REVIEW

ACCEPTED: September 2017
PUBLISHED ONLINE: October 2017
DOI: 10.5960/dzsm.2017.300

Stroehlein JK, van den Bongard F, Barthel T, Reinsberger C. Dose-response-relationship between physical activity and cognition in elderly. Dtsch Z Sportmed. 2017; 68: 234-242.

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Dose-Response-Relationship between Physical Activity and Cognition in Elderly

Dosis-Wirkungs-Beziehung zwischen körperlicher Aktivität und Kognitionen bei Älteren

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Summary

› **Background:** There is some evidence that regular physical activity has protective effects on cognitive functions in elderly people. The optimal dose of physical activity remains to be elucidated. We conducted a systematic literature research to detect a "dose-response-relationship" with quantitative measures between physical activity and cognitive performance.

› **Method:** We searched PubMed and Ovid for randomized controlled trials. Intensity and total number of minutes of exercise per week were converted into metabolic equivalent (MET) values per week. Standardized Mean Differences were calculated to determine the effect of the physical intervention on executive functions, attention, processing speed, verbal memory, short- and long-term memory. Methodological quality was assessed by risk of bias with the Cochrane Collaboration tool.

› **Results:** 13 studies were analyzed. Eight studies reached two and three points in the quality assessment, five studies reached between four and six points. Low, moderate and high MET/week values were related to marginal, small, medium and high effect sizes for each health status. Indications were found for a linear dose-response relationship between executive functions and MET/week for the MCI population, but not for healthy elderly and AD patients.

› **Conclusion:** A dose-response-relationship superior to other intensities was not found for any group. Consensus on cognitive outcomes and the exploration of the effects of different types of exercise in healthy elderly, MCI- and AD-patients might help to elucidate the optimal 'dose' of physical activity on age- and AD-affected cognitive functions.

KEY WORDS:
Dose-Response-Relationship, Cognitive Performance, Physical Activity, Metabolic Equivalent, Dementia

Zusammenfassung

› **Problemstellung:** Es existieren Hinweise, dass regelmäßige körperliche Aktivität protektiv auf kognitive Funktionen bei älteren Menschen wirkt, die optimale "Dosierung" ist jedoch unbekannt. Eine systematische Literaturrecherche mit einer quantitativen Beurteilung einer „Dosis-Wirkungs-Beziehung" wurde zwischen körperlicher Aktivität und kognitiver Leistungsfähigkeit bei älteren Menschen und Demenzpatienten durchgeführt.

› **Methodik:** Die Datenbanken PubMed und Ovid wurden nach randomisierten kontrollierten Studien durchsucht. Gesunde Ältere, Patienten mit leichter kognitiver Beeinträchtigung (LKB) und Patienten mit einer Demenz vom Alzheimer-Typ (DAT) wurden berücksichtigt. Intensität und Anzahl der Trainingsminuten wurden anhand des metabolischen Äquivalents (MET) pro Woche standardisiert. Die standardisierte Mittelwertdifferenz wurde berechnet, um den Einfluss der Interventionen auf exekutive Funktionen, Aufmerksamkeit, Informationsverarbeitungsgeschwindigkeit, Kurz- und Langzeitgedächtnis und das verbale Gedächtnis zu bestimmen. Die methodische Qualität der Studien wurde mit dem risk-of-bias-tool der Cochrane Collaboration bewertet.

› **Ergebnisse:** 13 Studien wurden analysiert. Acht Studien erzielten in der Qualitätsbewertung zwei und drei Punkte, fünf Studien erzielten zwischen vier und sechs Punkten. Kleine, mittlere und hohe MET-Werte/Woche zeigten in allen Probandengruppen ausbleibende, kleine, mittlere und hohe Effektstärken. Es wurden Hinweise bei LKB-Patienten auf eine lineare Dosis-Wirkungs-Beziehung für exekutive Funktionen gefunden, für gesunde Ältere und Demenzpatienten hingegen nicht.

› **Schlussfolgerung:** Auf Grundlage der analysierten Studien konnte keine den anderen Belastungsintensitäten überlegende Dosis-Wirkungs-Beziehung für gesunde Ältere, LKB- oder DAT-Patienten gezeigt werden. Die Untersuchung der Wirkmechanismen der verschiedenen Beanspruchungsformen und Konsensus über kognitive Endpunkte könnten bei der Erforschung einer optimalen Dosis-Wirkungs-Beziehung zwischen körperlicher Aktivität und alters- und demenzbetroffenen Hirnfunktionen helfen.

SCHLÜSSELWÖRTER:
Dosis-Wirkungs-Beziehung, kognitive Leistungsfähigkeit, körperliche Aktivität, metabolisches Äquivalent, Demenz

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Introduction

The world's population is aging: From now until 2050, the proportion of people older than 60 years will rise from 12% to 22% (35). In light of these demographic change and increasing incidence and prevalence of AD, the most common form of dementia, strategies are needed to improve cognitive functions in the demented and healthy elderly population.

