Author's response to reviews

Title: Generalized Joint Hypermobility in childhood is a possible risk for development of joint pain in adolescence: A cohort study

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Author's response to reviews: see over
Point-by point response to the comments regarding the paper: Generalized Joint Hypermobility in childhood is a possible risk for the development of joint pain in adolescence: A cohort study

Referee 1 (Verity Pacey)

Major revisions:

1. Throughout the discussion the authors refer to their results relating to children with GJH and no pain at baseline. I cannot locate anywhere in the methodology or results section that states children included in this study with GJH at baseline, also had no pain at baseline. If this is the case, it should be added within the methodology section (study population). If this is not the case, the discussion requires revision.

   Answer: We agree with the reviewer that it can be stated clearer, and this has now been done.

   Action: Added in line 110-111: “Participants for this study were selected according to their GJH status and pain status at baseline. All children of Caucasian origin, with no pain at baseline, and categorized..”

2. Within the methodology section of the paper the authors stated that statistical significance required that the 95%CI did not include 1. However, throughout the abstract, results and discussion of the paper, this interpretation of the results is usually not mentioned, in particular in the first two sentences of the discussion. Where it is mentioned it is often referred to as ‘close to significance’, which suggests to me that it would be significant with greater numbers. If this is what the authors believe is the case, it should be stated in the discussion. Suggestive terms such as ‘close to significance’ should be avoided being used so regularly throughout the paper.

Furthermore, much of the discussion within the body of this paper relates to these non-statistically significant results as if they are significant, e.g. line 253-254, and line 274-276. More discussion related to the results found to be statistically significant, rather than the interpretation of the non-significant findings as if they were significant, would strengthen the paper overall.

   Answer: We thank the reviewer for pointing this, and have performed a clearer distinction of significant, and non-significant. Also in the statistical section, it has now been defined more clearly, what is significant and what is defined as a tendency to significance.
Action: We have changed in the following sections:

Abstract:

Line 39-41: “Children with GJH had three times higher risk of developing joint pain in adolescence, although this association did not fully reach statistical significance (GJH5: 3.00, 95% [0.94-9.60])”

Line 46-50: “This study has suggested a possible link between GJH and joint pain in the adolescent population. GJH was both a contributing and a predictive factor for future pain. Further, adolescents with GJH had lower self-reported physical function and higher BMI, with no influence on measured physical function. Additional studies with larger sample sizes are needed to confirm our findings.”

Results:

Line 231-235: “In the unadjusted logistic regression analysis, children with GJH (independent of cut-off level) had three times higher risk of reporting joint pain at follow-up, although this association did not reach statistical significance (OR [95% CI]; GJH4: 2.76 [0.81-9.38], GJH5: 2.96 [0.84-8.60], GJH6: 2.77 [0.85-9.05]) (Table 2).”

Line 226-230: “In the longitudinal analysis, children with GJH based on the GJH5 definition at baseline had a threefold increased risk for developing joint pain at follow-up, although this association did not reach statistical significance (GJH5; 3.00 [0.94-9.60]) (Table 3).”

Line 243-244: “Children with GJH had a lower vertical jump height; however, the difference was not statistically significant (GJH4 p=0.33, GJH5 p=0.15, GJH6 p=0.12).”

Discussion:

Line 247-254: “The result of this study suggested that GJH5 without pain in childhood at eight or ten years of age is a possible predictive factor for developing joint pain in adolescence, although this association did not reach the predefined level of statistical significance. It also indicated that there was a positive association between GJH and experiencing joint pain at 14 years of age.”

Line 259-260: “More clearly, the current study proposes that GJH was a predictor...”

Line 268-269: “Our current results suggest that..”

Conclusion:

Line 324-330: “This study suggests a possible link between GJH in childhood and joint pain in adolescence.”
Children at eight or ten years of age with GJH5 and no pain at baseline were found to have a threefold increased risk of developing pain at 14 years of age. Although this association did not reach the predefined level of statistical significance future studies with a bigger sample size are needed to confirm these findings.

3. The reliability and validity has not been mentioned for many of the measures described within the Methodology section of the paper e.g. MABC, vertical jump height, RAOS-child. This information should be provided within this section.

Answer: We thank the reviewer for giving us the opportunity to add this important information to the study. This has now been added.

Action: Line 148-150: “Dynamic balance was measured using the zig-zag jumping test from Movement ABC-2 [28], which recently has been found to be a valid instrument for measuring activities among children [29].”

