PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Health-Related Quality of Life and its changes of Tibetan population in China: Based on the 2013 and 2018 National Health Services Surveys
AUTHORS	Dou, Lei; Shi, Zhao; Zhaxi, Cuomu; Cidan, Zhuoga; Li, Chaofan; Zhaxi, Dawa; Li, Shun-Ping

VERSION 1 – REVIEW

REVIEWER	Burtscher, Martin University of Innsbruck, Sport Science, Medical Section
REVIEW RETURNED	07-Apr-2023

GENERAL COMMENTS	The present study set out to evaluate altitude-dependent health-related quality of life (HRQoL) in residents (N = 14,752 in 2013 and 13,106 in 2018) of the Tibet Autonomous Region (TAR) (average altitude 4000 m), based on 2 cross-sectional population-based surveys (2013 and 2018). Individuals living between 3500–4000 m were found to have the best HRQoL, but changes from 2013 to 2018 were small. Although the authors deal with an interesting issue, there are several points that need to be addressed before a final recommendation can be made: In the introduction, the authors refer to (negative) health problems in people living at high altitude. This topic needs to be discussed in a more differentiated way as several studies found beneficial health effects when living at moderate and high altitude as well (e.g., PMID: 21406589, PMID: 24890677, PMID: 34083346). In addition, altitude my beneficially affect certain diseases and adversely others. A clear hypothesis is lacking, but should be stated after discussing more extensively potential health effects of high altitude living. Information on the sample analyzed is a bit confusing. In the abstract you refer to a sample of 14,752 and 13,106 participants and in the methods to 10,247 in 2013 and to 6436 participants in 2018. How many people have been included twice, in 2013 and 2018 as well? If you know this data, separate analyses should be performed. I suggest, to include some of the data provided in the supplementary Table 2 (at least total numbers of defined age groups for both sexes of different altitude ranges) into the main paper.

	Please, define the range < 3500 m and that of > 4000 m. Were these the same in 2013 and 2018? The effects of altitude on HRQoL becomes not entirely clear to me. Based on your discussion, it seems that socioeconomic status and related factors are most important determinants of QoL?! What about the "real" altitude-related effects (hypoxia, cold and dry air, UV radiation, etc.) on health and related QoL? If it's not high altitude per se that determines QoL the title should be changed. With regard to physical activity, you report that 92% never exercised, but physical activity (if meaning any movement of the body that requires energy expenditure) includes many activities which may importantly impact on health and QoL – in this regard your data seem unreasonable?! What are "usual activities" reported in Figure 1? Can you report/discuss "real" altitude effects (hypoxia, temperature, radiation, etc.) on Mobility Self-care, Usual activities, Pain/discomfort, Anxiety/depression? The meaning of some sentences is not easy to understand, e.g. "Other studies higher prevalence of oxygen-related cardiovascular diseases, chronic respiratory diseases, digestive diseases, and respiratory infections (e.g., high-altitude pulmonary oedema) with high-altitude". Do you mean hypoxia-related? Please, provide appropriate references for the statements. Please, try to better differentiate between "real" altitude effects and those related to tourism, infra- structures, job opportunities, social and health facilities, etc. In the "conclusions" you repeat the study limitations (which may be extended). Please, correct and provide a meaningful conclusion. Generally, proper proof reading is necessary.

REVIEWER	Ortiz-Prado, Esteban Universidad de Las Américas
REVIEW RETURNED	09-Apr-2023

GENERAL COMMENTS	Reviewer Report: Title: Effect of High-Altitude on Health-Related Quality of Life: Based on the 2013 and 2018 National Health Services Survey of Tibet, China General Comments: The study presented is well-written and the authors have made an effort to use clear and concise language. The objective of the study is not too clear although the methodology is interesting. The data analysis and interpretation appear to be appropriate. However, there are some areas where the authors could improve the manuscript to strengthen their arguments and address some questions. I have made some general and some specific comments Specific Comments:

