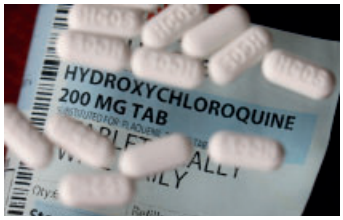
# research

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**ORIGINAL RESEARCH** Meta-epidemiological study

## Agreement of treatment effects from observational studies and RCTs evaluating medicines used in patients with covid-19

Moneer O, Daly G, Skydel JJ, et al

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**Study question** What is the agreement between treatment effects from individual or meta-analysed observational studies and randomised controlled trials (RCTs) evaluating the same covid-19 treatments, comparators, and outcomes?

**Methods** RCTs directly comparing any of the three most studied covid-19 treatments (hydroxychloroquine, lopinavir-ritonavir, dexamethasone) reported in a living review in *The BMJ*. Epistemonikos database was used to identify observational studies evaluating the same interventions, comparisons, and safety or efficacy outcomes. Outcomes from these studies were identified and treatment effects for dichotomous or continuous outcomes calculated and, if possible, meta-analysed to match treatment effects from trials or meta-analyses of trials reported in the living review with the same interventions, comparisons, and outcomes (matched pairs). Matched pairs were considered to be in agreement if both observational and trial treatment effects were significantly increased or decreased (P<0.05) or non-significant (P≥0.05).

**Agreement between treatment effect estimates from 27 matched observational study and RCT pairs**

| Observational study treatment effect estimates | RCT treatment effect estimates: Significant* increase/decrease | RCT treatment effect estimates: Non-significant† increase/decrease |
|---|---|---|
| **Matched pairs of meta-analyses of observational studies and meta-analyses of RCTs** | | |
| Significant increase* | 0‡/0 | 2/0 |
| Significant decrease* | 0/0‡ | 0/0 |
| Non-significant increase† | 0/0 | 4‡/2‡ |
| Non-significant decrease† | 0/1 | 5‡/3‡ |
| **Matched pairs with one observational study or RCT** | | |
| Significant increase* | 0‡/0 | 0/1 |
| Significant decrease* | 0/0‡ | 0/1 |
| Non-significant increase† | 1/0 | 3‡/1‡ |
| Non-significant decrease† | 0/0 | 1‡/2‡ |

*P<0.05. †P≥0.05. ‡Pairs classified as concordant.

**Study answer and limitations** 17 new, independent meta-analyses of observational studies of hydroxychloroquine, lopinavir-ritonavir, or dexamethasone versus an active or placebo comparator were matched and compared with 17 meta-analyses of RCTs reported in the living review. 10 additional matched pairs with only one observational study or trial were identified. 21 (78%) of the 27 matched pairs had treatment effects that were in agreement. Among the 17 matched pairs comprising meta-analyses of observational studies and meta-analyses of RCTs, 14 (82%) were in agreement; seven (70%) of the 10 matched pairs comprising at least one observational study or RCT were in agreement. This study was limited to three treatments and might generalise to other interventions with few or no RCTs.

**What this study adds** Accumulated evidence suggests that the direction and statistical significance of treatment effects from observational studies and RCTs for three covid-19 treatments generally are in agreement.

Funding, competing interests, and data sharing
See full paper on bmj.com for funding and competing interests.
Data are in the supplementary file.

# Preserving community mobility in vulnerable older people

**ORIGINAL RESEARCH** Randomised controlled trial

## Multicomponent intervention to prevent mobility disability in frail older adults

Bernabei R, Landi F, Calvani R, et al; on behalf of the SPRINTT consortium

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**Study question** Can a multicomponent intervention prevent mobility disability in older adults with physical frailty and sarcopenia?

