Author's response to reviews

Title: Care-seeking behaviour of adolescents with knee pain: a population-based study among 504 adolescents

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Author's response to reviews: see over
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Title: Care-seeking behaviour of adolescents with knee pain: a population-based study among 504 adolescents

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At first, we would like to express our thanks to the reviewers for their comments and suggestions for improving the manuscript. Reviewer 2 provided some excellent feedback for improving the manuscript. We have read through all of them thoroughly and made changes accordingly. We have provided a copy of the original comments below with our responses formatted in bold while in-text citations are in italic. Changes in the manuscript text have been marked using track changes. We have carefully addressed all comments from the reviewers and believe the manuscript has improved considerably. We hope the revision is satisfactory.

**Reviewer 1**
**Reviewer:** Gabriel Herrero-Beaumont

Reviewer's report:
Knee pain is a common condition among adolescents yet badly characterize. This aims to describe the determinants of care-seeking behaviour among adolescents with knee pain and to investigate how many adolescents with knee pain who are currently under medical treatment for their knee pain. It is the first study among adolescents recruited from a large population-based cohort.

1. The following sentence could be move to Results section: “A total of 11 adolescents could not remember if their knee pain was initiated by a traumatic event or it had an insidious onset why these 11…”

   **Response:**
   We acknowledge your point. Initially we discussed where the sentence would best belong in the manuscript. We believed the sentence was most closely related to the methodology of the study (the interpretation of responses that were later transformed into data that was used for our result section) and decided that the most logical place would be in the paragraph “Interpretation of the adolescents’ response”.

2. Regarding the statistical analysis it is not clear whether a Bonferroni adjustment was done.

   **Response:**
   Based on the suggestions from Rothman and colleagues (1990), no adjustments for multiple comparisons were applied.

Changes to text:
*P*<0.05 was considered statistically significant and no adjustments were made for multiple comparisons [22]. *Stata* (Version 11) was used for all statistical analyses.
Reviewer 2
Reviewer: Daniel McWilliams
Reviewer's report:
My understanding of this manuscript and general points This study examines risk factors for adolescents seeking medical advice about knee pain. It uses a nested design based upon sampling from an extant cohort of adolescents from 4 schools, and then examines some different research questions. I believe that some parts of this study are better designed, and the findings appear more robust, than other parts. I also believe that certain important biases will influence the findings, and that these need to be addressed. I have not read the papers describing the parent cohort for this study. I believe that any salient findings/descriptors should be mentioned in the text of this manuscript with a citation.

Main comments
1. The first part of the analysis focuses upon selecting adolescents with current knee pain and attempting to identify the cause or event associated with onset of knee pain. Traumatic and insidious onsets were not found to differ in some important ways, such as current pain severity. Table 2 describes this analysis, and it would be good to see significance highlighted on the table.
   Response
   We acknowledge that some readers would be more interested in p-values instead of precision as obtained from confidence intervals. We have added comparisons between groups stratified on gender.

Changes to text:
Data analysis
Demographics, participation in sports, pain severity, pain duration, percentage who sought medical care, percentage who were under treatment and EQ-5D score were stratified for gender and onset of knee pain. Adolescents with traumatic onset of knee pain were compared with adolescents with insidious onset of knee pain using Student’s t-test, Wilcoxon Rank Sum test or proportion test depending on data type.

P<0.05 was considered statistically significant and no adjustments were made for multiple comparisons [24]. Stata (Version 11) was used for all statistical analyses.

Also see changes to table 2.

2. The second set of analyses attempted to identify those with knee pain that sought medical care from their GP. In general, I thought that the risk factors for knee pain were fairly well controlled for (perhaps a better indicator of mental health might have been useful), but risk factors for consulting a GP did not appear to be controlled for. I think that people who have consulted their GP regularly or recently are more likely to consult their GP about a new problem. Also, the authors state that socioeconomic status does not influence GP consulting in a country with universal health care. In the UK, which also has universal health care, this is certainly not considered to be the case. So it would be really useful to see socioeconomic status controlled for.
   Response:
   Thank you for your comment on our well controlled analyses. We agree that it would have been advantageous to investigate if controlling for
individual socioeconomic state (SES) would alter our estimates and the conclusions. However no individual specific socioeconomic status was obtained from their parents. However, the four upper secondary schools where adolescents were recruited from all have students from low, middle and high socioeconomic status. We have reworded parts of the methods and discussion to avoid inferring that socioeconomic status does not influence contact to GP.

