Optimal dose and type of physical activity to improve functional capacity and minimise adverse events in acutely hospitalised older adults: a systematic review with dose-response network meta-analysis of randomised controlled trials

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ABSTRACT

Objective To identify the optimal dose and type of physical activity to improve functional capacity and reduce adverse events in acutely hospitalised older adults.

Design Systematic review and Bayesian model-based network meta-analysis.

Data sources Four databases were searched from inception to 20 June 2022.

Eligibility criteria for selecting studies Randomised controlled trials that assessed the effectiveness of a physical activity-based intervention on at least one functional outcome in people aged ≥50 years hospitalised due to an acute medical condition were included. Pooled effect estimates (ie, standardised mean differences for functional capacity and the ratio of means for adverse events) were calculated using random treatment effects network meta-analysis models.

Results Nineteen studies (3842 participants) met the inclusion criteria. Approximately 100 Metabolic Equivalents of Task per day (METs-min/day) (~40 min/day of light effort or ~25 min/day of moderate effort activities) was the minimal dose to improve the functional capacity of acute hospitalised older adults (standardised mean difference (SMD)=0.28, 95% credible interval (CrI) 0.01 to 0.55). The optimal dose was estimated at 159 METs-min/day (~70 min/day of light effort or ~40 min/day of moderate effort activities; SMD=0.41, 95% CrI 0.08 to 0.72). Ambulation was deemed the most efficient intervention, and the optimal dose was reached at 143 METs-min/day (~50 min/day of slow-paced walking; SMD=0.76, 95% CrI 0.35 to 1.16), showing a high evidential power (87.68%). The minimal effective ambulation dose was estimated at 74 METs-min/day (~25 min/day of slow-paced walking; SMD=0.25, 95% CrI 0.01 to 0.41). Physical activity interventions resulted in a decrease in the rate of adverse events compared with usual care at discharge (ratio of means=0.96, 95% CrI 0.95 to 0.97; median time 7 days).

Conclusions This meta-analysis yielded low to moderate evidence supporting the use of in-hospital supervised physical activity programmes in acutely hospitalised older adults. As little as ~25 min/day of slow-paced walking is sufficient to improve functional capacity and minimise adverse events in this population.

Trial registration number PROSPERO CRD42021271999.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hospitalised older adults spend most of their hospital time sedentary, usually in bed.
⇒ Exposure to long periods of almost total inactivity during hospitalisation leads to post-hospital deconditioning, disability, morbidity and mortality.
⇒ Despite its potential benefits, the type and optimal dose of physical activity to counteract the adverse events of prolonged bed rest during hospitalisation remains unknown.

WHAT THIS STUDY ADDS

⇒ Bed rest is less safe than staying active for acute hospital stays.
⇒ A small amount of slow walking (~25 min/day) is sufficient to improve function during acute hospital stays.
⇒ Optimal improvements in function are provided by either ~50 min/day of slow walking or ~40 min/day spent in multicomponent interventions (eg, ~20 min of resistance bands with ~20 min of aerobic activity).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Health care practitioners in hospital settings may capitalise on the information provided to improve mobility and health outcomes of hospitalised older adults.

INTRODUCTION

Hospitalised older adults, including those who can walk independently, spend most of their hospital time sedentary, usually in bed.[1] A study found that older adults spend only 45 min/day out of their hospital bed, less than 5% of a 24-hour period.[2]

Exposure to acute periods of almost total inactivity during hospitalisation plays a role in causing a condition known as post-hospital syndrome,[3] a critical 30-day post-discharge period associated with a general deconditioning. If not managed, this period of increasing vulnerability may lead to hospital readmission, disability, nursing home placement, morbidity and mortality.[3] These effects appear at least in part to be due to the admission itself rather than the condition that caused the initial admission.[4]

Recent meta-analytical evidence[5] has demonstrated the effectiveness of active interventions to prevent functional declines in older adults admitted to hospital. Martinez-Velilla *et al*[6] showed the benefits of an individualised multicomponent intervention to reverse the functional decline associated with acute hospitalisation in very elderly patients. Other studies have shown the feasibility of increasing mobilisation in hospitalised older adults, with positive outcomes such as improved functionality.[7] The world-first consensus-based statements from expert and stakeholder consultation recommend that hospitalised older adults should "be as physically active as their abilities and condition allows".[8] The same group of experts, however, flagged some key knowledge gaps that impede the effective application of physical activity as a critical clinical tool to prevent functional decline and adverse outcomes among hospitalised older adults. First, the most efficient type of physical activity intervention has not yet been identified. Second, the optimal dosage, which may be physical activity type-dependent, remains unknown. Finally, there is a common perception that physical activity may increase falls and other negative events (fostering the culture of 'bed rest' while in hospital).[7 9] Physical activity interventions often report no[6] or few adverse events.[7] Yet, there is no meta-analytical evidence assessing the number of adverse events from active interventions among hospitalised patients.

Using novel meta-analytical techniques (ie, model-based dose-response network meta-analysis under a Bayesian framework) and evidence from existing randomised controlled trials, the current report aimed to identify the optimal dose and type of physical activity to improve functional capacity and reduce adverse event outcomes in acutely hospitalised older adults. We also examined the time-course relationship of physical activity with functional capacity and adverse events.

METHODS

This pre-registered systematic review and meta-analysis (PROSPERO CRD42021271999) was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for network meta-analyses of healthcare interventions.[10] The methodological development of this work was guided by the technical support documents provided by the Decision Support Unit (DSU) of the National Institute for Health and Care Excellence (NICE).[11]

Search strategy

A systematic search was conducted in PubMed, Web of Science, Scopus and Embase databases from inception to June 2022. The specific search strategy for each database including search terms, dates and process are shown in online supplemental file 1. The reference lists of relevant articles and systematic reviews were also screened for additional studies. Two reviewers (DG-G and BdPC) independently screened the title/abstract and full texts, with disagreements resolved by discussion or adjudication by a third author (JdP-C).