Albeit not unequivocal, there is evidence for primary and secondary preventive effects of physical activity on cognitive performance and function in elderly people, especially for aerobic exercise (6, 8, 12, 25). Previous studies demonstrated that regular moderate aerobic exercise increases cerebral blood flow (21) which induces various neurobiological mechanisms like angiogenesis, neurogenesis, synaptogenesis and nerval growth factors (21–23, 26, 32) resulting in neuroplasticity on various levels (24). This "brain reserve" may compensate for at least some pathological changes and has the capacity to contribute to delaying the clinical onset of dementias (10). It remains unclear to what extend those mechanisms are applicable equally to patients with manifest AD, MCI as a pre-sequel of AD and healthy elderly alike.

Besides aerobic exercise, other types of physical activity were found to improve cognitive performance and function of AD-affected brain areas in healthy elderly, including high-intensive strength (14) and low-intensive coordination exercises (18, 19, 34).

However, the results of these studies are difficult to compare due to heterogeneous study designs and physical interventions as well as a high variability in cognitive endpoints. It still remains unclear which "dosage" of physical activity influences AD-affected cognitive functions most effectively.

Therefore, we systematically reviewed randomized controlled trials to examine an evidence based dose-response-relationship between physical activity and cognitive performance. We standardized physical interventions by extracting intensity and the total amount of minutes of exercising per week and converting them into MET-values per week. The Standardized Mean Difference (SMD) with a pre-test correction was calculated for each cognitive outcome to determine the effect of the intervention on the specific cognitive domains. Since the definition of cognition includes several cognitive domains (13), this review classified cognitive outcomes into the age- and AD- affected domains executive functions, processing speed and attention, short- and long-term memory and verbal memory.

To the best of our knowledge, no review or meta-analysis put different physical interventions on a comparable base and relate them to AD- and age-related cognitive domains.

The purpose of this review is to verify the hypothesis of an evidence based dose-response relationship between physical activity and cognitive performance. We also aim to identify potential limitations and the most effective "dosage" of physical activity on the specific cognitive domains.

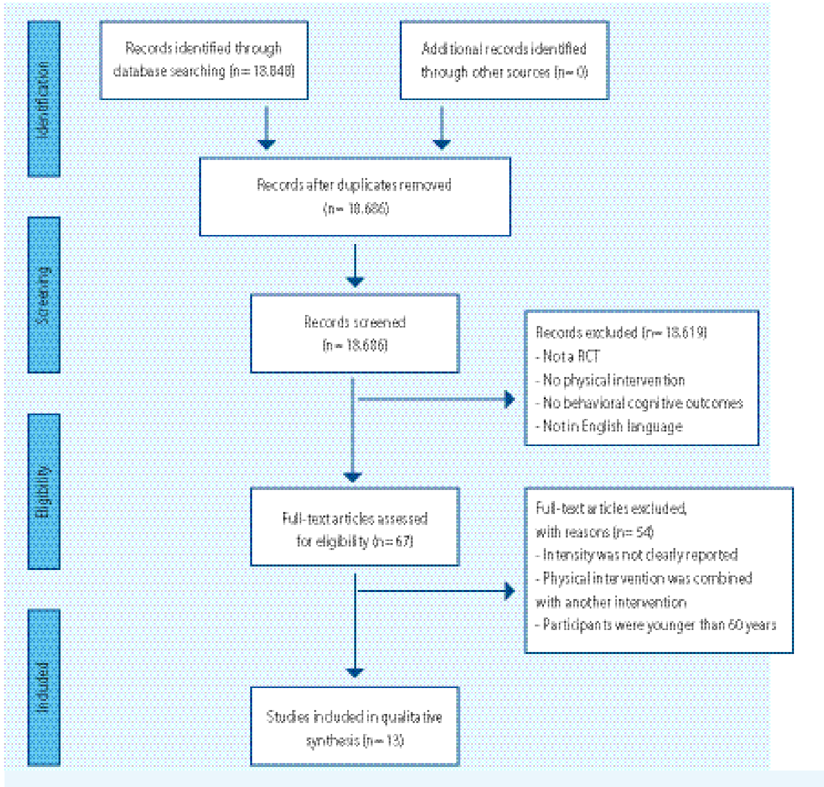

Figure 1

Modified PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram for the selection process.

