PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Observational evidence that urbanisation and neighbourhood deprivation are associated with escalation in chronic pharmacological pain treatment - a longitudinal population-based study in the Netherlands
AUTHORS	Leue, Carsten ; Buijs, Servaas; Strik, Jacqueline; Lousberg, Richel; Smit, Jasper; van Kleef, Maarten; van Os, Jim

VERSION 1 - REVIEW

REVIEWER	J B Kirkbride Sir Henry Wellcome Research Fellow University of Cambridge, UK No competing interests
REVIEW RETURNED	20-Feb-2012

REPORTING & ETHICS	No mention of ethical approval but assuming it was sought and obtained as appropriate. Editorial office may wish to check.
GENERAL COMMENTS	Comments for the authors Thank you for the chance to review your work on pain prescriptions, urbanization and deprivation. The hypothesis you present is interesting and the data you use allow for this type of investigation. To strengthen your work I have a number of suggestions and concerns which you should consider. I address these sequentially as I find them in your manuscript, with my most serious concerns denoted with a *. *1. Title – I do not believe this work can considered as a cohort study in the classic sense; you are not following up a group of individuals without the outcome at baseline, rather you link routinely collected statistics collected at a series of cross-sectional time points. *2. Abstract/Methods – definitions of urbanization and deprivation. In your abstract you mention a dichotomous deprivation variable, which is further elaborated upon in your methods. However, definitions of urbanization and deprivation are too vague, the sources from which the data come are not presented with sufficient detail and the reasons for their categorizations are not defined adequately in the text. Furthermore, I suspect there is a high degree of correlation between the two variables. This leaves the reader unable to assess the validity of your exposure variables for these analyses. To be more specific: you state that urbanization is defined according to five

	levels defined by the Dutch Central Bureau of Statistics, but how do they decide on these levels? Is it solely based on population density, or are other factors (correlated to your deprivation variable) also included? If it is solely based on population density (as alluded to in the description of your results, which talks about "deprivation and population density" (and not urbanization), then your data have a correlational problem because your measure of deprivation, as stated, considers population density. Controlling for each of these variables in the analysis does not necessarily overcome this issue, they could both remain significant predictions of escalation of analgesics, but still be measuring the same unidimensional construct. Further, deprivation also includes ethnic variation which seems unusual. There is nothing implicit about being from a particular ethnic group which indicates deprivation. It is a poor proxy. Finally, dichotomizing deprivation is not informative and a continuous or categorical variable should be used instead. Worse, no description of where the cut point between a deprived and a non-deprived neighbourhood is given. To significantly improve your paper, I would suggest (i) providing greater definitions or urbanicity and deprivation (ii) using a different measure of deprivation based on more accepted criteria – such as the Jarman or Mini (iii) classify deprivation as a continuous score or multi-categorical exposure variable. *3. Ecological fallacy and exposure misclassification – people's exposure to urban or deprived communities was categorized according to the location of their pharamacy. There is no way to ascertain whether this corresponds to an individual's residential neighbourhood. It could correspond to a pharmacy in their work locale, or their family's traditional pharmacy (particularly if people are really loyal to their pharmacy, ref 13). That people are loyal to a single surgery (ref 13) does not provide an argument to support linking pharmacy location to residence. A second issue relates to the ecological fallacy; people whose pharamacy is in a deprived or urban neighbourhood do not necessarily experience that level of deprivation or urbanicity. 4. Alternative modeling approach – a more sophisticated approach to their modeling of analgesic patterning over time would be some trajectory modeling (latent class analysis) to divide their sample into groups with distinct trajectories of analgesic use, if they have data on three or more time points for a large majority of the sample. This would allow you to move beyond simple (stronger, neutral, weaker analgesics to more realistic patterns, including those who moved onto stronger analgesics and then weaker ones (as symptoms remitted). P7. 5. P9-10: Sentence "The significance of the model and the adjusted R-squared were used to assess model reliability". What is model reliability? Do you mean model fit? If so, you also need to describe your modeling strategy, because the presentation of your results indicate you fitted a fully saturated model (all variables) without

	much actual fitting to find the best model. *6. Interpretation of results (1): The interpretation of your models is correct from a statistical point of view (not withstanding the aforementioned methodological concerns) but you may consider re-emphasising the importance of your paper in public health terms. The difference between analgesic escalation in the “urban (1)” vs. “less urban (2-5)” is 16.3% (starters) & 16.1% (continuation group) vs. 15.1%. This is a very small difference absolutely (though may still be important from a public health perspective). Some recontextualising the results in these terms would be useful. *7. Interpretation of results (2): Your last sentence of the discussion correctly states that your results do not speak of causal inference, but the first paragraph of the discussion erroneously assumes otherwise. As with the data on mental health (particularly psychotic disorders) and urbanization, your findings could be attributed to reverse causation – people with worsening pain move into more urban, deprived neighbourhoods as a consequence of not being able to hold down a regular job (due to ill health) or to be closer to specialist health services (traditionally located in inner cities). This possibility deserves some comment. 8. Interpretation of results (3): Non-affective psychotic disorders but not their affective counterparts or common mental disorders show patterning with urbanization and deprivation. Given the link between somatic pain and mental health might be stronger for common mental disorders than psychotic disorders, it is intriguing that their results show spatial patterning, but this is not seen at the level of common mental disorders. Some comment on this would be welcome. 9. Table 1: I think you have missed a row at the top of the table to distinguish between the starters and continuers. 10. Table 2: I don’t think anything would be lost by shortening Table 2 so that its presentation is more similar to that of Table 3. 11. Tables 2 & 3. The Odds ratio for escalation of analgesics in response to original level of analgesics – first exposure variable in each Table – is presumably just a ceiling effect – people already at level 5 have nowhere stronger to go; people at level 1 at baseline can fall further (into stronger meds). This is an obvious point, but perhaps the fact that this variable has little clinical significance should still be stated in your discussion for the reader unaware of floor/ceiling issues. 12. P12, line 18 “The majority was female…” – I think “was” should be “were”. 13. P12 line 58 and P13 line 5 – two references to population density and not urbanization – see comment 2. *14. P18, line 35 – references 3, 4 and 21 do not support the

	sentence and provide no original data relevant to their argument (the Ledebogen paper provides evidence of brain differences in people living in the city vs. those in rural areas but this is not the same as “poor mental health” – there is no evidence from this paper that these differences are in any way pathological. Better references would be the abundance of empirical data (or a systematic review) linking the social environment to (non-affective) psychotic disorders. Also, this sentence oversimplifies the literature and might mislead the reader; not all poorer mental health is linked to urbanization. 15. The second half of the discussion, beginning Line 16, p19, seemed fairly speculative.

REVIEWER	Dr Udo Reulbach Clinical Research Fellow Department of Public Health and Primary Care Trinity College Dublin
REVIEW RETURNED	28-Mar-2012

THE STUDY	1) Level of analgesic potency; figure 2: Is this an established classification? If so, please provide a reference? If not, please justify. 2) Statistical methods: I would suggest to calculate and display crude odds ratios and adjusted odds ratios. Multivariate modelling using stepwise regression models (e.g. forward selection or backward elimination) would be advisable.
RESULTS & CONCLUSIONS	1) Psychotropic prescribing (e.g. antidepressant or antiepileptics) is part of chronic pain treatment. Therefore, you would always expect that analgesic escalation is significantly associated with an increased prescribing rate of psychotropic medication 2) The title is perhaps misleading: "impact" could be misread as an indication of causation 3) I am not sure if the statements regarding "independently associated" are justified (at least by the information given in the article) 4) As mentioned in the box abocve, it might be easier for the reader (and perhaps more convincing) to: - display the crude odds ratio for factors - adjust for confounding factors - provide a stepwise regression model - calculate (if necessary) interaction terms 5) Please provide confidence intervals for proportions
REPORTING & ETHICS	A statement about research ethics should be included.
GENERAL COMMENTS	1) Please use either BE or AE spelling: e.g. urbanisation or urbanization 2) Try to simplify the talbes - they might be too busy for some readers 3) Think about providing a figure for the main finding: association urbanicity - analgesic escalation

REVIEWER	Aukje Mantel-Teeuwisse, PhD, PharmD Assistant professor Utrecht Institute for Pharmaceutical Sciences (UIPS) Pharmacoepidemiology & Clinical Pharmacology Utrecht, the Netherlands No personal conflict to disclose.
REVIEW RETURNED	19-Mar-2012