	It is not clear whether this study is a cross-sectional analysis or an epidemiological design. The authors should clarify this point. The authors should provide more detail about the surveys collected. Were the surveys collected from the same patients in 2013 and 2018 or are independent samples? The authors stratified the populations based on altitude, but there is no rationale for studying populations before and after i.e. 2013 versus 2018. The authors should explain why they compared two populations that can be totally different, and how this may be a confounding factor. I mean what is the main point comparing the effect of better economic situation of Nepal nowadays versus 2013 or are you interested in studying the effects of altitude o this population? The authors should provide statistical comparisons between the different altitude groups and have a stronger discussion on this topic, I was disappointed to see that no other factors are discussed The authors should include an analysis of the effect of environmental factors on high-altitude populations, and why there is a difference in perception of health and quality of life between different altitude groups. The authors should explain why they chose the 3L2018 value set for EQ-5D-3L over the 3L2014 value set. The authors should provide more details on the exclusion criteria and why they were chosen. The authors should discuss the limitations of their study and potential areas for future research. Limitations such as "we did not know if the patient were born at high altitude or was only living at high altitude ?" how you control this confounding ? Overall, the study presented an important sample , but the authors could improve the manuscript by addressing the points mentioned above. Minor comments: Some minor grammatical errors were found throughout the manuscript. Proofreading for grammatical errors and typos would be beneficial. The authors describe the exclusion criteria for the study; however, it would be helpful to include the number of participants excluded based on each criterion. The manuscript could benefit from additional detail regarding the demographic characteristics of the study population, such as the distribution of sex, age, and education level, as well as the number of participants in each category. A more detailed description of the sampling method would be beneficial, particularly for non-specialist readers. In terms of grammar, there are a few minor errors that could be corrected, such as missing articles (e.g., "A chronic condition" instead of "Chronic condition"), inconsistent capitalization (e.g., "Value set" vs. "value set"), and incomplete sentences (e.g., "In this study, we chose to adopt the 3L2018 value set, although the 3L2014 value set has been used more frequently than the 3L2018 value set"). However, overall the language is clear and easy to understand.

VERSION 1 – AUTHOR RESPONSE

Response to the Reviewer 1:
Dr. Martin Burtscher, University of Innsbruck

Q1: In the introduction, the authors refer to (negative) health problems in people living at high altitude. This topic needs to be discussed in a more differentiated way as several studies found beneficial health effects when living at moderate and high altitude as well (e.g., PMID: 21406589, PMID: 24890677, PMID: 34083346). In addition, altitude my beneficially affect certain diseases and adversely others.
A clear hypothesis is lacking, but should be stated after discussing more extensively potential health effects of high altitude living.
Response: Thanks for the comment.
Based on the previous literature, the conclusions on the effect of altitude on health are inconsistent. We were supposed to evaluate the effect of altitude on health-related quality of life (HRQoL), and the results showed that residents at 3500-4000 m altitude had the best HRQoL and those at 1500-3500 m and 4000-5000 m had poorer HRQoL. This can only reveal that there are differences in the HRQoL of residents at different altitudes, and cannot confirm the causal relationship between them. Therefore, we have revised the study objectives based on the reviewers' suggestions.
The objectives of the study was to assess the HRQoL of Tibetan population and its changes over time, and explore the differences in HRQoL for residents at different altitudes. The abstract, methods, results, discussion, and tables and figures in the manuscript have been revised accordingly.

Q2: Information on the sample analyzed is a bit confusing. In the abstract you refer to a sample of 14,752 and 13,106 participants and in the methods to 10,247 in 2013 and to 6436 participants in 2018. How many people have been included twice, in 2013 and 2018 as well? If you know this data, separate analyses should be performed.
Response: Thanks for the suggestion.
We have optimized the abstract and methods sections.
This study recruited 14752 participants in 2013 and 13106 participants in 2018, and after excluding observations with missing values for key variables, 10247 in 2013 and 6436 in 2018 were included in the study analysis.

Q3: I suggest, to include some of the data provided in the supplementary Table 2 (at least total numbers of defined age groups for both sexes of different altitude ranges) into the main paper.
Response: Thanks for the suggestion.
Since we modified the purpose of the study to assess the HRQoL of Tibetan population and its changes over time, and explore the differences in HRQoL for residents at different altitudes, the effect of altitude on HRQoL is no longer one of the study objectives. Based on the new objectives, we have added subgroups for different altitudes, as well as the demographic characteristics of the overall participants and the P-value in Table 1.

