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## Efficacy of exercise for functional outcomes in older persons with dementia

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# Chapter 6

## Summary and general discussion





## **Objectives of this thesis**

The objective of this thesis was to examine the efficacy of alternating aerobic and lower-limb strength exercise vs. control activities for physical and cognitive function in older persons with dementia (PwD). Furthermore, we examined anticholinergic and sedative drug burden, exercise type, exercise dose-parameters (program duration, session duration, frequency and intensity) and Apolipoprotein  $\epsilon 4$  (ApoE4) carriership as potential moderators and confounders of exercise effects on physical and cognitive function in PwD. Last, we examined the psychometric properties of a Flanker task as a measure of inhibitory control in PwD.

## **Summary of the main findings**

**Chapter 1** introduced physical inactivity as a risk factor for dementia and cognitive decline. Exercise was proposed as a potentially effective and safe alternative to pharmacological treatments to combat physical and cognitive decline in PwD. Anticholinergic and sedative drug burden, exercise type, exercise dose-parameters (program duration, session duration, frequency and intensity) and ApoE4-carriership were introduced as potential moderators and confounders of exercise effects on physical and cognitive function in PwD. Last, the need for an alternative test to the STROOP task to measure inhibitory control was put forward. A Flanker task was proposed as a suitable alternative to the STROOP task in PwD.

In order to determine whether anticholinergic and sedative drug burden could be a potential confounder of exercise effects on physical and cognitive function in PwD, **chapter 2** describes the results of a cross-sectional analysis into the associations between the Drug Burden Index (DBI, a measure of anticholinergic and sedative drug burden) with physical (gait speed, functional mobility, balance and grip strength) and cognitive (global cognition, verbal and visual memory, and information processing speed) functions in 140 nursing home (NH) PwD. There was no evidence for multivariate relationships between the total DBI, anticholinergic DBI and sedative DBI and the aforementioned physical and cognitive functions. Thus, anticholinergic and sedative drug burden could not be established as confounder of exercise effects on physical and cognitive function in PwD. Additionally, unpublished data from our RCT described in chapter 4 showed that the DBI did not moderate the effects of exercise on physical and cognitive function in PwD.

**Chapter 3** describes the results from a systematic review and meta-analysis into the dose-response relationships between exercise and cognitive function in old adults with and

without cognitive impairments. Cognitive status, exercise type, program duration, session duration, frequency and intensity were investigated as potential moderators of exercise effects. In healthy old adults, we found a small positive effect of exercise on executive function and memory. Exercise type and dose-parameters did not predict the strength of exercise effects on cognitive function. In older adults with cognitive impairments, exercise had a moderate positive effect on global cognitive function. Exercise programs with a short session duration ( $\leq 30$  minutes) and high frequency ( $\geq 4$ /week) predicted stronger effects on cognitive function. Thus, session duration and frequency were identified as moderators of exercise effects on cognitive function in old adults with cognitive impairments including dementia.

Chapter 3 confirmed the need for studies in which exercise intensities are compared among randomized PwD. This need provided the basis for the large randomized controlled trial (RCT) that is described in **chapter 4**. Participants were randomly assigned to an exercise intervention consisting of alternating walking and lower limb-strength exercises with a low vs. high-intensity component, or a control intervention of flexibility and recreational activities. Every participant was offered three weekly sessions of 30 minutes for 24 weeks. The aims of this RCT were to determine 1) the feasibility of low- (LI) vs. high-intensity (HI) alternating aerobic and strength exercise; 2) the effects of LI vs. HI alternating aerobic and strength exercise vs. a control intervention of flexibility and recreation on physical and cognitive function; 3) if LI vs. HI exercise had differential effects on physical and cognitive function, and 4) whether ApoE4-carriership moderated the effects of exercise in PwD. We analyzed the results from 69 PwD that were recruited from daycare and residential care facilities in the Northern Netherlands. The results showed a significant exercise effect on gait speed after higher exercise intensity. This effect declined after detraining, signifying the necessity for continuous exercise to protect against gait speed losses. For the other physical functions, exercise was slightly but non-significantly superior to control activities. There were no significant effects of the exercise vs. control intervention on any of the measured cognitive functions. ApoE4-carriership moderated at trend-level the effect of exercise on the Mini-Mental State Examination (MMSE, a measure of global cognition): ApoE4 non-carriers in the exercise group improved on the MMSE after 24 weeks, whereas MMSE scores for all other groups declined. Summarized, exercise vs. a control intervention had a significant positive effect on gait speed in PwD. Exercise intensity was identified as moderator of exercise effects on gait speed, potentially through strength increases in the HI phase. Exercise vs. a control intervention did not have significant positive effects on cognitive function. ApoE4

was carefully identified as moderator of exercise effects on global cognition in PwD.