Eligibility criteria

We included randomised controlled trials that involved individuals aged ≥50 years[12] admitted to either Intensive Care Units or general wards due to an acute medical condition and that used any form of physical activity as an intervention. Studies had to include a control group receiving usual care or another type of physical activity intervention as comparison. Studies also had to report on any assessment of functional capacity (ie, ability to perform daily-living activities independently and safely[5]) at baseline and, at least, at discharge. The number and type of adverse events (ie, functional decline, hospital re-admission, fall or death) at discharge or at any follow-up time point available were also recorded. We excluded studies with individuals admitted for reasons where acute physical activity is contraindicated: orthopaedic surgery wards, those admitted for a knee/hip replacement, with a stroke or with injuries (eg, fractures), and those who were admitted for long-term conditions. We also excluded studies detailing interventions that did not require physically active involvement of participants (eg, blood flow restriction or electrostimulation), or those that combined multiple treatments and for which the effects of physical activity could not be isolated.

Data extraction

Two authors independently extracted data from the included studies (DG-G and JdP-C) and disagreements were resolved by consensus between all authors. From each of the included studies we extracted data on functional capacity and adverse events at the different available time points. We also extracted the parameters of the intervention (ie, frequency, duration, intensity and type), key characteristics of included participants (ie, sex, age, body mass index and admission cause), functional capacity assessment tool, and any data that could be used to calculate effect sizes of interest based on the Cochrane Handbook for Systematic Reviews of Interventions.[13] When the minimally required data to conduct dose-response or time-course meta-analyses could not be retrieved from the published reports,[14–16] we contacted the authors and invited them to provide additional data. Of three studies for which further information was requested,[14–16] we could retrieve the required data from two studies.[15 16]

Data coding and management

We followed the principles described by Pedder *et al*[17 18] and prepared two datasets, one for dose-response analyses and another dataset for time-course analyses. The dataset used in the dose-response analyses included only data corresponding to admission (ie, baseline) and discharge time points. The time-course analysis dataset included additional data for all available follow-up time points. In both datasets, interventions were coded into three hierarchical levels[19]: first, we coded interventions as "physical activity" or "control" ("overall" level); second, interventions were coded considering the specific type of the intervention performed as "range of motion", "ambulation", "multicomponent" or "usual care" ("agent" level). We classified interventions as range of motion when participants, bedridden or not, performed assisted or independent exercises aimed to provide joints with a full range of motion movements. Ambulation was based on walking but could additionally include daily-living activities such as sit-to-standing or stepping on the site. Multicomponent interventions were based on various physical activity components applied during the same session (eg, resistance, aerobic and balance physical activities). Third, interventions were coded at the intersection of the specific type of intervention and dose ("treatment" level). For instance, the "Ambulation_50" code indicates 50 Metabolic Equivalents of Task per day (METs-min/day) of ambulation intervention.

The term dose used in this meta-analysis refers to energy expenditure, expressed as METs-min/day. We followed the validated approach by Ainsworth *et al*[20] to calculate the different doses associated with each of the included interventions in this meta-analysis. Next, we clustered the interventions into six pre-specified different groups by approximating the estimated METs-min/day to the closest convenient pre-specified grouping categories of 0 (control group: usual care and no intervention), 50, 100, 150, 200 and 250 METs-min/day. This approximation was done to facilitate the network connectivity, a necessary step to conduct a network meta-analysis.[21]

Data synthesis

Functional capacity

We used a random-effects Bayesian Model-Based Network Meta-Analysis (MBNMA)[22] to summarise the dose-response and time-course relationships between physical activity and functional capacity. No indication of violation of key assumptions for network meta-analysis (ie, connectivity,[23] consistency in the data, transitivity and homogeneity[24 25]) was found (see online supplemental file 2). Functional capacity was modelled using a normal likelihood with an identity link function. Predicted responses were calculated as pre–post change score for dose-response models to estimate the effects of physical activity at the discharge time point, and as pre-follow-up change score for time-course models to explore the physical activity effects at multiple follow-up times across the critical post-discharge period for this population. They were then standardised using the baseline SD of each study[11] and reported as standardised mean differences (SMD; Hedges' g form[26]); posterior medians are reported with 95% credible intervals (CrI) to assess the certainty of our estimates.[27] In addition, the 95% prediction interval was calculated to inform about potential effects to be expected in future trials. Finally, the statistical power of each treatment effect estimate was calculated to detect their evidential value (see online supplemental file 3).

Dose-response models

We first plotted the observed effects of different interventions on functional capacity to detect a potential dose-response functional pattern. Based on the observed shapes, a range of recommended non-linear functions (ie, log-linear, quadratic, Emax and splines[28]) were used to model the data. Next, we derived and compared different fit indices[29] (ie, Deviance Information Criterion (DIC), residual deviance and the number of data points, deviance of the model, and number of estimated parameters) as well as corresponding deviance plots[29] across all estimated models (see online supplemental file 4). For dose-response, natural cubic splines yielded the best fit at all levels (ie, fitted at overall and agent levels) and were therefore used to assess the non-linear dose-response associations (online supplemental file 4). Implementation parameters of the fitted models (ie, prior knowledge, Markov Chain Monte-Carlo iterations and convergence analysis) are also detailed in online supplemental file 4. Selecting for the model with the best fit and biological plausibility,[28] we placed knots at overall levels (ie, 20th and 75th percentiles) and at intervention-specific levels (ie, different knot locations for each intervention: 20th and 75th for usual care and ambulation, 50th for range of motion, and 20th and 60th for multicomponent) whenever data were available.[30] Beta coefficients from the spline models were used to estimate the physical activity dose at which the predicted maximal significant effect on functional capacity was achieved (referred to as the 'optimal dose'). This information was used to rank the analysed treatments (ie, type of intervention at a specific dose) based on their probability to enhance functional capacity, from worst to best. We also estimated the minimal dose associated with significant changes in the outcome of interest. Additionally, the maximal tolerated dose (ie, the dose from which there were null/worsening effects on our outcome of interest) was also calculated.