Q4: Please, define the range < 3500 m and that of > 4000 m. Were these the same in 2013 and 2018?
Response: Thanks for the suggestion. We have added the definition of altitude grouping in the manuscript, and the definition was consistent in 2013 and 2018.
"we divided the plateau areas into three altitude groups, high (1500–3500 m), very high (3500–4000m), and extreme altitude (4000-5000m). The altitude classification criterion was consistent in two waves of surveys."

Q5: The effects of altitude on HRQoL becomes not entirely clear to me. Based on your discussion, it seems that socioeconomic status and related factors are most important determinants of QoL?! What about the “real” altitude-related effects (hypoxia, cold and dry air, UV radiation, etc.) on health and related QoL? If it’s not high altitude perse that determines QoL the title should be changed
Response: Thanks for the comment. Through two rounds of survey data, we really could not determine the relationship between altitude and HRQoL, and the existing survey data were more related to socioeconomic status, so that we changed the title and the purpose of our study.
The effect of altitude on HRQoL is no longer one of our research objectives, and the title is now "Health-Related Quality of Life and its changes of Tibetan population in China: Based on the 2013 and 2018 National Health Services Surveys".
The study aimed to assess HRQoL of Tibetan and its changes over time, and to explore the differences in HRQoL for residents at different altitudes.

Q6: With regard to physical activity, you report that 92% never exercised, but physical activity (if meaning any movement of the body that requires energy expenditure) includes many activities which may importantly impact on health and QoL – in this regard your data seem unreasonable?
Response: Thanks for the comment. It is inaccurate to use physical activity in our article. In this study, the respondents were asked about the number of times they participated in physical activity per week, such as climbing, ball games, equipment exercise, swimming, jogging, etc. Therefore, we modified and used physical exercise instead of physical activity. The frequency of physical exercise was divided into three groups: never exercised, 1–5 times, and > 6 times.

Q7: What are “usual activities” reported in Figure 1?
Response: “usual activities” was one of dimension of EQ-5D-5L. The meaning of this dimension includes such as work, study, housework, family or leisure activities.
EQ-5D-5L has been developed to describe and value health across a wide range of disease areas. They are also frequently used in research into health in the general population. The EQ-5D-5L descriptive system comprises five dimensions (Mobility, Self-care, Usual activities, Pain/discomfort and Anxiety/depression), and each dimension now has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems.

Q8: Can you report/discuss “real” altitude effects (hypoxia, temperature, radiation, etc.) on Mobility Self-care, Usual activities, Pain/discomfort, Anxiety/depression?
Response: Thanks for the comment.
Environmental data are missing from both surveys, so we cannot report the“real” altitude effects (hypoxia, temperature, radiation, etc.) on Mobility, Self-care, Usual activities, Pain/discomfort, Anxiety/depression. We are aware of this problem, so during this revision of the manuscript, we modified the purpose of this study to assess the HRQoL of Tibetan population and its changes over time, and explore the differences in HRQoL for residents at different altitudes. The effect of altitude on HRQoL is no longer one of the study objectives.

Q9: The meaning of some sentences is not easy to understand, e.g. “Other studies higher prevalence of oxygen-related cardiovascular diseases, chronic respiratory diseases, digestive diseases, and respiratory infections (e.g., high-altitude pulmonary oedema) with high-altitude”. Do you mean hypoxia-related? Please, provide appropriate references for the statements.
Response: Thanks for the suggestion. We have reviewed the manuscript and revised some of the sentences that were not easy to understand. Since we revised the purpose of the study and the effect of altitude on HRQoL was no longer one of the purposes of our study, we removed this sentence in this discussion.

Q10: Please, try to better differentiate between “real” altitude effects and those related to tourism, infra- structures, job opportunities, social and health facilities, etc.

Response: Thanks for the comment. This comment is similar to Q8, and we were unable to distinguish the "real" altitude effects and those related to tourism, infra- structures, job opportunities, and social and health facilities based on the survey data. Therefore, we revised the study purpose, title, abstract, results, discussion, and corresponding figures and tables during this revision.

