Muscle Fitness as a Predictor for later Cognitive Performance

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Number of character (including spaces): 71.955

Thesis extent: 30 ECTS

Submitted: 01.06.2016

UNIVERSITY OF SOUTHERN DENMARK

This thesis is printed by Print & Sign, SDU

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Acknowledgements:

This thesis is based on the work conducted at the institute Centre of Research In Childhood Health, University of Southern Denmark during the period 2008-2015.

Especially I would like to thank:

Niels Wedderkopp, my supervisor, for your valuable inspiration, support, and supervision.

Anna Bugge, for your support, feedbacks, and constructive discussions.

Jakob Tarp, for your help with the statistics

All people in RICH, for receiving me with open arms

List of abbreviations:

ADHD	Attention Deficit Hyperactivity Disorder
AF	Aerobic Fitness
BDNF	Brain-derived Neurotrophic Factor
BMI	Body Mass Index
CI	Confidence Interval
CRF	Cardio-Respiratory Fitness
EF	Executive Functions
FGF-2	Fibroblast Growth Factor-2
FT	Flanker Task
HG	Hand Grip
IGF-1	Insulin-like Growth Factor-2
MEFT	Modified Eriksen Flanker Task
MF	Muscle Fitness
MSEC	Milliseconds
NS	Normal Schools
PA	Physical Activity
PF	Physical Fitness
PFC	Prefrontal Cortex
RA	Response Accuracy
RCT	Randomized Controlled Trials
RT	Reaction Time
SD	Standard Deviation
SR	Shuttlerun
SES	Socio-Economic Status
SS	Sports Schools
VEGF	Vascular Endothelial Growth Factor
WM	Working Memory

English summary:

Title: Muscle fitness as a predictor for cognition *by* Trine Muckert

Background: A great number of Danish students have problems in school. 15 % of the students do not have functional reading skills, and 17 % have a lack of mathematics and science skills when leaving the Danish primary school. Additionally the cost for special education in Denmark has increased from 5.1 % in 1995 to 13.3% in 2010 of the total expenses within the primary school area, which are equivalent to 5.5 billion kr. Furthermore, the prevalence of students who receive special education has been increasing during the period 2007-2009 from 27.207 to 32.159 students. Despite consensus of the positive effects related to PA and cognition, the impact of MF on cognition remains unclear.

Objective: To examine the associations of selected individual muscle fitness tests and overall muscle fitness with cognitive function, focusing on executive functions, in Danish children aged 5-17 years.

Methods: A retrospective cohort study was carried out. Cross-sectional and longitudinal analyses were conducted with data on 1327 (53% female) school children age 5-17 years (mean age 8.4-12.7 yr.) from 10 schools. Handgrip, Shuttlerun, and Vertical Jump were used to asses muscle fitness. A modified Eriksen Flanker task was used to assess inhibitory control, a key aspect of executive functions.

Results: Overall, the longitudinal and cross-sectional association between muscle fitness and cognition is weak and inconsistent without any trend, which is similar to other studies on children, but differ from those observed in elderly.

Discussion: This study has ability to provide new insight on the association between muscle fitness and cognition in children due to the large sample and the ongoing follow-ups, although Flanker is only measured once. The question is whether cognition and not fine motor skills and coordination are measured, when using Flanker and if the results is due to chance.

Perspective: This study may have educational relevance, but further research with baseline and follow-up measurements on cognition is needed.

Keywords: Muscle fitness, cognition, inhibitory control, executive functions, children

Dansk resume:

Titel: Muskel fitness som prædiktor for senere kognition *af* Trine Muckert

Baggrund: En stor del af danske elever har problemer i skolen. 15 % af eleverne har ikke tilfredsstillende læsefærdigheder, og 17 % har problemer med matematik og fysisk, når de forlader folkeskolen. Desuden er udgifterne til specialundervisning steget fra 5.1 % i 1995 til 13.3 % i 2010 af de totale udgifter til folkeskoleområdet, svarende til 5.5 milliarder kr. Endvidere er prævalensen af elever, der modtager specialundervisning, steget i perioden 2007-2009 fra 27.207 til 32.159 elever.

På trods af enighed om fysisk aktivitets positive effekt på kognition, er påvirkningen af muskel fitness stadig ukendt.

Målsætning: At undersøge associationen mellem udvalgte muskelstyrketests og samlet muskelstyrke og kognition med fokus på eksekutive funktioner.

Metode: Et retrospektiv kohortestudie blev gennemført. Tværsnits og longitudinal analyse af 1327 (53% piger) børn i alderen 5-17 år (mean age 8.4-12.7 år), fra 10 skoler. Hangrip, Vertical Jump og Shuttlerun blev brugt til at måle muskel fitness. En modificeret Eriksen Flanker test blev brug til at måle inhiberisk kontrol, et nøgleaspekt af eksekutive funktioner.

Resultater: Associationen mellem muskel fitness og kognition er svag og inkonsistent uden nogen trend både longitudinelt og tværsnits, hvilket er sammenligneligt med andre studier på børn men afviger fra fund på ældre.

Diskussion: Studiet har mulighed for at give indsigt i sammenhængen mellem muskel fitness og kognition hos børn pga. stor sample og gentagne opfølgninger. Spørgsmålet er, om der reelt måles på kognition og ikke finmotorik og koordination, og om fundene skyldes tilfældigheder?

Perspektivering: Studiet kan have uddannelsesmæssig relevans, men der er brug for yderligere forskning med baseline og follow-up måling på kognition.

Nøgleord: Muskelstyrke, kognition, inhibitorisk kontrol, eksekutive funktioner, børn

Introduction:

There is strong evidence linking physical activity (PA) and physical fitness (PF) to improved cognitive function, lower risk of obesity and diseases in both adults and children [1-3]. Recently, there has been an increased research studying the relationship between PF, including muscle fitness (MF) and cognitive functions in children. Cognitive function is associated with the abilities of knowledge, flexibility, collaboration, and innovative thinking, which is important in order to cope with the increasing demands of society, the labor market, and the global world. Furthermore, learning disabilities are a consequence of poor cognitive function, like learning is related to cognitive functions, which according to Adele Diamond have an impact on how you perform later in life e.g. better grades and education [4, 5]. Genes, phenotype, heredity, and parental stimulus are possible links to learning disabilities and executive functioning issues [6, 7]. A great number of Danish students have problems in school. 15 % of the students do not have functional reading skills, and 17 % have a lack of mathematics and science skills when leaving the Danish primary school [8, 9]. Additionally the cost for special education in Denmark has increased from 5.1 % in 1995 to 13.3% in 2010 of the total expenses within the primary school area, which are equivalent to 5.5 billion kr.[10]. Furthermore, the prevalence of students who receive special education has been increasing during the period 2007-2009 from 27.207 to 32.159 students [10]. Despite consensus of the positive effects related to PA and cognition [11], the impact of PF, defined as cardio-respiratory endurance, muscular endurance, MF, body composition, and flexibility [12] on cognition remains unclear.

Educational and health professionals have believed that children who are physical active and fit have a higher cognitive performance and perform better in school. Buck et al found cardio-respiratory fitness (CRF) to be positively associated with executive functions (EF) measured by Stroop task [13]. Additionally, Pontifex et al. supplemented that preadolescent children with high CRF perform better in inhibitory control measured by Flanker task (FT) compared to lower fit children [14]. According to Chaddock et al. children with higher level of CRF display better performance in task of executive control, memory [1], and inhibitory control [15]. Similarly, Scudder et al. highlights CRF being positively associated with EF measured by FT and n-back task in elementary school children [16]. In adolescent, Rutz et al. found that participation in leisure-time PA was associated with better cognitive performance, and cognitive function. However, no association was found between CRF, MF, and cognitive performance [17]. Therefore, several aspects of PF e.g. MF in relation to cognition and especially inhibition need further investigation because the function is crucial when to stay focused on a task and therefore the ability to learn [18].

Smith et al [2] and Khan et al [11] conducted systematic reviews examining the association between PA and MF and cognition. Additionally, a cohort study of Åberg et al. with conscripts detected no association between MF and cognition [19]. Despite the fact that cognition has been linked to four different health-related components of PF [12], most exercise interventional studies have used aerobic exercise when observing cognitive benefits, especially in task requiring executive control/EF [20, 21]. Therefore, less is known, about the association and correlation between MF, and cognition [22].

Recently research has been targeted at understanding the effects of PF and PA on cognitive functions and brain plasticity in children and older people. The evidence has linked aerobic PA to specific EF, but the current opinion remains divided as to the causal link between and gains from aerobic fitness and cognitive control [23-25]. There is an ongoing search for the potential mediators of PA's effect on cognition, and there is an emerging evidence pointing at the benefits of resistance training [26, 27]. Colcombe et al. highlights that the greatest effect of PA on cognition occurred when combining with resistance training [20] supported by Liu-Ambrose et al. and Cassilhas et al. showing that resistance training benefited the executive function (EF) of selective attention and conflict resolution [28, 29]. However, in men, an effect is shown after 6 months and in women, an effect is shown in 12 months. Therefore, it is also relevant to consider the importance of sex. It has to be noted that most of the studies on MF in relation to cognition are performed on older people aged 65 or more. Adolescence and old age are critical periods for brain development due to age-related changes where morphological, functional, hemodynamic, and psychological changes reduce the ability to adapt to the environment and the onset of pathological processes with muscle mass and strength decreasing [30]. Furthermore, aging is associated with a decrease of gray matter volume, which is closely related to cognitive functions [31, 32]. Therefore, these findings can not be generalized into children and more research is needed in order to draw any conclusion.

According to Hillman et al [13, 33, 34] PF and especially aerobic fitness (AF) can impact brain structure, brain functions, and cognition, because of increased blood flood of the brain [35], neural growth and the neural systems involved in cognitive processes e.g. learning and memory, especially EF [33]. AF at lactic acid stage releases hormones which improve the secretion of neurotransmitters in the Central Nervous System which contributes to an improved arousal followed by a reinforcement of the cognitive performance including the EF [36]. The level of synaptic proteins and several classes of growth factor e.g. brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) increase, which can enhance the plasticity of the brain, especially in the Hippocampus [37]. These are hormones which can be linked to MF, because moving muscles produces IGF-1 and Vascular

Endothelial Growth Factor (VEGF) that travel through the bloodstream and into the brain where they play a role in the mechanisms of cognition/cognitive performance [38]. This relates to the knowledge that higher level of AF is associated with significantly improved performance on the cognitive tasks [13, 34]. Furthermore, Kohl et al. has published a conceptual framework illustrating relationships among PA, PF, health, and cognitive function, which shows an independently relationship between PA, PF and health, and cognitive function/academic performance [39].

Overall, evidence showing an association between MF and cognitive function is scarce. A systematic search only found few studies investigating the possible association between MF and cognition in children and adolescents. Additionally, to our knowledge no evidence could be found that the relationship between MF/PF and cognition has been investigated in Danish children. The paucity of longitudinal and experimental studies prevents being able to draw a conclusion on causal relationship between MF and cognition. Therefore, longitudinal and cross-sectional studies analyzing the association between MF and cognition, especially EF are warranted. Furthermore, studies using a broader measure of cognition and current follow-ups are important to gain sufficient insight into the link between MF and cognition [40].

The present context of school and health issues in children makes examination of a possible relationship between MF and cognition timely, as politicians have increased pressure on teachers to produce students who achieve a basic level of especially reading, mathematics, and science [41]. Accordingly, the purpose of this thesis is to evaluate the longitudinal and cross-sectional association between MF and cognitive performance in Danish children.

