

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Diet Quality in Relation to Healthy Aging. The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.
AUTHORS	Goshen, Abigail; Goldbourt, Uri; Shohat, Tamar; Shimony, Tal; Keinan-Boker, Lital; Gerber, Yariv

VERSION 1 - REVIEW

REVIEWER	Pilleron, Sophie France
REVIEW RETURNED	17-Jul-2018

GENERAL COMMENTS	<p>Title: Dietary patterns in relation to healthy aging. The Israeli Longitudinal Study on Aging (ILSA): study protocol Major points Investigating the role of dietary pattern in relation to healthy aging is of great importance but it is also very complex. In its current form, the study's protocol is not clear enough to well understand what the authors are intended to do. What is the research question? What are the hypotheses? In the same logic, I don't understand very well what framework for analysis the authors plan to use. What is the operational definition of healthy aging? For instance, is mortality part of their definition (see specific objective 1)? Are frailty and cognitive health part of its definition? What about functional dependency? Another point is the lack of congruency across the different parts of the protocol. For instance, the authors mentioned that they will use logistic regression for their analysis while they plan to use more sophisticated analysis method in the core manuscript including Cox model, propensity score adjustment... It is not clear the link between background information and the study's plan. For instance, why did the authors introduce the concept of MCI while they don't plan to examine it as such? Another important point is that limitations of the study are not well addressed. For instance, examining trajectories of dietary pattern using 2 points of time is not realistic. The authors present the 10-year gap between the 2 waves as strength but to me, it is a limitation. This should be acknowledged as such. The "retrospective assessment" of frailty is a main limitation that has not been addressed as well. The dietary questionnaire to a proxy person may introduce an important bias that once again, has not been addressed.</p> <p>Minor points The protocol deserves thorough English editing. Commonly, baseline is referred as T0 and not T1. It is more and more recognized that the term "elderly" should be replaced by the one "older adults" or "adults aged XX years and</p>
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	older" that are considered as less stigmatising (please, see "Replacing the Elderly With Older Adults in JGSW Publications." (2015): 229-231.)
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REVIEWER	Yu-jintai Qingdao Municipal Hospital, China
REVIEW RETURNED	23-Jul-2018

GENERAL COMMENTS	<p>This is a well-designed, good-quality protocol that aimed to examine the roles of dietary factors in occurrence of frailty and cognitive decline. some minor suggestions are given:</p> <ol style="list-style-type: none"> 1. Page 8, line 10: you might want to describe more details on how you achieve a random sample. 2. Page 8, Line 41: MMSE score of less than 17 is defined as significant decline, how do you define the cutoff 17 ? 3. Page 9, Line 14: You might want to compare the basic characteristics (e.g., age, sex, etc.) between those included and those who refused to participate, especially considering that the response rate is estimated not very high. 4. Page 9, Line 45: Some information is reported by proxy but not the participant per se? this would increase the risk of information bias and you might control the percentage. 5. Page 10, line 17: information about consumption of fish should be also collected. 6. Page 10, Line 38: dietary recall is based on only 24h. I am not sure this is enough to objectively reflect the baseline dietary regular exposure. If you want to do some recommendations on the diet, a regular dietary pattern might be better. Thus, I will suggest that multiple collections of 24h recall be performed and after calculation of coefficient of variation (CV), indexes with score of smaller CV (e.g. <15%) should be included. Otherwise, you can use the average score. 7. Page 11, LINE 41: i think gender difference should be considered in the cutoff setting for other frailty indexes except physical activity. 8. Page 12, Line 4: The definition of cognitive decline based on MMSE should be education-tailored
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: PILLERON Sophie

Institution and Country: France

Major points

1. Investigating the role of dietary pattern in relation to healthy aging is of great importance but it is also very complex. In its current form, the study's protocol is not clear enough to well understand what the authors are intended to do.

RE: We thank the reviewer for this comment and have revised the manuscript thoroughly in order to better describe and clarify the study framework, hypotheses, and measured outcomes. We have

described in detail the changes that were made in the manuscript in the following replies to each reviewer comments.

2. What is the research question?

RE: Our main research objective is to investigate the relationship between overall dietary patterns as measured by the healthy eating index and healthy aging as defined by cognitive function and frailty. The research question has been further clarified in the revised manuscript (p. 7, "General objective").

3. What are the hypotheses?

RE: We hypothesize that diet quality in older adults is predictive of frailty state and cognitive changes. In the revised manuscript, we have added the research hypothesis on page 7, " Research hypothesis" paragraph.

4. In the same logic, I don't understand very well what framework for analysis the authors plan to use. What is the operational definition of healthy aging? For instance, is mortality part of their definition (see specific objective 1)? Are frailty and cognitive health part of its definition? What about functional dependency?

RE: We have addressed this issue in the revised manuscript in the background section (p. 4, "Healthy aging"), pointing out the lack of a "gold standard" definition to the concept of healthy aging, however there is some consensus that 'successful ager' outcome should measure the capacity to function well in domains of cognitive, physical and mental well-being. In our study, we intended to evaluate healthy aging outcome using assessments of cognitive function and frailty. Cognitive function will be assessed according to cognitive performance and preserved functional independence (T1). Frailty syndrome is defined as a progressive age-related cumulative decline in physical, physiological and functional abilities. These two outcomes comprise an adequate assessment of the concept of healthy aging. In the revised manuscript we define in detail how each outcome will be measured in "Data collection" section under "outcome variables" on page 11 (1st and 2nd paragraphs). Regarding research objective A, in order to assess prevalence of frailty at study entry, we intend to retrospectively assess frailty using the Accumulation of Deficits Index (i.e., frailty index) method and develop a frailty index based on T0 data. Due to the limitation of retrospectively assessing frailty, we would like to examine the index predictive value for all-cause and cause-specific mortality categories.

5. Another point is the lack of congruency across the different parts of the protocol. For instance, the authors mentioned that they will use logistic regression for their analysis while they plan to use more sophisticated analysis method in the core manuscript including Cox model, propensity score adjustment...

RE: In the section "Statistical analysis according to specific aims" pages 14-15 we elaborate the planned statistical methods which will include: Cox proportional hazards regression and multivariate logistic regression adjustment will be made for sociodemographic, clinical, and psychosocial variables, via either multivariable adjustment or propensity score. In the revised manuscript we have further indicated that several statistical models will be applied according to each specific objective (p. 3, "Abstract").

6. It is not clear the link between background information and the study's plan. For instance, why did the authors introduce the concept of MCI while they don't plan to examine it as such?

RE: We thank the reviewer for this comment. The background section of the protocol is divided according to the research objectives; First paragraph; general definition of healthy aging, i.e. research outcome, followed by a description of the specific assessments: frailty and cognitive function (2nd and 3rd paragraphs). The last paragraph includes a description of the exposure variable, i.e. dietary

patterns and the healthy eating index. In the revised manuscript we have further clarified and edited each section (p. 4-6, "Background"). The background section corresponds with the "Data collection" section of the Methods where each assessment (exposure and outcome) is described in detail: The healthy eating index score at baseline (exposure variable) and outcome variables which include frailty assessment (p. 11, 1st paragraph) and cognitive assessment (p. 11, 2nd paragraph) at T1. "Data collection" section was edited in the revised manuscript to allow a better understanding of the research framework analysis. In addition, in the revised manuscript we have clarified how MCI will be assessed (p. 12, "Cognitive assessment", 2nd paragraph). Generally, MCI will be assessed according to Peterson et al. (J Intern Med 2014;275(3):214-28) which includes: evaluation of poor performance on MMSE (i.e. a score of 1.5 standard deviations below the age- and education-specific mean) and preserved functional independence according to Katz et al's scale of activities of daily living (ADL) score. Furthermore, in the revised manuscript we re-edit the research design section on page 7 "Research design".

7. Another important point is that limitations of the study are not well addressed. For instance, examining trajectories of dietary pattern using 2 points of time is not realistic. The authors present the 10-year gap between the 2 waves as strength but to me, it is a limitation. This should be acknowledged as such.

RE: We agree, this is a limitation regarding trajectories of dietary pattern. In the revised manuscript we have added a paragraph regarding study limitations acknowledging this limitation (p. 17, "discussion"). However, using these two dietary measurements can be informative in order to examine the stability of general dietary patterns and malnutrition risk changes. We revised objective B and statistical analysis section indicating we intend to investigate long-term global changes of dietary patterns, consumption and nutritional status among study participants (p. 7, "Specific Aims" and p. 14-15, "Statistical analysis according to specific"). In addition, we would like to emphasize that only T0 dietary questionnaire provides the basis for nutritional exposure assessment that is subsequently linked to study outcomes.

8. The "retrospective assessment" of frailty is a main limitation that has not been addressed as well.

RE: We are aware of this limitation, and we would like to stress out that the retrospective assessment, as regards to our general study objective, is done in order to partly control for reverse causality and distinguish between prevalent and incident cases of frailty as written above (comment no. 4). At T1, frailty is assessed by both the Rockwood and colleagues' Deficit Index (J Gerontol A Biol Sci Med Sci, 2007; 62: 738-43) and the Fried and colleagues' Biological Phenotype framework (J Gerontol a-Biol, 2001; 56(3): M146-M56). In the revised manuscript we clarify this point on page 7, "Research design".

9. The dietary questionnaire to a proxy person may introduce an important bias that once again, has not been addressed.

RE: We agree and address this limitation in the revised manuscript in the discussion section indicating that self-report information and information from a proxy can lead to misclassification bias that may lead to under or overestimation of dietary recall, frailty and other outcomes (p. 17, "Discussion"). Generally, at T0 over 95% of dietary questionnaires were self-reported. At T1 we estimate about 85% of dietary questionnaires will be self-reported due to study population estimated average age of 84 years old, some living with a caregiver who is responsible for their daily nutrition. In this context, it is important to note that the initial (T0) –rather than the repeated (T1) – dietary questionnaire provides the basis for nutritional exposure assessment that is subsequently linked to study outcomes. Therefore, given the virtually complete self-reported nutritional data at T0, the suggested bias should be minimal. We have clarified this point in "Research design" section on page 7.

Minor points

10. The protocol deserves thorough English editing.

RE: According to the Reviewer's request, we re-edited the protocol.

11. Commonly, baseline is referred as T0 and not T1.

RE: We thank the reviewer for this comment and revised the manuscript accordingly.

12. It is more and more recognized that the term "elderly" should be replaced by the one "older adults" or "adults aged XX years and older" that are considered as less stigmatising (please, see "Replacing the Elderly With Older Adults in JGSW Publications." (2015): 229-231.)

RE: We thank the reviewer for this comment and revised the manuscript accordingly.

Reviewer: 2

Reviewer Name: Yu-jintai

Institution and Country: Qingdao Municipal Hospital, China

This is a well-designed, good-quality protocol that aimed to examine the roles of dietary factors in occurrence of frailty and cognitive decline. Some minor suggestions are given:

1. Page 8, line 10: you might want to describe more details on how you achieve a random sample.

RE: We thank the reviewer for this comment. The sampling framework was provided by the two major health funds in Israel; Clalit Health Services, and Maccabi Health Services, which represent 86.3% of all older adults citizens in Israel. Lists of members from each of the two health funds were divided into population groups (Jews and Arabs) according to name and identity number. The overall response rate from among successful contacts was 29.1% in the Jewish sector and 35.4% in the Arab sector. In the revised manuscript, we have added a brief description of the sampling method (p. 8, "Mabat Zahav" survey – study population").

2. Page 8, Line 41: MMSE score of less than 17 is defined as significant decline, how do you define the cutoff 17 ?

RE: A MMSE score of less than 17 is commonly defined as severe cognitive impairment (Folstein et al. Journal of the American Geriatrics Society 1985;33: 228-35; Crum et al. Jama-Journal of the American Medical Association 1993;269: 2386-91). Furthermore, this is the same exclusion criteria used at T0. We added the appropriate references in the revised manuscript (p. 8, "Exclusion criterion in current research stage").

3. Page 9, Line 14: You might want to compare the basic characteristics (e.g., age, sex, etc.) between those included and those who refused to participate, especially considering that the response rate is estimated not very high.

RE: We agree and intend to assess compliance and response rates and carry out statistical analysis of baseline characteristics across different response categories after data collection stage is done.

4. Page 9, Line 45: Some information is reported by proxy but not the participant per se? this would increase the risk of information bias, and you might control the percentage.

RE: We agree and acknowledged this limitation as written above (comment no.9 reviewer 1). In the revised manuscript this limitation was added in the discussion (p. 17, "Discussion").

5. Page 10, line 17: information about consumption of fish should be also collected.

RE: Information regarding consumption of fish is collected and is accumulated for in the Healthy Eating Index (HEI) component number 8: "seafood and plant proteins" (p. 10, "Exposure variable").

6. Page 10, Line 38: dietary recall is based on only 24h. I am not sure this is enough to objectively reflect the baseline dietary regular exposure. If you want to do some recommendations on the diet, a regular dietary pattern might be better. Thus, I will suggest that multiple collections of 24h recall be performed and after calculation of coefficient of variation (CV), indexes with score of smaller CV (e.g. <15%) should be included. Otherwise, you can use the average score.

RE: We agree and acknowledge this limitation in the revised manuscript indicating that dietary quality assessment (exposure variable) is based on a single 24-hour dietary recall. Although, evaluation of the HEI score is suitable for a single 24-hour recall of dietary intake (Guenther et al. J Am Diet Assoc 2008;108(11):1854-64; Guenther et al. The Journal of Nutrition 2014;144(3):399-407), individual diets can vary greatly from day to day. Furthermore, we cannot preclude that participants may have changed their dietary habits during the follow-up (p.17, "Discussion"). However, this dietary assessment was conducted by the Israel Center for Disease Control (ICDC) at study entry in 2005.

7. Page 11, LINE 41: i think gender difference should be considered in the cutoff setting for other frailty indexes except physical activity.

RE: According to Fried and colleagues' Biological Phenotype; grip strength, walking speed and physical activity are adjusted for gender. This has been further clarified on page 11, "Frailty assessment."

8. Page 12, Line 4: The definition of cognitive decline based on MMSE should be education-tailored.

RE: Indeed, MMSE scores are education-and age-standardized as written on p. 11, "Cognitive assessment."

VERSION 2 – REVIEW

REVIEWER	Sophie Pilleron France
REVIEW RETURNED	05-Nov-2018

GENERAL COMMENTS	<p>I really thank authors to have taken into account most of my comments. The manuscript is improved but still lacks clarity. The issues raised after the first review still remain in this version. I would advise authors to review their paper carefully.</p> <p>Page 6 lines 30-34: "However, little is ... in isolation": sentence not clear. Nutrients interact each other not dietary behaviour with diet quality!</p> <p>Page 6 line 39: Why talking about nutritional deficiency? Diet quality as assessed by HEI does not assess nutritional deficiency. Authors should be clear with the concepts.</p> <p>Page 7 lines 11-13: The authors should define better healthy aging. Is it defined by good cognitive function or/and absence of frailty? Why using these 2 markers? Why not functional status? Authors should read Rowe JW & Kahn RL (1997) Successful aging. Gerontologist</p>
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37, 433–440.

Page 7 line 19: I don't really understand why authors plan to analyse cause-specific mortality while they are interested in healthy aging. I suggest that they define a broader general objective including more outcomes. A minor point: authors should remove the word "category".

Page 7 line 29: Authors refer to dietary pattern while they refer to diet quality in the introduction. Once again, authors should be clear with the different concepts.

Page 7 lines 35-37: The hypothesis does not match to the general objective. No mention of general wellbeing or other clinical outcomes was done earlier in the paper.

Page 8 lines 7-13: The authors should introduce earlier that they plan to study depression and quality of life and why they plan to study these outcomes.

Page 8 lines 19-20: I don't understand why the authors want to use Fried's frailty they have only at one time while they have Rockwood's index at both times?

Page 8 line 22: I don't understand this sentence: "Follow-up of mortality, overall and across specific categories".

Page 8 lines 37-38: Authors should give more details on time for hospitalization. Does it refer to hospitalization at time of the study? Over the past six months?

Page 8 lines 47- so on: I really appreciate that authors gave more details on sampling. However, the sampling is not clear. Why 5100 people to select? How did you take into account this 2 stage sampling in the analysis? What is the population source? What are lists?

Page 9 line 22: This information was already given earlier. Authors should avoid repetitions.

Page 10 line 9: I would be interested to have more information about anthropometric measurements. Which ones? Which methods?

Page 10 line 11: What about English? It was mentioned earlier in the paper.

Page 10 line 30: What were the results of the pilot study? What was amended? What were difficulties encountered?

Page 12 lines 49-50: what does "recent trajectory" mean? What is the difference between "chronic disease" and "co-morbidity"?

Page 14 line 15: "Mortality" instead of "Mortailty"

Page 15: Statistical analysis plan does not correspond to objectives above. At no time, authors suggested to study malnutrition risk, or to do prediction modelling, or to study correlation between Rockwood and Fried scale. Once again, authors should be congruent throughout the manuscript.

Page 16: part D: The analyses planned are not clear. Authors should review this part.

Page 16 lines 30-40: What do authors plan in case of low missing data number?

Page 17 line 53: The statement "Both frailty and cognitive decline...older people" needs a reference. Functional status (but not frailty) is part of the definition of healthy aging based on Rowe et al. Functional status and frailty are two different concepts. Frailty predicts disability but are not equivalent to (see Fried et al. , 2001).

REVIEWER	Jin-Tai Yu Qingdao University
REVIEW RETURNED	21-Oct-2018

GENERAL COMMENTS	The authors have addressed my comments.
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VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: PILLERON Sophie

Institution and Country: France

I really thank authors to have taken into account most of my comments. The manuscript is improved but still lacks clarity. The issues raised after the first review still remain in this version. I would advise authors to review their paper carefully.

RE: We thank the reviewer. We have revised the manuscript in order to better describe and clarify the study. We have described in detail the changes that were made in the manuscript in the following replies to each comment.

1. Page 6 lines 30-34: "However, little is ... in isolation": sentence not clear. Nutrients interact each other not dietary behaviour with diet quality!

RE: We have rephrased the sentence, indicating that examining the intake of a single nutrient or food group does not account for the complexity of dietary intake, as food and nutrients are not eaten in isolation (p. 6, "Nutrition").

2. Page 6 line 39: Why talking about nutritional deficiency? Diet quality as assessed by HEI does not assess nutritional deficiency. Authors should be clear with the concepts.

RE: We have rephrased the sentence, stating that the concept of diet quality as a determinant of frailty development has not been investigated adequately (p. 6, "Nutrition").

3. Page 7 lines 11-13: The authors should define better healthy aging. Is it defined by good cognitive function or/and absence of frailty? Why using these 2 markers? Why not functional status? Authors should read Rowe JW & Kahn RL (1997) Successful aging. Gerontologist

37, 433–440.

RE: In the revised manuscript we have thoroughly edited the background section. On the first paragraph ("Healthy aging"), we have described our intention to conduct, among current participants, a comprehensive geriatric assessment including physical health, functional status, quality of life, social support, depression, and cognitive function. Since there is no "gold standard" definition to the concept of healthy aging, healthy aging will be assessed by various accepted aspects that will be measured in the study. In the second and third paragraphs ("Frailty" and "Cognitive function"), we tried to explain the focus on these two outcomes. References were added supporting the notion that frailty and cognitive function might be markers of successful aging. Functional status is part of both Mild cognitive impairment (MCI) and frailty index assessments (p.4-6 "Background" section). The predictive role of diet quality will be analyzed for each healthy aging outcome separately, i.e., non-frail

and preserved cognitive function. The "Statistical analysis according to specific aims" section was revised accordingly on page 14.

4. Page 7 line 19: I don't really understand why authors plan to analyse cause-specific mortality while they are interested in healthy aging. I suggest that they define a broader general objective including more outcomes.

RE: Our main objective in "specific aim A" is to assess the prevalence of frailty at study entry. In order to distinguish between prevalent and incident cases of frailty at T1. We intend to retrospectively assess frailty using the Accumulation of Deficits Index (i.e., frailty index) method and develop a frailty index based on T0 data. Due to the limitation of retrospectively assessing frailty, we would like to examine the index predictive value through survival analysis. This was previously suggested by Rockwood et al., as part of a standard procedure for creating a frailty index (BMC Geriatrics. 2008; 8:24). In the revised manuscript specific aim A has been modified accordingly on page 7, "Specific Aims" section.

