Author's response to reviews

Title: Predictors of Premature Mortality in Swedish Drug Abusers: A Prospective Longitudinal Study 1970 - 2006

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Predictors of Premature Mortality in Swedish Drug Abusers:
A Prospective Longitudinal Study 1970-2006
Anna Nyhlén, Mats Fridell, Martin Bäckström, Morten Hesse and Peter Krantz.
23 febr 2011

Dear Dr Odenwald/ Angelina Ilievska

1. Thank you for your comments. I will do my best to answer your editorial questions below. We made a general correction of some of our terms, like base-line, which can be misguiding since it is not an evaluation of treatment.

2. We ordered a new language check of the revised manuscript.

Our manuscript has now been revised according to the editorial comments and the comments from the four reviewers. The concerns are addressed with a point-by-point response below:

Editorial comments:

1. We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional copyediting service.

3. We have improved the style of the written English by copyedit the paper.

2. Please structure your manuscript according to our guidelines for Medical journals within the BMC series:

Manuscript sections - Manuscript sections should include (in the following order): Abstract; Background; Methods; Results; Discussion; Conclusions; Abbreviations (if any); Competing interests; Authors' contributions; Acknowledgements; References; Figure legends (if any); Tables (if any); Description of Additional files.
2 The manuscript is now structured according to your guidelines above.

3. We note that you have gained ethical approval for your study. Please do ensure that you remove this statement for you Acknowledgements and insert this into the Methods section of the manuscript. Please include the name of the body which gave approval, with a reference number where appropriate.

3 The ethical approval is inserted into the Methods section p.5, last para

4. Please also improve/add more depth to your Background/Aims section within your abstract.

4 We have added this in the new version of the Abstract

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

As substantial points were raised, we will need to seek further advice on the revised manuscript.

5. Please also highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

5. The changes in the text are highlighted in red colour

With best wishes,

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PS: The responses to the reviewers’ comments are attached as separate files and below on the following pages 3-18
This is an interesting paper, but I feel there are some major gaps in it which need to be addressed, and by so doing make it a stronger paper, and increase its external validity.

ANSWER FROM THE AUTHORS: We are grateful for you very thorough review and the many suggestions for improvement you provided.

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Major compulsory revisions

Abstract
1. Mention country of study site
ANSWER: We have added country to the abstract.

2. How do the findings compare to other cohort studies, especially SMRs, evolution of causes of death?
ANSWER: We have added some further references to the paper. Please see the new version of introduction p 3, para 2 and discussion p 13-14, para 1. The focus in this paper is on drug related and non drug related deaths and a thorough presentation of causes of death and the other drugs is dealt with in another paper.

Page 3, para 3, There are papers on the role of amphetamines, ecstasy and cocaine in causing death - these need to be cited e.g. papers by Schifano et al based on UK data.

ANSWER: The focus of this paper was factors associated with the difference between drug-related deaths and other causes of death. There was practically no cocaine in Sweden and it has not been a street drug in Sweden over the years. Ecstasy and cocaine is a very recent phenomenon and has played no part in our cohort. During the 1970s and 1980s there were still large variations of substances used in different regions of Sweden.

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Schifano F, Corkery JM, Cuffolo G. Smokable ("ice", "crystal meth") and non smokable amphetamine-type stimulants: clinical pharmacological and


ANSWER: As commented above, cocaine use is a very recent drug problem in Sweden and has more been common in some “jet-set” circles, not in our cohort (CAN). Crack has never been found among users in this or the next somewhat larger cohort from 1978-1995. Therefore, most of these references are not of central relevance to this paper.

We choose to include (introduction) the article by you and your colleagues from 2010 above.

Page 5, para 2 - where any lost to follow-up? If so, how many? (This needs to be clarified here not mentioned later on.

ANSWER: See results p 9-10 in the new version: Of the 561 included in the cohort, 11 individuals had either immigrated or could not be located by 2006. Information of date and place of death was available for 204 dead persons in the cohort. The information of the causes of death was missing in two cases. Due to the contact between the forensic department in Lund/ Sweden and forensic dept in Copenhagen/Denmark we obtained forensic autopsy protocols for patients who died in Denmark.

