PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	CHI study: protocol for an observational cohort study on ageing and mental health in community-dwelling older adults
AUTHORS	Lee, Rachael; Yu, Junhong; Rawtaer, Iris; Allen, Patrick; Bao, Zhiming; Feng, Lei; Feng, Qiushi; Lee, Jeong Kyu; Lim, Chin Tat; Ling, Lieng Hsi; Thang, Leng Leng; Naing, Thet; Wang, D. Y.; Yap, Kai Zhen; Kua, EH; Mahendran, Rathi

VERSION 1 - REVIEW

REVIEWER	Shannon Trecartin Andrews University USA
REVIEW RETURNED	26-Nov-2019

GENERAL COMMENTS	This is an important cohort multiple randomized control trial that incorporates multiple disciplines and a holistic conceptual model. The present protocol describes phase 1, a cohort baseline study and Does not include interventions. The variables are described well, though lack previously found reliability information regarding scales. Limitations are given. This study has the potential to provide significant information for improving mental and physical health in aging adults in Singapore.

REVIEWER	Sophie Holmes Yale University, USA
REVIEW RETURNED	28-Jan-2020

GENERAL COMMENTS	Cohort studies such as this are highly important in understanding the factors associated with aging and how best we can minimize adverse aging-related outcomes. Overall I think this is a highly worthwhile study. However, there are a few things that I think need to be considered/emphasised in the manuscript. Firstly, it would be helpful to understand how this protocol differs (or, more importantly, what it adds) in addition to other large, age-related cohort studies (such as AIBL and ADNI). In these cohort studies, they also collect comprehensive data on biological, lifestyle, psychological, social and demographic variables... They also include genetic and imaging data.

	I am also surprised that a huge aspect of aging - Alzheimer's disease and related dementias - are not mentioned. Please include some discussion around this. Have the authors thought about collecting genetic information from the blood draws? (apologies if I have missed this). In general, some more discussion around how the collected data will be used to inform interventions etc. would be helpful. This would also help readers understand why this study is important/what it adds. The authors do mention that a major limitation is the recruitment of people in a confined area, which, they correctly conclude limits generalizability. Other limitations should also be noted, eg. lack of genetic data. Further, the title includes 'mental health', however, the assessment of mental health does not appear to be that comprehensive, consisting of 2 self-report depression/anxiety measures. I understand that a lot of information is being collected, that subjects cannot realistically be given every measure and that in-depth psych assessments are very time-consuming. But given that mental health is in the title, an acknowledgment that administration of the SCID would be desirable. Finally, the stats are very vague - it is not clear what statistical tests will be run/what the outcomes will be. Which ties back to my previous point on how the data will be used to inform treatments/make a meaningful impact on the field.

VERSION 1 – AUTHOR RESPONSE

Authors' response to reviewers:

Reviewer: 1

Shannon Trecartin

Institution and Country, Andrews University, USA

Comments to Author:

This is an important cohort multiple randomized control trial that incorporates multiple disciplines and a holistic conceptual model.

The present protocol describes phase 1, a cohort baseline study and Does not include interventions. The variables are described well, though lack previously found reliability information regarding scales.

Limitations are given.

This study has the potential to provide significant information for improving mental and physical health in aging adults in Singapore.

Authors' response and actions

Thank you for your feedback on our manuscript. With regards to the validity information of the validated scales used in this study, we have added:

"These measures have been validated in the local context[15, 25-42]. It also comprises novel scales that will be used to test for validity in this sample." (Line 147-148 of marked copy)

Reviewer: 2

Sophie Holmes

Institution and Country, Yale University, USA

Comments to Author:

Cohort studies such as this are highly important in understanding the factors associated with aging and how best we can minimize adverse aging-related outcomes. Overall I think this is a highly worthwhile study.

However, there are a few things that I think need to be considered/emphasised in the manuscript.

