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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Sexual well-being among older adults in China (SWELL): protocol for a multicenter cross-sectional study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Wang, Bingyi; Peng, Xin; Liang, Bowen; Fu, Leiwen; Tian, Tian; Liu, Jiewei; Li, Yuwei; Li, Xinyi; Wang, Shihao; Zheng, Weiran; Xiao, Xin; Shi, Tongxin; Cao, Gaozhou; Ouyang, Lin; Wang, Ying; Tucker, Joseph; Tang, Weiming; Wu, Dan; Meng, Xiaojun; Yu, Maohe; Wu, Guohui; Cai, Yong; Zou, Huachun</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Hira, Subhash</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Washington, Global Health</td>
<td></td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>05-Oct-2022</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GENERAL COMMENTS</th>
<th>General Comments: It is a well-designed protocol for exploring sexual well-being of communities. However, authors have not included the questionnaire and descriptive tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods:</td>
<td>1. Line 237: Blood testing can be expanded to include HIV, HBs, HCV</td>
</tr>
<tr>
<td></td>
<td>2. Line 123: replace ‘region’ with ‘countries’</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
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<th>Lankowski, Alexander</th>
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<td>Fred Hutchinson Cancer Center, Vaccine &amp; Infectious Disease Division</td>
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<td>REVIEW RETURNED</td>
<td>24-Oct-2022</td>
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| GENERAL COMMENTS | General Comments: |
This protocol manuscript describes plans for a large, multi-center, cross-sectional study of sexual health and well-being among older adults in China, including a dedicated subgroup for people living with HIV that will comprise roughly one sixth of the overall sample. Data collection includes both a survey component (adapted from an existing sexual health survey from the U.K.) and a laboratory testing component to assess for comorbid medical conditions, including a limited STI evaluation (syphilis serology), and to measure sex hormone levels. The authors provide a well-stated rationale for why such a study is needed, and the study design and methodologies they outline appear to be sound. A particular strength is the multi-center, multi-stage sampling approach that the research team plans to employ, which seems likely to produce a broadly representative sample of the population of interest with regard to geographic region, age strata, and gender. The one area that stands out as needing further attention relates to the level of specificity of the research questions and the planned data analysis. The inclusion of additional details about the study’s main hypotheses, key variables of interest, and anticipated results would serve to further strengthen this otherwise solid manuscript.

Specific Comments:
1. Introduction (line 129): the authors list three “research questions”, but these are somewhat vague. As currently stated, these are not even really questions but rather general topic areas (e.g., “Sexual behaviors among older adults”). It would be helpful if the authors could provide a bit more detail here, perhaps by framing the research questions in terms of the specific key hypotheses that the study is seeking to test.
2. STROBE checklist item #7: also related to the previous comment, in general there is insufficient information provided about the key variables of interest (and their definitions). What are the main exposures (i.e., independent variables) of interest? What are the main ‘outcomes’ (i.e., dependent variables) of interest? And how are key variables of interest (e.g., “sexual dysfunction”) being defined? From the description of the sample size calculation, it can be inferred that “sexual dysfunction” is an important ‘outcome’ variable in the planned analysis, but there is no reference to how this is defined. Although it is not necessary to include an exhaustive list and description of every variable (the summary of variables on p.12 lines 204-207 is sufficient in most cases), a specific definition should be provided at very least for the set of key exposures/outcomes that are most relevant to the primary analysis.
3. STROBE checklist item #12: Insufficient detail is provided about the nature of the planned data analysis and statistical methods. For example, what (if any) subgroup or sensitivity analyses are planned? Presumably, this will be done for the OALHIV population, but what about other factors will be considered (e.g., age, gender, sexual orientation, geographic region, etc.)?
4. Methods + Analysis (line 145): the authors describe “meetings for stakeholders”, but it is unclear what kinds of individuals / groups are considered stakeholders (e.g., healthcare providers? research/clinical administrators? the study’s target population [older adults in the community]?)?
5. Table 1: it is unclear what the asterisk (*) next to the item “STI diagnosis and treatment, HPV vaccination, and cervical cancer screening” is meant to denote. Also, it is unclear why the Natsal-3 item “Use of recreational drugs” is omitted from the SWELL survey.
instrument. This is one of only two items that the researchers have chosen to omit (the other being fertility intentions, which seems reasonable to omit in this age group), but no explanation is provided. It seems like substance use would be an important co-factor to include here. Is there a specific reason for this omission?

