PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Frailty among middle-aged and older women and men in India: Findings from Wave 1 of the Longitudinal Aging Study in India
AUTHORS	Ghosh, Arpita; Kundu, Monica; Devasenapathy, Niveditha; Woodward, Mark; Jha, Vivekanand

VERSION 1 – REVIEW

REVIEWER	Beilby, Justin J.
REVIEW RETURNED	06-Feb-2023

GENERAL COMMENTS	This is a complex but important paper from LMIC. The analysis is based on the 2017 - 2018 Longitudinal Ageing Study in India (LASI) data. While the actual methodology for the LASI study is referenced it would help all readers to have more information as part of the paper (perhaps in a small box) regarding the LASI study. My other specific comments are : Abstract no comments. The strengths and limitations points are clear. Background I would have liked to know which other LMIC have gathered data on frailty - references added. Also was it possible to compare the findings from this study with the other data from LMIC countries later in the document? Methods nil to add except to note my earlier comments. Results This is a complex analysis. I wonder if a small section of key findings may help focus the reader. Discussion The section is well written. My only suggestion is use headings more clearly throughout the discussion - e.g Gender differences, 45 plus and over 60. Finally for readers who do not have a deep understanding of the Indian health system it maybe useful to add a small section outlining some strategies to tackle frailty.

REVIEWER	Lee, Yunhwan Ajou University School of Medicine and Graduate School of Medicine, Preventive Medicine and Public Health
REVIEW RETURNED	15-Mar-2023

GENERAL COMMENTS	This study examined the prevalence of frailty in India using the frailty index (FI). The study's strength is using a nationally representative sample of middle-aged and older populations.

	However, applying the frailty index in the younger population is problematic, as insufficient evidence supports that FI is a valid instrument for use in the middle-aged group. A fundamental question about frailty is whether FI is appropriate in determining frailty in non-older age groups, such as those middle-aged. As frailty is an age-associated syndrome, the accumulation of deficits in younger age groups may not correctly represent the concept of frailty. The younger age groups who fall into the frailty category would rather be considered to have comorbid conditions or have diseases of higher severity that adversely affect their overall functioning. This conceptual difference is brought to attention when considering the association between frailty and adverse outcomes, such as falls and hospitalizations. The magnitude of the associations was found to be higher in the middle-aged than in the older population. “We showed that frailty, usually assessed only in older adults, was also prevalent in 45-59-year-old middle-aged adults, and was associated with hospitalization, falls and poor cognitive functioning.” (p. 17, ln. 19-23) This may be because frailty is a concept developed for older people. I am just concerned whether “frailty” defined by the FI in the middle-aged is comparable to frailty in older people. One way to start testing the possible difference in the operationalization of frailty between the two age groups is to decompose the individual components included in defining frailty in the middle-aged and older age groups and compare them. Digging deeper into the conceptualization and operationalization of frailty might go beyond the scope of this paper. As the authors stated that “… there is but limited evidence to support the use of frailty index in middle-aged adults …” (p. 19, ln. 27), caution is warranted in using the FI in younger populations. p. 8, ln. 3: Please reference the cognitive exam on its validity and reliability. p. 9, ln. 22: About 12% (7,913 out of 65,562) of the study sample was excluded due to missing. The authors need to assess for potential selection bias. Please compare the sample characteristics between the participants and non-participants (those missing). Also, sensitivity analysis would help to determine the degree of the selection bias and the interpretation of the findings.

REVIEWER	Mishra, Anup K Mayo Clinic Rochester, Gastroenterology and Hepatology
REVIEW RETURNED	04-May-2023

GENERAL COMMENTS	Fix the error: Line 52 page 6 S1 Table. Error! Reference source not found. Overall, I believe, this is a solid manuscript with enough details and concise writing. I appreciate the authors for conducting this study as this is important for healthcare delivery. I believe this will receive great reception by the journal audience. Abstract: clear and to the point. I appreciate inclusion of key results concisely.