Page 7, line 3 - why are not licit/prescribed drugs discussed anywhere in this paper? There is no discussion of recreational drug use and death - another gap

ANSWER: This is an empirical study focusing on discriminating two causes of death. As described in the text, some of the deaths involved prescription drugs and alcohol. In the discussion it is already mentioned that licit drugs like barbiturates and benzodiazepines in combination with opiates were associated with increased risk of overdose ( p 15). Hypnotic and sedative drugs were prescribed to a minor extent during detoxification, and were not prescribed to drug addicts on an out-patient basis. Information about intake of not prescribed licit drugs in the cohort was not available. These substance dependent persons were hard core addicts and whether or not they had a period of recreational drug use, this preceded their admissions for detoxification by several years.

Licit drugs are not always prescribed. Licit drugs including alcohol were involved in about half of the drug related deaths (56 of 120) when found at autopsy examinations. This is published in another paper but we will comment upon it on your request.

Please see short comment on recreational use of cannabis in the new version of discussion, p.17.

Page 10, bottom para - What were the other causes of death in the drug-related
group? This is important information? Did these change over time?

ANSWER: please see new version p 11/ drug related death for causes of death. Please see fig 1 for the cumulative incidence over time for drug related deaths. A detailed analysis of the timing of specific causes of death other than drug related deaths would involve analyzing rare events in relation to their timing, and would not be statistically meaningful.

Page 11, first para - Again, it is important to tell us what these causes of death in the non-drug related death group were. What were they, and did they change over time?

ANSWER: Causes of deaths were sub grouped in drug related and non-drug related death. The non-drug related deaths were caused by somatic diseases (cardiovascular diseases 42%, infections 36%, and cancer 22% of the somatic deaths) and one third of the non-drug related deaths were violent (suicide, homicide and accidents). Please see the new version of the text p 11-12 describing non drug related death.

Please see fig 1 for the cumulative incidence over time for non-drug related deaths. The low prevalence of HIV in Sweden and the presence of harm reduction programs with needle exchange and hepatitis vaccination have probably contributed to the low incidence of premature death caused by these infections.

The pattern of non-drug related death causes was probably associated with age of death. However, as mentioned above an analysis of this issue is not feasible with this sample size. As it is known that incidence of cardiovascular diseases and cancer increase with age, it is very likely that these deaths occurred among older subjects in our sample as well. The violent deaths were probably not associated with age at death, but neither of these issues has been investigated.

Page 13 - Discussion - How does the length of this study's follow-up period compare to other cohort studies? What was the average length of follow-up? It

Answer: We thank the reviewer for this suggestion. We have mentioned that the present study is one of few studies with a follow-up period of more than 30 years. The mean observation time was 27.1 years, and this has been added to the text (Results, first para).

QUESTION: It would interesting to give SMRs for 5-year periods to see how they changed over time. This would also facilitate comparison with other studies, e.g. those on the addicts notified to the Home Office in the UK None of which have been cited). This will help improve the generalization of the study's findings.

Answer: The purpose of this study was to compare predictors of drug-related and non-drug related deaths. We may consider doing a study with a larger sample doing what the reviewer suggests. With this moderately large sample, estimates within individual years would be highly unstable

Page 16 - There is no discussion of the evolution of causes of death over time. What has been the effect of hepatitis, HIV/AIDS etc? As mentioned above – no
discussion of recreational drugs causing death, or of the role of prescribed, licit drugs.
ANSWER: Please see answer above. See fig 1 for the cumulative incidence over time for drug and non-drug related deaths.

The low prevalence of HIV in Sweden and the presence of harm reduction programs with needle exchange and hepatitis vaccination have probably contributed to the low incidence of premature death caused by these infections. However, substances contributed to death for those who died from liver diseases associated with hepatitis and/or chronic alcoholism, and for those who died from HIV associated causes (see discussion, p 19).

Very little discussion of how findings compare to other countries outside Scandinavia. We need to know to what extent these findings are similar/different to other regions of the world and/or time periods.
ANSWER: We have mentioned a considerable number of studies from other parts of the world, including USA, Australia, and Europe. A full comparative review goes beyond the scope of this empirical paper.