A minor point: authors should remove the word "category."

RE: In the revised manuscript, we have removed the word "category" (p. 7, "Specific aim").

5. Page 7 line 29: Authors refer to dietary pattern while they refer to diet quality in the introduction. Once again, authors should be clear with the different concepts.

RE: We have revised the manuscript, consistently using "diet quality" throughout the study protocol. Including the revised manuscript title: "Diet Quality in Relation to Healthy Aging" (p. 3, "Abstract").

6. Page 7 lines 35-37: The hypothesis does not match to the general objective. No mention of general wellbeing or other clinical outcomes was done earlier in the paper.

RE: In the revised manuscript, as the reviewer suggested, we have broadened the general research objective including more outcomes (p.7 "General objective"). A description of the study objectives and measurements was added to the background section as written previously on comment no. 3. The research hypothesis has been revised in order to correspond with the general objective of the study (p. 7, "Hypothesis").

7. Page 8 lines 7-13: The authors should introduce earlier that they plan to study depression and quality of life and why they plan to study these outcomes.

RE: We have re-edited the background section on page 4, indicating we intend to study specific age-related questionnaires including physical health, functional status, quality of life, depression and cognitive function as previously written on comment no.3.

8. Page 8 lines 19-20: I don't understand why the authors want to use Fried's frailty they have only at one time while they have Rockwood's index at both times?

RE: Methods to measure frailty vary widely throughout the literature, due to the absence of a "gold standard" measurement. The two most common frailty measurements are Fried's Biological Phenotype and Rockwood Frailty Index (Lancet. 2013; 381: 752-762), with Fried's Biological Phenotype being the most evaluated and frequently used measure of Frailty (BMC Geriatr. 2013; 13; 64). Measuring both at T1 will allow us to evaluate and compare these two models.

9. Page 8 line 22: I don't understand this sentence: "Follow-up of mortality, overall and across specific categories".

RE: We have revised the manuscript accordingly indicating that follow up of mortality will be conducted (p.8, "Research design").

10. Page 8 lines 37-38: Authors should give more details on time for hospitalization. Does it refer to hospitalization at time of the study? Over the past six months?

RE: In the revised manuscript, we have clarified the exclusion criteria that were used at T0. The exclusion criteria included significant cognitive reduction (MMSE<17) and hospitalization at the time of the study (p.8, "Mabat Zahav" survey – study population").

11. Page 8 lines 47- so on: I really appreciate that authors gave more details on sampling. However, the sampling is not clear. Why 5100 people to select? How did you take into account this 2 stage sampling in the analysis? What is the population source? What are lists?

RE: The sampling framework of T0 was carried out by the Israel Center for Disease Control (ICDC) and the Nutrition Department of the Israel Ministry of Health. The population source is older adults aged 65 and over insured by the two major HMO in Israel: Clalit Health Services, and Maccabi Health Services, representing 86.3% of all of the elderly in Israel. The joint list of insured older adults from both HMO was divided into population groups (Jews and Arabs) creating two new lists, one for Jews, and one for Arabs. We have further described the sampling framework and method in the revised manuscript (p. 8-9 "study population" section). In addition, in the revised manuscript (p. 14 "Statistical analysis according to specific aims"), we have added that when appropriate, the sampling approach will be accounted for through weighting.

12. Page 9 line 22: This information was already given earlier. Authors should avoid repetitions.

RE: The information on p.9 line 22 is the exclusion criteria for T1. Exclusion criteria for T0 is stated earlier in the manuscript (p.8 lines 33-40). In the revised manuscript we have further clarified this issue (p. 8, "Mabat Zahav" survey – study population").

13. Page 10 line 9: I would be interested to have more information about anthropometric measurements. Which ones? Which methods?

RE: Anthropometric measurements are described in detail in "Outcome variables" section under anthropometric measurements on page 13. In the revised manuscript we have further clarified the issue pointing out that anthropometric measurements are described in detail in the following sections (p.9, "Data collection").

14. Page 10 line 1c1: What about English? It was mentioned earlier in the paper.

RE: At T0 only two interviews were conducted in English (p. 9, "Mabat Zahav" survey – study population). At T1 we did not translate the questionnaire into English.

