PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: Korean Frailty and Aging Cohort Study (KFACS)
AUTHORS	Won, Chang Won; Lee, Seoyoon; Kim, Jinhee; Chon, Doukyoung; Kim, Sunyoung; Kim, Chang-O; Kim, Mi Kyung; Cho, BeLong; Choi, Kyung Mook; Roh, Eun; Jang, Hak Chul; Son, Sang Joon; Lee, Jin-Hee; Park, Yong Soon; Lee, Sam-Gyu; Kim, Bong Jo; Kim, Hyeon Ju; Choi, J; Ga, Hyuk; Lee, Kee Jae; Lee, Yunhwan; Kim, Miji

VERSION 1 – REVIEW

REVIEWER	Tu Nguyen The University of Sydney, Australia
REVIEW RETURNED	30-Nov-2019

GENERAL COMMENTS	This is a well-written manuscript. The KFACS will provide valuable data for investigating the risk factors of frailty and building an evidence base for the prevention and management of frailty for older people in Korea. Please find the following my comments: 1. Abstract: inclusion and exclusion criteria should be presented in the "Participants" section. 2. Page 8, lines 16-23: please provide justification for inclusion criteria. Why age 70-84? Why older people aged from 65 to 70 were not included? (the prevalence of pre-frailty may be high in people aged 65 to 70 years, which can be important for prevention strategy). Was serious cognitive impairment defined by MMSE? if yes please provide a cut-point 3. Page 8, lines 26-37: please provide a response rate. How many people were approached for the study and how many people agreed to participate? 4. Page 14, lines 30-31: please provide justification for the method of collecting medical conditions. Did the researchers use a pre-defined list of chronic health conditions?

REVIEWER	Minhui Liu Johns Hopkins University
REVIEW RETURNED	02-Dec-2019

GENERAL COMMENTS	The purpose of this study is to initiate a nationwide, population-based prospective cohort study of older adults living in the community to assess their frailty status and explore transitions between frailty states over time. The study is of interest to readers and also important in the field of frailty management in older adults. However, there are many methodological issues that should be resolved for publication. The English language should

	be edited before publication. Below are some comments for improvement. Abstract: 1. Participant section: what is the age eligibility criteria? Also, the authors should include some key characteristics that were used to define their target population. 2. Findings to date: the authors could have organized the variables in a more clear way, such as exposure and outcomes or independent and dependent variables. 3. Future plans: this part can be more specific; maybe the authors could link their future plans to their study aims: why they want to create this cohort study. Introduction 1. First paragraph: the authors mentioned percentages of older adults in different age range but it would be better if they could also add that the prevalence of frailty increases with age. 2. The rationale for creating this cohort study was not well explained. Certain things to consider: why a particular Korean cohort is needed? May the pathology of frailty in Korean population be different from older adults in other countries? What particular research questions related to the Korean population that they want to answer? How the proposed specific aims can be supported by current literature and research gaps? 3. For the research questions, did the authors have any particular risk factors in mind that they want to study in this cohort? Currently, it is like an explorative study. Cohort description 1. How were the 10 research centers selected? Please explain. 2. Why the age eligibility criteria was over 70 years? What is the definition of older adults in Korea? What is the prevalence rate of frailty among Korean adults between 65 and 70 years? Please explain how this criteria was decided. 3. Why the quota sampling is particularly used? Why older adults over 85 years old were excluded? Did the authors consider the ratio on some other characteristics, such as race and residential locatin (urban or rural)? 4. What did you mean by “move out?” Please be more specific. 5. How did they determine the cognitive function of older adults? 6. How did the research team approach and retain participants in this study? This paper lacks detail on certain methodological considerations. 7. Please correct “2109” and it should be “2019” on page 4. 8. The authors mentioned a list of key variables. Maybe they can explain why these are considered key variables and I think this should be linked to their research questions for study aims. 9. What are the interest of exposures and the potential confounders? 10. Data quality assurance: were two clinical research investigators at each of the 10 participating centers able to interview all participants? if not, who were other researchers and how the data quality was ensured on them? How did the researcher make sure the data quality and security? 11. Were the ethics approval addressed anywhere? Sorry if I missed it. 12. Suggest include brief analysis plans. Findings to date

	1. The design of the sub-cohorts should be put under cohort description and then here is to introduce the main findings to date. 2. What is the main finding for the main cohort? 3. Publications: does this subheading mean all the findings presented below are from the publications by the research team? This section is not that clear. Maybe they should organize this section by using some key variables or key associations. 4. The baseline results should be moved up to the beginning of this section. Strengths and limitations: 1. What are the meanings and implications of the two sub-cohort studies? Maybe it is better to clarify more details. 2. The last paragraph in this section does not quite fit into this section. Please consider removing it. Tables/figures: 1. Table 1 (Page9/27 Line31-34.): Same numbers among all the age groups? There may be copy errors.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name: Tu Nguyen
Institution and Country: The University of Sydney, Australia
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
This is a well-written manuscript. The KFACS will provide valuable data for investigating the risk factors of frailty and building an evidence base for the prevention and management of frailty for older people in Korea.