Q11: In the "conclusions" you repeat the study limitations (which may be extended). Please, correct and provide a meaningful conclusion.
Response: Thanks for the suggestion. It was our mistake. We have revised the conclusion.
"This study revealed the HRQoL of Tibetan population was lower than general Chinese population, and decreased over time between 5 years. There were differences in HRQoL among Tibetan at different altitudes, with residents living at 3500-4000m having the best quality of life. More attention should be paid to those Tibetans who are older, female, unemployed and without formal education. Targeted policies and strategies need to be strengthened, including plateau subsidies, poverty alleviation, primary health service capacity, standardized management of chronic diseases, and health education."

Response to the Reviewer 2:
Dr. Esteban Ortiz-Prado, Universidad de Las Américas, Universitat de Barcelona
Q1: It is not clear whether this study is a cross-sectional analysis or an epidemiological design. The authors should clarify this point.
Response: Thanks for the suggestion. The data used in this study were obtained from two cross-sectional surveys. We have revised in the "Methods" section and in the abstract.
"Data for the cross-sectional study were extracted from the fifth and sixth waves of the NHSS in Tibet, which were conducted in 2013 and 2018."

Q2: The authors should provide more detail about the surveys collected. Were the surveys collected from the same patients in 2013 and 2018 or are independent samples?
Response: Thanks for the suggestion. We have added more details and revised in the "Methods" section.
"Data for the cross-sectional study were extracted from the fifth and sixth waves of the NHSS in Tibet, which were conducted in 2013 and 2018. A multi-stage stratified cluster random sampling strategy was used to select representative participants. Each stage had a systematic random sampling approach. In the first stage, 24 counties were selected in 2013 and 25 counties were selected in 2018 from the seven cities in Tibet in proportion to their population size. In the second stage, 60 towns/sub-districts selected in 2013 and 59 towns/sub-districts were selected in 2018 using the random cluster method according to population size. In the third stage, three villages/communities were randomly selected from each town or sub-district, and 155 villages/communities were selected in 2013 and 159 villages/communities were selected in 2018. The majority of the counties, towns/ sub-districts, villages/communities sampled in 2018 were the same as those sampled in 2013. In the fourth stage, 20 households from each village of community were randomly selected for participation, and 4140 households were selected in 2013 and 4232 households were selected in 2018."
Although not all participants in two waves of the surveys were the same, the majority of the counties, towns/ sub-districts, villages/communities sampled in 2018 were the same as those sampled in 2013.

Q3: The authors stratified the populations based on altitude, but there is no rationale for studying populations before and after i.e. 2013 versus 2018. The authors should explain why they compared two populations that can be totally different, and how this may be a confounding factor.
Response: Thanks for the comment. In the study, data were extracted from the fifth and sixth waves of the NHSS in Tibet, which were conducted in 2013 and 2018. A multi-stage stratified cluster random sampling strategy was used to select representative participants. Although the populations were not identical, the majority of the counties, towns/sub-districts, villages/communities sampled in 2018 were

the same as those sampled in 2013, so that the participants may partly overlap. This is a limitation of the study.
We have added more details about the study design and population, and revised in the "Methods" section.
"Data for the cross-sectional study were extracted from the fifth and sixth waves of the NHSS in Tibet, which were conducted in 2013 and 2018. A multi-stage stratified cluster random sampling strategy was used to select representative participants. Each stage had a systematic random sampling approach. In the first stage, 24 counties were selected in 2013 and 25 counties were selected in 2018 from the seven cities in Tibet in proportion to their population size. In the second stage, 60 towns/sub-districts selected in 2013 and 59 towns/sub-districts were selected in 2018 using the random cluster method according to population size. In the third stage, three villages/communities were randomly selected from each town or sub-district, and 155 villages/communities were selected in 2013 and 159 villages/communities were selected in 2018. The majority of the counties, towns/ sub-districts, villages/communities sampled in 2018 were the same as those sampled in 2013. In the fourth stage, 20 households from each village of community were randomly selected for participation, and 4140 households were selected in 2013 and 4232 households were selected in 2018."

