Author’s response to reviews

Title: Chronic Mountain Sickness Caused Disease Burden among Chinese Young Male Population in Tibet

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Author’s response to reviews: see over
Dear Editor:

Good day!

Thank you very much for your timely feedback and comments on our manuscript, entitled “Burden of Disease Resulting from Chronic Mountain Sickness among Young Chinese Male Immigrants in Tibet” (MS: 1858169545586519), which we found very useful. According to the reviewers’ comments we have revised the manuscript thoroughly.

We submit this revised version for consideration for publication in BMC Public Health. This paper is new. Neither the entire paper nor any part of its content has been published or been accepted elsewhere. It is not being submitted to any other journal. All the authors have read and approved the content, and agree to submit the paper for consideration for publication in the journal. There are no ethical/legal conflicts associated with the article. We hope that the revised manuscript is acceptable for publication.

We would like to introduce the background to high altitude medical research in China. Owing to the importance of Tibet, China’s Party and government pays a great deal of attention to highland research, both on military personnel and civilians, and invests significant funding in this field of research. The academic field of high altitude medicine in China is relatively small; there are both civilian and military researchers and research institutes striving for development in the study field, thus there is not only specialization but also many intersection areas among them. Competition cannot be avoided entirely.

For historical reasons, the researchers in the field consist mainly of pathologists and physiologists; there are few scholars with a background in public health, medical sociology, or health service; and there is also a lack of public health studies in the field. Although there are a few institutes, like ours, which include public health or health service departments or researchers, public health research in the highlands has not been emphasized.

Mr. TY Wu, as we know, is an authoritative scholar who dominates the field of high altitude pathophysiology within high altitude medicine in China, especially with respect to civilian research. However, we consider that he might not have a sufficiently macroscopic view of public health, may not fully understand the methodology of a burden of disease study, and may also not truly recognize the importance of studies in highland military public health. Consequently, when he reviewed our manuscript some misunderstandings may have occurred. Hence, the authors wish to raise a complaint about Mr. Wu
and his comments. We request that you consider this fact during the editing process.

We attach the revised manuscript as a clean version (the changes have been colored red) in MS Word for your consideration. A detailed point by point response to the reviewers’ comments is attached below.

Once again, thank you for considering our manuscript for publication, and we would like to thank all the editors and reviewers for their efforts with the peer review and generous advice.

We are looking forward your reply.

Yours sincerely,

Yuqi Gao & Xiaoxiao Li
Dear Professors:

We would first like to express our sincere appreciation for your insightful comments, which have greatly improved our study. Accordingly, our manuscript has been revised thoroughly and we have addressed each reviewer’s comments point-by-point below.

To reviewer: Hwee Pin Phua

Major Compulsory Revisions

Point 1: Page 7, line 14: The authors had assumed the duration of one subject’s CMS symptoms was an entire one year and the severity of the CMS symptoms was averaged across the year. How was the severity of symptoms for a subject obtained across the year? There was no mentioned that the same subject was followed up across the year. Also, was the same duration assumed for each level of severity?

Reply: It would be very difficult to follow up a subject in the highland troops for an entire year, because it would cost too much money, time, and human resources, and the military population is dynamic. Thus, we adopted a cross-sectional investigation using one time period to represent the situation for the whole year. “The participants were asked to rate each symptom according to three severity levels … during the past month.” During each cross-sectional investigation we travelled more than 5000 km cumulatively on the Qinghai-Tibet plateau to visit the Chinese highland units. Each investigation took about 2–3 months. Each patient was investigated only once in each year. In the manuscript we described that “…assumed the duration of one subject’s CMS symptoms was one entire year and that the severity of the CMS symptoms was averaged across the year”, which means that we assumed that these patients’ symptoms were similar throughout the year, and that the severity of their symptoms was on average similar to the severity reported in the cross-sectional study. Although it may have caused some inaccuracy, we think that this was the most suitable method to use. We have added an explanation to the manuscript (page 7, paragraph 4, and lines 5–7). In the “limitations” section of the manuscript we have also discussed the short-comings of this assumption (page 15, the next to the last paragraph).

Minor Essential Revisions

Point 2: Page 3, 3rd Para: Some explanations are somewhat redundant. It would be good to rewrite this paragraph to explain clearly how the decline in health status caused by CMS has been underestimated in the past, and why it is important to evaluate the disease burden of CMS in the population of interest.

Reply: The paragraph has been rewritten according to your indication.

Point 3: Page 3, last Para, line 2: “…taking into account not only premature death but also physical impairments due to ill-health and the duration of illness.” Suggest the sentence to be changed to “…taking into account healthy years of life lost due to premature death as well as ill-health.”