GENERAL COMMENTS	**Leue et al.** **Urbanisation and neighbourhood deprivation impact chronic pharmacological pain treatment – a large scale longitudinal cohort study in the Netherlands** Carsten Leue *et al.* aimed to assess the impact of urbanization and neighbourhood deprivation on chronic pain treatment in terms of (de)escalation of analgesic treatment. Although they were able to use a large dataset and therefore showed statistically significant effects, the clinical relevance and (policy) impact of the results are less clear to me. Another important weakness of the current study is the way results are being presented – hampering full understanding of the results - and I question some of the methodological choices by the authors (see below). Major concerns: • A major issue throughout the whole paper is the outcome measurement. The dependent variable is not dichotomous, but consists of escalation, neutral and de-escalation. In tables 2 and 3, however, escalation is the main outcome of interest as far as I understand, meaning that the authors have grouped neutral and de-escalation as the other possible outcome (?). If they wish to study multiple outcomes, they should have used a multinominal logistic regression model. Or did the authors exclude patients who experienced a de-escalation from their analysis? In their methods section, the authors assume proportional odds in the escalation and de-escalation models. I am not convinced this assumption is valid and feel that the authors should show the results for de-escalation separately. Therefore, I also question some of the results, such as described in lines 44-49 on page 13 (“negative results with escalation, i.e. positive association with de-escalation, etc...”) • The objective (page 4 lines 38-58) is not in line with the methodological choices made by the authors. Here they say that “lower levels of urbanisation and neighbourhood deprivation would be associated with less potent analgesics”. They do not study this association! In addition, the second objective (escalation of analgesics would predict prescriptions of psychotropic medication) would in my view require a different analysis with prescription of psychotropic medication yes/no as dependent variable and escalation yes/no as independent variable. The current analysis assesses whether start of

	psychotropics (and other medication) leads to escalation of pain medication, which is a different research question. • The outcome measurement is based on the level of analgesic potency as described in Figure 2. No source is provided for this figure. I am not at all an expert in pain treatment, but I could not find an adequate source for this categorisation of pain levels. I do know the WHO pain ladder, which is different from Figure 2. Especially the inclusion of anti-epileptics as a separate category seems strange to me as they have a very different indication in pain treatment (neuralgic pain). In addition, paracetamol and NSAIDs are often combined as far as I know. As the main outcome measure is completely based on this figure, this is an important issue! • The authors do not state which calendar years are captured by the data. In relation to this, it is unclear to me whether they were able to use data on urbanisation and neighbourhood deprivation that originate form (approximately) the same year(s). Reference 15 for example is dated 1993, whereas reference 16 is dated 2008. • Did the authors consider conducting a multilevel analysis? If so, how did the multilevel results relate to the presented results? If not, why? I would suspect a clustering effect within general practices. • The authors included all variables in their final model, thereby treating them as (potential) confounders. Some of these variables may however <u>modify</u> the association between urbanisation and escalation. Did the authors check for interaction? • Table 1 shows that escalation occurs in 15.1% to 16.8% of all patients, depending on level of urbanisation and/or neighbourhood deprivation. Although this yields significant increased risks (not surprisingly, given the large numbers of patients included), I question whether these differences are of clinical relevance. The authors should at least discuss this issue in their discussion section. • In tables 2 and 3 only adjusted ORs are presented. To obtain a better understanding of the results, I would prefer to also see unadjusted ORs for the association between the main independent variables of interest (i.e. level of urbanicity and neighbourhood deprivation) and the dependent variable. • Given all shortcomings in the methodology mentioned above and the question whether escalation is a valid proxy for *poor* pain treatment (see below), it is difficult to assess the merits of the discussion and the conclusion at this point in time. Minor issues: • Title: a cohort study is a longitudinal study, so there is some redundancy here • Abstract: Data-analysis is missing in the abstract • Design: the authors have used a dispensing database, not a prescription database as far as I understand. This should be

	corrected throughout the paper. • The introduction is rather short (in itself not a problem); the authors do not clearly explain why they hypothesise that pain outcomes would be poorer in urban environments and disadvantaged neighbourhoods. Anything published in the area of pain treatment? In addition, they seem to suggest that escalation of pain treatment is a sign of poor pain treatment (stronger pain treatment necessary than initially given) whereas one could also argue that it is a sign of adequate treatment (at least the physician is treating the patient with a stronger analgesic instead of "doing nothing"). Is there any evidence that the first scenario is the case and not the latter? • Page 5, lines 44-46: I do not understand why potential bias caused by patients getting hospitalised, etc was minimised by studying chronic pain treatment. Or do the authors mean that they were sure that patients were still ambulant, alive and visiting the same pharmacy because there were dispensing records for these patients during the whole study period. If so, the authors may consider explaining more clearly. • Page 6, definition of Continuation group: It says (lines 23-25) "the latter group consisted of all patients who already received analgesics in the first month of the 6-months period. Why should patients receive analgesics in first month and not – for example – in month 2 and 3 prior to the observation period? Did the authors exclude patients who used analgesics prior to the observation period, but not in the first month? • Page 6, line 52. The sentence "Statistics were executed…. Etc" is unclear to me. • Page 7, last lines is a bit unclear. It reads: "comparison of potency at the first dispensing day and the last day of prescription". The authors probably mean last day of the last prescription within the observation period. • Page 10, lines 8-30: could the authors provide ATC codes (or other codes) used to identify the concomitant mediaction? • Presentation of data in Table 1 is unclear and data given in text are difficult to match with results displayed in the table.. No clear distinction is made between Starters and Continuous users in the header of the table. This table is further complicated by the fact that the authors try to display all characteristics by level of urbanicity and neighbourhood deprivation. For urbanicity, the choice for the current grouping (level 1 vs. level 2-5 combined) seems somewhat arbitrary, especially in the light of the trends displayed in tables 2+3. For neighbourhood deprivation, data are presented for the subgroup living in a deprived neighbourhood only which is also uncommon. I would suggest to present all baseline characteristics including urbanicity and neighbourhood deprivation for both starters and continuous users in one table (so one column for starters and one column for continuous users). In an additional table the main outcome measure (escalation, neutral de-escalation) can be shown by level of urbanicity and neighbourhood deprivation in more detail. • I would prefer to delete the column "significance" in tables 2 + 3,

	as the 95% confidence intervals also show whether the association is statistically significant or not. • As results in Table 2 + 3 show, the main “driver” of pain escalation is – not surprisingly - starting with a low level of pain treatment. The authors seem to ignore this finding. • In table 3, I am not sure I understand some of the results, e.g. for SNRIs. Total SNRI use is associated with escalation (OR=1.19; 95% CI 1.02-1.40) whereas both high dose (OR=0.95; 95% CI 0.82-1.10) and low dose (OR=0.99; 95%CI 0.89-1.11) are not. • Several references are incomplete, e.g. year is missing

VERSION 1 – AUTHOR RESPONSE

Reply to reviewer’s comments, suggestions and concerns regardingManuscript ID BMJopen-2011-000731 entitled "Urbanisation and neighbourhood deprivation impact chronic pharmacological pain treatment - a large scale longitudinal cohort study in the Netherlands".

Changes in the original manuscript are marked with “track changes”.

Reviewer: J B Kirkbride

1. Title - I do not believe this work can considered as a cohort study
in the classic sense; you are not following up a group of individuals without the outcome at baseline, rather you link routinely collected statistics collected at a series of cross-sectional time points.

Reply (1):
We agree we should have been more specific. Thus, we changed the title, which now reads: Observational evidence that urbanisation and neighbourhood deprivation are associated with escalation in pharmacological pain treatment - a longitudinal population-based study in the Netherlands

2. Abstract/Methods - definitions of urbanization and deprivation. In
your abstract you mention a dichotomous deprivation variable, which is further elaborated upon in your methods. However, definitions of urbanization and deprivation are too vague, the sources from which the data come are not presented with sufficient detail and the reasons for their categorizations are not defined adequately in the text.

Furthermore, I suspect there is a high degree of correlation between the two variables. This leaves the reader unable to assess the validity of your exposure variables for these analyses. To be more specific: you state that urbanisation is defined according to five levels defined by the Dutch Central Bureau of Statistics, but how do they decide on these levels? Is it solely based on population density, or are other factors (correlated to your deprivation variable) also included? If it is solely based on population density (as alluded to in the description of your results, which talks about "deprivation and population density" (and not urbanisation), then your data have a correlational problem because your measure of deprivation, as stated, considers population density.

Controlling for each of these variables in the analysis does not necessarily overcome this issue; they could both remain significant predictions of escalation of analgesics, but still be measuring the same

one-dimensional construct. Further, deprivation also includes ethnic variation, which seems unusual. There is nothing implicit about being from a particular ethnic group, which indicates deprivation. It is a poor proxy. Finally, dichotomizing deprivation is not informative and a continuous or categorical variable should be used instead. Worse, no description of where the cut point between a deprived and a non-deprived neighbourhood is given.

To significantly improve your paper, I would suggest (i) providing greater definitions or urbanicity and deprivation (ii) using a different measure of deprivation based on more accepted criteria - such as the Jarman or Mini (iii) classify deprivation as a continuous score or multi-categorical exposure variable.