Material and Method

Research Process, Key Words and Selection Criteria

We conducted a literature research on PubMed and Ovid until 17th July 2017. The search terms we used in different combinations were ("physical activity" OR exercise OR "physical exercise" OR physical training OR "aerobic exercise" OR "aerobic training" OR "resistance exercise" OR "resistance training" OR "coordination exercise" OR "coordination training") AND (brain OR cognition OR "cognitive performance" OR ageing OR "healthy elderly" OR elderly OR "mild cognitive impairment" OR dementia) AND "dose-response-relationship". Our selection criteria were (1) randomized controlled trial (2) physical intervention (3) clear documentation of intensity (by heart rate reserve (HRR), repetition maximum (RM) or VO_2max) and volume of the intervention) (4) behavioral cognitive outcomes (5) participants were at least 60 years (6) published in English language. The selection process following the PRISMA statement (17) is presented in fig. 1.

Quality of the studies was assessed by two independent reviewers for risk of bias by selection bias (two separated points: randomization sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other bias (9). One point was assigned for low risk of bias and zero points for unclear or high risk of bias. One point was awarded for each clearly satisfied criterion. Otherwise, no point was awarded (see table 1). Studies could reach a score between 0 and 7 points, with higher scores indicating less bias and better quality. For the purpose of this review, studies that scored four points or higher were considered to be of "high quality", while those scoring two points or less were considered to be of "low quality". Studies scoring three points were considered to be of "medium quality".

Calculation of Effect Sizes

Differences between samples were estimated by calculating effect sizes (ES). The dependent variables of the included studies were continuous and cognitive outcomes were different. Therefore, the SMD for each cognitive outcome was calculated using ReviewManager 5.3, utilizing the random effect model. To elucidate intervention effects, mean changes of the dependent variable from pre to post assessment depending on group allocation were calculated. For one study (33) only mean difference data was available. Therefore, we used the mean difference values for calculating the standard deviation and the SMD. In two studies (4, 5) we calculated the SMD using F-tests statistics. To assess ES we used the classification by Cohen (1988) due to the comparability with other studies and discrepancies of sample sizes. An ES lower than 0.2 indicates a small effect, 0.5 indicates a medium effect and 0.8 a high effect.

Table 1 - Part 1

Detailed description and risk of bias of the included studies. High or unclear risks (0 points) and the total score are presented. 1=Random sequence generation (selection bias), 2= Allocation concealment (selection bias), 3=Performance bias, 4=Detection bias, 5=Attrition bias, 6=Reporting bias, 7=Other bias. Higher scores are indicating less bias and better quality.

STUDY	INTERVENTION	COGNITIVE OUTCOMES	RISK OF BIAS (SCORE)
Alves et al. (2013) **RCT, single blinded** **56 older women** **mean age: 66.8 (60–80 years)**	24-weeks follow-up, 2 x week, 40 min each RT, 3 sets of 12 to 15RM, 7 whole-body exercises	Mini-Mental State Examination, Stroop Test, Trail Making Test, Digit Span Test, Delay Recall Test	2, 3, 4, 5 (3)
Arcoverde et al. (2013) **RCT** **20 mild AD patients, 4 with mixed dementia, mean age: 78.5 (64–81.2) years**	16-weeks follow-up (1 month familiarization), 2x week, 30 min each IG: Treadmill training, warm-up at 40% VO_2max (10 min), 60% of VO_2max (20 min), stretching exercises (5 min)	Cambridge Cognitive Examination, Clock Drawing Test, Verbal Fluency Test, Rey Auditory Verbal Learning Test (sum of round 1 – 5), Digit Span Test, Trail Making Test A, Stroop Test	1, 3, 4, 6 (3)
a) Baker et al. (2010) **RCT, single-blinded** **28 seniors with glucose intolerance** **range of age: 57–83 years**	24-weeks follow-up, Both groups: 4 x week, 45-60min each IG: Aerobic training on treadmill, stationary bicycle or elliptical trainer at 75-85% HRR CG: Stretching and balance exercises below 50% HRR	Trail Making Test A and B, Task Switching, Stroop Test, Self-Ordered Pointing Test, Verbal Fluency, Story Recall, List Learning	2, 4, 5, 6 (3)
b) Baker et al. (2010) **RCT, single-blinded** **33 adults with amnestic MCI** **mean age: 70 (55-85) years**	24-weeks follow-up, Both groups: 4x week, 45-60min each IG: Aerobic training on treadmill, stationary bicycle, or elliptical trainer at 75-85% HRR CG: Stretching and balance exercises below 50% HRR	Trail Making Test A and B, Stroop Test, Task Switching, Verbal Fluency, Symbol Digit Modalities, Story Recall, List Learning, Delayed-Match-To-Sample	2, 4, 5, 6 (3)
Davis et al. (2013) **RCT** **86 adults with MCI** **mean age: 75 years**	24-weeks follow up, All 3 groups: 2x week, 60min each (10min warm up, 40min core content, 10min cool down) RT: 7RM method (2 sets of 6-8 repetitions) AT: Walking program, progressing from 40% to 60% HRR CG: strength, balance and range-of-motion exercises, relaxation techniques	Stroop Test	2, 3, 4, 5, 6 (2)
Iuliano et al. (2015) **RCT** **80 healthy elderly** **mean age: 66.96 (11.73) years**	12-weeks follow-up, All groups exercised 3x week, 30-40min each RT: weeks 1-4 3 series with 12 repetitions at 60-70% of 1RM, weeks 5-8 3 series with 8 repetitions, 70-80% of 1RM, weeks 9-12 3 series with 6 repetitions at 80-85% of 1RM AT: aerobic exercise on the treadmill, bike-ergometer and ergometer for arms with increasing intensity (50-60% HRR to 70-80% HRR). Postural Training: flexibility, balance, respiratory and core stability exercises, muscle relaxing	Attentive Matrices Test, Raven's Progressive Matrices Test, Stroop Test, Trail Making Test A and B, Drawing Copy Test	2, 3, 4, 5, 6 (2)
Liu-Ambrose et al. (2010) **RCT, single-blinded** **135 community-dwelling older women** **mean age: 69.6 (2.9) years**	48-weeks follow-up, 1x or 2x week, 60min each RT groups: progressive, high intensity protocol with exercises for the whole body. 2 sets with 6-8 repetitions, training stimulus increased using the 7RM method Balance and tone group: stretching, range-of-motion, basic core strength and balance exercises as well as relaxation techniques	Trail Making Test A and B, Verbal Digit Span Forward and Backward Test, Stroop Test	2, 4, 5, 6 (3)