**Chapter 5** describes the results of a psychometric evaluation of a Flanker task in a sample of 22 PwD that participated in our RCT. We evaluated the feasibility, test-retest reliability and validity of a computerized Flanker task in relation to the MMSE and STROOP task. We found that the Flanker task was feasible in our sample. The Flanker task appeared to be a reliable measure of selective attention and inhibitory control. Although the Flanker task appeared to be a valid measure of selective attention, we could not establish its validity in measuring inhibitory control.

**Overall**, the current findings show the efficacy of alternating walking and lower limb strength exercise vs. a control intervention on gait speed, an important clinical measure in older adults. The superiority of exercise vs. control could not be established for other physical functions and cognitive function. Exercise intensity was established as potential moderator of exercise effects on gait speed in PwD. In addition, session duration and frequency were established as potential moderators of exercise effects on cognitive function in old adults with cognitive impairments including dementia. ApoE4 was established as potential moderator of exercise effects on global cognition (at trend-level), but caution is urged when interpreting this result as we found it for one test only. We could not establish anticholinergic and sedative drug burden, program duration or exercise type as moderators or confounders of exercise effects in PwD. Last, a Flanker task could be a suitable alternative to the STROOP task for measuring selective attention, but more research needs to be done to establish its validity in measuring inhibitory control in PwD.

## **General discussion**

### *Theoretical considerations*

The findings in chapter 4 show the efficacy of 24-weeks alternating walking and lower-limb strength exercise vs. a control intervention on gait speed in PwD. Gait speed has been dubbed ‘the sixth vital sign’ as it is consistently related to functional ability and overall health in various populations including old adults with and without cognitive impairment [1,2]. Therefore, improving gait speed is a treatment target in exercise studies with PwD. Our exercise participants’ gait speed improved by ~0.05 m/s on average which is considered clinically meaningful [3]. Thus, this finding strengthens the philosophy ‘Exercise as medicine’ that was introduced in chapter 1.

Higher exercise intensity moderated gait speed improvements in our sample. The contrast

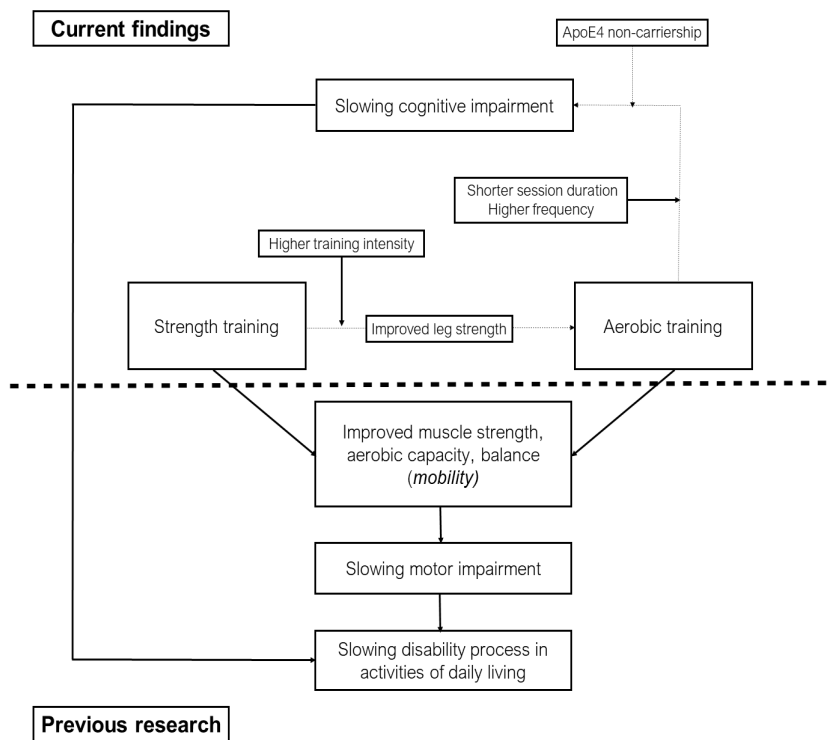
between LI vs. HI exercise was most pronounced for the lower-limb strength sessions as compared to the walking sessions in our sample. This finding supports previous evidence for gait speed improvements to be mediated by lower-limb strength improvements in PwD [4] and confirms the added value of lower limb strength training in exercise programs for PwD.