Line 157-160: “Muscle explosive force was measured using the child’s height and vertical jump on two legs (i.e. Abalakov’s test). This is a widely used test to investigate explosive strength or power, but to our knowledge reliability or validity has not been documented in children or adolescents [30].”

Line 166-172: “The KOOS-child has been validated in children aged 10-12 years, but only covers the knee [31]. The RAOS-child questionnaire consists of questions about the physical functioning of three body parts: the knee, hip and ankle. Similar modifications have been done to the KOOS questionnaire for adults [32], called RAOS [33] which has been found to be a valid, reliable and responsive outcome measurement. These properties have not been tested for the RAOS-child, but it is assumed that the questionnaire has similar properties as the adult version. “

4. Definitions need to be included for all terms within the tables i.e Table 1 dislocation/subluxation, soft tissue rheumatism; Table 4 all physical activity data; Table 5 the 95% area, ant-post range, med-lat range and COP path length. Where necessary, this information should also be included within the Methodology section.
**Answer:** We agree with the reviewer, and it is now stated both in the tables and in the methodology section.

**Action:** Added in tables:

Table 1:

1. BMI = Body Mass Index (calculated as = bodyweight in kg/ height in m*height in m)

2. Dislocation/subluxation is based on the question: ‘Have you experienced dislocation or subluxation in one joint’.

3. Soft tissue rheumatism is based on the question: ‘Have you experienced epicondylitis, tenosynovitis or bursitis?’

Table 2 and 3:

1. $<\text{GJH}_4 \text{ versus } \geq \text{GJH}_4 = 3 \text{ versus } 4 \text{ or more positive Beighton tests out of a maximum of } 9 \text{ Beighton tests}$

2. $<\text{GJH}_5 \text{ versus } \geq \text{GJH}_5 = 4 \text{ versus } 5 \text{ or more positive Beighton tests out of a maximum of } 9 \text{ Beighton tests}$

3. $<\text{GJH}_6 \text{ versus } \geq \text{GJH}_6 = 5 \text{ versus } 6 \text{ or more positive Beighton tests out of a maximum of } 9 \text{ Beighton tests}$

Table 4:

1. $<\text{GJH}_4 \text{ versus } \geq \text{GJH}_4 = 3 \text{ versus } 4 \text{ or more positive Beighton tests out of a maximum of } 9 \text{ Beighton tests}$

2. Activity level is based on the question: ‘At what level are you practising your primary sports activity?’ With the answering categories: Subelite, elite or exercise level.

3. Hours per week is based on the question: ‘How many hours a week are you practicing your primary sports activity?’ Measured as the group average.

Table 5:

1. 95% confidence ellipse area of the Center of Pressure ($\text{cm}^2$)

2. Anterior-posterior displacement (cm)

3. Medial-lateral range displacement (cm)

4. Centre of pressure path length (mm)

Added in method section:
Line 145-147: “The averages for these were used to calculate the following parameters: 95% confidence ellipse area of the centre of pressure (in cm²), anterior-posterior displacement (in cm), medial-lateral range displacement (in cm) and centre of pressure path length (in mm).”

Line 178-182: “Additional questions on musculoskeletal health in relation to prior injuries (‘Have you experienced dislocation or subluxation in one joint’ yes/no; ‘Have you experienced epicondylitis, tenosynovitis or bursitis?’ yes/no), physical activity (‘Do you do any sports in you spare time?’ yes/no; ‘At what level are you practising you primary sports activity?’ Elite/sub elite/exercise level; ‘How many hours a week are you practicing your primary sports activity?’ ).”

5. BJHS and the Brighton criteria is referred to within the abstract and background, however there are no results presented in relation to children with BJHS. Did any of the cohort meet the diagnostic criteria for BJHS at baseline, follow-up or both? If so, have they been included in or excluded from the analysis? This information should be provided to truly define the cohort being studied.

Answer: We agree that this information about BJHS seems to be a bit confusing, since we do not use this information in the selection of the participants. In this follow-up study we use one of the criteria from the clinical examination, namely arthralgia, in diagnosing BJHS as our primary outcome for joint pain. It will be stated clearer that the information from the examination for BJHS is used as an outcome measure for joint pain, and that the cohort is a group of children with no pain at baseline.