	Background: Included relavent articles and clear. Methods: Frailty definition is clearly provided, developed using 40 deficits Covariates and adverse outcomes were appropriately considered. Statistical analysis is appropriate and adequate. Information on missing data quantity and handling is provided. I appreciate the sex difference and sensitivity analysis. Figures and tables are concise and appropriate. Discussion section and conclusion are well written and appropriate.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Justin J. Beilby
Comments to the Author:
This is a complex but important paper from LMIC. The analysis is based on the 2017 - 2018 Longitudinal Ageing Study in India (LASI) data. While the actual methodology for the LASI study is referenced it would help all readers to have more information as part of the paper (perhaps in a small box) regarding the LASI study.

We now have included a description of the LASI study in the ***Data*** subsection of ***Methods*** section (page 5).
"We used data from Wave 1 of the Longitudinal Ageing Study in India (LASI), conducted in 2017-2019 in all of India's states and union territories.[27] Detailed descriptions of sampling design, participants, questionnaires and response rates and are available elsewhere.[28] Briefly, LASI is a nationwide panel survey of adults aged 45 and older and their spouses, designed to provide longitudinal data on the broad domains of social, health and economic wellbeing of the elderly Indian population. Data include demographics, household economic status, mental health, functional health, biomarkers, health insurance and healthcare utilization, family and social networks, welfare programmes, work and employment, retirement, and life satisfaction. While measures in LASI are specific and sensitive to the Indian context, they have been harmonized with international surveys on ageing and retirement. LASI adopted a multistage stratified cluster sampling design. Data from LASI wave 1 include 65,562 45-plus individuals from all states and union territories except Sikkim. Data are available in the public domain."
My other specific comments are :
Abstract
no comments. The strengths and limitations points are clear.
Thank you.
Background
I would have liked to know which other LMIC have gathered data on frailty - references added. Also was it possible to compare the findings from this study with the other data from LMIC countries later in the document?

We have added this information in second paragraph of ***Background*** section (page 4).
"Most studies on frailty are from high-income countries (HICs).[4] There exist several systematic reviews across geographical regions, but studies from low- and middle-income countries (LMICs) are limited and have used a variety of methods.[5] A few studies have shown that frailty prevalence and incidence are higher in LMICs compared to high-income countries.[4 6-8] In contrast, a multicounty study comparing 14 HICs and six LMICs (China, Ghana, India, Mexico, Russian Federation and South Africa) reported a higher mean frailty index in HICs compared with the LMICs.[9] However, interpretation of differences in prevalence between countries or regions is limited by the few data from LMICs. In a recent systematic review on the prevalence of frailty in LMICs, only one of the 56 studies was from a low-income country (Tanzania) and only two were from a lower middle-income country (India); the rest were from upper middle-income countries – Brazil, Colombia, Mexico, Chile, Cuba, China, Malaysia, Russia, Turkey and Lebanon.[5] Robust disaggregated data on frailty in the Indian population are rare,[10-14] whilst no studies have provided subnational estimates on the prevalence of frailty."

We have added a paragraph in ***Discussion*** section comparing findings from this study with that from other LMICs (page 18).
"Frailty prevalence in LMICs
"Based on a nationally representative sample of 45-plus-year-old Indian adults, we estimated a frailty prevalence of 29.5%, using a frailty index with 40 deficits. A recent systematic review in 62 countries across the world reported a pooled frailty index prevalence of 24% (95% CI = 22 – 26%) based on 71 studies.[4] Region-wise, these estimates were 38% (95% CI = 37 – 39%) in Sub-Saharan Africa, 30% (95% CI = 28 – 31%) in Latin America and the Caribbean, 25% (95% CI = 19 – 32%) in Asia, 22% (95% CI = 20 – 24%) in Europe and 21% (95% CI = 11 – 33%) in Northern America. Another systematic review focussing on LMICs reported a pooled prevalence of 18.0% (95% CI = 5.8 – 35.0%) based on 4 studies using a frailty index approach.[5] Comparison, however, is difficult because prevalence estimates vary greatly by frailty assessment method, and estimates from studies using frailty indices are available only from few LMICs.[4 5] It is further compounded by differences in the cut-off value and the type of study population."

