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Physical Fitness as a Protective Factor for Cognitive Impairment in a Prospective Population-Based Study in Germany

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Abstract. To evaluate the predictive effects of subjective measures of physical activity (PA) and objective measures of physical fitness (PF) on dementia risk, participants of the prospective population-based ILSE-study (*1930-1932; 12-year follow-up) were examined at three examination waves (t1 : 1993/94; t2 : 1997/98; t3 : 2005/07). 381 subjects of the original cohort ($n = 500$) were re-examined at t3. 29% of the subjects who were cognitively healthy at baseline received the diagnosis of mild cognitive impairment (MCI) and 7% of Alzheimer's disease (AD). Subjects were screened for physical and mental health using medical interviews, physical, and neuropsychological examinations. Participants completed a questionnaire on their current and past PA at t1. Subjects were classified as physically active if they reported a regular sport activity for at least 2 hours per week in the past year. Muscular strength (handgrip) and motor coordination (balance) served as objective indicators of PF. Subjects who passed the balance-test at t1 had a reduced risk of developing MCI/AD at t3 (OR = 0.35, 95%CI 0.19–0.66, $p < 0.01$) and performed significantly better on various neuropsychological measures. Muscular strength or subjective reports of PA did not predict MCI/AD development. Our results confirm the hypothesis that PF acts as a protective factor for the development of cognitive disorders. In our study context, motor coordination served as a better predictor than muscular strength or self-rated PA. Since subjects with cognitive disorders due to cerebral and/or systemic disorders were excluded from the analyses, our findings suggest that the effect of skill-related PF extends beyond the reduction of cardiovascular risk factors.

Keywords: Aging, Alzheimer's disease, cognition, cohort studies, physical activity, prevention

INTRODUCTION

The prevention of cognitive disorders in the elderly has become a major public health issue. Recent epidemiological studies have focused on the association between lifestyle habits and dementia risk. Several studies have reported a protective effect of cognitive and social activities [1, 2]. Although several studies support the hypothesis that physical activity (PA) enhances cognitive performance and reduces risk for dementia, other studies have failed to find an association. Thus, the protective nature of PA cannot yet be considered conclusive. In general, cognitive and physical decline are highly correlated in the aging process [3]. Previous studies investigating the relationship between PA and cognition in non-demented elderly subjects consistently report less cognitive decline among physically active subjects [4, 5] – especially in terms of executive functioning [6, 7].

Moreover, training aimed at increasing physical exercise improves both memory and attention in subjects diagnosed with mild cognitive impairment (MCI) [8, 9]. However, the beneficial effect of PA seems

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to be considerably dependent on the intensity of the performed activities. Kramer et al. [10] detected a significant improvement in executive function for subjects who participated in a walking intervention while subjects who completed a stretching program did not improve. The authors argue that aerobic training is likely to show a selective effect on frontal and prefrontal brain structures, which are associated with executive functioning. This hypothesis was supported by Colcombe et al. [11] who reported an increase in grey and white matter tissue in pre-frontal and temporal brain areas of subjects who participated in the aerobic training program. However, the exact mechanisms explaining the link between PA, brain structures and enhanced cognitive ability remain unclear.

Whereas studies investigating the relationship between PA and cognitive functioning in healthy controls and MCI subjects consistently show beneficial effects of PA, studies concerning the relationship between PA and dementia risk are rather inconsistent.

Most prospective studies hypothesize that regular engagement in PA delays the onset of dementia [12]. Accordingly, a significant protective effect of PA was reported in several [13–18] but not all [19–21] epidemiological studies.

The discrepancies in the reported research are likely related to methodological differences. Definitions of PA vary across epidemiological studies. Some studies focus on the impact of sport activities on dementia risk [12, 17] whereas others have examined the impact of low intensity PA [15]. Other studies consider non-aerobic activities – such as gardening or housekeeping – to be indicators of PA [16, 19]. While most of the cited studies asked for PA during leisure time one study also included occupation-based PA in their analyses [21]. These heterogeneous definitions are likely to result in heterogeneous results: A study by Andel et al. [22] showed that light PA (like gardening) significantly decreased their participants' dementia risk by 37% while regular sport activity resulted in a much higher risk reduction of 66%. Thus, protective effects of PA may be over- or underestimated depending on the applied criteria.

Another point to be considered refers to the question of how PA should be assessed. Currently, the most common form of assessment is self-report. However, this method has a number of potential biases. Social desirability might play an important role in answering questions on PA habits. On the other hand, subjects might forget to report about certain activities if they perform them on an irregular basis. This is especially relevant concerning retrospective data. Objective measures of PA and/or physical fitness (PF) have not been frequently used in previous prospective or retrospective longitudinal studies even though they are not affected by the bias problems of subjective measures. Biases related to subjective measures may be one explanation why some previous studies did not detect a protective effect of PA. Another advantage of objective measures is that they allow investigating and comparing different aspects of PF which may have differential effects on cognition (e.g., motor coordination versus muscular strength).