Q4: I mean what is the main point comparing the effect of better economic situation of Nepal nowadays versus 2013 or are you interested in studying the effects of altitude o this population?
Response: Thanks for the comment. The data were extracted from the fifth and sixth waves of the NHSS in Tibet of China. We originally intended to explore the effects of different altitudes on health-related quality of life in Tibetan populations, but we found that we could not draw clear conclusions based on the available data. Therefore, we have revised the study objectives, and the abstract, methods, results, discussion, and tables and figures in the manuscript have been revised accordingly. The objectives of the study was to assess the HRQoL of Tibetan population and its changes over time, and explore the differences in HRQoL for residents at different altitudes.

Q5: The authors should provide statistical comparisons between the different altitude groups and have a stronger discussion on this topic, I was disappointed to see that no other factors are discussed.
Response: Thanks for the suggestion. According to the new objectives, we added more statistical comparisons between the different altitude groups in Table 1 and Table 4, and added "HRQoL of participants at different altitudes" title and content in the "Results" section. We also revised some discussion about the different altitude groups in paragraphs 5 and 6 of "Discussion".

The following paragraph discusses the HRQoL of the 3500-4000m altitude group:
"Compared with other high-altitudes, we found that Tibetans living at 3500–4000 m had the best HRQoL. This could be attributed to Tibet's topography, population distribution, and socioeconomic status. The TAR is a vast territory with a sparse population with high-altitude in the northwest and low in the southeast. The region can be divided into three regions based on altitude. The Qiangtang Plateau in the north (> 5000 m), and the central basin region and Himalayan mountains (4000–5000 m on average). The valleys of the middle and lower reaches of the Yarlung Zangbo River and the three rivers in eastern Tibet have an altitude of 3000–4000 m, and 60% of the population is concentrated there. Of the seven cities surveyed, Lhasa, Shannan, Qamdo, and Shigaze have an average altitude of 3500–4000 m with their GDP ranking among the top four in Tibet according to the Seventh National Census in 2020. Similar results have been reported previously with socioeconomic status significantly associated with higher HRQoL[16]. Socioeconomic status is detrimental to health as it affects people's living and working conditions and restricts accessibility to medical care[35]. Moreover, socioeconomic status affects people's psychological state and cognition of the world around them[36]. During the few last decades, China has implemented strong policies to facilitate economic development in the Qinghai-Tibet plateau (e.g., the Strategy of the Development of China's West). The implementation of supportive strategies should help improve socioeconomic status in the

future, including improving public infrastructure, medical service capacity, and disease prevention improving HRQoL."

The following paragraph discusses the HRQoL of the 1500-3500m altitude group:
"Those living in low-altitude areas (1500–3500m) reported the most problems in anxiety/depression consistent with previous studies. A large sample survey of the prevalence of depression among Tibetans of the Qinghai-Tibet Plateau was 28.6%, higher than that in the general Chinese population and higher than that reported in a western study with high-altitude samples[37]. The prevalence of depression is significantly correlated with climatic pressure, particularly altitude[38]. Generally, the combined effects of harsh natural environment on the plateau, high-altitude hypoxia, low atmospheric pressure, intense ultraviolet radiation, relatively weak community support caused by low population density, and lack of access to mental health resources increases the severity of depression among those living in high-altitude areas[39-41]. In this study, the area with an altitude of 1500–3500 m was located southeast of the TAR. Nyingchi City, with an average altitude of 3100 m, has the lowest altitude and wettest climate in TAR. With convenient transportation and multiple splendid sceneries, tourism is the main source of income in this area, attracting millions of people traveling for sightseeing, mountaineering, and trekking every year[42]. Previous studies have reported a significant association between tourism impact and residents' quality of life[43, 44]. Tourism provides employment opportunities and tax revenues, supports economic diversity, and services and products enjoyed by residents[45, 46]. However, negative impacts of tourisms on residents' HRQoL have been reported including crowding, traffic and parking issues, criminality, and cost of living, changes in hosts' way of life, and friction between tourists and residents[47]. The perceived negative impacts, negative emotions, pressure, and relative deprivation of the residents will affect their subjective well-being, leading to psychological problems including anxiety and depression."