To assess the robustness of our estimates, we also conducted dose-response meta-analytical models (1) including only studies with a low risk of bias, and (2) using other dose-response functions that also fitted the data well as sensitivity analyses.

Time-course models

We first plotted the observed responses in each arm of each study over time to consider which functional forms were appropriate for modelling the time-course relationship.[28] Based on the available data, we used log-linear, quadratic and spline functions. A common-treatment effects spline time-course model was deemed optimal and was therefore used to model the time-course effects of physical activity interventions on functional capacity. Despite plans to explore these separately, intervention-level time-course models could not be conducted because of the paucity of available time-course data on some type-specific interventions.

Adverse events

We used a common-treatment effects MBNMA for modelling the time-course relationship between adverse events and overall physical activity using usual care as the reference treatment. Adverse event counts were assumed to be negatively binomially distributed and were modelled using a log link. The predicted responses were therefore expressed as a ratio of means (RoM), which has shown similar treatment effects and no large differences in heterogeneity compared with difference-based methods.[31] This effect measure can be interpreted as the coefficient between adverse events in the intervention arm and the control arm (ie, a RoM <1 favours the intervention and vice versa).

We originally planned to conduct similar analyses combining time-course and dose-response at deeper levels of intervention description (ie, type and dose of physical activity), but the paucity of data available (32 data points in total) prevented us from conducting such analyses. Instead, we carried out qualitative analyses to explore the distribution of adverse events across different types of interventions (ie, usual care, ambulation or multicomponent training). As an exploratory analysis, we plotted the number of adverse events in each study arm by dose and fitted a natural spline model to explore the potential dose-outcome trend association in an arm-based analysis that did not allow for between-study heterogeneity. Compared with contrast-based MBNMA, arm-based analyses such as this assume that prognostic factors and effect modifiers are the same across studies, and the results may therefore be affected by differences in prognostic factors between studies.[32] As sensitivity analysis, we used other smoothing techniques (ie, beta spline and locally weighted least squares regression (loess) functions) to assess the robustness of the estimated trend.

All analyses were performed in R 4.0.3.[33] We used the 'MBNMAdose' package[17] to perform Bayesian dose-response MBNMA models; the 'MBNMAtime' package[18] to perform Bayesian time-course MBNMA models; the 'metameta' package[34] to perform power analysis; and the 'ggplot2' package[35] for plotting and visualisation. The code and data necessary to reproduce

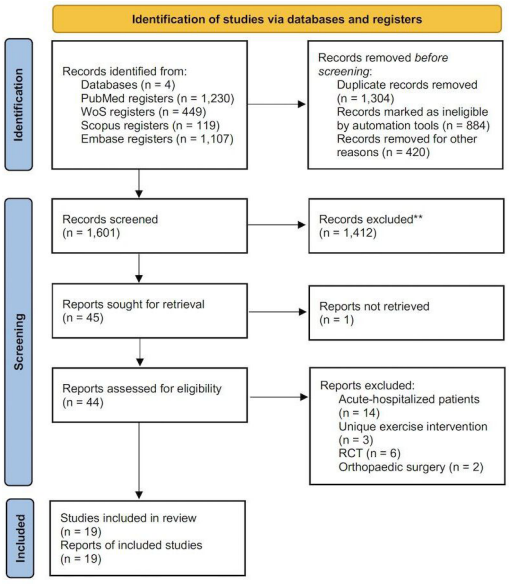

Figure 1 PRISMA flowchart of included studies. **Through title and abstract screening, we excluded 1,412 registers due to long-term hospitalised older adults (n = 633) and monocentric trial design (n = 779).

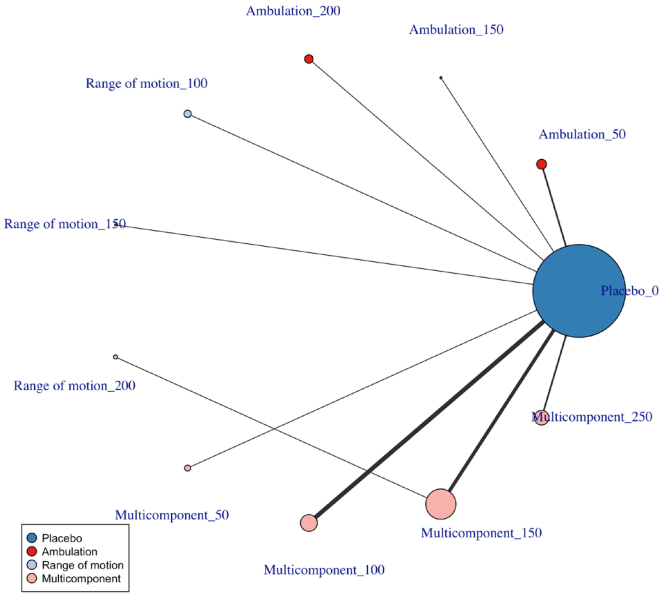

Figure 2 Network geometry at the treatment level. (Note: Treatment level is considered the combination of a specific type of intervention and dose).

the results presented in this paper are available through a public repository (https://github.com/dgalgom).

Risk of bias and certainty of evidence

Three reviewers (DG-G, JR-M and FA-B) assessed and rated the risk of bias in the included studies according to the Cochrane Risk of Bias tool criteria (Cochrane ROB tool).[36] The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to rate the certainty in estimates from our network meta-analysis.[37]

Equity, diversity and inclusion statement

Our research team included junior, mid-career and senior researchers from different disciplines (ie, physical therapy, physiology and biostatistics) and countries (ie, Spain, UK and Australia). Our study population included both male and female hospitalised older adults on an equivalent basis; however, in discussing the generalisability of our results and limitations of the findings, we acknowledge we did not examine the gender effect on our outcome of interest.

