Effect of home-based interventions on basic activities of daily living for patients who had a stroke: a systematic review with meta-analysis

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ABSTRACT

Objectives To investigate the effectiveness of home-based interventions in improving the ability to do basic activities of daily living in patients who had a stroke.

Methods Randomised controlled trials were searched through MEDLINE, Embase and CINAHL from their inception to 31 December 2021. We included studies involving home-based intervention prescribed by professionals and implemented at patients' homes. The characteristics of these studies were collected. Risk of bias of individual study was assessed by Physiotherapy Evidence Database scale. Meta-analyses were performed where studies reported comparable interventions and outcomes.

Results In total, 49 studies were included in the systematic review and 16 studies had sufficient data for meta-analyses. The short-term effect of home-based intervention showed no significant difference when compared with institution-based intervention (standardised mean difference (SMD)=0.24, 95% CI −0.15 to 0.62, I²=0%). No significant difference was found between home-based intervention and usual care for long-term effect (SMD=0.02; 95% CI −0.17 to 0.22; I²=0%). Home-based rehabilitation combined with usual care showed a significant short-term effect on the ability to do basic daily activities, compared with usual care alone (SMD=0.55; 95% CI 0.22 to 0.87; p=0.001; I²=3%).

Conclusion Home-based rehabilitation with usual care, which varied from no therapy to inpatient or outpatient therapy, may have a short-term effect on the ability to do basic activities of daily living for patients who had a stroke compared with usual care alone. However, the evidence quality is low because of the limited number of studies and participants included in the meta-analysis and the possible publication bias. Future research is needed to investigate the effectiveness of home-based rehabilitation in groups with stratification by stroke severity and time since stroke onset, with elaboration of details of the home-based and the control interventions. Moreover, more high-quality studies are required to prove the cost-effectiveness of newly developed strategies like caregiver-mediated rehabilitation and telerehabilitation.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Investigated the effectiveness of home-based rehabilitation in improving the ability to do basic activities of daily living in patients who had a stroke, compared with institution-based intervention, usual care and no intervention, respectively.

⇒ Updated some newly developed home-based treatment strategies such as telerehabilitation and caregiver-mediated intervention, and investigated their effectiveness.

⇒ The number of studies included in the individual meta-analysis was limited because of the inadequate data in the individual studies.

⇒ The clinical heterogeneity between studies in terms of severity of stroke, onset time of stroke, interventions and manner of delivery also compromised the evidence strength of our meta-analyses.

INTRODUCTION

Stroke is one of the major causes of death and is a leading cause of adult disability worldwide.¹ About half of patients who had a stroke are left with varying degrees of physical or cognitive impairments.² Previous studies have shown that 25%–74% of patients who had a stroke need assistance from caregivers for the activities of daily living,³ and the quality of life of both patients and caregivers is heavily impacted.⁴ Although the need for rehabilitation services for the patients who had a stroke after discharge from acute hospitals is widely recognised, outpatient and inpatient rehabilitation are often compromised for reasons such as lack of accessibility, increased costs and poor compliance.⁵,⁶ On the other hand, the ability to perform activities of daily living in an institution-based environment may not be generalised to the home environment, which is the final discharge destination for most patients who had a stroke.⁷ Moreover, the motor relearning of patients who had a stroke improves by context-specific training, and training in the patient’s own
environment is preferred. Early supported discharge from hospital with subsequent rehabilitation services at home has shown to be more cost-effective than usual care, with a lower caregiver burden and shorter length of stay in hospital. Therefore, a home-based rehabilitation programme could be a viable alternative to institution-based stroke rehabilitation.

A Cochrane review of home-based therapy programmes for upper limb functional recovery following stroke found that there was insufficient good-quality evidence to determine the relative effect of home-based upper limb programmes on performance of basic activities of daily living (BADL), compared with placebo, no intervention or usual care. The limited number of included studies and the heterogeneity in terms of the type of home-based therapy programmes limited the evidence strength. Apart from upper limb function, the ability to perform BADL in patients who had a stroke is influenced by much more factors such as mobility, cognition and communication, environmental limitation and psychological adaptation. Moreover, upper limb function is not linearly related to the actual performance of daily activities, and the improved upper limb motor capacity does not translate into the increased upper limb performance in daily life. Therefore, the effectiveness of home-based intervention including but not limited to upper extremity function training is needed to be investigated.