Action: Changed in abstract, line 31-37: “This was a longitudinal cohort study nested within the Copenhagen Hypermobility Cohort. All children (n=301) were examined for the exposure, GJH using the Beighton test at baseline at either 8 or 10 years of age and then re-examined respectively when they reached 14 years of age. The children were categorized into two groups based on their number of positive Beighton tests using different cut points (i.e., GJH4 defined as either < 4 or ≥ 4, GJH5 and GJH6 were similarly defined). The outcome of joint pain was defined as arthralgia as measured by the Brighton criteria from the clinical examination.”

Changed in methods, line 110-111: “Participants for this study were selected according to their GJH status and pain status at baseline. All children of Caucasian origin, with no pain at baseline, and categorized.”

Minor revisions:
6. There are a number of small grammatical errors throughout the paper, which would benefit from review. These errors do not result in any confusion with regards to the results, however would improve the ‘readability’ of the paper if corrected.

**Answer:** We agree in this comment.

**Action:** A native English speaker with scientific expertise has now edited the paper.

7. The paper would benefit from the use of “child-first language” consistently employed throughout eg ‘children with GJH’ rather than ‘this group’ line 71, ‘this children population’ line 131.

**Answer:** Thank you for this comment, we agree with the reviewer, this has now been changed.

**Action:** Changed in line: 76-77: “…preventive strategies for children with GJH.”
In line 140-141: “..satisfactory reproducibility for a children population aged 10-14.”
In line 184-185: “.. in a population of school children in 3rd and 5th grade”.

8. GJH4, GJH5, GJH6 requires explanation in the abstract before these abbreviations being used.

**Answer:** We agree with the reviewer and we have rewritten this section so that the abbreviations are clearer.

**Action:** Line 31-36: “This was a longitudinal cohort study nested within the Copenhagen Hypermobility Cohort. All children (n=301) were examined for the exposure, GJH using the Beighton test at baseline at either 8 or 10 years of age and then re-examined respectively when they reached 14 years of age. The children were categorized into two groups based on their number of positive Beighton tests using different cut points (i.e., GJH4 defined as either < 4 or ≥ 4, GJH5 and GJH6 were similarly defined).”

9. Line 60-61 states the prevalence of GJH4 for adolescents; however, the references used relate to children aged 8 and 10 years. The term adolescent should be revised.

**Answer:** Thank you, we agree with the reviewer.
**Action:** It has now been changed, line 65-66: “The prevalence of GJH4 for children has been estimated..”

10. Line 73-75. The second aim should be revised to be in line with the aims stated in the abstract

**Answer:** Thank you for the opportunity to correct this. We have changed this, so the aim in abstract and method are in accordance.

**Action:** In abstract it is now rewritten: line 28-30: “The aims for this study were to investigate the association between GJH and development of joint pain and to investigate the current GJH status and physical function in Danish adolescents”.

In methods line 84-87: “The current study had two aims. The first was to investigate the association between GJH and development of joint pain in adolescents. The second was to investigate the current GJH status and self-reported physical functioning and objectively measured physical function by re-examination, respectively, six and four years after the enrolment.”

11. Line 93-94. Clarification of the “need to notify” should be provided.

**Answer:** According to the Danish regulations/rules this examination of the cohort, both the physical examination and the questionnaires, were categorized as non-invasive, and therefore we got the answer from The Regional Scientific Ethical Committee that it was not necessary to apply for approval of the study.

**Action:** Changed in line 104-105: “The Regional Scientific Ethical Committee for Southern Denmark did not consider this study to be invasive and therefore, no ethics approval was warranted”

12. Line 195. The percentage of children participating is reported as 82%, which I calculate to be from the number invited to participate, however, 68% of those eligible to participate in the study were examined. This information is clearly provided in Figure 1 if you do the calculations, but would benefit from being stated clearly in this section of the text also.

**Answer:** We agree that this could be stated clearer.

**Action:** Information has been added in line 216: “In total, 301 (82% of invitees) children of ...”
13. Line 269 – 271 requires clarification within the text as to what association and risk is being referred to - joint pain

**Answer:** We are investigating one association throughout the article, the association between having GJH and developing joint pain. This association is investigated in two different ways, longitudinally and cross-sectionally. In the referred sentences we have now clarified that it is the longitudinal association between GJH and joint pain we are referring to.

**Action:** Added in line 295-296: “...could have weakened the association of having GJH as a child and developing joint pain in adolescence”

14. Line 292 of the Discussion states the same examiners performed the tests at follow-up and at baseline, however the Methods states they were all blinded to the baseline GJH status. Was a different examiner used for GJH at baseline and at follow-up?