Objectives:

The objectives of this thesis are to investigate whether in Danish children aged 5-17 years:

1. Selected individual muscle fitness tests are associated with cognitive function focusing on executive functions.
2. Overall muscle fitness is associated with cognitive function focusing on executive functions.

Hypothesis:

Based on the above mentioned objectives a hypothesis is made:

- Muscle fitness during childhood and youth is cross-sectionally and longitudinally associated with cognitive function.

Theoretical background:

MF, development of the cognitive functions, EF and inhibition will be described in this section. One of the challenges by studying cognition and executive functioning is, that there are different ways of describing the terms in order to understand, which mechanisms underlie the possible link/association between muscle fitness and EF. In this thesis, it has been chosen to base the theoretical background on the accepted theories of Adele Diamond, Akira Miyakes, and Charles H. Hillman, which is based on a great amount of research on EF and PA.

Cognition:

Cognition is a complex term and is a set of mental abilities and processes related to for example perception, attention, memory, EF, intelligence, and academic performance [42]. It is conscious and unconscious, concrete or abstract, as well as intuitive and conceptual and processes the use of existing knowledge and generates new knowledge. Cognition covers the way we process and use the information which is constantly received and processed by the human body [42]. Therefore, it is too simplistic relating to cognition as an overall term. In this thesis, focus will be on the EF and more specific, inhibition control because it is important in order to subvert behaviors that may interfere with task performance [18] and therefor may have an impact on learning and academic performance.

Executive Functions:

The EF, also called executive control, are higher levels of cognitive processes associated with the frontal lobe of the brain. It is an important but vague term for superior cognitive processes and refers to mental processes that control and co-ordinate more fundamental processes in the effortful pursuit of goals, and is needed when you have to concentrate and pay attention. It is a flexible system responsible for the control and regulation of cognitive processes [43]. Systematic research to specify the nature, organization, and role of these functions has begun within the last few years, although the importance of the EF in complex cognition has been recognized long time ago [44]. Therefore, the knowledge of EF is limited with a great number of unanswered questions [44].

Studies in rats, monkeys, and humans agree with the view that the prefrontal cortex (PFC) contributes to executive functioning [45], or in other words the set of cognitive processes that are necessary for optimal scheduling of behavior, planning, and decision making. These abilities are crucial to all forms of cognitive performance [46]. Therefore, when kids have issues with executive functioning, any task that requires planning, organization, memory, time management, and flexible thinking becomes a challenge. Having issues with executive functioning therefore makes it difficult to: Keep track of time, make plans, multitask, apply previously learned information to solve problems, analyze ideas, and look for help or more information when it is needed [47].

There is general agreement that there are three cores EF's [5, 48, 49]:

1. Inhibition (inhibitory control and self-control) and interference control (selective attention and cognitive inhibition): Important for controlling one's behavior, attention, thoughts, and emotions [5].
2. Working memory (WM): Refers to holding information in mind while mentally working with it or updating it, and is referred to as the central executive function [42].
3. Cognitive flexibility: The ability to change perspective, focus, or attention [6]

Even though the functions are a diverse, but related and overlapping set of skills, one can clearly distinguish between the above mentioned characteristics - they are dependent on one another [44].

Inhibition:

Inhibition or response inhibition implies the ability to control attention, conduct, thoughts and emotions and are regulated by the functions of the PFC [50], one of the last regions of the brain to reach functional and structural maturation [51]. Furthermore, studies using neuroimaging have shown that impulsivity and inhibitory control are regulated of the PFC [50]. Inhibition covers being able to resist first impulse and give a more considered response, stay on a task despite boredom or the temptation to go out and play and control one's attention despite distraction, also called selective and sustained attention. If one has weak ability to stop acting on impulses, one is called impulsive [47]. The ability is crucial in order to control attention and emotions, to make discipline, and to have social politeness, and focused attention. If we do not have the ability of inhibition, we will be controlled by external stimulus, emotions, or engrained behavioral tendencies [47].

Self-control/regulation entails inhibition of impulses, and there is therefore much overlap between EF and self-control, especially the inhibitory component [47]. Studies have shown that self-control is positively associated with leisure time PA, AF, and MF [52]. Additionally, inhibition is previously found jointly sensitive to fitness and sports skills [53], and studies have shown that inhibitory efficiency is predicted by how adolescence was able to perform strategic actions and to adapt motor coordination in response to perception of environmental cues (response orientation). Additionally, a theoretical model has linked inhibition to WM, and self-regulation of affect-motivation-arousal [54]. Furthermore, factors like lower-income, lower WM span and boys are associated with poor inhibitory control [4].

Development of cognition:

Since the age of onset of learning difficulties and cognitive problems is during the childhood, and in the view of the neurodevelopmental hypothesis, the time course of normal development of cognitive functions is important to consider when investigating and understanding the association between MF and cognitive and EF deficits in children. Improvement of EF in childhood is important, because EF deficits in childhood predict problems years later. Furthermore, the dysfunction does not disappear but may increase over time [5].

During normal brain development, some cognitive functions are fully developed when children are reaching school age, and others develop throughout adolescence into early adulthood. The elementary cognitive processes are fully developed by early childhood, at age 7, such as passively holding information available for a short period in the working memory and recognition and recall from the long term memory, which are memory functions that do not place large demands on strategic recalling [55]. However, the capacity for abstract thought, planning and cognitive flexibility develop throughout adolescence [56]. The PFC undergoes one of the longest periods of development of any brain region and continues to grow, as well as myelination of cells is increased and progresses until early adulthood [57].Furthermore, neural pathways between brain areas are further consolidated throughout adolescence [58, 59]. Marked changes occur in the abilities associated with PFC in the periods from 3-6 years and 7-11 years [55]. EF occurs in PFC, which is the thinking part of the brain, and can roughly be divided into; Lateral part of prefrontal cortex (behavioral control and planning) [60], medial part of prefrontal cortex (emotional regulation) and Cyrus cingula anterior (control of attention and autonomic nervous system) [42]. There are no primary sensory areas and storage of memory in the PFC [57]. Additionally, studies show that improvement in executive control task during childhood has been linked to development of the frontal lobe [61]. This is being supported by research of Duncan, who have examined what happens when people have a lesion in the frontal lobe. They end up with goal neglect, which can be associated with executive function capacity [62]. While some cognitive abilities, as mentioned above, develop early, EF do not reach their peak until early adulthood and puberty [63]. Studies have identified a stage-like development of EF beginning from the age of 12 months and almost all of the functions are "in action" at the age of eight. This development has been found to correlate with the development of the frontal brain region, focusing on increase on myelination and synaptogenesis [63]. The function inhibition is internalized through a cultural conditioned and social transmitted behavior [57].

Assessment of cognition and cognitive performance is not easy due to complexity. Furthermore, there are many challenges in testing children due to the biological development e.g. pubertal stages and environmental influence, which can make it difficult to assess cognition and especially EF [44, 64]. The field of cognitive psychology has developed during the last few years, and there are many ways in which assessment of cognition can be done and models and theories used in interpretating the result [64]. Despite that, there are theoretical issues or phenomena where much is unknown and one of the important ones is EF's [44]. A challenge when assessing and studying cognition is that many definitions tend to list sub-functions or sub-processes that may constitute EF. Therefore, there is no clear consensus of how to measure cognition and which task should be used in measuring EF's, and it's impossible to find a "pure" measure of the term/function [44]. Additionally, there is a great number of psychological tests e.g. Stroop task [65], Simon task [66], FT [67, 68], go/no-go tasks [69], and stop-signal tasks [70] measuring inhibitory control. There is a lack of consensus whether all these tests require and measure inhibitory control. The test used in this thesis is the Modified Eriksen Flanker task (MEFT), which is the most common used test when assessing cognitive functions in children [47, 71], which in the method section will be described extensively.

Physical fitness:

PF is defined as a state of physiologic well-being obtained by a combination of e.g. diet and physical activity. It is the ability to carry out daily tasks and perform physical activities without fatigue. The term covers AF, cardio-respiratory endurance, muscle strength and endurance. Recently the term MF is used to represent muscle strength, local muscular endurance, and muscular power [2]. According to the literature muscle strength is the ability to generate force with a group of muscles, or a muscle or the amount of external power a muscle can exert. Local muscular endurance is the ability to perform repeated contractions under submaximal load or successive exertions [12], and muscular power is equivalent to the energy output per unit of time/rate of doing the work [72]. Moving muscles produce proteins such as IGF-1 and VEGF that travels through the bloodstream and into the brain where they play a role in the mechanisms of cognition [38]. IGF-1, VEGF and BDNF are considered as key-proteins involved in various aspects of developmental and brain plasticity and are positively affected by PA [73, 74].

IGF-1 is a protein encoded by the IGF-1 gene playing an important role in childhood growth [75], and the highest rate of IGF-1 production occurs during the pubertal growth spurt [76]. The hormone stimulates cell growth and proliferation, division e.g. the AKT-signaling pathway and inhibition of cell death. Additionally, the hormone transports glucose to the muscles and the brain in cooperation with insulin [38]. IGF-1 has an impact on the increase of BDNF- receptors, which have a positive effect on the nerve cells. BDNF helps the brain increase the absorption of IGF-1 activating the production of neurotransmitters e.g. glutamate and serotonin, which have an increasing impact on neural activity of the brain [38].

Factors influencing the level of IGF-1 include e.g. insulin level, genes, age, sex, exercise status, Body Mass Index (BMI), and estrogen status [77]. IGF-1 is associated with muscle growth and strength gains [78], and the maintenance of muscle mass and strength are regulated by IGF-1 and myostatin pathways. Additionally, IGF-1 deficiency causes underdevelopment and weakness of the muscular system [75, 79]

BDNF is the neurotrophic factor that has drawn intensive attention from researchers. By activating the tropomyosin receptor kinase B, BDNF plays an important role in processes of the brain e.g. proliferation, protection of nerve cells, cognitive function, supporting growth, and the differentiation of the plasticity of the nerve cells, also called the neurogenesis [48, 80, 81]. BDNF is found in the nerve cells of the brain and is especially essential for the Hippocampus, situated in the PFC, which is associated with learning, memory and EF [33].

VEGF also known as vascular permeability factor is a signaling protein playing a role in physiological functions such as bone formation [82], neural development, developmental angiogenesis, growth [33, 83, 84] and formation of new blood. The protein also stimulates the growth of muscle after PA has been performed [85] and is upregulated with muscle contractions as a result of increased blood flow [74]. Studies have shown that IGF-1 was increased by training and markedly in subjects with high aerobic capacity [86].

Development of MF in children exhibits a gradual line increasing from age 3 until puberty for boys and until about 15 for girls [2]. Subsequently, boys increase in strength until the age of 17 and beyond, and girls show a plateauing and regression in late adolescence. The changes in MF are closely associated with changes in body size [87].

Studies on elderly have shown a positive association between cognitive performance and muscle strength [88]. Longitudinal studies have highlighted that handgrip strength is associated with accelerated decline in global cognitive performance [89, 90], higher risk of Alzheimer's disease and mild cognitive impairment [91, 92]. In relation to children, the association is yet unclear, but based on studies on elderly and the knowledge on cognitive development one will assume, the possibility for an association in children as well.

Methods:

Literature search and inclusion criteria:

PubMed, Cochrane, EMBASE, and PsykINFO were searched, and the search terms used to find the studies were variants of MF (e.g. muscular fitness, muscle strength, physical fitness) and cognitive performance (e.g. memory, cognition, executive functions, inhibition). The search terms were specially adjusted to each database and searched as free text and categorized subject term (e.g. MeSH in PubMed and keyword in EMBASE). The search covered the period from 1960 to 2015 since the number of articles published on the impact of PA and PF on cognitive functions and recently on EF has increased since the 1960s [93]. The search was performed during the period November 2015 – May 2016.

