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High-intensity exercise programs in people with dementia — a systematic review and meta-analysis

Electronic supplementary material

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Introduction

Dementia is one of the most common mental and neurological disorders affecting nearly 50 million people worldwide (Prince et al., 2015). The prevalence of dementia doubles every 5 years after the age of 65 (Fiest et al., 2016) meaning that more than two thirds of all affected individuals have already reached the age of 80. Due to demographic transition and increasing societal ageing, the financial burden of this disease will continuously grow in the coming years. In 2012, the World Health Organization (WHO) declared dementia a public health priority, highlighting the high global prevalence and economic impact (World Health Organization & Alzheimer's Disease International, 2012). Dementia is a syndrome which pathoetiologically affects the brain and is characterized by a progressive deterioration in intellect including memory, learning, orientation, language, comprehension and judgment (Hugo & Ganguli, 2014). Aside from cognitive decline, dementia is also associated with impaired motor function and difficulties in social and occupational functioning. Gait and balance disturbances increase the risk of falls (Kato-Narita, Nitrini, & Radanovic, 2011) and are related to reduced lower-limb muscle strength (Muehlbauer, Gollhofer, & Granacher, 2015), habitual physical activity (Morie et al., 2010), and the ability to perform activities of daily living (ADLs) independently (Wennie Huang, Perera, VanSwearingen, & Studenski, 2010).

There is currently no disease-modifying therapy available for any of the neurodegenerative types of dementia. Hence, the aim of existing therapies is to maintain general functions, facilitate independency, and to ensure quality of life (QoL) (Hildreth & Church, 2015; Hugo & Ganguli, 2014). There is a huge body of evidence suggesting that a higher amount of physical activity (PA) is associated with a reduced risk of cognitive impairments throughout the life span and that PA counteracts brain atrophy, one of the main features of Alzheimer's disease (Colcombe et al., 2006; Erickson et al., 2011; Erickson, Weinstein, & Lopez, 2012; Intlekofer & Cotman, 2013; Kirk-Sanchez & McGough, 2014; McGurran, Glenn, Madero, & Bott, 2019; Pini et al., 2016). Furthermore, a recent review reports on moderate evidence for exercise training interventions (structured programs) in improving cognitive function in people with dementia (Erickson et al., 2019). Thus, increasing PA and implementing exercise have been identified as protective factors as well as treatment strategies (Forbes, Forbes, Blake, Thiessen, & Forbes, 2015; Lam et al., 2018; Pitkälä, Savikko, Poysti, Strandberg, & Laakkonen, 2013). Nevertheless, to date, only limited data exist about the most effective exercise dose (e.g. intensity, modality, volume). Indeed, some but not all studies demonstrate higher effect sizes for endurance training (e.g. compared to resistance training) and higher volumes (at least 45 min for 6 months) (Erickson et al., 2019). In addition, a systematic review from 2019 dealing with exercise doses in people with cognitive impairment reports on superiority of short but more frequent exercise sessions (Sanders, Hortobágyi, La Bastide-van Gemert, Van der Zee, & Van Heuvelen, 2019). Thus, less is known about the significance of exercise intensity. Albeit, some basic research and intervention studies indicate that higher exercise intensities have beneficial effects on the expression of neuronal growth factors (Cabral-Santos et al., 2016; Jiménez-Maldonado, Rentería, García-Suárez, Moncada-Jiménez, & Freire-Royes, 2018) and protective vascular mechanisms (Ramos, Dalleck, Tjonna, Beetham, & Coombes, 2015; Way, Sultana, Sabag, Baker, & Johnson, 2019) which are related to cerebral blood flow and cognitive functioning (Davenport, Hogan, Eskes, Longman, & Poulin, 2012).

High intensity training (HIT) usually involves alternating short bursts of intense exercise with periods of rest or low-intensity exercise for recovery (Whitehurst, 2012). When applying HIT to older, diseased, and at-risk populations typically longer work intervals (2–4 min) were used, and it was not uncommon to approach 80–95% of a person's maximum heart rate in terms of endurance training (e.g. Costa et al., 2018; Hannan et al., 2018; Way et al., 2019; Weston, Wisløff, & Coombes, 2014). However, in literature, HIT also includes other types of exercise, such as functional or strength training. High-intensity resistance training is a form of strength training that usually involves short (6–8 repetitions) but intensive exercises at 85–90% of a person's one repetition maximum (1 RM) (Hagerman et al., 2000), while high-intensity functional training is a training type which consists of short bouts of repeated, multidirectional movements incorporating multiple joints, performed with high individual demands, and designed to improve parameters of general physical fitness (Feito, Heinrich, Butcher, & Poston, 2018). Generally, there is an age-related decline in motor and cognitive functions (Stöckel, Wunsch, & Hughes, 2017) and studies have shown high-intensity exercise programs to be effective in improving these functions in healthy elderly populations. More specifically, HIT improved walking endurance and functional mobility (Coetsee & Terblanche, 2017), muscular and cardiorespiratory fitness (Hurst, Weston, & Weston, 2019), and cognitive functions, such as attention and abstract reasoning performance (Iuliano et al., 2015). Since Littbrand et al. (2006) demonstrated the suitability of a strength and functional HIT program in older people with severe cognitive and physical impairments, a series of further HIT studies in people with dementia have been performed. However, at present, a synthesis of these data is still missing. Hence, the aim of this systematic review is to summarize existing data of HIT studies in people with dementia with special regard to physical performance, mental and cognitive health, ADLs, and QoL.

Methods

Search strategies and literature screening

This systematic and meta-analytical review was conducted in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009) and includes studies meeting the following eligibility criteria:

- Adults (≥18 years) with a clinical diagnosis of dementia made by a doctor or specialist and/or a validated test, such as the Mini-Mental State Examination (MMSE) according to Folstein, Folstein and McHugh (1975), the Clinical Dementia Rating (CDR) scale according to Hughes, Berg, Danziger, Coben, and Martin (1982), or the Alzheimer's criteria by the workgroup of the National Institute on Aging and Alzheimer's Association (McKhann et al., 2011) or its previous version the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984),
- Implementation of a HIT program in at least one intervention group,
- Outcome parameters, which include physical performance, mental and cognitive health, ADLs and QoL and
- A randomized controlled trial (RCT) study design.