We have added Sörensen et al (2005) and Hser et al (2001;2007) to the text. The problem is that there are very few cohort studies published were several different drugs are discussed. Most studies focus on opiate addicts, even though these are known to use other substances as well.

Minor essential revisions
Abstract - How many cases lost to follow-up? 11/561, see new version of abstract.

What was the average ages at recruitment and death?
ANSWER: See table 1: Average age at recruitment was 24.3 y (SD 7.2) Average age for drug related death, please see new version of results The average age of substance related death was 35.7 years (MD=34.9, SD=10.1).

At what level were the predictive factors/variables statistically significant?
ANSWER: please see table 2.

Page 3, para 2, line 1 - who states that the association is not clear?
ANSWER: This sentence is deleted.

para 2, line 3 - where was amphetamine the most common substance of abuse
ANSWER: Amphetamine abuse was diagnosed in 35-40% drug addicted patients admitted to hospital in the seventies, and in 42% in this cohort. This pattern of a high percentage of amphetamine abusers has been fairly stable up to middle of the 1990ties in Sweden.

para 2 - what is the literature on stimulants, barbiturates, benzos?
ANSWER: Stimulants; see p 3. Barbiturates and Benzodiazepines; see discussion page 18.
This study showed that in a few instances, cannabis was present along with other drugs among subjects in the general population who died of an accident. It does not show that, for instance, cannabis is present more often in fatal accidents than it is in the general population. The relevance to the question of cannabis-related mortality in the discussion is not exactly clear to us. However, the reference is included in the introduction.


Page 5, para 1, line 2 - what does 'heavy' use mean? Or do you mean 'Hard'?
ANSWER: Heavy drug use is in contrast with light or recreational drug use. The term is fairly commonly used. “Hard drugs” is normally used in contrast with “soft drugs”, which would generally be terms used to discriminate more from less stigmatized drugs. These last terms are avoided by us.

para 1 - It would interesting to know something of the nature of the region. e.g. is it rural or urbanised, what is employment like, what was the rate of co-morbidity/mental health issues in the recruitment period in the general population?
ANSWER: The region was urbanized with a very high level of employment. The unemployment rate was around 5% up to the 1980s, and this information has been added in Methods. Discussion about co-morbidity/ prevaence of psychiatric disorders in the general, local population; please see the new version of the discussion, p. 18.

Page 5, para 3 - Were any physical conditions/diseases diagnosed at recruitment?
ANSWER: Yes, please see new version.

Page 7, line 1 - is the second reference correct? No, It has been corrected in the new version
Page 8 - move Acknowledgements to end of paper. It has been corrected in the new version
Page 8, bottom para - Mention any loss to follow-up? Please, see new version
Page 9, para 1, line 4 delete 'a' before 'chronic' It has been corrected in the new version
line 8 - what are the p values for these results? Please, see the new version
The p-values are given either in the table or in the text.
para 2, line 5 - ? reverse 23% and 8% It has been corrected in the new version
para 3, lines 5 and following – presumably numbers 300.40 are ICD-8 codes? 
Yes, this is clarified in the text in the same para.
Page 10, para 2, first line - Replace 'in 2006' with 'by 2006'. Do not start a 
sentence with a number!
It has been corrected in the new version
Page 12, para 3 - suggest inserting 'Related to' at the start of the second 
sentence.
It has been corrected in the new version
Page 13, Para 3, lines 6-8 - Any references to support these claims ? ( Claims for 
what?)
No references as this is speculative, expressed by "might be one explanation"-
Page 14, para 2, line 4 - see reference to Oyefeso et al, above.
This reference is not strictly relevant for this study, as described above.
para 3, line 3 - How does this (psychiatric disorders) compare to the general 
population at the time?
please see the new version of the discussion, p. 18, the Lundby study.
Page 19 - Table 1 - what does 'mixed abuse' mean? Is it with other drugs or 
alcohol or both?
It means abuse of at least 2 substances at the same time, poly drug use. Poly 
drug use is mentioned in the text in Results , and in table 1. (it is with other drugs 
and/ or alcohol )
Page 20 - Table 2 - spell out what CS means (I note Dr Odenwald's quert)
It is central stimulants - It has been corrected in the new version
Page 22 - Figure 2 - as above It has been corrected in the new version
Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being 
published
ANSWER:
Please, see the new and corrected version of the paper.
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests

REPLY TO REVIEWER 2 ( P. 10-12)
Title: Predictors of Premature Mortality in Swedish Drug Abusers: A Prospective 
Longitudinal Study 1970 - 2006
Version: 3 Date: 23 November 2010
Reviewer: Thomy Tonia
Reviewer's report:

• Major Compulsory Revisions

1. The authors provide no reasoning behind their choice of the categories of mental disorders used in their model. The categories used are rather broad and -in my opinion- it is not safe to group together so different diagnoses under such big umbrellas. The authors need to justify how this categorization serves their purposes and maybe focus more on the other predictors.

ANSWER: We agree that our aggravations might be a bit crude. Apart from substance diagnoses, fewer persons were diagnosed with psychiatric diagnoses at that time. The diagnostic standard was ICD-8. Apart from the diagnoses of chronic psychoses many psychiatric categories were very broad at this time and in this particular cohort. Neurosis included depressions (minor and major without psychotic symptoms), and anxiety disorders and phobias. Among the personality disorders (pd) anti-social pd, was the most common with some additional hysterical and infantile pd:s. The psychoses will be dealt with in a forthcoming paper. Please see the new version of Methods p. 6, first para, last sentence, and in discussion/limitations.

2. The discussion is quite speculative at times and fails to convince. I would like to see more references in support of some of the authors' assumptions.

ANSWER: We agree that the discussion about cannabis is speculative, and this paragraph has been changed in the new version p 18. Mind that we do not discuss cannabis use as a recreational form of use.

Added to the discussion/limitations p 20, second para: Another limitation is that the psychiatric disorders were categorized in rather broad groups at time for inclusion and it is difficult to know how (more) specific diagnoses would influence/predict premature mortality.

3. It is not very clear to me how exactly the assessors used the autopsy and police reports and the hospital records. Were there any "preset" rules about how a drug-related death was to be identified, which documents had priority over the others etc? The somewhat "subjective" nature of your assessment of drug related deaths need to be addressed in the limitation (even if the inter-rater reliability was good).

ANSWER: The drug-related deaths were identified as described in Methods/coding and identifying causes of death, (p 7) and ref 13 p 7 (details, Degenhardt, preset rules). See added information in the new in Results/causes of death

4. There is no explicit reference in the abstract regarding the comparison with the case-finding study, even if this was one of the main aims of the study!

ANSWER: The aims of the study were to identify predictors of drug related premature mortality in the cohort. Please see the new version of introduction. The comparison with a case-finding study was performed to evaluate the representativity of the individuals in the cohort as drug dependent persons in the
studied area (ref23). We believe this kind of information is valuable.

• Minor Essential Revisions

1. You mention in page 5 that the national case-finding study estimated the number of abusers having a daily intake of illegal drugs. Were the participants in the cohort study abusing only illegal drugs too? This could affect the results.

ANSWER: The cohort had about 3% alcoholics and the case-finding study had none. As the case-finding study was not used to compare SMR:s it would not affect the results.

2. On page 7 you mention that a drug-related death is directly associated with illicit drug use. You also state that suicides were considered non-drug related deaths, if no drug or alcohol was involved in the death. Does this apply to both illicit and prescription drugs? Please specify. Same goes for page 14: were all suicides due to intoxication considered drug-related or only the ones involving illicit drugs?

ANSWER: Drug related deaths were considered drug related regardless of the legal status of the substance. This was an error. SUICIDES applies to both illicit and licit (not always subscribed for the individual her/himself) substances. This has been corrected in the new version.

3. There is some discrepancy regarding the reasons for exclusion of the 20 patients between pages 5 and 8, i.e. in page 8 there is no mention about patients refusing to take part in the study and in page 5 there is no mention of an incorrect identification number.

ANSWER: This has been corrected in the new version.

4. On page 5, the date of the data from the case finding study is reported as 1978, whereas on page 9 as 1980. Is that a mistake or was it really so?

ANSWER: Sorry the case-finding-study was conducted in 1978. But the publication is 1980. It has been corrected in the new version.