Another previous review found a significant short-term effect on functional independence in favour of home-based rehabilitation for community-dwelling people who had a stroke. However, the evidence was weak because the control interventions mentioned in the previous review were mixed with usual care, centre-based intervention and no intervention. Moreover, as the development of home-based treatment strategy and also for the purpose of reservation of medical services, novel home-based intervention strategies such as telerehabilitation and caregiver-mediated intervention have emerged nowadays. An updated review is needed to investigate the effectiveness of home-based interventions in improving the ability to perform self-care activities in patients who had a stroke.

The objective of this systematic review was to evaluate the effectiveness of home-based interventions in performance of BADL, when comparing with institution-based intervention, usual care and no intervention, respectively, in patients who had a stroke.

METHODS
The following items were reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Patient and public involvement
No patient involved.

Search strategy
The MEDLINE, Embase and CINAHL databases were searched through PubMed, Embase and EBSCOhost platforms, respectively, from inception to 31 December 2021. The search strategy is presented in online supplemental appendix 1.

Inclusion and exclusion criteria
We only included participants in home-based intervention groups who were living in their own home. Studies that included participants in home-based intervention groups who were living in care homes and other forms of supported or sheltered accommodation were excluded. We defined the home-based interventions as (1) prescribed by professionals and (2) implemented in the patient’s own home. Studies delivered solely in environmental modifications, ergonomic intervention, psychosocial interventions or medication were excluded. The comparison interventions included institution-based intervention, usual care and no intervention. We included studies which measured the ability to do BADL as one of the outcomes. Trials that studied solely instrumental activities of daily living were excluded. We only included peer-reviewed studies in English language. Grey literature like unpublished studies or conference abstracts were excluded.

Selection of studies
Two reviewers independently extracted randomised controlled studies from the three databases. The duplicate articles were deleted, and the obviously irrelevant studies were eliminated by screening the titles and abstracts. If any one of the reviewers considered one reference as eligible, the full text was assessed and two reviewers evaluated the study separately based on the inclusion and exclusion criteria. The two reviewers also searched for relevant reviews reported on the similar topic from the three databases. Reference lists of those reviews were examined, and citation searching and full-text assessment were conducted to identify the additional eligible studies. Only the studies identified by both reviewers were included in the review. Any disagreements between the two reviewers were resolved through discussion with the third reviewer.

Data extraction and management
Data were extracted from the included studies and recorded on a data extraction form by one reviewer and checked by another reviewer. The extracted information included the following items: (1) the total number of participants of each group; (2) characteristics of participants such as age, gender, disability level and time elapsed since stroke onset; (3) characteristics of home-based interventions and interventions in the control group, and details of home-based interventions; (4) outcome measures of performance of BADL and the time points of outcome measures; and (5) results of effectiveness.

Assessment of methodological quality
Two reviewers independently assessed the methodological quality of the included studies using the Physiotherapy Evidence Database scale (PEDro scale).
used the same measurement tool, we calculated a pooled standardised MDs (SMDs) instead of MDs. When different measurement tools were used, we used the means and SDs of outcome scores with the inverse variance method. The overall estimate of the treatment effect was calculated using the means and SDs of outcome scores with continuous data in the home-based intervention group and control group. Short-term effect and long-term effect were analysed by comparing the statistical difference between groups at treatment endpoint and at the last follow-up, respectively. Those studies with no mean or SD of outcome measure reported were excluded from the meta-analysis. For the studies that used the same measurement tool, we calculated a pooled estimate of the mean differences (MDs) with 95% CIs. When different measurement tools were used, we used the standardised MDs (SMDs) instead of MDs. Statistical heterogeneity was measured using the $I^2$ statistic. $I^2 >50\%$ was considered to indicate substantial heterogeneity, which would result in the use of a random-effects model for the meta-analysis. When $I^2$ was $\leq 50\%$, a fixed-effects model was used. Inverse variance method was used to estimate the treatment effect.

We planned to perform several meta-analyses to evaluate (1) the effectiveness of home-based intervention compared with institution-based intervention at treatment endpoint and follow-up; (2) the effectiveness of home-based intervention compared with usual care at treatment endpoint and follow-up; (3) the effectiveness of home-based intervention combined with usual care compared with usual care at treatment endpoint and follow-up; and (4) the effectiveness of home-based intervention compared with no intervention at treatment endpoint and follow-up.