Studies retrieved from the searches were screened using the following inclusion criteria: Studies had to investigate the relationship between MF and cognition in humans, or assess the relationship between PF and cognitive function in humans/animals; and the population had to be children or adolescents. Due to the scarce literature on MF and cognitive function in relation to children, studies based on elderly were used and selected based on the used tests and the outcome measures.

Study design and data collection:

This study is based on longitudinal data from the CHAMPS Study-DK. The study design of CHAMPS-DK has been reported elsewhere in detail [94]. Briefly, the CHAMPS-DK is a cohort study conducted from 2008-2015 including students from the preschool (age 5) till 10th grade (age 17) at public schools in Denmark.

Baseline measurements were performed in September 2008 and follow-ups were made annually in 2009, 2012, 2013, and 2015 and twice a year in 2010 and 2011. Height, weight, and waist were measured at every follow-up, but measurements on e.g. MF and cognition were not performed at every follow-up (table 2). The measurements were performed by university students (i.e. master's, graduate students, and Ph.D. students) who prior to test rounds were trained by experienced researchers.

Subjects:

1327 students (males=622) aged 5-17 years (mean age=8.41, SD=1.43) attending school classes in the country council of the municipality of Svendborg (43 school classes in 10 schools) were recruited to participate in the study. All 19 schools in the area were invited to participate in the project, of which six agreed to partake. 6 sports schools were created which were compared with 4 "normal" schools of the region using the design of a "natural experiment". See table 1 for participants' characteristic information.

The study flow diagram from the initial number of students involved in CHAMPS-DK is shown in figure 1. In the duration of the study, there was an ongoing inclusion and exclusion of students. The range of the participants in the test rounds were: VJ; 690-1232, HG; 699-1159 and SR; 669-1208.

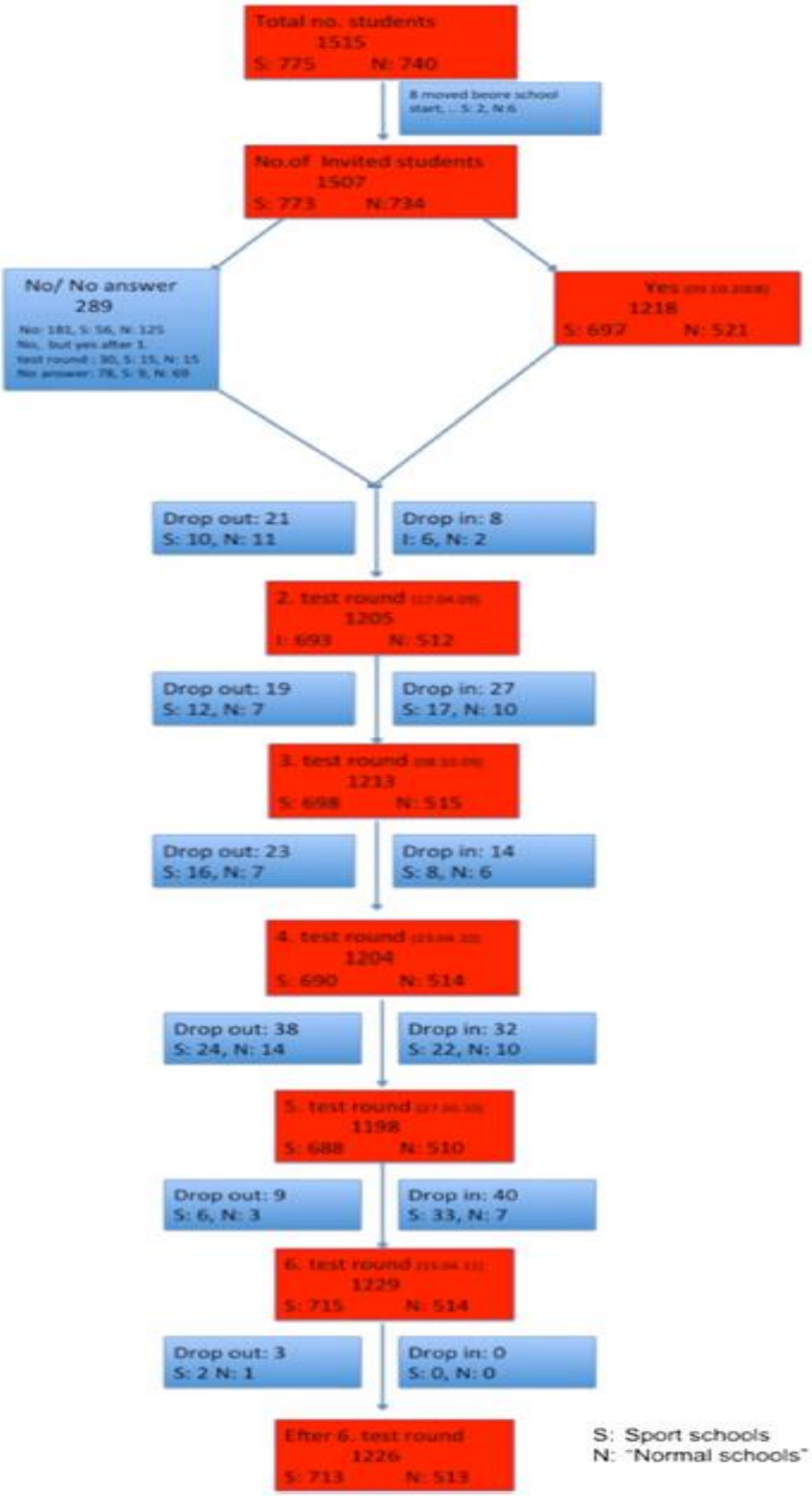

Figure 1 Flow chart of the CHAMPS-study DK, with Sport schools and normal schools.

Figure 1: Timeline of CHAMPS-DK [76]

Variables of interest:

Because the complete methodology has been previously published [95, 96], only methods and measurements pertinent to this thesis are described.

Anthropometrics:

Height and weight are measured by anthropometric standard methods. Height was measured to the nearest 0.5 cm without footwear and with light clothes on using Harpenden stadiometer (West Sussex, UK). Bodyweight was measured to the nearest 0.1 kg using an electronic scale (Tanita BWB-800, Tokyo, Japan). BMI was calculated as weight (kg) divided by height squared (m) [97].

Modified Eriksen Flanker task

Cognitive function (attentional inhibition) was assessed using a MEFT [67], which indexes the ability to resolve attentional conflict between different responses and to ignore task distracters [98] and measures EF. FT is a well-established test for higher cognitive functions such as attention and action monitoring [67] and has a high test-retest reliability and is a valid psychological test [99]. The test is previously described by Hillman [100]. Since children are tested, the task will employ arrows facing different directions rather than letters to reduce the WM requirements [101]. The task requires selective attention in order to focus on the centrally presented stimuli and to ignore the flanking stimuli surrounding it. Children have a natural tendency to focus on a salient stimulus when appearing, and in the FT children are instructed to inhibit this tendency e.g. in the incongruent trials. Incongruent trials requires higher amount of cognitive control in order to inhibit interference generated by the flanking stimuli. Therefore, children frequently will have a higher reaction time (RT) and lower response accuracy (RA) when doing the incongruent trials compared to the congruent. This difference, which is refereed as the flanker interference effect, is widely used as a measure of detection and resolution of response conflict [67]. Therefore, in this thesis the interference score of RT and RA will be interpreted as a measure of inhibition.

The task is a computer-based MEFT version consisting of congruent and incongruent trials. E-Prime 2.0 (Psychology Software Tools Inc., Sharpsburg, PA) was used for modifying and running the FT. Congruent trial consisted of five black horizontal arrows on a black screen facing the same direction (all stimuli facing the same direction), and incongruent trials consisted of four flanking arrows facing the opposite direction to that of the central arrow. Congruent stimulus is also referred to as the compatible condition and incongruent as the incompatible condition. Task difficulty is manipulated by whether the flanking arrow faces the same direction or the opposite direction to the middle arrow [95].

Participants were instructed to respond on the target arrow in the middle and respond as quickly and accurately as possible. An arrow pointing to the right “>” required a right button response, and a left arrow “<” required a left button response. The two flanker arrows on each side of the target arrow worked as distractors and would point in either same direction “>>>>>” (congruent) or opposite direction “<<><<” (incongruent). Participants received one block of 20 practice trials followed by a block of two blocks consisting of 75 trials consisting of the same amount congruent and incongruent randomized in each block. The congruent and incongruent conditions were randomly introduced. Each trial was presented for 120 milliseconds (msec) followed by a response window of 1350 msec. In order to perform a valid response, the student was to respond within 200 to 1470 msec post onset of stimuli. A random inter-stimulus interval of 1250 – 1550 msec separated each trial, and a break of 30 seconds separated each block of trials [102]. When possible, the students were tested alone in a quiet room, but due to large school classes students often were tested in a room with a few others.
Prior to testing, the instructions were given verbally [97].

The outcome measures are RT to the stimulus of the arrow (msec) and RA, which is percentage of possible trials where the correct response was selected. Students who achieved ≤ 50 % on RA where excluded from the analysis. The complete test, including rest between blocks, can be completed within 8 minutes.

In this thesis, interference score for Flanker RA, defined as congruent minus incongruent, and Flanker RT, defines as incongruent minus congruent are used as a measure of inhibition.

Assessment of muscle fitness and anaerobic fitness:

MF was assessed using the Handgrip (HG), Vertical jump (VJ), and Shuttlerun (SR), which are described in the following paragraphs.

Handgrip:

HG, which can be seen as an overall measure for static strength in the upper limb, is one of the most used methods for assessing MF [103] because it is has a low cost and can be used in a time-efficient manner with unsophisticated equipment (13). Therefore, the method has been used in many studies as a tool predicting several health outcomes primarily on elderly, but lately the test has been used for estimating health outcome and physical performance on children [104]. The test is from the Eurofit test battery [85] and HG has an test-retest reliability (r=0,94) [105] , which means that 94% of the observed variance is due to true score variance.

The students held the portable dynamometer (Smedley, spring) in the hand being tested, with the arm on the side of the body and the elbow slightly bent (appendix 1). The dynamometer was adjusted in order for the base to rest on the first metacarpal and the handle resting on middle of four fingers. Students were instructed to perform two maximal isometric contractions of the dominant hand and maintain it for minimum two seconds. There is a short break of one minute between the two attempts. During the test, no other body movement was allowed. Both results (kg) was recorded [97].

Vertical jump:

VJ, also called Sargent jump test [106], was used to assess the explosive strength in the muscles of the lower limb. The test has a validity (r=0.99, p=0.001), for intra-evaluator reproducibility (r=0.99, p=0.001) and for inter-evaluator reproducibility (r=1.0, p=0.001) [107], why the test is a valid and reproducible instrument measuring strength in homogenous groups.

In order to measure VJ a jump altimeter was used, consisting of 3 pieces of tape, a measuring tape and a waist belt. The latter was fastened to the belt and hereafter passed through an "eye" made of tape on the floor. The measuring tape was to be adjusted in order to get the edge of the "central" buckle to align with an even number on the measuring tape. The belt was placed around the waist of the student. 3 pieces of tape were placed across he measuring tape with an interval of 30 cm in order to get it to run perpendicularly to the floor. The student was instructed to stand straight without bending the knees. The feet were placed with forefoot on the inner tape strip to give a natural starting position, and the measuring tape was adjusted for the height of the student. Now the student was instructed to jump where after the result was read to the nearest 0.5 centimeter. The procedure was repeated three times, and all the attempts were noted. If the last attempt is the best one, the test will proceed until no further improvement is made [108].