Five exercise- and health-related databases (The Cochrane Library, Physical Education Index, PubMed, SPORTDiscus and Web of Science Core Collection) were systematically scanned by one author (JR) for eligible studies by title and abstract screening from inception of the respective journal until the deadline 31 July 2019. Each database was searched using the following combination of keywords and/or MeSH terms: "dementia" OR "alzheimer*" OR "cognitive impair*" OR "cognitive declin*" OR "cognition disord*" AND "high-intens*" OR "high" ("intens*" OR "impact" OR "dose" OR "amount") AND "physical" ("activ*" OR "exercise*" OR "therap*") OR "exercis*" OR "train*" OR "program*" OR "rehab*" OR "therap*". After the identification of relevant articles, two authors (JR and CP) performed an independent full text screening and discussed any deviations regarding inclusion and exclusion criteria. A final decision was based on consensus between the two authors. After study retrieval, additional studies

Abstract

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Abstract
Dementia is a syndrome characterized by a progressive deterioration of cognitive and physical functions. The aim of this systematic review was to investigate the effects of high-intensity exercise training (HIT) programs on cognitive and mental health, physical performance, activities of daily living (ADLs) and quality of life (QoL) in people with dementia. A systematic literature search for randomized controlled trials was performed until July 2019. We calculated mean difference (MD) or standardized MD (SMD) and the 95% confidence interval (CI), and assessed heterogeneity using I^2 statistic. Nine studies from three large-scale research projects which were based on the high-intensity functional exercise (HIFE) program incorporating strength, balance and mobility exercises of the lower limbs, including 456 participants (85.5 ± 7.0 years), were considered. There was an overall good study quality (mean PEDro score = 7.6 ± 0.7). Compared to seated control activities, strength and balance HIT resulted in statistically significant but small positive effects on balance performance (MD = 2.31, 95% CI = 0.44–4.17, $p = 0.02$; $I^2 = 73\%$) and on the abilities to independently perform ADLs (SMD = 0.28, 95% CI = 0.12–0.44, $p = 0.0006$; $I^2 = 0\%$). No differences were found in cognitive function, depressive symptoms and QoL. The qualitative analyses yielded sporadic beneficial results (mobility, psychological well-being and apathetic behaviour) in favour of HIT. There is only limited evidence for an intensity-related dose–response relationship. Further well-designed studies are needed to identify the best exercise type for different types and stages of dementia.

Keywords
Physical activity · Cognitive impairment · Strength training · Balance training · Exercise dosage

Table 1 Characteristics of included studies

Study; *Acronym*, country	Study design	Participants: Setting; sample size; mean age (years); female (%)	Groups (*N* included in the analysis): INT/CON	MMSE score or rating of dementia	Interventions	Outcomes	Intervention effect	Dropouts (%) to 1st follow-up: INT/CON	Follow-up
Littbrand et al. (2009) *FOPANU study*, Sweden	Stratified cluster-RCT	9 residential care facilities; *N* = 100; 84.7 ± 6.5; 72.8%	47/53	MMSE = N/A Dementia screening as per DSM-IV criteria	**INT** high-intensity functional exercise (HIFE) program **CON** topic-based and stimulating activity program while sitting	Barthel ADL Index (performance in ADLs, BI)	Significantly higher BI total score in favour of the INT groups at 3 months follow-up, but not at 6 months	4.4/5.7	3 and 6 months
Conradsson et al. (2010) *FOPANU study*, Sweden	a/a	a/a	a/a	a/a	a/a	GDS (depression) PGCMS (psychological state)	Subgroup analysis showed significant differences in PGCMS scores in favour of INT groups after 3 months, but not after 6 months and not in GDS scores	11.7/7.5	a/a
Littbrand et al. (2011) *FOPANU study*, Sweden	a/a	a/a	a/a	a/a	a/a	Berg Balance Scale (BBS)	The subgroup analyses for dementia revealed no statistically significant interaction on functional balance at 3 or 6 months	10.6/9.4	a/a
Telenius et al. (2015a) *EXDEM study*, Norway	Single-blinded parallel multicentre RCT	18 nursing homes; *N* = 170; 86.7 ± 7.4; 73.6%	81/79	MMSE = 15.7 ± 5.0 Mild or moderate dementia (CDR 1 or 2)	**INT** high-intensity functional exercise (HIFE) program **CON** light physical activity, reading, playing games, listening to music or having conversations	BBS BI MMSE 30-Second Chair Stand Test (leg strength and endurance, 30-CST) Normal walking speed (NWS) NPI-Q (behavioural symptoms) QUALID (quality of life) CSDD (depression)	Significant improvements of INT compared to CON groups for BBS, BI and NPI-Q sub-scores apathy and agitation after 12 weeks	12.5/7.2	12 weeks
Telenius et al. (2015b) *EXDEM study*, Norway	a/a	a/a	72/68 (Complete responder analysis)	a/a	**INT** after the 12-week HIFE program (Telenius et al., 2015a) the participants received no further intervention (12 weeks detraining period) **CON** no intervention		After 24 weeks, INT groups showed significant better improvements in BBS and NPI-Q sub-score agitation than CON groups	18.6/18.1 (at 2nd follow-up)	(12 and) 24 weeks
Study; *Acronym*, country	**Study design**	**Participants: Setting; Sample size; Mean age (years); Female (%)**	**Groups (*N* analysed): INT/CON**	**MMSE score or rating of dementia**	**Interventions**	**Outcomes**	**Intervention effect**	**Dropouts (%) to 1st follow-up: INT/CON**	**Follow-up**
Boström et al. (2016) *UMDEX study*, Sweden	Rater-blinded stratified cluster-RCT	16 residential care facilities; *N* = 186; 85.1 ± 7.1; 75.8%	92/92	MMSE = 14.9 ± 3.5 Dementia screening as per DSM-IV-TR criteria	**INT** high-intensity functional exercise (HIFE) program **CON** had conversations, sang, listened to music or readings on specific topics while seating	GDS MADRS (depression)	No differences in GDS and MADRS scores between INT and CON groups after 4 or 7 months	10.8/13.4	4 and 7 months
Toots et al. (2016) *UMDEX study*, Sweden	a/a	a/a	93/93	a/a	a/a	BBS BI FIM (functional status)	The difference between groups was significant for BBS at 4, but not at 7 months and not for BI and FIM	10.8/5.4	a/a

Table 1 (Continued)

Toots et al. (2017a) *UMDEX study*, Sweden	a/a	a/a	a/a	a/a	a/a	MMSE Verbal Fluency ADAS-Cog (cognitive functioning)	No between-group differences in MMSE, ADAS-Cog or VF after 4 and after 7 months of follow-up	12.9/8.6	a/a
Toots et al. (2017b) *UMDEX study*, Sweden	a/a	a/a	a/a	a/a	a/a	Gait Speed (GS) GS without walking aids	Exercise effects on GS significantly differed according to support, with larger effects in participants who walked unsupported compared with when walking aids or living support was used	17.2/15.1	a/a

a/a as above, *ADAS-Cog* Alzheimer's Disease Assessment Scale—cognitive subscale, *CSDD* Cornell Scale for Depression in Dementia, *DSM-IV-TR* Diagnostic and Statistical Manual of Mental Disorders—4th Edition—Text Revision, *FIM* Functional Independence Measure, *GDS* Geriatric Depression Scale, *MADRS* Montgomery—Åsberg Depression Rating Scale, *N/A* not available, *NPI-Q* Neuropsychiatric Inventory questionnaire, *PGCMS* Philadelphia Geriatric Center Morale Scale, *QUALID* quality of life in late-stage dementia scale, *INT* intervention, *CON* control, *RCT* randomized controlled trial

were identified by manually checking cross-references of the selected articles.

Data extraction

Data extraction was initially performed by one author (JR) and a second author (CP) reviewed the extracted data for its relevance, accuracy and comprehensiveness. In case of any disparities a third reviewer (CW) was asked to address any disparities, if necessary. A standardised data extraction sheet was created in dependence on a comprehensive checklist by Higgins and Green (2008) to collect the following data, if available:

- General information on study characteristics (**Table 1**), such as country of study center, study design, participant characteristics (setting and number of facilities, sample size, mean age, and sex ratio), number of participants analysed in the intervention (HIT) and control (CON) groups, diagnosis and classification of dementia, outcomes and length of follow-up,
- Specific information on HIT characteristics (**Table 2**), such as type of intervention and study name, intensity criteria, content of each intervention (exercises), frequency, length of intervention and number of sessions applied, time per session, group size and with or without supervision,
- Methodological quality of included studies, and
- Intervention effects including all available statistical data of individual studies and meta-analyses.

Assessment of methodological quality

Methodological quality was assessed independently by two reviewers using the Physiotherapy Evidence Database (PEDro) scale (Hegenscheidt, Harth, & Scherfer, 2008). Any disagreements were discussed and could be resolved. The PEDro scale comprises 11 dichotomous items and considers two aspects of study quality: firstly, the internal validity of the study, such as randomization, blinding and an adequate analysis (items 2–9) and secondly, whether the study contains sufficient statistical information to make its results interpretable, including between group comparisons, point estimations and dispersion measures (items 10 and 11). Item 1 refers to external validity and is not used to calculate the total score (10 points). The PEDro scale seems to be a valid measure of the methodological quality of clinical trials with a good total score reliability (de Morton, 2009; Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). Studies scoring 9 to 10 on the PEDro scale are often methodologically classified as *excellent*. Furthermore, Hariohm, Prakash and Saravankumar (2015) suggest that scores between 6 and 8 are considered to be of *good* quality, while studies scoring 4 or 5 were of *fair* quality, and studies scoring less than 4 are considered to be of *poor* quality.

Statistical analysis

The studies are described according to their characteristics (**Table 1**), interventions utilized (**Table 2**), methodological quality, and effectiveness of the intervention programs. Outcomes with sufficient quantitative data were analysed meta-analytically. If different studies used the same tool or test to measure the same outcome, the results for continuous variables are reported as mean difference (MD) and 95% confidence intervals (CI). Otherwise, the standardized mean difference (SMD) with 95% CI was calculated. As effect size for MD, Cohen's *d* was calculated and interpreted according to Cohen (1988). First, for each HIT and CON group, the mean change and its standard deviation (SD) was recorded or, if necessary, calculated. If the SD of mean change was not available but replaced by another statistical value, it was converted into a SD according to Higgins and Green (2008). If there were multiple tests measuring the same outcome construct within a study, a combined effect size across outcomes was computed before combining results over studies, so that certain studies were not over-weighted (Borenstein, Hedges, Higgins, & Rothstein, 2009). All statistical analyses were computed using the

Table 2 Characteristics of included high-intensity exercise interventions

Author (year)	Type of intervention (*study name*)	Intensity	Exercises	Frequency	Length of intervention (*N* sessions)	Time per session	Group size	Supervision	Additional notes
Littbrand et al. (2009)	High-intensity functional exercise program (*FOPANU study*)	*Strengthening* 8–12 RM (progression, if >12 repetitions possible) *Balance* Intended to fully challenge one's postural stability	Individual exercises for each person depending on their functional deficits	5×/2 weeks	13 weeks (29 sessions)	45 min	3–9	INT groups supervised by two PTs	Integration of physical tasks into daily life to maintain physical function during the 3-month follow-up period
Conradsson et al. (2010)									
Littbrand et al. (2011)									
Telenius et al. (2015a)	High-intensity functional exercise program (*EXDEM study*)	*Strengthening* 12 RM *Balance* Intended to be highly challenging	5 min warm-up At least two strengthening exercises for lower limb muscles and two balance exercises	2×/week	12 weeks (24 sessions)	50–60 min	3–6	All exercises were individually fitted, instructed and supervised (1 PT per 3 participants)	The 12-week HIT intervention was followed by 12 weeks of detraining (Telenius et al., 2015b)
Telenius et al. (2015b)									
Boström et al. (2016)	High-intensity functional exercise program (*UMDEX study*)	*Strengthening* Moderate intensity within the first two weeks (13–15 RM), following 8–12 RM (progression, if >12 repetitions possible) *Balance* Intended to fully challenge one's postural stability	Individual exercises for each person depending on their functional deficits	5×/2 weeks	16 weeks (40 sessions)	45 min	3–8	INT groups supervised by two PTs	–
Toots et al. (2016)									–
Toots et al. (2017a)									–
Toots et al. (2017b)									–

RM repetition maximum, *min* minutes, *PT* physical therapist, *INT* intervention, *CON* control, *HIT* high intensity training

Comprehensive Meta-Analysis software by Borenstein, Hedges, Higgins and Rothstein (2013). To quantify a given statistical heterogeneity, I^2 statistic was calculated (Higgins & Thompson, 2002). Corresponding to Higgins and Green (2008), we considered values of $I^2 > 30\%$ as moderate heterogeneity, $I^2 > 50$ as substantial heterogeneity, and $I^2 > 75\%$ as considerable heterogeneity. If any heterogeneity was present, the random-effects model was applied for statistical analysis as suggested by some authors (Borenstein, Hedges, Higgins, & Rothstein, 2010; Higgins, Thompson, Deeks, & Altman, 2003; Higgins & Green, 2008). In studies with multiple measurement time-points (baseline, 1st and 2nd follow-up measurement), only the baseline measurements and the first follow-up time-point were meta-analytically considered.

Results

The initial database search yielded 1484 articles from five databases. The identification and screening process is summarized in **Fig. 1**. After removing 402 duplicates, 1084 articles were checked for relevance based on the review of titles. The abstracts of the preselection were then screened for eligibility. In addition, two more studies were identified by checking for cross-references. The 15 remaining articles underwent a detailed full-text screening. Finally, 9 articles were included in the present review, which are solely based on the following three large-scale studies: (1) the *Frail Older People–Activity and Nutrition in Umeå* (FOPANU) study (Conradsson et al., 2010; Littbrand et al., 2011; Littbrand, Lundin-Olsson, Gustafson, & Rosendahl, 2009), (2) the *Exercise and Dementia* (EXDEM) study (Telenius, Engedal, & Bergland, 2015a, 2015b), and (3) the *Umeå Dementia and Exercise* (UMDEX) study (Boström et al., 2016; Toots et al., 2016, 2017a, 2017b; overview in Suppl. 1). The main characteristics of the included studies are summarized in **Table 1**. The FOPANU study also examined participants without dementia who were, however, analysed

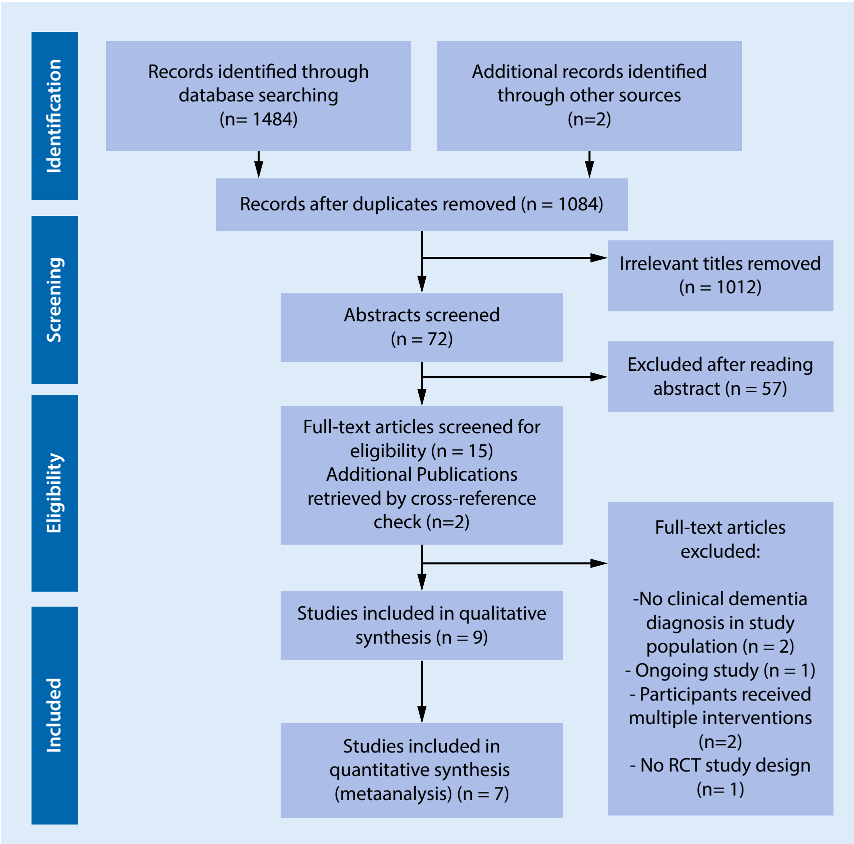

Fig. 1 ▲ Flow chart of literature search. *RCT* randomized controlled trial

separately and whose results have not been included in this review.

A total sample size of 456 participants suffered from dementia; 227 of them received a HIT intervention and 229 control activities. Approximately three quarters of the participants were women (74.1%). The overall mean age was 85.5 ± 7.0 years. Only the authors of the UMDEX study gave information about the type and distribution of the underlying dementia. Thus, 36% of the participants had Alzheimer's disease, 41.4% had vascular dementia and 8.1% had a mixed form of these two most common forms of dementia. 14.5% were affected by less frequent forms of dementia, including alcohol-related dementia (2.2%), Lewy body dementia (0.5%), frontotemporal dementia (2.2%), Parkinson's disease dementia (1.1%), vascular dementia mixed with another form other than Alzheimer's disease (3.1%) and nonspecific forms of dementia (5.4%). The MMSE was used in all studies to assess cognitive functioning. The average MMSE score was 15.7 ± 5.0 in the EXDEM and 14.9 ± 3.5 in the UMDEX study, indicating the severity of moderate dementia (Perneczky et al., 2006). The FOPANU study showed an average MMSE score of 17.8 ± 5.1; however, the values of the participants with and without dementia diagnosis were combined, so that no conclusion can be made about the actual dementia severity. About half of all participants (48.1%) showed depressive symptoms and, moreover, Telenius et al. (2015a, 2015b) reported that two thirds were restricted in their walking ability, of which 10% used a wheelchair. In the UMDEX study 78% of the participants were reliant on a walking aid or a wheelchair, and in the FOPANU study 63% of the subjects were able to walk independently within the nursing facilities with or without a walking aid.

Quality of the included studies

In all studies, group allocation was randomized and concealed. The mean study quality (PEDro score) was 7.6 ± 0.7 ranging from 6 to 8 which indicates an overall *good* methodological study quality (Suppl. 2). Subjects and therapists were not blinded in any of the studies. Six out of nine studies (Boström et al., 2016; Conradsson et al., 2010; Littbrand et al., 2009, 2011; Toots et al., 2016, 2017a) scored 8 points. Data by Toots et al. (2017b) revealed that more than 15% of the subjects initially allocated to groups dropped out after baseline measurements. In two studies, however, information was not conclusive; hence no scoring points were assigned (Telenius et al., 2015a, 2015b). Finally, in one study from Telenius et al. (2015b), data from participants were not analysed according to the intention-to-treat (ITT) method.

Funnel plots did not show a clear funnel-shaped scattering (Suppl. 3–5). Studies with smaller sample sizes (higher standard errors), constituting the basis of the funnel triangle, or large studies with small standard errors are missing. However, the number of studies on the left and right side of the vertical SMD line seems to be equally distributed.

HIT interventions

Each of the nine studies compared a HIT program with light and stimulating control activities in a sitting position. The characteristics of the exercise interventions are presented in **Table 2**. All exercise programs conducted in the three large-scale studies—the EXDEM, FOPANU and UMDEX study—are based on the High-Intensity Functional Exercise (HIFE) program described in detail by Littbrand, Rosendahl and Lindeloef (2014). According to the authors, the aim of the HIFE program is to improve the participant's lower-limb muscle strength, balance and mobility.

The intervention duration ranged from 12 to 16 weeks. The average training frequency was two to three sessions per week. All studies incorporated multicomponent exercise programs including a combination of strengthening and balance exercises. Individual training sessions were conducted in groups of three to nine participants, lasted 45–60 min, and were supervised by at least one experienced or instructed therapist. The FOPANU and the UMDEX study participants performed HIFE exercises according to their individual functional deficits. No information was provided by the authors about the number and type of exercises but a collection of exercises can be reviewed online (https://www.hifeprogram.se/en/download/). Each session in the EXDEM study included a 5 min warm-up, at least two strengthening exercises for lower-limb muscles and two balance exercises. In each study, the exercise intervention was followed by a 12-weeks detraining period. After completing the 3-month HIT intervention, the participants of the FOPANU study were taught to integrate physical tasks (e.g. walking, squats, and standing without balance support) into their daily life activities in order to maintain their physical functions. Adherence to these tasks was evaluated at the second follow-up.

Training intensities for strengthening exercises were determined by the multiple repetition maximum (RM). An intensity corresponding to 8–12 RM was considered to be high. Participants of the UMDEX study exercised at moderate intensity (13–15 RM) during the first two familiarization weeks. As soon as the participants were able to perform more than 12 repetitions, exercise loading was increased. Balance exercise intensities were intended to be "highly challenging" (Telenius et al., 2015a, 2015b) or "fully challenge postural stability" corresponding to Littbrand's (2014) intensity scale.

In this review, adherence to exercise interventions was defined by (1) the participation in each exercise session (attendance rate) and (2) the maintenance of intensity specifications (compliance). Telenius et al. (2015a) reported that participants of the EXDEM study attended an average of 18 ± 7 of 24 sessions (75%). Here, 70% of the training sessions were performed at high intensity levels and 2% at low intensity levels. The attendance rate of the UMDEX study amounted to 73% (Boström et al., 2016; Toots et al., 2016, 2017a, 2017b). Furthermore, strengthening exercises were performed at a moderate intensity level in 40% and at a high intensity level in 45% of the sessions, whereas balance exercises reached high intensities in 63% of the sessions. According to the FOPANU study authors, the attendance rate for participants with dementia was 72% (Conradsson et al., 2010; Littbrand et al., 2011; Littbrand, Lundin-Olsson, Gustafson, & Rosendahl, 2009). High intensities for strengthening exercises were achieved on average in 53% of the attended sessions, while compliance for balance exercises reached an average of 71%. After the 3-month HIT intervention, the participants of the FOPANU study completed an average of 2.0 ± 0.8 physical tasks. After 6 months the follow-up showed that 36% of the participants with dementia exercised as often as recommended, and 46% did not do any exercises at all anymore (Littbrand et al., 2009).

Effectiveness of intervention programs

Seven studies provided sufficient data for quantitative analysis. All other outcome data (effects on mobility, lower-extremity muscle strength, quality of life, behavioural symptoms, and psychological well-being) underwent an individual qualitative analysis. One study (Telenius et al., 2015b) only assessed the long-term effects of the EXDEM study, while a second study (Toots et al., 2017b) only assessed participants' walking ability in relation to walking aids. Finally, data on four continuous outcomes (balance performance, cognitive functioning, depressive symptoms and independence in ADLs) could be included in the meta-analysis (Fig. 2).

Effects on physical performance

A total of five publications refer to outcomes of physical performance. Littbrand et al. (2011), Telenius et al. (2015a), and Toots et al. (2016) used the 56-points Berg Balance Scale (BBS) to investigate whether a HIT program improves balance ability. In the HIT groups ($N = 204$), the overall mean change amounted to 2.38 ± 5.25 points, while the score of the CON groups ($N = 213$) changed by no more than 0.10 ± 4.67 points. The meta-analysis showed a significant difference in the total score of the BBS (mean difference [MD] = 2.30, 95% confidence interval [CI] = 0.44–4.16, $p = 0.02$; $I^2 = 73\%$; Fig. 2) in favour of the HIT groups compared to the CON groups with a small to moderate effect size ($d = 0.46$). Due to substantial heterogeneity ($I^2 = 73\%$) a random-effects model was calculated. While the long-term results remain positive in one study (Telenius et al., 2015b; $p = 0.031$), the second follow-up measurement by Toots et al. (2016) did not show significant between-group differences ($p = 0.98$) any longer after 12 weeks of detraining. In the study by Littbrand et al. (2011), the between-group difference was 1.78 points at the 6-month follow-up (no between-group *p*-value reported).

Three studies investigated mobility performance. Telenius et al. (2015a, 2015b) showed that the normal walking speed remained unchanged in both groups directly after the intervention ($p = 0.86$) and at the 24-month follow-up ($p = 0.685$) measured by the 6-metre walking test. Regarding the gait speed (GS) test, data from Toots et al. (2017b) revealed that there were no significant differences between the HIT and the CON groups. However, interaction analyses showed that intervention effects on GS differed according to additional support provided by, for example therapists or walking aids, with larger effects among participants who walked unsupported in the GS test after 4 ($p = 0.034$) and 7 ($p = 0.001$) months and in the GS test without walking aids (GS-noWA) after 7 ($p = 0.029$) months (Toots et al., 2017b). Subgroup analyses also showed—in both tests and both after 4 and 7 months—positive effects on GS in those participants of the exercise group who walked unsupported (GS test: $p = 0.009$ and $p < 0.001$, and GS-noWA test: $p = 0.011$ and $p = 0.029$, respectively).

Only subjects of the EXDEM study were assessed for lower-extremity strength and endurance performance using the

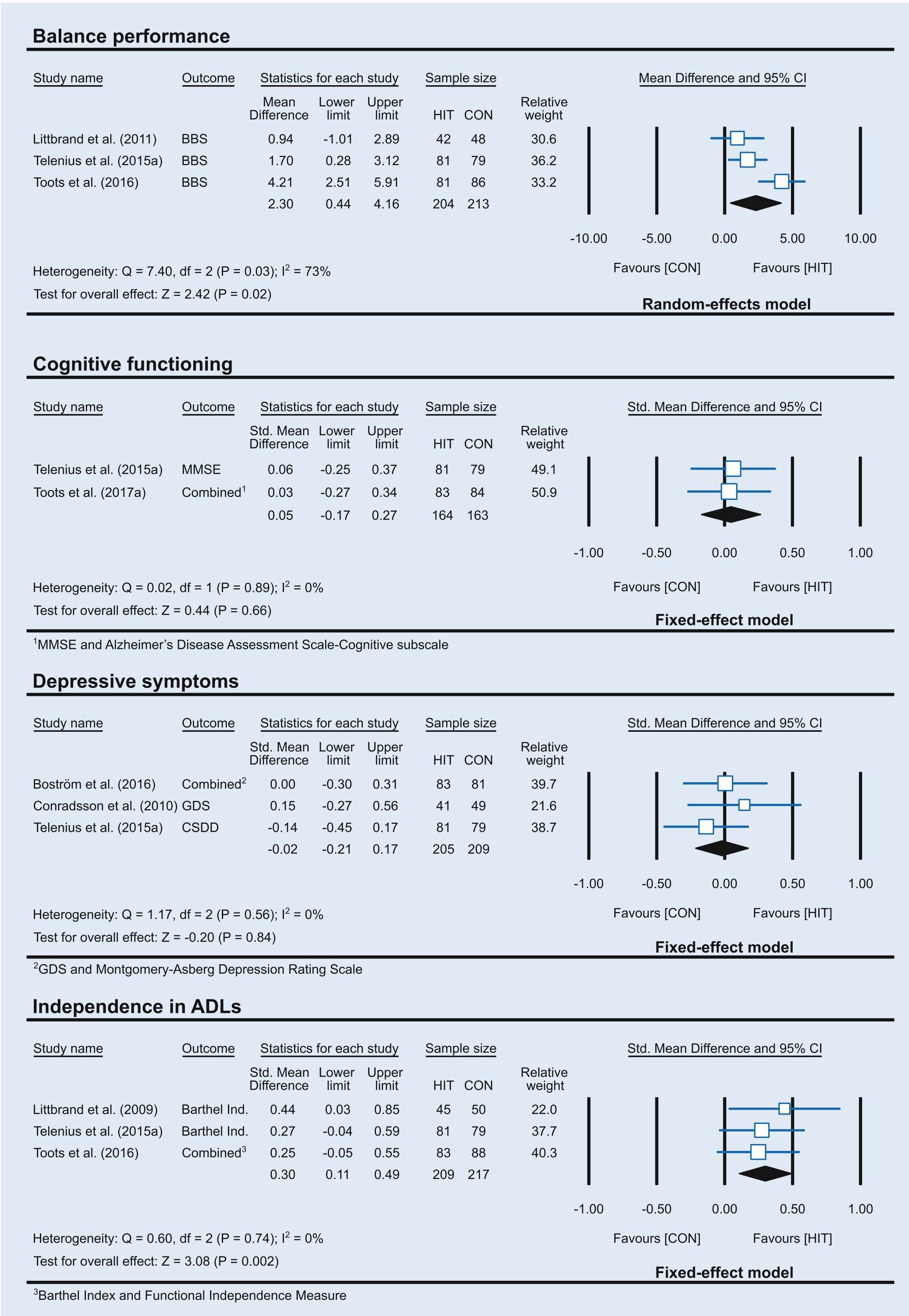

Fig. 2 ◀ Forest plots comparing balance performance, cognitive functioning, depressive symptoms and independence in activities of daily living (ADLs) for high-intensity training (HIT) versus control (CON) groups. *95% CI* 95% confidence interval, BBS Berg Balance Scale, *MMSE* Mini-Mental State Examination, *GDS* Geriatric Depression Scale, *CSDD* Cornell Scale for Depression in Dementia

30 s chair stand test. The average number of repetitions completed in 30 s improved by +1.0 repetitions due to HIT, while the number of repetitions in the CON groups increased by +0.4 repetitions only. The between-group differences were not significant at both the first and the second follow-up (Telenius et al., 2015a, 2015b).

Effects on mental and cognitive health

Five publications contained data about mental and cognitive health changes collected by specially trained research staff. Cognitive functions were recorded in three studies (Telenius et al., 2015a, 2015b; Toots et al., 2017a), effects on depressive symptoms in four (Boström et al., 2016; Conradsson et al., 2010; Telenius et al., 2015a, 2015b), and dementia-related behavioural disorders in three articles (Conradsson et al., 2010; Telenius et al., 2015a, 2015b). Cognitive functioning and the magnitude of depressive symptoms were analysed by fixed-effect meta-analyses. After the intervention period, no superior effects of HIT ($N = 246$) on cognitive functions (SMD = 0.05, 95% CI = –0.17 to 0.27, $p = 0.66$; $I^2 = 0\%$; ◘ Fig. 2) were observed in comparison to seated CON activities ($N = 246$) in people suffering from dementia. Similarly, after 24 (Telenius et al., 2015b) and 28 (Toots et al., 2017a) weeks of follow-up, the results of the MMSE showed no significant difference between the groups ($p = 0.492$ and $p = 0.056$, respectively). Furthermore, the meta-analysis yielded no significant between-group differences (HIT groups: $N = 288$; CON groups: $N = 289$) and no intervention effects on symptom scales of depression (SMD = –0.02, 95% CI = –0.21 to 0.17, $p = 0.84$; $I^2 = 0\%$; ◘ Fig. 2) at any follow-up point in time.

