PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Potentially Traumatic Interpersonal Events, Psychological Distress and Recurrent Headache in a Population-based Cohort of Adolescents The HUNT Study
AUTHORS	Stensland, Synne; Dyb, Grete; Thoresen, Siri; Wentzel-Larsen, Tore; Zwart, John-Anker

VERSION 1 - REVIEW

REVIEWER	Gretchen E. Tietjen, MD Professor and Chair, Department of Neurology University of Toledo, USA
REVIEW RETURNED	21-Apr-2013

RESULTS & CONCLUSIONS	Writing style is often unclear and it is important to note that the analysis of a cross-sectional study doesn't allow differentiation of mediating and confounding effects of 'psychological distress'
GENERAL COMMENTS	The paper is well constructed but the overly wordy writing style is sometimes at the expense of clarity and overall readability. *Article Summary* The language under the first bullet point of Article Focus is unclear. The main focus is to examine in a population based cohort of adolescents the associations between exposure to potentially traumatic interpersonal events and ICHD-II defined migraine and tension-type headache. The key messages would benefit from editing. The third key message could be eliminated. Under limitations: the cross-sectional design also does not allow the differentiation of confounding vs mediation. *Abstract* Authors' definition of psychological distress should be in abstract The work does not cover the spectrum of headache complaints but rather focuses on migraine and TTH The study examines the role of psychological distress as a **potential** mediator of the relationship, since it could also be a confounder. In the conclusion: It is not accurate to refer to posttraumatic psychological distress when the temporal relationship of events and psychological distress in uncertain. *Introduction* The second sentence is unclear.

The revised chronic migraine classification encompasses persons with tension type headache as well, as long as 8 or greater headaches/month of the 15 or more headaches/month required meet criteria for migraine. This raises a question as to whether the combined group of migraine and TTH is useful.

Methods

Any specific exclusion criteria, eg reading ability, since this is a self administered questionnaire ?

How is “other” headache defined? How is medication overuse headache handled?

The questions on PTIE do not distinguish between age of first exposure, frequency of exposure and over what ages did exposure occur. In addition the temporal relationship of age of exposure and age of onset of psychological distress (which only encompasses the prior 14 days) cannot be ascertained.

Statisitics

2nd paragraph. *Possible* mediation is tested. Attenuation of the OR when additionally adjusting for psychological distress could point to lack of power, mediation or confounding. Using a statistical test to look at the difference between the 2 models does not allow one to clarify whether the attenuation in OR is due to mediation or confounding.

Results.

What was the rationale for stratifying the main annalysis by sex, especially since table 1 showed similar patterns for both sexes?

No mention made of the importance of the type of PTIE.

The term chronic daily headache is introduced in this section without definition.

Table 1. Define ‘Other Headaches’

Table 2. Given that the OR and CI are given, the value of the “overall p-value” seems redundant, as does the Model 2/1 analysis. The first 2 columns are sufficient to be able to see that there is attenuation of OR in Model 2 (ie possible mediation), but that the PTIE association with recurrent HA is independent of psychological distress. I am not sure that inclusion of the data for age, family structure, family economy adds anything to the paper and these variable are included in the logistic regression models

Table 3 is difficult to look at. I suggest either leaving out the Model 2/1 column for each frequency or to simplify further as below

	Monthly HA	Weekly HA	Daily HA	OR (95% CI) for incr. HA frequency adjusted for sociodemographics	OR (95% CI) for incr. HA frequency adjusted for sociodemographics + psychological distress
0	N (%)	N (%)	N (%)		

	1	N (%)	N (%)	N (%)		
	2	N (%)	N (%)	N (%)		
	≥3	N (%)	N (%)	N (%)		

Table 4. I would suggest eliminating Model 2/1 column and showing data for TTH only (Model 1, Model 2), Migraine (model 1, model 2), and Migraine w. TTH (model 1 and model 2), and not show data for 'other headache' . Alternatively, combine analyses and show Relative Odds of Migraine vs TTH by number of traumatic event types for Model 1 and for model 2.

Table 5. Eliminate and describe in text as you have done on page 26.

Discussion. In the first paragraph the writing needs to be clearer. It is unclear what 'complaints' refers to. Is this headache frequency? And is major subtypes of complaints referring to PTIE subtypes or headache subtypes?

Limitation: it is uncertain the frequency/intensity of the exposures based on the questions. This is a weakness compared to tools like CTQ and ACE survey. The questions also don't cover the age or age span of events, perpetrator, and there are no questions specifically addressing emotional abuse.

The cross-sectional design also does not allow the differentiation of confounding vs mediation. This should be clearly stated.

