











important to note that the studies report different periods with regards to time from ICU admission to the start of early mobilisation, and time from randomisation to the start of rehabilitation, which might be different if there is a long period between ICU admission and randomisation into the study.

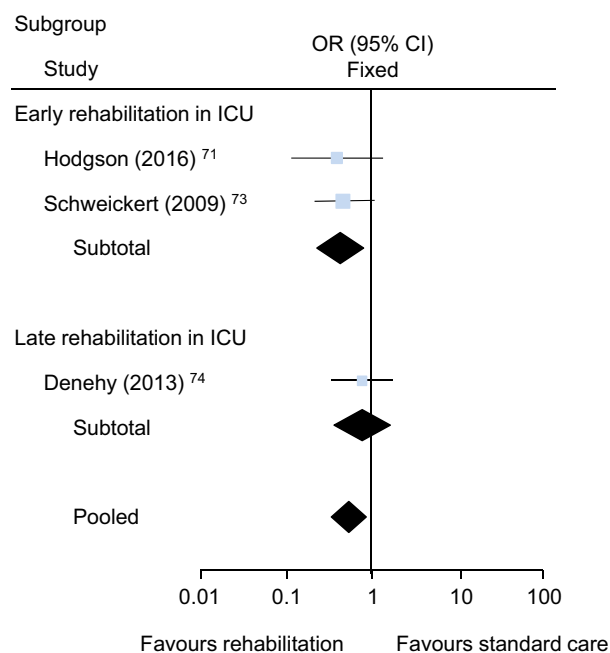
The results of the individual studies are conflicting, with some studies reporting no benefit,<sup>74–76</sup> whilst others report improved function at hospital discharge,<sup>73,77</sup> greater independent walking distance,<sup>73,78</sup> higher mobility milestones,<sup>71,77</sup> decreased duration of mechanical ventilation,<sup>73,79</sup> increased muscle strength<sup>80</sup> and improved quality of life of survivors<sup>72</sup> favouring the intervention group. One study reported significantly lower 6-minute walk test results in the early rehabilitation group compared with the control at ICU discharge (MD 42 m, 95% CI 4 to 79).<sup>74</sup> Whilst previous systematic reviews<sup>81,82</sup> have assessed the impact of mobilisation in the ICU, they have had limited ability to complete meta-analysis due to the heterogeneity in the study designs, in particular the outcome measures used and the timing of these assessments. To date, the significant results supporting mobilisation in the ICU with improvements in function, mobility and quality of life have been reported in studies that commenced the intervention early in the ICU stay.<sup>71–73,77</sup> This may demonstrate a greater ability for early mobilisation to prevent ICUAW and long-term functional impairments than to treat muscle weakness once it is established.<sup>83</sup>

A recent systematic review and meta-analysis of early rehabilitation during ICU stay on functional status demonstrated a greater probability of walking without assistance at hospital discharge in the early mobilisation group compared with the control group (pooled RR 1.42, 95% CI 1.17 to 1.71, four studies).<sup>81</sup> This systematic review and meta-analysis also reported the risk ratio for ICUAW between the intervention and control groups (pooled RR 0.75, 95% CI 0.51 to 1.09, three studies). However, this analysis pooled studies that included both electrical muscle stimulation and early mobilisation, and measured ICUAW at different points in the patient's trajectory. An updated pooled analysis of the proportion of patients who developed ICUAW in studies of early mobilisation demonstrates a lower risk of ICUAW in the early mobilisation group compared with the control group (OR 0.54, 95% CI 0.32 to 0.91) (Figure 4; for a detailed forest plot, see Figure 5 on the eAddenda).<sup>71,73,74</sup> The sensitivity analysis demonstrates that the results are driven by the two studies that commenced mobilisation within 3 days of ICU admission.<sup>71,73</sup>

We need to carefully consider strategies for retention of patients into studies that measure long-term outcomes after critical illness, including registry linkages.<sup>84,85</sup> To this end, there are excellent resources available from experts in the field that should be considered for use in ICU studies requiring follow-up.<sup>86</sup> Several recent studies of mobilisation and rehabilitation that measured long-term recovery after hospital discharge have demonstrated that a large number of participants were lost to follow-up or withdrew from the trial.<sup>54,74,75,77</sup> Finally, there is an urgent need for a large trial to confirm the impact of mobilisation in the ICU on patient-centred, long-term outcomes.<sup>83,84</sup> In some other areas of clinical practice, early mobilisation of acutely unwell patients has not demonstrated improved patient-centred outcomes,<sup>87,88</sup> and this may be true in specific ICU cohorts, for example patients with severe sepsis.<sup>72</sup>

