PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the Heart but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Postural tachycardia syndrome is associated with significant symptoms and functional impairment predominantly affecting young females – a UK perspective.
AUTHORS	NEWTON, JULIA; McDonald, Claire; Koshy, Sharon; Busner, Lorna; Kavi, Lesley

VERSION 1 - REVIEW

REVIEWER	Raj, Satish ***Vanderbilt University School of Medicine*** I have a conflict of interest. I serve on the Medical Advisory Board of POTS UK. My role has been largely to provide advice about online patient information content and review. I have not been involved in this study, and in fact I had no knowledge about this study until receiving this paper for review. I did mention this to the editors prior to accepting this review and I was still asked to review the manuscript.
REVIEW RETURNED	30-Apr-2013

GENERAL COMMENTS	McDonald et al. report on a survey study of patients with Postural Tachycardia Syndrome (POTS) in the United Kingdom. They recruited subjects from 2 sources: from the tertiary care Falls & Syncope clinic at Newcastle and from a national POTS patients support group (POTS UK). Through a series of self-reported questionnaires, they have captured a cross-sectional snapshot of the POTS patient experience in the United Kingdom. This information could prove quite useful. The main problem in reading through the manuscript is that seem to be a lot of stray facts, without a clear underlying story. Since this is a descriptive study, it might not be fair to expect a clearly stated hypothesis. However, the data could be better organized. For example, in reading through the manuscript, the most striking thing to me was how different the populations were between the support group and the clinic groups. Most of the POTS literature currently comes from 1 or more specialty referral clinics. These data suggest that the experience of the broader "POTS population" may be different from the experiences that are usually reported in the literature. I found that the authors had a tendency to vacillate between comparisons between the groups and trying to tell a combined story.

	If a comparison is to be made between POTS and chronic fatigue syndrome (CFS), then the authors need to make more effort to define these groups. The Newton group has published extensively on their cohort of patients with CFS and within this cohort, the sub-cohort with orthostatic intolerance/POTS. When comparing the 2 groups, did they exclude the CFS patients with OI/POTS from their analysis? The analysis can be done in many ways, but it needs to be clearly stated. Similarly, the points about CFS being a disorder characterized by autonomic dysfunction (pp. 9-10 and in the Discussion) are a little bit disingenuous. The references cited all allude to the orthostatic intolerance that likely identifies the subgroup with POTS. It is not reasonable to use these citations to justify the claim that CFS is an autonomic dysfunction disorder when it is being compared to POTS. There are specific issues that need to be addressed. The authors clearly state that the patients from Newcastle gave their informed consent. It is not clear if this is true for the POTS UK cohort. This needs to be clearly stated. Given the different numbers of subjects in each group, the relevant comparators are the percentages in each group, and not the absolute numbers of people. This should be reflected in the text. I am bothered by fact that 7 of the patients in the survey answered “I am not ill” to the question about the onset of their illness. This requires a better explanation. Are they stating that they were ill, but they are better? This question is under the “Onset of Illness” category, so I am left to wonder if they actually had POTS. Should they be excluded? I am also struck by the number of patients that are on no medications. This is very different from my clinic population. Again, these data may be able to teach us something that we cannot gain from a clinic experience alone. It would be interesting to segregate the group by those on no treatment (except salt) vs. on medications and compare those groups. Are the no treatment groups just earlier in the course of illness? Later in the course of illness? Less symptomatic? This analysis can be very revealing. I am not impressed that 4 patients used recreational marijuana. Is this higher than the use among young adults in the UK without POTS? Unless there is data to suggest that the answer is yes, any speculation about “underlying pathophysiology” is highly premature. The Discussion is written in a rather colloquial manner. For example, the last 2 lines of the 2nd paragraph of the Discussion (page 12; “POTS is clearly…) sounds like an advocacy statement or call to arms and not a reasoned scientific argument/statement. Similarly, there are statements later in the Discussion (p. 14, last paragraph) that are not supported by the authors’ own data or references. One example is the statement about the prognosis of “postviral onset POTS”. Reference 28 (page14) is listed in the text, but not in the Reference list (page 22).