REVIEWER	Dr.Shashi S. Seshia Dept. of Pediatrics (Division of Pediatric Neurology), University of Saskatchewan, Saskatoon, Canada. Declaration: No conflict of interest
REVIEW RETURNED	22-Apr-2013

THE STUDY	1. There are minor issues that do not detract from the overall excellence of this article. I have listed them separately in an attachment. I have also inserted comments into the manuscript-also attached. 2.Complex statistics have been used. I do not have the expertise to determine if the description is adequate, or usage and interpretation appropriate. PL. CONSULT A STATISTICAL EXPERT WHO IS FAMILIAR with the tests that have been used here, and in interpreting confidence intervals for precision. I have highlighted some of the CIs which seem relatively wide-to my knowledge, there are no clear guidelines to define 'wide' in confidence intervals (Glasziou and Doll 2006; Guyatt et al.2011)-so there is some subjectivity 3. With reference to the last question above- the authors have provided a CONSORT type flow diagram, used the STROBE

	checklist: these appear satisfactory. 4. The manuscript is extremely well written. However, some sentences are rather long and without commas or semi-colons, I found reading them difficult and the message confusing. As Editor, it is your call! I cannot claim to be an expert on the English language. I would suggest that all my suggestions/comments involve only minor revisions ie no major structural change in the manuscript
RESULTS & CONCLUSIONS	Again, a choice between a black and white "Yes" or "No" does not allow for commenting on the occasional sentences that one might question. I have inserted my comments in the manuscript- hopefully, I will be able to attach it successfully. I have also inserted a summary of my review.
GENERAL COMMENTS	**General Comments** 1. The HUNT data base has provided extremely valuable information on adolescent headache. The current paper is no exception. 2. The sample size is large (reflected, with a few exceptions, in the narrow confidence intervals). 3. The paper is generally well written. **Specific Comments** I have inserted detailed comments in “Sticky Notes” at places in the manuscript, I considered appropriate. Please refer to them. 1. There is considerable redundancy and repetition in the manuscript; if these can be eliminated then the paper would read even better. 2. Many of the sentences are long, hence the message can get confusing. The judicious use of shorter sentences, commas, semi-colons may be helpful. However, I am not an expert on the English language; hence, the authors should be guided by the editor. 3. I have made specific suggestions to improve the Methods Section. These include: (i) clearly specifying the age-range of the population under study, (ii) clearly stating if the information in the

	manuscript is based on data collected between 2006-2008 (or specifying the actual period)- if the former, then the authors will need to discuss (in discussion) if the questionnaire and information are *still relevant/complete* for 2013 (for this reason, in my clinic, we updated our questionnaires periodically) , (iii) defining the core terms such as PTIE and victimization, and ensuring that throughout the manuscript "trauma" is specified (i.e. use PTIE if that is what is meant) to avoid confusion with physical trauma, and explaining what Bootstrap is in relationship to CI and why the Bootstrap method was used: most clinical readers may be unaware. Given that narrow and wide with reference to confidence intervals are subjective, the authors should specify the range within which a value was considered to have high precision, and beyond which precision would be increasingly low. 4. I am not a statistical expert. The Statistics used are complex. Hence, usage and interpretation will need to be reviewed carefully by a statistical expert in the field. 5. I have expressed some reservations about incorporating headache frequency of >4/week under 'recurrent headache'-even if this has been stratified under 'daily' in the tables. Why not use 'daily' in the methods too? The clinical reason for differentiating between recurrent and daily is the crucial concept of transformation of the former to the latter. The issues addressed in the paper, are likely to be one of the common and important factors in transformation and persistence of (chronic) daily headache 6. The authors should address the issue of the precision (i.e. high low) for the confidence intervals. I have highlighted some that are relatively wide and the corresponding conclusions to be drawn (also

	needs to be addressed in Discussion). 7. There is considerable redundancy in the Discussion section. The authors have done an admirable task of highlighting the strengths and limitations of their study and data. If the information is based on that collected between 2006 and 2008, then the limitations of the questionnaire used then and relevance of their conclusion to current times (2013) should also be addressed. 8. The external validity of the information has not been well addressed. To which parts of the world will their data and conclusions apply? If all, then should be so stated. 9. The Questionnaire is excellent. However, the editors may wish to have an expert in the field of questionnaires in general and adolescents (and psychosocial stressors) in particular to comment on the strengths and weaknesses of the questionnaire- so that improvements can be made for future studies. On a personal note, I am pleased to see that the study provides better evidence for the clinical observational evidence that my colleagues in the Pediatric Headache field (Guidetti and group, Hershey/Powers, Wober-Bingol) and I have based our recommendations for a biopsychosocial approach to Childhood Headache, an approach our mentors and others followed without naming it as such.