6. Information about the anticipated dates/timeline for the study do not appear to be included in the manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Subhash Hira, University of Washington, Public Health Foundation of India

Comments to the Author:

General Comments: It is a well-designed protocol for exploring sexual well-being of communities. However, authors have not included the questionnaire and descriptive tools.

Response: Thanks for your comments. The vision of the SWELL Study is to provide a reference for future policy on sexual healthcare by collecting and analyzing data from a multi-center survey about the sexual health of older adults in China. As an innovative study among Chinese older adults, the SWELL Study draws on the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3) experience in the design phase of the survey instrument. Specifically, the survey instrument used in SWELL Study is adapted from the Nastal-3 survey instrument. We have re-clarified this point in the Survey Instruments subsection of the Methods section (Line 208-219). Based on your suggestions, we have added some additional notes on the content comparison (footnotes, Table 1).

Methods:

1. Line 237: Blood testing can be expanded to include HIV, HBs, HCV

Response: Thanks for the suggestion. There is no denying that HBV and HCV are equally important topics of concern to us in the SWELL Study. However, our testing programs were limited by funding. We had to make some trade-offs in the testing programs. The SWELL Study, a specialized survey, mainly focuses on sexual health. HBV and HCV are not classified as sexually transmitted diseases according to the Law of the People’s Republic of China on the Prevention and Treatment of Infectious Diseases. Therefore, HBV and HCV testing are not included. The survey instrument included HBV and HCV infection status as an alternative. Specifically, participants will be asked to report HBV and HCV infection status during the survey phase. We have added a description of the issue in Table 1.

HIV is indeed one of the blood testing programs in the SWELL Study. We skipped the description of HIV testing in the Specimen testing phase section. We have added it, as follows.
“HIV-1 Western Blot Bio-Rad assay (Bio-Rad Laboratories, Redmond, WA, USA) was used to confirm positive samples.” (Line 270-272)

2. Line 123: replace ‘region’ with ‘countries’

Response: Thanks for your comment. We have revised it.

“Much of the understanding of factors that explain variation in sexual health among older adults is mainly based on data from developed countries.” (Line 122-123)

3. Line 175: 600 adults with HIV will be added to the sample. Specific how many men and women with HIV will be recruited.

Response: Thanks for the reminder. We have added the relevant descriptions as shown below.

“600 OALHIV (400 males and 200 females) will be recruited to the SWELL Study.” (Line 180-181)

4. Line 261: add locally prevalent Opportunistic infections detected in patients

Response: Thanks for the suggestion. We have added the relevant descriptions as follows.

“For older adults living with HIV, the following clinical data will be retrieved from medical records: HIV-related medical history and laboratory testing results (e.g. time since HIV diagnosis, duration on ART, viral load, etc.), diagnosis of comorbidities (e.g. arthritis, heart attack, coronary heart disease, angina, other forms of heart disease, hyperuricemia, hypertension, stroke, diabetes, any other muscle or bone disease lasting longer than 3 months, and chronic airways disease.), sexually transmitted infections (e.g. syphilis, chlamydia, and gonorrhea) and opportunistic infections (e.g. herpes zoster, bacterial pneumonia, pulmonary and extra-pulmonary tuberculosis, oral and oesophageal candidiasis, pneumocystis pneumonia, toxoplasmosis, cryptococcal meningitis, non-Hodgkin’s lymphoma, and Kaposi’s sarcoma).” (Line 279-282)

5. Line 278: To be treated for syphilis at the first visit to the designated hospital.

Response: Thanks for the suggestion. We have revised the statement, as shown below.