REVIEWER	Colombo, Fernanda

	Heart Institute, University of Sao Paulo, Hypertension Unit
REVIEW RETURNED	10-May-2013

GENERAL COMMENTS	The present study brings important information related to Postural Tachycardia Syndrome in UK. The authors compared demographic characteristics, symptoms and treatment of POT subjects followed at two different institutions in UK (national UK registered small charity and a single hospital), and to compared their functional limitation with a cohort of patients chronic fatigue syndrome followed at the same hospital. The results show that PoTS patients have a high level of disability and comorbidity and highlight the necessity of a better understanding this pathology. It deserves to be publisher, but the manuscript needs some improvement to make it easier to read and understand. Major Comments: At the abstract– some points must be clarified: the meaning of the abbreviation “PoTS” . Objective: avoid expressions such as “explore clinic´s experience “ – please be more straightforward to the point – suggestion: to compare demographic characteristics, symptoms and treatment of POT subjects followed / or associated / or linked (etc…) at two different institutions in UK, and to verify if their functional limitation is similar to patients chronic fatigue syndrome. Clarify: 2 cohorts were studied ?? – there were 2 PoTS and 1 CFS At the Introduction: reinforce the gap in current knowledge that this study hope to address: suggestion: currently, health professional are not alert to the prevalence and function limitation of PoTs patient, what may cause a delay of the diagnosis and the therapeutic approach …., etc etc. Also, the information of a nation sample would add xxx in comparison to information of a single clinic xxx. Methods – please, clarify if patients with CFS also answered the same questionnaires and how it was performed. Results – Tables – add a list of abbreviations; Figure Legends – please, give information of abbreviations, include number of subjects of each group, and summarize the results Discussion – There are some repetitive phases, please, remove them. Add a paragraph with “limitations” of the study, and a final “conclusion”.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comments to the Author
McDonald et al. report on a survey study of patients with Postural Tachycardia Syndrome (POTS) in the United Kingdom. They recruited subjects from 2 sources: from the tertiary care Falls & Syncope clinic at Newcastle and from a national POTS patients support group (POTS UK). Through a series of self-reported questionnaires, they have captured a cross-sectional snapshot of the POTS patient experience in the United Kingdom. This information could prove quite useful.

We thank the reviewer for their positive comments.

The main problem in reading through the manuscript is that seem to be a lot of stray facts, without a clear underlying story. Since this is a descriptive study, it might not be fair to expect a clearly stated hypothesis. However, the data could be better organized. For example, in reading through the manuscript, the most striking thing to me was how different the populations were between the support group and the clinic groups. Most of the POTS literature currently comes from 1 or more specialty

referral clinics. These data suggest that the experience of the broader "POTS population" may be different from the experiences that are usually reported in the literature.

We thank the reviewer for their very helpful observations of our manuscript. We have now added more detail into the results and discussion as suggested to highlight the differences between the clinic and support group population.

I found that the authors had a tendency to vacillate between comparisons between the groups and trying to tell a combined story.

We apologise for this, have reread the manuscript and hope that we now present the data more emphatically.

If a comparison is to be made between POTS and chronic fatigue syndrome (CFS), then the authors need to make more effort to define these groups. The Newton group has published extensively on their cohort of patients with CFS and within this cohort, the sub-cohort with orthostatic intolerance/POTS. When comparing the 2 groups, did they exclude the CFS patients with OI/POTS from their analysis? The analysis can be done in many ways, but it needs to be clearly stated.

The reviewer raises an important point. We have clarified this in the methods section.

Similarly, the points about CFS being a disorder characterized by autonomic dysfunction (pp. 9-10 and in the Discussion) are a little bit disingenuous. The references cited all allude to the orthostatic intolerance that likely identifies the subgroup with POTS. It is not reasonable to use these citations to justify the claim that CFS is an autonomic dysfunction disorder when it is being compared to POTS.

We accept the reviewers point and have removed this from the manuscript.

There are specific issues that need to be addressed. The authors clearly state that the patients from Newcastle gave their informed consent. It is not clear if this is true for the POTS UK cohort. This needs to be clearly stated.

The POTS UK Cohort had not provided specific consent to be contacted. POTS UK placed information regarding the survey on their website and provided their members with the opportunity to download, complete and return the survey if they wished. No consent was obtained.

Given the different numbers of subjects in each group, the relevant comparators are the percentages in each group, and not the absolute numbers of people. This should be reflected in the text.