### Future directions for research and practice

There are several important considerations for the physiotherapy management of patients in the ICU who are at risk of developing ICUAW or who have been diagnosed with ICUAW. One of the criticisms of previous randomised trials assessing strength and function of patients in the ICU is the heterogeneous population. There is no measurement of baseline function that may affect the ability to recover, with evidence that patients who are older and with comorbid conditions are less likely to respond to interventions.<sup>89–91</sup>



**Figure 4.** Odds ratio (95% CI) of ICUAW with or without mobilisation and rehabilitation in the ICU. Overall, mobilisation and rehabilitation reduced the odds of ICUAW. When studies were subgrouped into mobilisation and rehabilitation started within 3 days of admission to ICU (early) or after more than 5 days in ICU (late), the odds of ICUAW were only significantly reduced with early mobilisation and rehabilitation compared with standard care. ICU = intensive care unit, ICUAW = Intensive Care Unit Acquired Weakness.

Similarly, the risks and benefits for specific diagnostic groups are currently unknown. One study demonstrated increased mortality in septic patients who received early mobilisation<sup>72</sup> (and direct communication with authors). Another study demonstrated increased mortality with inspiratory muscle training commenced after weaning from mechanical ventilation.<sup>42</sup> The study by Schweickert et al. that demonstrated improved recovery at hospital discharge included a heterogeneous population, but the participants were all functionally independent prior to ICU admission.<sup>73</sup> Another study in the surgical population demonstrated decreased length of hospital stay, with patients also functionally independent prior to ICU admission.<sup>77</sup> Therefore, there is an urgent need for future studies to identify responders and non-responders to mobilisation and rehabilitation in the ICU.<sup>90,92</sup>

Increasingly, physiotherapists have focused on exercise-based interventions in the ICU, including both bed exercises and mobilisation out of bed.<sup>81,82</sup> These have been shown to be safe and effective during the ICU stay<sup>4,68,93</sup> and there is evidence that they may reduce hospital length of stay and improve functional independence at hospital discharge.<sup>73</sup> This appears to be more apparent in studies that randomised patients early (within 3 days) of the ICU stay.<sup>71–73</sup> However, there is an urgent need for research that helps us to understand the risks versus the benefits of early mobilisation and rehabilitation on long-term outcomes and patient recovery beyond the hospital stay.<sup>84,85</sup> Until the long-term outcomes are assessed in an adequately powered, multi-centre trial, the safety of the intervention remains unclear.

In the past 12 months, several new randomised, controlled trials have assessed the effect of physiotherapy and early rehabilitation in patients with acute respiratory failure.<sup>75–77</sup> Whilst the number of studies in this field is increasing, there is no clear evidence of a dose-response in critically ill patients. Few of these studies have published precise data on the dosage of exercise per patient. Future studies could improve the understanding of the dose-response by providing this valuable information. This would require information about the timing and duration of exercise (minutes) and the type of exercise delivered, using a valid

measurement tool. There is an active international research agenda to develop a core set of outcome measures for patients after ICU.<sup>94-96</sup> This is urgently required because the larger trials that have measured long-term outcome have included different outcome measures of strength, physical function and health-related quality of life, therefore limiting the ability to pool the results.<sup>97</sup> In the future, ICU research assessing strength and function should include a core set of outcome measures to allow comparison between studies.<sup>94</sup>

In the clinical setting, physiotherapists have a growing body of evidence to guide practice when treating patients during critical illness (Figure 1). ICUAW is common and occurs rapidly during the ICU stay; however, the evidence for important benefits of early physiotherapy interventions in ICU is not strong.<sup>9</sup> It is possible that early interventions, including inspiratory muscle training, early mobilisation and cycle ergometry, reduce ICUAW and improve independence at hospital discharge; however, currently it is unclear which intervention, timing and dosage is best to prevent or treat ICUAW.<sup>83</sup> There are several ongoing studies that will inform long-term outcomes for patients in this area of practice in the future.





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