PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: The Mature Adults Cohort of the Malawi Longitudinal Study of Families and Health (MLSFH-MAC)
AUTHORS	Kohler, Iliana; Bandawe, Chiwoza; Ciancio, Alberto; Kämpfen, Fabrice; Payne, Collin F.; Mwera, James; Mkandawire, James; Kohler, Hans-Peter

VERSION 1 – REVIEW

REVIEWER	Rajat Das Gupta Arnold School of Public Health, University of South Carolina
REVIEW RETURNED	19-Apr-2020

GENERAL COMMENTS	Kohler et al. presented the profile of Malawi Longitudinal Study of Families and Health (MLSFH-MAC) cohort and presented some preliminary findings. Overall this manuscript has public health significance. However, I have some concerns and comments: 1. Study Population: “Enrollment is 1,266 in 2012, 1,257 in 2013, 1,606 in 2017, and 1,626 in 2018.” Please clarify the following questions and mention them in the manuscript: • Was it an open cohort? • Was it a cohort or a repeated cross sectional study? • How long the participants were followed? • Were the same participants enrolled in the three years or they were different? 2. Please provide the baseline characteristics of those who were dropped out and compared them with the main cohort to see whether they significantly differ or not? 3. Please include a data analysis section since the authors mentioned about some preliminary findings. 4. Findings and discussion section are presented together. They should be presented separately. 5. Please narrate some of the numerical findings in the result section, instead of only mentioning which one is more frequent. 6. Findings: “Longitudinal analyses of the age trajectories of mental health are shown in Figure 3. Importantly, the boxplots document an increase in the prevalence of depression as cohort members get older, confirming the above cross-sectional pattern: in all but the youngest age group, the median PHQ-9 depression score increased as cohort members aged, and in the oldest subset of MLSFH-MAC respondents (aged 75+ in 2018), more than 50% of the respondents experienced mild or worse depressive symptoms in 2018, an increase from only 33% in 2012, and 87% of respondents in this age group reported at least some depressive symptoms.”

	This is an important finding. Please describe the public health implications of this findings. 7. Physical health: “the vast majority of the MLSFH-MAC population has a grip strength below the median of the US population aged 55--64 years (red line), and more than 50% have a grip strength below the 25th percentile of the US population (blue line).” Rather mentioning what do to the red and blue line mean, that should be mentioned in the legend of the figure. 8. Physical health: “In addition, the cross-sectional decline of grip strength with age could reflect cohort differences, with older cohorts having weaker grip strength throughout life due to worse early life determinants of physical health.” Any reference in support of this findings? 9. Was ethical approval for this study taken from any IRB? Was written informed consent taken from the respondents before data collection? Please mention in the main text.

REVIEWER	Janet Seeley London School of Hygiene and Tropical Medicine, UK
REVIEW RETURNED	16-May-2020

GENERAL COMMENTS	This is a useful cohort paper which - with the supplementary material - provides a wealth of information on the cohort. There are a few areas that require attention. Please include a section in the main paper on the ethical scrutiny the research conducted in the cohort/data collection has received from establishment to date. That in itself could be a useful record of consent procedures etc. but also will give the reader information on the agreements reached with participants on the use and management of their data. At the moment `consent' is mentioned in the supplementary material with the bulk of that information being around consent for HIV counselling and testing.  On page 7 - line 49 - you refer to the interviewers as being `carefully-trained' - what does that mean? Page 10 - line 20 - you refer to the findings as being for older people `in Malawi' - elsewhere you are at pains to point out that the cohort is not representative of older people in all parts of Malawi. Please check the paper for places where you have implied the findings are generalisable. On page 11, in the discussion of HIV and older people, it would be helpful to include information on the dates of the roll out of different guidelines for ART, and information of when those different guidelines were implemented in each place and from where people accessed ART. This would provide helpful background information for a reader less familiar with the influence of ART roll out strategies on HIV care for older people. I am somewhat surprised that so few publications from the cohort are referenced in the main paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Rajat Das Gupta