“Participants diagnosed with syphilis will be treated for syphilis at the first visit to the designated hospital.” (Line 298-299)
6. Line 313: Suggest that authors add other software for qualitative studies eg such as Atlas.ti

Response: Thanks for the reminder. We have added the description of qualitative research software in this section.

“The qualitative analysis will be conducted by the qualitative analysis software, including Atlas.ti (v8.0), and NVivo (v12.0)).” (Line 334-336)

7. Line 349: add behavioral scientists to the list of experts.

Response: Thanks for your comment. We have refined the statement.

“The experts from multidisciplinary domains in SWELL Study, including Public Health, Clinical Medicine, Social Medicine, Health Service Management, Epidemiology, Behavioral Science, and Health Statistics, will provide optimal study oversight.” (Line 373-376)

Reviewer: 2

Dr. Alexander Lankowski, Fred Hutchinson Cancer Center

Comments to the Author:

General Comments:

This protocol manuscript describes plans for a large, multi-center, cross-sectional study of sexual health and well-being among older adults in China, including a dedicated subgroup for people living with HIV that will comprise roughly one sixth of the overall sample. Data collection includes both a survey component (adapted from an existing sexual health survey from the U.K.) and a laboratory testing component to assess for comorbid medical conditions, including a limited STI evaluation (syphilis serology), and to measure sex hormone levels. The authors provide a well-stated rationale for why such a study is needed, and the study design and methodologies they outline appear to be sound. A particular strength is the multi-center, multi-stage sampling approach that the research team plans to employ, which seems likely to produce a broadly representative sample of the population of interest with regard to geographic region, age strata, and gender. The one area that stands out as needing further attention relates to the level of specificity of the research questions and the planned data analysis. The inclusion of additional details about the study’s main hypotheses, key variables of interest, and anticipated results would serve to further strengthen this otherwise solid manuscript.

Response: We sincerely thank you for the reviewer’s comments, which have helped us improve the manuscript. We have revised the manuscript based on your comments. Below are the point-by-point responses.
Specific Comments:

1. Introduction (line 129): the authors list three “research questions”, but these are somewhat vague. As currently stated, these are not even really questions but rather general topic areas (e.g., “Sexual behaviors among older adults”). It would be helpful if the authors could provide a bit more detail here, perhaps by framing the research questions in terms of the specific key hypotheses that the study is seeking to test.

Response: Thanks for your comment. As you mentioned, we seem to propose only three relevant topic areas, which are the ones we are most concerned with. However, it may give the readers an unclear impression or even cause them to underestimate the significance of the SWELL Study. Therefore, following your suggestion, we have specificized our original research questions. In the revised version, we present four specific research questions to help the readers better understand our research hypothesis.

“The main research questions of the SWELL Study include three aspects:

1 What are sexual lifestyles among older adults, such as sexual experience, sexual behaviors, quality of sexual life, sexual needs, and attitude toward sex?

2 What are the correlates of sexual health among older adults?

3 How to improve sexual health among older adults?

4 What are the sexual health services that older adults prefer?” (Line 130-134)

2. STROBE checklist item #7: also related to the previous comment, in general there is insufficient information provided about the key variables of interest (and their definitions). What are the main exposures (i.e., independent variables) of interest? What are the main ‘outcomes’ (i.e., dependent variables) of interest? And how are key variables of interest (e.g., “sexual dysfunction”) being defined? From the description of the sample size calculation, it can be inferred that “sexual dysfunction” is an important ‘outcome’ variable in the planned analysis, but there is no reference to how this is defined. Although it is not necessary to include an exhaustive list and description of every variable (the summary of variables on p.12 lines 204-207 is sufficient in most cases), a specific definition should be provided at very least for the set of key exposures/outcomes that are most relevant to the primary analysis.

