability of measurements for DUP was 0.8 (ICC), and for diagnostic categories; K=0.9.”

1.7. - The rate of study refusals are very high – can you please explain if and why you believe the results are representative of the larger sample? This should be indicated under limitations. Also, any reason why people would refuse to participate?

Reply: The authors have clarified this in the manuscript:
Original text:
“In the case of refusers, diagnoses were either made through SCID by a member of the research team or clinical diagnoses from patients’ files.”

The following has been added/changed in the manuscript for clarification (page 7, lines 10-12)

“Demographic data was collected for all study eligible patients. Diagnoses for non-consenters, that is, patients who did not sign informed consent, were either made through SCID or clinical diagnoses from patients’ files.

And

Original text
“There is some uncertainty in the diagnoses of refusers as these are often based on initial interviews or clinical diagnoses from discharge letters.”

Changed text: (page 13, lines 8-11)
“The study is strengthened by having demographic data on all eligible patients. However, there is some uncertainty in the diagnoses of non-consenters as these are often based on initial interviews or clinical diagnoses from discharge letters.”

And

Original text:
“Our refusal rate was high in all groups, reflecting the arduousness of recruiting this patient-group into research as well as into the health care-system [48, 49].”

Changed text (page 13, lines 5-7):
“Our refusal rate was high in all groups, reflecting the arduousness of recruiting this patient-group into research as well as into the health care-system, as shown in other similar samples.”

And

Original text:
“Many patients are detected, assessed, but then discharge themselves against medical advice, or after the psychosis has resolved, without leaving any means of contact. This is confirmed in our sample where SIP patients have shorter admissions than the other groups, although this may also in part be due to the nature of SIP. The reasons for patients not engaging with services are likely to be diverse with some patients not acknowledging the need for help and others not wanting help or being too influenced by symptoms such as paranoia to be able to accept our offer for treatment.”

Changed text: (page 13, lines 13-16)
“Many patients are detected, assessed, but then discharge themselves against medical advice, or after the psychosis has resolved, without leaving any means of contact, possibly due to lack of insight or being too influenced by symptoms such as paranoia to be able to accept offers of treatment. This has also been found by others [3], and is confirmed in our sample where SIP patients have shorter admissions than the other groups.”

See also lines page 10, lines 4-5
“DUP remained significantly shorter in SIP patients, even when including patients who refused inclusion (table 2).”
1.8. Why were 5 people from the North included?

Reply: We take the reviewer’s comment on this being somewhat confusing, and have made the following changes to clarify:

Original text:
“TIPS was designed to identify and follow clinically epidemiologic samples of FEP patients from the Stavanger University Hospital catchment area, in the south sector of Rogaland County, Norway.

Changed text: (page 5, lines 18-20)
“TIPS was designed to identify and follow clinically epidemiologic samples of FEP patients from Rogaland County, Norway, in the Stavanger University Hospital catchment area in the south and Helse Fonna Hospital catchment area in the north.”

And deleted the following:
“..and also included a group of SIP patients from the north sector of Rogaland. “

See also lines page 9, lines 14-15.
“As the rate of detection from the North sector was uncertain, five patients from this area were included to enlarge sample size, but excluded from incidence calculations«

1.9. Are their profiles similar to the others?

Reply: The authors have looked at this and found no significant differences in terms of basic demographics or other characteristics between patients from the north sector and south sector.

The following has been added to the manuscript:
Lines page 9, lines 7-8:
“Patients from the north sector did not differ from remaining patients on any parameters.”

1.10. -Given the high rate of psychosis NOS diagnosed in your PS sample – this needs to be discussed more (wrong diagnosis, assessor really hesitant between SIP and PS?)... the results of the study are not as solid if the diagnoses used to split the groups are not clear and well-defined. This is an important limitation given the group comparisons... In fact, the PS and SIP groups appear quite similar in many ways ...

Reply: This is part of what the article aims to do. We have changed the text to clarify:

Original text:
“This is most likely to avoid over-diagnosing patients with primary psychotic disorders that in fact are the result of intoxication or withdrawal. “

Changed text: (page 12, lines 16-17)
“This is a limitation of our study, due to unwillingness to over-diagnosing primary psychotic disorders in patients possibly intoxicated or in withdrawal”

See also point 1.1.