Calculation of MET Values

Single MET-values for each workout session were determined with "the Compendium of Physical Activities- Tracking Guide" (1). Therefore, we considered the reported intensity of the intervention (heart rate reserve (HRR), repetition maximum (RM), VO_2max) the type of exercise and the duration of the workout session.

Standardization was obtained by total weekly MET values for each intervention group (including active control groups). ES demonstrating a better performance for the CG were recorded as 0 (no effect) in the overview.

Classification of Cognitive Outcomes

The cognitive measures were assigned to cognitive domains depending on the information provided in the studies. The domains were executive functions, processing speed and attention, short- and long-term memory and verbal memory.

Results

The research resulted in a total of 18.686 records. After screening titles and abstracts and excluding studies which were not a randomized controlled trial, had no physical intervention or behavioral cognitive outcomes and were not in English language, 65 records remained. After further analysis of full text we excluded 51 records, if the intensity and the volume of the intervention was not clearly reported or the intervention was combined with another intervention, and if the participants were younger than 60 years. Finally, a total number of 13 studies was analyzed (fig. 1).

The total score of the methodological quality assessment was seven points, studies scored between two and six points. One study reached six points (20) and two another studies five points (30, 33), with strengths in a clear randomization procedure, a single-blinded design and published study protocols. Four points were scored by two studies (28, 29) and six studies reached three points (2–5, 15, 16). Two studies reached two points (7, 11), with limitations regarding reporting bias, attrition bias as well as performance and detection bias. An overview is presented in table 1.

Description of Included Studies

The sample sizes within the 13 included studies ranged from 20 to 152 and observation periods from four to 48 weeks. Seven studies had a low-intensity placebo-treated control group (CG) (4, 5, 7, 15, 16, 29, 30). Treatment within the intervention groups differed. Eight of 13 studies performed an intervention to improve aerobic fitness (2, 4, 11, 15, 16, 20, 33) while six studies

Table 1 - Part 2

Detailed description and risk of bias of the included studies. High or unclear risks (0 points) and the total score are presented. 1*=Random sequence generation (selection bias), 2*= Allocation concealment (selection bias), 3*=Performance bias, 4*=Detection bias, 5*=Attrition bias, 6*=Reporting bias, 7*=Other bias. Higher scores are indicating less bias and better quality.