We also planned to perform a sensitivity analysis to diminish the influence of studies with poor methodological quality on the effect size estimate. The studies with poor PEDro score ($\leq 3$) were deleted from the meta-analysis. All of the statistical tests were two tailed, and $p<0.05$ represented statistical significance.

We planned to test for funnel plot asymmetry to assess the publication bias if there were more than 10 studies included in the meta-analysis.

**Assessment of certainty of the evidence**

Two reviewers independently assessed the quality of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Five factors result in rating down the quality of evidence including study limitations, inconsistency of results, indirectness of evidence, imprecision and publication bias. We rated the overall quality of evidence as high, moderate, low or very low for each outcome. We justified all decisions to downgrade the quality of evidence.

**RESULTS**

**Study identification**

The search of the electronic bibliographical databases identified 466 articles (MEDLINE=221, Embase=231, CINAHL=14). Five additional studies were identified through the reference lists of relevant articles and reviews. In total, 49 studies met the eligibility criteria and were included into this systematic review (figure 1).

**Study characteristics**

Twenty-one randomised controlled trials compared home-based rehabilitation with institution-based rehabilitation on an inpatient or outpatient basis. Fifteen randomised controlled trials compared home-based rehabilitation with usual care, which was provided according to routine practice without the involvement of the research team and might include no therapy, home care, instructions for home rehabilitation, inpatient therapy and outpatient therapy. Five randomised controlled trials evaluated the effect of specific home-based interventions by comparing with blank control or sham control. Ten randomised controlled trials compared home-based interventions combined with usual care with usual care alone. The main characteristics of the included studies are shown in online supplemental table 1. The summary of details of the home-based intervention in each included study according to the Template for Intervention Description and Replication is shown in online supplemental table 2.

There were various home-based interventions performed in the included studies. Twelve studies did not describe the details of treatment strategy. Among 37 studies which reported the details of treatment strategy, 19 studies provided physical exercise practice, 25 26 27 31 34–36 45–47 49 53 57–59 61 63 64 71 20 studies provided...
training of daily activities, and 2 studies provided constraint-induced movement treatment.

Other treatments like speech and communication therapy, psychosocial intervention, emotion management, electromyography-triggered neuromuscular stimulation, environmental modification, application of leisure activities, providing adaptive aids and equipment, providing fall prevention strategies, and providing splint or orthoses were also used as part of home-based interventions for patients who had a stroke.

The delivery strategy of home-based intervention has transformed in recent years. Before 2009, 24 out of 25 included studies reported that home-based interventions were provided by professionals during home visits. Among 24 studies published from 2009, 11 studies involved self/caregiver-mediated intervention, in which 4 studies provided telerehabilitation supervised by professionals.

**Risk of bias in included studies**
The methodological quality of the included studies is presented in table 1. Thirty-three out of the included 49 studies were of good methodological quality (PEDro score=6–8). Twelve studies were of fair quality (PEDro score=4–5) and four were of poor quality (PEDro score=1–3).