Reply (2i):
Thank you for these suggestions. We added more detail to the abstract. The main outcome measure now reads: … urbanisation (five levels) … .
Furthermore, definitions of urbanisation and neighbourhood deprivation are presented in the method section of the revised manuscript in more detail.
Page 9, lines 1 to 7 now reads (method section):
Urbanisation is defined by CBS as the number of addresses relative to the area surface, conform previous work with this variable in epidemiological studies22. Level 1 (i.e. highest level of urbanisation) consists of more than 2500 addresses per square-kilometre (km2); [level 2 = 1500 to 2500 addresses/km2, level 3 = 1000 to 1500 addresses/km2, level 4 = 500 to 1000 addresses/km2]. Level 5 (i.e. rural environment) consists of less than 500 addresses/km2; described in more detail elsewhere23. Neighbourhood deprivation was defined dichotomously (0=no, 1=yes).
Furthermore, page 9, lines 10 to 17 now reads (method section):
On the basis of empirical research in the Netherlands, NIVEL's neighbourhood deprivation index (NDI) is calculated as follows: NDI = ((ln percentage unemployed people – 3.0236)/0.37706) – ((ln average income – 2.8641)/0.14441) + ((ln population density – 7.0132)/1.06699) + ((ln percentage people of "non-western" ethnicity)/1.11147). NDIs were expressed continuously by NIVEL from low to high. Furthermore, NIVEL defined a dichotomous measure of deprivation at a cut-off of 5.5% (i.e. 885.000 people), in order to assess trends in the proportion of the Dutch population inhabiting an area with the highest NDI and for use in epidemiological research24.

Reply (2ii and 2iii):
Indeed, urbanisation and neighbourhood deprivation are representing partly overlapping constructs; nevertheless, 76.3% of the people living in an area of the highest level of urbanisation do not live in a deprived neighbourhood.
Page 9, lines 21 and 22 now reads:
… urbanisation. The majority (76%) of those living in an area of the highest level of urbanisation did not live in a deprived neighbourhood (Table 1).

Moreover, neighbourhood deprivation contains more than population density alone (see NIVEL's NDI-formula detailed above). Thus, it is informative to the reader to distinguish between both aspects. We added a Table (see below) (Table 1, page 10, line 1) to emphasize that living in a deprived neighbourhood not automatically indicates that the person in question is living at the highest level of urbanisation.

Table 1: Sample, stratified by Urbanisation and Neighbourhood Deprivation
(see original manuscript)

Legend:
The sample is described in absolute numbers for the Starter and the Continuation group, stratified by living in an urbanised area (level 1 to 5), and a dichotomous measure of neighbourhood deprivation. Furthermore, in the last two columns, tabulations are presented for living in a deprived neighbourhood

as a function of level of urbanization (e.g. 86.5% of the sample living in deprived neighbourhoods lived in an area with urbanisation level 1/Starter group) and for level of urbanisation as a function of living in a deprived neighbourhood (e.g. a minority (23.8%) of those living in an area pertaining to urbanisation level 1 lived in a deprived neighbourhood/Continuation group).

We used the dichotomous measure of deprivation by NIVEL, as this is the recommended measure in the Netherlands; this measure includes ethnic density variation based on the behavior of this variable in the correlation matrix of variables used. A description of where the cut-off point between a deprived and a non-deprived neighbourhood lies is now described in the method section, page 9 line 14 to 17 (see above).

3. Ecological fallacy and exposure misclassification - people's exposure to urban or deprived communities was categorized according to the location of their pharmacy. There is no way to ascertain whether this corresponds to an individual's residential neighbourhood. It could correspond to a pharmacy in their work locale, or their family's traditional pharmacy (particularly if people are really loyal to their pharmacy, ref 13). That people are loyal to a single surgery (ref 13) does not provide an argument to support linking pharmacy location to residence.

Reply (3a):
We agree that we cannot ascertain whether the location of a patient's pharmacy corresponds to the individual's residential neighbourhood. However, research from the Dutch "Foundation for Pharmaceutical Statistics" (Stichting Farmaceutische Kerngetallen (SFK)) shows that in the Netherlands, almost all patients make use of a pharmacy located in their area of living, 82% of patients living in a radius of 3 kilometres from their pharmacy (http://www.sfk.nl/nieuws-publicaties/PW/2003/2003-15.htm).
We added a sentence to the methods section, and completed the references (15. http://www.sfk.nl/nieuws-publicaties/PW/2003/2003-15.htm).
Page 5, lines 17 to 20 now reads (method section):
Research from the Dutch Foundation for Pharmaceutical Statistics (SFK) shows that in the Netherlands, almost all patients make use of a pharmacy located in their area of living, eighty-two percent of patients living in a radius of 3 kilometres from their pharmacy15.

A second issue relates to the ecological fallacy; people whose pharmacy is in a deprived or urban neighbourhood do not necessarily experience that level of deprivation or urbanicity.

Reply (3b):
We agree and now mention this limitation in the discussion:
Page 23, line 20 and 23 now reads:
The type of data used is subject to the possibility of ecological fallacy: people whose pharmacy is in a deprived or urban neighbourhood do not necessarily experience that level of deprivation or urbanicity.

4. Alternative modeling approach - a more sophisticated approach to their modeling of analgesic patterning over time would be some trajectory modeling (latent class analysis) to divide their sample into groups with distinct trajectories of analgesic use, if they have data on three or more time points for a large majority of the sample. This would allow you to move beyond simple (stronger, neutral, weaker analgesics to more realistic patterns, including those who moved onto stronger analgesics and then weaker ones (as symptoms remitted). P7.

Reply (4):
We appreciate this comment but we do not have enough data over three or more time points to allow such modeling including the majority of the sample. Also, while latent class analysis will obediently yield classes, this does not mean such classes really exist or indeed are valid. Our simple model of

escalation of analgesics in persistent pain states represents a realistic pattern of analgesic treatment that has clinical face validity.

5. P9-10: Sentence "The significance of the model and the adjusted R-squared were used to assess model reliability". What is model reliability? Do you mean model fit? If so, you also need to describe your modeling strategy, because the presentation of your results indicate you fitted a fully saturated model (all variables) without much actual fitting to find the best model.

Reply (5): (see also comments other reviewers regarding this point)
Fitting the best model:
In the current investigation, the fully saturated model was calculated. The only reason why we used the fully saturated model is that we did not want to withhold the reader relevant information by leaving out non-significant variables. However, all reviewers suggested we examine the best fitting model, and two reviewers requested a stepwise selection method additionally. In order to check the impact of such a method on our conclusions, we added the backward elimination method (BWE), which was additionally carried out in two separate analyses (one for the Starter group and one for the Continuation group).
Page 11, lines 6 to 9 now reads (method section):
The modeling strategy was to build, first, a fully saturated model (including all variables), in order to avoid missing relevant information by leaving out non-significant variables. Second, backward elimination was carried out to find the best model fit.

BWE for Starters:
In the fully saturated model, 31 out of all 43 available variables turned out to be significant. The BWE method delivered exactly the same 31 variables remaining significant. Thus, none of the original significant variables were omitted from the findings; no additional significant variables entered the BWE model.
Regarding adjusted ORs, most variables turned out to have exactly the same OR in both models, and those that differed did so in the second decimal digit. Thus, the original fully saturated model and the model after BWE revealed the same associations with escalation in chronic pain treatment for starters.
Page 16, lines 11 to 13 now reads (results):
In the Starter group, the original fully saturated model and the model after backward elimination revealed the same variables as associated significantly with escalation in chronic pharmacological pain treatment (Table 3).

BWE for the Continuation group:
Page 18, lines 17 to 23 now reads (results):
The saturated model showed that 22 out of 29 variables had significant associations. All these variables remained significant in the backward elimination approach. One additional variable displayed a significant association after backward elimination: ‘TCA high dosage’. The OR’s did not (16 variables), or only minimally (6 variables) differ between the fully saturated model and the backward elimination model. The only variable showing a degree of difference was ‘TCA total’ (fully saturated model: OR = 1.19 (CI: 1.06 – 1.32); backward elimination model: OR = 1.33 (CI: 1.29 – 1.36)) (Table 4).

6. Interpretation of results (1): The interpretation of your models is correct from a statistical point of view (not withstanding the aforementioned methodological concerns) but you may consider re-emphasizing the importance of your paper in public health terms. The difference between analgesic escalation in the "urban (1)" vs. "less urban (2-5)" is 16.3% (starters) & 16.1% (continuation group) vs. 15.1%. This is a very small difference absolutely (though may still be important from a public health perspective). Some recontextualising the results in these terms would be useful.

Reply (6): (see also referee Mantel-Teeuwisse comment 7))
We agree that from a public health perspective, the difference in analgesic escalation may be relevant, and have emphasized this in the discussion conform the reviewer's suggestion.
Page 21, line 9 to page 22, line 2 now reads (discussion section):
Although the absolute difference between analgesic escalation in the urban vs. less urban environments was small, this difference may be relevant from a public health perspective, given the high rate of painful conditions in the general population. Furthermore, prevention of persistent pain states is relevant with regard to costs40. A more effective treatment of persistent pain, including treatment of psychiatric comorbidity, may have a cost-saving effect. Targeting populations with painful conditions for early recognition and treatment of mental health problems may not only be cost-effective from a public health perspective, but also represent an area of considerable unmet clinical need, since opioid escalation is a frequent inflationary development in the treatment of painful conditions 41 42. Moreover, broadening the pain agenda to a better understanding of associated mental health problems could minimize failed surgery outcomes, for example in patients with undetected mental disorders. For instance, new surgical procedures were found to be more common in chronic back pain (CBP) patients with Post-traumatic Stress Disorder compared to CBP patients without43. Similarly, depression was demonstrated in 47.4 % of patients with low back pain who had no surgery, in 50% of those with one surgical procedure, and in 62.5 % of those who had undergone surgery more than once44. Influencing central pain sensitization by providing adequate antidepressant treatment in depressive conditions may help prevent surgical escalation.
Five references were added:
40. Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain 2000;84:95-103. 41. Seal KH, Shi Y, Cohen BE, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA 2012;307(9):940-7. 42. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011;305(13):1315-21.
43. Dersh J et al. Chronic pain and psychopathology: research findings and theoretical considerations. Psychosom Med 2002;64:773-86. 44. Edit V, Eva S, Maria K, et al. Psychosocial, educational, and somatic factors in chronic non-specific low back pain. Rheumatol Int 2012 Apr 3.[Epub ahead of print]

7. Interpretation of results (2): Your last sentence of the discussion correctly states that your results do not speak of causal inference, but the first paragraph of the discussion erroneously assumes otherwise. As with the data on mental health (particularly psychotic disorders) and urbanisation, your findings could be attributed to reverse causation - people with worsening pain move into more urban, deprived neighbourhoods as a consequence of not being able to hold down a regular job (due to ill health) or to be closer to specialist health services (traditionally located in inner cities). This possibility deserves some comment.