Shuttlerun:

SR (10x5 m) is designed to evaluate anaerobic capacity, speed, agility, and motor fitness [103, 109]. The test is valid an reliable, and the reliability does not differ between male and female adolescents [103]. Studies have indicated an increase in agility with age [110].

Two parallel lines were made on the floor with tape or chalk five meters apart. The lines were 120 cm wide, and the ends of each line was marked with cones. Students were instructed to run the distance (10 m) five times. Laps were counted loudly, and the test person was to encourage in order for the student to do the turns as quickly as possible. The time was noted with two decimals (1/100 sec, e.g. 21 sec and 16/100 of a sec). The test was repeated once [97].

Parental education and socioeconomics:

Information about parental education and household income was obtained by questionnaires (appendix 2) at baseline (2008) and follow-up (2015). This information was used as an indicator of parental socio- economic status (SES). The questionnaires were delivered to the parents through the schools at baseline in August 2008 to be returned by post, with separate questions for parents and children [111]. All questionnaires were paper based. The questionnaire is not validated and is made of questions from EYHS, CoSCIS and LCoMotion.

The parental education status was classified according to the International Standard Classification of Education (ISCED-97). The ISCED 7-level scale was combined into three groups (1= level 0-2; 2= level 3; 3= level 4-6). Accordingly, the education level was collapsed into three categories: (1) Basic school no more than 10 years, (2) High school or non-university-vocational programs, (3) College or university degrees.

Data management and treatment:

To minimize potential typing errors, two researchers independently entered the raw data using the EpiData Entry Client (EpiData Association, Odense, Denmark). The two entries were compared for consistency and the inconsistent data were manually checked and corrected based on the original data file and questionnaires.

The dataset was stored as a STATA file for statistical analysis.

Ethics:

The CHAMPS-DK study has been approved by the local ethics committee and by DPA. Written informed consent has been obtained from participating children’s parents or legal guardian, after provided with a detailed written explanation and the option to withdraw at any time. Additionally, verbal agreements from both child and parent were obtained before examinations. Sensitive information will be treated according to applicable rules and regulations.

Statistical analysis:

Descriptive statistics (mean, SD and frequencies) were summarized by school with baseline data and will be used to characterize data. The assumption of normal distribution of the residuals were examined using Q-Q plots because a Kolmogorov-Smirnow test of normality was deemed too conservative [85]. For continuous variables (e.g. VJ), group differences were evaluated using an independent sample t-test. Categorical values (e.g. sex) were assessed using chi-square test or Fishers exact test.

A composite score could be calculated, but since the correlation between the motor performance tests were 0.5, this was not performed in this thesis. Furthermore, the interaction between baseline and slope coefficient was tested. Due to non-significance, this was not included in the analysis.

Multilevel analyzes using the mixed command in STATA will be performed in order to evaluate the possible cross sectional and longitudinal association between MF and cognitive function on children.

Cross sectional analyzes will be performed using the last measurements in 2015. Longitudinal analyzes will be performed using the beta-coefficient for a regression for each child on the longitudinal data on HG, SR and VJ, this way analyzing the longitudinal association between change in MF during the 7 years with testing with cognition in 2015.

The longitudinal and cross sectional analyzes were adjusted for the co-variates age, sex, SES, and parental educational level, which are potential confounders in epidemiologic studies [4, 112] and when analyzing cognition, EF and MF.

The criteria for exclusion for data analysis, decided a priori, were as follows:

1. Data on MEFT was missing
2. Less than three observations on SR, VJ, and HG.

The number of students who completed various aspects of the data set varied from 1159-1327 students on variables e.g. age, and sex (see table 1) and 629 students on the variables of MEFT. A complete dataset was available for approximately 360 students.

All statistical analyses were conducted with STATA 14 for Windows (StataCorp LP, College Station, TX, USA), and the level of significance was set at 5% $P < 0.05$ (two-sided).

Results:

In this section, descriptive characteristics at baseline of the participants, respectively Sport Schools (SS) and Normal Schools (NS) included in the analysis, will be presented in table 1. Furthermore, development over time on selected characteristics will be presented in table 2.

Baseline characteristics:

Descriptive statistics for the variables used in this study are presented in table 1. 1327 participants were included in the analysis (SS n= 774 NS n= 553). There was no significant difference on selected characteristics (e.g. age, height, weight, HG, VJ, and SR) at baseline.

Overall, there is no difference between SS and NS, and the results imply that the two groups are alike, and an overall analysis can be performed on the measurements.

Table 1: Baseline characteristics

Characteristics	NS (SD) (n=489-553)	SS (SD) (n=677-774)	Total Sample (SD) (n=1159-1327)	P
Age (years)	8.46 (1.47) (553)	8,37 (1.41) (774)	8.41 (1.43) (1327)	0.27
Sex (no of students)	553	774	1327	
Female (%)	278 (50.2%)	426 (55 %)	704 (53%)	0.09
Male (%)	275 (49.7 %)	348 (45%)	623 (46.9%)	0.09
Parental education	146	303	449	
I (%)	4 (2.7%)	5 (1.65%)	9 (2.0%)	0.44
II (%)	77 (54.2%)	137 (46.3%)	214 (48.9%)	0.13
III (%)	65 (%)	161 (%)	226 (%)	0.09
Household income	441	634	1075	
I (>199.000)	7	22	29	0.06
II (200-299.000)	24	32	56	0.77
III (300-399.000)	34	67	101	0.11
IIII (400-499.000)	60	58	118	**0.02**
V (500-599.000)	87	144	231	0.24
VI (600-699.000)	72	135	207	**0.04**
VII (700-799.000)	80	69	149	**0.0007**
VII (<800.000)	77	107	184	0.80
Height (cm)	132.71 (10.16) (503)	132.49 (9.64) (677)	132.58 (9.68) (1180)	0,70
Weight (kg)	29.55 (7.20) (502)	29.11 (6.73) (677)	29.30 (6.94) (1179)	0.28
BMI (kg/m^2)	16.56 (2.13) (502)	16.38 (2.13) (676)	16.45 (2.13) (1178)	0.15
Handgrip (kg)	16.39 (4.30) (489)	15.16 (3.90) (670)	15.68 (4.12) (1159)	**0,00**
Slope Handgrip	1.52 (1.28) (507)	1.99 (1.42) (695)	1.79 (1.38) (1202)	**0,00**
Vertical jump (cm)	27.04 (6.85) (503)	27.45 (6.38) (668)	27.27 (6.59) (1171)	0.30
Shuttlerun (sec)	25.76 (3.59) (503)	25.61 (3.53) (667)	25.68 (3.55) (1170)	0.47

Abbreviation: BMI; Body Mass Index, NS; Normal School, and SS; Sports School
Data are expressed as mean (SD) for continuous variables and frequency (percent) for categorical variables.
Parental education was mainly based on mother's highest education ((I = Basic school no more than 10 years; II = High school or non-university vocational programs; 3.5 years of college education; III = College or University degrees).

Table 2 – Longitudinal development of the characteristics

Characteristics	F0 (SD) 2008 A	F1 (SD) 2009 S	F2 (SD) 2009 A	F3 (SD) 2010 S	F4 (SD) 2010 A	F5 (SD) 2011 S	F6 (SD) 2012	F7 (SD) 2013	F8 (SD) 2015
Age	8.41 (1.43)	8.93 (1.42)	9.41(1.43)	9.94 (1.43)	10.34 (1.43)	10.93 (1.43)	11.70 (1.36)	12.71 (1.37)	14.21 (1.27)
Height (m)	1.33 (0.1)	1.35 (0.1)	1.38 (0.1)	1.42 (0.1)	1.45 (0.1)	1.47 (0.1)	1.52 (0.1)	1.58 (0.1)	1.67 (0.1)
Weight (kg)	29.30 (6.94)	30.80 (7.16)	32.89 (7.76)	34.74 (8.37)	36.76 (8.90)	38.82 (9.63)	42.34 (10.37)	46.66 (10.86)	54.72(11.03)
Handgrip	15.58 (4.12)	16.49 (4.74)	17.67 (4.71)	18.26 (5.30)	NM	21.00 (5.98)	NM	27.09 (8.00)	32.98 (8.62)
Vertical jump	27.28 (6.57)	28.81 (6.9)	28.93 (6.11)	30.09 (5.96)	NM	33.40 (6.58)	33.51 (6.50)	37.73 (7.69)	41.37 (8.33)
Shuttlerun	25.68 (3.55)	24.70 (3.17)	23.77 (2.66)	23.22 (2.75)	NM	22.59 (2.34)	21.90 (2.22)	21.33 (2.07)	20.26 (2.02)
Mean RT cor_con									450.36 (57.40)
Mean RT cor_incon									542.00 (74.26)
AC con									96.09 (5.39)
AC incon									82.86 (11.4)
Flanker RT									91.64 (37.52)
Flanker AC									13.23 (9.33)

Abbreviation: A; Autumn, S; Spring, F; Follow-up, AC; Accuracy, RT; Reaction time, Con; congruent trial, Incon; Incongruent trial
Data are expressed as mean (SD) for continuous variables

Table 2 summarizes the results for baseline, follow-up, end-score, and changes in score of age, height, weight, HG, VJ, and SR as well as the baseline measure for the Flanker variables

Overall, there was an increase in all the variables over time. In regards to HG, the students have improved their score from 15.58 kg (SD 4.12) to 32.98 kg (SD 8.62), equal to an increase of 111.68 %.

In regards to VJ, the students have improved their score from 27.28 cm (SD 6.57) to 41.37 cm (SD 8.33), equal to an increase of 51.65 %.

In regards to SR, the students have improved their score from 25.68 sec (SD 3.55) to 20.26 sec (SD 2.02 sec, equal to a decrease of 21.10 %.

Table 3: Cross sectional analysis – association between MF and cognition

Characteristics	Mean RT cor_con (95% CI)	Mean RT cor_incon (95% CI)	AC con (95% CI)	AC incon (95% CI)	Flanker RT (95% CI)	Flanker AC (95% CI)
Vertical Jump F8						
Coef	-0,21 (-1.09 -0.68)	-0.18 (-1.29 – 0.92)	**0.11** (0.03 – 0.19)	**0.28** (0.11 – 0.45)	0.38 (-0.52 – 0.60)	**-0.17** (-0.31 - -0.03)
P	0.64	0.75	0.005	0.001	0.89	0.02
Handgrip F8						
Coef	-0.57 (-1.39 – 0.25)	**-1** (-2.03 – 0.03)	0.01 (-0.06 – 0.08)	0.08 (-0.08 – 0.34)	-0.42 (-0.94 – 0.10)	-0.06 (-0.19 – 0.07)
P	0.17	0.057	0.73	0.34	0.11	0.35
Shuttlerun F8						
Coef	**4.34** (0.86 – 7.81)	**4.52** (0.21 – 8.83)	**-0.30** (-0.60 - -0.003)	-0.47 (-1.12 – 0.18)	0.07 (-2.05 – 2.19)	0.16 (-0.38 – 0.70)
P	0.014	0.04	0.047	0.15	0.95	0.56

Abbreviation: RT; Reaction time, AC; Accuracy, Con; congruent trial, Incon; Incongruent trial, CI; Confidence interval, Coef; regression coefficient, P; p-value =0.05.
The table shows the association between Vertical jump, Handgrip and Shuttlerun, and Flanker measured at follow-up 8.