1.11. -There also needs to be more of an understanding of the sample. Other studies with substance abusers with psychosis have found extremely high rates of trauma and PTSD in that sample, which could explain somewhat why it is so hard to engage them in treatment. The discussion would benefit from more links to the literature, in order to better understand the results.

Reply: The authors thank the reviewer for her comments. This manuscript does not focus on trauma or PTSD, however, we have looked at the sample in relation to PTSD and significant life event, (as defined by DSM-IV) and there does not appear to be any significant differences between the groups (p>>.05). We have added the following for completion in our manuscript:

Page 10, lines 21-22:
“There were no differences between groups with regards to PTSD or significant life events (p>.05)” (DSM-IV life events)

1.12. -In the discussion, there is reference to a study using the BPRS (McKetin) – I haven’t checked the article but the BPRS is usually used for the past 2 weeks, maximum past month, never for the past year. If this is really what was done, the results are likely not reliable.

Reply: The authors agree with the reviewer on this, and included the McKetin study as an example of the heterogeneity of trials studying SIP. We feel this is one of the important reasons why we need more comparable studies on this group of patients.

We have altered the manuscript to clarify:

Original text:
“Different clinical assessment methods make it difficult to compare study findings. A study which applied the BPRS (Brief Psychiatric Rating Scale) [2], found that 23 % of users had experienced a clinically significant symptom of suspiciousness, unusual thought content or hallucinations in the past year. This would make the threshold for substance induced “psychosis” much lower than when adhering to DSM-IV-criteria. DSM-IV criteria would only consider hallucinations symptoms of substance induced psychosis when they occur in the absence of insight, in contrast to primary psychosis disorders. Most likely, the intent here is to eliminate the coding of “hallucinogen-induced psychosis” where hallucinations are the primary effect of the drug. However, several studies suggest that hallucinations are a key feature of SIP, with SIP patients being more likely to consider their symptoms psychotic [15, 16]. Intact insight in psychosis has also been reported as a common feature among most methamphetamine users with psychotic symptoms [50]. By excluding hallucinations in patients with insight for diagnostic purposes, DSM-IV risks excluding patients with distressing symptoms from receiving proper psychiatric treatment as their symptoms may be ruled clinically insignificant. “
“Hallucinations following the intake of drugs are quite common. Different assessment methods make it difficult to compare study rates. One study applying the Brief Psychiatric Rating Scale [4], found that 23% had experienced a symptoms of suspiciousness, unusual thought content or hallucinations in the past year. DSM-IV criteria only consider hallucinations due substance intake as psychotic when they occur in the absence of insight, in contrast to primary psychosis disorders. Most likely, this is to avoid over-diagnosing psychosis following drugs that commonly cause hallucinations. However, several studies suggest that hallucinations are a key feature of SIP, with SIP patients being more likely to consider their symptoms psychotic [5, 6]. Intact insight in psychosis has also been reported as a common feature among most methamphetamine users with psychotic symptoms [7]. By excluding hallucinations in patients with insight for diagnostic purposes, DSM-IV risks excluding patients with distressing symptoms from receiving proper psychiatric treatment as their symptoms may be ruled clinically insignificant. “

1.13. In the version I had, it jumps from table 2 to table 4 (no table 3). In table 4, does a higher score mean worse academic performance?

Reply: There seems to have been a formatting error with regards to table-numbering and the authors apologize for this. This has now been corrected.

The following has been added to the text: (page 7, lines 22-23)
“Each item is scored on a Likert-type scale of 0–6, where lower numbers indicate normal, healthy functioning and higher numbers suggest pathologic development.”

1.14. This result could also be discussed a bit because drugs during school impede academic success, and some people who later develop schizophrenia also have difficulties in school… Given we don’t know the age of substance abuse onset (and if they used at school) this result is not all that clear or well-explained.

Reply: The authors agree with the reviewers comment on this and have added the following to the manuscript:

Page 14, lines 19-20
“Our interpretation is, however, limited by not having data on onset of substance misuse.”