**Effectiveness of home-based intervention compared with institution-based intervention**
Twenty-one studies investigated the effectiveness of home-based intervention compared with institution-based intervention. Three studies did not specify the between-group statistical comparison. Fifteen studies found no significant difference between two groups in the ability to do daily living no matter at treatment endpoints or at follow-ups. While one study demonstrated the superiority of home-based intervention compared with institution-based intervention, one study showed an opposite result. Seven studies reported improvement in ability to do daily living in both groups.
| Studies                      | Items | Score (0–10) |
|------------------------------|-------|--------------|
| Asano et al23                | √     | 5            |
| Baskett et al24              | √     | 7            |
| Björkdahl et al25            | √     | 7            |
| Chen et al26                 | √     | 8            |
| Chen et al27                 | √     | 8            |
| Gladman and Lincoln28        | √     | 5            |
| Gladman et al29              | √     | 6            |
| Han et al30                  | √     | 7            |
| Hesse et al31                | √     | 7            |
| Hofstad et al32              | √     | 8            |
| Kalra et al33                | √     | 8            |
| Özdemir et al34              | √     | 5            |
| Pandian et al35              | √     | 2            |
| Redzuan et al36              | √     | 3            |
| Roderick et al37             | √     | 5            |
| Taule et al38                | √     | 5            |
| Thorsén et al39              | √     | 5            |
| von Koch et al40             | √     | 6            |
| von Koch et al41             | √     | 6            |
| Widén Holmqvist et al42      | √     | 6            |
| Young and Forster43          | √     | 6            |
| Barzel et al44               | √     | 8            |
| Chaiyawat and Kulkantrakorn45| √     | 7            |
| Chaiyawat et al46            | √     | 7            |
| Chen et al47                 | √     | 7            |
| Deng et al48                 | √     | 8            |
| Duncan et al49               | √     | 6            |
| Lincoln et al50              | √     | 4            |
| Lindley et al51              | √     | 7            |
| Mayo et al52                 | √     | 6            |
| Rasmussen et al53            | √     | 5            |
| Santana et al54              | √     | 6            |
| Walker et al55               | √     | 7            |
| Wolfe et al56                | √     | 5            |
| Azab et al62                 | √     | 1            |
| Batchelor et al63            | √     | 7            |
| Chumbler et al64             | √     | 7            |
| Corrand Bayer65              | √     | 5            |
| Goldberg et al67             | √     | 2            |
| Gilbertson et al66           | √     | 7            |
| Mandigout et al68            | √     | 6            |
| Ricauda et al69              | √     | 6            |
| Rudd et al70                 | √     | 5            |

Continued
Three studies with adequate data were included in the meta-analysis to evaluate the effect of home-based intervention compared with institution-based intervention.26 31 36 Two studies measured the performance of BADL at treatment endpoint,26 31 and one study measured at the follow-up after intervention.73 One study did the follow-up assessment during the treatment period.36 For the endpoint analysis, a fixed-effects analysis produced an insignificant result (SMD=0.24; 95% CI=−0.15 to 0.62; n=104; I²=0%) (figure 2).

At treatment endpoint, very low-quality evidence indicates the uncertainty of the effect of home-based intervention compared with institution-based intervention. The evidence was downgraded one level for publication bias and two levels for imprecision as the sample size is small and the 95% CI estimated includes both null effect and appreciable benefit or harm.

Effectiveness of home-based intervention compared with usual care

Fifteen studies investigated the effectiveness of home-based intervention compared with usual care. Ten studies found no significant difference between two groups in the ability to do daily living no matter at treatment endpoints or at follow-ups.32 38 44 49–54 56 Five studies showed significantly better improvement in the home-based intervention than in the usual care group.45–48 51

Six studies were pooled in the meta-analysis to evaluate the effect of home-based intervention compared with usual care.44 47 48 51 52 54 Four studies measured the performance of BADL at treatment endpoint.44 47 48 52 For the endpoint analysis, a random-effects analysis produced an insignificant result with high heterogeneity between studies (SMD=0.62; 95% CI=−0.07 to 1.31; n=475; I²=92%) (figure was eliminated). Three studies measured outcome at the follow-up after intervention.44 52 54 For the follow-up analysis (after intervention), a fixed-effects analysis produced an insignificant result with high heterogeneity between studies (SMD=0.02; 95% CI=−0.17 to 0.22; n=399; I²=0%) (figure was eliminated).

At treatment endpoint, very low-quality evidence indicates the uncertainty of the effect of home-based intervention compared with usual care. The evidence was downgraded one level for publication bias and two levels for imprecision as the sample size is small and the 95% CI estimated includes both null effect and appreciable benefit or harm.

At follow-up after intervention, very low-quality evidence indicates the uncertainty of the effect of home-based intervention compared with usual care. The evidence was downgraded one level for publication bias and two levels for imprecision as the sample size is small and the 95% CI estimated includes both null effect and appreciable benefit or harm.