Methods
nil to add except to note my earlier comments.

We have now added brief description of LASI study.

Results
This is a complex analysis. I wonder if a small section of key findings may help focus the reader.

We have added a box of key findings at the end of ***Results*** section (page 17).

Discussion
The section is well written. My only suggestion is use headings more clearly throughout the discussion - e.g Gender differences, 45 plus and over 60.
Finally for readers who do not have a deep understanding of the Indian health system it maybe useful to add a small section outlining some strategies to tackle frailty.

We have added the following headings in ***Discussion*** section to make things clearer.
Frailty prevalence in LMICs
Factors associated with frailty
Outcomes associated with frailty
Frailty in middle-aged adults
Strengths and limitations

We have the following sentences in ***Conclusion*** section (page 21) outlining some strategies to tackle frailty in India.
“In a resource-constrained setting such as India, the focus must be on prevention and early detection of frailty. Both management of risk factors and screening for frailty have to be implemented, preferably at the primary care level. Given the strong links between social inequalities and frailty, marginalized populations must be prioritized. ”

Reviewer: 2

Dr. Yunhwan Lee, Ajou University School of Medicine and Graduate School of Medicine
Comments to the Author:
This study examined the prevalence of frailty in India using the frailty index (FI). The study's strength is using a nationally representative sample of middle-aged and older populations. However, applying the frailty index in the younger population is problematic, as insufficient evidence supports that FI is a valid instrument for use in the middle-aged group.

A fundamental question about frailty is whether FI is appropriate in determining frailty in non-older age groups, such as those middle-aged. As frailty is an age-associated syndrome, the accumulation of deficits in younger age groups may not correctly represent the concept of frailty. The younger age groups who fall into the frailty category would rather be considered to have comorbid conditions or have diseases of higher severity that adversely affect their overall functioning. This conceptual difference is brought to attention when considering the association between frailty and adverse outcomes, such as falls and hospitalizations. The magnitude of the associations was found to be higher in the middle-aged than in the older population. "We showed that frailty, usually assessed only in older adults, was also prevalent in 45-59-year-old middle-aged adults, and was associated with hospitalization, falls and poor cognitive functioning." (p. 17, ln. 19-23) This may be because frailty is a concept developed for older people.
I am just concerned whether "frailty" defined by the FI in the middle-aged is comparable to frailty in older people. One way to start testing the possible difference in the operationalization of frailty between the two age groups is to decompose the individual components included in defining frailty in the middle-aged and older age groups and compare them. Digging deeper into the conceptualization and operationalization of frailty might go beyond the scope of this paper. As the authors stated that "… there is but limited evidence to support the use of frailty index in middle-aged adults …" (p. 19, ln. 27), caution is warranted in using the FI in younger populations.

Thank you for highlighting this point. We have expanded on this in the ***Discussion*** section (page 19-20).

"The frailty index has been validated in young and middle-aged adults in few studies and there exits limited evidence of predictive validity of frailty index in younger populations.[49 50] However, it is not clear if frailty, as a construct, is similar for older and younger adults.[51] Comparison of distribution of deficits in middle-aged and older adults (**S10 Table**) suggests that frailty in middle-aged adults is probably due to long-term health problems that adversely affect their overall functioning. More studies are needed to understand how frailty can be conceptualized and measured in middle-aged and younger adults, and whether assessing frailty in them makes any difference to their health or the care they receive."

p. 8, ln. 3: Please reference the cognitive exam on its validity and reliability.