Firstly, it would be helpful to understand how this protocol differs (or, more importantly, what it adds) in addition to other large, age-related cohort studies (such as AIBL and ADNI). In these cohort studies, they also collect comprehensive data on biological, lifestyle, psychological, social and demographic variables... They also include genetic and imaging data.

I am also surprised that a huge aspect of aging - Alzheimer's disease and related dementias - are not mentioned. Please include some discussion around this. Have the authors thought about collecting genetic information from the blood draws? (apologies if I have missed this).

Authors' response and actions

Thank you for your feedback.

Firstly, we would like to highlight some differences between the CHI study and other age-related cohort studies. The ADNI and AIBL are valuable studies that have made significant contributions through the use of imaging and genetic data, however they largely focused on treatment and progression of Alzheimer's Disease (AD). In contrast, the CHI study focuses on healthy ageing and its associated factors i.e. participants are likely to be recruited from the healthy ageing spectrum, given the community setting. Hence, AD and related dementias were not thoroughly discussed in the manuscript. Furthermore, this study covers a broader range of health-related measures that were absent in the ADNI and AIBL such as detailed oral examination, cardiovascular scans and biomarkers, speech ability, and olfactory status. Additionally, this study seeks to examine variables that are culturally relevant to the local/Asian context e.g. parenting styles, intergenerational communication and attitudes to ageing.

To provide further clarity to readers, we have included the following in the manuscript:

"Although other larger age-related cohort studies such as the Australian Imaging Biomarkers and Lifestyle study[10] and Alzheimer's Disease Neuroimaging Initiative[11] are notable studies that have collected a wide range of measures (e.g., clinical, cognitive, neuroimaging, lifestyle and genetic data), nonetheless the focus was largely on the treatment and progression of Alzheimer's Disease. Future research is needed to assess other health-related determinants of older adults in the healthy ageing spectrum such as oral health assessments, cardiovascular investigations, speech analysis and olfactory measures." (see Line 22 to 29 of marked copy)

"Although the aforementioned studies on older adults documented valuable findings, some of them mainly focused on the treatment and progression of AD, while most studies did not incorporate other important measures of health such as detailed oral health examination, cardiovascular assessments and biomarkers, olfactory measures or speech analysis. More observational studies using in-depth and culturally relevant assessments of older adults in the healthy ageing spectrum are needed. This calls for greater integration of health, psychosocial and environmental resources through close collaborations among clinicians, researchers and community partners. Thus, the CHI study aims to holistically investigate factors associated to healthy ageing in a community setting using a broad range of health-related measures." (Line 53 to 61)

In general, some more discussion around how the collected data will be used to inform interventions etc. would be helpful. This would also help readers understand why this study is important/what it adds.

Authors' response and actions

We have reworded the research aims and analyses of the manuscript, and included a discussion section to highlight the importance of this study, as follows:

Research aims

"Secondly, this study also acts as a recruitment platform for future interventional studies (e.g., feasibility or full-scale trial) to identify at-risk groups or normal ageing participants. The cohort data will enable the development and evaluation of pharmacological and psychosocial interventions targeted at improving health outcomes for older adults. Specifically, data will be used to identify at-risk groups such as (but not limited to) older adults with subsyndromal depression or anxiety, mild cognitive impairment, medical conditions (e.g., Hyperlipidemia, Diabetes, Hypertension), at-risk of cardiovascular diseases, oral diseases, speech impairment, or sleep apnea. Other future sub-studies will also explore culturally relevant psychosocial factors related to healthy ageing such as intergenerational communication, attitudes to ageing, social networks, satisfaction with life and many more. " (Line 72 to 81)

Analyses

"Specifically, group differences (between cognitive diagnoses or self-reported medical conditions) will be analysed using independent-samples t-tests and analysis of variance (ANOVAs). Relationships between physical and mental health, psychosocial and demographic variables will be analysed using multiple regressions and structural equation models. In addition, mixture models will be used to identify subgroups of participants based on their psychosocial, physical and mental health characteristics." (Line 167 to 172)