- The reviewer also provided marked-up PDF which are available on request from the publisher

REVIEWER	Rigmor Højland Jensen, Danish Headache Center, University of Copenhagen, Denmark No competing interests
REVIEW RETURNED	01-May-2013

THE STUDY	No these causal conclusions cannot be drawn in a cross sectional study as the present
RESULTS & CONCLUSIONS	Although the conclusions are careful the present data set cannot be taken into account for a causal relation as the applied methodology can be discussed.

VERSION 1 – AUTHOR RESPONSE

Dr. Gretchen E. Tietjen
Comments from referee
Writing style is often unclear and it is important to note that the analysis of a cross-sectional study doesn't allow differentiation of mediating and confounding effects of 'psychological distress' (See attached file).
Response 2
We have made revisions of the language throughout the document to enhance readability.
We fully agree with the reviewer that we cannot conclude on etiological pathways on the basis of a cross-sectional study. Our findings represent associations, and the paper has been changed to clarify this limitation. Limitations are particularly addressed on pp.4 and pp.39-40.

Comments from referee (attached comments)
The paper is well constructed but the overly wordy writing style is sometimes at the expense of clarity and overall readability. Article summary: The language under the first bullet point of Article Focus is unclear: The main focus is to examine in a population based cohort of adolescents the associations between exposure to potentially traumatic interpersonal events and ICHD-II defined migraine and tension-type headache.
Response 3
Thank you for enhancing readability of our paper. The language under the article focus is now changed in compliance with your suggestion (p. 3). For general readability, please see response 2.

Comments from referee (attached comments)
The key messages would benefit from editing. The third key message could be eliminated.
Response 4
We have edited the key messages, and the third key message has been removed, in accordance with your suggestions (pp.3 and 4).

Comments from referee (attached comments)
Under limitations: the cross-sectional design also does not allow the differentiation of confounding vs. mediation.
Response 5
Please see response 2.

Comments from referee (attached comments)
Abstract: Authors' definition of psychological distress should be in abstract.
Response 6
The abstract now includes a specification of psychological distress (p.6), and the origin of the measure has been specified within the methods section on psychological distress (p.15).

Comments from referee (attached comments)
The work does not cover the spectrum of headache complaints but rather focuses on migraine and TTH.
Response 7
Thank you for this remark. Changes have been made within the objectives section of the abstract

(p.6), followed by appropriate changes throughout the paper to clarify that the focus of this paper is on TTH and migraine.

Comments from referee (attached comments)
The study examines the role of psychological distress as a potential mediator of the relationship, since it could also be a confounder.
Response 8
Please see response 2.

Comments from referee (attached comments)
In the conclusion: It is not accurate to refer to posttraumatic psychological distress when the temporal relationship of events and psychological distress is uncertain.
Response 9
Thank you, the phrasing has been changed (p.7).

Comments from referee (attached comments)
Introduction: The second sentence is unclear.
Response 10
The sentence has been rephrased and separated into two sentences (p.8).

Comments from referee (attached comments)
The revised chronic migraine classification encompasses persons with tension type headache as well, as long as 8 or greater headaches/month of the 15 or more headaches/month required meet criteria for migraine. This raises a question as to whether the combined group of migraine and TTH is useful.
Response 11
Thank you for focusing on this complex issue related to chronification and terminology. We have chosen to present results, regarding the combined headache group (migraine with tension-type headache) in the paper, to enlighten possible differences in strength of associations between victimization and TTH, migraine only, and combined complaints. In the prospective Dunedin study young adults with a combined migraine and tension-type headache had higher functional impairment, poorer physical health and poorer mental health than both controls (asthmatics using medication), and adults with migraine or TTH only. This may imply that the combined group struggle more with their symptoms. On the basis of these prior findings we hypothesized that the association between PTIEs and combined headache would be stronger, compared to the associations between PTIEs and single-type headaches.

Comments from referee (attached comments)
Methods: Any specific exclusion criteria, i.e.reading ability, since this is a self administered questionnaire?
Response 12
We have added a reference to a recently published article on the methodology of the three young-HUNT studies, which thoroughly discuss potential selection-biases (Holmen et al.), in the first part of the methodology section. Minor changes have been integrated to clarify reasons for non-participation, p12.

Comments from referee (attached comments)
How is “other” headache defined?
Response 13
Thank you for commenting on the term ‘other’ headache. The term ‘Other headaches’ has now been changed into the term ‘non-classifiable headache’, in coherence with previous publications. The clinical headache interview of adolescents was the basis for categorization of subtypes of headache into migraine, tension-type headache and non-classifiable headache. Reported headache was

categorized as non-classifiable if the two descriptive texts did not fit with the adolescent's recalled experience of his or her headache, (pp.13-14).