	Comments raised by reviewer	**Response by author**	**Location in text: page and paragraph reference**
1	*Abstract: inclusion and exclusion criteria should be presented in the "Participants" section.*	Thank you for mentioning this important point. We agree, thus, revised the abstract. *"The inclusion criteria were: having an age of 70 – 84 years, currently living in the community, having no plans to move out in the next 2 years, having no problems with communication, and no prior dementia diagnosis."*	*The inclusion and exclusion criteria were added in abstract 'participants' section.* *– page 5, line 19-24*

2	*Page 8, lines 16-23: please provide justification for inclusion criteria. Why age 70-84? Why older people aged from 65 to 70 were not included? (The prevalence of pre-frailty may be high in people aged 65 to 70 years, which can be important for prevention strategy). Was serious cognitive impairment defined by MMSE? if yes please provide a cut-point*	Thank you for pointing this out. We agree that the justification of including older adults from aged 70 years should be further elaborated for clarification. We added explanation accordingly to the manuscript. Moreover, it was our intent to have an inclusion criterion of "serious cognitive impairment" to refer a person who can clearly state their intentions, and no problem with communications. We, therefore, have revised serious "cognitive impairment" to "no problems with communication with no prior dementia diagnosis". We have revised abstract and introduction section of the manuscript.	*- page 9 , line 27-49* *- page 5, line 22-24* *- page 9 , line 50*
3	*Page 8, lines 26-37: please provide a response rate. How many people were approached for the study and how many people agreed to participate?*	We appreciate the important point. We agree that it would be great to provide a response rate. However, South Korea has relatively strict Personal Information Protection Act, which deterred from us to approach individuals via letters, e-mails, or phone calls, and keep the information of the participants who did not agree. Therefore, after thorough discussion, we decided to use quota sampling, instead of random sampling like other general cohort studies; each center recruited participants by 1:1 face-to-face approach using quota sampling stratified by age and sex at local senior welfare centers, community health centers, apartments, housing complexes, and outpatient clinics. We have noted this point in the limitations section in the original manuscript.	

		"Second, the participants were not selected through probability sampling due to the strengthened data privacy laws that prevented researchers from acquiring the personal information of people living in the communities around the 10 centers." For details, please refer to our response on Dr. Liu's comment on *cohort description #3*. In fact, we had participants who disagreed to participate when we approached them 1:1 face-to-face, unfortunately, the ratio could not be collected due to the circumferences above.	*- page 24 ,* *line 39-42*
4	*Page 14, lines 30-31: please provide justification for the method of collecting medical conditions. Did the researchers use a pre-defined list of chronic health conditions?*	Thank you for your clarification. We have collected medical conditions of the participants as a self-reported physician's diagnosis of medical conditions. We used a pre-defined list of chronic health conditions, which are based on comorbidities according to Charlson's classification, which are categorized as cardiovascular, musculoskeletal/connective tissue, pulmonary, gastrointestinal, endocrine, neurologic, genitourinary, cancer, viral infection, and mental/behavioral disease to collect self-reported and physician-diagnosed chronic diseases. We have revised and its reference to the manuscript accordingly.	*- page 16* *line 48-51*
Dear Dr. Tu Nguyen			

On behalf of the KFACS team, we express gratitude for your insightful comments.

We, the KFACS team, have carefully reviewed your suggestions and revised the manuscript accordingly by incorporating changes.

We would like to inform you two changes that we have made in the manuscript aside from your comments.

First, as of beginning of the January, 2020, we have completed to record the data of the follow-up surveys that were conducted in 2019 (baseline survey conducted in 2017). Therefore, as the KFACS team, after the discussion, we have decided to incorporate our follow-up rates in 2019 with follow-up window time.

The manuscript was revised in page 13, line 21-40.

Secondly, please note that two authors (Dr. Jaekyung Choi, and Prof. Hyuk Ga) have joined in the authors of this manuscript by recognizing their contributions to the KFACS team, and we have made the changes in the authors list.

Again, we appreciate for your comments.

We look forward to hearing from you regarding our submission and would glad to respond to any further questions and comments you may have.

Sincerely,

The KFACS team

Reviewer 2

Reviewer Name: Minhui Liu
Institution and Country: Johns Hopkins University
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
The purpose of this study is to initiate a nationwide, population-based prospective cohort study of older adults living in the community to assess their frailty status and explore transitions between

frailty states over time. The study is of interest to readers and also important in the field of frailty management in older adults. However, there are many methodological issues that should be resolved for publication. The English language should be edited before publication. Below are some comments for improvement.		
Comments raised by reviewer	**Response by author**	**Location in text: page and paragraph reference**
Abstract		
1. Participant section: what is the age eligibility criteria? Also, the authors should include some key characteristics that were used to define their target population.	Thank you for pointing out. The age eligibility criteria and the key characteristics to define target population were added in abstract 'participants' section. Each center tried to recruit participants using quota sampling stratified by age (70 – 74, 75 – 79, and 80 – 84 years with a ratio of 6:5:4, respectively) and sex (male, female with same ratio). "*The inclusion criteria were an age of 70 – 84 years, currently living in the community, having no plans to move out in the next 2 years, and no problems with communication with no prior dementia diagnosis.*"	*The age criteria were added in abstract 'participants' section.* *– page 5, line 19-24*
2. Findings to date: the authors could have organized the variables in a more clear way, such as exposure and outcomes or independent and dependent variables.	Thank you for your suggestion. We agree that in the abstract, the main outcome should be stated in clearer way. Therefore, we have revised the variables to describe frailty for clarification. "*To define physical frailty, the KFACS used a modified version of the Fried Frailty Phenotype (FFP) consisting of five components of frailty: unintended weight loss, weakness, self-reported exhaustion, slowness, and low physical activity*."	*- page 5 , line 26-31*

	Along with the aim of identifying risk factors, outcomes, and transition of physical frailty, the KFACS strive to investigate correlation between other variables including social, nutritional, cognitive, health behaviors and components, environmental, physical components. Therefore, the key variables in a more clear way, it includes all the variables (independent, dependent, confound variables) that we collect.	
3. Future plans: this part can be more specific; maybe the authors could link their future plans to their study aims: why they want to create this cohort study.	We have added specific future plans by connecting with our aims in future plans section of the abstract: "*The KFACS plans to identify outcomes and risk factors associated with frailty by conducting a 10-year cohort study, with a follow-up every 2 years, using 3014 baseline participants.*"	*- page 5, line 43-46*
Introduction		
1. First paragraph: the authors mentioned percentages of older adults in different age range but it would be better if they could also add that the prevalence of frailty increases with age.	We agree. We have added how frailty prevalence increase by age. "*Many recent studies increasingly identify frailty as a major threat to healthy aging, as frailty prevalence increases with age [5-7]*"	*- page 7, line 25*
2. The rationale for creating this cohort study was not well explained. Certain things to consider: why a particular Korean cohort is needed? May the pathology of frailty in Korean population be	Thank you for pointing out. We agree that justification and the need of particular Korean frailty cohort study should be more elaborated.	*- page 7, line 56*

different from older adults in other countries? What particular research questions related to the Korean population that they want to answer? How the proposed specific aims can be supported by current literature and research gaps?	We have added explanations accordingly. "*Because the KFACS will be the first study to examine frailty specifically in a cohort of Korean subjects, it has several important implications for older Korean adults. Firstly, the KFACS will provide the natural history of frailty in Korea, which has never been studied. Secondly, the KFACS was constructed with in-depth considerations of the demographic characteristics of Korean adults – one of the fastest growing aging populations in the world. The KFACS specifically takes into account the rapid trend of increasing life expectancy and the corresponding increase in supportive care expenditures. Moreover, several potential risk factors for frailty are also considered including: nutrition (older Korean adults have relatively poor nutritional statuses, specifically consuming lower levels of protein and calcium, and having higher sodium intakes), physical function (sedentary lifestyle), and social aspects (high poverty and depression rates, and low social activity and participation rates).*"	*- page 8, line 4-27*
3. For the research questions, did the authors have any particular risk factors in mind that they want to study in this cohort? Currently, it is like an explorative study.	Thank you for your pointing out. The researchers at the KFACS team have strived to identify risk factors in diverse aspects to identify outcomes of physical frailty.	

Cohort description		
1. How were the 10 research centers selected? Please explain.	We are glad that you asked for further explanation. We have selected the centers by covering different residential locations (urban, suburban, and rural). We have added a line to explain how we selected. The sentences were modified accordingly.	*- page 9, line 4*
2. Why the age eligibility criteria was over 70 years? What is the definition of older adults in Korea? What is the prevalence rate of frailty among Korean adults between 65 and 70 years? Please explain how this criteria was decided.	Thank you for your comments. Older adult in Korea is defined as a person aged over 65. The latest prevalence rate of frailty among Korean adults are yet to be discussed due to lack of data and cohort studies in Korea, which leads to one of our aims to identify Korean frailty prevalence of Korean older adult population and its transition. By reference, the prevalence of frailty among adults between 65 and 70 was 3.7% based on living profiles of older people survey in 2008 in Korea. The prevalence was 7.4%, 11.6%, and 15.4% on 70-74, 75-79, and 80-84, respectively. Due to its relatively small number, and according to a frailty consensus, it suggested that all persons older than 70 years should be screened for frailty, we have set the starting age from 70 to 84 for this study. We have revised the manuscript accordingly. We agree to add justification of including older adults from aged 70 - 84 years for clarification. The modified and detailed explanation were added in the manuscript.	*- page 9, line 23 -27* *- page 9 , line 27-49*

3. Why the quota sampling is particularly used? Why older adults over 85 years old were excluded? Did the authors consider the ratio on some other characteristics, such as race and residential location (urban or rural)?	We are glad that you made a clarification. The sample frame could not be secured due to relatively strict Personal Information Protection Act in South Korea. (For detailed comments on Personal Information Act, please refer to our response to Dr. Nguyen #3) Therefore, with the reality that random sampling cannot be done, after in-depth debate, the KFACS team came up with quota sampling method in an effort to minimize selection bias by stratifying gender, age, and recruitment place. The justification for using quota sampling were added accordingly. Also, we did not include the oldest old, those aged 85 years or older, because of expected difficulties in enrollment; conducting tests (visits to the center, safety issues); and maintaining follow-up. We added the justification in the manuscript for clarification. South Korea is homogeneous society, where we have less than 4% of immigrants and Koreans with other race in Korea, and when considering elderly population, the proportion of immigrants and Koreans with other race account for less than 0.5%. Therefore, at this time of cohort, we have not considered the race yet, however, it is our intention to include various race in the future. (KOSIS 2582(Korean Statistical Information Service), 2018)	*- page 9, line 14-22* *- page 9 , line 34-49*
4. What did you mean by "move out?" Please be more specific.	Thank you for pointing out. We agree to further elaborate details on 'move out'. As we have aimed to recruit relatively healthy	

	community-dwelling older adults by prioritizing person who can visit the clinical sites, we made an inclusion criterion of a person who has no plans to move out in the next 2 years. In this case, move out refers to the relocation to areas other than three neighboring towns. We have made the changes accordingly.	*- page 9, line 53*
5. How did they determine the cognitive function of older adults?	Thank you for your clarification. It was our intent to have an inclusion criterion of "serious cognitive impairment" to refer a person who can clearly state their intentions, and no problem with communications. We, therefore, have revised serious "cognitive impairment" to "no problems with communication with no prior dementia diagnosis". We made changes in introduction accordingly.	*- page 9 , line 53*
6. How did the research team approach and retain participants in this study? This paper lacks detail on certain methodological considerations.	We appreciate your comment. The detailed methods of team approach and retaining participants in this study was added accordingly. "*Strategies promoting recruitment and retainment included enlisting caregiver assistance, providing transportation for center visit, explaining key test results, informing participants of identified health issues, maintaining regular communication (phone calls, greeting cards for holidays, and*	*- page 13 , line 40*

	birthday), and involving proxy respondents' answer."	
7. Please correct "2109" and it should be "2019" on page 4.	We apologize for the error. We have replaced "2109" with "2019"	*- page 13, line 19*
8. The authors mentioned a list of key variables. Maybe they can explain why these are considered key variables and I think this should be linked to their research questions for study aims.	Thank you for raising an important point. The lists of the variables depicted in the manuscript are the all the variables (independent, dependent, confound variables) that we collect and its references. To diminish further confusion, we decided to delete 'key' in front of variables. Differ from existing disease-oriented frailty cohorts, the uniqueness of the KFACS comes from its diversity in variables particularly representing Korean population; along with the aim of identifying risk factors, outcomes, and transition of physical frailty, other social, nutritional, cognitive, health behaviors and components, environmental, physical components and other studies are available, as it is open to all researchers. The KFACS is a frailty study, therefore, the main outcome would be frailty, focusing particularly Korean community dwelling older adult population.	*- page 14 , line 12* *- Table 2* *- page 16, line 37*
9. What are the interest of exposures and the potential confounders?	As far as we understand, this may have led you a confusion with the word 'key' variable that we indicated in this manuscript. We apologize for confusion. The variables in the manuscript refer to all the variables including independents, dependents and confounders. As the KFACS provide the open data to all the researchers upon request, the	