Discussion

"Using a cmRCT design, the CHI study seeks to explore vulnerability and resiliency factors associated with ageing with subsequent clinical trials of interventions and community programs that could potentially hold translational significance. The study intends to recruit a thousand older adults and collect a comprehensive set of biological, psychological and social data. Meaningful associations between outcomes measures found will provide significant information on the physical and mental health of older adults in Singapore. Results will also help identify at-risk groups of older adults and test out subsequent interventions targeted at improving health outcomes. In addition, having an interdisciplinary team of investigators enables the introduction of in-depth and novel health assessments such as oral examination, cardiovascular investigations, olfactory test and speech analysis. Given the limited sample size and cost considerations, this study excluded genetic and other in-depth measures (e.g., neuroimaging and Structured Clinical Interview for DSM-5) which could have added value to findings. Moreover, several ageing cohort studies in Singapore[79-81] have previously collected the above-mentioned data; hence due to limited resources, these measures were excluded in favour of other novel measures. Recruitment of participants in a confined area may also affect generalisability of results. Nevertheless, the CHI cohort is culturally relevant and will provide clinicians, researchers, and policy makers with information on improving the physical and mental health of older adults in Singapore." (Line 194 to 212)

The authors do mention that a major limitation is the recruitment of people in a confined area, which, they correctly conclude limits generalizability. Other limitations should also be noted, eg. lack of genetic data. Further, the title includes 'mental health', however, the assessment of mental health does not appear to be that comprehensive, consisting of 2 self-report depression/anxiety measures. I understand that a lot of information is being collected, that subjects cannot realistically be given every measure and that in-depth psych assessments are very time-consuming. But given that mental health is in the title, an acknowledgment that administration of the SCID would be desirable.

Authors' response and actions

Thank you for your suggestions.

Our study did not include neuroimaging, genetic data and SCID as cost, time and expected yield from genetic tests with small sample size were considered. Neuroimaging is relatively costly and there have already been several ageing cohort studies in Singapore with neuroimaging data. Hence, in view of limited resources, we have decided to include other novel measures instead. Given that genetic analyses require very large samples (Vacher et al., 2019; Wang et al., 2019), our expected sample size may be relatively small for such analyses to be worthwhile. Although this study did not include SCID, a second-level screening was conducted by a psychiatrist for participants reporting GDI and GAI scores above the local cut-off point.

We added the following in the manuscript:

Outcome measure (Table 1; Psychiatric symptoms)

"Participants with scores above the local cut-off point that signifies risk of depression and anxiety will undergo an assessment by a psychiatrist and referred for follow-up." (page 14)

Discussion

"Given the limited sample size and cost considerations, this study excluded genetic and other in-depth measures (e.g., neuroimaging measures and Structured Clinical Interview for DSM-5) which could have added value to findings. Moreover, several ageing cohort studies in Singapore[79-81] have previously collected the above-mentioned data; hence due to limited resources, these measures were excluded in favour of other novel measures. Recruitment of participants in a confined area may also affect generalisability of results. "(Line 204 to 210)

References:

Vacher M, Porter T, Villemange VL, et al. Validation of a priori candidate Alzheimer's disease SNPs with brain amyloid-beta deposition. Scientific Reports2019;9(17069) doi: 10.1038/s41598-019-53604-5

Wang T, Han Z, Yang Y, et al. Polygenic risk score for alzheimer's disease is associated with ch4 volume in normal subjects. Front Genet2019;10(519) doi:10.3389/fgene.2019.00519

Finally, the stats are very vague - it is not clear what statistical tests will be run/what the outcomes will be. Which ties back to my previous point on how the data will be used to inform treatments/make a meaningful impact on the field.

Authors' response and actions

This has been addressed as above under Analyses.

VERSION 2 – REVIEW

REVIEWER	sophie holmes Yale University, USA
REVIEW RETURNED	27-Feb-2020

GENERAL COMMENTS	Thanks for thoroughly addressing my comments.