Comments from referee nr 1 (attached comments)
How is medication overuse headache handled?
Response 14
Thank you for this comment, which raises an important issue. Medication-overuse was not included in this publication as we strictly focused on TTH and migraine as outcomes. Medication use and overuse is a complex issue in its own respect. Yet, as you point out, use of non-prescription and prescription medication within this population is of great medical interest and importance, especially as we know that many adolescents self-medicate, rather than seek medical attention for their headache complaints. Dr. Dyb, Holmen and Zwart have previously published on the use of analgesics in relation to headache within the young-HUNT2 cohort (data collected 1995-1997), although not in association to victimization. Thus, we agree that the issue of medication use, and overuse, is of great medical relevance also in association to victimization. To appropriately handle such a complex issue, this will be the topic of a subsequent publication.

Comments from referee (attached comments)
The questions on PTIE do not distinguish between age of first exposure, frequency of exposure and over what ages did exposure occur.
Response 15
This methodological restriction has been addressed within the limitations section (pp.39-40).

Comments from referee (attached comments)
In addition the temporal relationship of age of exposure and age of onset of psychological distress (which only encompasses the prior 14 days) cannot be ascertained.
Response 16
Please see response 2.

Comments from referee (attached comments)
Statistics: 2nd paragraph. Possible mediation is tested. Attenuation of the OR when additionally adjusting for psychological distress could point to lack of power, mediation or confounding. Using a statistical test to look at the difference between the 2 models does not allow one to clarify whether the attenuation in OR is due to mediation or confounding.
Response 17
Please see response 2 for the issue of mediation/confounding.
As you point out, a significant attenuation of the effect-size estimate (OR) for the association between exposure to PTIEs and recurrent headache, when adding psychological distress to the multivariate logistic regression model, may imply either a mediating or a moderating role played by psychological distress. Lack of power, on the other hand, would make the ORs less reliable and the CIs wider, but would not make the ORs systematically closer to, or further from, the value 1. We find it useful to formally test the significance of the impact of adjusting for psychological distress on the relationship between victimization and recurrent headache. Within the statistics section we have made changes to clarify the purpose and limitations of the test (pp.15-17).

Comments from referee (attached comments)
Results: What was the rationale for stratifying the main analysis by sex, especially since table 1 showed similar patterns for both sexes?
Response 18
The rationale for stratifying the main analysis by sex was to make analysis as transparent as possible, visualizing potential differences in strength of associations between sexes. We know that prevalence of PTIEs, psychological distress and recurrent headaches are sex-related. We therefore decided, that

within a large data-set like ours, we wanted to present data separately, to the extent possible (Table 2, p.25).

Comments from referee (attached comments)
No mention made of the importance of the type of PTIE.
Response 19
We included only potentially traumatic interpersonal events (PTIEs) in this study. The range of events (witnessing violence, exposure to violence, bullying, sexual abuse by peer and sexual abuse by adult) cover the most important violations experienced by adolescents, with a few exceptions (e.g. emotional maltreatment and peer emotional victimization such as cyber-bullying). All these events have previously been found to be more pathogenic than non-interpersonal potentially traumatic events. More comprehensive measures of the types of PTIEs (including severity, frequency and duration, relation to perpetrator, recency of events etc.) would have enabled a more specific analysis of the distinct impact of different types of PTIE. Restrictions related to our measures of PTIEs have been noted within limitations section on pp.39-40.

Comments from referee (attached comments)
The term chronic daily headache is introduced in this section without definition.
Response 20
For simplification we have omitted the term chronic headache from this paper. The issue of chronic headache in relation to victimization and medication-overuse will be a topic for a subsequent publication.

Comments from referee (attached comments)
Table 1. Define 'Other Headaches'
Response 21
Please see response 13.

Comments from referee (attached comments)
Table 2. Given that the OR and CI are given, the value of the "overall p-value" seems redundant, as does the Model 2/1 analysis. The first 2 columns are sufficient to be able to see that there is attenuation of OR in Model 2 (i.e. possible mediation), but that the PTIE association with recurrent HA is independent of psychological distress. I am not sure that inclusion of the data for age, family structure, and family economy adds anything to the paper and these variables are included in the logistic regression models. Table 3 is difficult to look at. I suggest either leaving out the Model 2/1 column for each frequency or to simplify further as below