Reply (7):
We agree with the reviewer that the findings could be attributed to reverse causation, although distances to specialist health services are universally small in the Netherlands (as evidenced by the highest rate of home births in primipara in Europe). Nevertheless, we added this possibility to the discussion section.
Page 20, lines 10 to 14 now reads (discussion section):
However, the findings could also be attributed to reverse causation, i.e. patients with worsening pain may move into more urban and deprived neighbourhoods as a consequence of being disabled due to ill health. Although unlikely to entirely explain the current findings, it cannot be excluded.

8. Interpretation of results (3): Non-affective psychotic disorders but not their affective counterparts or common mental disorders show patterning with urbanization and deprivation. Given the link between

somatic pain and mental health might be stronger for common mental disorders than psychotic disorders, it is intriguing that their results show spatial patterning, but this is not seen at the level of common mental disorders. Some comment on this would be welcome.

Reply (8):
Data from the Netherlands has shown spatial patterning at the level of common mental disorders including affective disorders. We added some words to the introduction, as well as the reference by Peen and colleagues who conducted a meta-analysis on this topic (11. Peen J, Schoevers RA, Beekman AT, et al. The current status of urban-rural differences in psychiatric disorders. Acta Psychiatr Scand 2010;121(2):84-93.)
Page 4, lines 6 and 7 now reads (introduction):
…, pain is strongly influenced by comorbid common mental disorders particularly affective disorders9 10. Given evidence of urban impact on risk for common mental disorders11, including psychiatric medication prescriptions12, …

9. Table 1: I think you have missed a row at the top of the table to distinguish between the starters and continuers.

Reply (9):
Thank you. This has been corrected [Table 2, page 13 of the manuscript].

10. Table 2: I don't think anything would be lost by shortening Table 3 so that its presentation is more similar to that of Table 4.

Reply (10):
We simplified table 3 in line with Kirkbride's (see also other reviewers) suggestions, which means that the column "Significance" was removed. However, table 2 (Starter group) differs essentially from table 4 (Continuation group), which means there still is some difference in the table layout; [Table 3, page 17 of the manuscript].

11. Tables 2 & 3. The Odds ratio for escalation of analgesics in response to original level of analgesics - first exposure variable in each Table - is presumably just a ceiling effect - people already at level 5 have nowhere stronger to go; people at level 1 at baseline can fall further (into stronger meds). This is an obvious point, but perhaps the fact that this variable has little clinical significance should still be stated in your discussion for the reader unaware of floor/ceiling issues.

Reply (11): (in line with suggestions other reviewers)
We agree that mentioning this point is relevant. Thus, we added text to the method, results and discussion sections.
Page 7 lines 11 to 22 now read (method section):
… in order of analgesic potency (Figure 2). Five escalation levels were provided, based on a minor adaptation of the 3-step WHO analgesic ladder16. Level 5 and 4 are identical to WHO steps 3 (strong opioids) and 2 (weak opioids), respectively. WHO step 1 (non-opioid analgesics) was refined, in order to enable further and clinically relevant differentiation between non-opioid analgesics (level 1: paracetamol, level 2: prostaglandin inhibitors, level 3: anticonvulsants)16-20. Furthermore, anti-epileptics were divided in anticonvulsants predominantly prescribed in pain conditions (level 3a: gabapentin and pregabalin) and anticonvulsants with best evidence for epilepsy treatment (level 3b: carbamazepine, valproic acid, lamotrigine)19-21. In order to avoid prescription for indications of mood stabilisation or epilepsy, the latter group was classified at level 3b only if prescribed in combination with analgesic medication at level 1 or 2 (i.e. pain indication) (Figure 2).
We changed Figure 2 accordingly (insert page 8 line 1).
Figure 2: 5 levels of analgesic potency, modified from the WHO-analgesic ladder16

(see original manuscript)

Legend:
Level 1 (lowest potency) to level 5 (highest potency)
(a) Gabapentine, pregabaline in the absence of other anti-epileptic drugs
(b) Carbamazepine, valproic acid, lamotrigine in combination with medication at level 1 or 2
(c) Tramadol, codeine
(d) Methadone, oxycodone, hydromorphone, morphine, buprenorphine, fentanyl, sufentanil, pethidine

Page 15, line 13 to 15 now reads (results):
… observed pain medication (highest adjusted Odds Ratio (OR) 58.23 at analgesic level 1, 95% Confidence Interval (CI) 53.60 to 63.27; lowest OR 1.36 at analgesic level 4, 95% CI 1.27 to 1.45; compared to reference level 5) (Table 3).

Page 18 lines 7 to 9 now read (results):
… observed analgesics (highest adjusted OR 16.00 at analgesic level 1; 95% CI 15.20 to 16.85; lowest OR 1.55 at analgesic level 4; 95% CI 1.50 to 1.61; compared to reference level 5) (Table 4).

Page 22 lines 3 to 10 now read (discussion section):
Odds ratios for escalation of analgesics in relation to original level of analgesics may represent ceiling effects in both starter and continuation groups - patients already at level 5 have nowhere stronger to go; treatment of patients at level 1 at baseline can escalate to stronger medication. Ceiling effects may reflect the pattern of prescribing analgesics in general practice. Given these, it has been suggested that the WHO analgesic ladder is in need of updating45. For example, Vargas-Schaffer is broadening the ladder with a 4th surgical step; in the current article, however, we guide attention to treatment aspects related to underestimated mental disorder comorbidity in persistent pain states. Seven references were added (16. World Health Organization. Traitement de la douleur cancéreuse. Geneva, Switzerland: World Health Organization; 1987.; 17. Wiffen PJ, Derry S, Moore RA, et al. Carbamazepine for acute and chronic pain in adults. Cochrane Database Syst Rev 2011;(1): CD005451.; 18. Wiffen PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. Cochrane Database Syst Rev 2011;(2):CD006044.; 19. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Sys Rev 2011;(3):CD007938.; 20. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. Cochrane Database Sys Rev 2009;(3):CD007076.; 21. Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. Lancet Neurol 2011;10(5):446-56.; 45. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? – Twenty-four years of experience. Can Fam Physician 2010;56:514-7.).

12. P12, line 18 "The majority was female..." - I think "was" should be "were".

Reply (12):
Correction was carried out.

13. P12 line 58 and P13 line 5 - two references to population density and not urbanization - see comment 2.

Reply (13):
Conform other studies concerning urban-rural contrasts in the Netherlands, urbanicity was defined in relation to population density. A textual change was introduced in the result section:
Page 14, line 16 now reads (results):
… 27.6% were living in an area of the highest level of urbanisation (level 1). …
Page 15 lines 6 to 8 now read (results):

… and in areas of the highest levels of urbanisation (16.8% and 16.1% in the Continuation group, respectively 16.5% and 16.3% in the Starting group) compared to rural areas (15.1%) and non-deprived neighbourhoods (15.3.%) …

14. P18, line 35 - references 3, 4 and 21 do not support the sentence and provide no original data relevant to their argument (the Lederbogen paper provides evidence of brain differences in people living in the city vs. those in rural areas but this is not the same as "poor mental health" - there is no evidence from this paper that these differences are in any way pathological. Better references would be the abundance of empirical data (or a systematic review) linking the social environment to (non-affective) psychotic disorders. Also, this sentence oversimplifies the literature and might mislead the reader; not all poorer mental health is linked to urbanization.

Reply (14):
We agree with this comment and changed text and references along with reviewer's suggestion. Two meta-analyses concerning urbanisation and psychotic as well as affective disorders were added: 11. Peen J, Schoevers RA, Beekman AT, et al. The current status of urban-rural differences in psychiatric disorders. Acta Psychiatr Scand 2010;121(2):84-93. 29. March D, Hatch SL, Morgan C, et al. Psychosis and place. Epidemiol Rev 2008;30:84-100.
Page 20, lines 15 to 17 now reads (discussion):
Regardless of the underlying mechanism, results clearly echo findings of unconfounded higher rates of mental ill health in areas of higher levels of urbanisation and greater neighbourhood deprivation11 29, and suggest that the outcome of mental disorder comorbidity associated with somatic disorders shows similar predictable variation.