Another issue that has not been considered by previous studies is that cohort effects might have influenced study outcomes, as earlier studies did not investigate birth cohorts. A birth cohort design provides the advantage of investigating subjects who grew up under similar life conditions, which allows for a more solid interpretation of the findings – especially with respect to the impact of education and lifestyle factors.

In the present study, we asked whether objective or subjective measures of PA and/or PF served as predictors for the development of MCI and Alzheimer's disease (AD). We investigated the association of sport activities, neuropsychological test performance, and cognitive impairment. The German Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE) served as the basis of our investigations.

MATERIALS AND METHODS

Subjects

The ILSE is a prospective study on adult development and aging in Germany based on two birth cohorts born between 1930–32 (C30) and between 1950–52 (C50), respectively [23]. Participants were randomly selected and recruited on the basis of community registers which comprise data on all inhabitants of German communities. This recruitment procedure resulted in a representative sample of 1002 participants for the respective communities (C30: $Nn = 500$; C50: $Nn = 502$). Subjects have been followed up since 1993/94 for an average time of 12 years within three examination waves (t1 : 1993/94; t2 : 1997/98; t3 : 2005/07). The present study is based on the results of 381 initially healthy participants from the 1930–32 birth cohort who completed the 3rd examination wave at an average age of 74 years. 119 subjects dropped out between t1 and t3 : 60 of them deceased, 59 did not participate because of relocation ($n = 13$), health problems ($n = 19$), lack of time and interest ($n = 15$) or

other reasons ($n = 12$). Subjects that dropped-out were significantly less educated than those who finished t3. Related to this, dropouts showed comparatively lower test results on most of the neuropsychological measures that are highly associated with educational attainment. However, participants who left the study did not differ in any other demographic (e.g., gender, age, socioeconomic status) or measured variable (subjective and objective measures of PA/PF at t1). The participants born between 1950 and 1952 were not considered in this study, as prevalence and incidence of cognitive disorders was very low for this cohort and our aims were specifically related to examining the protective effects of PF and PA on cognitive impairment. Participants were carefully screened for physical and mental health by extensive interviews, physical examinations and laboratory tests. In this context, Parkinson's disease and other neurological and mobility disorders were carefully excluded. Psychiatric disorders were assessed clinically and by using the Structured Clinical Interview for DSM-III-R [24]. The study was approved by the ethics committee of the University of Heidelberg. After complete description of the study to the subjects, written informed consent was obtained.

The neuropsychological test battery was administered by professional psychologists. Severity of cognitive deficits was assessed by the Mini Mental State Examination (MMSE) [25]. In addition, the subtest "logical memory" of the Wechsler Memory Scale (WMS) [26] and the Trail Making Test (TMT) [27] were applied to address memory and learning, as well as attention and cognitive flexibility. Additional neuropsychological tests were derived from the "Nürnberger-Alters-Inventar" [28] and the "Leistungsprüfsystem" [29], which are commonly used test batteries in Germany. The following subtests were applied for the present study [30]: *Memory* – immediate word list recall, delayed word list recognition; *Visuospatial functioning* – spatial orientation, block design; *Verbal comprehension* – information subtest; *Abstract thinking* – similarities subtest; *Speed* – number-connection test; *Attention/concentration* – D2[1]. In order to assess functional decline, subjects completed a self-rating scale within the "Nürnberger-Alters-Inventar" where they were asked to indicate recent cognitive and/or functional decline.

[1] D2 consists of 14 lines with the letters "d" and "p". Each letter is accompanied by 1–4 strokes. The task is to detect all ds with 2 strokes within a time limit of 20 seconds per line.

Assessment of subjective physical activity

In this study, PA was assessed with a questionnaire at t1. Participants were asked about their current and past sport activities using open-ended questions. Additionally, they were asked if they performed the respective activities on a regular basis and how many hours they spent on them per week. According to current WHO recommendations [31] subjects were classified as physically active if they reported at least one sport activity, for at least once a week for two hours over any year-long interval. Subjects were classified as physically active throughout their whole lifetime if they fulfilled the above criteria during childhood (6–14 years), youth (14–20 years), young adulthood (20–40 years), mid adulthood (40–60 years), and at t1. The remaining subjects were classified as "never" or "not continually physically active" according to their statements.

Assessment of objective physical fitness

Physical fitness (PF) combines cardio-respiratory and muscular endurance, muscle strength, body composition, and flexibility. While balance and motor coordination are regarded as skill-related components of PF, body composition and muscular strength are defined as health-related components.

Performance on the "one foot balance test" (OFBT) served as an objective skill-related indicator of PF in our study. Subjects were asked to balance on one foot for 15 seconds and were subsequently classified as successful or unsuccessful according to their performance. Balance tests are common measures of PF for older adults across epidemiological studies [3, 12, 15]. Additionally muscular strength is considered to be an important health-related aspect in the assessment of overall fitness [32]. In this study muscular strength was assessed with the aid of the "Martin-Vigorimeter" [33] Subjects were asked to press a ball alternating between the dominant and non-dominant hand for four trials. We chose the maximum grip strength for our analyses, which was defined as the best individual result out of the four trials. The widely used "Body-Mass Index" (BMI) served as an additional objective health-related indicator of PF measuring body composition. As the study protocol did not include aerobic or cardio-respiratory measures, we were not able to apply a more comprehensive assessment of PF. Although cardiorespiratory measures (i.e., VO_2 max) are often employed in RCT's they are not the most commonly used in longitudinal and epidemiological studies, as they are often both expensive and invasive.