RESULTS

Overall, 2905 records were identified through the initial electronic searches. After removing duplicates, 1601 records were screened for titles and abstracts and 44 full-text articles were screened for eligibility. In total, 19 studies[6 14–16 38–52] involving 3842 participants were included in the review. For the dose-response analyses, 39 data points (ie, effect sizes) were retrieved. For the time-course analyses, 49 data points were considered. The full screening and selection process is shown in figure 1.

Characteristics of included studies

The characteristics of the included studies are shown in online supplemental table 4. The year of publication ranged from 2000 to 2022. A total of 3783 participants were analysed, of whom 2087 (55.17%) were female. The median reported age was 78 (range 55–87) years. Participants were admitted to an ICU (758; 21.67%)[6 16 51] or general wards.[14 15 37–49 51] The median reported body mass index was 27 (range 24.5–33). The median length of stay of included participants was 7 days (range 4–42 days) and the median follow-up time after discharge was 68 days (range 34–365 days).

Two studies used range of motion,[38 49] four studies[16 39 43 47] used ambulation and 13 studies[6 14 15 39 41–43 45–47 50–52] used multicomponent interventions. The average duration of intervention sessions was 30 min. Specifically, the median duration of the intervention sessions was 25 min for range of motion (range 20–30 min), 37.5 min for ambulation (range 30–60 min) and 30 min for multicomponent interventions (range 20–60 min). The average frequency was 10 sessions per week for range of motion and ambulation, and eight sessions for multicomponent interventions. Estimated intervention doses were 100,[49] 150[38] and 200[43] METs-min/day for range of motion; 50,[44 48] 150[40] and 200[16] METs-min/day for ambulation; and 50,[14] 100,[40 41 50–52] 150[6 15 43 45 47] and 250[42 46] METs-min/day for multicomponent interventions. The network geometry combining all these treatments is shown in figure 2.

Several tools were used to assess functional capacity in the included studies: the 6 min Walking Test (6-MWT),[51] Activities of Daily Living,[15] the Barthel Index,[6 41 42 45 49] days to first out of bed,[16] the Morton Mobility Index,[39] Gait speed,[50] the Katz Index,[38 44] the Life-Space Assessment (LSA) questionnaire,[40]; the Short Physical Performance Battery (SPPB),[14 46–48] the Sit-to-Stand test[51] and the Timed-Up-and-Go (TUG) test.[43]

Functional capacity

Dose-response associations

We detected an inverted U-shaped dose-response relationship between increasing energy expenditure (ie, dose) and functional capacity (figure 3). The optimal dose was estimated at 159 METs-min/day (SMD=0.41, 95% CrI 0.08 to 0.72). The minimal dose associated with significant changes in functional capacity was predicted at 99 METs-min/day (SMD=0.26, 95% CrI 0.01 to 0.53). The maximal tolerated dose was observed at 184 METs-min/day (SMD=0.37, 95% CrI 0.01 to 0.72).

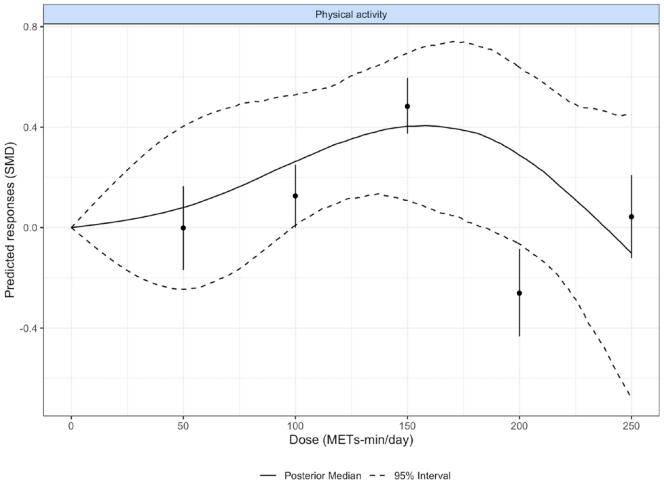

Figure 3 Dose-response relationship between physical activity dosage and functional capacity. (Note: Point estimates and credible intervals from a 'split' network meta-analysis in which each dose of physical activity is treated as an independent intervention).

Prediction intervals suggested that physical activity interventions could have a lower effect than that observed in the included trials (see online supplemental figure 8).

Intervention-specific dose-response relationships are shown in figure 4. The optimal response for ambulation was estimated at 143 METs-min/day (SMD=0.76, 95% CrI 0.35 to 1.16) and the optimal dose for multicomponent interventions was 174 METs-min/day (SMD=0.61, 95% CrI 0.46 to 0.77). For ambulation, the minimal effective dose was estimated at 74 METs-min/day (SMD=0.25, 95% CrI 0.01 to 0.50) and the maximal tolerated dose was estimated at 187 METs-min/day (SMD=0.21, 95% CrI 0.01 to 0.41). For multicomponent interventions, the minimal effective dose and the maximal tolerated dose were observed at 89 METs-min/day (SMD=0.15, 95% CrI 0.01 to 0.29) and 241 METs-min/day (SMD=0.15, 95% CrI 0.01 to 0.29), respectively. We did not detect a significant relationship between range of motion interventions and functional capacity. A league table showing comparisons of all between-treatment effects is shown in online supplemental file 6. Our ranking analysis showed that a dose of 150 METs-min/day for ambulation had the highest probability of retrieving the greatest response on

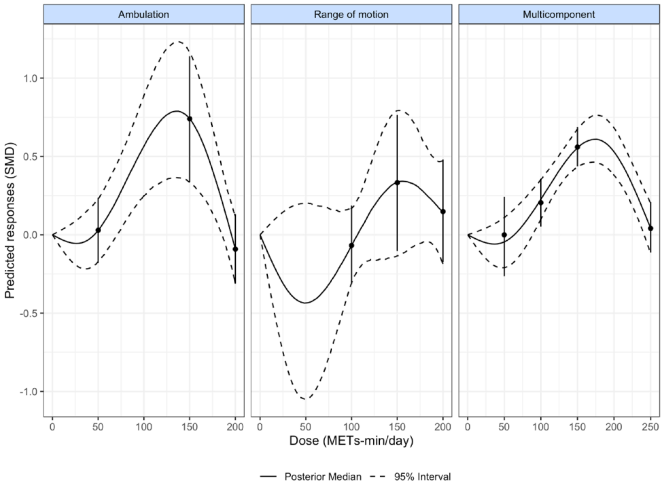

Figure 4 Intervention-specific dose-response relationship between physical activity dose and functional capacity.

