CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author:

Provisional Paper Title:	The physical fitness-cognition association from adolescence to midlife: Physiological mechanisms and sex differences
Proposing Author:	Andreas Stenling
Other Contributors:	Liana Machado, Magnus Lindwall, Richie Poulton, Terrie Moffitt
Potential Journals:	
Intended Submission Date	30/09/18

Please keep one copy for your records and return one to the proposing author

B. To be completed by potential co-authors:

[xx] Approved [ ] Not Approved [ ] Let's discuss, I have concerns

Comments: Thank you for the polishing of the concept paper. I look forward to the project. Temi

Please check your contribution(s) for authorship:

x	Conceptualising and designing the longitudinal study
x	Conceptualising and collecting one or more variables
x	Data collection
x	Conceptualizing and designing this specific paper project
	Statistical analyses
	Writing
x	Reviewing manuscript drafts
x	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature: Temi Moffitt 13 May, 2018

CONCEPT PAPER TEMPLATE	
Provisional Paper Title:	The physical fitness-cognition association from adolescence to midlife: Physiological mechanisms and sex differences
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P.I. Sponsor (if the proposing author is a student or colleague of an original PI)	Richie Poulton

Objective of the study:

A growing body of evidence suggests that higher physical fitness is associated with several health benefits, such as decreased risk of obesity, hypertension, and better cognitive function (Ross et al., 2016; Verburgh et al., 2014). However, the direction of associations remains unclear and we still have limited understanding of how associations might change across the life course (Bielak, 2010). Despite many studies showing positive effects of physical fitness on cognition, most of them are prone to the possibility of reverse causation as childhood cognitive function has been identified as a predictor of better physical and brain health later in life (cf. Belsky et al., 2015; Gow et al., 2012, 2017). In a recent study on the Dunedin Study cohort Belsky et al. (2015) addressed the issue of reversed causation by testing the hypotheses of neuroprotection and neuroselection in the physical fitness-cognition association. Using a between-person regression-based statistical approach they found support for a neuroselection effect, but not a neuroprotection effect, suggesting that people with better cognitive function early in life are selecting healthier lifestyles.

With the exception of Belsky et al. (2015) and studies on the Lothian Birth Cohort (e.g., Gow et al., 2012, 2017), very few studies have examined the effects of physical fitness on cognition while controlling for cognitive function early in life. Moreover, very little research has been conducted with young or middle-aged healthy adults (Etnier et al., 2016) and our understanding of the mechanisms and moderators of the physical fitness-cognition association is still limited (Etnier et al., 2016; Leckie et al., 2012; Stillman et al., 2016). In addition, few studies have compared between-person and within-person results. This is important because (a) inferences from cross-sectional studies seldom align with inferences from longitudinal data, (b) results are rarely decomposed into between- and within-person effects, which leads to results being interpreted as within-person changes even though they likely represent a mix of within- and between-person effects, and (c) very often results differ between the levels (Robitaille et al., 2014).

The present study investigates how between-person differences and within-person changes in physical fitness from adolescence (age 15) to midlife (age 38) predicts cognitive function at midlife, while controlling for cognitive function early in life (ages 7 to 13). It also examines whether between-person differences and within-person changes in blood pressure and body mass index mediate the effect of physical fitness on cognition (cf. Spirduzo et al., 2008; see also Chan et al., 2013; Falkner, 2010; Iadecola et al., 2016; Ross et al., 2016; and Wang et al., 2016, for reviews of the proposed associations in the current study). Finally, we will also examine if sex moderates the direct associations between physical fitness, blood pressure, body mass index, and cognition, and the indirect fitness-cognition association (cf. Etnier et al., 2016; Leckie et al., 2012). Previous research indicates that physical fitness may have sex-specific effects on cognitive functioning among older adults (e.g., Baker et al., 2010; Colcombe & Cramer, 2003). However, the role of sex as a moderator with younger samples has not been established (Etnier & Labban, 2012). A conceptual model is graphically depicted in Figure 1 outlining the hypothesized relationships.