15. The second half of the discussion, beginning Line 16, p19, seemed fairly speculative.

Reply (15):
We agree but would argue that observational research regarding clinical practice also serves the function of asking speculative questions, helping to generate new (re-)translational research theories, and helping clinicians to recognize patterns and variation that may be relevant for their particular clinical practice. Nevertheless, given the referee's comment, we shortened this part of the discussion substantially and deleted four references.
Page 22, line 11 to page 23, line 11 now reads (discussion section):
The –speculative– question remains to what degree escalation of analgesic treatment and its association with psychotropic medication reflects therapeutic paradigms to remedy pain, treatment of psychiatric comorbidity, or a cause of psychopathology. In the Starter and the Continuation group of chronic analgesic treatment, escalation of analgesics was consistently and positively associated with the use of TCA. This prescription habit may reflect routine off-label paradigms in the pharmacological treatment of pain syndromes10 46-48. However, given the evidence regarding TCA's efficacy in pain conditions, negative rather than positive associations with escalation of analgesics should have been expected. More likely, since the association with TCAs was as strong as the association of sedatives with analgesic escalation, it may be a reflection of affective or addictive comorbidity in persistent pain, for instance in vulnerable cases of opiate-induced sensitization, tolerance and hyperalgesia49-55. Our data indicate that escalation may represent an ongoing process after even months of treatment, which occurs not exclusively in the context of environmental deprivation. Escalation may also be driven to a degree by patient factors such as opioid tolerance, opioid-induced hyperalgesia52, or disease progression.
Given the literature on this topic46-50 56, negative associations of particularly antidepressants with escalation of chronic analgesic treatment would have been expected. Nevertheless, negative associations between escalation of chronic analgesic treatment were also found, for example, with migraine treatment (Tables 3 and 4). Moreover, the use of antipsychotics was negatively associated with analgesic escalation in the Starter group - if prescribed after start of analgesic treatment. In the

Continuation group, de-escalation was specifically associated with the use of second-generation antipsychotics. This outcome is interesting and deserves further investigation, given that limited evidence for the efficacy of antipsychotics in pain conditions already exists37 38.

Reviewer: A Mantel-Teeuwisse

Carsten Leue et al. aimed to assess the impact of urbanisation and neighbourhood deprivation on chronic pain treatment in terms of (de) escalation of analgesic treatment. Although they were able to use a large dataset and therefore showed statistically significant effects, the clinical relevance and (policy) impact of the results are less clear to me.

Remark (from Leue C et al): We thank the reviewer for these comments. Pain treatment typically is carried out from a physical perspective (anesthesiological, pharmacological, surgical, physical rehabilitational). Of course, this is a legitimate approach in acute pain and chronic cancer pain and to some extent in chronic non-malignant pain. However, in persistent non-malignant pain conditions, pathways are not well understood and include important psychological pathways. Broadening the pain agenda to an understanding which includes mental health perspectives will enhance understanding of central pain sensitization and could minimize negative classical pain treatment outcomes, for instance failed back surgery or negative opioid associated consequences, especially in patients with undetected mental disorders. From a public health and clinical perspective, a more effective treatment of persistent pain, including treatment of psychiatric comorbidity, may save costs. A new focus in populations with persistent pain states on early recognition and treatment of mental health problems not only may be cost-effective, but also represents an area of unmet clinical need (see also reply 6 and 11 to Kirbride's comments). We believe that articles such as the current manuscript add to this perspective.

Major concerns:
1. A major issue throughout the whole paper is the outcome measurement. The dependent variable is not dichotomous, but consists of escalation, neutral and de-escalation. In tables 2 and 3, however, escalation is the main outcome of interest as far as I understand meaning that the authors have grouped neutral and de-escalation as the other possible outcome (?). If they wish to study multiple outcomes, they should have used a multinominal logistic regression model. Or did the authors exclude patients who experienced de-escalation from their analysis? In their methods section, the authors assume proportional odds in the escalation and de-escalation models. I am not convinced this assumption is valid and feels that the authors should show the results for de-escalation separately. Therefore, I also question some of the results, such as described in lines 44-49 on page 13 ("negative results with escalation, i.e. positive association with de-escalation, etc...")

Reply (1):
We would like to suggest respectfully that there may be a misunderstanding here, for which we are to blame as we may not have provided sufficient detail. Thus, we did not exclude patients with de-escalation from the analysis. Furthermore, the referee assumes that we constructed escalation in pain treatment as a dichotomous or binary variable. This was not the case. Since our dependent variable has three categories of natural order, we used the ordered logistic model.
Page 11, lines 11 to 13 now reads:
The ordered logistic multivariable regression model was chosen above the multinomial model, as the latter does not consider the natural order in our data regarding development of chronic pain treatment, ranging from de-escalation to neutral to escalation. Proportional odds were assumed in the models of escalation and de-escalation of analgesic treatment, and analyses inspected for violation of this assumption.
Page 11, lines 15 to 17 now reads:

Test on the proportional odds assumption showed significance, which gave us the confidence to use the ordered logistic model. If a determinant was positively associated with escalation of analgesics, absence of this variable was associated negatively with escalation or positively with de-escalation in analgesic treatment (and vice versa). This offered advantage compared to separate models for escalation and de-escalation (such as consistency of model estimates) and avoided double use of patients with a neutral development of analgesic treatment.

2. The objective (page 4 lines 38-58) is not in line with the methodological choices made by the authors. Here they say "lower levels of urbanisation and neighbourhood deprivation would be associated with less potent analgesics". They do not study this association!
In addition, the second objective (escalation of analgesics would predict prescriptions of psychotropic medication) would in my view require a different analysis with prescription of psychotropic medication yes/no as dependent variable and escalation yes/no as independent variable. The current analysis assesses whether start of psychotropics (and other medication) leads to escalation of pain medication, which is a different research question.

Reply (2):
We agree we should have formulated the objectives more accurately.
Page 4, line 16 to page 5 line 2 now reads:
We examined the hypothesis that chronic pharmacological pain treatment of hospital outpatients and patients in primary care would show escalation of analgesics in association with the level of urbanisation and neighbourhood index of deprivation. It was predicted that the highest levels of urbanisation and neighbourhood deprivation would be associated with escalation of analgesic treatment to more potent pain medication (e.g. tramadol, morphine, methadone, etc.). Furthermore, we examined the hypothesis that prescriptions of psychotropic medication (e.g. antidepressants, antipsychotics, mood stabilizers, etc.) would be associated with escalation or de-escalation of analgesics in patients prescribed chronic analgesic treatment. Study hypotheses were specified before inspection of the data.
The abstract now reads:
Objective: To examine whether urbanisation and neighbourhood deprivation are associated with analgesic escalation in chronic pharmacological pain treatment, and whether escalation is associated with prescription of psychotropic medications.

3. The outcome measurement is based on the level of analgesic potency as described in Figure 2. No source is provided for this figure. I am not at all an expert in pain treatment, but I could not find an adequate source for this categorisation of pain levels. I do know the WHO pain ladder, which is different from Figure 2. Especially the inclusion of anti-epileptics as a separate category seems strange to me as they have a very different indication in pain treatment (neuralgic pain). In addition, paracetamol and NSAIDs are often combined as far as I know. As the main outcome measure is completely based on this figure, this is an important issue!

Reply (3):
(For justification of adapted WHO-analgesic ladder see reply 11 to Kirbride's comments, and manuscript changes (including new Figure 2, insert page 8 line 1, and added references).)
Chronic pharmacological pain treatment, in malignant and non-malignant pain states, includes conventional and unconventional (frequently off-label) approaches, with the WHO pain ladder as a starting point. Anti-epileptics are a part of this, not exclusively in neuropathic pain, which is deducible from the added references (see reply 11 to Kirkbride: 17. Wiffen PJ, Derry S, Moore RA, et al. Carbamazepine for acute and chronic pain in adults. Cochrane Database Syst Rev 2011;(1): CD005451.; 18. Wiffen PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. Cochrane Database Syst Rev 2011;(2):CD006044.; 19. Moore RA, Wiffen PJ, Derry S, et al.Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Sys Rev

2011;(3):CD007938.; 20. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. Cochrane Database Sys Rev 2009;(3):CD007076.).
Moreover, our data are confirming this prescription habit in general practice by revealing an escalation ceiling curve due to the adapted WHO steps presented in our article.

4. The authors do not state which calendar years are captured by the data. In relation to this, it is unclear to me whether they were able to use data on urbanisation and neighbourhood deprivation that originate form (approximately) the same year(s). Reference 15 for example is dated 1993, whereas reference 16 is dated 2008.

Reply (4):
All data captured a calendar period from May 2008 to September 2009. We added this sentence at page 6 line 15.
Actualization of the data was carried out on a yearly basis by CBS from 1993 until present.

5. Did the authors consider conducting a multilevel analysis? If so, how did the multilevel results relate to the presented results? If not, why? I would suspect a clustering effect within general practices.