**Changes to text:**
There are four upper secondary schools in the area where the study was conducted. The four schools all have students from low, middle and high socioeconomic status. However no individual specific socioeconomic status was obtained. All four schools agreed to participate and all adolescents were invited to answer an online questionnaire as part of their physical education lessons. Adolescents currently exempted from physical education because of pain or similar conditions still participated in the study.

One of the strengths of the study is that Danish citizens have free and unlimited access to health care through the GP. Therefore the care-seeking behaviour is not biased due to unequal access to health care. However, even though Denmark offers equal free access to health care through the GP, we cannot rule out that socioeconomic state may influence our results. Although the equal access improves the external validity of the results to countries with similar health care systems, our findings may not be generalisable to countries with unequal access to health care.

3. Cross-sectional studies are more likely to capture long-term cases of medical conditions. Were adolescents with previous knee pain (that had resolved) excluded? If not, this must surely be the strongest risk factor for current knee pain.

**Response**
In this cross-sectional study we included all adolescents with current knee pain. Therefore no adolescents without knee pain were included in any of the analyses. Based on the self-reported long pain duration we agree that our study most likely captures those with long-term knee pain. The study was designed to describe the determinants of care-seeking behaviour among adolescents with current knee pain and to investigate how many adolescents with current knee pain who are currently under medical treatment for their knee pain. When reading our manuscript we can see that there are several places were it would be relevant to emphasize that the study investigates current knee pain.

**Changes to text:**
See example from the purpose of the study:
The purpose of this study was therefore to describe the determinants of care-seeking behaviour among adolescents with current knee pain and to investigate how many adolescents with current knee pain are currently under medical treatment
for their knee pain.

4. The final analysis attempted to determine the risk factors for adolescents to have their knee pain treated by their GP. I found this to be the weakest of the analyses for a few reasons. Firstly, it had the lowest number of participants, because it was essentially a subgroup analysis. Also, there must surely be an interaction between adolescent and practitioner in deciding upon the course of treatment. Adolescents attending different clinics of GP’s were not controlled for (as far as I could see). This must be a large influence in deciding the course of treatment. Also, my reading of the methods suggested that some of the GPs decided upon referrals to hospitals or advised a period of inactivity. If the adolescent followed the GP’s advice, they were classified as being “not under treatment”. As far as I can tell, following GP’s advice should be the outcome measure for studying adolescents. Analysing GP practise should be out of this study’s remit, and it seems to be a very different outcome measure that was not well-described. I did not find the rationale for this analysis convincing, and I recommend that the authors reconsider the definition of the outcome measure in this section of the manuscript, and whether it should be included.

Response:
The regression analysis showing the association between “currently being under medical treatment” and key variables includes just as many adolescents as the first regression analysis (n=504). There is no subgroup analysis involved in this analysis. We have emphasized in the “Data analyses” that both regression analysis included all 504 adolescents.

We agree that there will likely be an effect of which general practitioner the adolescents is affiliated to. However in our analysis we were not interested in the effect of the approximately 60 different GPs the cohort was listed with, but to see how many adolescents from a population-based cohort that were currently being treated for their knee pain and which factors were associated to currently being treated. We agree with your point that an optimal design to investigate treatment (and if the adolescents follow the GP’s advice) will be in a prospective study. This is also why we suggest a prospective evaluation of the clinical pathway for adolescents with knee pain in future studies. We would like to keep the analysis in the manuscript as we believe the results are important as it shows that adolescents with an insidious onset are less likely to be under medical treatment, even after adjusting for pain severity and pain duration.

We have added a section in the discussion to emphasise that there could be an effect of which GP the adolescent is affiliated to, and that a prospective design would be a more appropriate approach to study treatment of adolescent knee pain.