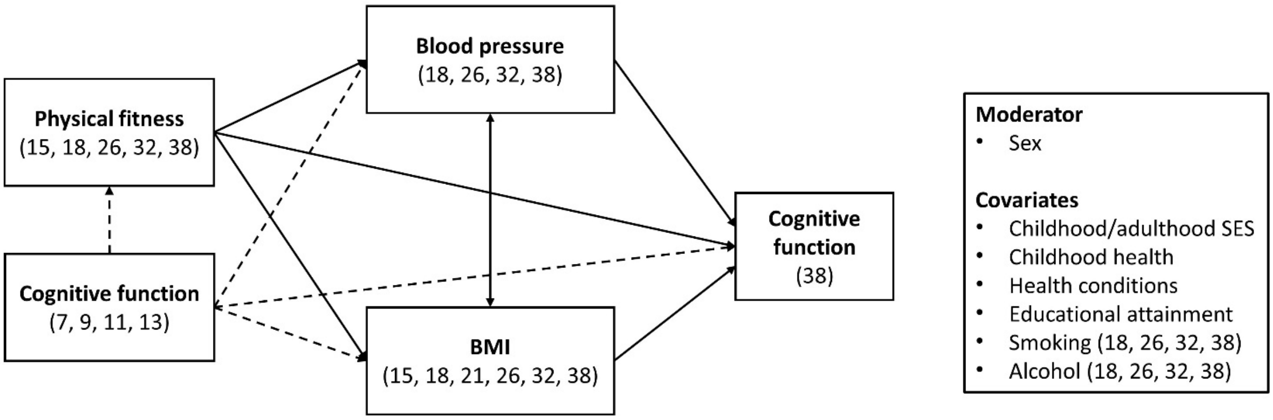

Figure 1. Conceptual model. Ages when the variables were measured are shown in the parentheses.

We propose the following hypotheses at the between-person level:

a) Higher physical fitness will be associated with lower blood pressure and lower BMI.

b) In line with Belsky et al. (2015), higher physical fitness will not be directly associated with midlife cognitive function when controlling for childhood cognitive function.

c) Lower blood pressure and BMI will be associated with better midlife cognitive function.

d) Higher physical fitness will be indirectly associated with better midlife cognitive function through blood pressure and BMI.

We propose the following hypotheses at the within-person level:

a) Higher physical fitness will be associated with lower blood pressure and BMI.

We propose the following hypotheses related to the associations of change from adolescence to midlife (i.e., using the within-person level slopes as predictors or mediators at the between-person level):

a) An increase (or a smaller decline) in physical fitness will be associated with a smaller increase in blood pressure and BMI.

b) An increase (or a smaller decline) in physical fitness will be associated with better midlife cognitive function.

c) Smaller increases in blood pressure and BMI will be associated with better midlife cognitive function.

d) An increase (or a smaller decline) in physical fitness will be indirectly associated with better midlife cognitive function through smaller increases in blood pressure and BMI.

Given the scarcity of research in younger samples we do not propose specific hypotheses about sex as a moderator. However, we follow suggestions in the literature that sex is important to consider when designing studies, analyzing data, and interpreting the results from studies on the fitness-cognition association (e.g., Leckie et al., 2012).

There are some similarities between the proposed study and Belsky et al. (2015), which also involved the Dunedin Study cohort, therefore we want to highlight some of the main differences between the two studies. In the present study we build on and extend the findings of Belsky et al. in the following ways:

- We will include physical fitness measures from earlier ages (from 15 to 38). The inclusion of fitness at earlier ages enables us to examine if changes in fitness over time are related to cognitive function in midlife. Level of and change in a variable can oftentimes show different associations with outcomes and very few studies have examined how changes in fitness over time are related to cognitive function. Changes in fitness over time can still be associated with midlife cognitive function, even if the association between fitness levels and cognitive function at age 38 is not statistically significant.
- We will examine sex differences by including sex as a moderator in the analyses. We are interested in whether males and females show similar (or different) developmental trajectories and associations between the variables over time. The inclusion of sex as a moderator will also allow us to examine moderated indirect associations (sometimes referred to as moderated mediation) between fitness and cognition over time. Furthermore, the statistical approach will allow us to examine sex differences in all of the main paths in the model.
- By using longitudinal multilevel modeling we will be able to decompose the effects into between-person and within-person parts. Analyses of between-person effects (when examining peoples' level compared to other peoples' level) often differ from analyses of within-person effects (when comparing people to their own mean over time), which indicates that they are two distinct types of effects that are important to distinguish.
- We will explore physiological (blood pressure and BMI) mediators of the fitness-cognition association. Direct associations are not a prerequisite for testing indirect associations, which makes it interesting to test for mediating variables even if the direct association between physical fitness and cognitive function is not statistically significant.

Data analysis methods:
The primary statistical analysis in the present study will be longitudinal multilevel structural equation modeling (MSEM) to decompose effects into between-person and within-person parts (Lüdtke et al., 2008). Multilevel mediation analysis, moderation analysis, and moderated mediation analysis will be conducted following recommended approaches proposed by Preacher et al. (2010) and Preacher et al. (2016). All repeatedly assessed variables will be examined for trends and detrending procedures will be used when appropriate (Wang & Maxwell, 2015). We will also use growth modeling to examine how changes in fitness are related to changes in blood pressure and BMI, and in turn, how these changes are related to cognitive function at age 38 (i.e., by using within-person level slopes as predictors and mediators at the between-person level), while controlling for early-life cognitive function.