1.15. Please re-read the article, a few language errors here and there (e.g. referred to our service in from August…).]

Reply: The authors take the reviewer’s point on this and have re-read and corrected grammatical errors.
Feedback from reviewer #2

2.1. “The way in which diagnoses were determined seems rather “loose” – it was either a SCID or record review. Some mention of this limitation or further explanation is necessary”

Reply: The authors take the reviewer’s comment to reflect need for clarification in the manuscript and have made the following alterations:

Original text:
“The Structured Clinical Interview for the DSM-IV (SCID) was used for diagnostic purposes [40]. If patients scored positive for abuse of drugs at intake, a longer period (> 4 weeks) of drug-free observation would be initiated before a diagnostic conclusion was made. In the case of refusers, diagnoses were either made through SCID by a member of the research team or clinical diagnoses from patients’ files.”

Changed text: (page 7, lines 4-12)
“The Structured Clinical Interview for the DSM-IV (SCID) was used for diagnostic purposes in all included patients [8] and performed by a member of the research team. SCID diagnoses were made on the basis of patients’ own account, co-lateral information and information from patients files. Strict DSM-IV criteria were applied for diagnoses. Patients were assessed by a member of the detection team within one week. If patients scored positive for abuse of drugs at intake, a longer period (> 4 weeks) of drug-free observation would be initiated before a diagnostic conclusion was made where possible. Demographic data was collected for all study eligible patients. Diagnoses for non-consenters, that is, patients who did not sign informed consent, were either made through SCID or clinical diagnoses from patients’ files”

See also,

Point 1.1

2.2. “In terms of the incidence data, the authors should further clarify how they’ve calculated incidence rates for those readers who are less familiar with this technique. Further, they should cite the source of the method for this calculation.”

Reply: The authors have made the following changes in the manuscript:

Original text:
“Age-specific incidence rates of first-episode psychosis were calculated in yearly bands and expressed per 100 000 person-years. The denominators for incidence calculation rates were based on estimated resident population figures for our catchment area, for each of the years 2007-2011, stratified by age. Treated incidence for the Stavanger sector was calculated as 6.5/100 000 person-years for SIP, 9.7/100 000 person-years for PS and 24.1/100 000 person-years for the PNS group (15-65yrs) (PNS> SIP and PS; p<.005). “

Changed text: (page 8, lines 18-20)
“Age-specific incidence rates of first-episode psychosis were calculated in yearly bands and expressed per 100 000 persons per year. The denominators for incidence calculation rates
were based on estimated resident mid-year population figures for our catchment area, for each of the years 2007-2011, stratified by age [9].

“And lines page 9, lines 12-14
“Treated incidence for the Stavanger University Hospital catchment area was calculated as 6.5/100 000 persons per year for SIP, 9.7/100 000 persons per year for PS and 24.1/100 000 persons per year for the PNS group (15-65yrs) (PNS> SIP and PS; p<.005).”

2.3. “The detected gender difference between groups is not adequately addressed. The authors did not statistically account for this (co-vary) nor did they discuss potential implications, or lack thereof, in the discussion. This should be addressed in some fashion.”

Reply: The authors greatly appreciate this comment from the reviewers, and have re-done all the data analyses with gender as a covariant. All results and significances remain the same with the exception of late adolescence academic performance on the PAS that showed an influence of gender.

We have added the following the manuscript:
Please see page 8, lines 15-16
“Outcome measures were corrected for the potential effect of gender differences applying ANCOVA (Analysis of covariance and log linear analysis, both with gender as a covariate.”

2.4. “However, the discussion lacks context and fails to convincingly integrate these findings into the current literature in a sophisticated manner. Further, they do not explicitly put forth how this ms. will serve to move the field forward. It is this reviewer’s impression the discussion can be made stronger through revision.”

Reply: The authors appreciate the reviewer’s comment and have re-written the discussion part of the manuscript to reflect this.

2.5 “While the authors took great care in the methods / results section to include describe differences between groups (such as symptoms, functioning, etc...), it is not clear to the reader how the findings address their initial hypotheses and why this is important.”