**Answer:** The same examiners performed the clinical tests at baseline and at follow-up with six and four years in between. Since each examiner examined a random number of adolescents, and therefore did not test precisely the same child at baseline and at follow-up, and the fact that there were six and four years in between, we do not expect the examiners to remember which status these children had at baseline when testing at follow-up. Therefore, we anticipate that the examiners to be blinded for health status at follow-up.

**Action:** Added in line 317-320: “The examiners performing the clinical tests were the same as in the baseline studies, and since each examiner tested a random number at baseline and at follow-up, meaning that they did not test precisely the same child at both test rounds, it is anticipated that examiners were blinded to the health status of the examined children.”
Referee 2 (Asharaf El Metwally)

The following comments are major 2, 4, 6, 7, 13, 14, 15. Other comments are minor.

Abstract

1. "Generalized Joint Hypermobility (GJH) is a risk factor for pain persistence". This is based on only one study, I would say "there is some evidence that....."

**Answer:** We thank the reviewer for pointing this and we have now changed this.

**Action:** Changed line 25-26: “There is some evidence that indicates that Generalized Joint Hypermobility (GJH) is..”

2. "and to re-examine their current GJH status and physical function" this has nothing to do with the background sentence. I would add another sentence before this to justify this aim.

**Answer:** We agree with this comment, and to clarify the aims for this study we have now changed it so the aim in abstract and method are in accordance.

**Action:** In abstract it has now been written: line 28-30: “The aims for this study were to investigate the association between GJH and development of joint pain and to investigate the current GJH status and physical function in Danish adolescents.”

In methods line 84-87: “The current study had two aims. The first was to investigate the association between GJH and development of joint pain in adolescents. The second was to investigate the current GJH status and self-reported physical functioning and objectively measured physical function by re-examination, respectively, six and four years after the enrolment.”

3. "among Danish adolescents previously...." I would remove this as this is mentioned later in methods.

**Answer:** Thank you for this comment.

**Action:** We have now removed this in line 30: “previously investigated”
4. "All children (n=301) were re-examined at 14 years". Reexamined means that they were examined before that time. No mention of the first assessment in the abstract. If you write reexamined, them you need to tell the reader about the first examination.

**Answer:** Thank you for pointing this and we agree with your comment. The section has now been rewritten to clarify the longitudinal and cross-sectional analyses/methodology used in this study.

**Action:** Line 32-38: “All children (n=301) were examined for the exposure, GJH using the Beighton test at baseline at either 8 or 10 years of age and then re-examined respectively when they reached 14 years of age. The children were categorized into two groups based on their number of positive Beighton tests using different cut points (i.e., GJH4 defined as either < 4 or ≥ 4, GJH5 and GJH6 were similarly defined). The outcome of joint pain was defined as arthralgia as measured by the Brighton criteria from the clinical examination. Other outcome measures of self-reported physical function and objective physical function were also collected. “

5. "GJH in childhood (eight and ten years) was a threefold (non-significant) risk factor". I would rephrase it. "Children with GJH had three times higher risk of developing joint pain in adolescence, although this association did not reach statistical significance (GJH5: 3.00, 95% [0.94-9.60])."

**Answer:** Thank you for this comment; we have now rewritten this sentence.

**Action:** Line 39-41: “Children with GJH had three times higher risk of developing joint pain in adolescence, although this association did not reach statistical significance (GJH5: 3.00, 95% [0.94-9.60]).”

6. "This study indicates a relationship between GJH and joint pain in adolescence both as a contributing and a predictive factor for pain development. Further, adolescents with GJH had lower self-reported physical function and higher BMI, but currently with no influence on measured physical function”. I would say "this study suggests a possible link between ,..... And ...... The study also shows that ....... Remove "but
We agree that the current text concludes too strong on results that are not significant, and it has now been rewritten.

Action: line 46-50: “This study has suggested a possible link between GJH and joint pain in the adolescent population. GJH was both a predictive and a contributing factor for future pain. Further, adolescents with GJH had lower self-reported physical function and higher BMI, with no influence on measured physical function. Additional studies with larger sample sizes are needed to confirm our findings.”

Introduction

7. Same comment as in abstract. The study has two aims, all background text is about the first aim and not the second. Please add a background paragraph for the second aim

Answer: Thank you for this comment; we have written in line 60-62 the prevalence background data regarding our second aim, and we have now also added a paragraph about physical function.