Assessment of covariates

Education and socioeconomic status (SES) were assessed in the course of an interview at t1 and cross-checked with the respective statements in a socio-demographic questionnaire. Education of participants – which was defined as years of formal education – was categorized as low (<10 years), medium (10–15 years), or high (>15 years). The assessment of participants' SES was based on their monthly household income at t1. Three categories were defined indicating a low (≤2000 Deutsche Mark (DM)), medium (2000–4000 DM), or high (≥4000 DM) SES. Depressive symptoms at t1 were determined with Zung's Self-Rating Depression Scale (SDS) [34]. Subjects were classified as having no depressive symptoms if they scored below 50 points.

Diagnostic categories

MCI was diagnosed according to the aging-associated cognitive decline (AACD) criteria as described elsewhere [35]; mild cognitive disorder (MCD) using ICD-10 criteria (for details see [30]). For the diagnosis of AD and vascular Dementia (VaD) the NINCDS-ADRDA and the NINDS-AIREN criteria were applied [36–37]. All diagnoses were undertaken by a consensus conference consisting of two specialists in psychiatry under supervision of a specialist in Old Age Psychiatry.

Statistics

SAS software (version 9.02; SAS Institute, Cary, NC, USA) was used for all statistical analyses; *p*-values less than 0.05 were considered significant. Group differences were calculated by univariate analyses of variance (ANOVAs) in case of continuous variables and chi-square tests in case of categorical variables. Group differences concerning neuropsychological test performance from t1–t3 were calculated by repeated multivariate analyses of variance (MANOVAs).

In order to assess the risk of MCI/AD associated with PA and PF, odds ratios (OR) were calculated. Logistic regression analyses were performed in order to determine statistical significance at 95% confidence intervals. In order to adjust for important potentially confounding variables, education, SES, gender, and depressive symptoms were included into the logistic regression model.

RESULTS

381 persons (76.2 %) of the 500 subjects initially recruited from 1993–94 were reassessed at the 3rd examination wave. Subjects who met the criteria for other mental disorders such as major depression ($n=6$), anxiety disorders ($n=16$), substance abuse ($n=3$), VaD ($n=4$), or MCD ($n=29$) at t3 were excluded from the analyses, leading to a reduced sample size of 323 subjects. Complete data sets were available for 300 participants: 24 subjects fulfilled criteria for AD, 102 for MCI, and for 174 control subjects with no mental disorders. All of these subjects were cognitively unimpaired at baseline.

Demographic and clinical characteristics of the diagnostic groups are provided in Table 1. There were no significant gender-specific differences in the remaining sample. AD patients were slightly older than controls; this difference gained significance due to the large sample size and low standard deviations. MMSE scores differed significantly among all three groups with AD patients scoring lowest, followed by the MCI and the control groups respectively. The mean SDS score of our sample was 33.4 points (SD = 6.7, Range: 20–52). MCI patients scored significantly higher on the SDS scale than AD patients and controls – however, their scores were still within the normal range ($M=35.3$, SD = 6.6).

Participants of the control group differed significantly from MCI/AD patients in terms of educational and socio-economic background. Our results show that controls enjoyed more years of education and were more likely to obtain a high SES score.

The number and type of self-reported sport activities are provided in Table 2. The percentage of subjects who reported to be physically active at t1 was higher in controls (35.6%) than in patients (MCI: 27.5%; AD: 33.3%); however this difference did not reach significance level ($\chi^2[2]=1.96$, $p=0.37$). Accordingly, no significant differences between the diagnostic groups were evident when comparing subjects concerning their self-reported lifetime PA ($\chi^2[4]=3.44$, $p=0.49$)[2]. The sample of our study showed a mean BMI score of 26.4 (SD = 3.5) which indicates preobesity according to WHO criteria [38]. Again, there were no significant differences between the diagnostic groups. Additionally no significant differences concerning handgrip strength were detected when comparing the diagnostic groups. However, con-

[2] Breaking up PA into quartiles did not change the pattern of results.

Table 1
Demographic and clinical characteristics of the diagnostic groups

Mean ± SD / n (%)	Controls (A)	MCI (B)	AD (C)	Tukey or χ^2	df	*Post-hoc* test
n	174	102	24			
Age	74.1 ± 1.1	74.4 ± 1.1	74.9 ± 1.1	F = 7.07**	2	A = B,B = C, *A* < C
Female sex	88 (50.6)	50 (49.0)	10 (41.7)	χ^2 = 0.68	2	
Education years	13.8 ± 3.0	12.1 ± 2.1	11.7 ± 2.4	F = 15.29***	2	A > B, C
SES						
High	49 (28.2)	15 (14.7)	1 (4.2)	χ^2 = 19.87***	4	
Medium	106 (60.9)	69 (67.6)	14 (58.3)			
Low	19 (10.9)	18 (17.7)	9 (37.5)			
T1 BMI	26.4 (3.4)	26.5 (3.2)	26.7 (4.9)	F = 0.09	2	
T1 Handgrip strength	86.3 (30.4)	84.4 (28.3)	86.4 (21.5)	F = 0.14	2	
T1 One foot balance test						
Successful	145 (83.3)	70 (68.6)	15 (62.5)	χ^2 = 10.70**	2	
Unsuccessful	29 (16.7)	32 (31.4)	9 (37.5)			
T1 Physical activity (PA)						
Active	62 (35.6)	28 (27.5)	8 (33.3)	χ^2 = 1.96	2	
Inactive	112 (64.4)	74 (72.5)	16 (66.7)			
T1 Lifetime PA						
Always active	18 (10.3)	8 (7.9)	4 (16.7)	χ^2 = 3.44	4	
Never active	46 (26.5)	34 (33.3)	8 (33.3)			
Not continually active	110 (63.2)	60 (58.8)	12 (50.0)			
SDS-Score	32.3 ± 6.3	35.3 ± 6.6	33.8 ± 8.1	F = 6.44**	2	A = C, *A* < B, *B* = C
T3 MMSE	28.9 ± 1.2	28.0 ± 1.4	23.9 ± 2.5	F = 125.63***	2	A > B > C
T3 WMS 1	25.5 ± 5.0	17.4 ± 4.6	10.5 ± 4.5	F = 143.13***	2	A > B > C
T3 WMS 2	22.5 ± 4.9	13.0 ± 4.3	5.9 ± 3.8	F = 197.08***	2	A > B > C
T3 TMT-A	33.3 ± 10.0	42.8 ± 15.4	69.7 ± 51.2	F = 36.39***	2	A < B < C
T3 TMT-B	91.1 ± 28.4	133.0 ± 49.3	219.7 ± 120.1	F = 66.93***	2	A < B < C

Abbreviations: AD = Alzheimer's disease; MCI = mild cognitive impairment; SD = standard deviation; *df* = degrees of freedom; SES = socioeconomic status; BMI = Body Mass Index; SDS = Self-rating Depression Scale; MMSE = Mini Mental State Examination; WMS = Wechsler Memory Scale; TMT = Trail Making Test; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2
Number and type of sport activities (t1)

	TOTAL	1 Activity	2 Activities	3 Activities	No Activity
N	300	67	45	42	146
Swimming	73	16	29	28	–
Gymnastics	55	17	14	24	–
Hiking	47	7	17	23	–
Cycling	33	5	7	21	–
Bowling	21	8	8	5	–
Skiing	15	3	2	10	–
Tennis	9	1	1	7	–
Fitness training	4	3	0	1	–
Others	26	7	12	7	–

Comment: Subjects were asked to indicate up to 3 sport activities using open-ended questions.

trol subjects were significantly more likely to pass the OFBT than subjects with an MCI/AD diagnosis ($\chi^2[2] = 10.70$, $p < 0.01$). Objective and subjective measures were not correlated except for very low correlations between t1 and lifetime PA, handgrip strength and PA as well as handgrip strength and OFBT (Table 3).

Next, a logistic regression analysis was performed in order to investigate the potential impact of the objective and subjective PA/PF scores at t1 regarding MCI/AD diagnosis at t3. As the correlations between the independent variables only ranged between $r = -0.14$ and $r = 0.18$ we decided to include all objective and subjective measures of PF into our regression model. Education, SES, BMI, gender and depressive symptoms were entered into the model as potentially confounding variables (Table 4). Subjects who passed the OFBT at t1 reduced their risk of developing MCI/AD by *65% (OR = 0.35, 95%CI = 0.19–0.66, $p < 0.01$). Moreover, high education and high SES showed an even stronger protective effect in our sample. However, handgrip strength and subjective

Table 3
Correlation between the subjective measures of physical activity and subjective measures of physical fitness (t1)

r/p	PA	Lifetime PA	BMI	OFBT	Handgrip strength
PA	1	**0.161**	0.028	–0.036	**0.179**
		0.005	0.630	0.536	**0.002**
Lifetime PA		1	0.019	0.022	0.098
			0.739	0.698	0.095
BMI			1	0.058	–0.063
				0.314	0.280
OFBT				1	**–0.141**
					0.016
Handgrip strength					1

Abbreviations: PA = physical activity; BMI = Body Mass Index; OFBT = One foot balance test.