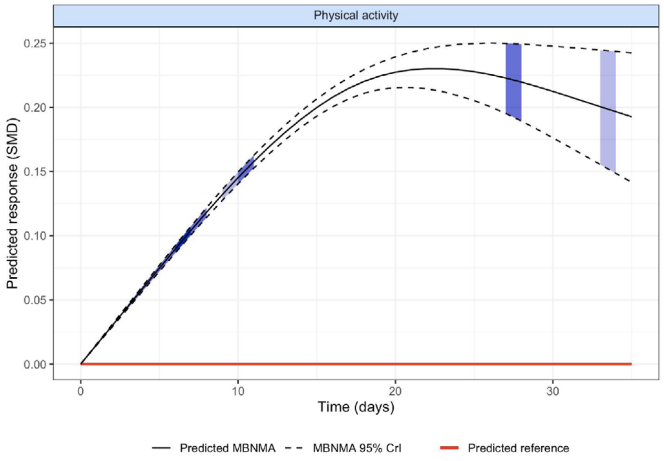

Figure 5 Time-course effectiveness. (Note. The shaded zones represent the number of observations in the original dataset at each predicted time point). MBMNA, Model-Based Network Meta-Analysis.

functional capacity (online supplemental file 6). Power analysis showed that ambulation (150 METs-min/day) and multicomponent treatments (100 and 150 METs-min/day) yielded the highest power values, although only ambulation presented an evidential power over 80%.

The dose-response model including only low risk of bias studies mirrored the pattern of association of our base case model (see online supplemental figure 15). The results were also robust to different modelling strategies (ie, natural spline assuming fixed-treatment effects, and quadratic functions; online supplemental file 7), although these were a poorer fit to the data.

Time-course effectiveness

The effectiveness of physical activity interventions increased from admission to discharge (SMD=0.11, 95% CrI 0.10 to 0.12; median time 7 days), and from this time point to approximately 2 weeks after discharge, achieving the greatest predicted effect at around 19 days after discharge (SMD=0.23, 95% CrI 0.20 to 0.25). From that time point, there was some indication that the effect may slightly decrease (figure 5).

Adverse events

We observed a decrease in the rate of adverse events in the active intervention groups when compared with usual care (figure 6). At discharge, the RoM was 0.96 (95% CrI 0.95 to 0.97). Corresponding outcomes were 0.94 at 1 week post discharge (95% CrI

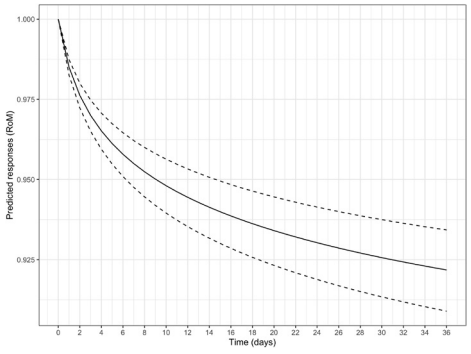

Figure 6 Ratio of means (RoM) between intervention and usual care groups. (Note: RoM <1 favours the intervention).

0.93 to 0.95), 0.93 at 2 weeks (95% CrI 0.92 to 0.95) and 0.92 at 4 weeks post discharge (95% CrI 0.91 to 0.93).

The distribution of different types of adverse events was similar across the different interventions, with falls being the main adverse event reported across studies and interventions (online supplemental figure 13). An inverted U-shape dose-outcome trend was observed, in which doses of physical activity between 100 and 150 METs-min/day had the lowest number of adverse events (online supplemental figure 14A). Sensitivity analyses using alternative smoothing techniques supported this trend (online supplemental figure 14).

Risk of bias

Domain level and overall level risk of bias judgements by reviewers' consensus are shown in online supplemental file 10. At the overall level, seven studies were classified as low risk of bias,[15 39 40 44 45 50 51] two studies as unclear risk of bias[14 52] and 10 studies as high risk of bias.[6 16 38 41–43 46–49]

Certainty of evidence

Summary of Findings (SoFs) tables are shown in online supplemental file 11. The evidence presented in this meta-analysis for functional capacity outcomes was classified as low to moderate. Six treatment estimates were deemed of low certainty of evidence due to imprecision (ie, 95% CrIs cross zero or are wide, suggesting uncertainty in the estimate) and risk of biased estimates. These include ambulation at 50 and 200 METs-min/day and multicomponent at 50, 100, 150 and 250 METs-min/day.

DISCUSSION

Main findings

The current study has several key findings with important clinical implications. First, our investigation confirms the benefits of physical activity interventions to reduce functional decline and adverse events associated with acute hospitalisation in older adults. Second, this dose-response meta-analysis highlights a novel non-linear relationship between physical activity dose and functional capacity. The minimal effective dose was estimated at ~100 METs-min/day (~40 min/day of light effort or 25 min/day of moderate effort activities) and the optimal response at 159 METs-min/day (~70 min/day of light effort or ~40 min/day of moderate effort activities). Doses higher than ~190 METs-min/day (more than ~90 min/day of light effort or ~60 min/day of moderate effort activities) did not show clear benefits. Third, we detected different dose-response patterns for each of the different types of physical activity interventions available in the literature. Fourth, our study highlights the superior effects of ambulation over other active intervention modalities. Last, physical activity interventions were effective in reducing the adverse events of older adults with acute hospitalisation. Taken together, these findings provide an evidence-based opportunity to inform physical activity-based interventions and change in care practice aimed to reduce the burden associated with acute hospitalisation in older adults, a growing public health problem.[52]

Strengths and limitations

There are several key strengths to our study. First, this study comprised a relatively large sample size of acute hospitalised older adults, which provided adequate statistical power for the study aims. Second, we applied current state of the art meta-analytical techniques[19] for pooling data from different studies to investigate the dose-response between physical activity dose and functional capacity. This novel method allowed us to determine the most efficient (optimal) dose of physical activity to improve functional capacity and reduce adverse events in the population under study. Third, through direct, indirect and network estimates, we were able to compare the relative efficacy of different active interventions, which led to the identification of ambulation as the most effective in-hospital intervention to improve the functional capacity of older adults. Fourth, we showed that the effect estimates of the optimal doses associated with ambulation and multicomponent (ie, the most effective interventions) suggested acceptable statistical power to detect significant 'true' effects. Last, our data enabled first-time modelling of the effects of physical activity on adverse events, a key factor in decision-making processes to support physical activity interventions in hospital settings.

This study also has some limitations. First, there was a paucity of available data related to follow-up time points after discharge and we could not model reliable time-course outcomes estimates for specific physical activity interventions. Second, studies considered here included only participants who had the minimum capacity to move on their own and hence generalisation to other populations is not possible. Third, the currently available aggregated data did not allow the modelling of covariate-specific dose-response patterns or ascertainment of the dose at the individual level. Finally, half of the studies in this review were classified with a high risk of bias. However, sensitivity analysis removing these studies showed similar dose-response association patterns.

Comparison with existing evidence

To date, only two systematic reviews have addressed the effectiveness of physical activity interventions to improve functional capacity outcomes in hospitalised older adults.[5 53] Although not directly comparable, the review by Scheerman *et al*[53] could not confirm the benefits of physical interventions, including exercise, to improve physical performance in older adults admitted to hospital. In contrast, more recent work by Valenzuela *et al*[5] concluded that inpatient supervised physical activity is effective in improving functional capacity in older adults and showed comparable effect sizes (SMD 0.57) to those reported in the current meta-analysis. Descriptively, the same review by Valenzuela *et al*[5] stated that in-hospital physical activity interventions are safe. Our review empirically showed the superior effects of physical activity over usual care to reduce the probability of adverse events at different follow-up time points. Although not formally tested, previous work[5] also suggests the existence of different responses to different physical activity interventions, an observation factually confirmed in our meta-analysis. Former research has also indicated the superior effects of multicomponent interventions.[5 6 15 48] Nevertheless, we provide for the first time meta-analytical evidence highlighting the value of ambulation over and above other physical activity interventions. This suggests that a change in hospital care practices that simply allow and promote patients to walk while in care might have very important benefits. This finding supports grass root clinician-led movements to promote ambulation in hospitals such as '#endpjparalysis'.[54] It is plausible that multicomponent intervention sessions result in compensatory behaviour with an overall (counterintuitive) increase in sedentary behaviour that might displace time previously dedicated to ambulation.[55] This in turn may limit the expected gains from engaging in such interventions. Future studies may want to test this hypothesis and, if true, plan more holistic (24-hour) interventions. In addition, we did not observe any benefits associated with a range of motion-based exercise programmes, which was also suggested by Valenzuela *et al*[5] in

their review. Nevertheless, our work and that of others suggests the need to incorporate feasible physical activity programmes into the daily routine care of older adults admitted to hospital.

Clinical implications and future research

This study helps inform the dose and type of physical activity which best improves functional capacity and reduces adverse events among acutely hospitalised older adults. Even low doses of ambulation (eg, ~25 min/day of slow walking or daily life activities such as sit-to-stand) may elicit significant changes in functional capacity, which supports the previously stated general recommendation of staying active while in hospital.[8] However, higher doses of ambulation (eg, ~50 min/day of slow walking) may result in optimal benefits. This strongly suggests that hospital care should be organised in such a way as to allow and promote older adult ambulation while in hospital. Similarly, short daily multicomponent intervention sessions may translate into functional capacity improvements (eg, ~15 min/day of resistance bands and ~10 additional min/day of aerobic activities such as assisted cycling with a device), although longer bouts may result in additional gains (eg, ~20 min/day of resistance bands with ~20 min/day of aerobic activities).

A key point to consider is the feasibility of in-hospital interventions. Multicomponent interventions require qualified personnel and multiple resources for their application, both of which are considered important barriers to the implementation of physical activity programmes in acutely hospitalised older adults.[56] In contrast, ambulatory activities may be easier and simpler to implement in hospital settings,[57 58] hence such interventions may be a cost-effective solution to reduce the negative consequences of excessive bed-time in hospitalised older adults.[59] Nevertheless, the information provided in this study supports tailored physical activity advice adapted to individual preferences, needs and availability of resources,[60] which may facilitate the adoption of a patient-centred care approach.[61]

Older adults are projected to comprise more than 60% of the total hospital inpatient population by 2030.[62] Based on the existing evidence to date, this review has shown the optimal type and dose of physical activity necessary to prevent functional decline and reduce adverse events in older adults admitted to hospital. These results may inform the design of new trials aimed to test the effectiveness of in-hospital physical activity interventions in older adults. Nevertheless, our findings warrant the collection of individual patient data to provide accurate subgroup-specific recommendations (eg, for specific medical conditions or baseline functional capacity level).[63] Adverse events should be more comprehensively reported in future trials.[64]

CONCLUSIONS

This novel systematic review with dose-response meta-analysis shows that relevant ranges of (type-specific) physical activity doses improve functional capacity and reduce the number of adverse events in acutely hospitalised older adults. If the most potent intervention is provided (ie, ambulation), the beneficial effects of in-hospital supervised physical activity programmes can be maximised with as little as ~25 min/day of slow-paced walking, an achievable target for most hospitalised older adults. Together, this meta-analysis has yielded critical information to support the use of physical activity as a core part of the daily routine of acutely hospitalised older adults.