Reply (5):
Multilevel analysis (MLA) or stratified approaches would make allowance for potential cluster effects within general practises. In theory, pain medication development can partly be influenced by general practitioners (GP) choices. The impact of this would implicate that true standard errors might be somewhat larger then the ones reported. However we do not have information allowing us to group patients at the level of GP practice. Thus, it is not possible to investigate this. Comparable to post-hoc subgroup analyses in RCTs, in observational research, MLA would help to identify and minimize confounding if carried out on a theory-driven basis. Otherwise, MLA would gain coincidental results without any practical application. As far as confounding factors are concerned, we dealt with all available information in the model.

6. The authors included all variables in their final model, thereby treating them as (potential) confounders. Some of these variables may however modify the association between urbanisation and escalation. Did the authors check for interaction?

Reply (6):
We did not carry out a posthoc interaction analysis, as this seems artificial and not hypothesis-driven. In our view, interactions should be considered if there is strong theory- driven grounds from pathways or practise to do this.

7. Table 2 shows that escalation occurs in 15.1% to 16.8% of all patients, depending on level of urbanisation and/or neighbourhood deprivation. Although this yields significant increased risks (not surprisingly, given the large numbers of patients included), I question whether these differences are of clinical relevance. The authors should at least discuss this issue in their discussion section.

Reply (7):
(Please see reply 6 to Kirkbride's comments)
We note that referee Kirkbride points to the public health relevance of these findings; clinical and public health relevance has been described in reply to Kirkbride's earlier comment, as well as the manuscript changes in relation to these.

8. In tables 3 and 4 only adjusted ORs are presented. To obtain a better understanding of the results, I would prefer to also see unadjusted ORs for the association between the main independent variables of interest (i.e. level of urbanicity and neighbourhood deprivation) and the dependent

variable.

Reply (8):
We decided to leave out crude ORs, as in our view they do not add information since they are not corrected for coincidental variation in the other variables. Given the amount of figures/tables, we refrained from adding non-vital information. However, we remain open to editorial advice on this issue.

9. Given all shortcomings in the methodology mentioned above and the question whether escalation is a valid proxy for poor pain treatment (see below), it is difficult to assess the merits of the discussion and the conclusion at this point in time.

Reply (9):
For changes regarding the discussion see reply to Kirkbride.

Minor issues:
10. Title: a cohort study is a longitudinal study, so there is some redundancy here.

Reply (10):
We agree there is some redundancy. Please see our reply to Kirkbride comment 1.

11. Abstract: Data-analysis is missing in the abstract

Reply (11):
The abstract now reads:
Methods: Ordered logistic multivariate model evaluating analgesic treatment.

12. Design: the authors have used a dispensing database, not a prescription database as far as I understand. This should be corrected throughout the paper.

Reply (12):
Data collection is described in the method section: … “This data source consists of anonymous longitudinal prescription records from a representative sample of pharmacies and dispensing GPs, covering 73% of the Dutch nationwide medication consumption of outpatients and primary care patients. The computerized medication-dispensing histories contain data regarding dispensed medications, type of prescriber, dispensing date, dispensed amount of medication, prescribed dosage, and length of prescription.” …
The abstract reads now:
Design: Longitudinal analysis of a population-based routine dispensing database in the Netherlands.

13. The introduction is rather short (in itself not a problem); the authors do not clearly explain why they hypothesize that pain outcomes would be poorer in urban environments and disadvantaged neighbourhoods. Anything published in the area of pain treatment? In addition, they seem to suggest that escalation of pain treatment is a sign of poor pain treatment (stronger pain treatment necessary than initially given) whereas one could also argue that it is a sign of adequate treatment (at least the physician is treating the patient with a stronger analgesic instead of "doing nothing"). Is there any evidence that the first scenario is the case and not the latter?

Reply (13):
Given the restricted word count, we decided to introduce the topic clearly but shortly. To our knowledge, there is no evidence linking chronic pain outcomes to urban environments.
Since affective mental disorders are associated with urbanicity (11. Peen J, Schoevers RA, Beekman

AT, et al. The current status of urban-rural differences in psychiatric disorders. Acta Psychiatr Scand 2010;121(2):84-93.) and pain conditions are frequently influenced by mental ill health, the question rises whether urban environments influence pain as well. This is of clinical importance since conventional chronic pain management may worsen outcome, especially in vulnerable populations (41. Seal KH, Shi Y, Cohen BE, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA 2012;307(9):940-7. 42. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011;305(13):1315-21.), and more targeted psychiatric treatment may be required. (see also reply to Kirkbride)

14. Page 5, lines 44-46: I do not understand why potential bias caused by patients getting hospitalised, etc was minimised by studying chronic pain treatment. Or do the authors mean that they were sure that patients were still ambulant, alive and visiting the same pharmacy because there were dispensing records for these patients during the whole study period. If so, the authors may consider explaining more clearly.

Reply (14):
Page 5 line 21 and 22 now reads:
… by studying chronic pharmacological pain treatment, because there were dispensing records for these patients during the whole study period.

15. Page 6, definition of Continuation group: It says (lines 23-25) "the latter group consisted of all patients who already received analgesics in the first month of the 6-months period. Why should patients receive analgesics in first month and not - for example – in month 2 and 3 prior to the observation period? Did the authors exclude patients who used analgesics prior to the observation period, but not in the first month?

Reply (15):
Indeed, the continuation group was selected as receiving analgesics in the first month of the 6-month period prior to the observation period, in order to build a contrast to the Starter group.
Page 19, lines 40 to 44 now reads: (results)
Over time, the escalation process continues even after the first 6 months of chronic analgesic treatment. In the Starter group, opioid-analgesics (level 4/5) were dispensed in 29.8% of patients living in a deprived neighbourhood. In contrast, 42.8% of patients in deprived neighbourhoods used opioids in the Continuation group, after one year of prescription. A similar, but attenuated development was seen at urbanisation level 1 and level 2 to 5 (Table 2).
Page 22, lines 22 to page 23, line 2 now reads: (discussion section)
Our data indicate that escalation may represent an ongoing process after even months of treatment, which occurs not exclusively in the context of environmental deprivation. Escalation may also be driven to a degree by patient factors such as opioid tolerance, opioid-induced hyperalgesia52, or disease progression. (see also Kirkbride)
Without contrasting both groups, these observations would have been missed.

16. Page 6, line 52. The sentence "Statistics were executed.... Etc" is unclear to me.

Reply (16):
We deleted this sentence.

17. Page 7, last lines is a bit unclear. It reads: "comparison of potency at the first dispensing day and the last day of prescription". The authors probably mean last day of the last prescription within the observation period.

Reply (17):
Page 8, lines 11 and 12 now reads:
Confirmation of escalation was based on the comparison of analgesic potency at the first dispensing day and the last dispensing day within the observation period.

18. Page 10, lines 8-30: could the authors provide ATC codes (or other codes) used to identify the concomitant medication?

Reply (18):
We can provide ATC codes on request but prefer not to add these to the text; ACT-codes won't inform the general practice reader further and would complicate the reading unnecessarily.

19 a. Presentation of data in Table 2 is unclear and data given in text are difficult to match with results displayed in the table.. No clear distinction is made between Starters and Continuous users in the header of the table. This table is further complicated by the fact that the authors try to display all characteristics by level of urbanicity and neighbourhood deprivation. For urbanicity, the choice for the current grouping (level 1 vs. level 2-5 combined) seems somewhat arbitrary, especially in the light of the trends displayed in tables 3+4. For neighbourhood deprivation, data are presented for the subgroup living in a deprived neighbourhood only, which is also uncommon.

Reply (19a):
We apologize - uploading the original word document to the journal PDF cut the header.
A new table is presented (including distinctive header for Starter and Continuation Group). See also reply 10 to Kirkebride's suggestions. In our opinion, arbitrary distinction between urbanisation levels helps to differentiate and cuts volume.

19 b. I would suggest presenting all baseline characteristics including urbanicity and neighbourhood deprivation for both starters and continuous users in one table (so one column for starters and one column for continuous users). In an additional table the main outcome measure (escalation, neutral de-escalation) can be shown by level of urbanicity and neighbourhood deprivation in more detail.

Reply (19b):
Thank you for your comment. In fact, we are not quite sure that we understand what you are suggesting. Would it mean one table more? Moreover, relevant information as mentioned in reply 15 regarding the contrast between Starter en Continuation groups would disappear….

20. I would prefer to delete the column "significance" in tables 3 + 4, as the 95% confidence intervals also show whether the association is statistically significant or not.

Reply (20):
The "significance" column was deleted from both tables.

21. As results in Table 3 + 4 show, the main "driver" of pain escalation is - not surprisingly - starting with a low level of pain treatment. The authors seem to ignore this finding.

Reply (21):
Thank you - please see reply 11 to Kirkbride's suggestions, where this issue also came up.

22. In table 4, I am not sure I understand some of the results, e.g.
for SNRIs. Total SNRI use is associated with escalation (OR=1.19; 95% CI 1.02-1.40) whereas both high dose (OR=0.95; 95% CI 0.82-1.10) and low dose (OR=0.99; 95%CI 0.89-1.11) are not.