Q6: The authors should include an analysis of the effect of environmental factors on high-altitude populations, and why there is a difference in perception of health and quality of life between different altitude groups.
Response: Thanks for the comment. Similar to the previous questions, we were unable to distinguish the effect of environmental factors on high-altitude population based on the available data. So that, we have revised the study objectives, and to assess the HRQoL of Tibetan population and its changes over time, and explore the differences in HRQoL for residents at different altitudes.
We also revised some discussion about the difference in perception of health and quality of life between different altitude groups in paragraphs 5 and 6 of "Discussion", which was the same as Q5.
The following paragraph discusses the HRQoL of the 3500-4000m altitude group:
"Compared with other high-altitudes, we found that Tibetans living at 3500–4000 m had the best HRQoL. This could be attributed to Tibet's topography, population distribution, and socioeconomic status. The TAR is a vast territory with a sparse population with high-altitude in the northwest and low in the southeast. The region can be divided into three regions based on altitude. The Qiangtang Plateau in the north (> 5000 m), and the central basin region and Himalayan mountains (4000–5000 m on average). The valleys of the middle and lower reaches of the Yarlung Zangbo River and the three rivers in eastern Tibet have an altitude of 3000–4000 m, and 60% of the population is concentrated there. Of the seven cities surveyed, Lhasa, Shannan, Qamdo, and Shigaze have an average altitude of 3500–4000 m with their GDP ranking among the top four in Tibet according to the Seventh National Census in 2020. Similar results have been reported previously with socioeconomic status significantly associated with higher HRQoL[16]. Socioeconomic status is detrimental to health as it affects people's living and working conditions and restricts accessibility to medical care[35]. Moreover, socioeconomic status affects people's psychological state and cognition of the world around them[36]. During the few last decades, China has implemented strong policies to facilitate economic development in the Qinghai-Tibet plateau (e.g., the Strategy of the Development of China's West). The implementation of supportive strategies should help improve socioeconomic status in the

future, including improving public infrastructure, medical service capacity, and disease prevention improving HRQoL."

The following paragraph discusses the HRQoL of the 1500-3500m altitude group:
"Those living in low-altitude areas (1500–3500m) reported the most problems in anxiety/depression consistent with previous studies. A large sample survey of the prevalence of depression among Tibetans of the Qinghai-Tibet Plateau was 28.6%, higher than that in the general Chinese population and higher than that reported in a western study with high-altitude samples[37]. The prevalence of depression is significantly correlated with climatic pressure, particularly altitude[38]. Generally, the combined effects of harsh natural environment on the plateau, high-altitude hypoxia, low atmospheric pressure, intense ultraviolet radiation, relatively weak community support caused by low population density, and lack of access to mental health resources increases the severity of depression among those living in high-altitude areas[39-41]. In this study, the area with an altitude of 1500–3500 m was located southeast of the TAR. Nyingchi City, with an average altitude of 3100 m, has the lowest altitude and wettest climate in TAR. With convenient transportation and multiple splendid sceneries, tourism is the main source of income in this area, attracting millions of people traveling for sightseeing, mountaineering, and trekking every year[42]. Previous studies have reported a significant association between tourism impact and residents' quality of life[43, 44]. Tourism provides employment opportunities and tax revenues, supports economic diversity, and services and products enjoyed by residents[45, 46]. However, negative impacts of tourisms on residents' HRQoL have been reported including crowding, traffic and parking issues, criminality, and cost of living, changes in hosts' way of life, and friction between tourists and residents[47]. The perceived negative impacts, negative emotions, pressure, and relative deprivation of the residents will affect their subjective well-being, leading to psychological problems including anxiety and depression."

Q7: The authors should explain why they chose the 3L2018 value set for EQ-5D-3L over the 3L2014 value set.
Response: Thanks for the suggestion. We have added and revised more explanations in the manuscript.
"The main reason for the choice was based on the participants in the $3L_{2014}$ value set being selected conveniently from big cities in urban areas through quota sampling. While the $3L_{2018}$ value set, a more representative sample of respondents was obtained from both rural and urban areas using a random sampling method[22]. The rural population accounts for half of the Chinese population, and large disparities exist in socioeconomic status, lifestyle, and health status between urban and rural areas in China[23]. In the two waves of NHSS in the TAR, more than 75% of participants were from farming and pastoral areas. Therefore, the $3L_{2018}$ value set, which more closely matches the distribution of the Tibetan population, was used in this study."