5. Page 14: “it is possible that the more passive lifestyle...often violent deaths”. The use of word “passive” is a bit strange here. Are heroin users considered to have an active lifestyle in comparison? Also, you mention “drug related, often violent deaths”. Could you provide an example of what kind of violent death would be considered drug related? Would it include, for instance, being murdered during drug dealing even if no illegal drug was found in the system?

ANSWER: Well, after having worked with many of these patients over many years one could seldom apply the word passive to the heroin users, even though we understand what you mean.

It will depend on your definition of “active” or “passive”. The heroin users that we have come across have not had a lot of idle time. They generally spend a considerable amount of time actively pursuing money and drugs before the next abstinence symptoms strike. Clinically there were very substantial differences between heroin och amphetamine users and cannabis users. The latter were often more similar to patients dependent on sedatives and/or analgetics. But of
course the conclusion is a bit speculative, but the best we can find. Please see the new discussion, p18-19.

Mind also, that the comparisons are made within the group of heavy substance users and may not apply to the population at large.

6. Maybe I just don’t read it right, but I am not sure I understand your reasoning on page 15: if the cohort and the case finding study had similar age, how can you justify your statement that “the rate of injection use might…...and inhaled substances rather than injected them”?

ANSWER: Maybe it would be more correct to state that The case- finding study find a more diversified pattern of substance abuse than is the case with patients who are admitted to treatment. We think that the wording: “in an earlier phase of the drug career” was exaggerated since the difference is not that large.

7. The acknowledgements should be moved at the end of the manuscript.
ANSWER: This has been corrected in the new version.

• Discretionary Revisions
1. I think that fact that the informed consent was just verbal should be more clearly stated (as it stands now you say that patients were asked if they agreed to participate; asking could be either verbal or written).
ANSWER: At that time only a verbal consent was required. Mind that this is not a treatment study, in which case the regulation should be much stricter.

P 6, first para.

2. Maybe the authors could consider some minor revisions of their English and their writing
ANSWER: Yes, definitely. Please see the new version. We made a new language revision.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests.

REPLY TO REVIEWER 3 (P. 13-15)
Reviewer's report -´
Title: Predictors of Premature Mortality in Swedish Drug Abusers: A Prospective Longitudinal Study 1970 - 2006
Version: 3 Date: 24 November 2010
Reviewer: Fabrizio Schifano
Reviewer's report:
1. Is the question posed by the authors well defined? Yes it is
2. Are the methods appropriate and well described? Yes, but a better description
   of the comparator sample is needed
3. Are the data sound? Yes they seem to be
4. Does the manuscript adhere to the relevant standards for reporting and data
   deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported
   by the data? Overall, yes (pls see below for further comments)
6. Are limitations of the work clearly stated? Yes
7. Do the authors clearly acknowledge any work upon which they are building,
   both published and unpublished? A few more updated references are needed
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? Some editing is clearly needed

More in particular; the paper is interesting and presents with a number of
strengths. However, some revision may be needed to improve even further the
quality of the document.

Editing: it is baseline and not base-line; page 1 is interpretation and not
interpretation etc etc (I am not identifying here all the areas that need to be
addressed)

ANSWER: Thanks for commenting upon it. This is messy, and the word base-line
of course divert the ideas of the reader to a treatment study, which is it not. This
issue has been addressed, please see the new version. We also do a new
language finish. We changed the term also in the abstract.

Abstract: I would avoid the term ‘angoris’ (only very few readers would be able to
understand this)

ANSWER: True this is the term in ICD-8 and we tried to stay with the older term,
but of course it is dated. This is corrected in the new version.

Page 3; apart from reference 13, pls include more recent data re: cocaine and
amphetamine mortality. The very recent EMCDDA report contains some of these
data but there are specific research publications as well from the last 1-2 years

ANSWER: This has been corrected in the new version, p 4, first para.

Page 7, line 1: I think that Degenhardt is reference 13 and not 24
ANSWER: This has been corrected in the new version

Page 8, middle of the page; pls explain better which are the levels of ethnic
diversity in Sweden at present

ANSWER: In the late sixties and early seventies there was an immigration wave
from Yugoslavia, Greece and Italy. This immigration was however very modest
compared to other countries in Europe except the Scandinavian countries. There
was about 5% of immigrants in Sweden at that time which increased in the 1990s
and 2000s to 15% today. In the cohort of patients, only 0.3% had two parents born outside Sweden. About 15% had one parent born abroad.