Table 4
Subjective and objective indicators of physical activity (t1) and prevalence of MCI/AD (t3). OR scores adjusted for gender, education, SES and depressive symptoms

	OR	95 % CI	χ^2
Education			
high versus low	**0.15**	**0.06 – 0.40**	14.20***
high versus medium	**0.22**	**0.11 – 0.46**	16.16***
medium versus low	0.68	0.32 – 1.44	1.02
SES			
high versus low	**0.32**	**0.13 – 0.83**	5.45**
high versus medium	0.50	0.24 – 1.06	3.28
medium versus low	0.64	0.31 – 1.32	1.45
T1 BMI	1.01	0.94 – 1.09	0.10
T1 Handgrip strength	1.00	0.99 – 1.01	0.91
One foot balance test (OFBT)			
successful versus unsuccessful	**0.35**	**0.19 – 0.66**	10.63**
Physical activity			
active versus inactive	0.93	0.45 – 1.90	0.04
Lifetime PA			
always versus never	1.25	0.38 – 4.06	0.14
always versus not continually	1.24	0.46 – 3.32	0.18
not continually versus never	1.01	0.54 – 1.90	0.00

Abbreviations: OR = Odds ratio; CI = confidence interval; PA = physical activity; SES = Socioeconomic Status; BMI = Body Mass Index; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

measures of PA at t1 did not predict MCI/AD development at t3.

In order to investigate the association of the performance on the OFBT at t1 and neuropsychological test scores over time, a repeated MANOVA was calculated. The OFBT (t1) and the cognitive diagnosis (t3) served as independent variables while neuropsychological test scores (t1, t2, t3) were used as dependent variables (Table 5). The main effect of the cognitive diagnosis was significant for all neuropsychological measures. MCI/AD subjects scored significantly lower at all examination waves when compared to healthy controls even though all the participants were initially healthy. Moreover, subjects who did not pass the OFBT at t1 scored significantly lower on most neuropsychological measures. Interaction effects between time and diagnosis were significant for spatial orientation, abstract thinking, and the number connection test. Significant interactions between time, diagnosis and OFBT were detected for the number connection test and the word list immediate recall task.

DISCUSSION

The present study revealed the following major findings: Participants who passed the OFBT at t1 lowered their risk of developing MCI/AD by 65% in the 12-year follow-up. Moreover, they showed better test performance on most neuropsychological measures throughout the three examination waves. This effect was independent from the participants' cognitive status at t3. In contrast, handgrip strength, as well as self-reported current and lifetime PA, at t1 did not predict the development of MCI/AD at t3. Moreover, there were no significant differences in the neuropsychological test performance of self-reported active compared to inactive subjects (data not provided).

Our results indicate that objective, skill-related measures of PF serve as better predictors of cognitive impairment than health-related objective measures of PF and self-reported measures of PA in our sample. This result may be one explanation why some previous studies detected a protective effect of PA [13–18] while others did not report an association [19–21]. Subjective measures are likely to be biased by social desirability as subjects may tend to report being more physically active than they actually are. The assessment of lifetime PA by retrospective data may be even more biased – especially when considering that episodic memory declines with age. Another possibility why PA was not predictive of cognitive impairment, as it has been demonstrated by prior studies, is that the effect sizes of subjective measures are relatively small so that more participants would be needed to detect an effect. Another possibility is that our questions differed from previous studies and thus no effect of PA was detected. Moreover, differences concerning the self-perception of PA across countries cannot be completely ruled out, as this is the first study on PA which refers to a German cohort.

In our study context, motor coordinative aspects of PF predicted MCI/AD development while muscular strength did not show a predictive effect. This result suggests that even small dysfunctions in motor coordination might be a very sensitive and useful tool to

Table 5
Repeated multivariate analysis of variance (MANOVA): OFBT (t1), cognitive diagnosis (t3) and neuropsychological measures (t1-t3)