Table 4. I would suggest eliminating Model 2/1 column and showing data for TTH only (Model 1, Model 2), Migraine (model 1, model 2), and Migraine w. TTH (model 1 and model 2), and not show data for 'other headache'. Alternatively, combine analyses and show Relative Odds of Migraine vs. TTH by number of traumatic event types for Model 1 and for model 2. Table 5. Eliminate and describe in text as you have done on page 26.
Response 22
Thank you for these comments on the presentation of data.
We agree that a p-value is made redundant by the whole confidence distribution, but not necessarily by a single (usually 95%) CI. In this case, on the other hand, we have chosen to report the overall p-value, in addition to odds ratios related to specific contrasts of PTIEs (1, 2, and 3 or more PTIEs, in comparison to no exposure). The p-value here is related to the 4 category PTIE variable as a whole; not to individual contrasts from a reference category.
Further, as you point out, the ratio of odds ratio test does not differentiate between mediating and confounding effects. Nevertheless, by estimating the ratio of odds ratio (OR2/OR1), with corresponding bootstrap 95% percentile CIs, we may assess whether adjustment for psychological

distress significantly alters the strength of associations between exposure to PTIEs and recurrent headache. CIs not crossing the value 1 indicate a significant difference between the two models. The bootstrap test used here is currently recommended for estimation of these confidence intervals. Please also see response 17, concerning the inclusion of the ratio of odds ratio test. Changes have been incorporated in the statistical section of the paper (pp.15-17).
In line with the reviewer's recommendations, results of the comparison of ORs (Model2/Model1) have been excluded from the tables 2, 3 and 4, to simplify presentation of data (pp. 25, 30 and 34). Results of the test are reported in brief in the result section of the paper. Table 5 has been removed. We have also omitted the test of proportional odds assumption to enhance readability of the statistics section of the paper (p.16). Thus, tables A1 and A2, for online publication only have also been removed. Analysis comparing strength of associations between exposure to PTIEs and frequencies of headache are reported in the result section, but kept as a table for online publication only (Old supplementary Table A3, now labeled table A1). Likewise, analysis comparing strength of associations between exposure to PTIEs and subtypes of headache are reported in the result section, but kept as a table for online publication only (Old supplementary Table A4, now labeled table A2).
Regarding presentation of the ORs for the background variables in table 2, the reasons why we presented these were to enable transparency of data and comparison between studies. We realize that the presentation of these background variables may interfere with readability, and the ORs in question have therefore been omitted (Table 2, p.24).
Within the revised tables minor changes to enhance readability and precision have been highlighted. Data on migraine with aura has been omitted.

Comments from referee (attached comments)
Discussion: In the first paragraph the writing needs to be clearer. It is unclear what 'complaints' refers to. Is this headache frequency? And are major subtypes of complaints referring to PTIE subtypes or headache subtypes?
Response 23
Thank you for commenting on lack of readability and clarity. The paragraph has been revised (p.37).

Comments from referee (attached comments)
Limitation: it is uncertain the frequency/intensity of the exposures based on the questions. This is a weakness compared to tools like CTQ and ACE survey. The questions also don't cover the age or age span of events, perpetrator, and there are no questions specifically addressing emotional abuse.
Response 24
Please see responses 15 and 19.

Comments from referee (attached comments)
The cross-sectional design also does not allow the differentiation of confounding vs. mediation. This should be clearly stated.
Response 25
Please see response 2.

Referee nr 2, Dr.Shashi S. Seshia
Comments from referee
There are minor issues that do not detract from the overall excellence of this article. I have listed them separately in an attachment. I have also inserted comments into the manuscript-also attached. Complex statistics have been used. I do not have the expertise to determine if the description is adequate, or usage and interpretation appropriate. PL. CONSULT A STATISTICAL EXPERT WHO IS FAMILIAR with the tests that have been used here, and in interpreting confidence intervals for precision. I have highlighted some of the CIs which seem relatively wide-to my knowledge, there are no clear guidelines to define 'wide' in confidence intervals (Glasziou and Doll 2006; Guyatt et al.2011)-so there is some subjectivity. With reference to the last question above- the authors have

provided a CONSORT type flow diagram, used the STROBE checklist: these appear satisfactory. The manuscript is extremely well written. However, some sentences are rather long and without commas or semi-colons, I found reading them difficult and the message confusing. As Editor, it is your call! I cannot claim to be an expert on the English language. I would suggest that all my suggestions/comments involve only minor revisions i.e. no major structural change in the manuscript. Please see comments inserted as Sticky Notes to manuscript and a summary of my comments: two files being attached.
Response 26
Thank you for these remarks. Please see specific responses below.

Comments from referee (attached comments)
General Comments
1. The HUNT data base has provided extremely valuable information on adolescent headache. The current paper is no exception.
2. The sample size is large (reflected, with a few exceptions, in the narrow confidence intervals).
3. The paper is generally well written.
Specific Comments
I have inserted detailed comments in “Sticky Notes” at places in the manuscript, I considered appropriate. Please refer to them.
There is considerable redundancy and repetition in the manuscript; if these can be eliminated then the paper would read even better.
Many of the sentences are long; hence the message can get confusing. The judicious use of shorter sentences, commas, semi-colons may be helpful. However, I am not an expert on the English language; hence, the authors should be guided by the editor.
Response 27
Thank you for these general comments, and specific remarks. Please see response 2 concerning redundancy and language.

