
13-May-2021
BMJ-2021-065492 entitled "Terminal decline in objective and self-reported measures of motor function over 10-years before death: results from the Whitehall II cohort study"

Dear Dr. Landré,
I write with some good news. We sent your paper for external peer review and have discussed it our manuscript meeting. We would like to proceed with the paper, provided you can revise it to address the comments of reviewers and editors.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Thank you very much for entrusting us with your work! Please feel free to reach out to me with any questions or concerns.

Yours sincerely
Nazrul Islam, MBBS, MSc, MPH, PhD
Research Editor, The BMJ
nislam@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: John Fletcher (Chair), Tim Cole (Statistician), Wim Weber, David Ludwig, Di Wang, Joseph Ross, Tiago Villanueva, Helen MacDonald, Jessica Kimpton, Nazrul Islam, Mark Richards

Decision: Put points
BMJ-2021-065492

Detailed comments from the meeting:

* Authors should be very clear as to how this single cohort study advances the field in the context of there being multiple systematic reviews and meta-analyses of nearly a dozen other cohort studies published in BMJ and JAMA.

* Of 10,308 recruited at baseline, ~50% were analysed in this study. Could you please elaborate on the potential impact of that on the findings. On this note, could you consider an alternative approach such as multiple imputation.

* Multiple measurements on the motor functions is a strength of the study. The Editors think it would be more interesting to examine the association between the 'changes in motor functions' and all-cause mortality. Such analysis will make the best use of longitudinal measurements.

* Could you please elaborate on the generalisability of the findings given the study population were predominantly men (n=4106, 73%), white (n=5244, 92.9%), high SES (43.9%), active (57.3%), which limits the generalisability of the findings.

* How did you measure timings for walking speed? Will this test be representative for patient's 'normal walking speed?' I can imagine some participants will be fine over 8ft but not further. Is 8 ft even long enough to gather momentum for 'normal walking speed.'

* As the reviewer Xu points out, it would be better to identify changes in physical function that predict mortality in individuals, or the patterns that predict a longer survival, for example.

* How well do the curves in Figure 1 fit – what % of variance is explained?

* Re BMI, the dose-response curve is potentially complex - very low BMI is a very strong predictor of mortality, and high BMI to a lesser extent. So BMI should either be in 3-4 groups or quadratic - but certainly not dichotomised.

* eTable 1 is uninformative.

* eTable 2 is virtually identical to Table 2 (age vs time in Cox regression). Please consider taking it off.

* "5-chair rises" looks like raising 5 chairs. Please consider "5 chair-rises" or just "chair rises".

*Could you please define the 'period leading to death' more precisely ?

* Typo: 6chair rise (last sentence).

* The phrase "terminal decline" sounds as if it is referring to time immediately preceding deaths. Could you elaborate on this, and make sure it is used properly.

* The use of both measured motor activity markers and self-reported markers is quite interesting. Could the authors provide correlation matrices for patients to show the inter-relationship between them?

* Clarify when self-reported measures were measured - was it 3 times, like the motor activity measures, or just once, or annually?

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Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
This study on age-related decline in motor function, with emphasis on terminal decline, towards the end of life, is an important and timely piece of work. The topic is relevant, as the population ages, and ways of identifying and therefore potentially reducing age-associated morbidity and frailty, are becoming more necessary. The work is clearly presented, and adds new findings to this area of research, as well as emphasising the overall importance of motor function as an indicator of health status.

Some points to consider: is this population representative of the UK population, making the results generalisable? Could some comments be included on this ?

The population is relatively young, from a geriatrician's perspective. Was the rate of death expected for this age group?

It is interesting that walking speed differences did not increase in the period before death. Is there any hypothesis as to why this is the case? Was there any way of capturing whether people became bedbound/unable to walk?

Minor point = typo line 56.

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Institution: King's College London

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Recommendation:

Comments:
RE: "Terminal decline in objective and self-reported measures of motor function over 10-years before death: results from the Whitehall II cohort study" by Landre et al.