Q8: The authors should provide more details on the exclusion criteria and why they were chosen.
Response: Thanks for the suggestion. We have added and revised more details in the Manuscript.
"The exclusion criteria in this study were as follows: (1) participants aged < 15 years were excluded since the EQ-5D-3L is recommended to be used among ≥15 years by the user guide (n=3412 in 2013 and n=2677 in 2018); (2) participants who did not answer the questionnaires by themselves were excluded since the EQ-5D-3L need to be self-complete (n=1001 in 2013 and n=3798 in 2018); (3) participants with missing values for key variables including socio-demographic characteristics were excluded (n=4 in 2013 and n=1 in 2018); (4) participants with ethnicities other than Tibetan were excluded (n=88 in 2013 and n=194 in 2018). Overall, final sample size of 10247 in 2013 and 6436 in 2018 were included in this study for analysis."

Q9: The authors should discuss the limitations of their study and potential areas for future research. Limitations such as "we did not know if the patient were born at high altitude or was only living at high altitude ?" how you control this confounding ?

Response: Thanks for the suggestion. We have added and revised this point in the limitations.
"Second, the participants recruited in the surveys were those had lived in Tibet for more than six months; however, we could not determine if they were born in Tibet or came to work from other low-altitude areas. A small-scale survey could be conducted to refine the participant inclusion criteria to validate the study findings in the future."

Q10: Some minor grammatical errors were found throughout the manuscript. Proofreading for grammatical errors and typos would be beneficial.
Response: Thanks for the suggestion. We have Proofread some grammatical errors and typos.

Q11: The authors describe the exclusion criteria for the study; however, it would be helpful to include the number of participants excluded based on each criterion.
Response: Thanks for the suggestion. We have added and revised more details in the Method section.
"The exclusion criteria in this study were as follows: (1) participants aged < 15 years were excluded since the EQ-5D-3L is recommended to be used among ≥15 years by the user guide (n=3412 in 2013 and n=2677 in 2018); (2) participants who did not answer the questionnaires by themselves were excluded since the EQ-5D-3L need to be self-complete (n=1001 in 2013 and n=3798 in 2018); (3) participants with missing values for key variables including socio-demographic characteristics were excluded (n=4 in 2013 and n=1 in 2018); (4) participants with ethnicities other than Tibetan were excluded (n=88 in 2013 and n=194 in 2018)."

Q12: The manuscript could benefit from additional detail regarding the demographic characteristics of the study population, such as the distribution of sex, age, and education level, as well as the number of participants in each category.
Response: Thanks for the suggestion. We added some demographic characteristics of the overall population, the distribution of the population in the three altitude groups in Table 1. Additional details were also added in the "Results" section of the manuscript.
"Participant characteristics
The characteristics of the participants are listed in Table 1. In 2013, more than half of the participants were in the 15–44 years age group (56.2%), and older participants accounted for < 15% of the participants (11.0%) and less than half of the participants were male (46.5%). Moreover, 57% of participants had never received education and 14.98% of the participants were unemployed. More than four out of five participants resided in rural areas (84.9%) with an average altitude of 3838 ± 526 m. Overall, 11.35% of participants reported having a disease during 2 weeks before data collection, while, more than half of participants (65.6%) had no chronic diseases during the past 6 months.
In 2018, the sociodemographic characteristics of the participants were basically the same as those in 2013. The average age was 45.22 ± 14.71 years, and more than half of the participants were female (56.6%). Of the participants, 52.0% never had education, 81.2% were employed, 78.3% were married, and 77.5% lived in rural areas with an average altitude of 3903 ± 495 m. Most of the participants (85.1%) were non-smokers, and 62.3% had never engaged in weekly physical exercise during the past 6 months. Compared two waves of surveys, participants in the 2018 were more female (P<0.001), reported a higher level of education (P<0.001), had a lower employed proportion (P=0.008), more lived in urban with more high altitude (P<0.001)."