Reply: The authors consider the reviewer’s comment and have changed the following to make the results clearer:

Original text:
“It is likely that SIP is associated with more acute onset due to a proximal trigger (substance misuse) and that more severe symptoms propel patients into care more rapidly. Pre-morbidly, SIP patients had the poorest scores on early and late adolescent academic levels, suggesting that there are problems in this group from adolescence on. This is supported by other studies [18, 21] and would, in itself potentially increase risk of substance use. “

Changed text: (page 14, lines 16-19)
“Our results suggests that that SIP is associated with more acute onset due to a proximal trigger (substance misuse) and that more severe symptoms propel patients into care more rapidly. SIP patients performed poorer academically than the two other groups in early adolescence, a finding that is supported by other studies [10, 11] and would, in itself potentially increase risk of substance use.”

And page 14, lines 22-23 and page 15, lines 1-3
“Guidelines for assessment and treatments of these patients as a group are needed as SIP patients may need different medications, brief medication or no medication and they may be more susceptible to the adverse effects of antipsychotic treatment. Future research should focus on a common methodology to determine incidence rates and characteristics of SIP patients necessary to inform best delivery of care but also to shed light on the trajectory from substance abuse to primary psychosis.”

2.5.” There are a few typos that need to be corrected (such as on page 3 – toward bottom, extra bracket; spelling errors, confusing sentences top of page 4, etc...). The authors should ensure their formatting is appropriate for BMC Psychiatry.”

Reply: The authors have corrected typos and reviewed formatting of the manuscript

2.6. “Table 1 provides diagnostic description for SIP. However, it seems that the paper focuses so heavily on looking at differences between this group and that of primary focus – including descriptions of the other two diagnoses may be of use to the reader.

Reply: The authors take the reviewer’s comment into consideration and have decided to remove table 1 as information presented in the table was also written in the text.

We have added the following to the text: (page 9, lines 20-22)
“The PS groups had a greater proportion of schizophreniform psychosis, whilst PNS patients had a higher degree of major depressive disorder. Both groups had similar rates of schizophrenia.”

Table 3 describes diagnoses for the PNS and PS groups.

2.7 Further, there was little discussion as to why the table was included. Appeared to be some formatting issues with Table 1. Therefore, consolidating / thinning the table to reflect the most important or relevant data would make it more convincing and palatable to the reader.

Reply: See 2.6

2.8 Additionally, the formatting of all Tables could be improved to reflect a more professional style (i.e. removing box outlines). The column with only descriptors of the stats could be eliminated and that information could be consolidated either in the table legend or in the note.
*The Tables seem to be mis-numbered, with Table 3 potentially missing? The authors will need to fix this issue prior to consideration for publication."

Reply: The authors apologise for the inconvenience regarding formatting and have now updated the manuscript to reflect BMC psychiatry standards. Boxes in Figure 1 were included for clarity and the authors wish to keep these.

2.11. “The authors clearly outline why they think that distinguishing between SIP and primary psychosis is important, highlighting the need for the present work. As currently worded, the hypothesis includes expectations about investigative and treatment approaches. However, it is unclear if these are of primary interest/directly tested in the present manuscript.”

Reply: The authors take the reviewers point on this. The above sentence was added to describe the study’s main outcomes, but has now been altered to reflect the current article only.

Original text:
“We wanted to investigate this in a well-defined catchment area and explore the differences in baseline characteristics compared with primary psychosis patients with and without substance misuse aiming for a better understanding of characteristics, investigative and treatment approaches.”

Changed text: (page 5, lines 4-7)
“We wanted to investigate this in a well-defined catchment area and explore the differences in baseline characteristics compared with primary psychosis patients with and without substance misuse aiming for a better understanding of characteristics and symptom patterns.”

2.12. “The methods seem mostly appropriate. However, as described in other sections of this review – further detail will be needed on some aspects, such as calculating base rates. The authors will need to modify the methods to ensure clarity and the capacity for replication.”

See point 2.2.

2.12. “the paper examines a uniquely well characterized sample. The study was designed to examine a particular catchment area – which is likely a strength, in terms of the homogeneity of their sample, but clearly a weakness in terms of generalizability. Some discussion of this is warranted.”

Reply: The authors appreciate the reviewer’s comments and have added the following into the discussion part.