Missing data will be handled by using either the full information maximum likelihood (FIML) estimation or multiple imputation (MI), which produces unbiased estimates under the assumption that the data is missing at random (MAR; Enders, 2010). FIML estimation and MI uses all available data in the analyses, hence, participants with partial missing data will not be excluded from the analyses. We will also examine the dropout pattern across waves and if the data is not MAR, we will use missing not at random (MNAR) models to analyze the impact of the missing data pattern on the parameter estimates (Enders, 2010, 2011).

Independent variable:

- Physical fitness at ages 15, 18, 26, 32, 38

Mediators:

- Blood pressure at ages 18, 26, 32, 38
- Body mass index at ages 15, 18, 21, 26, 32, 38

Dependent variables:

- Cognitive function at age 38
- Cognitive complaints at age 38

Moderator:

- Sex

Covariates: childhood cognitive function, childhood and adulthood socioeconomic status, childhood health, health conditions, educational attainment, smoking, alcohol consumption

Variables needed at which ages:

- Physical fitness – predicted maximum oxygen uptake [VO2max] (ages 15, 18, 26, 32, 38; see e.g., Hancox & Rasmussen, 2018)
- Blood pressure (ages 18, 26, 32, 38; see Theodore et al., 2015)
- BMI (ages 15, 18, 21, 26, 32, 38; see Williams et al., 2017)
- Cognitive function (all ages of WISC and WAIS, the Rey Auditory Verbal Learning Test, the Trail Making Test, and the Grooved Pegboard Test; see Belsky et al., 2015)
- Cognitive complaints (age 38; questions COG1-COG21)
- Childhood socioeconomic status (from Belsky et al., 2015)
- Adulthood socioeconomic status (ages 26, 32, 38; see Shearer et al., 2017)
- Childhood health index (from Belsky et al., 2015)
- Health conditions at age 38 (asthma, type 1 or 2 diabetes, arthritis, cancer, Crohn disease, hepatitis C, lupus, multiple sclerosis, and insomnia; see Goldman-Mellor et al., 2014).
- Educational attainment (from Belsky et al., 2015)
- Alcohol consumption (ages 18, 26, 32, 38; see Theodore et al., 2015)
- Smoking (ages 18, 26, 32, 38; see Theodore et al., 2015)
- Age
- Sex

Significance of the study (for theory, research methods or clinical practice):

The significance of this project is both for theory development and clinical practice. We will test parts of Spirduso et al.'s (2008) conceptual model of mediators as resources and reserves in the fitness-cognition association. It will shed light on physiological (blood pressure and BMI) factors that potentially mediate the effects of physical fitness on cognition, which have been called for in the literature but seldom addressed (Stillman et al., 2016). The ability to account for early-life cognitive function also addresses the question of reverse causation in the fitness-cognition association and provides a rigorous test of the direct and indirect effects of physical fitness on cognition from adolescence to midlife. The decomposition of between- and within-person effects can show whether the associations are similar when individuals are compared to other individuals (i.e., between-person effects) and when they are compared to themselves over time (i.e., within-person effects). In addition, the present study will not only address the question "if" fitness is related to cognition, it will also address "how" fitness relates to cognition (i.e., mediating effects), and "for whom" the effects are weaker or stronger (i.e., moderating effects), providing knowledge that can be used to tailor future interventions.

Data from this study may be subjected to integrative data analysis (IDA; Curran & Hussong, 2009; Hofer & Piccinin, 2009) by pooling the data with data from other birth cohort studies "to maximize opportunities for replication and extension of findings across longitudinal studies…" (Hofer & Piccinin, 2009, p. 150). A separate concept paper will be submitted for the use of Dunedin Study data in an IDA study.

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Data Security Agreement (customize as necessary)

A

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Proposing Author	Andreas Stenling
Today's Date	10/May/2018

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement

My project is covered by Dunedin Study's ethics approval *OR* I have /will obtain ethics approval from my home institution.

I will treat all data as "restricted" and store in a secure fashion.

I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.

I will not post data online or submit the data file to a journal for them to post.
Some journals are now requesting the data file as part of the manuscript submission process. Data from the Dunedin Study cannot be shared because the Study Members have not given informed consent for unrestricted open access. Speak to Richie Poulton, DMHDRU Director for strategies for dealing with data sharing requests from Journals.

Before submitting my paper to a journal, I will submit my draft manuscript and scripts for data checking, and my draft manuscript for co-author mock review, allowing three weeks.

I will not submit my paper until I have received final approval from the Director, Richie Poulton, as per Unit policy

I will submit analysis scripts and new variable documentation to DMHDRU data manager after manuscript gets accepted for publication.

I will return all data files to the PI responsible and/or DMHDRU Data Manager after the project is complete. The data remains the property of the Study and cannot be used for further analyses without express, written permission.

Signature: