PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	ACUTE CORONARY SYNDROMES PRESENTATIONS AND CARE OUTCOMES IN WHITE, SOUTH ASIAN, AND CHINESE PATIENTS: A COHORT STUDY
AUTHORS	King-Shier, Kathryn; Quan, Hude; Kapral, MK; Tsuyuki, Ross; An, Libin; Banerjee, Suvro; Southern, Danielle; Khan, Nadia

VERSION 1 – REVIEW

REVIEWER	Genovefa Kolovou Onassis Cardiac Surgery Center, Athens, Greece
REVIEW RETURNED	19-Mar-2018

GENERAL COMMENTS	The manuscript entitled: ACUTE CORONARY SYNDROMES PRESENTATIONS AND CARE ACCESS IN WHITE, SOUTH ASIAN, AND CHINESE PATIENTS: A COHORT STUDY is interesting and practical, well written and well presented

REVIEWER	Ling Zhang The University of Sydney, Australia
REVIEW RETURNED	05-May-2018

GENERAL COMMENTS	Overall, this is an informative paper and it provides useful information for the health professionals dealing with ACS patients from a diverse ethnic background. There are few suggestions: 1. In the ' abstract' and 'statistical analysis' sections, the authors mentioned that the models were adjusted for (age, sex, education------ and level of education). Were both education (year) and education level be adjusted? any particular reason? 2. In the ‘result' section, If authors could provide the actual number and percentage in the text that will be much easier for the readers. There are some vague expressions such as 'most all participant (Pg9, line 43), 'most patients' (Pg 10 line 13). 3. Please check the content in the text with the content in the table. For an example, authors reported ‘the most common presenting symptom in each ----(90.4%)’, but there were 1191 out of 1334 (89.3%) patients reported mid-sternal pain. 4. Please check the results in Table 2, there were no significant differences between groups in terms of shortness of breath and diaphoresis according to the P value, but the authors reported the significant differences in the text (Pg 10 line 20). 5. The 'discussion' section, there is a repetition of the results. For example, 'South Asian who had-----than those with typical symptoms' (Pg 16 line 38), please make it more succinct. 6. The 'limitation' section, personally prefer to describe limitations first, then justify with the efforts which minimising the impact of these limitations. It's just different writing style.

REVIEWER	Bank, Ingrid St. Antonius Ziekenhuis Nieuwegein, The Netherlands
REVIEW RETURNED	12-Jul-2018

GENERAL COMMENTS	The authors aim to investigate possible ethnic variations in ACS symptoms in white, south Asian and Chinese patients in Canada. 1. The use term "care access" in the title of the manuscript is somewhat confusing to me as the paper is solely based on data of patients who had access to care. No data are available on the patients who did not or were not able to seek medical help, as was stated in the limitations section. Throughout the paper the authors more often use the term "care outcomes". Could you please clarify what you exactly mean with these two terms? 2. One of the main conclusions of the paper, as presented in the abstract, is that atypical presentations were associated with longer delays in South Asians (Table 4). However, from the same table 4 we can learn that the mean/median time to ER presentation is even longer in Chinese with atypical complaints, and that the difference in delay between Chinese patients with atypical vs typical complaints is similarly big. Unfortunately, in Chinese patients this is not a statistically significant finding probably due to the lower number of Chinese ACS patients included. Could you please explain why you chose underline the findings in south Asians (and not in Chinese vs whites) 3. page 16, line 45. "The reasons for this difference are not clear". Performing coronary revascularization with either PCI or CABG depends on the presence/absence and location of significant coronary artery stenosis. No data are provided on the presence of 1-, 2-, or 3 vessel disease (and left main/proximal LAD involvement) in the 3 ethnic groups. Could you please provide us with a table showing this data for the subset of patients who underwent CAG, possibly stratified by atypical vs typical symptoms or by type of ACS.

REVIEWER	Mathias Schlögl, MD, MPH Department of Geriatrics and Aging Research, University Hospital Zurich, Zurich, Switzerland
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	In this cross-sectional analysis of 1334 patients with an ACS (acute coronary syndrome), the authors investigated potential ethnic variations in ACS symptoms in white (n = 630), south Asian (n= 488) and Chinese (n= 216) patients. The literature review seems current and places the study in appropriate context. The methods, analyses, tables and figures are (mostly) valid and clear. In summary, after addressing the comments below this paper will be a useful original contribution appropriate for the BMJ Open audience. Writing: • The writing is clear and concise. However, the authors should check for minor typos, e.g. page 4, line 2 (…) syndrome (ACS) is substantial is now…" or page 6, line 2 (…) interpretation of this stuy (…).