In the trials from Telenius et al. (2015a, 2015b) the Neuropsychiatric Inventory Questionnaire (NPI-Q), a short proxy-reported questionnaire filled in by professional caregivers, was used. No significant differences were found between HIT and CON groups in the total score after 12 ($p = 0.17$) and 24 weeks ($p = 0.059$). However, regarding specific symptomatic domains, positive effects in favour of the HIT groups on agitation showing a trend after 12 weeks ($p = 0.07$) and a significant difference after 24 weeks ($p = 0.045$) were demonstrated. In addition, participants of the HIT groups were significantly less apathetic compared to those of the CON groups after 12 weeks ($p = 0.048$), but not after 24 weeks ($p = 0.688$). At no point in time were statistically significant differences found in the domain of affectivity.

Psychological well-being was assessed in one study by means of the Philadelphia Geriatric Center Morale Scale (Conradsson et al., 2010). The interviewer-administered scale with yes/no answers demonstrated a significantly higher score after 3 months of training compared to CON activities ($p = 0.03$).

Effects on ADLs

Scales for the assessment of independency and self-reliance performing ADLs were included in three studies. For this purpose, trained physical therapists interviewed care staff familiar with participants' need for assistance in ADLs (Littbrand et al., 2009; Toots et al., 2016) or professional caregivers assessed the ADL questionnaires based on their observations of the participants (Telenius et al., 2015a). All intervention effects of the first follow-up on ADLs were considered in a fixed-effect meta-analysis. For this purpose, data of 292 participants of the HIT groups and 305 participants of the CON groups were analysed. As a result a highly significant, but small effect ($d = 0.28$) was identified in performing ADLs (SMD = 0.30, 95% CI = 0.11–0.49, $p = 0.002$; $I^2 = 0\%$; ◘ Fig. 2) in favour of HIT interventions. However, at the second follow-up measurement, there was no longer any significant difference between HIT and CON groups concerning Barthel Index (BI) and Functional Independence Measure (FIM).

Effects on QoL

No differences were found between the HIT and CON groups based on the results of the proxy-rated QoL in late-stage dementia (QUALID) scale at any timepoint of follow-up. The representative assessors were professional caregivers who knew the patients well (Telenius et al., 2015a, 2015b).

Discussion

The aim of the present systematic and meta-analytical review was to summarise existing evidence of HIT programs in people with dementia about the effects on physical performance, mental and cognitive health, ADLs, and QoL. Over the last decade, research has increasingly addressed the issue of exercise programs in people with cognitive impairments and dementia. Several reviews have been published assessing the effects on these pathologies (e.g. Forbes et al., 2008, 2015; Gogulla, Lemke, & Hauer, 2012; Lam et al., 2018; Pitkälä et al., 2013). However, this is the first systematic review on HIT in people with dementia.

Results and relevance

The present data support that HIT regimens led to greater improvements on balance performance and the ability to perform ADLs independently than seated control activities. Pooled effect estimates showed nearly moderate statistical effects on balance performance ($d = 0.46$) measured by BBS, but demonstrated considerable heterogeneity ($I^2 = 73\%$), and small effects on ADLs ($d = 0.30$) measured by BI and FIM. A sensitivity analysis of the pooled effects on ADLs showed that SMD remained almost stable ($d = 0.32$) when FIM data by Toots et al. (2016) was excluded. The mean change in the HIT groups' BBS score was 2.38 ± 5.25 points from baseline to the first follow-up. However, an intrarater test–retest reliability assessment by Conradsson et al. (2007) showed that due to high intrapersonal variabilities a change of 8 BBS points is required to reveal a genuine change in function among older people who are dependent in ADLs and living in residential care facilities. Considering only BI data, from a potential total of 20 points the score decreased by an average of 0.27 ± 2.35 points in the HIT and by an average of 1.06 ± 2.39 points in the CON groups. Consequently, the small effect observed in favour of HIT is attributed to a lower progression in the loss of independence among older people with dementia. However, there is evidence that the BI might be less reliable in patients with cognitive impairments (Sainsbury, Seebass, Bansal, & Young, 2005). Furthermore, a reliability study by Collin, Wade, Davies, and Horne (1988) outlined that only a change of more than two points (10%) in the overall BI score reliably reflects probable changes in functional status.

Qualitative analyses of physical performance outcome parameters did not reveal major differences in favour of HIT, neither in mobility nor in lower-extremity muscle strength. However, several interaction analyses conducted as part of the UMDEX study by Toots et al. (2017b) showed superior effects on GS in favour of the HIT groups, if the participants were able to walk independently during the 6-metre walking test which is in line with the results of Sanders et al. (2020). Nevertheless, 78% of the UMDEX and 68% of the EXDEM study participants (Telenius et al., 2015a, 2015b) were unable to walk without support. The lack of positive exercise effects on mobility, despite significant improvements in balance performance, is consistent with the results of a study by Schwenk, Schmidt, Pfisterer, Oster, and Hauer (2011). The authors observed that testing gait speed in people using walking aids adversely affected the assessment of changes over time in gait and mobility performance, and reduced the responsiveness of the tests. They concluded that this might lead to concealments of actual intervention benefits.

There were no treatment effects in favour of HIT interventions on cognitive functioning and depressive symptoms as shown by the present meta-analyses. In addition, the EXDEM study indicates that QoL was not affected by HIT. This is partly in line with a recent meta-analysis by Ojagbemi and Akin-Ojagbemi (2019) as their results show that specific aerobic exercises may produce larger effects on QoL compared to other exercise types. Anyhow, limited evidence from our qualitative analysis demonstrates that psychological well-being indicated by higher PGCMS scores as well as specific dementia-related behavioural disorders were positively influenced by HIT (solely at 3 months follow-up). HIT had, for instance, a positive impact on the extent of apathy which is associated with faster cognitive and functional decline, depression and increased mortality (Helvik, Engedal, Benth, & Selbæk, 2014; Tagariello, Girardi, & Amore, 2009).