### Table 1

| Studies               | Items | Score (0–10) |
|-----------------------|-------|--------------|
| Wong and Yeung71      | √     | √            | √           | √       | √       | √       | √       | √       | 8      |
| Koç57                 | √     | √            | √           | √       | √       | 5       |
| Lin et al68           | √     | √            | √           | √       | √       | √       | √       | 8       |
| Wade et al69          | √     | √            | √           | √       | √       | √       | √       | 6       |
| Walker et al60        | √     | √            | √           | √       | √       | 6       |
| Wang et al61          | √     | √            | √           | √       | √       | 6       |

Rating items: 1—eligibility criteria and source of participants; 2—random allocation; 3—concealed allocation; 4—baseline comparability; 5—blinded participants; 6—blinded therapists; 7—blind assessors; 8—adequate follow-up; 9—intention-to-treat analysis; 10—between-group comparisons; 11—point estimates and variability. Item 1 evaluates external validity, does not contribute to the total score.

### Figure 2

Forest plot comparing the effectiveness of home-based intervention with institution-based intervention at treatment endpoint.

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Qin P, et al. BMJ Open 2022;12:e056045. doi:10.1136/bmjopen-2021-056045
At follow-up during the intervention period, very low-quality evidence indicates the uncertainty of the effect of home-based intervention compared with usual care. The evidence was downgraded one level for publication bias, one level for inconsistency because of the heterogeneity between results, and one level for imprecision as the 95% CI estimated includes both null effect and appreciable benefit or harm.

**Effectiveness of home-based intervention compared with no intervention**

Five studies investigated the effectiveness of home-based intervention compared with no intervention. Four out of five included studies showed significantly greater improvements of BADL in home-based intervention group than in the control group. Studies demonstrated significant improvements on the BADL in home-based intervention but not in the control group.

Four studies were pooled in the meta-analysis to evaluate the effect of home-based intervention compared with no intervention. All of them measured the performance of BADL at treatment endpoint, and a random-effects analysis produced an insignificant result with high heterogeneity between studies (SMD=0.84; 95% CI=0.38 to 2.05; n=231; I²=94%) (figure was eliminated).

At treatment endpoint, very low-quality evidence indicates the uncertainty of the effect of home-based intervention compared with no intervention. The evidence was downgraded one level for publication bias, one level for inconsistency because of the heterogeneity between results, and two levels for imprecision as the sample size is small and the 95% CI estimated includes both null effect and appreciable benefit or harm.

**Effectiveness of home-based intervention addition to usual care compared with usual care**

Ten studies investigated the effectiveness of home-based intervention addition to usual care. Seven studies found no significant difference between groups in the ability to do daily living no matter at treatment endpoints or at follow-ups. Two studies demonstrated significantly greater improvement in home-based intervention group than control group. Wong and Yeung and Ricauda et al. found significant improvement in both groups, while Batchelor et al. showed there was no significant improvement either in home-based intervention group or in the control group.

Four studies were pooled in the meta-analysis to evaluate the effect of home-based intervention addition to usual care compared with usual care. Two studies measured the performance of BADL at treatment endpoint, and a fixed-effects analysis produced a significant result (SMD=0.55; 95% CI=0.22 to 0.87; n=152; I²=3%) (figure 4). All of them measured at the follow-up, and a random-effects analysis produced an insignificant result with high heterogeneity between studies (SMD=0.23; 95% CI=−0.16 to 0.62; n=545; I²=77%) (figure was eliminated).

At treatment endpoint, low-quality evidence indicates the home-based intervention addition to usual care may have little or no effect on BADL compared with usual care alone. The evidence was downgraded one level for publication bias and one level for imprecision as the sample size is small.

At follow-up after intervention, very low-quality evidence indicates the uncertainty of the effect of home-based intervention addition to usual care compared with usual care alone. The evidence was downgraded one level for publication bias, one level for inconsistency because of the heterogeneity between results, and one level for imprecision as the 95% CI estimated includes both null effect and appreciable benefit or harm.
Subgroup analysis
We were unable to conduct subgroup analyses according to the level of disability of the patients who had a stroke, the onset time of stroke, type of intervention or manner of delivery of the treatment because of the clinical diversity between studies, the insufficient information in the individual study and the limited number of included studies.

Sensitivity analysis
We were unable to conduct sensitivity analyses because there was no low-quality study included in the meta-analyses.

Assessment of reporting bias
We were unable to conduct the funnel plot to assess the reporting biases because of the limited number of included studies in each meta-analysis.