Comments from referee (attached comments)
I have made specific suggestions to improve the Methods Section. These include: (i) clearly specifying the age-range of the population under study, (ii) clearly stating if the information in the manuscript is based on data collected between 2006-2008 (or specifying the actual period)- if the former, then the authors will need to discuss (in discussion) if the questionnaire and information are still relevant/complete for 2013 (for this reason, in my clinic, we updated our questionnaires periodically), (iii) defining the core terms such as PTIE and victimization, and ensuring that throughout the manuscript “trauma” is specified (i.e. use PTIE if that is what is meant) to avoid confusion with physical trauma, and explaining what Bootstrap is in relationship to CI and why the Bootstrap method was used: most clinical readers may be unaware. Given that narrow and wide with reference to confidence intervals are subjective, the authors should specify the range within which a value was considered to have high precision, and beyond which precision would be increasingly low.
Response 28
Regarding lack of information on the participants’ age, and when the data was collected, changes have been done to meet with the reviewer’s requirements (p.12). Please also see response 12. Within the limitations section of the paper we have included lack of assessment of cyber-bullying. Please see response 19.
Our definition of the term PTIE has been included within the methods section of the paper, in line with the reviewer’s recommendations (p.14). The defined term replace the use of unspecified ‘trauma’ throughout the manuscript, as suggested. Our operationalization of the term can be found on pp.14-16. Further, we now consistently use the term PTIE/PTIE exposure when referring to our findings, whilst the more commonly used and general term victimization encompass exposure to PTIEs, and is kept within the discussion section without a definition.
Please see response 17 and 22 for statistics on bootstrap methodology and CIs. Wide CIs may be

observed in relation to analysis lacking power, due to low numbers or measurements uncertainties, whilst a higher numbers and more precise (reliable) measures result in tighter CIs.

Comments from referee (attached comments)
I am not a statistical expert. The Statistics used are complex. Hence, usage and interpretation will need to be reviewed carefully by a statistical expert in the field.
Response 29
Please see response 17, 22 and 28.

Comments from referee (attached comments)
I have expressed some reservations about incorporating headache frequency of >4/week under 'recurrent headache'-even if this has been stratified under 'daily' in the tables. Why not use 'daily' in the methods too? The clinical reason for differentiating between recurrent and daily is the crucial concept of transformation of the former to the latter. The issues addressed in the paper, are likely to be one of the common and important factors in transformation and persistence of (chronic) daily headache
Response 30
The term chronic headache has been omitted from this paper for simplification. Please see response 20.

Comments from referee (attached comments)
The authors should address the issue of the precision (i.e. high low) for the confidence intervals. I have highlighted some that are relatively wide and the corresponding conclusions to be drawn (also needs to be addressed in Discussion).
Response 31
Please see response 28.

Comments from referee (attached comments)
There is considerable redundancy in the Discussion section. The authors have done an admirable task of highlighting the strengths and limitations of their study and data. If the information is based on that collected between 2006 and 2008, then the limitations of the questionnaire used then and relevance of their conclusion to current times (2013) should also be addressed.
Response 32
Thank you for this timely comment. Changes have been done in the limitations section of the paper (pp.39-40).

Comments from referee (attached comments)
The external validity of the information has not been well addressed. To which parts of the world will their data and conclusions apply? If all, then should be so stated.
Response 33
Thank you for this comment. Your point has been added on page 40.

Comments from referee (attached comments)
The Questionnaire is excellent. However, the editors may wish to have an expert in the field of questionnaires in general and adolescents (and psychosocial stressors) in particular to comment on the strengths and weaknesses of the questionnaire- so that improvements can be made for future studies. On a personal note, I am pleased to see that the study provides better evidence for the clinical observational evidence that my colleagues in the Pediatric Headache field (Guidetti and group, Hershey/Powers, Wober-Bingol) and I have based our recommendations for a biopsychosocial approach to Childhood Headache, an approach our mentors and others followed without naming it as such.
Response 34

Thank you for this comment. The appropriate reference has been added.

Comments from referee (sticky note 1, in second key message)
The 2nd and 3rd lines reflect speculation
Response 35
Please see response 4.

Comments from referee (sticky note 2, in third key message)
Traditional dichotomization may need to be defined/ meaning made more explicit-readers may not understand; perhaps the sentence could be worded positively i.e. advocating a biopsychosocial approach? Is that the intent?
Response 36
Please see response 4.

