REPLY

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Comment on "Effects of Vivifrail multicomponent intervention on functional capacity" by Casas-Herrero et al.—The authors reply

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In this response letter, we would like to clarify some aspects related to the methodology and inferences derived from our work entitled 'Effects of Vivifrail multicomponent intervention on functional capacity',[1] which was aimed at investigating the effects of a home-based multicomponent individualized exercise programme (Vivifrail) on the functional capacity of frail older adults with mild cognitive impairment/dementia. Yan et al.[2] raised concerns related to the amount of data missingness and methods used to handle it in our study. Although we addressed this issue as a limitation of the Discussion section of the original report, we now take the opportunity to further discuss its implications.

The first concern raised by Yan et al. relates to the potential impact of the high percentage of dropouts (37%) over the 3-month follow-up period on the inferences derived from the study. First, we would like to emphasize that our randomized clinical trial was designed to evaluate the Vivifrail multicomponent exercise programme in a sample of very old, community-dwelling frail cognitively impaired older adults (mean age $>$ 84 years) with multiple comorbid conditions. Dissimilarly to laboratory-, hospital-, nursing-home- or day hospital-based supervised exercise studies where continuous support (and follow-up) is feasible, subject retention in our unsupervised, home-based intervention presented challenges, as did requiring very old participants to attend centre-based evaluations. While this may limit internal validity, it provides a more realistic picture of the potential and feasibility of implementing such programmes in real-world settings, offering information on what clinicians, policymakers and funding agencies can expect. In fact, recent studies investigating the effect of unsupervised exercise interventions in frail older individuals have reported comparable, and even higher, attrition figures among those intervened on remotely.[3,4] This illustrates the difficulties of retaining very old, frail individuals in longitudinal studies. Additionally, many participants could not attend final visits during the COVID-19 outbreak due to infection concerns and lockdown policies. However, we believe our study still makes a valuable contribution given the limited evidence on the topic.

In relation to missing data handling, Yan et al. referred to a previous report on a randomized clinical trial that used different approaches and found opposite conclusions, to illustrate that varying strategies can impact the results. However, unlike the example provided by Yan et al. (in which model- and different-imputation-based approaches are compared), our work benefits from the use of likelihood-based linear mixed models in the data analyses, which has been recently incorporated as an alternative path for trial-based repeated measures intention-to-treat analyses with missing data.[5,6] In fact, mixed models without ad hoc imputation may provide more powerful inference than simple imputation approaches at varying missing data rates.[7]

Nonetheless, we agree that a sensitivity analysis could be informative and reinforce our conclusions. Following Yan et al.'s suggestions, we implemented a controlled multiple imputation approach to explore whether our results could be impacted by not-at-random data missingness.[8] This illustrated how outcomes would change across a range of imputed values in both groups. As shown in *Figure 1*, the statistical significance of our results would only fade in the very