Cross-sectional Analyses

Overall, in mixed model analyses, the cross sectional association between MF and Flanker is weak and inconsistent. The analysis was adjusted for age, sex, and SES. The results of the longitudinal analysis are shown in Table 3.

VJ was associated with Flanker AC in the congruent (95% CI=0.03 – 0.19, P=0.005) and incongruent (95% CI=0.11 – 0.45, P=0.001) trials, as well as the Flanker AC interference score (95% CI=-0.31 - -0.03, P=0.02). The coefficient of Flanker AC interference score was minus 0.17 meaning that an increase of one-unit in vertical jump score was positively associated with a better Flanker effect. A decrease in flanker score equals a better inhibition.

The variable sex was statistical significant in AC incongruent (P=0.003), AC congruent (P=0.015), and Flanker RT (P=0.023), hence a stratified analysis was performed. None of these results was statistically significant.

There was no association between HG and Flanker except between mean RT in the incongruent trial (95% CI=-2.03 – 0.03, P=0.057). The coefficient was minus 1 meaning that a one-unit increase in Handgrip was associated with a decrease in mean RT.

The variable sex was statistically significant in Flanker RT and borderline in AC incongruent, hence a stratified analysis was performed. The analysis showed a difference between boys and girls, and the coefficient for boys is twice the measure for girls, although there is no statistical significance. These findings results from ancillary (post hoc) analysis and are intended to generate new hypotheses that boys may react differently than girls.

SR was associated with mean RT in the congruent (CI=0.86 – 7.81, P=0.014) and incongruent trials (CI=0.21 – 8.83, P=0.04), as well as in Flanker AC in congruent (CI=-0.60 - -0.003, P=0.047). The coefficient in mean RT was positive meaning that a one-unit increase in SR was associated with an increase in mean RT and a decrease in congruent AC.

Table 4: Longitudinal analysis – association between MF and cognition

Characteristics	Mean RT cor_con (95% CI)	Mean RT cor_incon (95% CI)	AC con (95% CI)	AC incon (95% CI)	Flanker RT (95%CI)	Flanker AC (95% CI)
Vertical Jump baseline						
Coef	-0,89 (-2.20 - 0.42)	-0.58 (-2.22 - 1.06)	0.18 (0.07- 0.29)	0.39 (0.14 – 0.64)	0.25 (-0.56 – 1.06)	**-0.22** (-0.24 - -0.01)
P	0.18	0.49	0.002	0.002	0.55	0.04
Slope						
Coef	0.02 (-5.43 – 5.47)	0.97 (-6.66 – 6.95)	0.29 (-0.18 - 0.76)	0.68 (-0.37 – 1.72)	0.15 (-3.26 – 3.55)	- 0.41 (-1.27 – 0.45)
P	0.99	0.15	0.22	0.20	0.93	0.35
Handgrip baseline						
Coef	**2.53** (0.02 – 5.03)	**3.07** (-0.05 – 6.18)	0.16 (-0.03 – 0.35)	**0.52** (0.06 -0.98)	0.60 (-0.93 – 2.14)	-0.36 (-0.74 -0.01)
P	0.048	0.05	0.11	0.028	0.44	0.06
Slope						
Coef	**-11.09** (-19.15 - -3.02)	**-15.74** (-25.78 - -5.69)	0.45 (-0.18 – 1.08)	-0.20 (-1.74 – 1.33)	-4.61 (-9.67 – 0.45)	0.65 (-0.60 – 1.90)
P	0.007	0.002	0.64	0.80	0.07	0.31
Shuttlerun baseline						
Coef	1.55 (-0.51 – 3.61)	**2.80** (0.25 – 5.35)	**-0.27** (-0.45 - -0.09)	**-0.66** (-1.05 - -0.26)	1.16 (-0.12 – 2.43)	**0.38** (0.06 – 0.71)
P	0.14	0.031	0.003	0.001	0.075	0.019
Slope						
Coef	9.63 (-9.29 – 28.5)	12.55 (-10.86 – 35.96)	-0.65 (-2.29 – 0.99)	1.77 (-1.86 – 5.40)	3.30 (-8.46 – 15.06)	-2.43 (-5.41 – 0.55)
P	0.32	0.29	0.44	0.34	0.58	0.11

Abbreviations: : RT; Reaction time, AC; Accuracy, Con; congruent trial, Incon; Incongruent trial, CI; Confidence interval, Coef; regression coefficient, P; p-value =0.05.
The table shows the association between Vertical jump, Handgrip and Shuttlerun at baseline, Slope and Flanker measured at follow-up 8.

Longitudinal Analyses:

Overall, the longitudinal association between MF and Flanker was weak and inconsistent. The results of the longitudinal analysis are shown in Table 4.

There was an association between VJ at baseline and Flanker AC in both the incongruent (95% CI=0.14 – 0.64, P=0.002) and congruent (95% CI= 0.07- 0.29, P=0.002) task, as well as in Flanker AC interference score (95% CI= -0.24 - -0.01, P=0.04). There was no significant association between Slope on VJ and Flanker variables.

Additionally, there was an association between HG at baseline and mean RT of the congruent (95% CI=-0.24 - -0.01, P=0.048) and incongruent (95% CI=-0.05 – 6.18, P=0.05), and incongruent AC (95%CI=0.06 - 0.98, P=0.028). Furthermore, Slope was positively associated with mean in RT both in the congruent and incongruent trials.

The variable sex was statistically significant in Flanker RT (P=0.029), therefore a secondary analysis was performed, stratified for sex. On boys the association between Slope and interference score Flanker RT was statistically significant (P=0.044), but not on girls (P=0.14), meaning there was an association between development in handgrip and Flanker RT on boys.

SR at baseline was associated with mean in RT in the incongruent task (95% CI=0.25 – 5.35, P=0.031), AC in the congruent (95% CI=-0.45 - -0.09, P=0.003) and incongruent trials (95% CI=-1.05 - -0.26, P=0.001), as well as in Flanker AC interference score (95% CI=0.06 – 0.71, P=0.019). There was no significant association between Slope and SR, and Flanker variables.

Discussion:

To our knowledge, this is the first study to investigate the association between MF and cognitive performance in children. The results from this study, and the longitudinal and cross-sectional analyzes indicate that individual MF tests and overall MF may be related to cognition, although the associations were low or non-existent and without a trend. These results parallel similar observations on young adults in the study of Åberg et al [19] and a review by Smith et al [2] . The study of Åberg et al is performed on conscripts aged 18 years, and measures AF and cognitive performance. It is not clearly described how MF and cognitive performance are measured, other than data was collected during conscription examination[19]. The strength of the study is the ability to include information from a large sample, but since only male subjects were analyzed, the results may not be applicable to women and children, and therefore not the target population of this study. Furthermore, information regarding more specific neurological functions e.g. EF was lacking. Therefore, direct comparison between the study of Åberg and the results of this study is not possible, or should be done with this in mind.

The review of Smith et al only used six cross-sectional studies investigating the association between MF and cognition. Only one study had low risk of bias, and there was considerable heterogeneity between the measures used to assess cognitive ability. Making a comparison was problematic, and therefore the results must be interpreted with caution when comparing to the findings in this study. Additionally, 5/6 of the studies measured academic performance and not cognitive performance [2]. One can discuss if cognitive performance may be used as a proxy for academic performance, if one believes that the ability to inhibit is important for one's possibility to learn and thereby obtain better academic achievement. Bangirana et al. found an association between cognition and academic performance on children, although it is performed on a small sample of children previously affected by malaria [113]. Therefore, this finding must be interpreted with caution because malaria is associated with cognitive impairment [114]. Additionally, a limitation in the literature is found concerning the reliance on standardized academic measures, providing limited information about the relationship between PF e.g. AF and MF, and the underlying cognitive processes supporting cognitive and academic performance [100]

Unlike in children, prior research has demonstrated that elderly adults with higher MF have better cognition [115]. Raji et al. found a significant cross sectional and longitudinal association between MF, measured with HG, and cognition measured with Mini-Mental State Examination (MMSE) [115]. The longitudinal association remained significant when controlling for age, sex, and education as done in this thesis. Although, the population is different from Danish school children, the results show that it is crucial, for elderly, to remain physical active in order to maintain MF and thereby prevent a decrease in cognitive performance. The association between HG and cognition is not evident in children, which may be explained by the fact, that for elderly MF is associated with their general physical health and ADL ability, which is compatible with the findings of Raji et al. This is not the case for children, because they are overall more physical active, and their cognitive performance is not decreasing due to age-related changes. Furthermore, cognition in this study not measured with FT, but MMSE which is a test for dementia [116] and not an expression for cognitive function, although the test is used in order to detect cognitive dysfunctions.

Opposed to research on MF, several cross-sectional studies have documented corroborating results to the positive link between AF and aspects of cognitive control on children with evidence indicating that higher fit children exhibit increased improvements in learning on memory tasks compared to lesser-fit children [117, 118]. Moreover, EF appears more sensitive than other aspects of cognition to aerobic exercise training [20], like Davis et al. found a dose-response relationship between aerobic exercise and improvements in math, EF, and cognitive performance [119]. Furthermore, Dustman et al. found AF to be associated with significantly reduced interference score in Stroop task, whereas no such effect was observed for strength and flexibility training [120]. This finding is supported by Colcombe [20] and Cramer and Hillman et al [121], who found that AF is more beneficial for tasks requiring EF e.g. planning, and inhibition, which may be linked to increased blood-flow of the brain, which not happens in relation to MF and might explain the inconsistent findings of this study.

Stroop is comparable to the FT, because the incongruent trial of a FT requires greater amount of interference control similar to the incongruent condition of a Stroop task [13]. When comparing studies on children, it is noticeable that several studies have indicated that Stroop task performance increases with age (7) because of interference and RT (15), which suggests a curvilinear relationship between age and interference control across the lifespan. On the other hand, on elderly, RT is also found to exhibit a marked decrease with age. Taken together, these findings are likely to reflect the structural development of the brain, which intermediates functions related to both Stroop and FT, such as response inhibition, interference resolution, and reading ability (1, 22). This may explain the findings of this study, and why the association between MF in elderly is significant and is stronger than in children.

On the other hand, Machetti et al. showed findings that provide an overall association between motor coordination and EF [53]. When assessing MF, one cannot rule out a possible link between motor coordination and MF and the tests in this study also may involve coordination e.g. SR [122] and FT. Additionally, there is differential between specific EF and aspects of physical and motor fitness measures. It can be suggested that the cognitive demands inherent in sensorimotor learning, performing a complex movement, and participating in sports task may be responsible for the positive, but weak, associations between MF and inhibition in this study. This is being supported by Spitzer et al., who highlights that PA enhance inhibitory control, especially RT, in a group of 10-18 years old [123].

Although the hypothesis of this thesis was, that there was an association between MF and cognition due to the knowledge of how MF may have an impact on different hormones, this was not confirmed.

Sex-related differences in muscular development contributes to differences in physical performance, which can explain some of the disparities between boys and girls in the tests scores [124] and may be due to hormones, which corroborate with some of the findings of this study.
The extern validity of this study is limited because the independent variables depend on other factors, and the findings need to be verified in a similar population.

Methodological considerations:

Despite the contribution regarding the association between MF and cognition, several limitations and strengths of the study are warrant mention.

Strengths:

The strengths of this study are the large sample of children and that the independent variables are assessed once a year using objective measuring methods, which can be quantified, are validated and have a high reliability. Additionally, whenever testing, the same test protocol was used and the assessors were blinded, which gives a high intern validity.