Changes to text:
No information was collected on which specific GP the adolescent was listed with. There may be a wide variation in GPs’ diagnosis and prescribed treatments and
future studies should control for the potential heterogeneity between GPs.

A large percentage of the adolescents had sought medical care, but only 18% were currently being treated, even though they all reported current knee pain. Future studies should aim to prospectively describe the clinical pathway of adolescents with knee pain in primary care and survey the number of consultations, the types of prescribed treatment and compliance. Further, we need to describe the reasons for treatment termination in primary and secondary care and investigate if it is related to an absence of pain or because no further reductions in pain can be achieved by intervening.

5. One general point with both of the first two analyses is that 4 different schools were analysed, but school was not controlled for in the analyses. Ideally, multi-level modelling is supposed to be most appropriate for examining school-associated effects. Alternatively, describing the school populations would be useful. If this has been performed in previous studies published from this cohort, it can be summarised in the text with a citation. Other major comments

Response:
We acknowledge your suggestion. After consulting our statistician he suggested us to adjust for the potential cluster effect between adolescents within each school. We have updated all the analyses and added the information to “Data analyses”. The adjustment for cluster effect only caused small changes to the estimates in the regression analysis why our conclusions are identical to the previous ones.

Changes to text:
Estimates in table 3 and 4 have been updated.

The association between “seeking medical care” and “currently under treatment”, respectively, and the dependant variables: gender, EQ-5D (categorised in quartiles based on EQ-5D index score), body mass index (BMI; categorised into quartiles), pain duration, onset of pain (traumatic versus insidious onset) were tested through logistic regression analyses using robust variance estimates that adjust for within-cluster correlations within schools [22]. All 504 adolescents were included in both logistic regression analyses. Categorical dependent variables were entered into the logistic regression analyses by using dichotomous indicator variables using the built-in indicator function of Stata.

6. The EQ5D in table 4 seems to be the opposite of a dose-response gradient. Can this be explained?

Response:
After the cluster adjustment and switching the reference group to the lowest quartile of BMI, there is no longer any significant difference between the four quartiles. The reference group was changed so both BMI and EQ-5D use the lowest quartile as reference group.

7. In table 4, “contact to GP” is significant. I did not notice this variable in the methods. Can
you clarify please?

Response:
If students reported knee pain in the online questionnaire, they were asked if they had contacted their general practitioner (GP) because of their knee pain. As contacting their GP most likely increases the odds of receiving treatment, we included this variable in the analysis. We have added this information to the manuscript.

Changes to manuscript:
Furthermore “Contact to GP” was included into model with the independent variable “currently being under treatment”.

- Minor Essential Revisions
1. Univariate analyses should be briefly described in the text before the adjusted statistics are described.

   Response
   These have been added.

Changes to the text:
Seeking medical care
59% of the adolescents sought medical care for their knee pain. The unadjusted analysis showed that EQ-5D, pain severity, onset of knee pain and pain duration were associated with seeking medical care.

2. P values should be 3 decimal points every time.
   Response:
   Three decimals have been added for all comparisons throughout the manuscript.

3. All the empty cells in table 3 should be filled with the appropriate analyses.
   Response:
   The reason for the empty cells is that interaction was found between gender and onset of knee pain in the multivariate analysis. The interaction is not possible to model in the univariate analysis. To fill out 2x2 cells in the univariate column we would need to conduct a separate analysis stratified on gender. The stratified analysis would not be comparable to the other univariate analysis as they include both males and females. To ensure all analyses were done properly we consulted our statistician.

4. Multivariate analysis has more than one dependent variable, or repeated measures. Multivariable analysis has more than one independent variable, but one dependent variable. Can you make sure that the terminology is correct.
   Response
   We have altered the terminology to dependent/independent variables.

5. Problems with written English. Abstract, Introduction, sentence #2. Background,
paragraph#1, last sentence “An insidious onset….etc”. (The use of “why” is incorrect).
Background, paragraph#3, sentence#1 “The purpose…..”. Methods, Interpretation of
Adolescents Response, paragraph#1, last sentence “A total of 11…” (The use of ‘why’ is
incorrect). Discussion, Care seeking behaviour sentence#1, ‘Almost 60%…’. Discussion,
Implications for clinical researchers, sentence beginning with ‘This means that 40%.’?

Response
A native English speaker has proof-read the entire manuscript to ensure
no grammatical errors.

6. What % of the APA2011 cohort was approached to perform this study?

Changes to text
Adolescents were recruited from a population-based cohort (Adolescent Pain in
Aalborg 2011, the APA2011-cohort), which consists of 4,007 adolescents aged 12-19
years. In this analysis, only adolescents from the upper secondary schools were
included (2,846 adolescents, 71% of the entire cohort) [16]. Two papers have
previously been published from the APA2011-cohort. They describe pain and
muscular mechanisms in the subsample diagnosed with PFP [8, 17].

7. Describe socioeconomic variation within the study population.

Response:  
The four schools all have students from low, middle and high socio
economic status. However no individual specific socioeconomic status
was obtained.

Changes to text:
There are four upper secondary schools in the area where the study was conducted. 
The four schools all have students from low, middle and high socioeconomic
status. However no individual specific socioeconomic status was obtained. All four
schools agreed to participate and all adolescents were invited to answer an online
questionnaire as part of their physical education lessons.

8. Did adolescents not taking physical education (due to poor health) miss the opportunity
to register for the study?

Response:  
Students exempt from physical education because of knee pain or
similar still had the opportunity to answer the online questionnaire, as
they were required to participate in the first part of the physical
education lessons.

Changes to text:
Adolescents currently exempted from physical education because of pain or similar
conditions still participated in the study.

9. Pain data was collected for the whole body. Will pain data for other body sites be
published elsewhere? Has it already been published elsewhere? If so, please cite all
Response
Prevalence rates of self-reported pain from the other regions are under review. The previous 2 papers this cohort have been added to the method section.

Changes to text:
Adolescents were recruited from a population-based cohort (Adolescent Pain in Aalborg 2011, the APA2011-cohort), which consists of 4,007 adolescents aged 12-19 years. In this analysis, only adolescents from the upper secondary schools were included (2,846 adolescents, 71% of the entire cohort) [16]. Two papers have previously been published from the APA2011-cohort. They describe pain and muscular mechanisms in the subsample diagnosed with PFP [8, 17].

10. Were previous knee injuries recorded?
Response:
No. Previous knee injuries were not recorded. In this cross-sectional study we were only interested in current knee pain.

Changes to text:
See changes to text under “Major comments number 3”.

11. Please define endpoint of “under treatment”, perhaps giving examples.
Response:
The different responses interpreted as “under treatment” is given in the section called “Interpretation of the adolescents’ response”. However, we are in doubt if we have misinterpreted your comment. Please allow us to correct if necessary.

12. state what p value is taken as significance in the methods (ie. P<0.05).
Response:
We have added this information to the data analysis section.

Changes to the manuscript:
P<0.05 was considered statistically significant.

13. In non-responder analysis, please give the numerical values of the data for each group, instead of just p values. Some p values are almost significant.
Response:
Numerical values have been added.

Changes to text:
Responders (n=504) had a higher pain severity with 28% reporting daily pain versus only 15% among non-responders (the other categories were: more than once per week 19% vs. 15%, weekly 29% vs. 22%, monthly 24% vs. 47% (p<0.001). No difference was observed in gender distribution (70.5 vs. 73%, p=0.583), median BMI (21.58 vs. 21.38, p=0.934) or average EQ-5D index score (0.75 vs. 0.78, p=0.093) compared to non-responders (n=166).
14. In Discussion, please report primary outcomes first, then report secondary and post hoc subgroup analyses.
   
   Response:
   We have rewritten the beginning of the discussion.

Changes to text:

The main findings are that lower EQ-5D index score, higher pain severity and traumatic onset of knee pain were associated with both seeking medical care and being under treatment. Females with insidious onset of knee pain do not seek medical care as often as females with traumatic onset and adolescents of both genders with insidious onset are less likely to be under medical treatment.