Action: Line 78-83: “The connection between GJH and physical functioning has been investigated. Some studies have shown an association between GJH with neuromuscular and motor development dysfunction [16-18] as explained by a poor proprioception [19, 20]. Other studies have found conflicting evidence where children with GJH had a higher vertical jump height, had better static balance, had faster speed skills, and faster reaction skills than children without GJH [8][7].”

8. Language checking and editing by a native speaker would improve the clarity of information.

Answer: We agree with this comment.

Action: A native English speaker with scientific expertise has now edited the paper.

Methods
9. Clear to me and good methodology, stat analysis plan seems reasonable. Only comment is language editing to improve clarity.

Answer: Thank you very much for this comment, and regarding the language it has now been edited.

Action: A native English speaker with scientific expertise has now edited the paper.

Results

10. Line 211. It says "and therefore no adjusted model", not clear what it means

Answer: In line 175-77 we defined the variables (age and sex measured at baseline), that we would use to test for confounding. In line 188-191 we explain how we have analysed to find the confounders and which criteria we have used as confounders. When testing, respectively, age (baseline) and sex, the $\beta$-coefficient of GJH did not change more than 10%, and therefore there were no confounders for this association. In addition, in table 3 it is written as NR (not reported). We have rewritten this sentence now to clarify this both in the sentence and in table 3.

Action: line 229-230: “..and therefore, it was not possible to conduct an adjusted model.”. In table 3: NC = not conducted.

11. Line 220: "There was non-significantly lower vertical jump height in children with GJH" do your mean statistical significance? In that case it should be written it was lower in children with GJH. However the difference was not statistically significant ($P=,,,,$)

Answer: We intended to write that the children with GJH had a lower vertical jump height, but the findings were not statistically significant. We have now changed it, to avoid any misinterpretation, and the p-values for the three different cut-offs have now been added.

Action: line 243-244: “Children with GJH had a lower vertical jump height; however, the difference was not statistically significant (GJH4 p=0.33, GJH5 p=0.15, GJH6 p=0.12).”
12. Review by native speaker needed to improve clarity although results in general add to our understanding in this field of research.

**Answer:** Thank you for this comment, and we are honoured that you find the results interesting.

**Action:** A native English speaker with scientific expertise has now edited the paper.

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**Discussion**

13. First paragraph. We have to standardize this. If you say was predictive it means it reached statistical significance. If it did not reach significance, then you have to continue the sentence by saying although this association did not reach the predefined level of statistical significance.

**Answer:** Thank you for this comment, and we agree that it seems to be written too conclusive. We have now rewritten this section so it is in accordance with the findings that are not significant.

**Action:** Line 248-251: “The result of this study suggested that GJH5 without pain in childhood at eight or ten years of age is a possible predictive factor for developing joint pain in adolescence, although this association did not reach the predefined level of statistical significance. It also indicated that there was a positive association between GJH and experiencing joint pain at 14 years of age.”

14. Study limitations: the width of confidence intervals in the study is big. There must be an issue of statistical power to answer the research question. This should be discussed in the discussion section, why the CI is wide? Please justify this.

**Answer:** We agree with the reviewer, the CI is big and of course in affects the statistical power. We have now rewritten the paragraph of this impact of the results.

**Action:** Added in line 288-293: “The estimates for both the cross-sectional as well as for the longitudinal analyses have wide CI’s. This affects the statistical power of the results negatively, and weakens the association of GJH and developing joint pain. The small sample size and low number of outcome events must be an explanation for this and why these associations should be confirmed in a larger study.”
Conclusion

15. Please see comments in abstract. The current conclusion does not give guide for future research. Please add recommendations based on your results, I would add future bigger studies are needed to confirm results.

**Answer:** We agree that the conclusion of our results suggests a link, while it is not strong enough to guide future research. We have now changed the conclusion.

**Action:** line 324-330: “This study suggests a possible link between GJH in childhood and joint pain in adolescence. Children at eight or ten years of age with GJH5 and no pain at baseline were found to have a threefold increased risk of developing pain at 14 years of age. Although this association did not reach the predefined level of statistical significance future studies with a bigger sample size are needed to confirm these findings.

Furthermore, adolescents at 14 years of age with GJH have higher BMI, lower self-reported physical function and experience daily pain more frequently, but GJH does not seem to influence measured physical function at 14 years of age.”