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REFERENCES

1 Baldwin C, van Kessel G, Phillips A, *et al*. Accelerometry shows inpatients with acute medical or surgical conditions spend little time upright and are highly sedentary: systematic review. *Phys Ther* 2017;97:1044–65.
2 Brown CJ, Redden DT, Flood KL, *et al*. The underrecognized epidemic of low mobility during hospitalization of older adults. *J Am Geriatr Soc* 2009;57:1660–5.
3 Krumholz HM. Post-hospital syndrome — an acquired, transient condition of generalized risk. *N Engl J Med* 2013;368:100–2.
4 Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009;360:1418–28.
5 Valenzuela PL, Morales JS, Castillo-García A, *et al*. Effects of exercise interventions on the functional status of acutely hospitalised older adults: a systematic review and meta-analysis. *Ageing Res Rev* 2020;61:101076.

6 Martínez-Velilla N, Casas-Herrero A, Zambom-Ferraresi F, *et al*. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern Med* 2019;179:28–36.
7 Greysen SR. Activating hospitalized older patients to confront the epidemic of low mobility. *JAMA Intern Med* 2016;176:928–9.
8 Baldwin CE, Phillips AC, Edney SM, *et al*. Recommendations for older adults' physical activity and sedentary behaviour during hospitalisation for an acute medical illness: an international Delphi study. *Int J Behav Nutr Phys Act* 2020;17:69.
9 Flaherty JH, Rodin MB, Morley JE. Changing hospital care for older adults: the case for geriatric hospitals in the United States. *Gerontol Geriatr Med* 2022;8:23337214221109004.
10 Lee SW, Koo MJ. PRISMA 2020 statement and guidelines for systematic review and meta-analysis articles, and their underlying mathematics: life cycle committee recommendations. *Life Cycle* 2022;2.
11 Dias S, Welton NJ, Sutton AJ, *et al*. *NICE DSU technical support document 1: Introduction to evidence synthesis for decision making*. University of Sheffield, Decision Support Unit, 2011: 1–24.
12 Rotermann M. High use of acute care hospital services at age 50 or older. *Health Rep* 2017;28:3–16.
13 Higgins JPT, Thomas J, Chandler J, *et al*. *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons, 2019.
14 Campo G, Tonet E, Chiaranda G, *et al*. Exercise intervention to improve functional capacity in older adults after acute coronary syndrome. *J Am Coll Cardiol* 2019;74:2948–50.
15 Siebens H, Aronow H, Edwards D, *et al*. A randomized controlled trial of exercise to improve outcomes of acute hospitalization in older adults. *J Am Geriatr Soc* 2000;48:1545–6.
16 Morris PE, Goad A, Thompson C, *et al*. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238–43.
17 Pedder H. MBNMAdose: an R package for incorporating dose-response information into network meta-analysis. In: *Evidence synthesis and meta-analysis in R Conference 2021*. 2021. Available: https://research-information.bris.ac.uk/en/publications/mbnmadose-an-r-package-for-incorporating-dose-response-informatio
18 Pedder H. MBNMAtime: an R package for time-course Model-Based Network Meta-Analysis models. 2021. Available: https://research-information.bris.ac.uk/en/publications/mbnmatime-an-r-package-for-time-course-model-based-network-meta-a
19 Gallardo-Gómez D, Del Pozo-Cruz J, Noetel M, *et al*. Optimal dose and type of exercise to improve cognitive function in older adults: a systematic review and Bayesian model-based network meta-analysis of RCTs. *Ageing Res Rev* 2022;76:101591.
20 Ainsworth BE, Haskell WL, Herrmann SD, *et al*. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011;43:1575–81.
21 Higgins JPT, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98–110.
22 Mawdsley D, Bennetts M, Dias S, *et al*. Model-based network meta-analysis: a framework for evidence synthesis of clinical trial data. *CPT Pharmacometrics Syst Pharmacol* 2016;5:393–401.
23 Ter Veer E, van Oijen MGH, van Laarhoven HWM. The use of (network) meta-analysis in clinical oncology. *Front Oncol* 2019;9:822.
24 Wheeler DC, Hickson DA, Waller LA. Assessing local model adequacy in Bayesian hierarchical models using the partitioned deviance information criterion. *Comput Stat Data Anal* 2010;54:1657–71.
25 White IR, Barrett JK, Jackson D, *et al*. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3:111–25.
26 Hedges LV, Olkin I. Meta-analysis in the physical and biological sciences. *Stat Methods Meta-Anal* 1985:311–25.
27 Etzioni RD, Kadane JB. Bayesian statistical methods in public health and medicine. *Annu Rev Public Health* 1995;16:23–41.
28 Pedder H, Dias S, Bennetts M, *et al*. Modelling time-course relationships with multiple treatments: model-based network meta-analysis for continuous summary outcomes. *Res Synth Methods* 2019;10:267–86.
29 Evans NJ. Assessing the practical differences between model selection methods in inferences about choice response time tasks. *Psychon Bull Rev* 2019;26:1070–98.
30 Harrell FE. Springer series in statistics. In: *Regression modeling strategies*. 2001.
31 Friedrich JO, Adhikari NKJ, Beyene J. Ratio of means for analyzing continuous outcomes in meta-analysis performed as well as mean difference methods. *J Clin Epidemiol* 2011;64:556–64.
32 Dias S, Ades AE. Absolute or relative effects? Arm-based synthesis of trial data. *Res Syn Meth* 2016;7:23–8.
33 R Foundation for Statistical Computing. *R: a language and environment for statistical computing. R Foundation for Statistical Computing*. Vienna, Austria, 2020. Available: https://www R-project org/