Reply (22):
As mentioned earlier (see reply 4 to Kirkbride's comment), we unfortunately do not have enough data on three or more time points for a large majority of the sample, in order to deliver a more sophisticated approach including more time points. This would have helped us to understand more detailed aspects of prescription habits (like low dose start of TCA for instance [due to neuropathic pain indication] or possible dose upgrading in case of depression manifesting itself later in course). Given absence of these longitudinal data, no useful interpretation of dose differences is possible. Thus, we deleted low and high doses from table 4.

23. Several references are incomplete, e.g. year is missing.

Reply (23):
Thank you spotting this. We have corrected.

Reviewer: U Reulbach

1) Level of analgesic potency; figure 2: Is this an established classification? If so, please provide a reference? If not, please justify.
Reply: See reply 11 to Kirkbride, and reply 3 to Mantel-Teeuwisse.

2) Statistical methods: I would suggest calculating and displaying crude odds ratios and adjusted odds ratios.
Reply: See reply reply 8 to Mantel-Teeuwisse.

Multivariate modelling using stepwise regression models (e.g. forward selection or backward elimination) would be advisable.
Reply: See reply 5 to Kirkbride.

3) Psychotropic prescribing (e.g. antidepressant or antiepileptics) is part of chronic pain treatment. Therefore, you would always expect that analgesic escalation is significantly associated with an increased prescribing rate of psychotropic medication.
Reply: We agree, however the question remains whether this association represents escalation or de-escalation, as discussed in our manuscript. Furthermore, based on that, the debate needs guidance with respect to psychiatric treatment in vulnerable cases of persistent pain

4) The title is perhaps misleading: "impact" could be misread as an indication of causation.
Reply: See reply 1 to Kirkbride, and reply 10 to Mantel-Teeuwisse.

5) I am not sure if the statements regarding "independently associated"
are justified (at least by the information given in the article).
Reply: We deleted "independently" from the abstract and the article.

6) As mentioned in the box above, it might be easier for the reader
(and perhaps more convincing) to:
- Display the crude odds ratio for factors
Reply: see # 2.
- Adjust for confounding factors
Reply: See reply 5 and 6 to Mantel-Teeuwisse.
- Provide a stepwise regression model
Reply: see # 2 (reply 5 to Kirkbride)
- Calculate (if necessary) interaction terms

Reply: See reply 5 and 6 to Mantel-Teeuwisse.

7) Please provide confidence intervals for proportions
Reply: It is possible to provide CIs for proportions in table 2. However, with regard to table complexity, as mentioned by reviewer Mantel-Teeuwisse, this would not enhance reading comfort. Therefore we have not included CI's but remain open to editorial advice on this issue.

8) A statement about research ethics should be included.
Reply: Data were anonymous, reflecting routine GP practice. In the Netherlands, no ethical commission approval is required in these circumstances.

9) Please use either BE or AE spelling: e.g. urbanisation or urbanization.
Reply: British English has been applied.

10) Try to simplify the tables - they might be too busy for some readers.
Reply: the "significance" column has been deleted from both tables. Furthermore, we removed high and low dosage in the antidepressants rows.

11) Think about providing a figure for the main finding: association
urbanicity - analgesic escalation.
Reply: Unfortunately we cannot comply as we have already included the maximum number of figures/tables allowed.

VERSION 2 – REVIEW

REVIEWER	James B Kirkbride Sir Henry Wellcome Research Fellow University of Cambridge, UK
REVIEW RETURNED	06-Jun-2012

THE STUDY	The authors' use of deprivation as a dichotomous variable is unsatisfactory but could be easily remedied.
RESULTS & CONCLUSIONS	Table 1 requires improvement.
REPORTING & ETHICS	No mention of any ethical approval is given in the main body of the manuscript I reviewed.
GENERAL COMMENTS	Dear authors The revised version of your paper is much clearer and you have attempted to address many of the comments you received. The paper is the better for it. Having read your work I still have the following concerns: 1. P9, line 7-9: the new sentence beginning "Urbanisation is defined by CBS…" does not read correctly in English after the comma, and should be corrected. 2. Neighbourhood Deprivation Index – thank you for providing the additional information about this variable. However, I am unsure of the utility of using this variable in your analysis. This dichotomized variable only distinguishes between the upper most deprived neighbourhoods (5.5%) and the remainder. It would be preferable to use the raw scores from NIVEL, rather than this dichotomous variable. Furthermore, the NDI includes population density in it as a measure, which means your urbanicity and deprivation variables are likely to be highly correlated.

	3. Table 1 – the presentation of the data in this table is very unclear. I cannot see easily how the %s add up or why the NDI only appears on the first two rows of the urbanicity variable. This needs greater clarification 4. P20, line 32-33. Line beginning “Although unlikely to entirely explain the current findings…”. Why would this be unlikely? It could be entirely possible. You have no way of deducing the strength of this possibility in the data you have presented. It is important to have acknowledged the possibility of reverse causation, thank you for doing so, but I would drop this line. 5. A statement on ethical approval for this study is required according to the BMJ Open reviewer criteria, but I couldn’t see one. This could be easily addressed, I’m sure. Well done again on all the changes, the paper reads extremely well now, and will be further improved after consideration of the above points.

REVIEWER	Reulbach, Udo Trinity College Dublin, Public Health and Primary Care There are no competing interests.
REVIEW RETURNED	25-May-2012

GENERAL COMMENTS	The authors have responded sufficiently to all my queries. I have no further comments. From my point of view, the quality of the article has greatly improved.

REVIEWER	A.K. Mantel-Teeuwisse, PhD Assistant professor Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands
REVIEW RETURNED	23-May-2012

GENERAL COMMENTS	The manuscript has been improved by the clarifications given and changes made by the authors. In my view, the paper still lacks sufficient focus, especially in the discussion section. It is clear that the authors advocate to “broaden the pain agenda to an understanding that includes mental health perspectives”. However, at least I missed a clear and concise link with the aim of this study – to assess whether the level of urbanization and neighbourhood deprivation are associated with analgesic escalation. One may hypothesise that mental illness comes into play, but this has not been studied as such in detail. For example, the authors conclude “Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of adding psychotropic medications, suggesting pain outcomes in part reflect area influences affecting mental health.” I am not sure the last part of this sentence can be concluded from the presented data. The increased risk of escalation when using psychotropic medication is an independent risk, adjusted for many factors including level of

	urbanization and neighbourhood deprivation. Similarly, both urbanization and neighbourhood deprivation are independently associated with escalation as well (although I am not sure the remark by Dr Kirkbride about the high correlation between these two has been sufficiently addressed). But this does not necessarily mean that low level of urbanization and neighbourhood deprivation lead to use of psychotropic medication (as a proxy for mental illness) which then leads to dose escalation. Maybe I am missing the point here; I would be happy if the authors could further share their thoughts on this. I am also still a bit puzzled by the definition of "continuous use". I now understand that the authors wish to compare starters with those who have started 6 months earlier. Did all of the continuous users use analgesics during the whole period of six months prior to the observation period? If that was a requirement (I suppose so), it may be helpful to amend Figure 1 to reflect this use during all of these months. Table 2: I do understand that the authors need to make some choices in which data to present. However, I feel that the main study outcome, % of escalation, neutral or de-escalation is now a bit "hidden" in table 2. The justification for comparing level 1 with levels 2-5 is still lacking (why not another combination?). Ideally, these % would therefore be presented for each level and for neighbourhood deprivation yes/no. In the current table, % are not displayed for those not living in a deprived neigbourhood, which hampers proper interpretation of the % escalation in deprived neighbourhoods. Tables 3-4: If the editor agrees I would prefer to present unadjusted ORs as well. The absolute risk difference of (approximately) 1.5% in escalation between different levels of urbanicity would mean that for every 67 patients treated with analgesics, 1 additional escalation would be expected in the lowest level of urbanicity as compared to levels 2-5. One may indeed argue that this is important from a public health perspective. The discussion of the clinical implications of this finding could be a bit more focused in my opinion. The authors now directly assume that this is due to mental illness and elaborate on that (e.g. page 21, lines 46 and further). But I am not completely convinced this can be concluded – see comment above – and would therefore refrain from too much elaboration in that direction.

VERSION 2 – AUTHOR RESPONSE

Reply to reviewer's comments regarding Manuscript ID BMJopen-2011-000731.R1 entitled "Observational evidence that urbanisation and neighbourhood deprivation are associated with escalation in chronic pharmacological pain treatment - a longitudinal population-based study in the Netherlands" (after reviewer's recommendation for publication).

Changes in the original manuscript are marked with "track changes".

Reviewer Udo Reulbach

The authors have responded sufficiently to all my queries. I have no further comments. From my point of view, the quality of the article has greatly improved.

Reviewer A.K. Mantel-Teeuwisse

-The manuscript has been improved by the clarifications given and changes made by the authors. In my view, the paper still lacks sufficient focus, especially in the discussion section. It is clear that the authors advocate to “broaden the pain agenda to an understanding that includes mental health perspectives”. However, at least I missed a clear and concise link with the aim of this study – to assess whether the level of urbanization and neighbourhood deprivation are associated with analgesic escalation.