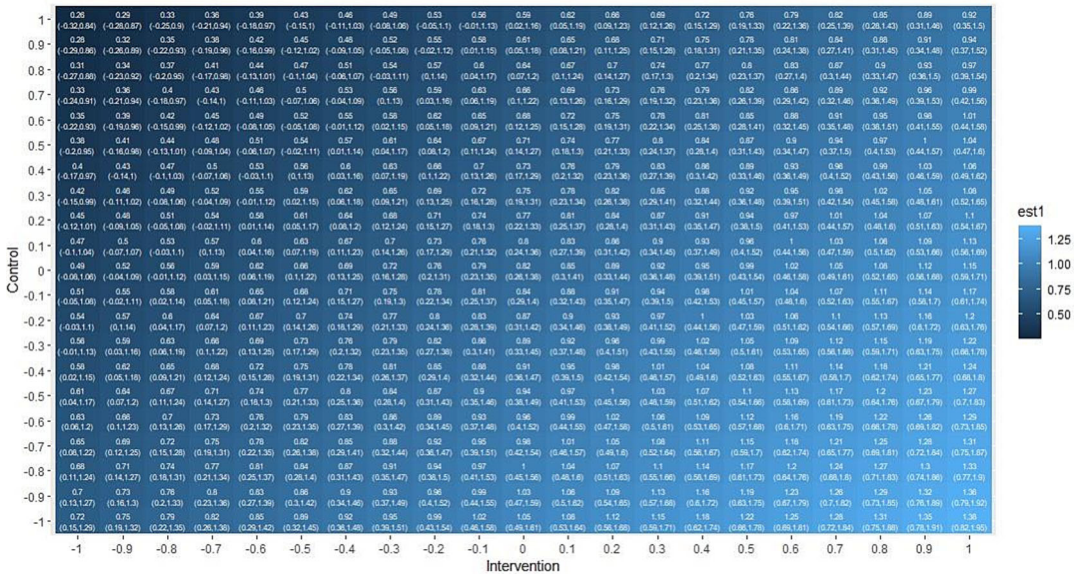

Figure 1 Sensitivity analyses exploring potential tipping point by controlled multiple imputation at the 3-month follow-up.

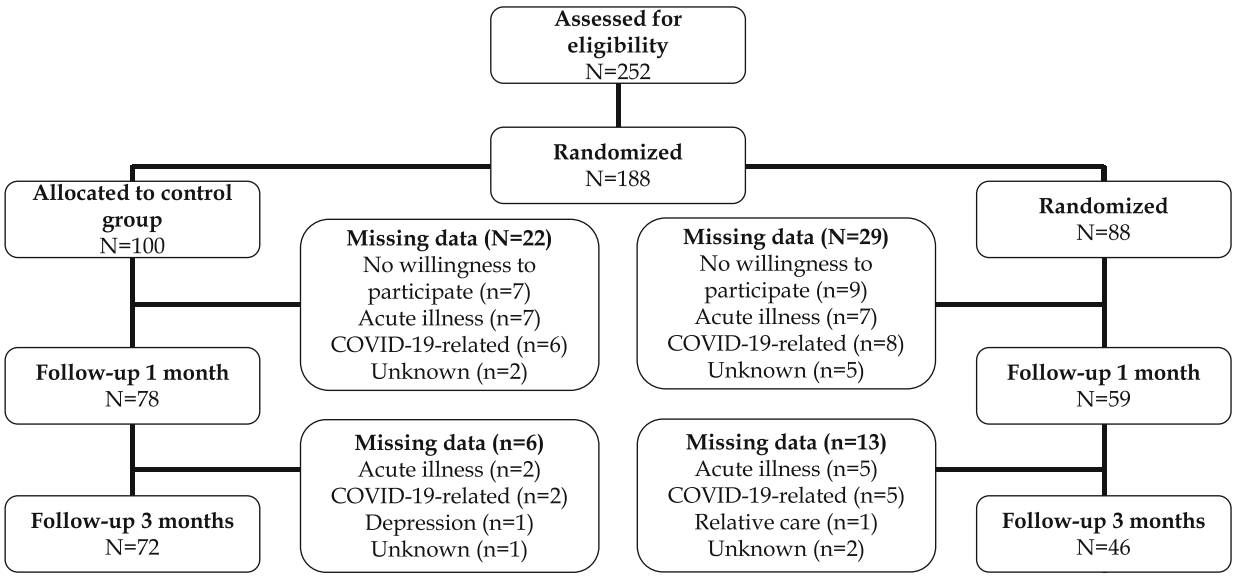

Figure 2 Flow diagram of the individuals included in the study.

unlikely scenario in which individuals with missing scores in the intervention group experience an evolution 1.4 points worse than control counterparts, which provides robustness to our conclusions by supporting at-random data missingness. *Figure S1* shows the sensitivity analysis for the 1-month follow-up. Second, Yan et al. expressed their concerns around the feasibility of the promotion of the programme as a greater number of individuals dropped out in the intervention group compared with their control counterparts. As detailed in *Figure 2*, we did not observe differential reasons for discontinuation implying programme stress. Certainly, adoption may be limited in older adults without prior exercise experience, given barriers like low motivation, impairment and inadequate support.[9] Individual circumstances should be considered by clinicians, supervisors and relatives when prescribing exercise in general and specifically the Vivifrail exercise programme, given the high rates of participation (79% of exercise sessions completed) among those remaining in the study. In addition, supervised modalities might be more suitable and effective among individuals