Reply: The sentence has been replaced. (Page 4, paragraph 2, line 2)

Point 4: Page 4, 3rd Para on “Selection of population groups”, line 2: It was stated that the conditions in the areas selected as the study areas were considered to be representative. Please specify explicitly what these conditions are.

Reply: The conditions of the area cannot be expressed in a few words. There are three strategic roads that supply the main areas of Tibet. These roads are, from west to east, the Xinjiang-Tibet road, Qinghai-Tibet
road, and Sichuan-Tibet road. These roads connect most cities, towns, airports, and strategic locations in Tibet. For military needs and logistic support reasons, Chinese highland units are distributed mainly along and around these strategic roads. Most Chinese highland units are located in these areas, not only in different types of unit but also in different locations (city, rural, or wasteland) and at different altitudes. However, the detail and numbers of each condition were not allowed to be published.

For this study we believed that the Xinjiang-Tibet road and Qinghai-Tibet road areas are representative and these were selected for investigation. First, the two roads run north and south across many degrees of longitude. Second, these two road areas enjoy higher altitude that considered being more representative. Third, there are more military units distributed in these areas at different altitudes. Fourth, the situations of these areas around the two roads are more representative. The Xinjiang-Tibet road connects the areas of the China–India border that still are disputed, while the Qinghai-Tibet road runs with the only railroad in Tibet and the oil pipeline to Lhasa. Thus there is a larger population (troops) and more types of unit in these areas. By contrast, the Sichuan-Tibet Road runs east–west; its average altitude is lower than those of the others; and it has a smaller population and number of unit types. Thus, it was considered not to be more representative than the others.

We consider that the situation and reasons abovementioned are sufficient to point out the relevance of our selection. Of course, there are also some other important reasons for the selection of these areas. However, these include some military concerns. We think that this article should be a purely academic one. We do not want to describe military affairs in it, which may cause unnecessary and unforeseen problems. We appreciate your understanding on this point.

Point 5: Page 5, line 1: What are the other severe chronic diseases excluded?
Reply: These diseases mainly included chronic skin diseases, chronic oral diseases, chronic digestive diseases, chronic musculoskeletal disorders, and chronic soft tissue injury. We have modified this passage in the manuscript (page 5 paragraph 2, last line).

Point 6: Page 7, line 10 from the bottom: Please elaborate further on the formula used in the multiplicative adjustment method or provide example to show how it is applied in this study.
Reply: According to your comment the adjustment formula has been included in the text (page 8, lines 2–6).

Point 7: Page 9, line 11: “Finally, there was no significant difference between the regular infantry and the support categories.” What is not significantly different between the two categories? Please state.
Reply: We apologize for this lack of clarity. In this sentence we wanted to say that there are no significant differences between the regular infantry and the support group with respect to the rate of CMS. The text has been modified (page 9, last line but four). It also should be pointed out that in Table 3 “Occupation” categorizes the results of the comparison, using the chi-square test, among three occupational groups, while this result is for a comparison between two groups.

Discretionary Revisions
Point 8: Page 4, 3rd Para on “Selection of population groups”, last line: What exactly constitute each unit and how were the servicemen assigned to each unit?
Reply: There were several kinds of highland military unit in this study. For example, frontier station, regular barrack, depot, service station, etc. However, it is forbidden to publish the exact details of the
category of highland unit and the number of each kind of unit, or the exact constitution of each unit. We can only classify the servicemen crudely into the three categories of highland troops. In each unit there are several kinds of servicemen, according to the needs of the unit’s mission; among the different kinds of unit the constituents and their ratios are different; but the details are not suitable for publication.

**Point 9: Page 10, 2nd last Para on “Discussion”:** Are there other locally derived disease weights for disease conditions other than CMS in Tibet? If so, how does these weights compare with those derived for CMS in this study?

**Reply:** To our knowledge, in the past the burden of disease study has been overlooked in public health research on the effects of high altitude in China, therefore there is no other disease weighting in Tibet to compare with ours.
To reviewer: Kaliannagounder Krishnamoorthy
Thank you for your serious review of our manuscript, and thank you for your fair appraisal of our work. We believe that you have a real understanding of the meanings and values of this study without prejudice.
To reviewer: TY Wu

Major comments

First, a larger question is that of the diagnosis of CMS: I believe that the reported CMS cases may be correctly diagnosed as subacute mountain sickness. The reported soldiers were resided in the highland for more than six months; however, more details on length of residence were not clear. Previous studies among Han Chinese immigrants in Tibet has been suggested that CMS requires years of residence at high altitude, healthy Han lowland person can develop CMS during his continuously living at altitudes for 15-20 years, whereas a Tibetan, the period necessary is more than 35-40 years.[1,2] As for Chinese young soldiers, their term of military service is not more than three years. So the time course of altitude residence for developing CMS are shorter in these reported young soldiers. However, they may be consistent with the Indian young soldiers stationed in the Himalayas, healthy lowland soldiers stationed at extreme altitude between 5800 and 6700 m (mean 6060±281 m) for a mean duration of 4.5 months (note: not more than 1 yr), and diagnosed as subacute mountain sickness. [3,4] Although the “consensus statement on chronic and subacute high altitude diseases”[5] haven’t a definite length of residence for CMS, most findings suggestive of both people native to high altitude and lowlanders resident at high altitude for several years are at risk of developing CMS.

Second, in fact, this is an epidemiological study, risk factors such as higher residential elevation, more advanced age (in young soldiers will not significantly contribute to the statistical model), longer highland service years, smoking, and heavy exercise performance (Table 1—6) has been reported previously and repeatedly. Higher BP and higher HR are clinical manifestations of CMS only, not a burden of disease.

Finally, the specific magnitude of the study are limited, as the effects felt apply only to this very specific place and population (young soldiers) so no general public health significance. In addition, Even if the authors used a series of statistically analyses, there was no an important innovation of the epidemiology or pathophysiology of subacute mountain sickness or CMS, and that is not publishable.

Reply:

Thank you for your detailed review of our manuscript and helpful comments. We admit that there are many disputes about the diagnostic criteria for CMS. However, we believe that the disease diagnostic criteria should be open-ended for all scholars, and that the diagnostic criteria used in this study were appropriate for the purpose of the study. In this study we referred some published article and selectively adopted some criteria in our views, although there are something could be discussed. We did not want to develop generalized criteria that could be accepted by the academic circle, but to attempt to evaluate the health of the highland servicemen, because every definition has its limitations. We believe that the duration of highland exposure is not an absolute definition of CMS; by contrast, we believe that there is no threshold between “sub-acute mountain sickness” and CMS, all the concepts are defined relatively. As you know, there are many different diagnostic criteria used in different research articles published, thus we only can make a coherent diagnosis within our own research. In our study, the criterion of “half a year” was effectively sanctioned by its long usage in Chinese military highland research, which should be beyond reproach. We also believe the excessive hypercythemia is a gold standard for the diagnosis of CMS, and if combined with low oxygen saturation it could give an appropriate definition of CMS. In The World Health Organization (WHO) ICD-10, to which we referred, the disease is listed as “secondary polycythemia due to high altitude” and there are no other names for CMS or sub-acute mountain sickness; thus we believe that the disease can be diagnosed in this way. In addition, in many Chinese military health investigation practices, we and our (military) partners have found that exposure to the highland environment for half a year is sufficient to cause a considerable level of excessive hypercythemia in the population of servicemen.
Moreover, the true situation is not that “every soldier serves not more than three years” and “details on length of residence were not clear”. The length of residence in the military population is very easy to define. In highland military units it is very clear when a serviceman enters the highlands and how long he remains there, because the military units are compact organizations with rigorous discipline. Private soldiers may serve for no more than 2 years; non-commissioned officers can serve for a long time, generally 3–8 years or more than 10 years; highland unit officers may live in the highlands longer, sometimes for more than 20 years.

Far more importantly, our study was not, or was not only, an epidemiological study to identify risk factors for CMS but was designed mainly to establish a tool, according to the methodology of WHO, for quantitative estimation of the disease burden in highland troops. Until now, to our knowledge, there has been no study that has used the WHO burden of disease study methodology and the concept of disability adjusted life years in a public health study at high altitude. Although our target population was specific, the military population is one of the largest populations of highland immigrants and therefore deserves specific study, especially in Tibet. The authors believe that generalizability and specificity are both important to all studies; however, it is hard to imagine that one study can be generalized easily and entirely to both the civilian and military populations in Tibet, because the natures of the populations are very different. As a health service department in a military medical study institute, our aim is to develop the policy of the health service troops with regard to health promotion and occupational compensation, and this is sufficient. We also believe that Western scholars will be interested in the public health of Chinese highland troops in Tibet. Moreover, our study is not only the first to establish the disease weights (according to the methodology of WHO) for CMS in troops in Tibet, but also provides a novel view of public health to encourage further study focusing on the disease burden of other highland immigrant populations. Hence, we believe that the work is of academic value and worthy of publication in a high quality international public health journal.

In our study we performed a series of statistical analyses. In fact the aim was not to identify the risk factors for CMS, but to test the validation of the disease burden values and the quantitative relationship between the burden value and these factors. Thus we have not repeated previous research.

Finally, thank you again for your kind comments.