Mean ± SD	Controls		MCI / AD		Main effect diagnosis (D)	Main effect OFBT	Main effect time (T)	Interactions
	OFBT+ $n = 145$	OFBT – $n = 29$	OFBT+ $n = 85$	OFBT – $n = 41$				
Word list immediate recall								
T1	5.7 ± 1.1	5.8 ± 1.0	5.0 ± 1.2	4.4 ± 1.3	F = 28.12***	F = 3.78*	F = 16.45***	T*D: $F = 0.20$
T2	5.8 ± 1.5	5.8 ± 1.1	5.2 ± 1.5	4.6 ± 1.2				T*OFBT: $F = 0.21$
T3	5.4 ± 1.7	4.8 ± 1.7	4.3 ± 1.4	4.3 ± 1.7				T*D*OFBT: 4.00*
Word list delayed recognition								
T1	6.3 ± 2.3	7.1 ± 2.2	5.3 ± 2.5	5.8 ± 2.8	F = 37.17***	F = 0.64	F = 0.19	T*D: $F = 2.06$
T2	6.8 ± 2.2	7.3 ± 2.3	5.3 ± 5.5	5.3 ± 3.0				T*OFBT=0.60
T3	6.7 ± 2.4	7.5 ± 1.9	5.4 ± 2.3	4.9 ± 3.2				T*D*OFBT: 0.61
Spatial orientation								
T1	24.3 ± 5.1	22.0 ± 6.0	19.9 ± 6.6	18.9 ± 6.9	F = 27.99***	F = 7.82**	F = 34.67***	T*D: $F = 5.46$**
T2	23.2 ± 5.8	21.3 ± 5.3	18.2 ± 6.8	16.4 ± 7.1				T*OFBT: $F = 1.36$
T3	22.4 ± 5.7	20.2 ± 5.6	17.9 ± 7.6	14.0 ± 7.1				T*D*OFBT: 2.17
Information								
T1	17.3 ± 4.4	16.6 ± 3.5	14.6 ± 5.0	12.8 ± 4.8	F = 33.26***	F = 9.01**	F = 1.34	T*D: $F = 2.27$
T2	17.7 ± 4.0	17.6 ± 3.3	14.8 ± 5.1	12.8 ± 4.5				T*OFBT: $F = 0.42$
T3	18.0 ± 3.7	16.9 ± 3.8	15.1 ± 5.1	12.1 ± 4.4				T*D*OFBT: 0.91
Attention/Concentration (D2)								
T1	412.2 ± 77.4	404.0 ± 70.6	329.3 ± 66.6	345.3 ± 65.0	F = 53.15***	F = 0.00	F = 80.22***	T*D: $F = 0.18$
T2	412.5 ± 75.0	403.5 ± 63.6	330.3 ± 73.2	325.8 ± 76.1				T*OFBT: $F = 0.24$
T3	366.2 ± 73.7	365.5 ± 53.6	285.8 ± 74.2	281.6 ± 77.2				T*D*OFBT: 0.60
Abstract thinking								
T1	27.4 ± 3.2	26.5 ± 3.3	23.5 ± 6.0	21.9 ± 6.4	F = 60.86***	F = 8.09**	F = 10.43***	T*D: $F = 7.66$**
T2	27.1 ± 3.6	26.0 ± 4.5	22.4 ± 6.6	19.8 ± 6.9				T*OFBT=0.27
T3	27.0 ± 4.1	26.4 ± 3.0	22.0 ± 6.5	18.9 ± 7.3				T*D*OFBT: 1.77
Block Design								
T1	30.3 ± 8.1	28.3 ± 7.7	24.4 ± 7.2	24.6 ± 7.7	F = 22.69***	F = 4.58*	F = 39.03***	T*D: $F = 2.80$
T2	27.7 ± 7.9	23.4 ± 8.7	22.0 ± 8.0	21.1 ± 8.0				T*OFBT: $F = 1.60$
T3	27.3 ± 7.0	25.4 ± 6.0	21.4 ± 9.5	19.3 ± 7.4				T*D*OFBT: 1.24
Number-Connection Test								
T1	20.9 ± 6.7	22.1 ± 7.9	26.1 ± 8.6	27.4 ± 9.1	F = 43.86***	F = 3.63*	F = 9.37***	T*D: $F = 11.01$***
T2	21.2 ± 7.7	25.9 ± 12.2	27.1 ± 8.1	27.3 ± 9.1				T*OFBT: $F = 1.19$
T3	21.8 ± 4.9	21.8 ± 4.5	29.6 ± 9.7	32.1 ± 12.0				T*D*OFBT: 7.00**

Abbreviations: OFBT = One foot balance test; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

predict cognitive disorders in the elderly. Our results are supported by other studies which showed that motor coordination dysfunctions as assessed by neurological soft signs [39, 40] and poor equilibrium and limb coordination [41] are associated with MCI/AD. The association between muscle strength and MCI/AD risk has been rarely addressed. Our study contradicts the results of a previous study which reported an association between poor muscle strength and AD risk [42]. However, this study relied on a complex muscle strength measures covering the whole body, which might explain the differential results.

Our results indicate that skill-related PF acts as an independent protective factor preventing MCI/AD development. The protective effect of skill-related PF remained significant after accounting for gender, education, SES, and depressive symptoms, thereby confirming the variable's protective impact. Skill-related PF, education and SES independently acted as protectors against MCI/AD development. This result supports the findings of other studies that reported a protective impact of education [1, 14] and SES [43, 44], but is in contrast to other studies which only considered SES to be a protective factor when education was not accounted for as a confounder [45, 46]. We consider our results to be important when addressing the question whether early or late life variables have a stronger effect on dementia risk. Even though education as an early-determined variable showed the strongest protective impact in our analysis (OR = 0.15) the subjects' fitness level and SES at an average age of 62 had comparable effects on dementia risk (OR = 0.35/OR = 0.32). High education and SES might not only improve life conditions in general but may facilitate the ability and motivation to participate in certain beneficial activities which prevent cognitive disorders.

One methodological strength of our study is that we were able to prospectively investigate the impact of PF/PA on MCI/AD risk within a relatively young, initially healthy birth cohort whereas most previous studies started their first examination at a much higher average age [2, 19] or had a wide range of ages in their sample [15, 17]. The examination of birth cohorts is advantageous because it allows for the exclusion of age and cohort effects, which facilitates the interpretation of the findings – especially with respect to age-related diseases.

Another advantage of this study is the consideration of MCI as a potential prodromal state of AD in the scope of our analyses. This is especially noteworthy as other studies in this field only focused on AD as an outcome measure [2, 16]. Yet, the consideration of MCI is very important, as subjects with this diagnosis are very likely to develop subsequent AD. The strength of the reported effects might even be underestimated, as our patients have not been severely impaired at t3. Further examinations planned within the next few years might yield interesting findings with respect to this issue.