Gait speed declined after 12 weeks of detraining (at follow-up) by  $\sim 0.09$  m/s. This rate of decline was steeper than the rate of decline in the control group from T24 to follow-up ( $\sim 0.06$  m/s). Gait speed declines  $\geq 0.05$  m/s are considered functionally meaningful [3] and classify participants as ‘fast decliners’ [5], although it is uncertain whether this also applies to detraining effects. Yet, the overall decline in gait speed from baseline to follow-up was  $\sim 0.04$  m/s in the exercise group and  $\sim 0.12$  m/s in the control group. These findings highlight the importance of continuous physical exercise for PwD.

ApoE4 was established as potential moderator of exercise effects on global cognition: MMSE scores for non-carriers in the exercise group improved whereas MMSE scores declined for all other groups. This was in line with the results of a previous RCT in old adults at risk for Alzheimer’s Disease (AD) [6]. As discussed in chapter 1, ApoE4 has deleterious effects on neurocognitive health [7,8]. Therefore presence of the ApoE4 allele may negate the beneficial effects of exercise. However, caution is urged when interpreting this result as we found it for one test only and it was only trend-level significant. Furthermore, sex differences can confound the effects of exercise for ApoE4 carriers vs. non-carriers differentially (see [9] for a review) but the low sample size in the study presented in chapter 4 did not allow for further investigation of this hypothesis. Last, it is uncertain whether dose-response relationships between exercise and physical and cognitive function differ for ApoE4 carriers vs. non-carriers. To be able to personalize exercise treatments for each individual, such knowledge would need to be acquired by future studies.

In chapter 3 it was shown that exercise programs with short sessions ( $\leq 30$  minutes) and high frequency ( $\geq 4$  times/week) generated the highest cognitive effect sizes in old adults with cognitive impairments including dementia. Shorter sessions may protect PwD against fatigue and loss of motivation after exercise. A higher frequency perhaps decreases overall sedentary time.

In Figure 1, the model that was introduced in chapter 1 is adjusted to incorporate the abovementioned findings.



**Figure 1.** Relationships between exercise, physical function and cognition in PwD including moderators. Continuous lines represent evidence-based relationships whereas dotted lines represent hypothesized relationships. ApoE4 = Apolipoprotein  $\epsilon$ 4.

### *Exercise and cognition in PwD*

Chapter 4 shows a lack of exercise vs. control effects on cognitive function in PwD. Recently, several of the largest exercise studies in PwD to date also showed little to no effect of exercise vs. control on cognitive function in PwD [10-13]. These results are in contrast with our review (chapter 3) and two recent reviews that concluded exercise to have significant moderate effects of exercise on cognitive function in PwD [14,15]. Inspection of the forest plots in these reviews shows that 10/22 interventions in PwD had significant positive effects of exercise