Table 1 Baseline features of individuals by group and attrition

Variable	Control group		Intervention group	
	Complete follow-up $n = 72$	Dropout $n = 28$	Complete follow-up $n = 46$	Dropout $n = 42$
Demographic data				
Age, years	83.33 ± 4.43	86.31 ± 5.45	83.34 ± 4.22	85.73 ± 5.40
Women, *n* (%)	49 (68.18%)	19 (68.18%)	32 (68.75%)	38 (90%)[a]
<12 education years, *n* (%)	59 (82.05%)	18 (63.64%)	36 (77.59%)	28 (66.6%)
Living alone, *n* (%)	19 (26.92%)	6 (22.73%)	10 (22.41%)	8 (15.38%)
Clinical data				
MCI, *n* (%)	44 (61.19%)	19 (68.18%)	25 (55.10%)	22 (55.33%)
Mild dementia, *n* (%)	28 (39.39%)	9 (31.82%)	21 (42.86%)	20 (47.62%)
Fried frailty criteria, *n* (%)				
Pre-frail	47 (65.38%)	17 (59.09%)	32 (68.97%)	24 (56.67%)
Frail	25 (34.62%)	11 (40.91%)	14 (31.03%)	18 (43.33%)
Endpoints				
CIRS score, median (IQR)	5.0 (3.0–7.0)	6.0 (4.0–8.0)	7.5 (5.0–11.0)	7 (5.0–9.0)
SPPB score	7.92 ± 2.51	7.04 ± 2.25	6.72 ± 2.87	7.1 ± 2.24
MEC Lobo score	27.15 ± 4.68	27 ± 3.86	27.03 ± 5.10	25.2 ± 5.62
Barthel Index score	93.26 ± 9.00	86.13 ± 12.43	91.81 ± 8.56	89.83 ± 10.54
Handgrip, kg	19.76 ± 7.40	17.15 ± 8.60	20.92 ± 6.19	16.92 ± 6.93
Yesavage GDS score	3.36 ± 2.94	3.38 ± 2.85	3.56 ± 2.82	4.6 ± 3.05
QoL (EQ-VAS) score	70.72 ± 18.30	73.71 ± 18.22	71.50 ± 15.74	68.75 ± 27.88

Note: Data are mean (SD), unless otherwise stated.
Abbreviations: CIRS, Cumulative Illness Rating Scale; EQ-VAS, visual analogue scale of the Euro-QoL questionnaire; IQR, interquartile range; MCI, mild cognitive impairment; MEC, Mini-Mental Cognitive Exam; QoL, quality of life; SPPB, Short Physical Performance Battery; Yesavage GDS, Yesavage Geriatric Depression Scale.
[a]Significant differences between subjects who withdrew in the control versus intervention groups.

presenting lack of motivation or greater cognitive impairment.[10] Better understanding of the factors that might predict the engagement in exercise programmes by frail older adults will assist in the identification of the best strategy oriented to optimize exercise prescription. Understanding predictors of engagement will optimize strategies to maximize adherence.

Finally, Yan et al. wondered if greater dropout could artificially favour the intervention group if completers had higher baseline values. As shown in *Table 1*, we found no imbalance between groups, including the primary outcome measure (Short Physical Performance Battery score). This suggests that results did not derive from follow-up bias. Overall, comparable groups at baseline and our statistical approach reinforce the validity of our findings, despite substantial missing data.

Acknowledgements

We would like to show our gratefulness to Yan et al. for the attention paid to our work, believing that the clarifications made will allow potential readers to better understand the significance of our results and their true potential considering its intrinsic limitations.

Conflict of interest statement

Juan Luis Sanchez, Mikel Izquierdo, Mikel L. Sáez de Asteasu, Iván Antón-Rodrigo, Arkaitz Galbete, Alejandro Álvarez-Bustos and Álvaro Casas-Herrero declare that they have no conflict of interest.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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