DISCUSSION
Our review found that home-based intervention combined with usual care may have short-term benefits for patients who had a stroke compared with usual care alone. However, the evidence was weak because of the limited number of studies and participants included in the meta-analysis and the possible publication bias. We speculated the intensive dosage of intervention attributes to the effect of home-based intervention combined with usual care. Most included studies conducted the professional-mediated home-based intervention to participants and the usual care was also provided, which ensured the high intensity of therapy to improve the recovery of patients who had a stroke.

There was insufficient evidence to determine the short-term effect of home-based intervention compared with the institution-based intervention, or to determine the long-term effect of home-based intervention compared with the usual care, because of the limited number of studies and participants included in the meta-analyses. There was insufficient evidence to prove the short-term effect of home-based intervention on the performance of activities of daily living in patients who had a stroke, when compared with no intervention. There was insufficient evidence to suggest the short-term effect of home-based intervention compared with usual care, or to suggest the long-term effect of home-based intervention addition to usual care compared with usual care. The heterogeneity between the studies limited the conclusions that could be drawn.

Many current rehabilitation interventions are developed in clinical setting, and some are translated to home. Home-based intervention strategies vary in type, duration, intensity, frequency and delivery manner. This systematic review revealed that exercise physiology practice and training of activity of daily living were commonly performed as home-based interventions which are supported by current evidence. American Heart Association/American Stroke Association (AHA/ASA) guideline suggested that lower extremity strengthening exercise and cardiovascular exercise are beneficial to improve gait capacity of patients who had a stroke and can also improve their ability to perform gait-related mobility tasks. Moreover, training of activities of daily living is strongly recommended for community-dwelling patients who had a stroke. Some newly developed home-based interventions like caregiver-mediated rehabilitation and telerehabilitation have emerged for the past two decades to replace the traditional home visits by professionals. A Cochrane systematic review found that the caregiver-mediated rehabilitation did not increase the caregiver burden but the effectiveness in the ability to perform BADL in patients who had a stroke was uncertain. One large study found that the lower dose of caregiver-guided rehabilitation training and non-multidisciplinary coordination might decrease the efficacy of caregiver-mediated home-based interventions. Telerehabilitation seemed to be a good alternative to traditional rehabilitation. Chen et al delivered the same treatment strategy to home-based telerehabilitation group and institution-based rehabilitation group. At the end of intervention and at follow-up, both groups showed significant improvement in the ability to do activities of daily living, and there was no significant difference between two groups throughout the time. Similarly, when comparing with the traditional face-to-face way of home-based intervention performed by professionals, home-based telerehabilitation showed equal positive effect on enhancing the ability to do activities of daily living of patients who had a stroke. More high-quality studies and practice are required to prove the effectiveness of those new strategies.

Limitations
There is no sufficient study to determine the effectiveness of home-based intervention compared with other approaches. Although 49 studies were included in the review, many of them did not report adequate data so they were not included in the meta-analyses; therefore, only two to four studies were included in each meta-analysis. Moreover, among the 49 included studies, several studies of the original study and their follow-up study shared the same study population, including two studies conducted by Chaiyawat et al, four studies conducted by von Koch et al and two studies conducted by Gladman et al. Therefore, only 44 trials were included. Nearly half of studies included in the meta-analyses had sample size smaller than 30. The clinical heterogeneity between studies in terms of severity of stroke, onset time of stroke, interventions and manner of delivery also compromised the evidence strength of our meta-analyses. Estimation of publication bias using funnel plots failed because of the insufficient number of included studies in each meta-analysis. Publication bias was possibly increased as we have not searched for the grey literature.
CONCLUSION
Our finding reveals that the home-based intervention combined with usual care may be more effective than usual care alone for the short-term effect. However, the evidence is weak. Future research with larger sample size is needed to investigate the effectiveness of home-based rehabilitation, including (1) on groups with stratification of stroke severity defined by Brunnstrom stage; (2) on groups with stratification of acute, subacute and chronic stroke; (3) with elaboration of the details of the home-based interventions and the control interventions. Moreover, more high-quality studies are required to prove the cost-effectiveness of newly developed strategies like caregiver-mediated rehabilitation and telerehabilitation.

Contributors XJW and PQ designed the review. PQ and CXC screened and selected the study. PQ and CC rated the study quality and extracted the data. PQ analysed the data and drafted the paper. XJW revised the paper. All authors acknowledged and agreed with the format and content of the paper before submission for publication. XJW is the guarantor and responsible for the overall contents of this study.

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