vs. control on cognitive function in PwD [16-25]. Determining shared study characteristics may help discover the determinants of exercise effects on cognitive function in PwD. Within the aforementioned ten interventions, the number of participants was generally low (N~30 for 9/10 interventions); baseline MMSE scores were for the greater part indicative of low-moderate dementia (6/8 interventions for which baseline MMSE was known); the majority of participants were institutionalized (7/10 interventions); program duration ranged between 9-24 weeks for almost all (9/10) interventions; exercise programs mostly consisted of aerobic training with (5/7 interventions) or without (2/7 interventions) added strength, balance or cognitive components; attendance was high to excellent (range >70 – 100% attendance when reported); and control groups performed usual daily activities (6/10 interventions) or social visits (3/10 interventions; 1/10 undetermined). Summarized, the effects of exercise on cognition may be largest for patients with higher dementia severity, living institutionalized, who participate in multimodal interventions compared to a control program of usual activities, and show high attendance. However, several methodological issues need to be taken into account when interpreting the results presented in the reviews. First, the large heterogeneity between studies complicates interpretation of findings. Second, the included studies were RCTs with small sample sizes. Smaller RCTs tend to show larger effect sizes, but are affected by high heterogeneity, lower reliability of results and lower quality in design [26]. Third, nearly all (9/10) control groups showed marked declines in cognitive function determined through visual inspection (6/9 control groups) or statistical significance (3/9 control groups). Such a notable decline in cognitive function within the control group was not seen in our study and other studies [10,12,13] that failed to show an effect of exercise vs. control on cognitive function in PwD. Especially in PwD it may be difficult to determine to what extent control group behavior predicts exercise effects. Control group declines may be ‘natural’, or determined by the type of or lack of control activities. In our study, it is possible that the control activities (flexibility exercises and recreational activities) contributed to stabilization of functional outcomes in the control group. Furthermore, it is possible that our control participants performed more non-study-related activities than intervention participants. This could have positively affected functional outcomes. Normative data on functional outcomes in PwD is needed to determine to what extent control group behavior is influenced by study participation. Such normative data could be acquired by future studies. Fourth, cognitive measurements may be less reliable in PwD compared to healthy old adults, especially in later stages of dementia [27]. The within-person variability in cognitive performance is generally larger in PwD due

to dementia- and drug-related fluctuations in cognitive function [28]. As discussed in chapter 5, there is a scarcity of data on the psychometric properties of cognitive tests for PwD. Furthermore, we are unsure what change in cognitive test scores constitutes a clinically relevant change. In healthy old adults a change of MMSE between 2-4 points may be considered a functionally meaningful change [29,30]. In PwD a larger change in MMSE may be necessary to conclude a change to be functionally meaningful. Because of the low reliability of cognitive tests in PwD future researchers could consider other ways of measuring cognition in PwD. For example, subjective caregiver assessments of cognitive function may be a more reliable estimate of a patients' cognitive function than patients' performance on a cognitive test [31]. Also, observation of behavior can help determine a patients' functional status and wellbeing. Methods such as subjective caregiver assessment of cognition and observation of behavior are most feasible in smaller studies. Smaller studies do also allow for gathering of information from different sources, i.e., cognitive assessment, medical information, and case history. To avoid the limitations of small RCTs, future researchers should consider conducting multiple case studies instead of RCTs [32]. Last, the effects of exercise may be larger in PwD in later stages of dementia living institutionalized due to minimization of confounding factors such as life events or disease awareness. However, the finding that the effects of exercise may be strongest in later stages of dementia should be cautiously interpreted due to the low reliability of cognitive tests in PwD in later stages of dementia. Thus, we cannot support nor reject the recommendation of initiating exercise treatments in the earliest stages of the disorder (in line with [33] for pharmacological treatments). Summarized, the evidence for beneficial effects of exercise vs. control on cognitive function in PwD is unconvincing. Methodological issues complicate interpretation of findings. Future researchers are encouraged to find other methods to measure cognitive function in PwD, perhaps best performed in multiple case studies instead of RCTs.

#### *Exercise characteristics for PwD*

In chapter 4, we selected intervention characteristics (i.e., alternating walking and lower limb strength training, 3 individually supervised sessions/week, 30 minutes per session for 24 weeks) that previously showed the highest efficacy for physical and cognitive function in PwD [17,34]. We focused on exercise intensity as moderator because higher exercise intensity is related to better physical fitness, health variables, and neuroplasticity that may mediate exercise effects on physical and cognitive function [35-39]. The current two-group design

allowed participants to ease into higher intensity exercise while heterogeneity was minimized (as compared to a three-group LI exercise vs. HI exercise vs. control design). The finding that exercise intensity did not moderate exercise effects on cognition was reaffirmed by the meta-analytic results described in chapter 3. Instead, in chapter 3 short session duration ( $\leq 30$  minutes) and high frequency ( $\geq 4$ /week) were shown to moderate exercise effects on cognition. It should be noted that only one of the three studies with a frequency of  $\geq 4$  times/week was performed in PwD [17]. Thus, future studies could investigate exercise frequency as moderator of exercise effects on physical and cognitive function in PwD specifically. However, given the moderate attendance rate within our RCT sample ( $\sim 60\text{-}70\%$ ) we doubt whether a higher frequency would be feasible in a daycare or residential care setting. Given the lack of intensity effects, and uncertain feasibility of higher frequency exercise, future studies on moderators of exercise effects in PwD are perhaps best focused on the type of activities instead of dose-parameters. Multimodal treatments including exercise, cognitive stimulation, social stimulation and sensory enrichment may be required to stimulate functional outcomes for PwD [40]. Given the large diversity in symptom etiology and presentation in PwD it is preferable that such treatments are individually tailored. For personalization of treatments it is helpful to know the characteristics of responders and non-responders to a given treatment. Therefore, future researchers are encouraged to collect data on the characteristics of responders and non-responders to lifestyle treatments including but not limited to exercise.