15. Page 10 line 30: What were the results of the pilot study? What was amended? What were difficulties encountered?

RE: The research questionnaires undertook minor adjustments after the pilot study. Mostly regarding general instructions for the interviewers. We believe it was because the current study questionnaire (T1) duplicates most parts of the original (T0) questionnaire (p. 7, "Research design" and Fig.1). In the revised manuscript we have clarified this issue (p. 10, "Data collection").

16. Page 12 lines 49-50: what does "recent trajectory" mean?

RE: In the revised manuscript we have rephrased the sentence. Self-rated health questions refer to current status and recent changes (e.g., a year ago, in the last month) (p. 12, "Health status evaluation").

17. What is the difference between "chronic disease" and "co-morbidity"?

RE: We have removed "co-morbidity" in the revised manuscript to avoid repetition. (p.10, "Data collection" and p. 12, "Health status evaluation").

18. Page 14 line 15: "Mortality" instead of "Mortailty"

RE: We corrected the mistake in revised the manuscript (p.13, "Outcome variables").

19. Page 15: Statistical analysis plan does not correspond to objectives above. At no time, authors suggested to study malnutrition risk, or to do prediction modelling, or to study correlation between Rockwood and Fried scale. Once again, authors should be congruent throughout the manuscript.

RE: We have revised the statistical analysis section to better correspond with the revised objectives. We rephrased specific aim B indicating that we intend to examine the predictive role of diet quality in development of frailty, cognitive changes and other healthy aging outcomes among study participants (p. 7, "specific aims"). Assessment of malnutrition risk is included in objective C as part of assessing "nutritional status" among study participants (p.7, "specific aims"). Nutritional status assessments are further described on data collection section (pages 10-11) and eventually on the statistical analysis section (pages 14-15). We have further clarified the planned statistical analysis for each objective (p. 14-15, " Statistical analysis according to specific aims").

20. Page 16: part D: The analyses planned are not clear. Authors should review this part.

RE: We have thoroughly reviewed the statistical analysis section and further clarified the planned statistical analysis for objective C (previously marked D) on p. 14, "Statistical analysis according to specific aims" section.

21. Page 16 lines 30-40: What do authors plan in case of low missing data number?

RE: In case of low missing data, a complete case analysis will likely be performed, i.e., removal of subjects where any of the predictor variables are missing. We have revised the manuscript accordingly (p. 15, "Approach to missing data").

22. Page 17 line 53: The statement "Both frailty and cognitive decline...older people" needs a reference. Functional status (but not frailty) is part of the definition of healthy aging based on Rowe et al. Functional status and frailty are two different concepts. Frailty predicts disability but are not equivalent to (see Fried et al. , 2001).

RE: In the revised manuscript, we have added appropriate references (pages 16-17, "Discussion"). We have thoroughly modified the manuscript in order to better describe and clarify the study framework and objectives as described previously in replay to each comment. Hopefully, we were able to satisfactorily address most concerns pointed out.

VERSION 3 - REVIEW

REVIEWER	Sophie Pilleron IARC, Lyon, France
REVIEW RETURNED	12-Feb-2019

GENERAL COMMENTS	I'm happy with this version. I thank authors for taking into account my (numerous) previous comments. I would just suggest: 1 - to remove the survival analysis from the hypothesis as it was not introduced before
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	<p>2 - to add a reference for the formula used to estimate the height from ulna length; 3 - remove all "scientifically recognized measures".</p> <p>Thank you for this interesting study that I will follow.</p>
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VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Sophie Pilleron

Institution and Country: IARC, Lyon, France

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I'm happy with this version. I thank authors for taking into account my (numerous) previous comments. I would just suggest:

1 - to remove the survival analysis from the hypothesis as it was not introduced before

RE: In the revised manuscript, we have removed survival analysis from the research hypothesis (p. 7, "Hypothesis").

2 - to add a reference for the formula used to estimate the height from ulna length;

RE: In the revised manuscript, we have added the appropriate reference for estimated height calculation according to ulna length (p. 13, "Anthropometric measurements").

3 - remove all "scientifically recognized measures".

RE: We have removed the phrase in the revised manuscript (p. 4, " Background" and p. 7, "Specific aim").

Thank you for this interesting study that I will follow.