**Methods** A randomised controlled trial was conducted in 16 clinical sites across 11 European countries. The study sample comprised 1519 community dwelling men and women aged 70 years or older with physical frailty and sarcopenia. Participants randomised to the multicomponent intervention (n=760) engaged in moderate intensity physical activity twice weekly at a study centre and up to four times weekly at home. Actimetry data were used to tailor the intervention. Participants also received personalised nutritional counselling. Control participants (n=759) attended workshops on healthy ageing once a month. Interventions and follow-up lasted for up to 36 months. The primary outcome was mobility disability (inability to independently walk 400 m in ‹15 minutes). Primary comparisons were conducted in participants with a score on the short physical performance battery (SPPB) of 3 to 7 at baseline (n=1205). Those with a score of 8 or 9 (n=314) were analysed separately for exploratory purposes.

**Study answer and limitations** During 2.2 years of follow-up, mobility disability occurred in 283/605 (46.8%) participants with an SPPB score of 3 to 7 assigned to the multicomponent intervention and 316/600 (52.7%) assigned to lifestyle education (hazard ratio 0.78, 95% confidence interval 0.67 to 0.92; P=0.005). In the exploratory group with an SPPB score of 8 or 9, mobility disability occurred in 46/155 (29.7%) participants assigned to the multicomponent intervention and 38/159 (23.9%) assigned to lifestyle education (1.25, 0.79 to 1.95; P=0.34). The risk of serious adverse events was comparable between intervention groups irrespective of baseline SPPB score category. Results might not be generalisable to non-white people, those with major cognitive deficits, or those who are unable to independently walk 400 m.

**What this study adds** Findings indicate that a multicomponent intervention reduces the risk of mobility disability in older adults with physical frailty and sarcopenia and SPPB scores of 3 to 7. This condition could be targeted to preserve mobility in vulnerable older people.

**Funding, competing interests, and data sharing** This work was funded by a grant from the Innovative Medicines Initiative Joint Undertaking.
See full paper on bmj.com for competing interests.
Anonymised raw trial data can be shared on request to Luca Mariotti (luca.mariotti1@unicatt.it).
**Study registration** ClinicalTrials.gov NCT02582138.

**COMMENTARY** Fresh evidence confirms the benefits of structured physical activity

Preserving independent mobility is central to maintaining a good quality of life, including retention of many activities, such as walking to a bus stop or around a neighbourhood, that older adults need to stay fully engaged in their communities.[1] Loss of mobility in community living people is associated with multiple adverse outcomes, including worsening disability and morbidity, increases in healthcare utilisation and costs, admission to residential care, and death.[2-6]

The linked study by Bernabei and colleagues provides additional evidence that a structured moderate intensity physical activity programme can preserve mobility, defined as the ability to independently walk 400 m in less than 15 minutes, in community living older adults.[7]

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### Loss of mobility in community living people is associated with multiple adverse outcomes

This evidence comes from a well designed and rigorously executed randomised controlled trial that was conducted at 16 clinical sites across 11 European countries.

The authors found that the multicomponent intervention, which included personalised nutritional counselling in addition to aerobic (walking), strength, flexibility, and balance exercises, reduced the occurrence of mobility disability over the course of three years by 22% among community living older people with a condition that the authors call “physical frailty and sarcopenia.”

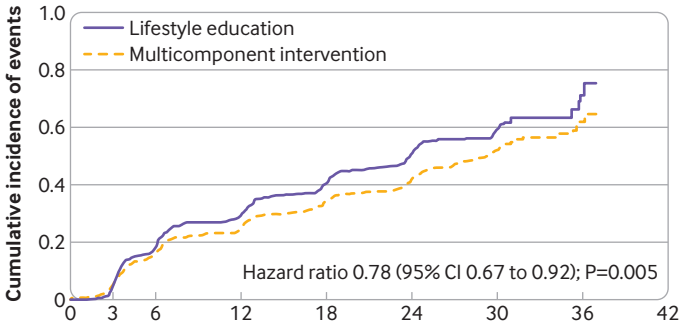
These findings are consistent with those from an earlier US based multicentre trial, the LIFE Study,[8] that evaluated physical activity as the sole intervention among sedentary older people with functional limitations.