This has been added in the new version

Page 9, after ‘insert table 1 here’: pls describe better the sample of the case finding study. Furthermore, the following statement is either somewhat unclear or needs some editing (is it 8% vs 23% or the 23% vs 8%?)

ANSWER: 23% vs 8%. This has been corrected in the new version

Page 10, first line: the ‘persona pathologica’ term may be intelligible to only few Professionals.

ANSWER: True, the term is ICD-8 and could is replaced by anti-social personality disorder, which was the most common category followed by infantile and hysterical. See new version p.6, last para

Page 10 Mortality rates, page 10; did you mean people who had died in 2006 or by 2006?

ANSWER: by 2006, This has been corrected in the new version.

A few lines below, same page: you already commented about the k=0.98 level of inter-rater reliability.

ANSWER: We have done both. This is inter-rater reliability concerning causes of death, on p 11 (in new version) it concerned diagnoses at intake.

Page 11: Gender and age paragraph: pls check the editing of this paragraph.

ANSWER: This has been corrected in the new version.

Page 12, drug type/drug abuse paragraph: pls edit; it is somewhat unclear.

ANSWER: This has been corrected in the new version.

Page 13: you mention that stimulant misuse was not associated with any impact on premature mortality, but you failed to comment about this issue (which is quite important and somewhat unexpected) in the discussion.

ANSWER: This has been corrected in the new version, p 16, second para.

Page 13: ‘..inexperience might also contribute to the hazards..’: no reference given here; no evidence provided here for this statement; better to be deleted.

ANSWER: Agree, this is our own way to understand and we have seen no other authors having drawn the same conclusion. This has been corrected in the new version.

Page 14; negative association between THC misuse and premature mortality occurrence: Pls expand on this important issue. Explanations here provided seem to be over simplistic

ANSWER: Please see p 16-17 in the new version

Page 14: barbiturates and opiates (with no capital words) causing respiratory depression: no reference provided to support this statement

ANSWER: Again, this has been corrected in the new version. It is however quite clear that these are the pharmacological effects of opiates as well as
barbiturates. So in a way we feel references could be left out on this bit of information, but a ref (White, 1999) is added.

In short: the paper is worthy publishing, but only after a revision.

REPLY TO REVIEWER 4 (P. 16-18)
Reviewer’s report –
Title: Predictors of Premature Mortality in Swedish Drug Abusers: A Prospective Longitudinal Study 1970 - 2006
Version: 3 Date: 16 December 2010
Reviewer: Heinrich Kufner
Reviewer’s report:
General remark
The topic is interesting for the addiction field, the data base is clearly defined, but not comprehensive and the methodological approach to analyse predictors of drug related mortality is convincing regarding statistical methods. Besides the strengths of the study three major points and several minor points for revision are described in the following.

Major revision
1. During the long follow-up period many episodes e.g. treatment episodes or life events e.g. death of relatives or friends may have occurred in the life period of the patients which could influence drug-related mortality and could modify the impact of the analysed predictors in different ways (see Flynn et al 2003). Of course, in case of deaths the dead drug addicts cannot be asked any more about their treatment episodes, but there are other sources of getting data from relatives or friends or from health insurance companies or other documentation systems. If there are no such data available this should be discussed at least as limitations of the study. If there are data, then it must be argumented for not having included these data in the study.

ANSWER: Unfortunately we do not have this kind of data. When starting the research process very modestly in the late 1970s our preliminary intention was to try to identify various forms of psychopathology. This was possible to do with the psychoses and in a forthcoming publication we are updating all types of psychoses to ICD-10 standard from a data in the hospital records. But the data you mention we did not have. I admit this is particularly problematic with patients who have committed suicide. We have studied suicide attempts back in 1993-1997 from a well conducted five-year follow-up. We had a lot of data there, but not exactly the data you ask for.
2. The data of ICD diagnoses were filed at discharge (page 6) and it may be assumed that there are other data at discharge available e.g. dropout of treatment which is presumably in general one of the best predictors of treatment outcome and may be a predictor for drug-related deaths, too (Simpson DD et al.) This issue is not discussed. If data about premature discharge are available they should be included in the analyses, if not this should be discussed, at least.