	interest of exposures and its confounders may vary according to the researchers and it may be difficult to be defined.	
10. Data quality assurance: were two clinical research investigators at each of the 10 participating centers able to interview all participants? if not, who were other researchers and how the data quality was ensured on them? How did the researcher make sure the data quality and security?	We are glad that you asked for the clarification. Two clinical research investigators from each of the 10 centers, thereby having 20 clinical research investigators in total, who carried the study procedures. Therefore, we have modified the manuscript for clarification accordingly.	*- page 21, line 22-33*
11. Were the ethics approval addressed anywhere? Sorry if I missed it.	The ethic approval was addressed under ethics statement on page 16 line 54, which are as follows: The KFACS protocol was approved by the institutional review boards (IRBs) of the clinical research ethics committees of all 10 participating centers, including the coordinating center, Kyung Hee University Hospital, Seoul, Korea (IRB number: 2015-12-103). All participants provided written informed consent. This report was exempted from approval by the IRB of the Clinical Research Ethics Committee of Kyung Hee	

	University Hospital (IRB number: 2019-08-072).	
12. Suggest include brief analysis plans.	We appreciate for your suggestion. We agree to include brief analysis plans in the manuscript. It was added under '*brief analysis plans*' section.	*- page 22, line 38-52*
Findings to date		
1. The design of the sub-cohorts should be put under cohort description and then here is to introduce the main findings to date.	Thank you for your suggestion. We have relocated the design of sub-cohorts under cohort description.	*- page 20*
2. What is the main finding for the main cohort?	Thank you for your clarification. We consider identifying prevalence of frailty among Korean older adult as the main finding. We have stated detailed explanation under findings to date section.	*- page 21, line 44*
3. Publications: does this subheading mean all the findings presented below are from the publications by the research team? This section is not that clear. Maybe they should organize this section by using some key variables or key associations.	We appreciate your clarification. Our intention was to introduce the findings and the articles presented by our researchers using the KFACS data. We apologize with confusion. We have modified this section heading from "publications" to "Publications and findings using KFACS data"	*- page 22, line 7*
4. The baseline results should be moved up to the beginning of this section.	Thank you for your suggestion. We have relocated the baseline results moved to the beginning of the section.	*- page 21, line 44*
Strengths and limitations		
1. What are the meanings and implications of the two sub-cohort studies? Maybe it	We are glad that you pointed out. We agree to put more details on implications and the meaning of	

is better to clarify more details.	two sub-cohort studies. It was added under '*sub-cohort*' section.	*- page 20, line 44-48* *- page 21, line 9-15*
2. The last paragraph in this section does not quite fit into this section. Please consider removing it.	Thank you for your suggestion. After consideration, we decided to remove the last paragraph in this section.	
Tables/figures		
1. Table 1 (Page9/27 Line31-34.): Same numbers among all the age groups? There may be copy errors.	We apologize for the error. We have revised the table accordingly.	*- page 11,* *line 31-34 (Table 1)*

Dear Dr. Minhui Liu

On behalf of the KFACS team, we express gratitude for your insightful comments.

We, the KFACS team, have carefully reviewed your suggestions and revised the manuscript accordingly by incorporating changes.

We would like to inform you two changes that we have made in the manuscript aside from your comments.

First, as of beginning of the January, 2020, we have completed to record the data of the follow-up surveys that were conducted in 2019 (baseline survey conducted in 2017). Therefore, as the KFACS team, after the discussion, we have decided to incorporate our follow-up rates in 2019 with follow-up window time.

The manuscript was revised in page 13, line 21-40.

Secondly, please note that two authors (Dr. Jaekyung Choi, and Prof. Hyuk Ga) have joined in the authors of this manuscript by recognizing their contributions to the KFACS team, and we have made the changes in the authors list.

Again, we appreciate for your comments.

We look forward to hearing from you regarding our submission and would glad to respond to any further questions and comments you may have. Sincerely, The KFACS team

VERSION 2 – REVIEW

REVIEWER	Tu Nguyen The University of Sydney, Australia
REVIEW RETURNED	21-Jan-2020

GENERAL COMMENTS	The manuscript is well written and revised. I have nothing to add.