Institution and Country: Arnold School of Public Health, University of South Carolina
Please state any competing interests or state 'None declared': None Declared
Please leave your comments for the authors below
Kohler et al. presented the profile of Malawi Longitudinal Study of Families and Health (MLSFH-MAC) cohort and presented some preliminary findings. Overall this manuscript has public health significance. However, I have some concerns and comments:
1. Study Population: "Enrollment is 1,266 in 2012, 1,257 in 2013, 1,606 in 2017, and 1,626 in 2018." Please clarify the following questions and mention them in the manuscript:
• Was it an open cohort?
Yes, MLSFH-MAC is an open cohort that allows the population to grow over time and enrolls new cohort members when they reach eligibility to be included in the cohort (that is, they turn 45 years of age in the year of the respective cohort follow-up and have participated in the 2008 and 2010 MLSFH data collections.
We have clarified this aspect in the manuscript by inserting the following additional text marked in yellow in section "Cohort Description: Study Population": "The MLSFH-MAC is an ongoing open population-based cohort study of mature adults aged 45 years and older. Enrollment is 1,266 in 2 012, 1,257 in 2013, 1,606 in 2017, and 1,626 in 2018 when last surveyed."
We also clarified this in the abstract by adding "open to "cohort study" in the description of the "Participants".
• Was it a cohort or a repeated cross sectional study?
MLSFH-MAC is a longitudinal cohort study, not a repeated cross-section study. This has been now been clarified at several places in the paper, including in the description of the study population: "[…], the MLSFH-MAC provides two decades of longitudinal cohort data across mid- to older ages, […]". The longitudinal aspect of the cohort is also emphasized in the description of the eligibility criteria to enter the cohort (e.g., being age 45 upon enrollment and being interviewed in both 2008 and 2010) and these eligibility criteria are described in the section "Study population".
In response to the reviewer comments, we have also made the following additions in the manuscript:
We added a statement that the MLSFH Mature Adults Cohort is "an open cohort and allows the enrollment of new cohort members (see changes made to respond to Reviewer's 1 previous comment). As a result, the newly added cohort members are observed and surveyed for a shorter period of time compared to those who were enrolled upon establishing MLSFH-MAC."
A further clarification of this point is also provided in our response to the next comment raised by Reviewer 1.
• How long the participants were followed?
We have clarified this aspect. The duration of follow-up and waves of cohort follow-up since establishing MLSFH-MAC are now specified in several places in the manuscript, such as the description of the "Study population" and Figure 1 that presents the initial MLSFH-MAC sample selection, additional enrollments, mortality and sample attrition during 2012-2018.
Members of the MLSFH-MAC continue to be surveyed. We had planned a 2020 data collection that had to be postponed due to the Covid-19 pandemic 2021 19 (the respective text has been updated in the manuscript). We also clarified the MLSFH-MAC follow-up waves abstract and in the introduction, and the former for instance now includes the following modified text: "The cohort has been followed up in 2013, 2017 and 2018, with a planned data collection in 2021."
In addition to the above revisions, we also highlight in the manuscript more precisely that MLSFHMAC is an ongoing cohort study and the cohort members will continue to be surveyed. For instance, we modified the first sentence in Section "Cohort Description: Study population" as following:
"The MLSFH-MAC is an ongoing open population-based cohort study of mature adults aged 45 years and older. Enrollment is 1,266 in 2,012, 1,257 in 2013, 1,606 in 2017, and 1,626 in 2018 when last surveyed."
• Were the same participants enrolled in the three years or they were different?
The response to this question is very much related to our responses above and has been clarified