Please see page 12, lines 4-7
“This is further strengthened by a stable population with low migration numbers, as one gets a non-selected/"real world scenario”. Furthermore, the mix between rural and urban environments is viewed as very representative of the general Norwegian population [12].”
2.13. “The comparison of the TIPS I and TIPS II phases of study are, at times, confusing. The authors should consider carefully if they need to include the additional data. If it wasn’t included, would the findings still be of significance.”

Reply: The authors appreciate the reviewer’s comment and have changed the manuscript accordingly.

Information on the original TIPS study is included for informational purposes, but does not alter significances as the current sample does not include any data from previous samples.

Original text:
“TIPS was designed to identify and follow clinically epidemiologic samples of FEP patients from the Stavanger University Hospital catchment area, in the south sector of Rogaland County, Norway. The sector population of 185 337 (15-65 years) [36] live mainly in urban and suburban areas. The general medical system in Norway is nationalized, as is secondary psychiatric care. Psychiatry in Rogaland is sectored and all admissions present to the regional hospital.

TIPS II [35] (2002-ongoing) is a continuation of the early detection TIPS I study (1997-2000) [18, 37-39]. From 2007 onwards, TIPS entered a new phase, including substance induced psychosis patients, dividing patients into three groups consisting of SIP patients and primary psychosis patients with and without substance misuse (PS and PNS respectively).”

Changed text: (page 5, lines 18-21 and page 6, lines 1-2)
“TIPS was designed to identify and follow clinically epidemiologic samples of FEP patients from Rogaland County, Norway, in the Stavanger University Hospital catchment area in the south and the Health Fonna Hospital catchment area in the north. The population of 185 337 in the south sector and 66 255 in the north sector (15-65 years) [13] live mainly in urban and suburban areas. The general medical system in Norway is nationalized, as is secondary psychiatric care. All hospital admissions and secondary care out-patient treatment are referred to the two sector hospitals.

TIPS II [2] (2002-ongoing) is a continuation of the early detection TIPS I study (1997-2000) [10, 14-16]. From 2007 onwards, TIPS entered a new phase, including new patients, and for the first time also substance induced psychosis patients, dividing patients into three groups consisting of SIP patients and primary psychosis patients with and without substance misuse (PS and PNS respectively).”

2.14. “Finally, a demographic characteristic difference was ignored after being detected.”

Reply: The authors recognize that a significant finding was excluded from the discussion and have added the following:

Please see page 11, lines 12-13
“…and more positive psychosis symptoms.”
2.15. “In terms of specific points where improvement could be possible in the methods section, please consider the following: a) on page 10, there is a sentence that reads “Most of our patients use cannabis...” It is unclear to the reader what patients they are referring to? Is this anecdotal clinical info? Or are they referring to the data?”

Reply: The authors take the reviewers point on this being unclear. The cited statement refers to the data in the presented sample. The following have been added to the manuscript:

Original text:
“Most of our patients use cannabis or amphetamines, or a combination of several substances.”

Changed text: (page 11, lines 16-17)
“Most of the patients in our sample reported use of cannabis, amphetamines, or a combination of several substances.

2.16 “b) a more complete description of statistical analyses would be useful”

Reply: The authors have taken the reviewers point on this and altered the manuscript to clarify

Please see page 8, lines 10-20
“Analyses were performed using the SPSS Statistical Program Package v 20.0 [48]. Mean values are reported with standard deviations in parentheses, with median values applied for skewed variables. DUP was log transformed prior to analysis with ANOVA. Parametrical tests were used for normally distributed data whereas non-parametric tests were applied for all univariate tests to ensure a uniform analysis strategy. Categorical variables in 2x2 crosstabs were analyzed using Fisher’s exact test. All tests are two-tailed. Outcome measures were corrected for the potential effect of gender differences applying covariant analysis to continuous data and log linear analysis for categorical variables.

Age-specific incidence rates of first-episode psychosis were calculated in yearly bands and expressed per 100 000 persons per year. The denominators for incidence calculation rates were based on estimated resident mid-year population figures for our catchment area, for each of the years 2007-2011, stratified by age [49]."

2.17. “c) naming the diagnostic procedures as a potential limitation should be more explicit”

Reply: The authors take the reviewer’s point into consideration, and refer the reviewer to point 1.1., 1.10. and 2.1.