STUDY	INTERVENTION	COGNITIVE OUTCOMES	RISK OF BIAS (SCORE)
Liu-Ambrose et al. (2012) **RCT, single-blinded** **52 community-dwelling older women** **mean age: 69.3 (3.0) years**	See above (Liu-Ambrose et al. 2010)	Eriksen Flanker Task	2, 4, 5, 6 (3)
Nouchi et al. (2013) **RCT, single-blinded** **64 healthy elderly** **mean age: 67.06 (2.82) years IG and 66.75 (4.61) years CG**	24-weeks follow-up, 3x week, 30min each IG: Combination of aerobic, strength and stretching in a circuit style, each workout consists of 12 strength exercises at 60-80% HRR and 30s breaks. The participants did a standardized whole-body stretching training consisting of 12 exercises at the end of each session.	Verbal Fluency Task, Stroop Test, Logical Memory, First and Second Names, Digit Span Forward and Backward, Digit Cancellation Task	4 (6)
Suzuki et al. (2013) **RCT, single-blinded** **100 adults with MCI** **mean age: 75 years**	24-weeks follow-up, 2x week, 90min each IG: Combination of aerobic exercise, muscle strength training, postural balance and dual-task training.10 min warm-up with stretching exercises and 20 min strength training, followed by 60 min aerobic exercises, postural balance and dual-task training at approximately 60% HRR.	MMSE, Alzheimer's Disease Assessment Scale-Cognitive Subscale, Logical Memory WMS-LM I and II	2, 4, 5 (4)
Ten Brinke et al. (2014) **RCT, single-blinded** **29 adults with MCI** **mean age: AT 76.07 (3.43), RT 73.75 (3.72) and BAT 75.46 (3.93)**	24-weeks follow-up, 2x week, 60 min each (10min warm up, 40min of core content and 10min cool down) RT: Exercises for the whole body with free-weights and Keiser-based exercises. 2 sets with 6-8 repetitions, training stimulus increased using the 7RM method. AT: Outdoor walking program, trainings stimulus was 40% HRR at the beginning and progressed during the observation period to 70-80% HRR Balance and tone group: stretching, range-of-motion, basic core strength and balance exercises as well as relaxation techniques	Rey Auditory Verbal Learning Test	2, 4, 5 (4)
Van Uffelen et al. (2008) **RCT, double-blinded** **152 adults with MCI** **range of age: 70-80 years**	48-weeks follow-up, 2x week, 60min each AT: Walking program at moderate intensity (>3 MET), participants were able to talk to each other, but also showed since of moderate intensity activity (breathing frequency). The placebo activity program consisted of non-aerobic exercises (<3 MET), including relaxation, activities of daily living, balance, flexibility and postural exercises. Between both groups participants were randomized to vitamin B (folic acid, B 12, B6) or placebo supplementation	Auditory Verbal Learning Test, Verbal Fluency Test, Digit Symbol Substitution, Abriged Stroop Color Word Test	2, 4 (5)
Vidoni et al. (2016) **RCT, single-blinded** **65 healthy seniors** **mean age: 75 min/w 73.5 (5.9), 150 min/w 72.5 (5.7), 225 min/w 73.2 (5.3), CG 72.5 (5.8)**	26-weeks follow up, 4 different intervention arms: 1) 75min/week aerobic exercise, 2) 150min/week aerobic exercise, 3) 225min/week aerobic exercise, 4) inactive CG In the first 4 weeks, intensity was 40-55%. At weeks 19-26, intensity increased to 60-75% HRR. Aerobic exercise included treadmill walking or different aerobic modality (e.g. elliptical).	Logical Memory, Delayed Logical Memory, Selective Reminding Task, Boston Naming Test, Block Design, Stroop Color Reading, Digit Dymbol Substitution, Trail Making Test A, Digit Span Forward and Backward, Letter Number Sequencing, DKEFS Card Sort, Category Fluency, Inductive Reasoning Letter, Inductive Reasoning Word, Matrix Reasoning	2, 4 (5)

performed resistance training (RT) (2, 7, 11, 15, 16, 29) and two studies engaged in a mixed program including coordination exercises, too (20, 28). Seven of 13 studies included healthy elderly participants (2, 4, 11, 15, 16, 20, 33), five included MCI patients (5, 7, 28–31) and one study AD patients (3). Detailed descriptions of the interventions and cognitive outcomes are presented in table 1.

Dose-Response Relationship

ES are presented as SMD with 95% CI (see table 2). Squares indicate results for AD patients, triangles indicate results for MCI patients and circles indicate results for healthy elderly (see fig. 2).

Executive Functions

The following cognitive measures were assigned to the domain executive functions: Stroop Test (Victoria Version), Trail Making Test, Clock Drawing Test, Task Switching Test, Stroop Color and Word Interference Test, Self-Ordered-Pointing Test, Verbal Fluency Task, Verbal Digit Span Test, Eriksen Flanker Task, Stroop Color Reading Test and Digit Symbol Substitution.

We found heterogeneous results for seven studies with healthy elderly participants (2, 4, 11, 15, 16, 20, 33): No effects were found in five groups. In the other groups, eight marginal ES were achieved at 5 MET, 5.25 MET, 6 MET, 7.2 MET and 7.6 MET, 8.48 MET, 10.5 MET, 12 MET 21 MET, 27.6 and 28.5 MET. Nine small and ten moderate ES were found at 5.25 MET, 6 MET, 7.2 MET, 8.5 MET, 12 MET, 21 MET, 24 MET, 27.6 MET and 28.5 MET. Three large ES were found at 12 MET, 21 MET and 24 MET.

The three studies with MCI patients (5, 7, 30) showed no effects in two groups. Two marginal ES between 5 MET to 8.48 MET were found in the other groups. One small and two moderate ES were found at 12 MET and 27.6 MET. Three large ES were found at 27.6 MET in one study (5).

We found a moderate and two large ES for one study with AD and mixed dementia patients at 3.8 MET (3).

Processing Speed and Attention

The following outcomes were assigned to the cognitive domain processing speed and attention: Digit Span Forward and Backward, Digit Span Score, Symbol Digit Modalities, Digit ›

Table 2

Overview of effect sizes (ES) with 95% confidence intervall (CI) for the cognitive domains executive functions, processing speed and attention, short-, long-term and verbal memory. MCI = mild cognitive impairment, AD = Alzheimer's disease.

EXECUTIVE FUNCTIONS	MARGINAL ES	SMALL ES	MODERATE ES	LARGE ES
Healthy elderly	-0.11 [-0.95, 0.73] (20)	-0.23 [-0.65, 0.18] (16)	0.70 [0.14, 1.54] (4)	0.90 [0.38, 1.43] (20)
	0.01 [-0.41, 0.43] (16)	0.32 [-0.18, 0.83] (20)	0.62 [0.02, 1.23] (33)	-0.81 [-1.46, -0.16] (11)
	0.15 [-0.27, 0.56] (16)	-0.23 [-0.85, 0.4] (11)	-0.65 [-1.51, 0.22] (2)	0.86 [0.21, 1.50] (33)
	-0.10 [-0.72; 0.52] (11)	-0.22 [-0.84, 0.4] (11)	-0.77 [-1.65, 0.11] (2)	
	-0.05 [-0.67, 0.57] (11)	-0.36 [-0.99, 0.26] (11)	-0.46 [-0.88, -0.04] (16)	
	0.03 [-0.51, 0.56] (30)	0.37 [-0.26, 0.99] (33)	-0.47 [-0.89, -0.05] (16)	
	0.10 [-0.49, 0.69] (33)	0.24 [-0.68, 1.16] (4)	0.36 [-0.14, 0.87] (20)	
	0.17 [-0.42, 0.77] (33)	0.25 [-0.67, 1.17] (4)	0.51 [-0.15, 1.17] (33)	
		0.22 [-0.7, 1.14] (4)	0.60 [-0.07, 1.26] (33)	
			-0.73 [-1.45, -0.01] (15)	
MCI	0.08 [-0.35, 0.52] (30)	0.23 [-0.29, 0.75] (7)	0.43 [-0.10, 0.96] (7)	0.86 [-0.06, 1.67] (5)
	0.03 [-0.51, 0.56] (30)		0.68 [0.1, 1.46] (5)	1.03 [-0.23, 1.83] (5)
				0.84 [-0.04, 1.64] (5)
AD			0.76 [-0.15, 1.68] (3)	0.87 [-0.06, 1.80] (3)
				-0.83 [-1.75, 0.09] (3)
PROCESSING SPEED AND ATTENTION	**MARGINAL ES**	**SMALL ES**	**MODERATE ES**	**LARGE ES**
Healthy elderly	0.09 [-0.75, 0.93] (2)	0.33 [-0.18, 0.83] (20)	0.73 [-1.45, -0.01] (15)	1.17 [0.49, 1.84] (11)
	0.09 [-0.56, 0.71] (11)	-0.25 [-0.87, 0.37] (11)	0.41 [-0.10, 0.92] (20)	
	0.12 [-0.5, 0.74] (11)			
	0.14 [-0.48, 0.76] (11)			
	-0.19 [-0.69, 0.32] (20)			
MCI	0.02 [-0.42, 0.46] (30)	0.35 [-0.09, 0.79] (30)		0.80 [-0.003, 1.6] (5)
	-0.10 [-0.63, 0.43] (30)	0.20 [-0.33, 0.74] (30)		
	-0.10 [-0.54, 0.33] (30)	-0.31 [-0.84, 0.23] (30)		
	-0.08 [-0.62, 0.45] (30)	-0.23 [-0.67, 0.21] (30)		
AD			0.41 [-0.48, 1.30] (3)	
SHORT-, LONG-TERM AND VERBAL MEMORY	**MARGINAL ES**	**SMALL ES**	**MODERATE ES**	**LARGE ES**
Healthy elderly	-0.07 [-0.58, 0.43] (20)	0.30 [-0.48, 1.08] (4)	0.70 [0.18, 1.21] (20)	
	0.03 [-0.53, 0.59] (33)	0.22 [-0.34, 0.77] (33)		
	0.09 [-0.46, 0.65] (33)	0.23 [-0.33, 0.79] (33)		
	-0.04 [-0.53, 0.45] (33)	0.38 [-0.17, 0.93] (33)		
		0.39 [-0.18, 0.95] (33)		
MCI	-0.06 [-0.91, 0.8] (29)	0.36 [-0.05, 0.77] (28)	-0.60 [-1.11, -0.08] (30)	
	-0.07 [-0.51, 0.37] (30)	0.30 [-0.11, 0.71] (28)		
	-0.07 [-0.06; 0.47] (30)	0.37 [-0.55, 1.29] (29)		
		-0.27 [-0.71, 0.17] (30)		
AD		0.27 [-0.61, 1.15] (3)		

Cancellation Task, Digit Symbol Coding, Symbol Search, Attentive Matrices Test (time and target), Digit Symbol Substitution Test, Abridged Stroop Color and Word Test, Digit Span Numbers Forward and Backward

In four studies with healthy elderly (2, 11, 15, 20) no effects were found in five groups. Five marginal ES were found at 5 MET, 5.25 MET, 6 MET, 7.2 MET, 12 MET and 24 MET in the other groups. Two small and two moderate ES were presented at 24 MET. One large ES was found at 10.5 MET.

The two studies with MCI patients (5, 30) showed no effects in three groups and four marginal ES at 5 MET, 7.6 MET and 8.48 MET in the other groups. Four small ES were found at 5 MET and 7.6 MET. A large ES was found at 27.6 MET in one study (5).

No effects as well as a moderate ES was found for one study with AD and mixed dementia patients (3) at 3.8 MET.

Short- and Long-Term Memory, Verbal Memory

The following outcomes were assigned to the cognitive domain short- and long-term memory, verbal memory, Logical Memory Wechsler-Memory-Scale III (immediate and delayed recall), Rey Osterrieth Complex Figure (copy, immediate and delayed recall), Letter Fluency, Rey Auditory Verbal Learning Test, (sum of words of round 1 – 5), Story Recall and List Learning, Reading Ability, First and Second Names, Boston Naming Test, Selective Reminding Task.

In three studies (4, 20, 33) with healthy elderly no effects were found in four groups and four marginal ES were found at 8.48 MET, 8.5 MET, 21 MET, 24 MET, 27.6 MET and 28.5 MET in the other groups. Five small and one moderate ES were found at 8.5 MET, 21 MET, 24 MET and 28.5 MET.

The four studies with MCI patients (5, 28–30) showed no effects in six groups and three marginal ES at 5 MET, 7.6 MET 12 MET, 8.48 MET and 27.6 MET in the other groups. Four small and one moderate ES were found at 5 MET, 7.6 MET and 12 MET.

A small ES was found in one study with AD and mixed dementia patients (3) at 3.8 MET.

Discussion

The purpose of this review was to verify the hypotheses of an evidence-based dose-response-relationship between cognitive functions and physical activity. The results of the seven included studies with healthy elderly were heterogeneous in terms of ES and MET values. Even small and high MET/week values showed no intervention effect as well as marginal, small, moderate or large ES for all cognitive domains. Most of the studies with healthy elderly were of low or medium quality, scoring two or three points in the risk of bias assessment (see table 1) (except for (20, 33)). An unclear randomization procedure, lack of double-blinding and a missing study protocol resulted in an increased risk for selection bias, performance and detection bias as well as reporting bias. Thus, it is not possible to determine a clear dose-response relationship between MET/week and cognitive performance in healthy elderly for any of the examined cognitive domains.

We found some indications for a linear dose-response relationship between executive functions and MET/week for the MCI population: the lower the MET/week value, the lower the ES, and vice versa the higher the MET/week values, the higher the ES (see figure 2). However, these results are based on only three studies of low (two points (7)), medium (three points (5)) and high (six points (30)) methodological quality. A dose-response-relationship between MET/value per week and cognitive performance in the MCI population could not be determined for the other cognitive domains, due to few heterogeneous results. Methodological quality of the other MCI studies was high (four points (28, 29)).

Only one study with AD patients fulfilled the inclusion criteria for this review. Predominantly moderate to large ES were found at a small level of MET values per week. The study was of medium quality (3 points).

In conclusion, low, moderate and high MET/week values may improve cognitive performance in healthy elderly, MCI and AD patients. However, negative results were also found on each level. Our findings also indicate that executive functions benefited more than the other cognitive functions from physical activity. This is in line with findings from other studies (4, 6).

Probably, the most effective 'dosage' of physical activity on specific cognitive functions is highly individual and influenced by the physical fitness level of the participants, the number of various cognitive outcomes and the heterogeneous physical interventions. The majority of the analyzed studies applied aerobic and strength exercise – probably as a consequence of our selection criteria ("criterion 3: intensity of the intervention is documented"). The brain's reaction to an increased energy metabolism includes an increase in cerebral blood flow which induces several neurotrophic factors, as brain derived neurotrophic factor, insulin-like growth factor and vascular endothelial growth factor (26). These neuroprotective mechanisms lead to an enhanced synthesis of cerebral tissue (21).

Therefore, aerobic and strength exercise programs can lead to an increased brain reserve capacity, maintaining a healthy function for the aging brain and delaying the onset of clinical symptoms in MCI or AD (10, 27). However, until now there is only modest evidence for aerobic and strength exercise programs on cognitive performance for people who already suffer from AD (23).

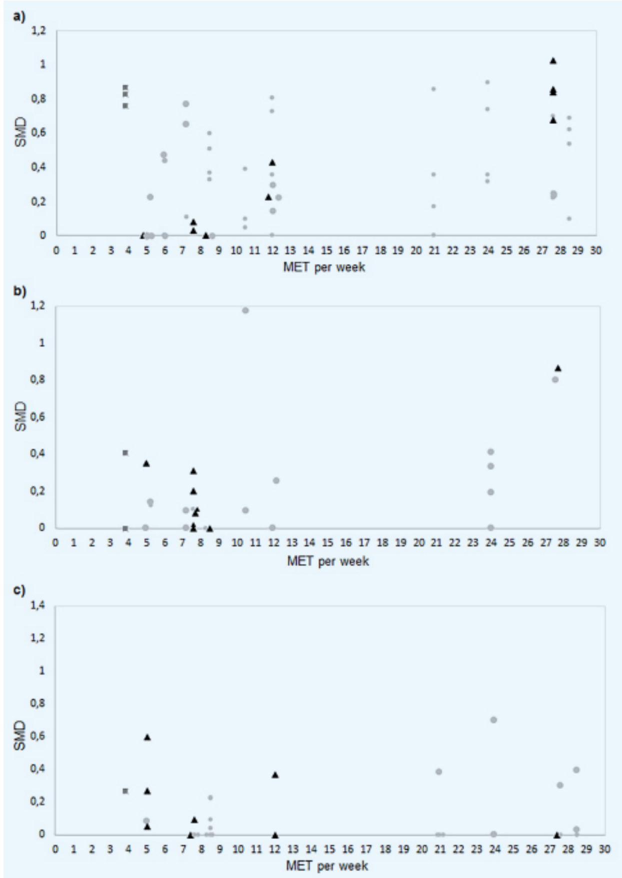

Figure 2

Dose-response relationship between MET-values per week and the SMD of the cognitive outcomes. We differentiated between the cognitive domains (a) executive functions b) processing speed and attention c) short-, long-term and verbal memory) and health status (circles: healthy elderly, triangles: MCI patients, squares: AD patients).

Previous studies found that even low-intensity exercise, such as coordination training can improve cognitive performance and alter brain structures and functions that are involved in cognitive processes and pathology (18, 19, 34). Seven control groups of the included studies received a low-intensity placebo treatment, including stretching, postural and balance exercises as well as calisthenics and relaxation techniques. Even those low-intensity groups, designed to exclude the benefit from a social/group activity factor, demonstrated small ES for short and long-term memory and verbal memory, processing speed and attention in MCI patients as well as for executive functions in healthy elderly. These findings indicate that the amount and intensity of physical activity might not be the sole factor determining effects on brain function and structure, but rather supports the importance of the conducted type of the intervention. Based on the 13 analyzed studies, aerobic exercise interventions demonstrated the largest ES, followed by strength and multicomponent exercise, while ES for low-intensity exercise were rather small.

It remains to be elucidated, how different types of exercise (e.g. aerobic, strength and coordination exercise) influence the specific cognitive functions in healthy elderly, MCI- and AD-patients. Moreover, consensus on cognitive outcomes may help identifying a more detailed signature of exercise interventions that have optimal effects on the specific cognitive functions.

Limitations

This review is limited by its focus on behavioral cognitive outcomes to elucidate the dose-response-relationship between physical activity and cognitive performance. Moreover, the assignment of the cognitive outcomes to the specific cognitive domains was inconsistent within the analyzed studies, which have probably influenced our results. Because of our selection criteria, mainly aerobic exercise interventions were included, raising the risk for selection bias. A further limitation is the transformation of the physical intervention into MET. To get exact MET values, the metabolic rate of each subject is needed. To account for this problem, we estimate approximate MET values for each physical activity according to "The Compendium of Physical Activities Tracking Guide".

Conclusion

We could not determine a clear dose-response-relationship between the amount of physical activity per week and the cognitive domains executive functions, attention and processing speed, short- and long-term memory and verbal memory based on randomized controlled trials. However, cognitive functions were improved by physical exercise at each intensity level.

The amount and intensity of physical activity were probably not the key factors for determining the effects on brain structures and functions. Consensus on cognitive outcomes and the exploration of the effects of different types of exercise in healthy elderly, MCI- and AD-patients might help to elucidate the optimal 'dose' of physical activity on age- and AD-affected cognitive functions.

Acknowledgement

We thank Lisa M. Stroehlein for reading and correcting the paper.

Conflict of Interest

The authors have no conflict of interest.

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