### *Exercise and quality of life in PwD*

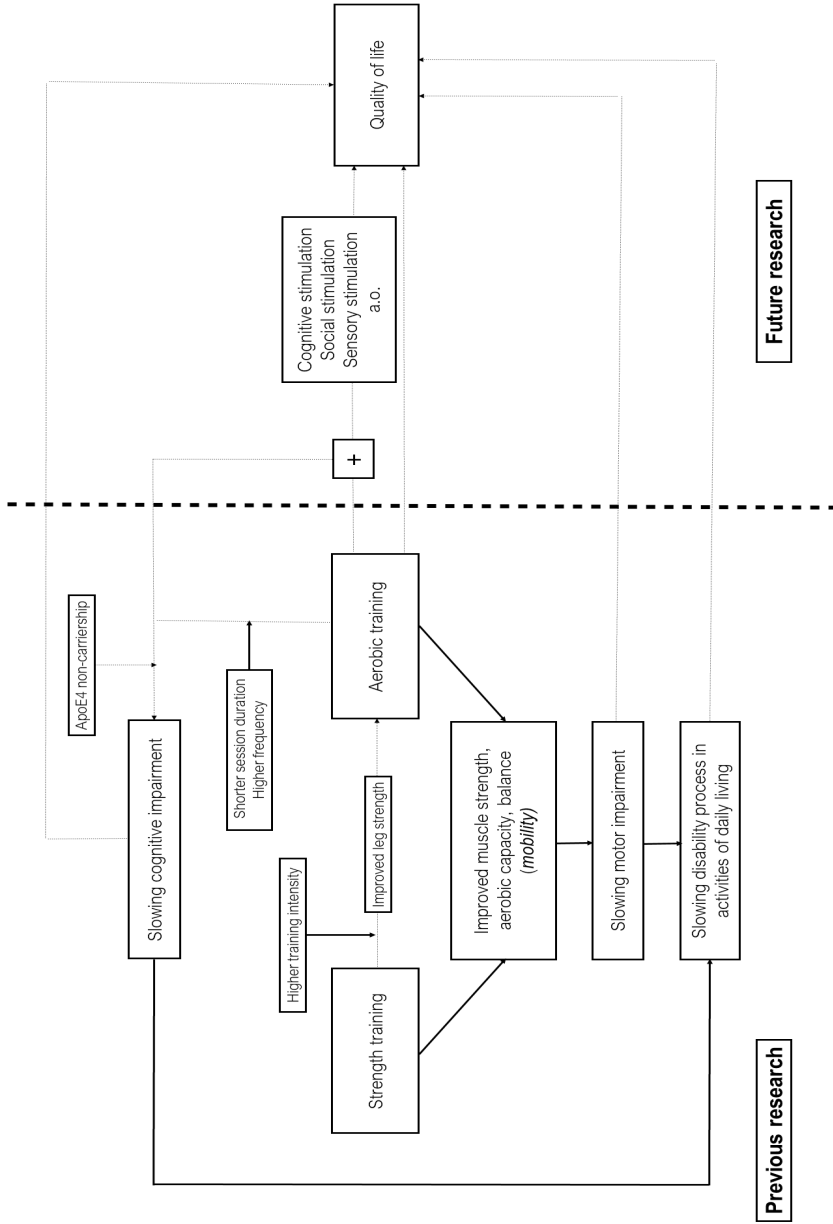
In order to have a meaningful impact on the lives of PwD and their caregivers we should determine the efficacy of exercise for quality of life (QoL). The World Health Organization defines QoL as ‘an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’. Changes in dementia-related variables such as declining health, loss of independence and increase in neuropsychiatric symptoms may negatively impact QoL of PwD [41]. Potential effects of exercise on QoL may be mediated by exercise-induced changes in physical and/or cognitive functions and activities of daily living [41,42]. Exercise may also exert a beneficial effect on QoL directly. Unfortunately only a handful of RCTs have investigated the effects of exercise on QoL directly in PwD [6,43,44] with conflicting findings. Interpretation of results regarding exercise effects on QoL is further complicated by heterogeneity between QoL-measures. It is important that future exercise studies investigate