A critical point is that a low level of PF and/or PA might be a consequence rather than a cause of cognitive decline in the preclinical phase of AD. Of course, causal relationships are very difficult to determine and other, unmeasured third variables might be contributing to the reported associations. However, our prospective study relied on data of carefully screened, initially healthy subjects. In order to control for depressive symptoms, health related factors and mobility issues at t1 we adjusted our data for SDS scores and excluded participants with Parkinson's disease and other neurological and mobility disorders. As our results still remained significant, it is unlikely that these factors can explain low PF and/or PA of subjects within our sample. Another critical point is that participants that dropped-out were less educated than those that stayed involved in the study. Thus, we cannot completely rule out that our results might be biased by a more educated sample.

In summary, this study showed a significant reduction of MCI/AD risk during 12 years of follow-up in 300 initially healthy, community-dwelling subjects who passed a motor-coordinative PF test at the beginning of the study. In contrast, muscle strength and self-reported levels of PA did not predict the development of cognitive impairment. Our findings suggest that objective skill-related measures of PA/PF may be a much more useful tool than relying on self-reported measures. Moreover, our results underline the importance of choosing sensitive measures of objective PF as motor-coordination but not muscle strength predicted MCI/AD development. Along these lines, aerobic capacity is another important component of PF and has been shown to be related to both cognitive and brain function in non-demented adults [11], but was not measured in this study. As some research suggests that aerobic fitness might be more important than non-aerobic fitness for the presentation of cognitive impairment and brain atrophy [10], it will be important for future studies to examine the effect of objective measures of aerobic fitness in comparison to the effect of motor-coordination measures as studied here. Thus, we would suggest to include objective measures of motor-coordination and aerobic capacity in future studies when examining the impact of PA on dementia risk. However, our finding that a relatively simple measure of balance as a marker for PF could be predictive of dementia is very important and one that needs to be studied further. Detecting safe and inexpensive predictors for dementia is surely relevant for both, clinical practice and epidemiological studies with large sample sizes.

The reported findings have very important practical implications with regard to prevention and early intervention strategies. Promoting the importance of PF during leisure time (e.g., by training motor-coordination) might be a successful prevention strategy which can be carried out relatively easily on an individual level.

Further studies need to be undertaken for a better understanding of the underlying mechanisms which mediate the protective impact of PF on brain structures. Particularly, physical training studies will be very important as they have the potential to identify and verify long-term beneficial effects originating from PF and PA.

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REFERENCES

[1] Fratiglioni L, Wang H-X (2007) Brain Reserve Hypothesis in Dementia. *J Alzheimers Dis* **12**, 11-22.

[2] Karp A, Paillard-Borg S, Wang H-X, Silverstein M, Winblad B, Fratiglioni L (2006) Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dement Geriatr Cogn Disord* **21**, 65-73.

[3] Tabbarah M, Crimmins EM, Seeman TE (2002) The Relationship Between Cognitive and Physical Performance: MacArthur Studies of Successful Aging. *J Gerontol A Biol Sci Med Sci* **57**, 228-235.

[4] Yaffe K, Barnes D, Nevitt M, Lui L-Y, Covinsky K (2001) A Prospective Study of Physical Activity and Cognitive Decline in Elderly Women: Women Who Walk. *Arch Intern Med* **161**, 1703-1708.

[5] Weuve J, Kang JH, Manson JE, Breteler MMB, Ware JH, Grodstein F (2004) Physical Activity, Including Walking, and Cognitive Function in Older Women. *JAMA* **292**, 1454-1461.

[6] Colcombe SJ, Kramer AF (2003) Fitness effects on the cognitive function of older adults: A Meta-Analytic study. *Psychol Sci* **14**, 125-130.

[7] Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer AF, Greenough WT (2002) Exercise, experience and the aging brain. *Neurobiol Aging* **23**, 941-955.

[8] Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP (2008) Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA* **300**, 1027-1037.

[9] van Uffelen JGZ, Chinapaw MJM, van Mechelen W, Hopman-Rock M (2008) Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. *Br J Sports Med* **42**, 344-351.

[10] Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR (1999) Ageing, fitness and neurocognitive function. *Nature* **400**, 418-419.

[11] Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, Elavsky S, Marquez DX, Hu L, Kramer AF (2006) Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* **61**, 1166-1170.

[12] Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W (2006) Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med* **144**, 73-81.

[13] Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K, Sueishi K, Tsuneyoshi M, Fujishima M (1995) Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: The Hisayama Study. *Neurology* **45**, 1161-1168.

[14] Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I (2002) Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* **156**, 445-453.

[15] Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H (2004) Walking and dementia in physically capable elderly men. *JAMA* **292**, 1447-1453.

[16] Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, Lyketsos CG (2005) Physical activity, APOE genotype, and dementia risk: Findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol* **161**, 639-651.

[17] Rovio S, Kåreholt I, Helkala E-L, Viitanen M, Winblad B, Tuomilehto J, Soininen H, Nissinen A, Kivipelto M (2005) Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol* **4**, 705-711.

[18] Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* **58**, 498-504.

[19] Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Ambrose AF, Sliwinski M, Buschke H (2003) Leisure activities and the risk of dementia in the elderly. *N Engl J Med* **348**, 2508-2516.