15. Clearly label 95% CIs and IQRs in the tables.
   
   Response:
   We have added 95% CIs and IQR to all variables.

Changes to manuscript:

See changes table 3

16. Pain duration in months (median seems to be 24) is difficult to interpret as each significant OR is only 1.01. Perhaps division into tertiles would be easier to interpret?
   
   Response:
   As suggested we have changed the analyses so the odds refer to every 10 month increase in pain duration.

Changes to text:

See table 3 and 4.

17. Please clarify in the statistical methods section how each stratum of each co-variable has its own OR (95% CI) in the multivariable analysis. When I perform logistic regression (on SPSS), a single OR (95% CI) is yielded for each variable (ie. Average change across all strata). Were the variables entered more than once?
   
   Response:
   To use a categorical variable as a dependant variable within a regression analysis you can use categorical predictor variables (also called indicator variables or dummy variables) which is a standard feature in Stata. It transforms the categorical variable into multiple dichotomous variables that allows for direct input and interpretation in the multivariate analysis. For more information see "Multivariable Analysis: A Practical Guide For Clinicians By Mitchell H. Katz or Applied Regression Analysis and Other Multivariable Methods by Kleinbaum. We acknowledge this was not clear in the previous version of our manuscript and we have added the information to the "Data analysis" section.

Changes to text
Categorical dependent variables were entered into the logistic regression analyses by using dichotomous indicator variables using the built-in indicator function of Stata.

- Discretionary Revisions
Please report percentages of all important numbers in the Results.
  Response:
  Percentages have been added to all important numbers in the result section of the manuscript.

Changes to text
The majority of the sample was female with a median age of 17 (Table 1). A total of 158 (31.7%) reported knee pain with traumatic onset while 346 (68.3%) reported insidious onset of pain (Table 2). An unadjusted analysis showed no difference in pain frequency between those with traumatic onset of pain and those with insidious onset of pain (p=0.589).

Treatment
47 adolescents with an insidious onset of knee pain were currently under treatment with 38 (81%) of those receiving exercise, with or without the addition of surgery. An additional 6 (13%) adolescents were referred for further investigation at the hospital and 3 (13%) received advice from their GP on reducing their activity level. Among adolescents with traumatic onset of knee pain, 41 were currently under treatment with 34 (83%) receiving exercise, with or without the addition of surgery. An additional 8 (20%) adolescents were referred for further investigation at the hospital (Figure 1).

Give prevalence of PFP in adolescents in Introduction.
  Response:
  This has been added.

Changes to text:
Between 19 and 31% of adolescents report knee pain [3, 5, 6] with Patellofemoral Pain (PFP) being one of the most common knee conditions among adolescents with a prevalence of approximately 7% [6-8].

Did the adolescents have low BMI values? Are other classification criteria, rather than the WHO, appropriate? Maybe tertiles?
  Response:
  As with the EQ-5D score we have redone the analyses and converted the BMI values into quartiles.

Changes to text:
The association between “seeking medical care” and “currently under treatment”, respectively, and the dependant variables: gender, EQ-5D (categorised in quartiles based on EQ-5D index score), body mass index (BMI; categorised into quartiles),
pain duration, onset of pain (traumatic versus insidious onset) were tested through logistic regression analyses using robust variance estimates that adjust for within-cluster correlations within schools [22].

Also, see changes in table 3 and 5.
Reviewer 3
Reviewer: Gulcan Gurer
Reviewer's report:

I read the manuscript titled "Care-seeking behaviour of adolescents with knee pain: a population-based study among 504 adolescents". They had performed an online questionnaire to 2,846 adolescents aged 15-19 in four upper secondary schools and had interrogated specifically the knee pain of participants. In outcome, they had found that females with insidious onset of knee pain didn't seek medical care as often as those with traumatic onset and adolescents of both genders with an insidious onset were less likely to be under medical treatment.

Subject of the article is not interesting but I think this manuscript can be published in your journal.

Response to reviewer:
Thank you for your comment.