throughout the manuscript. For instance, the eligibility criteria and follow up of cohort members have now been modified as follows:
“At each follow up, all existing MLSFH-MAC-eligible respondents were reinterviewed (or approached for interview), and newly-eligible MLSFH respondents were added to the MLSFH-MAC cohort. The largest number of respondents was added in 2017 (423 new respondents), while few respondents newly reached eligibility in 2013 and 2018 (12 and 56 respectively.)”
Since this is an open cohort study design, as a result some MLSFH-MAC study participants have been
observed for shorter period of time. However, even for those who have joint the cohort in 2017 or 2018, we have observations in 2008 and 2010 since this is one of the eligibility requirements to enter the cohort.
We addressed Reviewer’s 1 comment by adding the following underlined text (also marked in yellow in the manuscript) to the original text in Section “MLSFH-MAC Data Collections”: “At each follow up, all existing MLSFH-MAC-eligible respondents were reinterviewed (or approached for interview), and newly-eligible MLSFH respondents were added to the MLSFH-MAC cohort. The largest number of respondents was added in 2017 (423 new respondents), while few respondents newly reached eligibility in 2013 and 2018 (12 and 56 respectively. As a result of this open cohort design, some MLSFH-MAC cohort members have participated in fewer study follow-ups.”
2. Please provide the baseline characteristics of those who were dropped out and compared them with the main cohort to see whether they significantly differ or not?
This information is provided in detail in the “Supplemental Materials”. Specifically, we discuss in the Supplemental Materials:
1. Comparisons of the MLSFH-MAC study population with national representative samples such as the nationally representative survey “Integrated Household Survey” (IHS3) (Section S2 in the Supplemental Materials) and in Section S3 and S3.1 in Supplemental Materials
2. Attrition (and possibility selection) at the initial enrollment in the MLSFH-MAC study in 2012, but comparing all 2008-10 MLSFH study participants who were eligible for inclusion in the MLSFH with the participants who were ultimately enrolled in the MLSFH-MAC baseline survey in 2012.
3. Analyses of attrition in MLSFH-MAC during 2012-18, that is during the course of the MLSFHMAC follow-ups.
Because of the length limitations of BMJ Open manuscripts, there is no enough space to include these results and comparisons in the main text. Yet, Reviewer 1 correctly pointed out that these finding need to be summarize din the main text, and we have therefore included a short discussion of attrition in the main text as part of the Section on “MLSFH-MAC Data Collections”. Specifically we added the following text:
“Additional analyses show that the MLSFH-MAC study baseline population closely matches the rural sub-sample in the 2010 nationally representative Integrated Household Survey IHS3 in key observable characteristics (Supplemental Materials).”
These additional analyses to which we refer in the cited text above are shown in Table S4 in the Supplemental Materials.
And we also included the following text:
“Supplemental analyses show that that the initial enrollment is not selective, and that attrition is positively related to several baseline (2012) characteristics such as being male, being older, having no formal schooling, not being married in 2012, being poor, scoring low on the indicators of subjective well-being, mental or physical health, and being depressed (Supplemental Materials). Of the 181 respondents lost to follow-up during 2012–18, the majority (149) died, and many of the characteristics predicting attrition are predictors of mortality as the most important reason for attrition in the MLSFH-MAC cohort during 2012–18.”
These additional analyses to which we refer in the cited text above are shown in Table S10 in the Supplemental Materials.
3. Please include a data analysis section since the authors mentioned about some preliminary

findings.
This comment was not addressed since following the Editor's comment. Specifically, this comment is related to formatting of the manuscript and is against the instructions for authors.
4. Findings and discussion section are presented together. They should be presented separately.
This comment was not addressed since we followed the editor's comment. Specifically, this comment is related to formatting of the manuscript and is against the instructions for authors.
5. Please narrate some of the numerical findings in the result section, instead of only mentioning which one is more frequent.
In response to this comment, we introduced an additional section that elaborates some of the key findings and their importance and the changes are clearly marked in the manuscript. This addition includes the following text:
"Overall relevance of findings: The gains in adult life expectancy foreshadow a new challenge for which SSA LICs are ill prepared: the shifting disease burden in SSA towards chronic noncommunicable diseases, which has been described as the new frontier in global health.20 The growing emphasis on NCDs in global health is due to at least two reasons: First, NCDs---among the MLSFH-MAC study participants and in SSA LIC populations more generally---are primarily CVD, hypertension, and NCDs-associated functional disabilities. These NCDs increasingly contribute to disease burdens, thereby becoming leading causes of adult morbidity and mortality in SSA, while disease burdens attributable to communicable diseases have been decreasing. Second, NCDs and associated functional disabilities and physical health limitations that have been documented using the MLSFH-MAC have important limiting effects on adult economic activities, which in turn is likely to hamper benefits in SSA of a demographic dividend during which a growing population-share of economically-active adults provides.21 Scholars and NGOs have therefore argued that health research and policies in SSA LICs devote far too few resources to NCDs and their determinants/consequences.22 As a result, studies such as the MLSFH-MAC are critically important to fill very basic knowledge gaps continue to exist with respect to the prevalence of NCDs, their risk factors, and the driving forces behind their relatively recent dramatic increase in SSA LICs. The current knowledge is also very inadequate for understanding the consequences of these shifting disease burden, and for developing adequate public health policy and health-system responses in SSA LICs, including those highlighted in the Malawi National Health Sector Strategic Plan. Such context-specific evidence is necessary as findings from more developed contexts is generally not sufficient for addressing the distinctive knowledge gaps about NCDs in SSA LICs as epidemiological, market, policy and resource contexts differ so much that useful guidance cannot simply be transferred from high-income country research studies."
6. Findings: "Longitudinal analyses of the age trajectories of mental health are shown in Figure 3. Importantly, the boxplots document an increase in the prevalence of depression as cohort members get older, confirming the above cross-sectional pattern: in all but the youngest age group, the median PHQ-9 depression score increased as cohort members aged, and in the oldest subset of MLSFH-MAC
respondents (aged 75+ in 2018), more than 50% of the respondents experienced mild or worse depressive symptoms in 2018, an increase from only 33% in 2012, and 87% of respondents in this age
group reported at least some depressive symptoms."
This is an important finding. Please describe the public health implications of this findings.
We agree with the reviewer that this is an important finding. We have therefore highlighted the public health implications of this research by adding the following text:
"In summary, the above findings indicate a relatively high prevalence of poor mental health among mature adults in rural Malawi that increases strongly with age and affects women more than men. Currently, poor mental health is inadequately addressed by health systems and health policies in Malawi and most other low-income countries, and our findings highlight for the urgency of expending these services."
7. Physical health: "the vast majority of the MLSFH-MAC population has a grip strength below the

median of the US population aged 55--64 years (red line), and more than 50% have a grip strength below the 25th percentile of the US population (blue line).” Rather mentioning what do to the red and blue line mean, that should be mentioned in the legend of the figure.
The meaning of the red and blue lines is denoted in Figure 4 to which we refer here. Following your suggestion, we just removed the respective text (“red line” and “blue line”) in the main text.
8. Physical health: “In addition, the cross-sectional decline of grip strength with age could reflect cohort differences, with older cohorts having weaker grip strength throughout life due to worse early life determinants of physical health.” Any reference in support of this findings?
We now support our findings with additional references as follows:
Kämpfen, Fabrice; Kohler, Iliana V.; Bountogo, Mamadou; Mwera, James; Kohler, Hans-Peter; Maurer, Jü & rgen (2020). Using grip strength to compute physical health-adjusted old age dependency ratios. SSM - Population Health, 11, 100579 DOI: https://doi.org/10.1016/j.ssmph.2020.100579
Kuh, Diana; Hardy, Rebecca; Butterworth, Suzanne; Okell, Lucy; Wadsworth, Michael; Cooper, Cyrus & Aihie Sayer, Avan (2006). Developmental origins of midlife grip strength: findings from a birth cohort study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, Oxford
University Press 61(7), 702-706 DOI: https://doi.org/10.1093/gerona/61.7.702
Sayer, Avan Aihie; Syddall, Holly; Martin, Helen; Patel, Harnish; Baylis, Daniel & Cooper, Cyrus (2008). The developmental origins of sarcopenia. The Journal of Nutrition Health and Aging, Springer 12(7), 427 DOI: https://doi.org/10.1007/BF02982703
9. Was ethical approval for this study taken from any IRB? Was written informed consent taken from the respondents before data collection? Please mention in the main text.
This is a very important point and we should have included the reference to the ethical approvals of our study in the initial submission. Form the beginning to present, all data collections for the MLSFH-MAC study cohort have been approved by both, the IRB at the University of Pennsylvania, the Ethics Committee of the College of Medicine, Malawi and the National Health Sciences Research Committee (NHSRC). Additional details on the informed consent process and training of the survey team members are provided in the Supplemental Materials.
The main body of the manuscript now includes the following new paragraph on IRB approval and human subjects protection, with additional details being provided in the Supplemental Materials:
“Ethics Approval and Informed Consent Procedures: The data collections of the MLSFH-MAC and MLSFH have been approved by the IRB Board at the University of Pennsylvania (IRB Protocols #815016 and #826828), and in Malawi, the MLSFH-MAC and MLSFH research has been approved by
the Ethics Committee of the College of Medicine, Malawi (COMREC, Protocols #P01/12/1165 and #P.04/17/2160) and the National Health Sciences Research Committee (NHSRC, Protocol #19/01/2214). “
Reviewer: 2
Reviewer Name: Janet Seeley
Institution and Country: London School of Hygiene and Tropical Medicine, UK
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
This is a useful cohort paper which - with the supplementary material - provides a wealth of information on the cohort. There are a few areas that require attention. Please include a section in the main paper on the ethical scrutiny the research conducted in the cohort/data collection has received from establishment to date. That in itself could be a useful record of consent procedures etc. but also will give the reader information on the agreements reached with participants on the use and management of their data. At the moment `consent' is mentioned in the supplementary material with the bulk of that information being around consent for HIV counselling and testing.
This is a very important point that was also raised by Reviewer 1. Form the beginning to present, all data collections for the MLSFH-MAC study cohort have been approved by both, the IRB at the

University of Pennsylvania, the Ethics Committee of the College of Medicine, Malawi and the National Health Sciences Research Committee (NHSRC). Additional details on the informed consent process and training of the survey team members are provided in the Supplemental Materials and because of the length limitation we included only the following text:
“Ethics Approval and Informed Consent Procedures: The data collections of the MLSFH-MAC and MLSFH have been approved by the IRB Board at the University of Pennsylvania (IRB Protocols #815016 and #826828), and in Malawi, the MLSFH-MAC and MLSFH research has been approved by
the Ethics Committee of the College of Medicine, Malawi (COMREC, Protocols #P01/12/1165 and #P.04/17/2160) and the National Health Sciences Research Committee (NHSRC, Protocol #19/01/2214).”
On page 7 - line 49 - you refer to the interviewers as being `carefully-trained' - what does that mean?
By “carefully trained” we meant “extensively trained” in the survey methodology, interviewer’s techniques, research ethics, etc. We clarified this point by making the following changes in the text:
“Surveys have been conducted in the local languages (Chichewa, Chiyao and Chitumbuka) by experienced interviewers and/or HIV testing counselors who are extensively trained in the study methodology and instruments at each data collection round.”
Page 10 - line 20 - you refer to the findings as being for older people `in Malawi' - elsewhere you are at
pains to point out that the cohort is not representative of older people in all parts of Malawi. Please check the paper for places where you have implied the findings are generalisable.
We have clarified this throughout the text. Narrowly defined the data represent mature adults in the 3 study regions. Comparisons with nationally representative samples have confirmed that the study population is statistically indistinguishable in key characteristics from older individuals in the rural areas in Malawi, where 85% of the population lives. These comparisons with nationally representative samples are included in the supplemental materials.
In addition, in the section “Strengths and Limitations” we discuss this issue, and have included the following text:
“Some weaknesses of the MLSFH-MAC are noteworthy. The cohort is not a nationally representative sample, but instead represents mature adults in rural Malawi (specifically, rural areas in the three study districts).”
On page 11, in the discussion of HIV and older people, it would be helpful to include information on the dates of the roll out of different guidelines for ART, and information of when those different guidelines were implemented in each place and from where people accessed ART. This would provide
helpful background information for a reader less familiar with the influence of ART roll out strategies on HIV care for older people.
Space constraints prevent a detailed discussion of this important issue. To our knowledge there have not been specific ART initiatives and programs that targeted specifically older individuals. We cited two additional papers in addition to our initially included references by Payne and Kohler 2017, that provide a detailed discussion of the ART roll-out in Malawi in general. These references are as following:
Baranov, Victoria & Kohler, Hans-Peter (2018). The Impact of AIDS Treatment on Savings and Human Capital Investment in Malawi. American Economic Journal: Applied Economics, 10(1), 266-306 DOI: 10.1257/app.20150369
Harries, A.D., Ford, N., Jahn, A. et al. Act local, think global: how the Malawi experience of scaling up antiretroviral treatment has informed global policy. BMC Public Health 16, 938 (2016). https://doi.org/10.1186/s12889-016-3620-x
I am somewhat surprised that so few publications from the cohort are referenced in the main paper.
We added two additional recent MLSFH-MAC publications:
Kämpfen, Fabirce; Kohler, Iliana V.; Bountogo, Mamadou; Mwera, James; Kohler, Hans-Peter; Maurer, Jürgen (2020). Using grip strength to compute physical health-adjusted old age dependency

ratios. SSM - Population Health, 11, 100579 DOI: https://doi.org/10.1016/j.ssmph.2020.100579
Ohrnberger, Julius; Anselmi, Laura; Fichera, Eleonora & Sutton, Matt (2020). Validation of the SF12 mental and physical health measure for the population from a low-income country in sub-Saharan Africa. Health and Quality of Life Outcomes, 18(1), 78 DOI: 10.1186/s12955-020-01323-1.
Several additional papers using the MLSFH-MAC data are either under review, revise and resubmit or in progress. Because of the length limitations for the manuscript we emphasized the currently in our opinion most relevant findings. The 2012 data are publicly available, and the other rounds are available upon request, and several researchers, in the USA as well as in Malawi, are currently utilizing these data that we hope will result in future publications. If this manuscript is accepted for publication after this revision, we hope that MLSFH-MAC will be "publicized" this way and the data will be more broadly utilized.

VERSION 2 – REVIEW

REVIEWER	Rajat Das Gupta Anrold School of Public Health, University of South Carolina
REVIEW RETURNED	21-Jul-2020

GENERAL COMMENTS	The authors have addressed all the comments. The manuscript is in a good shape to be published.

REVIEWER	Janet Seeley London School of Hygiene and Tropical Medicine, UK
REVIEW RETURNED	27-Jul-2020

GENERAL COMMENTS	Thank you for addressing the comments. Please proof read carefully before final submission - a few errors appear in the new text.