Response: Thank you for your suggestion. We have added descriptions of the most important outcome variables in the SWELL Study, as shown below.
“Sexual lifestyles characteristics were the most significant outcome variables. In SWELL Study, older adults who reported recent sexual activity (including vaginal, oral, or anal sex) in the past years were categorized as sexually active. Sexual function was assessed by the Natsal-SF and the lowest quintile of the gender-specific population score distribution was considered low sexual function, as defined by previous studies [19].” (Line 220-225)

3. STROBE checklist item #12: Insufficient detail is provided about the nature of the planned data analysis and statistical methods. For example, what (if any) subgroup or sensitivity analyses are planned? Presumably, this will be done for the OALHIV population, but what about other factors will be considered (e.g., age, gender, sexual orientation, geographic region, etc.)?

Response: Thanks for the comment. Subgroup analysis is indeed an important part of the statistical analysis plan. We have added it to the revised version.

“Meanwhile, the associations between independent variables (e.g. sociodemographic characteristics and general health status) and the outcome variables (e.g. sexual lifestyles characteristics and sexual health indicators) will be analyzed by multivariable logistics models. Subgroup analysis will be performed by studying the differences between age, sex (female/male), HIV status (i.e., OALHIV and older adults living in the community), and geographic region (East, West, South, and North China).” (Line 337-343)

4. Methods + Analysis (line 145): the authors describe “meetings for stakeholders”, but it is unclear what kinds of individuals / groups are considered stakeholders (e.g., healthcare providers? research/clinical administrators? the study’s target population [older adults in the community]?).

Response: Thank you for the reminder. We have added details about stakeholders.

“During the planning phase, meetings for stakeholders (including older adults in the community, older adults living with HIV, healthcare providers, social workers, and research administrators from SWELL Study) are held to discuss the feasibility of the SWELL Study.” (Line 148-151)

5. Table 1: it is unclear what the asterisk (*) next to the item “STI diagnosis and treatment, HPV vaccination, and cervical cancer screening” is meant to denote. Also, it is unclear why the Natsal-3 item “Use of recreational drugs” is omitted from the SWELL survey instrument. This is one of only two items that the researchers have chosen to omit (the other being fertility intentions, which seems reasonable to omit in this age group), but no explanation is provided. It seems like substance use would be an important co-factor to include here. Is there a specific reason for this omission?
Response: Sorry for our negligence. We skipped the footnotes in Table 1. We have now added footnotes. For the topic “STI diagnosis and treatment, HPV vaccination, and cervical cancer screening”, questions about HPV vaccination were not applicable in the SWELL Study because the study population exceeded the maximum age for HPV vaccination. GlaxoSmithKline’s Cervarix®, a bivalent vaccine (2vHPV), and Merck’s Gardasil®, a quadrivalent vaccine (4vHPV), were approved for use in women in China by the China Food and Drug Administration in July 2016 and April 2017, respectively. Merck’s Gardasil®9, a 9-valent HPV vaccine (9vHPV), was licensed in May 2018. Each of the three vaccines is licensed for different age ranges, with 2vHPV recommended for ages 9 through 25 (the recommended age was extended to 45 years by the China Food and Drug Administration on July 2018), 4vHPV recommended for ages 20 through 45, and 9vHPV recommended for ages 16 through 26 (Lin, Yulan et al. doi:10.1016/j.vaccine.2019.09.026). Besides, the pre-survey showed that the prevalence of “Use of recreational drugs” was too low (< 1%, sample size 200), and our expert team supported the results of our pre-survey. So, the topic “Use of recreational drugs” was excluded from the SWELL Study. (Footnote, Table 1)

6. Information about the anticipated dates / timeline for the study do not appear to be included in the manuscript.

Response: We have added the planned start and end dates for the study in the methods section, as follow.

“The planned start and end dates for this study are June 2021 and June 2023, respectively.” (Line 145-146)