#### Frailty and sarcopenia

Physical frailty and sarcopenia was operationalised as the co-occurrence of functional limitations, defined as a short physical performance battery (SPPB) score of 3 to 9 (as in the LIFE Study) and low appendicular lean mass, assessed by dual energy x ray absorptiometry (DEXA). Although this definition is rigorous and appropriate for an efficacy trial, its clinical utility is uncertain for several reasons. Firstly, the SPPB, which includes a short distance walk, five chair stands, and a set of balance manoeuvres, requires considerable staff training and up to 15 minutes to safely and effectively complete. Secondly, DEXA scans are not readily available in many clinical settings, and they add expense and radiation exposure. Thirdly, operationalising sarcopenia on the basis of muscle mass, rather than muscle strength, has lost favour based on mounting evidence from epidemiological studies and clinical trials.[9]

The SPRINTT trial was not designed to determine whether nutritional counselling added any benefit to structured physical activity. This is important since the nutritional component adds costs and complexity. Previous research, dating back to the seminal trial by Fiatarone and colleagues published in 1994, has shown that the value of physical activity is much greater than that of nutrition for improving functional outcomes in vulnerable older people.[10]

Among participants with SPPB scores less than 8, the rates of mobility disability in the control groups were comparable between SPRINTT (51.5%, mean follow-up 2.2 years) and LIFE (46.8%, mean follow-up




**No at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multicomponent intervention | | | | | | | |
| 605 | 547 | 474 | 413 | 346 | 259 | 106 | 18 |
| Lifestyle education | | | | | | | |
| 600 | 537 | 452 | 378 | 299 | 196 | 98 | 13 |

**No of events**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multicomponent intervention | | | | | | | |
| 0 | 28 | 93 | 141 | 195 | 231 | 267 | 281 |
| Lifestyle education | | | | | | | |
| 0 | 26 | 103 | 163 | 222 | 270 | 299 | 313 |

**Kaplan-Meier curves for incident mobility disability in participants with baseline short physical performance battery (SPPB) score of 3-7. The graph is truncated at 36 months, after which two additional mobility disability events were recorded in the multicomponent intervention group and three in the lifestyle education group. CI=confidence interval**

2.6 years), suggesting that the additional low appendicular lean mass requirement in SPRINTT did not add much prognostic information. Whether a muscle strength requirement would add useful prognostic information is uncertain.

Translating findings from even the best designed efficacy trials to clinical practice can be challenging for several reasons, including eligibility criteria that are difficult to implement and interventions that are overly complex and expensive. Collectively, trial findings provide compelling evidence that mobility in the community can be preserved among vulnerable older people through structured physical activity, with walking as the primary modality.

To enhance clinical feasibility, slow gait speed rather than the complete SPPB could be used to identify older people who are at high risk of losing independent mobility.[11] Ideally, these individuals could be referred to structured physical activity programmes in the community. In the US, many Medicare plans offer SilverSneakers, a free health and fitness programme where older people can exercise at a fitness centre, such as a gym or community centre, or at home, or both by accessing on-demand videos, classes, and workouts.[12]

The cost effectiveness of the LIFE structured physical activity programme was found to be comparable to that of many commonly recommended medical treatments.[13] Confirming these findings in SPRINTT would further strengthen the case for developing, implementing, and supporting community based physical activity programmes to preserve independent mobility among vulnerable older people.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.o1084

# Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure

Urner M, Barnett AG, Bassi GL, et al; on behalf of the COVID-19 Critical Care Consortium Investigators