This study examined motor function in relation to mortality based on the Whitehall II cohort study including 6194 participants with a mean age of 65 at baseline. The results showed that physical function decline is associated with mortality. Following comments may help to improve this study.
Major concerns
Originality. A number of studies have shown that physical function decline or impairment has been associated with higher mortality risk and adverse health outcomes. It would be more interesting to show the patterns of changes in physical function predicting mortality in healthy older adults, and decline in function related to mortality reflects medical conditions, instead of mortality.
Study population. 1) The original study participants were 10308, and only 6194 were included in the current study. The authors may want to discuss how the dropouts would affect the results and the generalizability. 2) Participants with function impairment/disability or dementia should have been excluded from the study population (i.e., disability-free participants), as these conditions might have driven the observed associations. 3) The flow chart (eFig 1) is very difficult to understand and seems to show 3 separate populations without showing how many people with all repeated measurements of function. In fact, the flow-chart in this manuscript should not be called a flow-chart, which should show the populations that remained, died, and dropped out at each examination time). The authors should consider improving the Fig.
Assessment of physical function. ADL and IADL should not be combined as they measure the different activities of daily living with different scales, and ADL disability indicates a more advanced disability than IADL. Otherwise, they should be merged after standardizations.
The outcome. It is interesting to show function changes related to cause-specific mortality by stratified analysis. The validation of the registry-based ascertainment of death should be reported.
Statistical analysis. 1) I would be more clinical relevant to identify a cut-off of function decline that may predict mortality 10 years later for people with and with multimorbidity. 2) Stratified analysis in people with and without chronic diseases would show different associations between function decline and mortality. Cognitive function should have been taken into account in the analysis. 3) As data on healthy lifestyle factors are available, the authors may want to identify which lifestyle factors may counteract function decline to prolong survival.
Minor comments.
1. Using BMI as the covariate instead of obesity, as obesity is reversely related to both physical function and mortality among older people.
2. Number of people with dementia or depression might have been underestimated due to the ascertainment of the conditions based on medical records.

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Please enter your name: Weili Xu

Job Title: Associate Prof

Institution: Karolinska Institutet

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Reviewer: 3

Recommendation:

Comments:
Terminal decline in objective and self-reported measures of motor function over 10-years before death:
results from the Whitehall II cohort study This study is a helpful addition to the body of evidence on ageing, supporting the case for early interventions to address future decline and I believe the inclusion of
self reported subjective measures is a positive one - it gives participants agency, places their lived experience at the centre of the research and gives a richer understanding of changes to an individual

person's function over time. While the authors report no current public involvement in the Whitehall II cohort study I strongly believe there would be considerable value in future public involvement. I would encourage them to consider options to draw in public views that could help identify priorities for further
research and recommend strategies to effect change in policy and practice. My comments relate to representativeness of the cohort and the generalisability of the findings to the wider population. Although
many of these issues have been raised before, they they are still relevant. Changes in the makeup of the
working population and changes to the nature of employment in the last 30+ years are significant and should be acknowledged. Such secure employment is now much less common. The Whitehall II study is
an occupational cohort of people working in the civil service in London, and women and minority ethnic
populations are underrepresented. The ethnicity of the cohort is here identified as white or non-white - the
very low percentage of workers identified as non-white makes it incredibly difficult if not impossible to translate findings in order to understand variations between individual ethnic populations e.g. people of
South Asian heritage who are known to have higher rates of CVD. Identifying if studies meet the needs of
different populations equally is a topic of great urgency and importance and it's important to identify gaps
in what we know and to call for further research that can address disparities and gaps in our understanding. Moreover, the study participants are geographically bound to London and the protective
effect of walking to and from work in the work-life patterns of commuting workers in London has already
been identified as specific and not representative of wider population across the UK. Recruitment practices have changed significantly since the beginning of this cohort study and equality legislation has
been strengthened meaning that the current intake of civil servants are more likely to include people with
disabilities. It would also be hugely helpful to know the experiences of people with caring responsibilities -
previous research shows that carers have less opportunity to look after their own health. All of these issues may need to be teased out - it would be helpful to explore the differences in the cohort with members of the public who reflect the diverse populations living in and around London in order to identify
the relative importance of those differences and what they may imply for findings of this study. I do think
these potential limitations should be acknowledged in the discussion. One minor typo - the link to the participant portal doesn't work in the document https://www.ucl.ac.uk/whitehallII/participants/.

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