[20] Wilson RS, Mendes de Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA (2002) Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* **287**, 742-748.

[21] Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G (2003) Association between dementia and midlife risk factors: The Radiation Effects Research Foundation Adult Health Study. *J Am Geriatr Soc* **51**, 410-414.

[22] Andel R, Crowe M, Pedersen NL, Fratiglioni L, Johansson B, Gatz M (2008) Physical exercise at midlife and risk of dementia three decades later: A population-based study of Swedish twins. *J Gerontol A Biol Sci Med Sci* **63**, 62-66.

[23] Martin P, Martin M. (2000) Design und Methodik der Interdisziplinären Längsschnittstudie des Erwachsenenalters In *Aspekte der Entwicklung im mittleren und höheren Erwachsenenalter: Ergebnisse der Interdisziplinären Längsstudie des Erwachsenenalters (ILSE)*, Martin P, Ettrich KU, Lehr U, Roether D, Martin M, Fischer-Cyrulies A, eds. Steinkopff, Darmstadt, pp. 17-27.

[24] Wittchen HU, Zaudig M, Sprengler P eds. (1991) *SKID: Strukturiertes klinisches Interview für DSM-III-R*, Beltz Test, Weinheim.

[25] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state" : A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[26] Wechsler D (2000) *Wechsler Gedächtnistest - revidierte Fassung. Deutsche Adaption der revidierten Fassung der Wechsler Memory Scale*, Huber, Bern,Göttingen Toronto.

[27] Reitan C (1992) *The Trail Making Test: Manual for administration and scoring*, The Reitan Neuropsychological Laboratory, Tucson.

[28] Oswald WD, Fleischmann VM (1991) *Nürnberger-Alters-Inventar*, Universität Erlangen-Nürnberg, Erlangen-Nürnberg.

[29] Horn WC (1983) *Leistungsprüfsystem*, Hogrefe, Göttingen.

[30] Schönknecht P, Pantel J, Kruse A, Schröder J (2005) Prevalence and natural course of aging-associated cognitive decline in a population-based sample of young-old subjects. *Am J Psychiatr* **162**, 2071-2077.

[31] Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, Buchner D, Ettinger W, Heath GW, King AC, Kriska A, Leon AS, Marcus BH, Morris J, Paffenbarger RS, Jr, Patrick K, Pollock ML, Rippe JM, Sallis J, Wilmore JH (1995) Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* **273**, 402-407.

[32] Innes E (1999) Handgrip strength testing: A review of the literature. *Aust Occup Ther J* **46**, 120-140.

[33] Martin Medizin-Technik ed. (1999) *Vigorimeter - Gebrauchsanweisung*, Eigendruck, Tuttlingen.

[34] Zung WW (1965) A self-rating depression scale. *Arch Gen Psychiatry* **12**, 63-70.

[35] Schröder J, Kratz B, Pantel J, Minnemann E, Lehr U, Sauer H (1998) Prevalence of mild cognitive impairment in an elderly community sample. *J Neural Transm Suppl* **54**, 51-59.

[36] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[37] Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo J-M, Brun A, Hofman A, Moody DM, O'Brien MD, Yamaguchi T, Grafman J, Drayer BP, Bennett DA, Fisher M, Ogata J, Kokmen E, Bermejo F, Wolf PA, Gorelick PB, Bick KL, Pajeau AK, Bell MA, DeCarli C, Culebras A, Korczyn AD, Bogousslavsky J, Hartmann A, Scheinberg P (1993) Vascular dementia: Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop. *Neurology* **43**, 250-260.

[38] Weltgesundheitsorganisation, BMI classification, http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed 22.06.2010.

[39] Seidl U, Thomann PA, Schroder J (2009) Neurological soft signs in nursing home residents with Alzheimer's disease. *J Alzheimers Dis* **18**, 525-532.

[40] Schröder J, Niethammer R, Geider FJ, Reitz C, Binkert M, Jauss M, Sauer H (1991) Neurological soft signs in schizophrenia. *Schizophr Res* **6**, 25-30.

[41] Franssen EH, Souren LE, Torossian CL, Reisberg B (1999) Equilibrium and limb coordination in mild cognitive impairment and mild Alzheimer's disease. *J Am Geriatr Soc* **47**, 463-469.

[42] Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA (2009) Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. *Arch Neurol* **66**, 1339-1344.

[43] Anttila T, Helkala EL, Kivipelto M, Hallikainen M, Alhainen K, Heinonen H, Mannermaa A, Tuomilehto J, Soininen H, Nissinen A (2002) Midlife income, occupation, APOE status, and dementia: a population-based study. *Neurology* **59**, 887-893.

[44] Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R (1994) Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* **271**, 1004-1010.

[45] Karp A, Kareholt I, Qiu C, Bellander T, Winblad B, Fratiglioni L (2004) Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease. *Am J Epidemiol* **159**, 175-183.

[46] Evans DA, Hebert LE, Beckett LA, Scherr PA, Albert MS, Chown MJ, Pilgrim DM, Taylor JO (1997) Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. *Arch Neurol* **54**, 1399-1405.