ANSWER: This cohort study did not have treatment as the major interest. In this cohort there were 20 patients not entering treatment before having the initial physical examination completed. These 20 have not been included, since we are not sure whom they were in several cases. From the group admitted (n=561) there were an initial physical and psychiatric examination and urine samples. After having been admitted, about 39% of the patients did not complete detoxification, while the remaining 60% did complete detoxification and some 25% also completed more extensive goals with a prolonged stay.

Simpson, DeLéon, and a number of researchers in institutional treatment in the 1960s-1980s wrote extensively on predictors of drop-out. I think you refer to the article of Simpson from 1997 where he and others defined early drop-outs as those leaving before 3 months. But the conclusion from many researchers at that time was that there were no definite predictors of drop-out apart from situation related ones. Today we would probably say that this was related to craving.

3. The sample is rather heterogeneous regarding different types of drugs and different dependencies. Especially, the small group of alcoholics with 2% deaths may be different as to treatment outcome and as to the long term course of the patients including spontaneous remission (see Klingemann & Sobell, 2007). Although different drugs as predictors are analysed the group of chronic alcoholics with 3% related to the total sample is small. Again, the heterogeneity should be discussed, at least, regarding the impact on results.

ANSWER: The intention was to use the detoxification ward as a unit where the patients resembled the street addicts in the region as close as possible. It is true that there are several substances and so is also the case in the case-finding study. Other authors have focused on opiate addicts like Hser with a 33 year follow-up., but we feel it is valuable to see how different drugs and problems associated to them influence outcome.

On the issue of alcohol dependence, patients with chronic alcohol dependence as their major addiction was to a less extent admitted to the treatment unit after 1975. We are just like you quite convinced that there are many characteristics which differ between drug and alcohol dependent persons. The more recent American NESARC-study give support to the findings that drug abusing and alcohol abusing patients differ as regard to type and magnitude of psychopathology.

Minor revisions

4. How long had patients stayed in treatment? (page 4)

ANSWER: Please see p. 9, last para, 31% discontinued detoxification treatment
prematurely. Of these 20% dropped out within 6 days and another 11% within two weeks. The average treatment time at the unit was 24 days (MD=23 days). During the early 1970s, patients from forensic psychiatry were treated in the unit over 6 months or longer. In this group there were some patients with Schizophrenia.

4. In table 1 not only percentages, but also absolute frequencies should be presented.

ANSWER: Has been corrected

5. For easier reading of the tables, the definitions mentioned in the text (e.g. mixed abuse) could be presented in the legend, too.

ANSWER: Please see new versions of tables

6. In table 2 only the Beta’s are represented, at page 12 risks are mentioned not clearly defined. In epidemiological studies it is usual to apply the OR (=Exp(B) mentioned at page 11) to characterize the effect of predictors or to use other risk coefficients if available. Therefore, in table 2 the OR should be included.

ANSWER: True, we change these labels

7. The abbreviation CS in table 2 and figure 2 may be substituted by the full name of the substance group.

ANSWER: Please see new versions of table 2, fig 2

8. The authors say (page 15) that the study sample is similar to a national case finding study in that area. Usually, the rate of alcoholics in the European countries is clearly larger than that of drug addicts, which is not the case in the study sample. There should be some explanation for the stated similarity.

ANSWER: Sorry if we were not clear about this. The case-finding study was aiming for drug use and especially hard drug use in the region. Persons with alcohol problems were not a major target. If we compare the two groups, the incidence of chronic alcohol abuse is much higher, around 7% of the population or 70000 adults in the region compared to about 1.500 heavy drug users.

9. Gender and age paragraph. Please check the editing of this paragraph.

ANSWER: We had misplaced the heading and have moved it down.

Pate 12. Drug type/drug abuse paragraph: please edit, it is somewhat unclear.

ANSWER: This has been edited.

Pate 14: negative association between THC misuse and premature mortality occurrence: Please expand on this important issue. Explanations here provided seem to be over simplistic.

ANSWER: It is a striking finding, but in fact, we have no strong theory to explain why this negative association came up. We agree that our suggestions for this finding are speculative, and have addressed this issue in the new version, p 16-17.