Limitations:

The limitations of this study are that a full dataset is only available on approximately 360 children, equivalent to 27 % of the eligible children. Therefore, the results could be affected by selections bias. Imputation of data may have solved the problem, but this was not performed in this study. A response analysis could have been performed to control for the children analyzed being representative for the study sample. This was not deemed necessary, since this study was used to generate a hypothesis and not to look for effect of intervention. Moreover, cognition was only measured once in 2015, meaning that we do not know the level of cognitive function in 2008.
Furthermore, the FT is modified fitting it to the study population, children. Zeischka et al. has investigated the congruency effect in different versions of the FT and found increased congruency effect when using arrows, as compared to e.g. letters and colors [125]. Therefore, this test may show a more positive result in comparison to if another test, had been used. Furthermore, the MEFT was performed in rooms together with other children. If children have problems with inhibition they may score lower compared to "normal" children if the level of disturbing factors had been lower. However it was not possible to adjust for in this thesis. Besides, there is no golden standard measure of EF, and a variety of cognitive tasks have been used to assess the association between MF and cognition. These cognitive tasks tap various aspects of EF and require different cognitive skill demands. This may explain part of the reason for the inconsistent findings, which have characterized the field of research and this study. Furthermore, when assessing cognition with MEFT, it can be discussed whether the

task is an expression for cognition and not fine motor skills and hand-eye-coordination. Children, who play a lot of games e.g. PlayStation may have an advantage when being tested with MEFT cracking the code how to increase their performance, and because they perhaps have better fine motor skills and hand-eye-coordination. Therefore, the factor "time spent playing PlayStation" may have been relevant to check for in order for this to be taking into account when analyzing for an association. Additionally, by definition, EF operate on other cognitive processes, wherefore a large proportion of the variance in e.g. inhibition or any of the other EF is dependent on each other and therefore interacting [47]. Accordingly, when assessing EF it is important to consider the functions of the different parts of EF. Furthermore, children may have different strategies when performing the MEFT, meaning that a child can respond quickly and thereby risk a poorer RA. On the other hand, a child may have a strategy to be as accurate as possible and thereby obtain a lower RT. Additionally, Bunge et al. found left-PFC activation on children compared with right-PFC activation during performance of a MEFT [126], indicating differential cognitive strategy between adults and children supporting the findings of Davidson et al. [127]. Moreover, children react more impulsively and with poorer graduation of the RT than adults, indicating RA to be a more informative scale/measure when assessing inhibition on children [127]. Even though Davidson et al has used the Simon task and not the FT, this may indicate that one prospectively should focus on RA. Furthermore, when assessing inhibition with FT, one has to notice that the task is sensitive to developmental improvements in childhood and adolescence [128, 129]. Therefore, it would be relevant to control for Tanner Stages [130] i.e. pubertal development, but this was not possible due to lack of data. Additionally, it would have been relevant to take BMI into account since changes in MF are closely associated with changes in body size [87].

The validity of HG as a measure of general muscle strength has been questioned, as the strength of the forearm muscles may not necessarily represent the strength of other muscles [131]. Additionally, performing HG with the elbow extended is the most appropriate way to assess maximal HG in adolescents [132], which is not done in this study according to the protocol [97]. Furthermore, there is considerable variation in current methods of assessing HG, e.g. with regard to choice of dynamometer and the measurement protocol, which has the potential to introduce measurement errors [133].

In the statistical analysis, a composite score could be calculated, but due to close correlation between the tests, there was a risk of the tests not being independent of each other, because they explain 25 percent of the variance of each other. When tests are too alike, there is a risk of overfitting, meaning that the difference between "top and bottom" may increase. On the other hand, if the tests were more diverse, calculation of a composite score would be relevant, because a composite measure may be more powerful than their constituent parts when detecting change [134]. E.g. if one constituent test has a good precision for children with high levels of MF or EF, and another has a good precision on children with poor MF or EF, combining them can result in a "test" that is good on children with both high and low levels of EF and MF ability. When looking at children, there is a good chance of finding children both in the high and low function. Moreover, the use of a composite may increase measurement precision and limit the number of statistical tests needed, compared to analyzing the tests separately. It would have been possible using more cognitive tests, but due to a limited timeframe, this was not possible although data on Word Recall and Switch were available. When doing this, one has to be sure that the 3 tests are not alike and a measure of the same, although EF composites have proven useful for investigating change over time [135].

Although the present study may provide an additional knowledge to the understanding of a possible relationship between MF and childhood cognition, the use of a longitudinal design raises the possibility that the observed association can be caused by another factor e.g. genes, nutrition, intellectual stimulation, and level of PA [6, 7]. Furthermore, individuals may modify their behavior after initial and ongoing measurements. Therefore, randomized controlled trials (RCT) are necessary to account for potential bias such as difficulties to maintain consistency of measurements and outcomes over time.

Perspectives:

This study confirms that the longitudinal and cross-sectional association between MF and cognition is weak and inconsistent, but findings may be due to chance. Because the slope is not significant, the changes in MF may happen before the assessments. Therefore, it may be relevant to include younger children e.g. from kindergarten and see, if MF has an impact on cognition. Doing that one has to consider the challenges, e.g. is it possible to measure MF in that age, can they stay motivated, and is it possible to find quantifiable and reproducible tests for children age 3-5. The relationship between MF, motor skills, and FA is a self-fulfilling prophecy because an increase in FA will have a positive impact on MF and motor skills and vice versa. Yet, we do not know if children by being active obtain better intelligence. Therefore, RCT are warranted to see if being more active and doing strength training have an impact on present and later intelligence, learning, and academic performance. In order for this to be relevant, the effect size crucial. If it is necessary to exercise e.g. 200 students to obtain an educational relevant effect on one child, it may not be worth it. This knowledge could carry significant educational implications, and the notion that a higher level of MF may enhance cognitive performance may be relevant for educators and sport coordinators. If the two parameters are related, MF could be a relevant factor for physiotherapists and psychologists to test on children with learning/executive difficulties. Furthermore, perhaps developing a comprehensive EF test battery that consists of relatively simple tasks may be one of the top priorities for future research.

Due to cross sectional nature of the current study and the missing baseline measure on cognition it is not possible to determine a causal association. Continued research is needed to gain a causal understanding of the relationship between MF and cognition on children. Future research should address which parameters of PF obtain the greatest impact on cognition and examine the effects of strength training compared to aerobic exercise on cognition. Therefore, longitudinal and intervention studies of similar design but with baseline measure of cognition should be conducted in order to determine, if any, the causal relationship and an association between MF and cognition.

References:

1. Chaddock, L., et al., *A review of the relation of aerobic fitness and physical activity to brain structure and function in children.* J Int Neuropsychol Soc, 2011. **17**(6): p. 975-85.

2. Smith, J.J., et al., *The health benefits of muscular fitness for children and adolescents: a systematic review and meta-analysis.* Sports Med, 2014. **44**(9): p. 1209-23.

3. Hillman, C.H., N.A. Khan, and S.C. Kao, *The Relationship of Health Behaviors to Childhood Cognition and Brain Health.* Ann Nutr Metab, 2015. **66 Suppl 3**: p. 1-4.

4. Diamond, A. and K. Lee, *Interventions shown to aid executive function development in children 4 to 12 years old.* Science, 2011. **333**(6045): p. 959-964.

5. Diamond, A., *Activities and Programs That Improve Children's Executive Functions.* Current Directions in Psychological Science, 2012. **21**(5): p. 335-341.

6. Kjærgård, H.e.a., *Barnets lærende hjerne – børneneuropsykologi, kognition og neuropædagogik*. Vol. 3. 2016, Frederiksberg: Borgforlaget Frydenlund.

7. Friedman, N.P., et al., *Individual Differences in Executive Functions Are Almost Entirely Genetic in Origin.* Journal of Experimental Psychology: General, 2008. **137**(2): p. 201-225.

8. OECD, *PISA 2009 Results: What Students Know and Can Do: Student Performance in Reading, Mathematics and Science (vol. I).* 2010.

9. (EVA), D.E., *Undervisningsdifferentiering som bærende pædagogisk princip - En evaluering af sammenhænge mellem evalueringsfaglighed og differentieret undervisning*. 2011.

10. Bækgaard M, J.S., *Ekskluderende specialundervisning. Hvem får det, og hvilke forskelle er der mellem kommunerne?* 2011, KREVI, Det Kommunale og Regionale Evalueringsinstitut: Århus.

11. Khan, N.A. and C.H. Hillman, *The relation of childhood physical activity and aerobic fitness to brain function and cognition: a review.* Pediatr Exerc Sci, 2014. **26**(2): p. 138-46.

12. Caspersen, C.J., K.E. Powell, and G.M. Christenson, *Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.* Public Health Reports, 1985. **100**(2): p. 126-131.

13. Buck, S.M., C.H. Hillman, and D.M. Castelli, *The relation of aerobic fitness to stroop task performance in preadolescent children.* Medicine and Science in Sports and Exercise, 2008. **40**(1): p. 166-172.

14. Pontifex, M.B., et al., *Cardiorespiratory fitness and the flexible modulation of cognitive control in preadolescent children.* J Cogn Neurosci, 2011. **23**(6): p. 1332-45.

15. Chaddock, L., et al., *Childhood aerobic fitness predicts cognitive performance one year later*. J Sports Sci, 2012. **30**(5): p. 421-30.

16. Scudder, M.R., et al., *Aerobic capacity and cognitive control in elementary school-age children.* Med Sci Sports Exerc, 2014. **46**(5): p. 1025-35.

17. Ruiz, J.R., et al., *Physical activity, fitness, weight status, and cognitive performance in adolescents.* J Pediatr, 2010. **157**(6): p. 917-922.e1-5.

18. Best, J.R., P.H. Miller, and L.L. Jones, *Executive Functions after Age 5: Changes and Correlates.* Dev Rev, 2009. **29**(3): p. 180-200.

19. Åberg, M.A.I., et al., *Cardiovascular fitness is associated with cognition in young adulthood.* Proceedings of the National Academy of Sciences of the United States of America, 2009. **106**(49): p. 20906-20911.

20. Colcombe, S. and A.F. Kramer, *Fitness effects on the cognitive function of older adults: a meta-analytic study.* Psychol Sci, 2003. **14**(2): p. 125-30.

21. Fragala, M.S., et al., *Resistance exercise may improve spatial awareness and visual reaction in older adults.* J Strength Cond Res, 2014. **28**(8): p. 2079-87.

22. Padilla-Moledo, C., et al., *Associations of muscular fitness with psychological positive health, health complaints, and health risk behaviors in Spanish children and adolescents.* Journal of Strength and Conditioning Research, 2012. **26**(1): p. 167-173.

23. Etnier, J.L., et al., *A meta-regression to examine the relationship between aerobic fitness and cognitive performance.* Brain Res Rev, 2006. **52**(1): p. 119-30.

24. Angevaren, M., et al., *Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment.* Cochrane Database Syst Rev, 2008(3): p. Cd005381.

25. Smiley-Oyen, A.L., et al., *Exercise, fitness, and neurocognitive function in older adults: the "selective improvement" and "cardiovascular fitness" hypotheses.* Ann Behav Med, 2008. **36**(3): p. 280-91.

26. Voss, M.W., et al., *Exercise, brain, and cognition across the life span.* J Appl Physiol (1985), 2011. **111**(5): p. 1505-13.

27. Forte, R., et al., *Enhancing cognitive functioning in the elderly: multicomponent vs resistance training.* Clinical Interventions in Aging, 2013. **8**: p. 19-27.

28. Liu-Ambrose, T., et al., *Resistance training and executive functions: a 12-month randomized controlled trial.* Arch Intern Med, 2010. **170**(2): p. 170-8.

29. Cassilhas, R.C., et al., *The impact of resistance exercise on the cognitive function of the elderly.* Medicine and Science in Sports and Exercise, 2007. **39**(8): p. 1401-1407.

30. Roubenoff, R., *Sarcopenia and its implications for the elderly.* Eur J Clin Nutr, 2000. **54 Suppl 3**: p. S40-7.

31. Weinstein, A.M., et al., *The association between aerobic fitness and executive function is mediated by prefrontal cortex volume.* Brain Behav Immun, 2012. **26**(5): p. 811-9.

32. Ruscheweyh, R., et al., *Executive performance is related to regional gray matter volume in healthy older individuals.* Hum Brain Mapp, 2013. **34**(12): p. 3333-46.

33. Hillman, C.H., K.I. Erickson, and A.F. Kramer, *Be smart, exercise your heart: Exercise effects on brain and cognition.* Nature Reviews Neuroscience, 2008. **9**(1): p. 58-65.

34. Hillman, C.H., D.M. Castelli, and S.M. Buck, *Aerobic fitness and neurocognitive function in healthy preadolescent children.* Medicine and Science in Sports and Exercise, 2005. **37**(11): p. 1967-1974.

35. Knudsen, A. *Hjerne og motorik. Styrk hjernen - brug kroppen*. Available from: www.Ann.E.Knudsen.dk.

36. Anish, E.J., *Exercise and its effects on the central nervous system.* Curr Sports Med Rep, 2005. **4**(1): p. 18-23.

37. Cotman, C.W., N.C. Berchtold, and L.A. Christie, *Exercise builds brain health: key roles of growth factor cascades and inflammation.* Trends Neurosci, 2007. **30**(9): p. 464-72.

38. Ratey, J., *Spark!: How exercise will improve the performance of your brain*. 2010, London: Quercus.

39. Kohl HW III, C.H., *Educating the Student Body: Taking Physical Activity and Physical Education to School*. 2013, Washington: National Academies Press (US).

40. Chaddock-Heyman, L., et al., *III. The importance of physical activity and aerobic fitness for cognitive control and memory in children.* Monogr Soc Res Child Dev, 2014. **79**(4): p. 25-50.

41. Regeringen, *Gør en god skole bedre - et fagligt løft til folkeskolen*. 2012.

42. Gade, A., *Hjerneprocesser. Kognition og neurovidenskab*. Vol. 1. 1998: Frydenlund Grafisk.

43. Alloway, T.P., et al., *A structural analysis of working memory and related cognitive skills in young children.* Journal of Experimental Child Psychology, 2004. **87**(2): p. 85-106.

44. Miyake, A., M.J. Emerson, and N.P. Friedman, *Assessment of executive functions in clinical settings: problems and recommendations.* Semin Speech Lang, 2000. **21**(2): p. 169-83.

45. Dalley, J.W., R.N. Cardinal, and T.W. Robbins, *Prefrontal executive and cognitive functions in rodents: Neural and neurochemical substrates.* Neuroscience and Biobehavioral Reviews, 2004. **28**(7): p. 771-784.

46. Bialystok E., C.I.M.F., *Lifespan cognition - mechanisms of change* 2006, New York: Oxford Univeristy Press Inc.

47. Diamond, A., *Executive Functions.* Annual review of psychology, 2013. **64**: p. 135-168.

48. Fredens, K., *Mennesket i hjernen*. Vol. 1. 2012, København: Hans Reitzels Forlag.

49. Best, J.R., *Effects of Physical Activity on Children's Executive Function: Contributions of Experimental Research on Aerobic Exercise.* Developmental review : DR, 2010. **30**(4): p. 331-551.

50. Fino, E., et al., *Executive functions, impulsivity, and inhibitory control in adolescents: A structural equation model.* Advances in Cognitive Psychology, 2014. **10**(2): p. 32-38.

51. Horn, N.R., et al., *Response inhibition and impulsivity: an fMRI study.* Neuropsychologia, 2003. **41**(14): p. 1959-66.

52. Kinnunen, M.I., et al., *Self-control is associated with physical activity and fitness among young males.* Behavioral Medicine, 2012. **38**(3): p. 83-89.

53. Marchetti, R.e.a., *Physical and Motor Fitness, Sport Skills and Executive Function in Adolescents: A Moderated Prediction Model.* psychology 2015(6): p. 1915-1929.

54. Barkley, R.A., *Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD.* Psychological Bulletin, 1997. **121**(1): p. 65-94.

55. Diamond, A., *Normal Development of Prefrontal Cortex from Birth to Young Adulthood: Cognitive Fuctions, Anatomy, and Biochemistry.* Principles of Frontal Lobe Function, ed. K.R. Stuss DT. 2002, Oxford: Oxford University Press.

56. Levin, H.S., et al., *Developmental changes in performance on tests of purported frontal lobe functioning.* Developmental Neuropsychology, 1991. **7**(3): p. 377-395.

57. Hart, S., *Den følsomme hjerne*. Vol. 1. 2009, København: Hans Reitzels Forlag.

58. Fuster, J.M., *Frontal lobe and cognitive development.* J Neurocytol, 2002. **31**(3-5): p. 373-85.

59. Luna, B., et al., *Maturation of widely distributed brain function subserves cognitive development.* NeuroImage, 2001. **13**(5): p. 786-793.

60. Tanji, J. and E. Hoshi, *Role of the lateral prefrontal cortex in executive behavioral control.* Physiological Reviews, 2008. **88**(1): p. 37-57.

61. Diamond, A., *The early development of executive functions.* Lifespan cognition: Mechanisms of change, 2006: p. 70-95.

62. Duncan, J., P. Burgess, and H. Emslie, *Fluid intelligence after frontal lobe lesions.* Neuropsychologia, 1995. **33**(3): p. 261-268.

63. De Luca, C.R., et al., *Normative data from the CANTAB. I: development of executive function over the lifespan.* J Clin Exp Neuropsychol, 2003. **25**(2): p. 242-54.

64. Lezak MD, H.D., Bigler ED, Tranel D:, *Neuropsychological Assessment,*. Fifth Edition ed. 2012, NY, USA;: Oxford University Press,.

65. MacLeod, C.M., *Half a century of research on the Stroop effect: an integrative review.* Psychol Bull, 1991. **109**(2): p. 163-203.

66. Hommel, B., *The Simon effect as tool and heuristic.* Acta Psychol (Amst), 2011. **136**(2): p. 189-202.

67. Eriksen, B.A. and C.W. Eriksen, *Effects of noise letters upon the identification of a target letter in a nonsearch task.* Perception & Psychophysics, 1974. **16**(1): p. 143-149.

68. Mullane, J.C., et al., *Interference control in children with and without ADHD: A systematic review of flanker and simon task performance.* Child Neuropsychology, 2009. **15**(4): p. 321-342.

69. Cragg, L. and K. Nation, *Go or no-go? Developmental improvements in the efficiency of response inhibition in mid-childhood.* Dev Sci, 2008. **11**(6): p. 819-27.

70. Verbruggen, F. and G.D. Logan, *Automatic and controlled response inhibition: associative learning in the go/no-go and stop-signal paradigms.* J Exp Psychol Gen, 2008. **137**(4): p. 649-72.

71. Chen, C., et al., *Correlating Gray Matter Volume with Individual Difference in the Flanker Interference Effect.* PLoS ONE, 2015. **10**(8): p. e0136877.

72. Sapega, A.A. and G. Drillings, *The definition and assessment of muscular power.* J Orthop Sports Phys Ther, 1983. **5**(1): p. 7-9.

73. Szuhany, K.L., M. Bugatti, and M.W. Otto, *A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor.* Journal of Psychiatric Research, 2015. **60**: p. 56-64.

74. Prior, B.M., H.T. Yang, and R.L. Terjung, *What makes vessels grow with exercise training?* J Appl Physiol (1985), 2004. **97**(3): p. 1119-28.

75. Laron, Z., *Insulin-like growth factor 1 (IGF-1): a growth hormone.* Molecular Pathology, 2001. **54**(5): p. 311-316.

76. Kanbur, N.O., O. Derman, and E. Kinik, *The relationships between pubertal development, IGF-1 axis, and bone formation in healthy adolescents.* J Bone Miner Metab, 2005. **23**(1): p. 76-83.

77. Scarth, J.P., *Modulation of the growth hormone-insulin-like growth factor (GH-IGF) axis by pharmaceutical, nutraceutical and environmental xenobiotics: an emerging role for xenobiotic-metabolizing enzymes and the transcription factors regulating their expression. A review.* Xenobiotica, 2006. **36**(2-3): p. 119-218.

78. Auld, A. *New Gene Release: IGF1 and IGF1_2*. 17.03.2016 09.05.2016]; Available from: https://fitnessgenes.com/blog/igf1-and-increased-muscle-growth/.

79. Brat, O., et al., *Muscle force and endurance in untreated and human growth hormone or insulin-like growth factor-I-treated patients with growth hormone deficiency or Laron syndrome.* Horm Res, 1997. **47**(2): p. 45-8.

80. Hofer, M.M. and Y.A. Barde, *Brain-derived neurotrophic factor prevents neuronal death in vivo.* Nature, 1988. **331**(6153): p. 261-262.

81. Monteggia, L.M., et al., *Essential role of brain-derived neurotrophic factor in adult hippocampal function.* Proc Natl Acad Sci U S A, 2004. **101**(29): p. 10827-32.

82. Gerber, H.P., et al., *VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation.* Nat Med, 1999. **5**(6): p. 623-8.

83. Reichardt, L.F. and K.J. Tomaselli, *Extracellular matrix molecules and their receptors: functions in neural development.* Annu Rev Neurosci, 1991. **14**: p. 531-70.

84. Duffy AM, B.-H.J., and Harmey HJ., *Vascular Endothelial Growth Factor (VEGF) and Its Role in Non-Endothelial Cells: Autocrine Signalling by VEGF*, in *Madame Curie Bioscience Database*. 2011, Landes Bioscience. p. 133-144.

85. ; Available from: http://www.topendsports.com/testing/eurofit.htm.

86. Timmons, J.A., et al., *Human muscle gene expression responses to endurance training provide a novel perspective on Duchenne muscular dystrophy.* Faseb j, 2005. **19**(7): p. 750-60.

87. Beunen, G. and M. Thomis, *Muscular strength development in children and adolescents.* Pediatric Exercise Science, 2000. **12**(2): p. 174-197.

88. Taekema, D.G., et al., *Temporal relationship between handgrip strength and cognitive performance in oldest old people.* Age and Ageing, 2012. **41**(4): p. 506-512.

89. Taekema, D.G., et al., *Handgrip strength as a predictor of functional, psychological and social health. A prospective population-based study among the oldest old.* Age Ageing, 2010. **39**(3): p. 331-7.

90. Alfaro-Acha, A., et al., *Handgrip strength and cognitive decline in older Mexican Americans.* J Gerontol A Biol Sci Med Sci, 2006. **61**(8): p. 859-65.

91. Atti, A.R., et al., *Anaemia increases the risk of dementia in cognitively intact elderly.* Neurobiology of Aging, 2006. **27**(2): p. 278-284.

92. Go, A.S., et al., *Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure - The anemia in chronic heart failure: Outcomes and Resource Utilization (ANCHOR) Study.* Circulation, 2006. **113**(23): p. 2713-2723.

93. Audiffren, M. and N. André, *The strength model of self-control revisited: Linking acute and chronic effects of exercise on executive functions.* Journal of Sport and Health Science, 2015. **4**(1): p. 30-46.

94. Wedderkopp, N., et al., *Study protocol. The Childhood Health, Activity, and Motor Performance School Study Denmark (The CHAMPS-study DK).* BMC Pediatr, 2012. **12**: p. 128.