34 Quintana DS. A guide for calculating study-level statistical power for meta-analyses. *Open Science Framework* [Preprint] 2022.
35 Wickham H. Ggplot2. *WIREs Comp Stat* 2011;3:180–5.
36 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
37 Brignardello-Petersen R, Bonner A, Alexander PE, *et al*. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol* 2018;93:36–44.
38 Blanc-Bisson C, Dechamps A, Gouspillou G, *et al*. A randomized controlled trial on early physiotherapy intervention versus usual care in acute care unit for elderly: potential benefits in light of dietary intakes. *J Nutr Health Aging* 2008;12:395–9.
39 Braun T, Grüneberg C, Süßmilch K, *et al*. An augmented prescribed exercise program (APEP) to improve mobility of older acute medical patients – a randomized, controlled pilot and feasibility trial. *BMC Geriatr* 2019;19:240.
40 Brown CJ, Foley KT, Lowman JD, *et al*. Comparison of posthospitalization function and community mobility in hospital mobility program and usual care patients: a randomized clinical trial. *JAMA Intern Med* 2016;176:921–7.
41 Bürge E, Berchtold A, Maupetit C, *et al*. Does physical exercise improve ADL capacities in people over 65 years with moderate or severe dementia hospitalized in an acute psychiatric setting? A multisite randomized clinical trial. *Int Psychogeriatr* 2017;29:323–32.
42 de Morton NA, Keating JL, Berlowitz DJ, *et al*. Additional exercise does not change hospital or patient outcomes in older medical patients: a controlled clinical trial. *Aust J Physiother* 2007;53:105–11.
43 Haines TP, Hill KD, Bennell KL, *et al*. Additional exercise for older subacute hospital inpatients to prevent falls: benefits and barriers to implementation and evaluation. *Clin Rehabil* 2007;21:742–53.
44 Hu F-W, Huang Y-T, Lin H-S, *et al*. Effectiveness of a simplified reablement program to minimize functional decline in hospitalized older patients. *Geriatr Gerontol Int* 2020;20:436–42.
45 Jones CT, Lowe AJ, MacGregor L, *et al*. A randomised controlled trial of an exercise intervention to reduce functional decline and health service utilisation in the hospitalised elderly. *Australas J Ageing* 2006;25:126–33.
46 Kitzman DW, Whellan DJ, Duncan P, *et al*. Physical rehabilitation for older patients hospitalized for heart failure. *N Engl J Med* 2021;385:203–16.
47 Martínez-Velilla N, Abizanda P, Gómez-Pavón J, *et al*. Effect of an exercise intervention on functional decline in very old patients during acute hospitalizations: results of a multicenter, randomized clinical trial. *JAMA Intern Med* 2022;182:345–7.
48 Ortiz-Alonso J, Bustamante-Ara N, Valenzuela PL, *et al*. Effect of a simple exercise programme on hospitalisation-associated disability in older patients: a randomised controlled trial. *Geriatric Medicine* 2019.
49 Padula CA, Hughes C, Baumhover L. Impact of a nurse-driven mobility protocol on functional decline in hospitalized older adults. *J Nurs Care Qual* 2009;24:325–31.
50 Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, *et al*. Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: secondary analysis of a randomized trial. *PLoS Med* 2019;16:e1002852.
51 Torres-Sánchez I, Valenza MC, Cabrera-Martos I, *et al*. Effects of an exercise intervention in frail older patients with chronic obstructive pulmonary disease hospitalized due to an exacerbation: a randomized controlled trial. *COPD* 2017;14:37–42.
52 Troosters T, Probst VS, Crul T, *et al*. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;181:1072–7.
53 Scheerman K, Raaijmakers K, Otten RHJ, *et al*. Effect of physical interventions on physical performance and physical activity in older patients during hospitalization: a systematic review. *BMC Geriatr* 2018;18:288.
54 Chastin SFM, Harvey JA, Dall PM, *et al*. Beyond '#endpjparalysis', tackling sedentary behaviour in health care. *AIMS Med Sci* 2019;6:67–75.
55 Hartman SJ, Pekmezi D, Dunsiger SI, *et al*. Physical activity intervention effects on sedentary time in Spanish-speaking Latinas. *J Phys Act Health* 2020;17:343–8.
56 Geelen SJG, van Dijk-Huisman HC, de Bie RA, *et al*. Barriers and enablers to physical activity in patients during hospital stay: a scoping review. *Syst Rev* 2021;10:293.
57 Holst M, Hansen PL, Pedersen LA, *et al*. Physical activity in hospitalized old medical patients; how active are they, and what. *J Aging Res Clin Pract* 2015;4:116–23.
58 Gill TM. Preserving community mobility in vulnerable older people. *BMJ* 2022;377:1084.
59 Garrett S, Elley CR, Rose SB, *et al*. Are physical activity interventions in primary care and the community cost-effective? A systematic review of the evidence. *Br J Gen Pract* 2011;61:e125–33.
60 Lange E, Palstam A, Gjertsson I, *et al*. Aspects of exercise with person-centred guidance influencing the transition to independent exercise: a qualitative interview study among older adults with rheumatoid arthritis. *Eur Rev Aging Phys Act* 2019;16:4.
61 NEJM Catalyst. What is patient-centered care?; 2017.
62 American Hospital Association. *When I'm 64: How boomers will change health care*. Chicago, Illinois: American Hospital Association, 2007.
63 Riley RD, Debray TPA, Fisher D, *et al*. Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: statistical recommendations for conduct and planning. *Stat Med* 2020;39:2115–37.
64 Xu C, Yu T, Furuya-Kanamori L, *et al*. Validity of data extraction in evidence synthesis practice of adverse events: reproducibility study. *BMJ* 2022;377:e069155.