Comments from referee (sticky note 3, in conclusion, abstract)
The biopsychosocial approach, at least to childhood headache, has been highlighted by others: Guidetti, Seshia (especially for chronic daily headache)
Response 37
Please see response 34

Comments from referee (sticky note 4, in first section, introduction)
There seems to be some repetition of clinical background in the introduction-perhaps redundancy could be eliminated?
Response 38
Thank you for commenting on the matter of redundancy. We have made changes to enhance readability and avoid redundancy throughout this revised version of the paper. Please see response 2.

Comments from referee (sticky note 5, in first section, methods)
upper age limit needs to be stated? The age range for definition of adolescents needs to be specified; I believe the questionnaire refers to 13-19 years
Response 39
Please see response 12 and 28 (p.12).

Comments from referee (sticky note 6, in first section, methods)
Recruitment was done between 2006-2008; authors need to specify when the information that forms the basis for the present paper, was gathered. If the information is based on that recorded between 2006-2008 then it should be so stated. While we were aware of bullying during that period, cyber-bullying and abuse/victimization through the Internet have become subjects of intense public, health care and official debate. This has coincided with the increasing sophistication of cell/mobile phones (which can take high quality embarassing pictures including video clips), and social sites such as Facebook etc. More importantly, most teenagers even in developing economies such as India, possess cell/mobile phones and use social sites.
Response 40
Please see response 28 regarding when the study was conducted, and response 19 regarding limitations related to the types of PTIEs assessed.

Comments from referee (sticky note 7, in recurrent headache, methods)
By convention, once recurrent headaches occur on 15 or more days a month-the term "chronic daily headache" is used: albeit not recognized in ICHD-II , or chronic headache (ICHD-IIR). I would question incorporating a frequency of 4 days/week under "recurrent." Perhaps, the authors have a reason?

Response 41
Please see response 20.

Comments from referee (sticky note 8, in recurrent headache, methods)
Reference 40 i.e. McGrath et al. may not be the most appropriate to use to justify incorporating a frequency of more than 4 days/week headache under 'recurrent.'
Response 42
Thank you for this remark. You are perfectly right. The reference has been omitted.

Comments from referee (sticky note 9, in Potentially Traumatic Interpersonal Events, methods)
I have reviewed the Questionnaire at the end of the manuscript. I have a few general comments: (i) I may have missed it, but I could not find any questions dealing with bullying, cyber-bullying and internet abuse: all increasingly common in recent years. From the questionnaire, I am unable to determine what would be classified as a PTIE, "victimizations" and believe these need to be specified clearly for the readers to be meaningful. I have also stated elsewhere that the authors should avoid using "trauma" or "traumatic" without qualification (why not use PTIE?) since readers could rightly misinterpret as physical trauma (example head injury); trauma in relationship to abuse should be specified as such
Response 43
Thank you for this comment. Bullying is included in our study. Items on cyber-bullying and internet abuse were unfortunately not included in the questionnaire. Please see response 19 regarding limitations to the PTIE measures (i.e. not including cyber-bullying), and response 28 for definition and consistent use of the terms PTIEs and victimization.

Comments from referee (sticky note 10, in Potentially Traumatic Interpersonal Events, methods)
I believe there should be a definition for the term 'potentially traumatic interpersonal events' and all that it incorporates. The use of the word 'trauma' without qualification could cause some readers to assume it refers to physical trauma i.e. head injury etc. There should also be a definition for 'victimizations' and all it encompasses. I am confused if the authors are using 'PTIEs' and 'victimizations' interchangeably. This paper is of great relevance to clinicians-hence, the importance of terms that may have standard definitions in psychological literature.
Response 44
Please see response 28.

Comments from referee (sticky note 11, in statistics)
This section and the statistical analyses will need careful review by a statistical expert well versed in the techniques described (I am finding out that there is as much sub-specialization in Statistics as there is in Medicine)
Response 45
Please see response 17, 22 and 28.

Comments from referee (sticky note 12, in statistics)
Not all clinical readers will know the term 'bootstrap' in relationship to CI. a line to explain why 'bootstrap methods' and not plain CI calculations were done, will be helpful.
Response 46
Please see responses 17, 22 and 28.

Comments from referee (sticky note 13, in Table 1)
Some of the SDs are large
Response 47
Please see responses 22 and 28 describing the statistics.

Comments from referee (sticky note 14, in Table 2)
The CIs in table 2 are narrow suggesting high precision
Response 48
Please see responses 22 and 28 describing the statistics.

Comments from referee (sticky note 15, in Table 3)
Some of the CIs in this table are relatively wide-see highlighted, suggesting relatively low or lower precision (irrespective of the p value). Would this need some elaboration by the authors i.e., define what range of CI was considered high precision and address the significance and relevance of those values that exceeded the range? Precision will impact on the 'strength' of the inference being drawn
Response 49
Please see response 28 describing the statistics.