QoL directly, preferably by proxy- and self-report, using standardized methods. Alternatively, a more individualized approach could be considered whereby QoL is defined subjectively for each individual participant. Equivalent to the effects of exercise on functional outcomes in PwD, a multimodal approach including exercise, cognitive stimulation, social stimulation and sensory enrichment may be required to stimulate QoL for PwD.

Figure 2 illustrates the recommendations for future studies.

#### *Generalizability of the current findings*

Figure 1 in chapter 4 shows that only ~10% of people assessed for eligibility could participate in our RCT. The question arises whether the target population is able to participate in exercise programs. We deem it unlikely that the included sample of PwD had a significantly higher ability to exercise than the target population. The only physical function prerequisite that was required for study participation was the ability to complete the Timed Up&Go (TUG) with or without walking aid. Within the included sample the level of physical function varied. 38% of our sample had gait speed scores  $\leq 0.8$  m/s, reflecting low mobility [45]. Also, the mean SPPB score in our sample at baseline of ~8.3 classifies participants at high risk of mobility disability [46,47]. Indeed, in chapter 4 it was shown that a combination of walking and lower limb strength exercise was feasible for PwD, even for those with low levels of physical function. The low percentage of included participants may have resulted from the requirement to be able to participate in a scientific study including all assessments. Especially a neuropsychological assessment can be burdensome for PwD as participants may be confronted with a lack of ability to correctly complete the task. In addition, participants have to be able to sufficiently understand instructions and be comfortable with the idea of participating in a scientific study. Furthermore, both participants and their informal caregivers had to consent to study participation. This limits the generalizability of the findings in this thesis to PwD who are able to participate in research, with informal caregivers that were supportive of study participation. Furthermore, within all chapters the generalizability of our findings is limited to PwD who enjoy PA enough to participate in exercise studies. Whether or not a person enjoys PA may determine the beneficial effects of PA on health outcomes [48]. This should be taken into account when interpreting the results of this thesis.



**Figure 2.** Recommendations for future research. a.o. = and others. Continuous lines represent evidence-based relationships whereas dotted lines represent hypothesized relationships.

### *Suggestions for the implementation of exercise in health care practice*

In chapter 1 it was shown that PwD are less physically active and more sedentary as compared to their healthy peers [49,50]. Increasing PA in this population may help ameliorate the detrimental effects of physical inactivity on health. Indeed, increasing PA reduces the risk of mortality, cancer, cardiovascular disease, diabetes and neuropsychiatric disorders in old adults [51]. Furthermore, the current thesis shows that exercise may have beneficial effects on gait speed in PwD. Therefore, we support the recommendation for movement-oriented health care for PwD. The implementation of continuous and structured exercise in daily health care practice is necessary for lasting health benefits. We have previously identified a number of barriers and facilitators for PA for PwD (unpublished data sourced from interviews with formal caregivers of the participants after the study, questionnaires, observation, and evaluation of implementation protocols; for more information on barriers and facilitators of PA in PwD see Van Alphen et al. [52] and Karssemeijer et al. [53]). One of the most prominent barriers for PA participation was the formal caregivers' perception that PwD may be too vulnerable for PA due to poor physical health, low cognitive function and fatigue. In addition, caregivers often reported a lack of knowledge on how to embed PA in daily routine. Thus, there is a need for the dissemination of knowledge on how to be physically active with PwD and how to structurally embed PA in everyday care. Caregivers need information on what exercises to do with PwD, how to tailor those exercises to PwD specifically, how to approach PwD, how to incorporate PA moments in everyday routine, and what to do when a person has limited physical capacity for PA. This knowledge needs to be aimed at staff, who work closely with PwD such as nursing assistants and living assistants. Such knowledge could be widely spread using e-learning modules that are specifically tailored to the target audience. We recommend that such e-learning modules incorporate the use of visual information with a hands-on approach. Initiatives as the one described above may facilitate movement-oriented health care for PwD in the Netherlands and abroad.

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