One may hypothesise that mental illness comes into play, but this has not been studied as such in detail. For example, the authors conclude “Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of adding psychotropic medications, suggesting pain outcomes in part reflect area influences affecting mental health.” I am not sure the last part of this sentence can be concluded from the presented data. The increased risk of escalation when using psychotropic medication is an independent risk, adjusted for many factors including level of urbanization and neighbourhood deprivation. Similarly, both urbanization and neighbourhood deprivation are independently associated with escalation as well (although I am not sure the remark by Dr Kirkbride about the high correlation between these two has been sufficiently addressed). But this does not necessarily mean that low level of urbanization and neighbourhood deprivation lead to use of psychotropic medication (as a proxy for mental illness) which then leads to dose escalation. Maybe I am missing the point here; I would be happy if the authors could further share their thoughts on this.

Reply: We agree this needs further clarification. Our argument was based not only on the independent risks linking urban environment and escalation on the one hand and psychotropic medication and escalation on the other, but also on published findings on links between urban environment and mental health on the one hand and urban environment and use of psychotropic medication on the other (11. Peen J, Schoevers RA, Beekman AT, et al. The current status of urban-rural differences in psychiatric disorders. Acta Psychiatr Scand 2010;121(2):84-93. 12. Crump C, Sundquist K, Sundquist J, et al. Neighborhood deprivation and psychiatric medication prescription: a Swedish national multilevel study. Ann Epidemiol;21(4):231-7.). Given these findings, the abstract conclusion now reads as follows:
“Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of adding psychotropic medication prescriptions. These findings suggest that pain outcomes and mental health outcomes share factors that increase risk and remedy suffering”.

-I am also still a bit puzzled by the definition of “continuous use”. I now understand that the authors wish to compare starters with those who have started 6 months earlier. Did all of the continuous users use analgesics during the whole period of six months prior to the observation period? If that was a requirement (I suppose so), it may be helpful to amend Figure 1 to reflect this use during all of these months.

Reply: In order to ensure comparability, we measured analgesics’ escalation during an interval of the same length for the Starter and the Continuation group. Regarding “continuous use”, yes, we wished to compare starters with those who had started analgesic treatment six months earlier. No, we did not follow up whether the Continuation group used analgesics over the entire six month interval prior to the observation period. The Starter group, however, did not use any analgesics during the six month

interval prior to the observation period. Technically, we could have measured escalation of continuing patients over a longer time interval, but then the definition of escalation between both groups would be different and a direct comparison of starters and continuing patients would have become difficult. We added the following text to the legend of Figure 1: “Patients in the Continuation group received first prescription of analgesics in month 1 of the pre-observation period; there was no follow-up whether analgesics were continued over the entire six-month interval prior to the observation period. The Starter group did not use any analgesics during the six month interval prior to the observation period”.

-Table 2: I do understand that the authors need to make some choices in which data to present. However, I feel that the main study outcome, % of escalation, neutral or de-escalation is now a bit “hidden” in table 2. The justification for comparing level 1 with levels 2-5 is still lacking (why not another combination?). Ideally, these % would therefore be presented for each level and for neighbourhood deprivation yes/no. In the current table, % is not displayed for those not living in a deprived neighbourhood, which hampers proper interpretation of the % escalation in deprived neighbourhoods.

Reply: We added a column % of escalation in “non deprived neighbourhoods” to Table 2. Given the small difference with column “urbanicity level 2-5” our choice to summarize levels of urbanisation is justifiable. Please note that we had to make choices regarding data presentation in order to guarantee overview and to avoid diluted results. In our opinion, this table now makes for comfortable reading, without withholding any relevant information.
Thus, table 2 now reads: See page 13 of the original manuscript (also up-loaded Reply2-(Word)-Table2).

-Tables 3-4: If the editor agrees I would prefer to present unadjusted ORs as well.

Reply: Of course we remain open to editorial advice in this issue. As we stated earlier, we decided to leave out crude ORs, as in our view they do not add information since they’re not corrected for coincidental variation in the other variables. Given the already large amount of figures/tables, and the amount of information that would need to be added, we refrained from adding non-vital information. With regard to the complexity of the tables, as mentioned earlier by reviewer Mantel-Teeuwisse and Reulbach, our aim is to guarantee overview and readability.

-The absolute risk difference of (approximately) 1.5% in escalation between different levels of urbanicity would mean that for every 67 patients treated with analgesics, 1 additional escalation would be expected in the lowest level of urbanicity as compared to levels 2-5. One may indeed argue that this is important from a public health perspective. The discussion of the clinical implications of this finding could be a bit more focused in my opinion. The authors now directly assume that this is due to mental illness and elaborate on that (e.g. page 21, lines 46 and further). But I am not completely convinced this can be concluded – see comment above – and would therefore refrain from too much elaboration in that direction.

Reply: Given the well-known increase of health care costs in complex patients with frequent utilization of health care, with or with out psychiatric comorbidity, only a small number of patients is required to cause relevant clinical cost changes (41. de Jonge P, Huyse FJ, Stiefel FC. Case and Care Complexity in the Medically Ill. Med Clin N Am 2006;90:679-92.). Thus, even without psychiatric comorbidity, escalation of analgesics in chronic pain states is of clinical relevance. See also up-loaded Reply2-(Word)-PDF-Figure, which is not added to the origianal manuscript; adapted from de

Jonge et al. Med Clin N Am 2006.
Regarding somatic and psychiatric multi-morbidity, please see our reply above on first comment of reviewer Mantel-Teeuwisse.
We added a sentence to the discussion (page 21, lines 13 to 16 of the original manuscript): “Given the well known increase of health care costs in complex patients with frequent utilization of health care, with or with out psychiatric comorbidity, only a small number of patients is required to cause relevant clinical cost changes 41”.

Reviewer James B Kirkbride

1. P9, line 7-9: the new sentence beginning “Urbanisation is defined by CBS…” does not read correctly in English after the comma, and should be corrected.

Reply: P9, original manuscript line 6-8 reads correctly in English now: “Conform previous work, and in line with the classification developed by CBS, level of urbanisation was defined as the number of addresses relative to area surface 22”.

2. Neighbourhood Deprivation Index – thank you for providing the additional information about this variable. However, I am unsure of the utility of using this variable in your analysis. This dichotomized variable only distinguishes between the upper most deprived neighbourhoods (5.5%) and the remainder. It would be preferable to use the raw scores from NIVEL, rather than this dichotomous variable. Furthermore, the NDI includes population density in it as a measure, which means your urbanicity and deprivation variables are likely to be highly correlated.

Reply: Unfortunately, as we stated in the reply to reviewers’ comments regarding Manuscript ID BMJopen-2011-000731 (03-May-2012), we do not have raw NDI scores from NIVEL. Although neighbourhood deprivation and urbanicity are correlated, additional association of deprivation with escalation of analgesics exists over and above urbanisation, indicating that other parameters than population density are involved too.
We added a sentence to the discussion (page 20, lines 10 to 13 of the original manuscript): “Furthermore, although neighbourhood deprivation and urbanicity are correlated, additional association of deprivation with escalation of analgesics exists over and above urbanisation, indicating that other parameters than population density are involved too”.

3. Table 1 – the presentation of the data in this table is very unclear. I cannot see easily how the %s add up or why the NDI only appears on the first two rows of the urbanicity variable. This needs greater clarification

Reply: (See also up-loaded Reply2-(Word)-Table1) We hope the presentation of the data is clear now. The NDI itself is not available in our data but the dichotomous variable Neighbourhood Deprivation (yes/no) is. All percentages are added up to clarify their calculation. Adapted Table 1 and the legend are added to the original manuscript (original manuscript page 10, line 7 to 27).
The legend now reads: “The sample is described in absolute numbers for the Starter and the Continuation group, stratified by living in an urbanised area (level 1 to 5), and a dichotomous measure of neighbourhood deprivation. Furthermore, in the last column, tabulation is presented for living in a deprived neighbourhood as a function of level of urbanisation (e.g. in the Starter group, 86.5% of the sample living in deprived neighbourhoods lived in an area with urbanisation level 1)”.

4. P20, line 32-33. Line beginning “Although unlikely to entirely explain the current findings…”. Why would this be unlikely? It could be entirely possible. You have no way of deducing the strength of this possibility in the data you have presented. It is important to have acknowledged the possibility of reverse causation, thank you for doing so, but I would drop this line.

Reply: P20, line 13-15 of the original manuscript now reads: “However, the findings could also be attributed to reverse causation, i.e. patients with worsening pain may move into more urban and deprived neighbourhoods as a consequence of being disabled due to ill health”.
Thus, we dropped the line suggested by reviewer Kirkbride.

5. A statement on ethical approval for this study is required according to the BMJ Open reviewer criteria, but I couldn’t see one. This could be easily addressed, I’m sure.

Reply: A statement on ethical approval is added at the end of the article now: “Data were anonymous, reflecting routine general practice. In the Netherlands, no ethical commission approval is required for analyses using anonymous data acquired in routine practice” (page 25, line 17 to 19 of the original manuscript). This statement is identical to what has been stated earlier (reply to reviewers’ requests concerning manuscript ID BMJopen-2011-000731, and the submission format, which has already been noticed by the editor).

-Well done again on all the changes, the paper reads extremely well now, and will be further improved after consideration of the above points.

Reply: Thank you for the compliment!