Comments from referee (sticky note 16, in Table 4)
Some CIs relatively wide in table 4 also ...comments made earlier apply to all situations were CIs relatively wide
Response 50
Please see responses 22 and 28 describing the statistics.

Comments from referee (sticky note 17, in section on subgroup analysis in results)
Did the authors mean "attenuated" (i.e. weakened or reduced?) If so, why the word "Nonetheless" in the next line? Could these lines be made more explicit/clear?
Response 51
Thank you for this remark. Changes have been done to comply with the reviewer's suggestions (p.35).

Comments from referee (sticky note 19, in Table 5)
CIs in relatively narrow range
Response 52
Please see responses 22 and 28 describing the statistics.

Comments from referee (sticky note 20, in Discussion)
Discussion is v good, but I would suggest attention to a couple of points may further improve readability: (i) There is repetition of information and message: please try and minimize; (ii) some sentences are too long and the message becomes confusing; shorter sentences or use of commas, semi-colons may help. I would ask the editor/s to comment on these issues- since they and other reviewers may not share my opinion
Response 53
Please see response 2 and 38.

Comments from referee (sticky note 21, in Strengths and Limitations, Discussion)
If the authors are referring to posttraumatic stress (as defined in psychological and psychiatric literature) they should use the full term. Simply using 'trauma' implies physical trauma (head injury) I suggest the authors define the term 'posttraumatic stress' in Methods, and be consistent in the use of the term throughout; I addresses this issue with a "sticky note' in the Methods section
Response 54
Thank you for commenting on this. We have changed the wording to posttraumatic stress reactions, where appropriate, throughout the manuscript. Regarding the use of the term 'trauma', see response 28. Regarding the use of the term 'psychological distress' see response 6.

Comments from referee (sticky note 22, in Discussion)
Did the authors define 'interpersonal trauma'- if not this should be defined in Methods; please see

earlier comments
Response 55
Please see response 28.

Comments from referee (sticky note 23, in Discussion on temporality)
'some evidence' rather than 'scarce'?
Response 56
The wording has been changed on p.42.

Comments from referee (sticky note 24, in Discussion)
see earlier comment regarding use of the word 'trauma' in isolation
Response 57
Please see response 28.

Comments from referee (sticky note 25, in Discussion)
do the authors mean the association was strongest with combined migraine and TT? If so why not delete the initial part of the sentence which makes for confusing reading. (referring to: This discrepancy between tension-type headache and migraine seemed to be explained largely by the stronger association between trauma exposure and combined migraine with tension-type complaints.)
Response 58
Suggested changes have been done on p.42.

Comments from referee (sticky note 26, in Discussion)
I found this sentence difficult to understand; I think I know what the authors are trying to say, but am unsure...in general, longer sentences are more likely to cause confusion for readers. (refering to : 'These findings may reflect a pattern where exposure to interpersonal trauma predispose for more severe headache complaints, and comorbidity in the form of multiple types of pains,[55] reflecting a similar pattern as that observed in the relationship between trauma exposure and psychopathology.[29]')
Response 59
The sentence has been revised (p.42).

Comments from referee (sticky note 27, in Discussion, conclusion and implications)
It is considered improper for a referee to draw attention to his or her own paper. However, the term "biopsychosocial" was used in our 2008 paper (published in Dev Med Child Neurol); and I am aware that Professor Guidetti and his group in Italy, and Wober-Bingol and her group in Austria have referred to the importance of psychological/psychiatric-medical approach for assessment and management, in their writings. The current study provides good evidence for such an approach
Response 60
Please see response 34.

Comments from referee (sticky note 27, in Discussion, conclusion and implications)
We agree that while individual groups may use and advocate a biopsychosocial approach to childhood headache, health services generally still function as silos.
Response 60
Please see response 34.

Comments from referee (sticky note 28, in Questionnaire)
Is there a specific question to address bullying in general (especially at school), and cyber-bullying or internet 'abuse' in particular?
Response 60

Please see response 19 and 28.

Referee nr 3, Professor Rigmor Højland Jensen
Comments from referee
No these causal conclusions cannot be drawn in a cross sectional study as the present
Although the conclusions are careful the present data set cannot be taken into account for a causal relation as the applied methodology can be discussed.
Response 61
We fully agree with the reviewer that within the given constraints of this study we can only assess associations, and cannot conclude on etiological pathways. We have therefore made changes to the paper, to comply with the methodological restrictions of the study. Please see response 2.

VERSION 2 – REVIEW

REVIEWER	Gretchen Tietjen, MD; Professor and Chair, Neurology, University of Toledo, USA I have no competing interests
REVIEW RETURNED	09-Jun-2013

GENERAL COMMENTS	Excellent revision. All my concerns and questions have been addressed.