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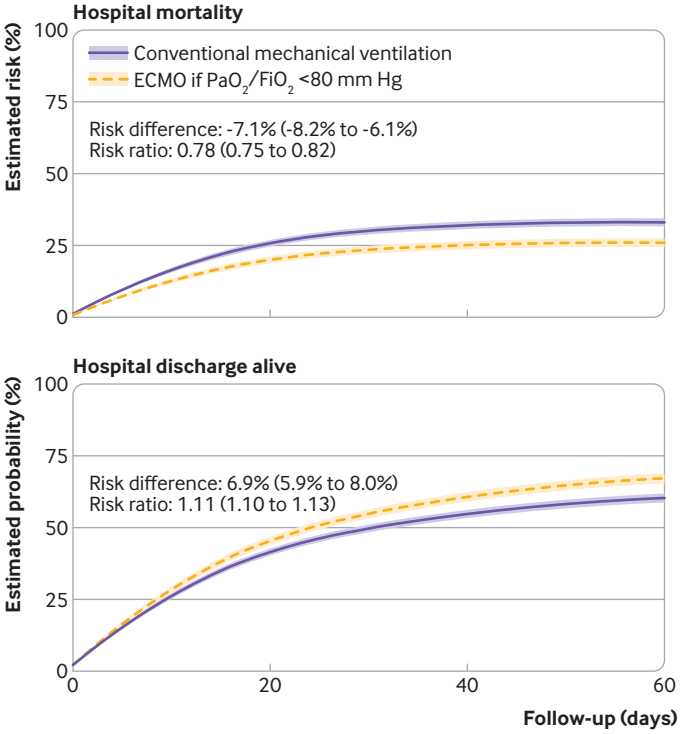
**Study question** What is the effect of treatment with extracorporeal membrane oxygenation (ECMO) on outcomes of patients with covid-19 associated respiratory failure compared with conventional mechanical ventilation?

**Methods** Using registry based data from the COVID-19 Critical Care Consortium recorded in 30 countries across five continents, ECMO in patients with a partial pressure of arterial oxygen to fraction of inspired oxygen ($PaO_2/FiO_2$) ratio ‹80 mm Hg was compared with a treatment strategy where all patients received conventional treatment without ECMO. The primary outcome was mortality in adults with suspected or confirmed SARS-CoV-2 infection and acute respiratory failure within 60 days of admission to the intensive care unit. Adherence adjusted estimates for the treatment effect were calculated using marginal structural models with inverse probability weighting, accounting for competing events (hospital discharge) and baseline and time varying confounding.

**Study answer and limitations** 844 of 7345 eligible adults (11.5%) received ECMO at any time point during follow-up. Adherence adjusted mortality was 26.0% (95% confidence interval 24.5% to 27.5%) for a treatment strategy that included ECMO if the $PaO_2/FiO_2$ ratio dropped below 80 mm Hg compared with 33.2% (31.8% to 34.6%) had patients received conventional treatment without ECMO (risk difference −7.1%, 95% confidence interval −8.2% to −6.1%; risk ratio 0.78, 95% confidence interval 0.75 to 0.82). In secondary analyses, ECMO appeared to be most effective in patients aged ‹65 years and with a $PaO_2/FiO_2$ ‹80 mm Hg or with driving pressures ›15 $cmH_2O$ during the first 10 days of mechanical ventilation. The findings were robust in sensitivity analyses to detect the potential influence of residual confounding or missing data.




**Treatment with extracorporeal membrane oxygenation (ECMO) if ratio of partial pressure of arterial oxygen to fraction of inspiratory oxygen ($PaO_2/FiO_2$) was ‹80 mm Hg compared with treatment with conventional mechanical ventilation without ECMO. Adherence adjusted estimates are reported for differences in hospital mortality and probability of hospital discharge alive in 7345 patients with covid-19 associated acute respiratory failure. Shaded areas represent 95% confidence intervals**

**What this study adds** ECMO was associated with a reduction in mortality in well selected patients with covid-19 associated respiratory failure. Age, severity of hypoxaemia, and duration and intensity of mechanical ventilation were found to be modifiers of treatment effectiveness and should be considered when deciding on ECMO in patients with covid-19.

**Funding, competing interests, and data sharing** See full paper on bmj.com for funding and competing interests. Deidentified registry data may be obtained for research purposes on approval of a formal proposal.