95. Bugge, A., et al., *LCoMotion - Learning, Cognition and Motion; a multicomponent cluster randomized school-based intervention aimed at increasing learning and cognition - rationale, design and methods.* BMC Public Health, 2014. **14**: p. 967.

96. Larsen, L.R., et al., *Motor Performance as Predictor of Physical Activity in Children: The CHAMPS Study-DK.* Med Sci Sports Exerc, 2015. **47**(9): p. 1849-56.

97. *Testprotokol CHAMPS-III, Svendborgprojektet*, SDU, Editor. 2015.

98. Najmi, S., A.C. Hindash, and N. Amir, *Executive Control of Attention in Individuals with Contamination-Related Obsessive-Compulsive Symptoms.* Depression and anxiety, 2010. **27**(9): p. 807-812.

99. Wostmann, N.M., et al., *Reliability and plasticity of response inhibition and interference control.* Brain Cogn, 2013. **81**(1): p. 82-94.

100. Donnelly, J.E., et al., *Physical activity and academic achievement across the curriculum (A + PAAC): rationale and design of a 3-year, cluster-randomized trial.* BMC Public Health, 2013. **13**: p. 307.

101. Hillman, C.H., et al., *Aerobic fitness and cognitive development: Event-related brain potential and task performance indices of executive control in preadolescent children.* Dev Psychol, 2009. **45**(1): p. 114-29.

102. *Kognition protolol (CHAMPS 3)*, RICH, Editor. 2015.

103. Ruiz, J.R., et al., *Field-based fitness assessment in young people: The ALPHA health-related fitness test battery for children and adolescents.* British Journal of Sports Medicine, 2011. **45**(6): p. 518-524.

104. Matsudo, V.K.R., et al., *Handgrip strength as a predictor of physical fitness in children and adolescents.* Revista Brasileira de Cineantropometria e Desempenho Humano, 2014. **17**(1): p. 1-10.

105. Tsigilis, N., H. Douda, and S.P. Tokmakidis, *Test-retest reliability of the Eurofit test battery administered to university students.* Percept Mot Skills, 2002. **95(**3 Pt 2): p. 1295-300.

106. DA, S., *The Physical Test of a Man.* American Physical Education Review, 1921. **26**: p. 188-194.

107. de Salles, P.G., et al., *Validity and reproducibility of the sargent jump test in the assessment of explosive strength in soccer players.* J Hum Kinet, 2012. **33**: p. 115-21.

108. *SÅDAN UDFØRES MÅLING AF HOPPEHØJDE – SARGENT JUMP TEST*. Sund Skole Nettet.

109. Ortega, F.B., et al., *Physical fitness in childhood and adolescence: a powerful marker of health.* Int J Obes (Lond), 2008. **32**(1): p. 1-11.

110. Canhadas, I.L., et al., *Anthropometric and physical fitness characteristics of young male soccer players.* Revista Brasileira de Cineantropometria e Desempenho Humano, 2010. **12**(4): p. 239-245.

111. Wedderkopp, N.e.a., *Appendices CHAMPS Study-DK*. 2012.

112. Portney, L., Watkins, MP, *Foundations os Clinical Research Applicatons to Practice*. 3 ed. 2014, Harlow,Essex: Pearsons Education Limited. 842.

113. Bangirana, P., et al., *The Association between Cognition and Academic Performance in Ugandan Children Surviving Malaria with Neurological Involvement.* PLoS ONE, 2013. **8**(2).

114. Fernando, S.D., C. Rodrigo, and S. Rajapakse, *The 'hidden' burden of malaria: cognitive impairment following infection.* Malar J, 2010. **9**: p. 366.

115. Raji, M.A., et al., *Cognitive status, muscle strength, and subsequent disability in older Mexican Americans.* J Am Geriatr Soc, 2005. **53**(9): p. 1462-8.

116. O'Bryant, S.E., et al., *Detecting Dementia with the Mini-Mental State Examination (MMSE) in Highly Educated Individuals.* Archives of neurology, 2008. **65**(7): p. 963-967.

117. Herting, M.M. and B.J. Nagel, *Aerobic fitness relates to learning on a virtual Morris Water Task and hippocampal volume in adolescents.* Behavioural Brain Research, 2012. **233**(2): p. 517-525.

118. Raine, L.B., et al., *The Influence of Childhood Aerobic Fitness on Learning and Memory.* PLoS ONE, 2013. **8**(9): p. e72666.

119. Davis, C.L., et al., *Exercise Improves Executive Function and Achievement and Alters Brain Activation in Overweight Children: A Randomized, Controlled Trial.* Health Psychology, 2011. **30**(1): p. 91-98.

120. Dustman, R.E., et al., *Age and fitness effects on EEG, ERPs, visual sensitivity, and cognition.* Neurobiol Aging, 1990. **11**(3): p. 193-200.

121. Hillman, C.H., et al., *Physical activity and cognitive function in a cross-section of younger and older community-dwelling individuals.* Health Psychol, 2006. **25**(6): p. 678-87.

122. Bianco, A., et al., *A systematic review to determine reliability and usefulness of the field-based test batteries for the assessment of physical fitness in adolescents - The ASSO Project.* International Journal of Occupational Medicine and Environmental Health, 2015. **28**(3): p. 445-478.

123. Spitzer, M.W.H. and M. Furtner, *Being physically active versus watching physical activity - Effects on inhibitory control.* Trends in Neuroscience and Education, 2016. **5**(1): p. 30-33.

124. Kohl HW III, C.H., *Educating the Student Body: Taking Physical Activity and Physical Education to School*. 2013, IOM (Institute of Medicine). Washington, DC. p. 503.

125. Zeischka, P., et al., *Reduced congruency effects only for repeated spatial irrelevant information.* European Journal of Cognitive Psychology, 2010. **22**(8): p. 1137-1167.

126. Bunge, S.A., et al., *Immature frontal lobe contributions to cognitive control in children: evidence from fMRI.* Neuron, 2002. **33**(2): p. 301-11.

127. Davidson, M.C., et al., *Development of cognitive control and executive functions from 4 to 13 years: Evidence from manipulations of memory, inhibition, and task switching.* Neuropsychologia, 2006. **44**(11): p. 2037-2078.

128. Luna, B., *Developmental Changes in Cognitive Control through Adolescence*, in *Advances in Child Development and Behavior*. 2009. p. 233-278.

129. Luna, B., et al., *Maturation of cognitive processes from late childhood to adulthood.* Child Dev, 2004. **75**(5): p. 1357-72.

130. Tanner, J., *Growth at adolescence; with a general consideration of the effects of hereditary and environmental factors upon growth and maturation from birth to maturity*. Vol. 2. 1962, Oxford: Blackwell Scientific Publications.

131. Wood, R. *Handgrip Strength Test*. 2008 31.05.2016]; Available from: http://www.topendsports.com/testing/tests/handgrip.htm.

132. España-Romero, V., et al., *Elbow position affects handgrip strength in adolescents: Validity and reliability of jamar, dynex, and TKK dynamometers.* Journal of Strength and Conditioning Research, 2010. **24**(1): p. 272-277.

133. Roberts, H.C., et al., *A review of the measurement of grip strength in clinical and epidemiological studies: Towards a standardised approach.* Age and Ageing, 2011. **40**(4): p. 423-429.

134. Crane, P.K., et al., *Composite scores for executive function items: Demographic heterogeneity and relationships with quantitative magnetic resonance imaging.* Journal of the International Neuropsychological Society, 2008. **14**(5): p. 746-759.

135. Gibbons, L.E., et al., *A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment.* Brain Imaging and Behavior, 2012. **6**(4): p. 517-527.

List of appendences:

Appendix 1: -illustration of HG

The picture is from the protocol CHAMPS – III [97]

Appendix 2: Questionaire

The students and parents have filled in 2 questionnaires. It is chosen to cut out the relevant questions for this thesis.

32) Hvad er jeres højeste uddannelsesniveau

a) Skriv for mor (f.eks. folkeskole

EFG, HG, gymnasial, bachelor, ____________________

master eller kandidat)

b) Skriv for far (f.eks. folkeskole,

EFG, HG, gymnasial, bachelor, ____________________

master eller kandidat)

36) Hvor stor var husstandens bruttoindkomst i år 2007, dvs. før skat og andre fradrag er trukket fra?

(1) ❑ Mindre end kr. 199.000

(2) ❑ Kr. 200.000 - 299.000

(3) ❑ Kr. 300.000 - 399.000

(4) ❑ Kr. 400.000 - 499.000

(5) ❑ Kr. 500.000 - 599.000

(6) ❑ Kr. 600.000 - 699.000

(7) ❑ Kr. 700.000 - 799.000

(8) ❑ Mere end kr. 800.000

26) Hvad er den højest bestående uddannelse (angiv ikke eventuelt igangværende uddannelsesforløb)?

26a) Mor/kvindelig værge

(1) ❑ Folkeskole (9. klasse)
(2) ❑ 10. klasse
(3) ❑ Gymnasial uddannelse (f.eks. HHX, HTX, HH)
(4) ❑ Erhvervsuddannelse (f.eks. HG, handelsuddannelse, tømrer, murer, erhvervspraktisk uddannelse, social- og sundhedshjælper)
(5) ❑ Kort videregående uddannelse (f.eks. tandplejer, byggetekniker, handelsøkonom, datamatiker)
(6) ❑ Mellemlang videregående uddannelse (f.eks. lærer, fysioterapeut, sygeplejerske, bachelor, diplomingeniør)
(7) ❑ Lang videregående uddannelse (f.eks. kandidatgrad, læge, civilingeniør)

26b) Far/mandlig værge

(1) ❑ Folkeskole (9. klasse)
(2) ❑ 10. klasse
(3) ❑ Gymnasial uddannelse (f.eks. HHX, HTX, HH)
(4) ❑ Erhvervsuddannelse (f.eks. HG, handelsuddannelse, tømrer, murer, erhvervspraktisk uddannelse, social- og sundhedshjælper)
(5) ❑ Kort videregående uddannelse (f.eks. tandplejer, byggetekniker, handelsøkonom, datamatiker)
(6) ❑ Mellemlang videregående uddannelse (f.eks. lærer, fysioterapeut, sygeplejerske, bachelor, diplomingeniør)
(7) ❑ Lang videregående uddannelse (f.eks. kandidatgrad, læge, civilingeniør)

Vedrørende udlån af opgave

Undertegnede, Trine Muckert

(navn(e) med blokbogstaver), har indleveret:

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- [ ] Hovedopgave
- [ ] Prisopgave
- [ ] Masterafhandling
- [ ] Ph.d.-afhandling

med titlen: Muscle fitness as a predictor for cognition

med henblik på erhvervelse af graden / titlen: Cand Scient Fys

til godkendelse ved center / institut/ fakultet: Sundhedsvidenskabelige fakultet

(stempel)

Såfremt vejleder er tilknyttet andet center / institut, angiv da hvilket: ____________________

Undertegnede tillader, at ovennævnte opgave efter godkendelse stilles til rådighed for en udlånsordning i form af benyttelse på læsesal på danske (og evt. udenlandske) biblioteker:

[x] JA (straks), eller først efter [ ] 5 år, [ ] 10 år regnet fra udgivelsesåret.

[ ] NEJ. Hvorfor ikke tilgængeligt? [ ] Fortrolige oplysninger, [ ] Påtænker fortsat forskning indenfor området, [ ] Andet.

Undertegnede tillader, at opgaven eller dele af den må kopieres til eget brug:

- [x] JA
- [ ] NEJ

Dato: 24.05.2016 Underskrift(er): Trine Muckert

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