Limitations of primary studies

Generally, six out of nine included studies achieved *good quality* (8 points) on the PEDro scale even though a blinding of subjects and therapists in exercise intervention studies is very difficult to implement. Only one study did not analyse participants according to their initial group allocation (ITT analysis) (Telenius et al., 2015b). The dropout rate amounted to more than 15% in one study (Toots et al., 2017b) but could not be clearly determined due to a lack of information in two studies (Telenius et al., 2015a, 2015b). In addition, due to the small number of studies (3 or 4 per meta-analysis), the identification of publication bias using funnel plots must be critically judged.

Moreover, the adherence to the exercise protocols has to be addressed. On average, the overall attendance rate of HIT participants was 73% which is, according to a systematic review with institutionalized older people living with dementia, in the upper range (40–80% respectively, Vseteckova et al., 2018) suggesting that a HIT program is accepted by older people with dementia. However, another systematic review and meta-analysis of 47 RCTs examining factors affecting exercise attendance and exercise completion among sedentary older adults reports a higher attendance rate of 86% (Hong, Hughes, & Prohaska, 2008). This might have been due to a lower overall health status among the patients included in this review since physical health and mental wellbeing represent potential barriers to group exercise interventions (Vseteckova et al., 2018). Nevertheless, the most common reason for absence in both groups of the EXDEM study was an acute illness (Telenius et al., 2015a).

Furthermore, no common definition for HIT in patients can be deduced from the literature. Rather, there is huge heterogeneity in all key variables, e.g. exercise intensity, volume, duration and frequency of the intervals and sessions or resting time. Due to these discrepancies, the comparability of study results is generally limited. Nevertheless, the present systematic review overcomes this limitation, since all HIT interventions were based on the same (HIFE) program (Littbrand et al., 2014). In this sense, the intensity of the exercises was determined by the number of repetitions completed. According to a predefined scale, the intensity of the strength and balance exercises was then classified as low, moderate or high. When combining the values recorded by all three large-scale studies, on average 63.5% of the exercises were actually performed with high intensities, which is a limitation and might lead to an overestimation of high-intensity effects per se. However, this score is comparable to the results of a recent study by Reitlo et al. (2018), in which participants of a HIT intervention achieved a score of 60%. Chong et al. (2014) demonstrated that people with cognitive impairments prefer simple, light and safe exercises. Consequently, the high intensities of the included studies may have had a negative impact on the patients' motivation to participate. In contrast to this finding, the HIT group participants of the UMDEX study explained in a postevaluation report that despite their challenging character, the exercises were achievable and gave them pleasure as they improved their mental and physical capacity (Lindelöf, Lundin-Olsson, Skelton, Lundman, & Rosendahl, 2017). Furthermore, the suitability study of Littbrand et al. (2006) reports pain as main cause for not achieving high intensities during strengthening exercises of the lower extremity.

The reporting of underlying dementia types was insufficient as only four out of nine studies presented this information. The study of Toots et al. (2016) demonstrated that exercise effects on balance and ADL independence were exclusively limited to patients with non-Alzheimer's dementia. It was also shown that baseline cognitive function has a moderator effect since impairments in memory and motor learning differ between such entities (Van Halteren-van Tilborg, Scherder, & Hulstijn, 2007). Thus, future studies should differentiate exercise-induced effects on different dementia types and consider subgroup analyses accordingly.

In addition, all HIT programs correspond to a multimodal exercise training approach. Thus, it cannot be identified if one training modality was superior to the other (strength vs. balance training) or if the improvements were rather the effect of the sum of both exercise training modalities. Furthermore, each HIT intervention was only compared with seated control activities in order to avoid confounding effects by social support and attention from therapists and other patients. Consequently, the study arms did not only differ in exercise intensity but also in the exercise types, e.g. weight bearing exercises vs. seating, which could bias our results. We therefore recommend future studies to compare single component exercise programs with similar neuromuscular movement patterns but differences in exercise intensity (high, moderate and low) for deriving a dose–response relationship of exercise interventions in people with dementia. Finally, from this review it remains unclear whether the HIFE program is superior over other types of exercise training (e.g. endurance training) since there were no such comparisons.

Limitations of the review

This systematic review provides a comprehensive overview of current findings regarding the effects of HIT on a variety of health and functional outcomes in older people with dementia. It was conducted in accordance with the PRISMA statement, which guarantees an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (Moher et al., 2009). Nevertheless, some limitations have to be addressed. At first, all included studies exclusively stem from three large-scale research projects (FOPANU, UMDEX, and EXDEM study; Suppl. 1) which were conducted in Sweden and Norway and built on each other. Many of the study personnel and article authors were incorporated in more than two of the included studies, which limits the generalizability of the review results. The funnel plots revealed an unclear picture of publication bias due to the small number of studies per outcome measure ($n = 3$). Yet, it cannot be excluded that this review missed relevant studies which incorporated high intensity exercise but did not outline respective terms in their title or abstract. The selection of English publications only could be another source of publication bias. Unfortunately, we had a lag time bias since we did not include a recent and relevant RCT from Sanders et al. (2020) in our review. Since we could not identify any published study protocols a selective reporting assessment was not feasible.

Conclusion

The literature regarding the effectiveness of HIT in people with dementia is mixed with regard to the results. From good-quality studies, there is evidence of no effect for cognitive function and depressive symptoms, and weak evidence for improved balance performance and abilities to perform ADLs independently, especially in non-Alzheimer's disease patients or those with higher baseline cognitive function. Qualitative analyses from individual studies demonstrated slight improvements in mobility, an increased overall psychological well-being and lesser apathetic behaviour in people who performed HIT. As none of the included studies compared to weight-bearing control activities and only about two third of all training sessions were accomplished at high intensity, our confidence in an intensity-related dose–response relationship is severely limited. Exercise training is recommended for treating the symptoms of dementia, but additional and well-designed studies would be helpful to identify the most effective exercise factors for different types and stages of dementia.

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Compliance with ethical guidelines

Conflict of interest. J. Russ, C. Weyh and C. Pilat declare that they have no competing interests.

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