Q13: A more detailed description of the sampling method would be beneficial, particularly for non-specialist readers.
Response: Thanks for the suggestion. We have added and revised more details about the sampling method in the Method section.
"A multi-stage stratified cluster random sampling strategy was used to select representative participants. Each stage had a systematic random sampling approach. In the first stage, 24 counties were selected in 2013 and 25 counties were selected in 2018 from the seven cities in Tibet in

proportion to their population size. In the second stage, 60 towns/sub-districts selected in 2013 and 59 towns/sub-districts were selected in 2018 using the random cluster method according to population size. In the third stage, three villages/communities were randomly selected from each town or sub-district, and 155 villages/communities were selected in 2013 and 159 villages/communities were selected in 2018. The majority of the counties, towns/sub-districts, villages/communities sampled in 2018 were the same as those sampled in 2013. In the fourth stage, 20 households from each village of community were randomly selected for participation, and 4140 households were selected in 2013 and 4232 households were selected in 2018."

Q14: In terms of grammar, there are a few minor errors that could be corrected, such as missing articles (e.g., "A chronic condition" instead of "Chronic condition"), inconsistent capitalization (e.g., "Value set" vs. "value set"), and incomplete sentences (e.g., "In this study, we chose to adopt the 3L2018 value set, although the 3L2014 value set has been used more frequently than the 3L2018 value set"). However, overall the language is clear and easy to understand.
Response: Thanks for the suggestion. We reviewed the manuscript and made changes to some grammar, sentences, spelling, etc.

VERSION 2 – REVIEW

REVIEWER	Burtscher, Martin University of Innsbruck, Sport Science, Medical Section
REVIEW RETURNED	26-Jul-2023

GENERAL COMMENTS	I appreciate the efforts made by the authors in order to revise their manuscript. It has really improved and I only have 2 minor suggestions: 1) Despite focusing on QoL, you should consider previous findings on general health effects of living at moderate and high altitudes (in the intro and discussion section as well). 2) Your definition of high-altitude ranges "high (1500–3500 m), very high (3500–4000m), and extreme altitude (4000-5000m)" is very uncommon and arbitrary. You should at least refer to that and better justify the chosen classification.

VERSION 2 – AUTHOR RESPONSE

Response to the Reviewer 1:

Dr. Martin Burtscher, University of Innsbruck

Q1: Despite focusing on QoL, you should consider previous findings on general health effects of living at moderate and high altitudes (in the intro and discussion section as well).

Response: Thanks for the suggestion.

We have added some previous findings on general health effects of living at moderate and high altitudes in the Introduction and Discussion.

“High-altitude areas present a complex ecology in physical environment and population characteristics including genetics, lifestyle, socioeconomic factors, and access to medical care[9], directly or indirectly impact health[10]. Previous studies have reported that high-altitude is strongly associated with the many health issues including psychiatric disorders [11, 12], hypertension[6, 13], and cardiovascular diseases[10].”

“This could be attributed to many reasons. First, most Tibetan tend to stay at their altitude of residence for extended periods of time, the complex interaction between genetic and environmental influence led to the extraordinary ability to adapt to their hypoxic environment, and less susceptible to chronic mountain sickness[41].”

Q2: Your definition of high-altitude ranges “high (1500–3500 m), very high (3500–4000m), and extreme altitude (4000-5000m)” is very uncommon and arbitrary. You should at least refer to that and better justify the chosen classification.

Response: Thanks for the suggestion.

We have added explanation of the reasons for the altitude groupings, as well as some supporting literature.

“The average altitude of Tibet is above 4000 m, and the high altitude (3500-5000 m) and extreme altitude areas (> 5000 m) account for 93.69% of the land area of the TAR[29]. The altitude range of the two surveys was 1974 ~4936 m, and the average altitude was 3863 ± 515 m, with no extreme altitude areas. In addition, we considered the number of villages and participants in different altitude groupings. Therefore, we divided the plateau areas into three altitude groups, high (1500–3500 m), very high (3500–4000 m), and extreme altitude (4000-5000 m) based on the China’s policy of subsidizing plateau areas in this study [30].”