	Methods: • Based on the STROBE protocol potential bias should be mentioned on page 7 of the manuscript, which (so far) is not clear for me. Please revise. • The authors should comment on their handling of potential missing data and state the numbers for excluded patients due to mixed-race and/or cognitive deficits. Furthermore I encourage the authors to highlight the importance of the reporting and appropriate handling of missing data in scientific journals in their discussion section. • The authors should provide information on how diabetes and chronic renal disease has been defined. Discussion: • The author should highlight the cross-sectional study design, which provides no basis for temporal ordering of the observed associations and do not imply causation. However, caution in drawing conclusions concerning causality does not lessen the value of the findings included, but points to the need for more methodologically rigorous designs in future research to advance our understanding for this important matter. Furthermore, I suggest that the authors add a comment about possible biases (e.g. selection bias) due to the study design. • So far, the age of the participants has been not highlighted in the discussion. As mentioned previously (e.g.: Schlögl M et al., BMJ Case Reports 2018), the clinical symptoms of an acute myocardial infarction differ significantly between age, gender and ethnicity, which will have significant clinical implications especially for elderly women from ethnic minorities. • So far, the authors only highlighted the potential cultural aspect for their main finding. However, enhanced physiological pain sensitivity in minority groups has been proposed as a contributing factor that might partially explain the observed ethnic differences in clinical pain reports.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

The manuscript entitled: ACUTE CORONARY SYNDROMES PRESENTATIONS AND CARE ACCESS IN WHITE, SOUTH ASIAN, AND CHINESE PATIENTS: A COHORT STUDY is interesting and practical, well written and well presented.

Thank you very much!

Reviewer #2

In the ' abstract' and 'statistical analysis' sections, the authors mentioned that the models were adjusted for (age, sex, education------ and level of education). Were both education (year) and education level be adjusted? Any particular reason?

This was a typographical error. The models were adjusted only for level of education. The duplication in the abstract and in the text (page 8) have been corrected. The footnotes at the end of the tables were correct.

In the ‘result' section, if authors could provide the actual number and percentage in the text that will be much easier for the readers. There are some vague expressions such as 'most all participant (Pg9, line 43), 'most patients' (Pg 10 line 13).

It was somewhat challenging to balance being repetitive with providing sufficient detail. We did not want to be repetitive in the reporting, given that the tables will be so proximal to the text. However, we appreciate the reviewers comment and have provided more detail in the ‘baseline characteristics’ section on pages 10 and 11.

Please check the content in the text with the content in the table. For an example, authors reported ‘the most common presenting symptom in each ----(90.4%)’, but there were 1191 out of 1334 (89.3%) patients reported mid-sternal pain.

The reviewer is absolutely correct. Please pardon our mathematical error. The sentence has been re-written….The most common presenting symptom across ethnic groups was mid-sternal pain/discomfort of any intensity (89.3%) followed by left shoulder pain/discomfort (46.6%)….on page 10. We also noted an error in the sentence above, which has now been corrected.

Please check the results in Table 2, there were no significant differences between groups in terms of shortness of breath and diaphoresis according to the P value, but the authors reported the significant differences in the text (Pg 10 line 20).

Again, we appreciate this feedback. The sentence has been re-written….There were significant differences between groups in reporting these symptoms with whites reporting more dizziness, and nausea or vomiting. We have reviewed all tables for accuracy.

The 'discussion' section, there is a repetition of the results. For example, 'South Asian who had-----than those with typical symptoms' (Pg 16 line 38), please make it more succinct.

We have changed the wording on page 14 (to which we refer in the discussion) to ‘south Asians were LEAST likely’ because all groups were less likely to receive PCI when having atypical symptoms.

On page 17, we deleted the sentence in which we re-reported unadjusted analyses and retained only the following edited sentence: Overall, and after adjustment, south Asians with atypical symptoms were least likely of the ethnic groups to receive PCI than those with typical symptoms. We hope by doing so, that the point is more clear and succinct.

The 'limitation' section, personally prefer to describe limitations first, then justify with the efforts which minimising the impact of these limitations. It's just different writing style.

We have re-ordered the elements of this section to address the reviewer’s concern.

Reviewer #3

The use term "care access" in the title of the manuscript is somewhat confusing to me as the paper is solely based on data of patients who had access to care. No data are available on the patients who did not or were not able to seek medical help, as was stated in the limitations section. Throughout the paper the authors more often use the term "care outcomes". Could you please clarify what you exactly mean with these two terms?

We appreciate this comment. The term ‘clinical care outcomes’ has now been defined and used consistently throughout the manuscript. The title is now changed. The abstract contains a definition of clinical care outcomes. Changes have also been made throughout the manuscript for consistency.

One of the main conclusions of the paper, as presented in the abstract, is that atypical presentations were associated with longer delays in South Asians (Table 4). However, from the

same table 4 we can learn that the mean/median time to ER presentation is even longer in Chinese with atypical complaints, and that the difference in delay between Chinese patients with atypical vs typical complaints is similarly big. Unfortunately, in Chinese patients this is not a statistically significant finding probably due to the lower number of Chinese ACS patients included. Could you please explain why you chose underline the findings in south Asians (and not in Chinese vs whites)

We appreciate the reviewer's comment. In part, we focused the abstract on the findings from south Asians because of the limited word count, south Asians were most consistently different (at risk) relative to whites, the differences were statistically significant, and the differences were potentially more clinically meaningful.

page 16, line 45. "The reasons for this difference are not clear". Performing coronary revascularization with either PCI or CABG depends on the presence/absence and location of significant coronary artery stenosis. No data are provided on the presence of 1-, 2-, or 3 vessel disease (and left main/proximal LAD involvement) in the 3 ethnic groups. Could you please provide us with a table showing this data for the subset of patients who underwent CAG, possibly stratified by atypical vs typical symptoms or by type of ACS.

Thank you. We have presented the 'extent of coronary artery disease' data in Table 1. There was no association between extent of coronary artery disease and having classic symptoms in whites, south Asians or Chinese. This information has been included on page 10, para 1. We have also adjusted the models presented in Table 3 (with no change in outcome) and Table 5 (south Asians with atypical symptoms now less likely to receive PCI).

Reviewer #4

The writing is clear and concise. However, the authors should check for minor typos, e.g. page 4, line 2 (…) syndrome (ACS) is substantial is now…" or page 6, line 2 (…) interpretation of this stuy (…).

Thank you. We have made the corrections as indicated and have also had the manuscript proof read.

Based on the STROBE protocol potential bias should be mentioned on page 7 of the manuscript, which (so far) is not clear for me. Please revise.

Thank you. The following statements were added on page 7:

There was potential for bias when using this design and data collection method. This was a self-selected group of patients (i.e., selection bias) who agreed to participate in the study. Also, the retrospective nature of the design could lead to recall bias given that patients were asked about their symptoms up to 5 days post hospital admission.

The authors should comment on their handling of potential missing data and state the numbers for excluded patients due to mixed-race and/or cognitive deficits. Furthermore I encourage the authors to highlight the importance of the reporting and appropriate handling of missing data in scientific journals in their discussion section.

Each variable had a 'not entered' category – in binary variables of present/not present, not entered was assumed to be not present. Unfortunately, we did not keep records of the number of patients excluded for various reasons. We are sorry that this information cannot be included in the manuscript. This is now included in page 7, para 3.

We appreciate the importance of 'missing data' in scientific reporting. However, this was not a major problem in our study and for space reasons, we have not opted to include a discussion about it.

The authors should provide information on how diabetes and chronic renal disease has been defined.

These were defined as in the Charlson Co-morbidity Index. This information is located now on page 8, para 1.

The author should highlight the cross-sectional study design, which provides no basis for temporal ordering of the observed associations and do not imply causation. However, caution in drawing conclusions concerning causality does not lessen the value of the findings included, but points to the need for more methodologically rigorous designs in future research to advance our understanding for this important matter. Furthermore, I suggest that the authors add a comment about possible biases (e.g. selection bias) due to the study design.

Thank you. We have added the concern about cross-sectional study design to the study limitations section on page 17. The concerns about bias have been identified on page 7, as indicated above.

So far, the age of the participants has been not highlighted in the discussion. As mentioned previously (e.g.: Schlögl M et al., BMJ Case Reports 2018), the clinical symptoms of an acute myocardial infarction differ significantly between age, gender and ethnicity, which will have significant clinical implications especially for elderly women from ethnic minorities.

Thank you for this comment. We would like to point out that our analyses were controlled for age and sex as well as age, sex, and other known co-variates, based on their known association with symptoms.

So far, the authors only highlighted the potential cultural aspect for their main finding. However, enhanced physiological pain sensitivity in minority groups has been proposed as a contributing factor that might partially explain the observed ethnic differences in clinical pain reports.

Thank you for this important comment. We have added some text on page 16, para 2 to address the potential ethnic differences in pain tolerance/sensitivity and subsequent reporting. We believe this contributes well to the overall findings.

VERSION 2 – REVIEW

REVIEWER	Mathias C. Schlögl, MD, MPH Department of Palliative Care, University Hospital Zurich, Switzerland
REVIEW RETURNED	15-Oct-2018

GENERAL COMMENTS	The authors addressed all my previous concerns sufficiently. I recommend this paper for publication.