We have added this information in ***Methods*** section (page 7).
"Cognitive measures in LASI were derived from the cognition module of the Health and Retirement Study – Harmonized Cognitive Assessment Protocol.[35] A detailed description of the different cognitive domains measured in LASI is presented in **S3 Table**."

p. 9, ln. 22: About 12% (7,913 out of 65,562) of the study sample was excluded due to missing. The authors need to assess for potential selection bias. Please compare the sample characteristics between the participants and non-participants (those missing). Also, sensitivity analysis would help to determine the degree of the selection bias and the interpretation of the findings.

We have included comparison of sample characteristics between excluded participants (missing frailty information) and participants included in analyses (with non-missing frailty index) in S4 Table. We present this in first paragraph of ***Results*** section (page 8).

"7,913 participants for whom information related to frailty was missing were excluded from analyses, resulting in a total sample of 57,649 participants. Participants were further excluded while studying associations with outcomes, because of missing outcome data (**S1 Fig**). There were small differences between participants with missing frailty information and those included in analyses (**S4 Table**). Participants with missing frailty data (n=7,913) were more likely to be older, residing in urban areas, living with children and/or others and not working currently."

To understand the pattern, we examined missingness in deficits that comprised the frailty index and constructed an alternative frailty index based on non-missing deficits.
In sub-subsection ***Assessment of frailty*** in subsection ***Variables*** in ***Methods*** section on page 8, we wrote,
"Also, an alternative approach to calculating the frailty index that accounts for missing deficit scores was examined – up to 3 deficits were allowed to be missing and the frailty index for an individual was calculated by summing the non-missing health deficit scores and then dividing by the total number of deficits measured in that individual."

In ***Sensitivity analyses*** subsection in ***Results*** section on page 16, we wrote

"Of the 40 deficits considered, all deficits, except body mass index, grip strength and gait speed, were missing in <2% of the 45-plus participants; and these three measurements were missing in 10-11% of participants (**S3 Fig**). The frailty index calculated using non-missing health deficit scores allowed up to 3 deficits to be missing and therefore could be calculated for 64,331 participants, resulting in <2% with missing frailty index (n=1,231). There were small differences between participants with frailty index missing (n=1,231) or not (n=64,331) (S4 Table). This alternative construction made no difference tthe prevalence estimates – 17% of middle-aged adults and 44% of older participants were frail using this metric (**S8 Table**). ORs for the association between frailty and adverse outcomes were also similar (**S9 Table**), suggesting that findings hold true irrespective of the proportion missing frailty information."

Reviewer: 3
Dr. Anup K Mishra, Mayo Clinic Rochester Comments to the Author:
Fix the error: Line 52 page 6 S1 Table. Error! Reference source not found.

We have fixed this.

Overall, I believe, this is a solid manuscript with enough details and concise writing.
I appreciate the authors for conducting this study as this is important for healthcare delivery. I believe this will receive great reception by the journal audience.

Abstract: clear and to the point. I appreciate inclusion of key results concisely.

Background: Included relavent articles and clear.

Methods: Frailty definition is clearly provided, developed using 40 deficits

Covariates and adverse outcomes were appropriately considered. Statistical analysis is appropriate and adequate.

Information on missing data quantity and handling is provided.

I appreciate the sex difference and sensitivity analysis.

Figures and tables are concise and appropriate.

Discussion section and conclusion are well written and appropriate.

VERSION 2 – REVIEW

REVIEWER	Beilby, Justin J.
REVIEW RETURNED	25-Jun-2023

GENERAL COMMENTS	I have now reviewed the authors responses to the reviewers. I believe that the authors have responded to all requests in a logical and appropriate manner. I have no further comments. I believe the manuscript is now ready for final review,.

REVIEWER	Lee, Yunhwan Ajou University School of Medicine and Graduate School of Medicine, Preventive Medicine and Public Health
REVIEW RETURNED	10-Jul-2023

GENERAL COMMENTS	The authors have sufficiently addressed all my concerns.