The reviewer is correct, we have changed this in the revised manuscript.

I am bothered by fact that 7 of the patients in the survey answered "I am not ill" to the question about the onset of their illness. This requires a better explanation. Are they stating that they were ill, but they are better? This question is under the "Onset of Illness" category, so I am left to wonder if they actually had POTS. Should they be excluded?

The reviewer is correct, and this is interesting. The responses are to the specific question 'I am not ill' and we would suggest could reflect the individuals perception of their symptoms. i.e. they could be symptomatic however it might be that they do not consider themselves to be ill. We have added this to the discussion.

I am also struck by the number of patients that are on no medications. This is very different from my clinic population. Again, these data may be able to teach us something that we cannot gain from a clinic experience alone. It would be interesting to segregate the group by those on no treatment (except salt) vs. on medications and compare those groups. Are the no treatment groups just earlier in the course of illness? Later in the course of illness? Less symptomatic? This analysis can be very revealing.

The reviewer is correct – we too were surprised at the proportion taking no medication (and as a consequence have in fact begun to change our approach to 'rushing' straight to medication. We have

run the analyses as suggested and included these in the results section.

I am not impressed that 4 patients used recreational marijuana. Is this higher than the use among young adults in the UK without POTS? Unless there is data to suggest that the answer is yes, any speculation about "underlying pathophysiology" is highly premature.

We accept the reviewers point and have removed this.

The Discussion is written in a rather colloquial manner. For example, the last 2 lines of the 2nd paragraph of the Discussion (page 12; "POTS is clearly…) sounds like an advocacy statement or call to arms and not a reasoned scientific argument/statement. Similarly, there are statements later in the Discussion (p. 14, last paragraph) that are not supported by the authors' own data or references. One example is the statement about the prognosis of "postviral onset POTS".

We apologise and have reread the discussion and changed it to make it more reasoned.

Reference 28 (page14) is listed in the text, but not in the Reference list (page 22).

We apologise for this oversight and have now added this to the reference list.

Reviewer: 2
Comments to the Author
General comments:
The present study brings important information related to Postural Tachycardia Syndrome in UK. The authors compared demographic characteristics, symptoms and treatment of POT subjects followed at two different institutions in UK (national UK registered small charity and a single hospital), and to compared their functional limitation with a cohort of patients chronic fatigue syndrome followed at the same hospital.
The results show that PoTS patients have a high level of disability and comorbidity and highlight the necessity of a better understanding this pathology.
It deserves to be publisher, but the manuscript needs some improvement to make it easier to read and understand.

We thank the reviewer for their positive comments and hope that with revision our manuscript if now suitable for publication.

Major Comments:
At the abstract– some points must be clarified: the meaning of the abbreviation "PoTS" .

We apologise for this oversight and have amended in the revision.

Objective: avoid expressions such as "explore clinic´s experience " – please be more straightforward to the point – suggestion: to compare demographic characteristics, symptoms and treatment of POT subjects followed / or associated / or linked (etc…) at two different institutions in UK, and to verify if their functional limitation is similar to patients chronic fatigue syndrome.

We thank the reviewer and have amended the text as suggested.

Clarify: 2 cohorts were studied ?? – there were 2 PoTS and 1 CFS

The abstract states that there are 2 PoTS cohorts which are matched to a CFS cohort – we have changed this inaccuracy in the text.

At the Introduction: reinforce the gap in current knowledge that this study hope to address: suggestion: currently, health professional are not alert to the prevalence and function limitation of PoTs patient, what may cause a delay of the diagnosis and the therapeutic approach …., etc etc. Also, the information of a nation sample would add xxx in comparison to information of a single clinic xxx.

We had added this detail as suggested.

Methods – please, clarify if patients with CFS also answered the same questionnaires and how it was performed.

The CFS patients completed the same symptom assessment tools but not the details of the history. We have added this detail to the methods.

Results – Tables – add a list of abbreviations;

We apologise for this oversight and have added this as suggested.

Figure Legends – please, give information of abbreviations, include number of subjects of each group, and summarize the results

We have added this as requested.

Discussion – There are some repetitive phases, please, remove them. Add a paragraph with "limitations" of the study, and a final "conclusion".

We have made these changes as recommended.